Evaluation of Clinical Data

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Content

1 Background: the medical use of cannabinoids and their side effects

The Volcano inhalation system is intended for the inhalation of cannabinoids from the cannabis plant (Cannabis sativa L.), either for the inhalation of single cannabinoids (mainly dronabinol) or for the inhalation of ingredients of products of the whole cannabis plant. This chapter summarizes accepted medical uses of single cannabinoids and whole plant preparations, possible side effects and the legal framework for the medical use of dronabinol and cannabis in several countries.

1.1 Cannabis, the cannabinoids and dronabinol - explanation of terms

Cannabis sativa L. is the botanical name and Latin binomial of hemp. Cannabis is among the very oldest of economic plants, providing fibre, edible seed, and drug resin. Human selection for varying uses and natural selection pressures imposed by diverse climates have resulted in a wide variety of growth forms and chemical compositions. The production of cannabinoids is unique to cannabis, and cultivars with specific chemical profiles are being developed for diverse potential pharmaceutical uses. Natural cannabis based medicines approved for medical use in several countries are Marinol®, which contains the cannabinoid dronabinol, and Sativex®, a cannabis extract containing equal amounts of the cannabinoids dronabinol and cannabidiol.

Dronabinol is the International Non-proprietary Name (INN) of the (-)-*trans*-isomer of Δ^9-tetrahydrocannabinol (Δ^9-THC), the primary psychoactive compound in botanical cannabis. Marijuana (marihuana) is a colloquial name for dried leaves and flowers of cannabis varieties rich in dronabinol (1-25% dronabinol). Hashish is an Arabic name for cannabis resin or compressed resin glands, containing 5-20% dronabinol. Depending on dronabinol and cannabidiol content "hemp" can be divided into fibre and drug types. There are regional differences in the employment of the terms cannabis, hemp and marijuana. In the USA and Canada the term "hemp" is usually only applied to fibre hemp in contrast to the term "marijuana", while in many regions of Europe hemp ("Hanf") can be applied to drug types as well (in the sense of the old term "Indian hemp"). While in the United Kingdom the term cannabis is preferred in the context of medical use, in the USA and Canada the term marijuana ("medical marijuana") is used most often.

In a more narrow sense the term "cannabinoid" designates the natural phytocannabinoids of the cannabis plant. In the broadest sense, it includes all ligands of the cannabinoid receptors of the human body and related compounds. In the context of this paper the term cannabinoid refers to natural phytocannabinoids of the cannabis plant. In the plant variable amounts of dronabinol are accompanied by significant quantities of cannabigerol (CBG), cannabidiol (CBD), and cannabichromene (CBC). There are over 60 cannabinoids present in the plant, although most of these, plus about four hundred other compounds, exist only in small to minuscule quantities, relative to the four major cannabinoids and their sporadically occurring propyl, and rare methyl, C-3 homologs.

Figure 1: Chemical structure of dronabinol according to two different numbering systems

1.2 Medical uses of cannabis based medicines

Mechanisms of action of cannabinoids are complex, not only involving activation of and interaction at the cannabinoid receptors of the human body, but also increase of endocannabinoid concentration - endocannabinoids are endogenous ligands of cannabinoid receptors -, antioxidant activity, metabolic interaction with other compounds, and several others.

Currently two cannabinoid receptor agonists, dronabinol and nabilone, as well as a cannabis extract (Sativex®), are in medical use. In addition, cannabis herb produced ac-cording to pharmaceutical standards and supervised by the Office of Medicinal Cannabis of the Dutch Health Ministry is available in pharmacies of the Netherlands (Grotenhermen 2005). In some countries the possession of small amounts of cannabis either for recreational or medicinal use is allowed or tolerated, such as in the Netherlands, Spain, Belgium and some regions of Switzerland. Twelve states of the USA (Alaska, California, Colorado, Hawaii, Maine, Montana, Nevada, New Mexico, Oregon, Rhode Island, Vermont, Washington) have legalized the medical use of cannabis under state law, while it remains illegal under federal law. In Canada it is possible to apply for a certificate of exemption to use otherwise illegal cannabis for medical purposes, and the Health Ministry (Health Canada) sells cannabis herb to these patients if they do not want to grow it themselves.

In 1985 the Food and Drug Administration (FDA) of the United States approved Marinol® Capsules, which contain synthetic dronabinol (2.5 mg, 5 mg or 10 mg), for nausea and vomiting associated with cancer chemotherapy in patients that had failed to respond adequately to conventional anti-emetic treatments. Marinol® is manufactured by Unimed Pharmaceuticals, a subsidiary of Solvay Pharmaceuticals. Marinol® has been on the market in the USA since 1987. In 1992 the FDA approved Marinol® Capsules for the treatment of anorexia associated with weight loss in patients with AIDS. Marinol is also available on prescription in several other countries including Canada and several European countries. In Germany and Austria dronabinol, which is manufactured by the two German companies THC Pharm and Bionorica Ethics, may be bought by

pharmacies to produce dronabinol capsules or solutions, which may be taken orally (oily solutions) or inhaled (alcoholic solutions) by using a vaporizer.

In 1985 the FDA also approved Cesamet® Capsules for the treatment of nausea and vomiting associated with chemotherapy. Cesamet® made by Eli Lilly and Company contains nabilone, a synthetic derivative of dronabinol. However, it was not marketed in the USA and Lilly discontinued the drug in 1989. Cesamet® is also available in the United Kingdom marketed by Cambridge Laboratories and in several other European countries. In 2006 nabilone (Cesamet®) again got approval by the FDA as a prescription treatment for nausea and vomiting associated with chemotherapy. It is marketed by Valeant Pharmaceuticals International, which bought the drug from Eli Lilly in 2004 and also sells it in Canada.

In 2005 Sativex® received approval in Canada for the symptomatic relief of neuropathic pain in multiple sclerosis. Sativex® is produced by the British company GW Pharmaceuticals and marketed in Canada by Bayer Health Care. Sativex® is a cannabis extract, which is sprayed in the oro-mucosal area and contains approximately equal amounts of dronabinol and cannabidiol. There is also limited access to Sativex® in the UK, Luxembourg and Spain.

Preparations under investigation in clinical phase II or III studies include the capsulated cannabis extract Cannador®, which contains dronabinol and other cannabinoids in a ratio of 2 to 1 and is being investigated by the Institute for Clinical Research in Berlin, Germany, and the pharmaceutical company Weleda, and ajulemic acid, a synthetic derivative of THC-COOH, which is also called CT3 or IP751 and is being investigated by Indevus Pharmaceuticals.

Possible indications for cannabis preparations have been extensively reviewed (British Medical Association 1997, Grinspoon & Bakalar 1993, Grotenhermen 2002, House of Lords Select Committee on Science and Technology 1998, Joy et al. 1999, Mechoulam 2007, Guy et al. 2004, Russo & Grotenhermen 2006). To do justice to the scientific evidence with regard to different indications, a hierarchy of therapeutic effects can be devised, with established effects, effects with clinical and preclinical confirmation and effects based

on preclinical, mechanistic studies. Data on established effects are briefly reviewed in the following paragraphs.

Dronabinol (Marinol®) is approved in several countries for the medical use in refractory nausea and vomiting caused by anti-neoplastic drugs used for the treatment of cancer and for appetite loss in anorexia and cachexia of HIV/AIDS patients. These effects can be regarded as established effects for dronabinol and cannabis. Nabilone (Cesamet®) is the second cannabinoid available on prescription, against nausea and vomiting associated with cancer chemotherapy.

In more than 30 studies dronabinol and nabilone have been shown to have a similar anti-emetic efficacy as the phenothiazines (for review see: Plasse 2002). In the 1980s several clinical studies with smoked cannabis have been performed in the USA, in which smoked cannabis was similar effective as dronabinol (for review see: Musty & Rossi

2001). In a clinical setting 5-HT3 antagonists are usually superior to dronabinol, but the cannabinoid has proven to be effective at least in some cases of intractable nausea and vomiting (Gonzalez-Rosales & Walsh 1997). Dronabinol was demonstrated to be as effective as ondansetron in delayed nausea and vomiting after chemotherapy and the addition of low doses of dronabinol to the standard medication improved the outcome of acute nausea and vomiting (Meiri et al. 2007). Dronabinol was shown to have therapeutic value also in nausea and vomiting due to other causes, due to antiretroviral therapy (Anderson 2000), after surgery (Layeeque et al. 2006) and in nausea of patients with liver metastases in melanoma (Zutt et al. 2006). The use of cannabis was reported to be associated with an improved compliance in patients with hepatitis C, who underwent a treatment with interferon and ribavirin, which was attributed to the anti-emetic effects of cannabis, among others (Sylvestre et al. 2006).

Dronabinol is effective in AIDS wasting (Beal et al. 1995, Beal et al. 1997, Dejesus et al. 2007, Haney et al. 2007) and cancer cachexia (Jatoi et al. 2002).

Neuropathic pain is another indication, which can be regarded as established for a treatment with cannabis-based medicines. Sativex is available in Canada for the relief of neuropathic pain in multiple sclerosis. Several case reports and small clinical studies indicate that dronabinol, nabilone and cannabis may be effective in treating several chronic pain conditions (Abrams et al. 2007a, Seeling et al. 2006, Holdcroft et al. 2006, Schley et al. 2006, Pinsger et al. 2006, Beaulieu 2006, Wissel et al. 2006, Rog et al. 2005, Berman et al. 2004, Svendsen et al. 2004, Wade et al. 2003, Krenn et al. 2003, Lynch & Clark 2003, Elsner et al. 2001, Hamann & di Vadi 1999, Holdcroft et al. 1997, Maurer et al. 1990, Noyes et al. 1975a, Noyes et al. 1975b, Petro 1980).

1.3 Possible side effects of the medical use of cannabis and dronabinol

The side effects of recreational cannabis use have been extensively reviewed (e.g. Hall & Solowij 1998, House of Lords 1998, Joy et al. 1999, Ashton 2001, Kalant 2004, Grotenhermen 2007). A widely accepted opinion has been expressed in the report of the U.S. Institute of Medicine of 1999 on the medical use of cannabis: "Marijuana is not a completely benign substance. It is a powerful drug with a variety of effects. However, except for the harms associated with smoking, the adverse effects of marijuana use are within the range of effects tolerated for other medications" (Joy et al. 1998).

In principle, the side effects associated with the medical use of cannabis and dronabinol are similar to those observed with recreational use of cannabis, except that due to several factors side effects are less common with medical use. Among these factors are lower doses with medical use resulting in fewer and less intense acute psychological side effects, higher age of medical users resulting in fewer psychiatric side effects (e.g. dependency), more oral intake and less intake by smoking resulting in fewer respiratory problems.

Because the prevalence of cannabis use has in recent years been on the rise in Europe

and North America and because the potency of cannabis preparations has increased in the past decades there is growing concern about potentially harmful effects of this drug and an ongoing debate on the policy implications of these developments and of our scientific knowledge on the health effects of cannabis (Hall & Degenhardt 2006). During the past decade the literature on adverse effects of cannabis and cannabinoids in humans had focused on effects that are thought to be mediated by the CB1 receptor, including effects on cognitive function, psychiatric effects, and dependence and decline of psychomotor performance that may result in traffic accidents (Kalant 2004). In addition, there is a discussion on the pulmonary and cancer causing effects of smoking cannabis. These are not attributed to any inherent cannabis compounds but to combustion products generated when dried plant material is smoked rather than taken orally or through other advisable modes of administration (Grotenhermen 2004). Scientists generally agree on the acute and short-lasting effects of cannabis, while questions and controversy remain regarding possible chronic and long-term effects.

One cannot easily draw a clear line between desired medicinal and undesirable side effects of cannabis and THC, and this line may vary with the indication. Desirable effects in one case may be unwanted in another. This is not only the case for psychological effects, such as euphoria and sedation, but also for somatic effects such as increase in appetite or muscle relaxation, which are regarded as therapeutic in most cases but may be unwanted in others. For example some patients find sedation or somnolence desirable under certain circumstances, e.g. during chemotherapy (Tramer et al. 2001). In severe illness such as AIDS and cancer not only the physical effects (analgesia, appetite enhancement and anti-emetic effects) but also psychological effects (mood enhancement and anxiolytic action) may be of great value (Joy et al. 1999).

1.3.1 Acute side effects

The acute toxicity of dronabinol is low. Acute lethal human toxicity for cannabis has not been substantiated. The median lethal dose (LD_{50}) of oral dronabinol in rats was 800-1900 mg/kg depending on sex and strain (Thompson et al. 1973). There were no cases of death due to toxicity following the maximum THC dose in dogs (up to 3000 mg/kg THC) and monkeys (up to 9000 mg/kg THC) (Thompson et al. 1973).

Above a person's individual threshold, consumption of cannabis and isolated dronabinol may cause adverse effects on the central nervous system and peripheral organ systems, of which possible unwanted effects on psyche and circulation are the most relevant for the health of the user. The large intra-individual variation of this threshold is illustrated by the different daily doses tolerated by patients in clinical studies. In a study by Wade et al. (2004) with 160 multiple sclerosis patients who received an oral cannabis extract, the maximum daily doses varied between 2.5 and 120 mg dronabinol. Hagenbach et al. (2006) studied the effects of dronabinol in 25 patients with spinal cord injury; maximum daily oral doses varied between 15 and 60 mg. With inhalation the threshold for psychological effects is lower (a single dose of about 2-3 mg dronabinol) compared to oral intake (a single dose of usually about 5-20 mg THC).

Since tolerance develops to dronabinol in the central nervous system and regarding several other effects, regular cannabis users may tolerate considerably higher doses. In a study by Bowman and Pihl (1973) on cognitive performance of cannabis users in Jamaica, participants reported a mean daily intake of about 24.5 g cannabis, corresponding to about 1000 mg dronabinol.

Consumer self-reports of acute clinical effects of cannabis in low to medium doses (2-10 mg inhaled THC) mostly point to qualitative changes in sensory perception with a heightened external and internal sensitivity, especially with regard to visual stimuli, and to distortions of the subjective perception of time. Further effects comprise feelings of well-being, of mild euphoria (the "high"), of relaxation, anxiolysis and sedation (Abood & Martin 1992). However, the individual response to cannabinoids varies between subjects (Hollister 1986).

Inhaled doses of medium strength (10-20 mg THC) may lead to an intensification of emotional responses and reactivity and to more prominent changes in perception and transient hallucinatory experiences (Julien 1998). But these effects are usually avoidable if users inhale cannabis whereby the fast bioavailability gives the consumer good individual control of these responses. In a therapeutic context users should slowly increase the oral dose to avoid overdosing.

Serious unwanted effects generally occur at high single inhaled doses of more than 20 mg THC, but due to the high inter-individual variability, some persons may also experience such effects at lower doses. The most frequent unwanted psychic response is an acute panic reaction, that occurs most often in inexperienced users or at high doses of cannabis (Halikas 1974). The most prominent sign of a panic reaction is the users concern of losing control. It usually remits spontaneously. In a small number of cases, longer lasting or recurrent experiences of depersonalization have been observed. However, as for the more frequent panic reaction and because of their generally mild severity, experiences of depersonalisation in acute cannabis intoxication rarely require further pharmacological intervention (Hollister 1986).

Psychotic symptoms following acute cannabis consumption have been described. Their severity, duration and frequency heavily depended on cultural and personality-related factors as well as on the frequency and intensity of previous cannabis consumption (Bron 1982). A toxic delirium due to cannabis has been observed hitherto only after ultra-high dosages. It becomes manifest by disturbances of memory function, of orientation and of consciousness (Meyer 1974).

THC impairs perception, psychomotor performance, cognitive and affective functions, which all may contribute to a driver's increased risk of causing a traffic accident. A fatal accident is the most serious acute adverse consequence of cannabis use, which may not only harm the user but also other subjects involved. After alcohol, cannabis and benzodiazepines are the drugs most frequently found in impaired drivers and in drivers involved in accidents (Laumon et al. 2005). The detection of THC or THC metabolites in a driver's body usually results from illegal use and rarely from medicinal use. In clinical studies with therapeutic doses of dronabinol or cannabis psychomotor and cognitive

performance were not reduced, suggesting that driving skills may not be impaired by these doses (Haney et al. 2007, Mueller-Vahl et al. 2003).

Dronabinol produces reversible and dose-dependent tachycardia with increased cardiac labour and oxygen demand and increased diastolic blood pressure (in horizontal position) associated with a decreased parasympathetic tone (Clark et al. 1974). Due to tolerance to these effects, chronic use can lead to bradycardia (Jones et al. 1981). At higher dosages, orthostatic hypotension may occur due to a dilation of blood vessels, which may result in dizziness and syncope. Myocardial infarction may be triggered by THC due to these effects on circulation (Bachs & Morland 2001, Mittleman 2001). Dilation of blood vessels also causes conjunctival reddening. THC has a cholinergic effect on the salivary glands leading to hyposalivation and dry mouth. Rare adverse effects are headache or nausea and vomiting. The relaxation of muscles may be accompanied by a reduction in strength and impaired coordination, leading to possible falls. Cannabis rarely causes allergies.

Reports on the effects of cannabinoids on platelet aggregation are conflicting. While Formukong et al. (1989) reported an inhibition by cannabigerol, cannabidiol, THC and cannabinol in *in vitro* studies, Deusch et al. (2004) observed procoagulatory effects of THC in human platelets *in vitro*. The clinical significance of these observations is unclear. In clinical studies laboratory investigations did not reveal any trends of clinical significance in haematological parameters, including parameters relevant for coagulation (Sativex Product Monograph 2005).

In one study the THC derivative nabilone deteriorated choreatic movements in Huntington`s disease (Mueller-Vahl et al. 1999). Thus, cannabinoid receptor agonists may be contraindicated in Huntington's disease.

Cannabinoid-1 receptors are present throughout the gastrointestinal tract. However in the colon and the stomach the densities are the highest. Cannabinoid receptor agonist were shown to inhibit secretory activity and motility of the gut (Coutts & Izzo 2004). They promote inhibition of gastric emptying (Landi et al. 2007) and inhibition of intestinal motility and food transit through the intestines (Izzo et al. 2001, Manara et al. 2002).

1.3.2 Chronic adverse effects

The long-term use of cannabis was not associated with an increased mortality in animals (Chan et al. 1996) and humans (Sidney et al. 1997). A multitude of chronic effects of cannabis use on the immune and endocrine systems, respiratory tract (when inhaled), psyche, cognition, and psychomotor performance have been described. Adverse effects of medical cannabis use are within the range of effects tolerated for other medications (Joy et al. 1998, House of Lords 1999).

There is some biological plausibility from the role of the endocannabinoid system in dopaminergic actions that exogenous ligands of the CB1 receptor may play a causal role in the development of psychosis. On the other hand, increased levels of endocannabinoids in cerebrospinal fluid in patients with schizophrenia may reflect

compensatory adaptation to the disease state (Giuffrida et al. 2004). Evidence from several longitudinal studies published in recent years suggests that the use of cannabis predicts an increased risk of a schizophrenia diagnosis or of reporting symptoms of psychosis (Arsenault et al. 2002, Ferdinand et al. 2005, Fergusson et al. 2003, Henquet et al. 2004, Stefanis et al. 2004, van Os et al. 2004, Zammit et al. 2004). In their review Arseneault et al. (2004) concluded that cannabis use confers an overall twofold increase in the relative risk for later schizophrenia and that it appears to be neither a sufficient nor a necessary cause for psychosis but a component cause, part of a complex constellation of factors leading to psychosis. Degenhardt and Hall (2006) concluded that it is most likely that cannabis use precipitates schizophrenia in individuals who are vulnerable because of a personal or family history of schizophrenia.

Adolescents are thought to be more susceptible to possible toxic effects of cannabis to the brain. Kumra et al. (2005) presented data at the 2005 Meeting of the Radiological Society of North America according to which cannabis use may damage certain brain regions applying diffusion tensor imaging (DTI) (Kumra et al. 2005). They concluded that in addition to interfering with normal brain development, heavy cannabis use in adolescents may also lead to an earlier onset of schizophrenia in individuals who are genetically predisposed to the disorder. In contrast to this result, Delisi et al. (2006) did not find any differences in brains of individuals who were frequent cannabis users in adolescence and control subjects using magnetic resonance imaging (MRI) (Delisi et al. 2006). They concluded that frequent cannabis use is unlikely to be neurotoxic to the normal developing brain refuting the hypothesis that cannabis alone can cause a psychiatric disturbance such as schizophrenia by directly producing brain pathology.

It is generally agreed that cannabis use increases the incidence of psychosis in high-risk groups and worsens the course of psychosis.

It is well established that persons with mental disorders such as schizophrenia, anxiety and depression have a higher rate of tobacco use, cannabis use and alcohol dependence and some scientists have proposed causal relationships between these disorders and alcohol dependency and cannabis use (Degenhardt et al. 2001). Particularly, the use of cannabis by young people may have negative effects on their mental and social development. In his review of 48 long-term studies on cannabis use and psychological and social problems Macleod et al. (2004) did not find a strong support for an important causal relation between cannabis use by young people and psychosocial harm, but could not exclude the possibility that such an association exists. Others see a strong support for a causal relationship (de Irala et al. 2005).

Cannabis use seems to have less effects on the mental health of adults than on adolescents (Harder et. al. 2006, Chen et al. 2002). After adjusting for differences in baseline risk factors of cannabis use and depression, past-year cannabis use did not significantly predict later development of depression in 8759 adults (age range 29-37 years) (Harder et. al. 2006). In a sample of 6792 young adults a small but significant increase in the risk of developing a major depression was found among current cannabis users (Chen et al. 2002). Green and Ritter (2000) found a weak association between

adult cannabis use and depression in 1941 participants of a representative sample of U.S. males from the 1944-1954 birth cohort, but the association disappeared after adjustment for educational attainment, employment status, marital status, and other drug use, notably alcohol and tobacco use (Green & Ritter 2000). Depression was associated with earlier age of first cannabis use rather than with the current level of use. In an Australian twin study Lynskey et al. (2004) found a substantial contribution of genetic vulnerabilities to the association between cannabis use and depression (Lynskey et al. 2004).

Neuropsychological studies have indicated that chronic heavy users may, depending on intensity and duration of use, show impairments of memory, attention, and ability to organize and integrate complex information. A partial explanation for cognitive impairment may be the influence of cannabis use on blood flow in the brain. Cerebrovascular resistance and systolic velocity were significantly increased in cannabis users compared to control subjects and these increases persisted in very heavy users (131 joints per week on average) after a month of monitored abstinence (Herning et al. 2005). In a meta-analysis of studies on cannabis use and cognitive function Grant et al. (2003) found only a small effect of the drug on long-lasting deficits, which would offer an acceptable margin of safety if the drug is used medicinally (Grant et al. 2003). The effect of the drug on cognitive performance may be more pronounced in adolescence (Fergusson et al. 2003, Pope et al. 2003).

Humans can develop tolerance to cannabis-induced cardiovascular and autonomic changes, decreased intraocular pressure, sleep and sleep EEG, mood and certain behavioural changes (Jones et al. 1981).

Clinical long-term studies with THC and cannabis in patients suffering from multiple sclerosis (Zajicek et al. 2005, Wade et al. 2006, Rog et al. 2007), spasticity and pain (Maurer et al. 1990) and AIDS (Beal et al. 1997) did not find tolerance to the medicinal effects of moderate doses (usually 5-30 mg THC daily) within 6-24 months. As with tolerance, withdrawal symptoms are dose-dependent (Budney et al. 2004). Among withdrawal symptoms are irritability, restlessness, insomnia, anorexia, nausea, sweating, salivation, altered sleep, tremor, and weight loss (Jones et al. 1981, Budney et al. 2003). They usually occur after long-term use of higher doses, but may also be observed with low intensity after the long-term use of low doses (Wade et al. 2006, Abrams et al. 2007a).

The U.S. National Comorbidity Study indicated that 9 per cent of lifetime cannabis users met DSM-R-III criteria for dependence at some time in their life, compared to 32 per cent of tobacco users, 23 per cent of opiate users and 15 per cent of alcohol users (Anthony et al. 1994). In a representative Australian sample of 10.641 adults 1.5% were dependent according to DSM-IV and 0.7% were diagnosed with cannabis abuse (Swift et al. 2001). In long-term heavy cannabis users the percentage of dependency may be up to 50% (Swift et al. 2000).

Cannabis and Δ^9-THC act on the hypothalamic-pituitary adrenal axis and in animal studies a multitude of endocrine processes are influenced by the drug, thus affecting

sexual and other hormones (ACTH, TSH, HGH, melatonin) as well as glucose metabolism (Murphy 2002). Changes in human hormone levels due to acute cannabis or THC ingestion are minor and usually remain in the normal range (Hollister 1986). Tolerance develops to these effects and even regular cannabis users demonstrate normal hormone levels.

The endocannabinoid system plays a crucial role in pregnancy. Cannabis use may be associated with a shorter gestation (Fried et al. 1998). THC rapidly crosses the placenta and the course of THC levels in foetal blood coincides well with that in the maternal blood, though foetal plasma concentrations are lower than maternal level in rats (Hutchings et al. 1989). There is evidence of subtle disturbances of cerebral development resulting in cognitive impairment in offspring of cannabis users from two longitudinal studies conducted in Canada and the USA (Fried et al. 2003, Richardson et al. 2002).

Daily cannabis use was a risk factor for progression of fibrosis in chronic hepatitis C in one epidemiological study, while occasional use was not (Hézode et al. 2005).

1.3.3 Risks of cannabis smoking

One of the greatest concerns about chronic effects of recreational cannabis use pertains to the inhalation of combustion products that may damage the mucous membranes, if the drug is smoked as a cannabis cigarette ("joint") or in a pipe. Pyrolysis creates at least 200 thermal degradation products in smoke not found in cannabis, including mutagenic polycyclic hydrocarbons such as benz[α]anthracene, benzo[α]pyrene, naphthalene, and several cresols and phenols (McPartland 2002). The composition of these combustion products is at least qualitatively similar to that of tobacco smoke or that of the smoke generated from other dried plant material, despite some minor differences (British Medical Association 1997). Thus, one would expect similar damage to the mucosa by cannabis smoke as following the use of tobacco. Indeed, signs of airway inflammation (vascular hyperplasia, submucosal oedema, inflammatory cell infiltrates, and goblet cell hyperplasia) were found in bronchial biopsies of cannabis smokers similar to the changes in tobacco smokers (Roth et al. 1998). Regular cannabis smoking in young adults was associated with wheezing, shortness of breath during exercise and the production of sputum as it is known for tobacco smokers (Taylor et al. 2000). Another group found that heavy cannabis smokers had a significantly higher prevalence of chronic cough (18% vs. 0%, respectively), chronic sputum production (20% vs. 0%), wheeze (25% vs. 3.5%) and episodes of acute bronchitis (13% vs. 2%) than non-smokers, while the prevalence of symptoms of chronic and acute bronchitis were not significantly different between cannabis and tobacco smokers (Tashkin et al. 1987).

Biopsies from cannabis smokers have also yielded a higher rate of precancerous pathological changes compared to non-smokers (Barsky et al. 1998), which is suggestive of an increased cancer risk of the respiratory tract and other cancers. So far,

the epidemiological data is inconclusive. A review of two cohort studies and 14 case-control studies by the International Agency for Research on Cancer (IARC) did not find a clear association between cannabis use and cancer (Hashibe et al. 2005). Authors noted that sufficient studies are not available to adequately evaluate the impact of cannabis smoking on cancer risk and available studies often have limitations including too few heavy cannabis users in the study samples. The largest epidemiological study conducted so far with 1212 incident cancer cases and 1040 cancer-free controls did not find a positive association between cannabis smoking and the investigated cancer types (mouth, larynx, lung, pharynx) (Hashibe et al. 2006). There was no dose-effect relationship and even heavy use was not associated with an increased risk. Some smaller studies found a dose-dependent lung cancer risk (e.g. Voirin et al. 2006).

1.3.4 Adverse effects of cannabis and dronabinol in clinical studies

The most frequent adverse effects of cannabis and dronabinol in clinical studies comprise effects on psyche and cognition (euphoria, dizziness, anxiety, sedation, depression etc.) and dry mouth. In addition, nausea may be observed in a considerable number of patients, but it is unclear why it is observed in some studies (see Table 1) but nearly absent in others (Tables 2 and 3). Other acute effects, including spasms and pain differed much as a function of disease and showed no relevant difference between verum and placebo. This supports the assumption that these effects are often not caused by the treatment but the underlying disease (Tables 1-3).

Tables 2 and 3 show adverse drug events for dronabinol (Marinol®) observed in controlled clinical studies. Adverse events from oral cannabis preparations are presented in Table 1 (Sativex®) and Table 2 (Cannador®). Sativex is applied as an oro-mucosal spray and Cannador as well as Marinol in capsules. Events from smoked cannabis are presented in Table 3. Comparisons between cannabis and dronabinol are presented in Tables 2 and 3. Table 2 also compares the frequency of side effects caused by cannabis, dronabinol and a placebo observed in a short study of 15 weeks and a follow-up study of 52 weeks in duration.

There was little difference in side effect profiles between an oral cannabis extract (Cannador) and dronabinol (Marinol) (Table 2) and smoked cannabis vs. dronabinol (Table 3). Compared to a short-term study in patients with multiple sclerosis a long-term therapy with cannabis and dronabinol over a course of 12 months resulted in a dramatic reduction of adverse effects (Table 2). This may be due to the development of tolerance for some symptoms and to the establishment of an individual tolerable dose for every patient. Many clinical acute studies with cannabis or dronabinol start with low doses and slowly increase the dose until side effects appear or a maximum daily dose is reached. Thus, side effects are expected to be observed frequently in acute studies. However, they are usually mild or moderate in intensity (Zajicek et al. 2003). In the long-term study by Zajicek et al. (2005) with 502 patients the incidence of side effects was no longer higher in the verum groups (dronabinol and cannabis) compared to the placebo group except for the events "dizzy or lightheadedness" and "falls" (Table 2) (Zajicek et al.

2005). In studies with dronabinol taken by patients with HIV, similar observations of a reduction in frequency of side effects were made. While about 25% of patients reported a minor CNS-related adverse drug event during the first 2 weeks, only about 4% reported such an event during each of the following six weeks (Marinol 2007).

Table 1: *Side effects of the cannabis extract Sativex® according the product information of the approval in Canada (*Sativex product monograph 2007*). Data were taken from clinical studies with 166 patients treated with Sativex and 162 patients treated with placebo. The table lists all side effects that were observed in 2% of the cases or more.*

Adverse event	**Cannabis (n=166)**	**Placebo (n=162)**
Dizziness	41,6%	13,0%
Fatigue	11,4%	5,6%
Nausea	10,2%	7,4%
Somnolence	8,4%	3,1%
Dry mouth	7,8%	1,9%
Application site pain	7,8%	6,8%
Feeling drunk	7,2%	0,6%
Oral pain	6,6%	6,8%
Disturbance in attention	6,6%	0,0%
Diarrhoea	6,0%	3,1%
Euphoric mood	5,4%	0,6%
Disorientation	4,8%	0,0%
Dysgeusia (abnormal taste)	4,2%	2,5%
Weakness	3,6%	1,2%
Appetite increased	3,6%	1,9%
Pharyngitis	3,6%	1,9%
Mouth ulceration	3,0%	0,6%
Fall	3,0%	1,2%
Lethargy	3,0%	0,6%
Thirst	3,0%	0,0%
Dissociation	3,0%	0,0%
Vomiting	2,4%	0,6%
Sensation of heaviness	2,4%	0,6%

Cough	2,4%	1,9%

In addition to the adverse events reported in these controlled acute studies the following adverse events were observed in patients (>2%) on long-term treatment with Sativex®: headache (8.7%), balance impaired (5%), depressed mood (4%), memory impairment (3.1%) and oral mucosal disorder (3.1%).

Table 2: *Adverse events observed in a 15-week study (Zajicek et al. 2003) and in a 12-month follow-up study (Zajicek et al. 2005) in MS patients who received either the cannabis extract Cannador®, THC (dronabinol, Marinol®) or placebo. In the short-term study 611 patients and in the long-term study 502 patients were evaluable. In the short-term study doses were slowly increased up to the occurrence of side effects or until the maximum dose (10-25 mg THC (dronabinol) depending on body weight daily) was reached.*

Adverse event	**Short-term study (15 weeks)**		**Long-term study (52 weeks)**			
THC	**Cannabis**	**Placebo**	**THC**	**Cannabis**		**Placebo**
Dizzy or lightheadedness	59%	50%	18%	8%	10%	2%
Sleep	35%	40%	33%	8%	8%	9%
Spasms or stiffness	34%	33%	33%	14%	15%	14%
Gastrointestinal tract	30%	37%	20%	9%	12%	7%
Miscellaneous	28%	30%	22%	7%	7%	7%
Pain	26%	24%	32%	10%	17%	10%
Dry mouth	26%	20%	7%	2%	1%	1%
Weakness or reduced mobility	25%	23%	20%	10%	12%	16%
Bladder	24%	26%	23%	10%	12%	15%
Infection	15%	16%	17%	9%	11%	11%
Tremor or lack of coordination	12%	10%	8%	5%	2%	2%
Depression or anxiety	10%	9%	8%	6%	6%	5%
Numbness or paraesthesia	9%	7%	7%	5%	4%	4%
Vision	6%	8%	2%	2%	2%	0%

MS-relapse or exacerbation *)	-	-	-	5%	6%	6%
Falls *)	-	-	-	4%	7%	3%
Memory or concentration *)	-	-	-	2%	2%	1%
Other skin problems *)	-	-	-	1%	5%	6%
Pressure sores *)	-	-	-	0%	1%	3%

*) Not measured in the short-term study

Table 3: *Side effects observed in a state clinical trial on oral THC (dronabinol) and smoked cannabis conducted in California in the 1970s (cited according to Musty & Rossi 2001).*

Adverse event	**Smoked cannabis (n=98)**	**Oral THC (n=257)**
Dry mouth	56.5%	44.8%
Sedation	52.1%	64.0%
Dizziness	33.1%	26.8%
Ataxia	27.1%	12.8%
Elated mood	26.6%	24.4%
Confusion	26.6%	31.6%
Anxiety	20.2%	18.8%
Depressed	18.1%	13.2%
Perceptual	15.9%	22.8%
Fantasizing	10.7%	11.6%
Orthostatic	7.5%	12.8%
Panic/Fear	7.5%	7.6%
Tachycardia	6.4%	10.0%

2 Pharmacokinetics of cannabinoids and routes of administration

Cannabis products are commonly either inhaled by smoking a cannabis cigarette, taken orally as dronabinol capsules (Marinol®) or in baked foods or liquids, or absorbed by the

mucous membrane of the mouth (Sativex®) (see Figure 2). Various other routes of administration and delivery forms have been tested for therapeutic purposes. The rectal route with suppositories has been applied in some patients (Brenneisen et al. 1996). Dermal (Valiveti et al. 2004) and intranasal (Valiveti et al. 2007) administration are under investigation. Other methods include eye drops to decrease intraocular pressure (Merritt et al. 1981), as well as aerosols (van Drooge et al. 2005, Naef et al. 2004) and inhalation by using vaporizers to avoid the harms associated with smoking (Abrams et al. 2007b, Zuurman et al. 2008, Hazekamp et al. 2006).

Serum protein binding Lipoproteins, albumin ***Tissue storage*** Fat, protein Hair, saliva, sweat THC concentration in extracellular water***Absorption***THC concentration at site of action***Metabolism*** Hepatic microsomal, non-microsomal, extrahepatic Metabolites ***Biliary excretion*** Enterohepatic recirculation ***Renal excretion*** Glomerular filtration, tubular secretion, passive reabsorption Lung, mouth, intestine, colon, skin***Administration***THCCannabinoid receptors,other targets of action THC effects

Figure 2. Pharmacokinetic properties of THC (modified according to Grotenhermen 2003).

The pharmacokinetics of THC is briefly reviewed with emphasis to differences between routes of administration, allowing for an assessment of advantages and disadvantages of different routes with regard to onset, magnitude, and duration of the pharmacodynamic effects of THC and cannabis. (for extended reviews please see: Grotenhermen 2003, Hawksworth and McArdle 2004, Huestis 2005).

2.1 General features of THC pharmacokinetics

Distribution: After absorption the lipophility of THC with high binding to tissue and in particular to fat causes a change of distribution pattern over time (Ryrfeldt et al. 1973). THC rapidly penetrates highly vascularized tissues, among them liver, heart, lung, jejunum, kidney and spleen, resulting in a rapid decrease in plasma concentration after

inhalation (Ho et al. 1970). Subsequently intensive accumulation occurs in less vascularized tissues and finally in body fat, the major long-term storage site (Kreuz & Axelrod 1973, Johansson et al. 1989).

Metabolism: Metabolism of THC occurs mainly in the liver by microsomal hydroxylation and oxidation catalysed by enzymes of the cytochrome P-450 complex (Matsunaga et al. 1995).

Major metabolites are monohydroxylated compounds. In man C-11 is the major site attacked (Wall 1971, Widman et al. 1978). Hydroxylation results in 11-hydroxy-THC (11-OH-THC) and further oxidation in 11-nor-9-carboxy-THC (THC-COOH) that may be glucuronated to 11-nor-9-carboxy-THC glucuronide.

Plasma clearance: Average plasma clearance rates have been reported to be 197±50 ml/min for females and 248±62 ml/min for males (Wall et al. 1983), while others determined higher mean clearance rates of about 600 ml/min for naive THC users and about 1000 ml/min for chronic users (Hunt & Jones 1980). The latter values are similar to the volume of hepatic blood flow, indicating that the limiting step of the metabolic rate is controlled by hepatic blood flow. These high clearance rates explain the high degree of first pass metabolism and the much higher concentration of 11-OH-THC after oral administration compared to inhalation.

Elimination from plasma: About 6 hours after intravenous dosing of THC a pseudoequilibrium is reached between plasma and tissues (Chiang & Rapaka 1987). Concentration in plasma usually has dropped below 2 ng/ml at this time and than decreases more slowly with increasing time from use (Huestis et al. 1992). After smoking a low dose cannabis cigarette (about 16 mg THC) the detection limit of 0.5 ng/ml THC in plasma was reached after 7.2 h (range: 3-12 h) and following a high dose cigarette (about 34 mg THC) a plasma concentration of 0.5 ng/ml THC was reached within 12.5 h (range: 6-27 h) (Huestis et al. 1992). The true elimination half-life of THC from the plasma is difficult to calculate, as the concentration equilibrium ratio plasma/fatty tissue is only slowly reached, resulting in very low plasma levels that are difficult to analyse.

Excretion with urine and faeces: THC is excreted within days and weeks, mainly as acid metabolites, about 20-35% in urine and 65-80% in faeces, less than 5% of an oral dose as unchanged drug in the faeces (Hunt & Jones 1980, Wall et al. 1983). After three days overall excretion rates were about 65% following oral and about 45% with intravenous administration (Wall et al. 1983).

2.2 Pulmonary administration (inhalation)

Absorption: THC is detectable in plasma only seconds after the first puff of a cannabis cigarette with peak plasma concentrations being measured 3 to 10 minutes after onset of smoking (Huestis et al. 1992). Systemic bioavailability generally ranges between about 10 and 35%, and regular users are more efficient (Lindgren et al. 1981). About 30% is assumed to be destroyed by pyrolysis. With smoking, additional THC is lost in

the butt, in side-stream smoke, and by incomplete absorption in the lungs.

Course of plasma concentration: The course of plasma THC levels after inhalation resembles that after i.v. administration. Smoking a single cannabis cigarette containing about 16 or 34 mg THC caused average peak levels of 84.3 ng/ml (range: 50.0-129.0 ng/ml) for the lower dose and 162.2 ng/ml (range: 76.0-267.0 ng/ml) for the higher dose, then rapidly decreased to low levels of about 1-4 ng/ml within 3-4 h (Huestis et al. 1992). The maximal THC plasma level after smoking a cannabis cigarette (3.55% THC) was reported to exceed the maximal THC-COOH level by threefold and 11-OH-THC by twentyfold. Peak concentrations for THC were observed 8 min (range: 6-10) after onset of smoking, while 11-OH-THC peaked at 15 min (range: 9-23) and THC-COOH at 81 min (range: 32-133) (Huestis et al. 1992).

Correlation of time and effects: Effects set in within seconds or a few minutes after the first puff from a cannabis cigarette. Peak psychic effects after pulmonary administration were noted after 20-30 min and decreased to low-level after 3 h and to baseline after 4 h (Chiang & Barnett 1984, Hollister et al. 1981, Lindgren et al. 1981). Maximum increase of heart rate was noted earlier, within a few minutes (1-5 min) decreasing to baseline after 3 h (Lindgren et al. 1981). Conjunctival injection was noted within a few minutes as well and subsided in some participants by 3 h after smoking (Ohlsson et al. 1982). Duration of maximal effects is dose dependent and was found to be 45 min after 9 mg THC (Harder & Rietbrock 1997) and more than 60 min with higher doses (Robbe 1994).

2.3 Oral administration

Absorption: With oral use, absorption is slow and erratic, resulting in maximal plasma concentrations usually after 60-120 minutes (Ohlsson et al. 1980, Timpone et al. 1997). In several studies, maximal plasma levels were observed as late as 4 h (Law et al. 1984) and even 6 hours in some cases (Frytak et al. 1984, Ohlsson et al. 1980, Sporkert et al. 2001).

Δ^9-THC is expected to be degraded by the acid of the stomach and in the gut (Garrett and Hunt 1974). Absorption seems to be nearly complete in different vehicles. 95% of total radioactivity of radiolabeled THC was absorbed from the gastrointestinal tract in an oil vehicle (Wall et al. 1983) and 90-95% if taken in a cherry syrup vehicle (Lemberger et al. 1972), but it is unclear from these data how much of this radioactivity belongs to unchanged THC and how much to breakdown products.

An extensive first pass liver metabolism reduces oral bioavailability of THC. Systemic bioavailability was reported to be very low, 6±3% (range: 4-12%) (Ohlssen et al. 1980) or 7±3% (range: 2-14%) (Sporkert et al. 2001), respectively, with a high interindividual variation.

Course of plasma concentration: After oral application the THC plasma concentration shows a flat course with peaks ranging from 4.4-11 ng/ml following 20 mg THC (Ohlsson et al. 1980), from 2.7-6.3 ng/ml with 15 mg THC (Frytak et al. 1984), and from 0.58-12.48 ng/ml with 2.5 mg THC (Timpone et al. 1997). Much higher amounts of 11-OH-

THC are formed than with inhalation or intravenous administration (Frytak et al. 1984, Wall et al. 1983). The course of THC plasma concentrations shows a high interindividual variation.

Correlation of time and effects: After oral use (20 mg THC in a cookie) reddening of the conjunctivae occurred within 30-60 min and was maximal from 60-180 min, gradually lessening thereafter (Ohlsson et al. 1980). As with inhalation the pulse rate often returned to baseline or below even while the participants felt "high" (Ohlsson et al. 1980). Psychic effects after oral use set in after 30-90 minutes (Hollister et al. 1981, Wall et al. 1983), were maximal between 2 to 4 h, and declined to low levels after 6 h (Hollister et al. 1981).

2.4 Oromucosal Administration

In 2005 Sativex® received approval in Canada for the symptomatic relief of neuropathic pain in multiple sclerosis. Sativex® is a cannabis extract, which is sprayed in the oromucosal area and contains approximately equal amounts of dronabinol (THC) and cannabidiol (CBD).

Absorption and course of plasma concentration after oromucosal administration is much similar to oral administration with maximal THC plasma concentrations after 60-120 minutes and a great interindividual variability (Guy & Flint 2003, Guy & Robson 2003). In one study the mean maximal THC plasma levels were reached after 100 minutes (Guy & Flint 2003). These results indicate that only a small proportion of THC is absorbed by the mucosa of the mouth and most of it is swallowed.

Maximum THC plasma levels after administration of therapeutic doses (up to 20 mg) were reported to be similar to levels after oral administration (Guy & Flint 2003). THC plasma concentrations of up to 14 ng/ml were noted (Notcutt et al. 2001).

The onset of therapeutic effects of Sativex was reported to be after 15-40 minutes (Robson & Guy 2004), somewhat faster than after oral administration, which may be due to the small proportion absorbed by the oral mucosa.

2.5 Rectal Administration

With rectal application, systemic bioavailability strongly differed depending on suppository formulations. Among formulations containing several polar esters of THC in various suppository bases, THC-hemisuccinate in Witepsol H15 showed the highest bioavailability in monkeys and was calculated to be 13.5% (ElSohly et al. 1981). The rectal bioavailability of this formulation was calculated to be about as twice as high as oral bioavailability in a small clinical study (Brenneisen et al. 1996). However, in one clinical study with patients suffering from spinal cord injury higher doses were needed for rectal administration compared to oral administration, which was attributed to loss of material on administration (Hagenbach et al. 2007).

2.6 Dermal Administration

Experimental studies investigated the skin permeation behaviour of THC, suggesting that cannabinoids may be administered transdermally (Touitou & Fabin 1988, Touitou et al. 1988, Stinchcomb et al. 2004, Valiveti et al. 2004). In a study using the more stable Δ^{8}-THC isomer the permeability coefficient of THC was significantly enhanced by water and by oleic acid in propylene glycol and ethanol (Touitou et al. 1988). Significant THC concentrations in the blood of rats treated with formulations containing 26,5 mg/g THC were measured. Ethanol concentrations of 30 to 33% (Stinchcomb et al. 2004) and ethosomal carriers (Lodzki et al. 2003) also significantly increased the transdermal flux of cannabinoids.

Using a transdermal delivery system a mean steady-state level of 4.4 ng/mL was reached within 1.4 h and was maintained for at least 48 h for THC in guinea pigs (Valiveti et al. 2004). Upon transdermal application of the ethosomal system to the abdomen of mice for 72 h, steady-state levels were reached at about 24 h and lasted at least until the end of the experiment, at 72 h (Lodzki et al. 2003).

2.7 Ophthalmic Administration

A study in rabbits with THC in light mineral oil determined a variable systemic bioavailability of 6-40% with ophthalmic administration (Chiang et al. 1983). Plasma concentrations peaked after one hour and remained high for several hours.

2.8 Intranasal administration

A first study that investigated the potential of the nasal route for systemic delivery of THC and a synthetic cannabinoid (WIN55,212-2) in rats showed that this route may also result in concentrations of therapeutic relevance with a maximum concentration for THC after 1.5-1.6 h (Valiveti et al. 2007).

2.9 Summary of pharmacokinetics and routes of administration for THC

Depending on route of administration the onset and duration of action caused by THC differ considerably. With oral use onset of action is slow but lasts longer than after pulmonary administration. With pulmonary administration onset of action is similar to onset after intravenous administration. With oromucosal administration onset of action is somewhat faster than after oral administration, but still considerably more delayed than after pulmonary administration. If fast onset of THC effects is required, e.g. as with pain that sets in fast (e.g. in migraine) or an attack of spasms in multiple sclerosis, or if titration of dose in dependency of perceived effects is necessary, the pulmonary route is advantageous, while the oral or the oromucosal routes are preferable if a long

continuous action is required, e.g. for pain relief during the night or stimulation of appetite.

3 Results of preclinical studies with the Volcano vaporization system

There are two preclinical studies with the Volcano with relevance to safety and efficacy of this delivery system (Gieringer et al. 2004, Hazekamp et al. 2006).

The first one by Dale Gieringer and colleagues was conducted at Chemic Laboratories, Inc. (Canton, Massachusetts, USA) (Gieringer et al. 2004). It mainly evaluated the question, whether and to what extent the device reduced the presence of toxic combustion products in the vapour generated from cannabis with the Volcano vaporization system, compared to the smoke, which is generated when cannabis is smoked. The samples used in this study were herbal cannabis with a mean THC concentration of 4.15% (range 4.0-4.3%) provided by the National Institute on Drug Abuse (Baltimore, USA). In brief, the results demonstrated a drastic reduction in pyrolytic smoke compounds by using the Volcano compared to smoke after combustion of cannabis herb.

The second one by Arno Hazekamp and colleagues was conducted at the Devision of Pharmacognosy of the Institute of Biology at Leiden University (Leiden, The Netherlands) (Hazekamp et al. 2006). It mainly evaluated the efficiency and intra- and inter-device reproducibility of THC delivery by the Volcano vaporization system to humans. Pure THC (purity ≥ 98%), solved in ethanol at a concentration of 50 mg/mL was used. By changing parameters such as temperature setting, type of evaporation sample and balloon volume, the vaporization of THC was systematically improved to its maximum, while preventing the formation of breakdown products of THC, such as cannabinol or delta-8-THC. In brief, the final pulmonal uptake of THC was comparable to the smoking of cannabis, while avoiding the respiratory disadvantages of smoking.

3.1 Study on the reduction of pyrolytic compounds of cannabis by using the Volcano compared to cannabis smoking (Gieringer et al. 2004)

The study by Gieringer et al. (2004) was published in the Journal of Cannabis Therapeutics under the title "Cannabis vaporizer combines efficient delivery of THC with effective suppression of pyrolytic compounds". The following texts on this study were partly taken from this publication, from the study protocol and from the signed final report and partly rewritten by the author of this review of the clinical data on the Volcano.

3.1.1 Summary

Title: Cannabis vaporizer combines efficient delivery of THC with effective suppression

of pyrolytic compounds.

Identification of the medical device: Volcano® (Storz & Bickel GmbH & Co. KG, Tuttlingen, Germany, http://www.storz-bickel.com).

Name of sponsor: Multidisciplinary Association for Psychedelic Studies (MAPS), Sarasota, Florida, USA.

Objectives: The study was designed to evaluate the efficacy of the Volcano® with regard to the delivery of cannabinoids and to the reduction in pyrolytic smoke compounds.

Methodology: Three 200 mg samples of standard cannabis provided by NIDA (National Institute on Drug Abuse) were vaporized at the highest temperature setting of the device resulting in temperatures of between 155° and 218°C. For comparison, smoke from combusted samples was also tested. The study consisted of two phases: (1) a quantitative analysis of the solid phase of the vapour using HPLC-DAD-MS (High Performance Liquid Chromatograph-Diode Array-Mass Spectrometry) to determine the amount of cannabinoids delivered; (2) a GC/MS (Gas Chromatograph/Mass Spectrometer) analysis of the gas phase to analyze the vapour for a wide range of toxins, focusing on pyrene and other polynuculear aromatic hydrocarbons (PAHs).

Results: The HPLC analysis of the vapour found that the Volcano delivered 36%-61% of the THC in the sample, a delivery efficiency that compares favourably to that of cannabis cigarettes. The GC/MS analysis showed that the gas phase of the vapour consisted overwhelmingly of cannabinoids, with trace amounts of three other compounds. In contrast, over 111 compounds were identified in the combusted cannabis smoke, including several known PAHs.

Conclusions: The results indicate that vaporization can deliver therapeutic doses of cannabinoids with a drastic reduction in pyrolytic smoke compounds. Vaporization therefore appears to be an attractive alternative to smoked cannabis for future medical cannabis studies.

Authors of report: Dale Gieringer, Joseph S. Laurent, Scott Goodrich

Publication date: 2004

3.1.2 Introduction

Cannabis vaporization is a relatively new technology aimed at suppressing respiratory toxins by heating cannabis to a temperature where cannabinoid vapours form (typically around 180-190°C), but below the point of combustion where smoke and associated toxins are produced. The purpose of this is to permit the inhalation of medically active cannabinoids while avoiding noxious smoke compounds that pose respiratory hazards.

One of the greatest concerns about chronic effects of cannabis use by smoking pertains to the inhalation of combustion products that may damage the mucous membranes. The cannabis plant contains about 500 chemical compounds, most of which are also found in

other organisms such as hydrocarbons, terpenes, amino acids, flavonoids, fatty acids, and sugars, among others (ElSohly 2002). Pyrolysis creates at least 200 thermal degradation products in smoke not found in cannabis. The composition of these combustion products is at least qualitatively similar to that of tobacco smoke or that of the smoke generated from other dried plant material, despite some minor differences (British Medical Association 1997). Thus, one would expect similar damage to the mucosa by cannabis smoke as following the use of tobacco.

In principle, vaporization offers patients the advantages of inhaled routes of administration: rapid onset, ease of self-titration and concomitant avoidance of over- and under-dosage, high systemic bioavailability, while avoiding the respiratory disadvantages of smoking. In practice, the major question concerning vaporization comes down to feasibility. How well can one design a vaporizer that reliably produces "smokeless," toxin-free cannabinoid vapours from cannabis products and are these vapours indeed toxin-free?

3.1.3 Materials and methods

The study by Gieringer et al. (2004) was designed to measure how efficiently the device delivered delta-9-tetrahydrocannabinol (THC) and other cannabinoids, and how effectively it suppressed other, non-cannabinoid compounds from the vapour. The study consisted of two phases: (1) a quantitative analysis of the solid phase of the vapour using HPLC-DAD-MS (High Performance Liquid Chromatograph-Diode Array-Mass Spectrometry) to determine the amount of cannabinoids delivered; (2) a GC/MS (Gas Chromatograph/ Mass Spectrometry) analysis of the gas phase to analyze the vapour for a wide range of toxins, focusing on pyrene and other polynuculear aromatic hydocarbons. Vapour was generated by loading the Volcano with 200 mg samples of NIDA cannabis. For comparison, a combusted control using 200 mg of cannabis burned in a glass pipe bowl was also tested.

Temperature setting of the Volcano

The temperature control of the Volcano® ranges from 1 to 9, which is said by the manufacturer of the Volcano to correspond to temperatures of about 130° to 226°C. The manufacturer suggests using a temperature setting of 7, corresponding to a nominal 202°C. As a worst-case test of the Volcano's safety, it was set at its highest setting to ascertain whether pyrolytic byproducts might result. Two thermocouples were placed in the vaporizer above and below the sample to determine the actual operating temperature. The temperature was found to be stable, measuring 155°C on the top surface of the sample and 218°C on the screen closest to the heater.

Cannabis sample

The sample consisted of standard NIDA cannabis supplied through an independent

laboratory. Portions were prepared in 1.7 gram batches by gently sifting through a 2 mm sieve screen and mixing. The baseline concentrations of cannabinoids in the sample were analyzed by Soxhlet extraction for THC, cannabidiol (CBD) and cannabinol (CBN). Three separate samples of 200 mg were extracted in 250 ml ethanol under heat for 2 hours, concentrated by rotary evaporation, and analyzed by HPLC-DAD-MS. The mean concentration of THC was 4.15% (range 4.0%-4.3%), consistent with NIDA standards. CBD and CBN were detected in only trace amounts, with the CBD showing a wide range of variance: 0.0428%-0.128% (mean 0.075%). CBN ranged more tightly from 0.086% to 0.10% (mean 0.094%). The water content of the sample was measured by heating a prepared 0.56 gram sample for 30 minutes at 140°C and measuring the weight loss. The water content was found to be 11.9% by weight.

Phase 1: cannabinoid recovery analysis

Vapour from the Volcano was analyzed to determine the cannabinoid delivery efficiency of the vaporizer. A 200 mg sample was loaded into the Volcano and exposed to heat for 45 seconds, enough to fill the collection balloon. The vapour was then transferred from the balloon over a period of approximately 15 minutes by a vacuum pump into a solvent reservoir containing 50 ml of methanol. Three balloons were collected from each sample. The three balloon quota was based on preliminary tests, which found that most of the cannabinoids were delivered in the first two balloons, with just trace amounts in the third. The vapour is typically visible as a light gray wispy haze and has a distinct cannabis terpene odour. In order to facilitate maximal vaporization, the manufacturer recommends stirring the sample around after inhaling a few balloons, then repeating. However, this procedure was not followed in these tests since relatively small amounts of sieved material was used. The dissolved vapour from the Volcano was subjected to quantitative analysis on the HPLC-DAD. Two separate samples of 1.5 ml were tested from each dissolved sample as a consistency check. The entire process was repeated for three different 200 mg samples of cannabis.

To analyse the smoke of combusted cannabis, the samples were not rolled into cigarettes, but combusted in a glass pipe bowl. Each sample was ignited by exposure to an electric radiant heater placed over the bowl, and the smoke was drawn through a tube directly into the methanol. The dissolved smoke was assayed for cannabinoids as previously described. This process was also repeated for three different 200 mg samples of cannabis.

Phase 2: Gas phase GC/MS analysis

The second phase of the study analyzed the gas phase of the vapour for a broad spectrum of compounds via GC/MS. The GC/MS was outfitted with a DB-XLB analytical separation column (DB-xtra low bleed, 30 M x 0.25 mm, 0.25 µm film), which is especially suited for the detection of polynuclear aromatic hydrocarbons.

A PAH reference stock solution was used that included analytes for naphthalene,

acenaphthalene, anthracene, chrysense, benzo(a)pyrene, benzo(k)fluoranthene, 1,1,2-benzoperylene, indeno(1,2,3-c,d)pyrene, ancenaphthylene, fluorene, phenanthrene, pyrene, 1,2-benzanthracene, benzo(b)fluroanthene, and 1,2,4,6-dibenzanthrancene. Pyrene was used as a reference standard.

The evolved vapour from the Volcano was transferred from the collection balloon via vacuum directly to a 250 ml volatile gas trap. A 2.0 ml portion of the gaseous sample was then transferred using a headspace syringe directly onto the chromatographic system and assayed. In addition, the condensed residue that had adhered to the gas trap was analyzed by adding 2.0 ml of methanol to the trap to dissolve it. Subsequently, 1 µl of the solution was injected directly into the GC/MS. This process was repeated for three samples with three balloons from each sample, making a total of nine runs with gas samples and nine more with the condensed residue.

The gas was analyzed qualitatively and semi-quantitatively for polynuclear aromatic hydrocarbons at sample concentrations of 2.25-125 µg/ml. The GC/MS operated at a thermal gradient of 110°-320°C over 53 min. Different compounds were qualitatively identified by comparing their response peaks with an NBS reference library. Compounds that demonstrated greater than 70% match quality in comparison to the NBS mass spectral standard were reported as identified isolated compounds. Their mass concentrations were estimated from the response peak area in terms of the calibrated reference standard for pyrene. This yielded approximate, semi-quantitative mass determinations.

3.1.4 Results

Phase I: With regard to the tests with the vaporizer, on average, the recovered THC amounted to 1.95% of the original weight of the sample, or 47% of the original THC in the crude sample. There was a large variance in the percentage of THC recovered in the three different vaporizer test runs, ranging from 36% to 61%.

The combusted samples registered a relatively high THC delivery efficiency of 78%. The variance was low for the three different test runs.

All of the vaporized and combusted samples were also assayed for CBD and CBN. The amount of CBD delivered was unexpectedly somewhat higher for both the vaporized and combusted samples. For CBN, there was no significant change under vaporization. In contrast, the level of CBN was twice as high in all three combusted samples, with little variance.

Phase II: A review of the data showed that the Volcano vapour was overwhelmingly dominated by THC, with trace amounts of a handful of other compounds. Aside from THC, one other cannabinoid, CBN, was detected. No CBD was detected. This was not unexpected, since the GC/MS analysis was much less sensitive to cannabinoids than to PAHs. In general, the GC/MS analysis was intended to measure PAHs but did not provide an accurate measure of cannabinoids. For the latter, it was necessary to use the HPLC.

Aside from the cannabinoids, only three other compounds were tentatively identified in the vapour gas, and one in the solvated condensate. The three were caryophyllene (an aromatic terpene found in cannabis and other plants) plus two other compounds of undetermined origin (2-Methyl-2, 4 (2H-1-benzopyran-5-ol), 5-[(Acetyl benz [e] azulene-3,8-dione), the first of which also appeared in the condensate.

An estimated 1.7% of the weight of the 200 mg sample was recovered in the solvated condensate, as approximately quantified in terms of the pyrene standard. THC accounted for a nominal 94.3% of the inferred estimated mass. That the apparent concentration of THC inferred in the GC/MS analysis (3.2 mg/g) was much lower than in the HPLC (19.5 mg/g), was partly an artifact of the mathematical representation of THC in terms of pyrene, and partly due to the lack of applicability of the GC/MS system to THC due to low volatility and to sorbation characteristics of the analytic column.

The gaseous headspace was more tenuous, yielding an estimated recovered mass of just 0.04% of the sample weight. Once again, the sample was overwhelmingly dominated by THC.

A striking result in both analyses was a lack of significant quantities of pyrolytic-induced analytes in the vapour.

Comparison runs using combusted cannabis presented a strikingly different picture. Review of the data from the gaseous headspace detected 111 tentatively identified compounds, including THC and CBN. Included were five known PAHs. Cannabinoids represented only 12% of the inferred recovered mass; the remaining 88% consisted of extraneous products of combustion.

The solvated extract yielded 37 tentatively identified compounds, including five known PAHs. THC and CBN constituted 90% of the estimated recovered mass. (When combusted, the product saturated the chromatographic system, producing a distorted response; hence the apparently elevated concentration of THC (57.9 mg/g); as noted above, the GC/MS did not provide an accurate measurement of cannabinoids.) Altogether, eight different PAHs were identified in the solvated extract and the gaseous headspace.

3.1.5 Discussion

The high efficiency of 78% with combustion of cannabis may be explained by the fact that the laboratory conditions minimized loss of sidestream smoke; the sample was completely consumed with no "butt" remaining; and the pipestem led directly into the solvent so as not to cause excessive loss by adhesion to the walls. The amount of THC lost (22%) in combustion was consistent with the losses attributed to pyrolysis in other studies. It has been estimated that 23-30% of the THC in combusted cannabis is destroyed by pyrolysis, while as much as 40-50% can be lost in sidestream smoke (Perez-Reyes 1990). In a study with a smoking machine, patterns of cannabis smoking were simulated with regard to puff duration and volume (Davis et al. 1984), resulting in 16 to 19% of THC in the mainstream smoke. If the whole cigarette was smoked in one

puff the percentage of THC in the mainstream increased to 69%. Smoking a pipe that produces little side stream smoke may also result in high effectiveness with 45% of THC transferred via the mainstream smoke in one smoker tested (Agurell et al. 1971).

The results of the study suggest that the efficiency of vaporization to deliver cannabinoids is highly sensitive to variations in the sample and micro-conditions of its environment. These results compare favourably to the delivery efficiencies of cannabis cigarettes as measured in other studies. THC efficiencies of 34% to 61% were reported in studies of cannabis cigarettes smoked via a smoking machine under varying conditions of puff duration and air speed (Fehr and Kalant 1972). Efficiencies of up to 50% were obtained using a machine designed to mimic human cannabis cigarette smoking (Manno et al. 1970). A systemic bioavailability of 23±16% (Lindgren et al. 1981) and 27±10% (Ohlsson et al. 1982) for regular users versus 10±7% and 14±1% for occasional users of the drug was reported. Theoretically, the vaporizer might have been expected to realize a higher THC delivery efficiency than combustion, since it should have avoided loss of THC by pyrolysis. That this was not observed indicates that there were other inefficiencies in the vaporization process. The most likely explanation would seem to be incomplete vaporization, due to lack of uniform thorough heating and ventilation of the sample. It is certainly possible that higher efficiencies might have been achieved by stirring the sample and drawing another balloon from the vaporizer, as recommended by the manufacturer.

Numerous unexplored variables could conceivably affect the efficiency and output of vaporization. Included are variations in temperature; differences in the density, weight, and consistency of material in the chamber; differences in the variety and potency of cannabis used; and use of different preparations such as hashish, hash oil, etc.

The major finding of this study was a drastic quantitative reduction in non-cannabinoid compounds in the vapour from the Volcano. This strongly suggests that vaporization is an effective method for delivering medically active cannabinoids while effectively suppressing other potentially deleterious compounds that are a byproduct of combustion.

The vaporized cannabis does not turn to ash, but retains its original shape, as discussed above. A microscopic examination reveals the physical nature of the process. The cannabinoids in cannabis are borne in droplets of resin, known as glandular trichomes, which coat the exterior structures of the flowering tops, and the leaves to a lesser extent. The trichomes resemble small stalks or protuberances, appearing like dewy-capped mushrooms under a microscope. After vaporization, the resin has evaporated and trichomes have withered, while the underlying vegetative matter remains intact. This confirms that vaporization is essentially a different physical process than combustion. This study was not designed to measure the presence of toxic gases with low molecular weight, such as ammonia, hydrogen cyanide and carbon monoxide, which are known to be produced by cannabis cigarettes (Huber 1991). Previous studies have indicated a qualitative decrease in CO with vaporization, but this remains to be quantitatively measured (see the study by Abrams et al. 2007 in the section on clinical studies with the

Volcano, which investigated the reduction of CO compared to cannabis smoking). Neither did this study analyze the solid tar phase of the vapour for non-cannabinoids. However, there is sound reason to believe that the total amount of tar was drastically reduced, given the absence of detectable combustion. Unlike the combusted cannabis, which turned to ash, the vaporized sample remained greenish- brown and intact, though clearly dessicated.

In summary, there is good reason to believe that vaporization is a highly effective method of smoke harm reduction.

A major goal of this study was to pave the way for vaporizers to be introduced into human studies, in particular studies of medical cannabis that are now normally conducted using NIDA cigarettes. Data from this study have been submitted to the FDA in support of an application for an investigational device exemption (IDE) to permit the Volcano to be used in a study by Donald Abrams of the University of California, San Francisco (see below Abrams et al. 2007).

3.2 Study on the efficiency and intra- and inter-device reproducibility of THC delivery by the Volcano (Hazekamp et al. 2006)

The study by Hazekamp et al. (2006) was published in the Journal of Pharmaceutical Sciences under the title "Evaluation of a vaporizing device (Volcano®) for the pulmonary administration of tetrahydrocannabinol". The following texts on this study were partly taken from this publication and were partly rewritten by the author of this review of the clinical data on the Volcano.

3.2.1 Summary

Title: Evaluation of a vaporizing device (Volcano®) for the pulmonary administration of tetrahydrocannabinol.

Identification of the medical device: Volcano® (Storz & Bickel GmbH & Co. KG, Tuttlingen, Germany, http://www.storz-bickel.com).

Name of sponsors: The Volcano vaporizers were provided by Storz & Bickel GmbH & Co. Medical grade cannabis plant materials were provided by Bedrocan BV (The Netherlands). Farmalyse BV (Zaandam, The Netherlands) supported the development of the procedure to produce clinical grade cannabinoid samples of THC and THCA.

Objectives: The goal of this study was to evaluate the performance of the Volcano vaporizer in terms of reproducible delivery of the bioactive cannabinoid tetrahydrocannabinol (THC) by using pure cannabinoid preparations, so that it could be used in a clinical trial.

Methodology: By changing parameters such as temperature setting, type of evaporation sample and balloon volume, the vaporization of THC was systematically improved to its maximum, while preventing the formation of breakdown products of THC,

such as cannabinol or Δ^{8}-THC. Inter- and intra-device variability was tested as well as relationship between loaded- and delivered dose.

Results: It was found that an average of about 54% of loaded THC was delivered into the balloon of the vaporizer, in a reproducible manner.

Conclusions: The results show that with the Volcano a safe and effective cannabinoid delivery system seems to be available to patients. The final pulmonal uptake of THC is comparable to the smoking of cannabis, while avoiding the respiratory disadvantages of smoking.

Authors of report: Arno Hazekamp, Renee Ruhaak, Lineke Zuurman, Joop van Gerven, Rob Verpoorte

Publication date: 2006

3.2.2 Introduction

Vaporization offers patients who use medicinal cannabis the advantages of the pulmonary routes of administration, while avoiding the respiratory disadvantages of smoking. In a series of studies the vaporizing of cannabis samples was systematically tested to show its advantage over smoking. When a variety of smoking devices (including water pipes) were compared, specifically examining THC and solid smoke tars, it was found that only vaporizers were capable of achieving reductions in tar relative to THC when compared to direct smoking of cannabis (Gieringer 1996, McPartland and Pruitt 1997). A follow-up study tested a vaporizer that was found to deliver THC while completely eliminating three specific toxins (naphthalene, benzene, and toluene) in the solid phase of the vapour (Chemic Laboratories 2000). The study also detected a ≥56% reduction in tars and a qualitative reduction in carbon monoxide, but did not test for any other chemicals (Gieringer 2001). In a more recent study, GC-mass-spectrometry was used to analyze the gas phase of vaporized cannabis for a wide range of toxins, particularly concentrating on the highly carcinogenic polynuclear aromatic hydrocarbons (PAHs) (Gieringer et al. 2004, see above chapter 3.1 of this report). The vaporizer that was used was the Volcano. Although a large variety of vaporizing devices is available on the market, the Volcano is one of the few devices that have been tested scientifically to some extent.

Because of the paucity of data it has so far been difficult to show that the Volcano vaporizer can be used as a reliable tool for the reproducible administration of THC or other cannabinoids. A solution to this would be in the use of pure cannabinoid preparations of known concentration to guarantee an exact and reproducible loading of cannabinoids. In this study the Volcano vaporizer was evaluated as a novel method for the administration of THC. Pure cannabinoid preparations were used in order to obtain quantitative results in terms of efficiency and reproducibility of THC delivery into the balloon of the Volcano. By changing parameters such as temperature setting, type of evaporation sample, and balloon volume, the vaporization of THC was systematically improved to its maximum yield, while preventing the formation of degradation products.

Factors that resulted in loss of THC by condensation, that is, storage time of the balloon and use of the filling chamber, were evaluated. The inter-device reproducibility of THC vaporization under optimized conditions was determined. Finally, the results of this study were used for the clinical administration of THC by vaporizing. The amount of exhaled THC was determined and compared to the dose, which was inhaled through the Volcano.

3.2.3 Materials and methods

Materials

All organic solvents were HPLC or analytical grade, and were purchased from J.T. Baker (Deventer, The Netherlands). Anthracene (min. 99% purity) was purchased from Aldrich (St. Louis, MO). Deuteriated chloroform ($CDCl_3$) was from Eurisotop, Gif-sur-Yvette, France. Glass fibre filters (Cambridge type, borosilicate glass, 92 mm diameter) and tightly fitting filter holders for vapour extraction were obtained from Borgwaldt Technik GmbH (Hamburg, Germany). Cannabis plant material (female flowertops) was medical grade and obtained from Bedrocan BV (Veendam, The Netherlands). It had a water content of about 8%, a THCA (THC acid) content of about 12%, and virtually no free THC. Purified THC and THCA (purity ≥98%) were produced and quantified as reported earlier (Hazekamp et al. 2004a, 2004b). THC was of pharmaceutical grade. The cannabinoids were stored as ethanolic solutions at -20°C at a concentration of 50 mg/mL.

The Volcano Device

The Volcano® was obtained from Storz & Bickel GmbH & Co. (Tuttlingen, Germany) and was used according to the manual as provided by the manufacturer. Unless otherwise stated, a balloon length of 55 cm (around 8 L) was used, as recommended by the manufacturer. Before each new set of experiments the whole device was thoroughly cleaned with ethanol. At the start of each evaporation the Volcano was preheated until the indicator light showed that the target temperature was reached. The balloon, connected to the filling chamber, was then immediately placed onto the Volcano and the ventilation was started. When the balloon was completely inflated, ventilation was stopped and the content of the balloon was processed for analysis within 5 min, unless stated otherwise. All laboratory experiments were carried out in a standard laboratory fume hood under constant ventilation with an ambient room temperature of about 22°C and a humidity of 40-60%. The air was not conditioned (e.g., by HEPA filters).

Use of the Liquid Pad

The pure cannabinoids THC or THCA were used as ethanolic solutions. For these liquid samples an adapted filling chamber was used, containing a removable disc made of tightly packed stainless steel wire mesh (liquid pad), obtained from the manufacturer of

the Volcano. For each experiment the appropriate amount of the cannabinoid was dissolved in a final volume of 200 ml of ethanol for application onto the liquid pad and ethanol was allowed to evaporate for 10 min under ambient conditions. A new liquid pad was used for each experiment.

Extraction of THC from the Vapour and the Liquid Pad

Cannabinoids were recovered from the vapour phase inside the balloon by condensation onto glass fibre filters, designed to capture particles >0.1 microns. Vapour was slowly aspired through the glass-fibre filter which was then extracted twice with 15mL of methanol/chloroform (9:1, v/v) under ultrasonication. After evaporating the extraction solvent, samples were reconstituted in 5 mL of ethanol for analysis by HPLC or NMR. These ethanolic samples will be further referred to as vapour extracts. Residual THC on the liquid pad was recovered by extracting the liquid pad twice using methanol/ chloroform (9:1, v/v) under ultrasonication. Extracts were further handled as described above for the vapour extracts. Recovery was determined by spiking filters or liquid pads with THC (2 mg) and performing the described extraction procedure. To assess the efficiency of condensation of cannabinoids onto the glass fibre filter, a wash bottle filled with ethanol was placed after the filter. The escaping gases were bubbled through this liquid which was thereafter analyzed by HPLC to measure untrapped cannabinoids.

Quantitative ^{1}H-Nuclear Magnetic Resonance Spectroscopy (NMR)

Quantification of THC in the extracts was done by quantitative ^{1}H-NMR using a Bruker 300 MHz NMR apparatus as described by Hazekamp et al. (2004b). In short, an exact volume of the sample was mixed with 1.0 mg of anthracene as internal standard for quantification. The sample was then evaporated to dryness under vacuum and reconstituted in chloroform (deuteriated) for ^{1}H-NMR analysis.

High Pressure Liquid Chromatography (HPLC)

HPLC was used for both qualitative and quantitative analysis of the obtained extracts. The HPLC profiles were acquired on a Waters (Milford, MA) HPLC system consisting of a 626 pump, a 717 plus autosampler, and a 2996 diode array detector (DAD), controlled by Waters Millennium 3.2 software. Full spectra were recorded in the range of 200-400 nm. The analytical column was a Vydac (Hesperia, CA) C18, type 218MS54 (4.6x250 mm, 5 µm), with a Waters Bondapak C18 (2x20 mm, 50 µm) guard column. The mobile phase consisted of a mixture of methanol-water containing 25mM of formic acid in gradient mode; methanol:water in ratios from 65:35 to 100:0 over 25 min, then isocratic to 28 min. The column was reequilibrated under initial conditions for 4 min. Flow-rate was 1.5 mL/min and total runtime was 32 min. All determinations were carried out at ambient temperature. The main neutral and acidic cannabinoids were well separated with this method (Hazekamp et al. 2005). Analyzed concentrations were well above the

limit of quantification of the used method.

Evaluation of Temperature Control

Temperature control was evaluated at setting 1, 3, 5, 7, and 9 of the Volcano device. Time needed to reach target temperature, and accuracy and stability of target temperature were determined using an electronic thermometer (response time; 250 ms). Temperature was measured in the middle of the filling chamber, on top of the liquid pad, and each measurement was started by switching on the airflow directly after the indicator light of the heater had switched off. Inter-device variability for the same parameters was tested for four different Volcano devices. All experiments were repeated three times.

Optimization of Vaporizing Parameters

(a) Temperature: Cannabis plant material, and pure cannabinoids THCA and THC were vaporized at temperature settings 1, 3, 5, 7, and 9 in order to determine the delivery into the balloon as well as the formation of degradation products. Vapour extracts were qualitatively analyzed by HPLC for detection of degradation products, while quantitative analysis by NMR was used for determination of delivery.

(b) Heating time: In order to determine the minimal time that is needed to reach maximal evaporation of THC, the following experiment was performed: THC (2 mg) was applied onto the liquid pad and the ventilation was activated for a duration ranging from 10 to 300 s, without balloon attached to the device so THC could evaporate freely. Subsequently, residual THC was extracted from the liquid pads and extracts were quantitatively analyzed by NMR.

Relationship Between Loaded Dose and Delivery

The relationship between quantity of THC loaded onto the filling chamber and delivery into the balloon was determined in the range of 2-8 mg of THC. Vapour extracts were analyzed by NMR and HPLC, and each experiment was performed threefold.

Inter-Device Variability

Using the optimized parameters as determined in this study, four Volcano devices were finally evaluated for inter-device variability in THC delivery. Samples of 4 mg of THC were used for vaporizing and each Volcano was tested on five occasions. Vapour extracts were analyzed by NMR.

Condensation of THC onto the Balloon and Filling Chamber

The effect of storage time of the balloons on condensation of THC was determined by storage of the balloon at room temperature for a duration of up to 180 min after vaporizing (2 mg THC). The vapour extract was then collected for analysis. Each experiment was performed threefold. Throughout this study balloons were always processed within 5 min after vaporizing. Therefore, it was determined more exactly how much THC was lost due to condensation onto the walls of the balloon after 5 min of storage by carefully cutting the balloon (n=5) into pieces and extracting twice with ethanol under ultrasonication. In order to determine the amount of THC that condensated onto the filling chamber (excluding liquid pad) and valve, after some experiments these parts were extracted twice with ethanol under ultrasonication. Finally, extracts were concentrated and THC was quantified by NMR.

3.2.4 Results

Trapping and Recovery of THC for Analysis

Since no trace of THC could be found in the ethanol fraction of the wash bottle inserted after the filter, it was concluded that THC was completely trapped onto the used type of filter. Recovery of THC was found to be 99.3 (±1.1)% from the filter and 83.0 (±2.5)% from the liquid pad. All measurements were corrected for these values.

Accuracy of the Temperature Setting

At all tested temperature settings it was found that temperature reached a first plateau after about 30 s. After that temperatures remained relatively stable for some time, but kept below accepted limits (target temperature ±4°C, as claimed by the manufacturer) for all tested settings. However, after about 45-60 s, depending on the setting, the heating element was activated again by the temperature sensor, and about 20 s later temperatures increased by a few degrees bringing the temperature within specified limits. It must be concluded that the liquid pad and the filling chamber need some time to heat up to the target temperature.

Reproducibility of the Vaporizer

When four different Volcano devices were evaluated under equal conditions to evaluate interdevice variability, some small differences in heating profile were found. Only temperature setting 9 was evaluated here after it had been shown to be the optimal temperature for THC delivery. Although two devices reached target temperature (accepted variation ±4°C) already after 30 s, the two others needed 60 s or more to do so. For two devices the temperature increased above the maximum limit of target temperature in the 90 s duration of this experiment. In conclusion each individual Volcano device shows little variability during sequential uses (intradevice variability), although small differences do exist between different devices (inter-device variability).

Optimizing of Vaporizing Parameters with Different Substrates

THCA: Under the influence of heat THCA can be converted into THC by decarboxylation. Indeed, when THCA was used it was observed that this conversion increased with temperature and maximum delivery of THC was about 33% at the highest temperature setting. However, conversion was not complete and THCA was present in the vapour extracts at a level of about 5.5 (±1.3)% relative to THC.

Crude flower tops: The use of plant material (200 mg at 12% THCA) resulted in a maximum THC delivery of only 29%. In fresh cannabis plant materials THC is present in the form of its acidic precursor THCA and the use of plant material resulted in an incomplete decarboxylation with about 3.8% residual THCA present in the vapour. Besides THC, several other cannabinoids as well as a range of other plant components were detected.

Pure THC: Evaporation of THC was shown to increase with temperature with a maximal delivery of about 53% at setting 9, while no degradation products (delta-8-THC (Δ^8-THC), cannabinol (CBN), or other unknown peaks in the HPLC-chromatogram) were observed at any setting. Therefore, using the Volcano device, it was concluded that the highest delivery yield was achieved with an ethanolic solution of pure THC. When liquid pads were extracted after vaporizing it showed a very low amount of residual THC, indicating a very high yield of evaporation, at the highest temperature setting. This strongly suggests that nondelivered THC does not remain on the liquid pad, but is probably lost by condensation after initial evaporation.

Minimum time was determined for the maximal evaporation of THC from the liquid pad by measuring residual THC after vaporizing. The amount of residual THC rapidly decreases between 20 and 40 s after starting of the vaporizing. This corresponds with the observation that in the same time-period the (near) target temperature of the Volcano is reached. After 45 s most of the THC is evaporated and just a small fraction of THC can be found in the liquid pad extract, indicating that vaporizing time should be at least 45 s. In a preliminary test when using a temperature setting of 9 with a balloon volume of 4 L (filling time around 30 s), a low THC delivery (only 30% for 8 mg of THC) with a high dose variability (relative SD ±22%) was observed indicating that the maximum delivery yield was not yet reached.

It was observed that the maximal evaporation of THC is reached after 120 s. Since the Volcano is blowing air at a constant rate of about 9 L per min, this corresponds to a balloon volume of about 18 L. However, by empirical testing in the laboratory (data not shown) it was found that a maximum volume of about 8 L could be inhaled within 3 min when following the protocol of the clinical trial. Therefore, a balloon volume of 8 L (filling time of about 55 s) was selected for further study. Under these conditions, only about 5% THC remained on the liquid pad.

Relationship between Loaded Dose and Delivery under Optimal Conditions

With a Volcano operating under the aforementioned optimized conditions (temperature setting 9, balloon volume 8 L) the delivery was determined with an increasing amount of THC ranging from 2 to 8 mg. The delivery was proportional to the loaded dose of THC; a linear curve was obtained with a regression coefficient (R^2-value) of 0.99. From the slope of the line, a mean delivery yield of 57.8 (±6.9)% could be calculated. Four available devices were then tested under conditions as mentioned above using a sample of 4 mg of THC. Differences in delivery between the Volcano devices were relatively small. Average delivery of all four Volcanos was 53.9 (±8.1)%, and this value was taken as the average delivery for further considerations.

Condensation onto balloon and filling chambers

Loss of THC during experiments could partially be accounted for by incomplete evaporation and condensation onto parts of the Volcano vaporizer. Prolonged storage of the balloon at room temperature after vaporizing led to a steadily increasing loss of THC by condensation up to the point that after 180 min almost no THC could be detected anymore in vapour extracts. However, if the balloon was extracted within 5 min after vaporizing, less than 2% of the total dose was recovered from the inner surface of the balloon. Condensation of THC onto the other parts of the Volcano setup was found to be of significant importance. Visual inspection of the filling chamber shows the presence of a condensate mostly on the inside of the filling chamber just above the liquid pad. Extraction of the filling chamber together with the valve, but excluding the liquid pad, showed that an average of 23.6 (±14.1)% of the loaded THC had condensated onto these parts of the Volcano, and could therefore account for a large part of the nondelivered THC.

3.2.5 Discussion and conclusion

The Volcano® vaporizer was validated for the efficient and reproducible delivery of delta-9-THC, and was found to be able to deliver an average amount of about 54% of applied dose of THC into the balloon for inhalation. Systemic bioavailability with smoking cannabis generally ranges between about 10 and 35%, and regular users are more efficient (Lindgren et al. 1981). Using the Volcano device for pulmonary administration of THC, a delivery is reached that is somewhat superior to smoking, and without the presence of degradation products or harmful byproducts in significant amounts.

Loading the Volcano with Cannabis plant material or pure THCA resulted in a residual amount of THCA in the vapour in the order of 5% relative to THC. THCA is known to be not psychoactive but to have some pharmacological effects, that are also known from cannabis, e.g. anti-inflammatory and analgesic effects (Burstein 2002). Although in this study cannabis plant material was used only for comparative reasons, it is clear that a variety of cannabinoids and other compounds such as terpenoids are present in the vapor.

With pure THC as the loading sample, temperature setting and balloon volume were

optimized for a maximal, reproducible delivery of THC without formation of detectable amounts of degradation products. Using the highest temperature setting together with a balloon volume of 8 L was found to yield optimal results. Balloon volumes over 8 Lwere not tested because of restraints in the clinical trial protocol. The target temperature of the Volcano was found to be not completely accurate and stable. Possibly this is a contributing factor to the relative variability in the delivery of THC, which was about 15% at setting 9. However, this is reasonable when compared to the variability that has been previously found in smoking studies of cannabis plant material. Accuracy of temperature control therefore does not seem to be of crucial importance under these conditions, although a more accurate temperature control might result in an even lower variability in THC delivery.

In the range of 2-8 mg of THC, the delivery was found to be linear with the amount of THC used. Prolonged storage of the balloon before inhalation resulted in an increasing loss of THC by condensation inside the balloon and after 3 h almost no THC could be recovered from the vapour in the balloon. However, if the content was extracted within 5 min after vaporization not more than 2% of THC present was lost. Vaporized THC was visible inside the balloon as a thin gray mist which was absent in placebo balloons, so during the clinical trial balloons had to be blinded with a black plastic cover.

During the clinical administration, it was found that about 35% of total THC was exhaled directly after inhalation and was therefore not absorbed by the lungs. When the efficiency of delivery during vaporizing and incomplete absorption by the lungs is considered, the final administered dose equaled about 6-8 mg of THC of the total amount of 20 mg loaded. The subjective effect upon the subjects seemed to be in accordance with such a dose as described in other papers (Leweke 2002, Abood & Martin 1992). So it seems that a final uptake of 30-40% was reached (relative to loaded amount of THC), which is somewhat higher compared to the usual efficiency reached by smoking of cannabis.

What is currently needed for optimal use of medicinal cannabinoids is a feasible, nonsmoked, rapid-onset delivery system. With the Volcano a safe and effective cannabinoid delivery system seems to be available to patients. Although the study by Hazekamp et al. (2006) has concentrated on the delivery of THC, it should be noted that other cannabinoids might also have a role to play for some indications. In several medical studies, the effect of THC or dronabinol alone could not match the effect of a total cannabis preparation, indicating there might be other active cannabinoids needed for a full range of effects (Williamson & Evans 2000). The next step in the evaluation of the Volcano vaporizer should therefore include the study of mixtures of pure cannabinoids.

4 Results of clinical studies with the Volcano vaporization system

Two clinical studies have been conducted with the Volcano and three papers have been

published on their results (Abrams et al. 2007b, Strougo et al. 2008, Zuurman et al. 2008). Two of these papers are relevant for the subject of this review (Abrams et al. 2007b, Zuurman et al. 2008).

The first one by Abrams et al. (2007b) was conducted at the San Francisco General Hospital (San Francisco, California, USA). The main aim of this study was a comparison of the pharmacokinetics of smoked cannabis with a standard cannabis cigarette and of inhaled cannabis using the Volcano system in healthy volunteers. Expired carbon monoxide (CO), physiologic and neuropsychologic effects were also measured. In brief, peak THC plasma concentrations, area under the curve of THC plasma concentrations were similar and CO levels were reduced with vaporization compared to smoking.

The second study by Zuurman et al. (2008) was conducted at the Centre for Human Drug Research (Leiden, the Netherlands). In this study increasing doses of dronabinol (THC) (2, 4, 6 and 8 mg) were administered by inhalation with the Volcano at 90-minute intervals and compared to vehicle on a separate, randomised occasion, as placebo. Pharmacodynamic measurements were obtained frequently after each dose. In brief, the measured pharmacodynamic parameters such as heart rate and body sway showed dose-related changes compared to placebo. Plasma THC concentrations showed little inter-individual variation. Five of the twelve participants had to cough when inhaling THC with the Volcano.

4.1 Clinical study on a comparison between smoked cannabis and inhaled cannabis by using the Volcano in healthy subjects (Abrams et al. 2007b)

The study by Abrams et al. (2007b) was published in Clinical Pharmacology & Therapeutics under the title "Vaporization as a smokeless cannabis delivery system: a pilot study". The following texts on this study were taken from this publication and were partly rewritten by the author of this review of the clinical data on the Volcano.

4.1.1 Summary

Title: Vaporization as a smokeless cannabis delivery system: a pilot study.

Identification of the medical device: Volcano® (Storz & Bickel GmbH & Co. KG, Tuttlingen, Germany, http://www.storz-bickel.com).

Name of sponsor: University of California Center for Medicinal Cannabis, National Institutes of Health, USA (Grant 5-MO1-RR00083).

Objectives: The study was designed to investigate vaporization using the Volcano device as an alternative means of delivery of inhaled cannabis herb compared to smoking.

Subjects: 18 healthy subjects between the ages of 21 and 45 years who were current cannabis users and had smoked cannabis within the past 30 days but in an amount

totalling less than 10 cannabis cigarettes or the equivalent.

Methodology: On 6 study days participants received one of three strengths of cannabis (1.7, 3.4, or 6.8% THC) either smoked or inhaled by using the Volcano at a temperature setting of 6 (190°C). THC concentrations in blood were measured 2, 30, 60, 180, and 360 minutes after smoking. Expired CO was measured before inhalation, and 2, 30, 60, 180, and 360 minutes after inhalation. Subjects rated the maximum intensity of psychological effects on a visual analogue scale. All adverse events were spontaneously reported by the subject or observed by the study personnel, documented and evaluated according to standardised criteria in terms of severity, frequency, duration, and relationship to study drug.

Results: Peak plasma concentrations and 6-h area under the plasma concentration-time curve of THC were similar. CO levels were reduced with vaporization. No adverse events occurred.

Conclusions: Vaporization of cannabis is a safe and effective mode of delivery of THC. Further trials of clinical effectiveness of cannabis could utilize vaporization as a smokeless delivery system.

Authors of report: Donald I. Abrams, Hector P. Vizoso, Starley B. Shade, Corinne Jay, Michael E. Kelly and Neal L. Benowitz

Publication date: 2007

4.1.2 Introduction

The report by the US Institute of Medicine on Marijuana as Medicine of 1999 recommended that clinical trials of cannabinoid drugs for symptom management should be conducted with the goal of developing rapid onset, reliable, and safe delivery systems (Joy et al. 1999). While acknowledging therapeutic potential, the IOM report stressed that cannabis is not a completely benign substance, but a powerful drug with a variety of effects, but "except for the harms associated with smoking, the adverse effects are within the range of those tolerated for other medications."

A recent evaluation of the Volcano vaporizer device used herbal cannabis or pure cannabinoid ethanolic solution preparations to test the efficacy and reproducibility of THC delivery into the balloon receptacle (Hazekamp et al.2006). The results validated the Volcano vaporizer as an efficient and reproducible mode of delivery of Δ^9-THC. This clinical study by Abrams et al. (2007) investigated vaporization using the Volcano device compared to smoked cannabis. This is the first pharmacokinetic and pharmacodynamic evaluation conducted in humans to determine whether the Volcano may be an appropriate system for use in clinical effectiveness studies.

4.1.3 Materials and methods

Study patients

Participants were healthy adults between the ages of 21 and 45 years who were current cannabis users and had smoked cannabis within the past 30 days but in an amount totalling less than 10 cannabis cigarettes or the equivalent. Subjects with active substance abuse (e.g., recurrent or continuous drug and/or alcohol use) or diagnosed with cannabis dependence as defined in DSM-IV were excluded. Subjects were required to abstain from smoking cannabis for 48 h before their admission to the San Francisco General Hospital (SFGH). The study was approved by the Institutional Review Board at the University of California San Francisco, the Research Advisory Panel of California, the Drug Enforcement Administration, the Food and Drug Administration, and the National Institute on Drug Abuse. Written informed consent was obtained from all patients. The trial was monitored by an independent Data Safety Monitoring Board (DSMB) established by the University of California Center for Medicinal Cannabis Research.

Study medication

The National Institute on Drug Abuse provided pre-rolled cannabis cigarettes, weighing on average 0.9 g and containing 1.7, 3.4, and 6.8% Δ^9-THC, respectively. The cigarettes were kept in a locked and alarmed freezer until they were dispensed to a locked freezer in the San Francisco General Hospital General Clinical Research Center where the in-patient study was conducted. The cigarettes were bisected; one half to be smoked and the contents of the other half to be vaporized. The half cigarettes were rehydrated in a humidifier overnight before their use. Patients were housed in a room with a fan ventilating to the outside. Research staff monitored patients during smoking sessions, weighed cigarettes immediately before and after they were administered to patients, and returned all leftover material to the pharmacy. To maximize standardization of inhaled doses, patients followed the Foltin uniform puff procedure where inhalation for 5 s is followed by a 10 s breath hold, then exhalation; the entire process is repeated after 45 s (Foltin et al. 1988). Study participants smoked or vaporized cannabis once a day. Subjects were instructed to continue puffing until they exhausted smoke or vapour from the delivery device or until they had inhaled as much as they could tolerate.

The vaporizer device

The Volcano vaporizers were obtained from Storz & Bickel GmbH & Company (Tuttlingen, Germany) and were employed according to the manual provided. Temperature setting 6 was chosen, which corresponds to a maximum temperature of 190°C according to the manufacturer. This is considerably lower than used in the preclinical study by Gieringer et al. (2004), who conducted their study with a temperature setting of 9 (see chapter 3.1 of this review).

Study design and procedures

The study was a 6-day "proof of concept" pilot study to investigate the delivery of cannabinoids by way of vaporization of cannabis compared to cannabis smoked in a standard cigarette. The in-patient setting permitted us to measure plasma THC concentration over time and to rigorously assess the primary and secondary outcome variables in a controlled clinical environment.

Screening visit

Once a subject for the protocol had been identified, details of the study were carefully discussed and the subject was asked to read and sign a consent form. Subjects were asked questions about their medical history including psychiatric illness and substance abuse. Subjects were asked to abstain from smoking or ingesting cannabis 48 h before their hospitalization based on prior studies by Abrams and colleagues which indicated that after 24 h of abstinence, plasma THC concentrations are sufficiently low so that the concentration time curve could be determined after the experimental exposure.

GCRC in-patient hospitalization (days 1-6)

Subjects inhaled three strengths of cannabis (1.7, 3.4, and 6.8% THC) as smoked cigarettes and three as vaporized cannabis using the Volcano device. Half of one cigarette was inhaled via one of the two delivery systems on each of the 6 in-patient GCRC days. The uniform puff procedure described above was utilized to attempt to standardize inhalation. Blood was drawn at 2, 30, 60, 180, and 360 min after smoking on each of the 6 inhalation days to measure the concentrations of THC. Expired CO was measured using the Ecolyzers before inhalation, and 2, 30, 60, 180, and 360 min after inhalation. Subjects rated the subjective "high" they experienced using a 100 mm visual analogue scale anchored by "none" and "highest ever". On day 5 before discharge, subjects were asked to choose which inpatient day they preferred. Subjects were asked to rate their preferences from 1 to 5 with 1 indicating very satisfied and 5 indicating very dissatisfied.

All adverse events were spontaneously reported by the subject or observed by the study personnel and/or GCRC nursing staff, documented along with any medical intervention, and evaluated according to standardized criteria in terms of severity, frequency, duration, and relationship to study drug. Adverse events were graded using the NIH Division of AIDS table for scoring severity of adult adverse experiences.

Randomization

The order of administration of the six combinations of THC strength and delivery method for the 18 participants was randomized in three 6x6 Latin squares. This ensured balance in the sense that each of the six combinations occurred exactly three times on day 1, exactly three times on day 2, and so on. In addition, the orders were restricted so that the two delivery methods for the same strength always occurred on consecutive days.

This was to prevent patients from developing an early preference for one delivery method if it was used with a higher strength cigarette than the other. Randomization was computer-generated, and study drug distribution was managed by a research pharmacist. Subjects and study personnel were blinded to the THC strength.

Statistical analysis

The 18-patient target sample size was based on a standardized effect size to calculate sample size and power for the study. With a sample of 18 subjects, there is an 80% power to detect a true standardized effect size (E/S) of 0.70, using an α of 0.05, where E is the effect size and S is the standard deviation of the paired differences. This calculation assumes use of a paired t-test using data at a single concentration of THC.

The primary outcome was the within-person ratio for the 6-h area under the curve (AUC0-6) for plasma concentration of THC, comparing the vaporizer with smoking cannabis cigarettes. AUC0-6 was computed using the linear trapezoidal method, assuming zero THC concentration at baseline. This assumption was based on previous research that observed undetectable plasma concentration of THC 8 h after smoking in all subjects (Abrams et al. 2003). For each mode of administration and THC strength, the mean and 95% confidence intervals of the observed values at each time point were plotted. To assess the within person ratio comparing vaporization to smoking, each outcome (AUC0-6, C2, C30, C60, C180, C360, number of puffs, AUC0-6 per THC percent, and AUC0-6 per puff) was log transformed for analysis using mixed effects models. The overall effect of vaporization compared to smoking for each parameter was assessed by fitting a fixed effect term for randomization (vaporization vs smoking), controlling for strength of THC (indicators for 3.4% THC and 6.8% THC cannabis, relative to 1.7% THC cannabis). Each patient was treated as a random effect. Another model was fit to assess THC strength-specific effects of vaporization compared to smoking. This model included fitting additional fixed effects for the use of the vaporizer at each strength of THC (vaporization at 1.7% THC, vaporization at 3.4% THC, and vaporization at 6.8% THC).

The potential presence of order effects due to the study day of observation was also assessed, as well as potential practice effects due to additional experience using the vaporizer. To assess the presence of order effects, additional variables were added to both the overall and strength-specific models to assess whether day of observation impacted the outcomes, as well as whether there was a difference in measurements taken on the first day of the study compared to other study days. In these models, day of observation was treated as a linear variable with and without an additional indicator variable for the first study day. Similarly, to assess the presence of practice effects, additional variables were added to both the overall and strength-specific models to assess whether previous use of the vaporizer impacted the outcomes. These models included either a linear variable for how many days the participant had used the vaporizer or separate indicator variables for each day of vaporizer use.

To explore possible evidence of titration of THC intake and dose-dependent changes in bioavailability, additional mixed models for number of puffs and AUC0-6 per THC percent were created, which included fixed effects, as above, for randomization (vaporization vs smoking), as well as linear terms for strength of THC, and the interaction between randomization and strength of THC. As above, these models included a random effect for each patient. These models assess not only whether the ratio of the number of puffs or the AUC per THC percent differs during vaporization and smoking but also whether the ratio increases or decreases with increasing strength of cannabis, and whether this increase or decrease differs during vaporization compared to smoking.

The observed values for expired CO and self-reported high using similar methods were compared. The mean and 95% confidence intervals of response measures at each time point for each mode of administration and THC strength were plotted. Mixed models for the 6-h AUC for expired CO and self-reported high were fit, as described above, to compare within-person effects using vaporization and smoking. For 6-h AUC for CO, models for the within-person arithmetic difference in effects were fit, because it was not possible to fit models for the ratio of effects for 6-h AUC for CO due to the presence of many negative values (and therefore non-valid log transformation of these values) during vaporization. For 6-h AUC for self-reported high, models for the within-person ratios in effects were fit, as above. All analyses were conducted using SAS 8.2.

4.1.4 Results

Baseline characteristics of study subjects

A total of 68 patients were screened for eligibility between August 2004 and May 2005. Of these, 47 were not enrolled (33 patients were unavailable to commit to a 6-day hospitalization, 10 patients were excluded as a result of their medical history or concurrent illness, and four patients were excluded because of active substance abuse). Twenty-one patients were randomly assigned; however, three patients did not complete the intervention of the study phase (one patient for non-adherence to the General Clinical Research Center (GCRC) rules of comportment, one patient for acute influenza, and one patient withdrew consent), leaving 18 total patients for analysis.

Participants were predominately men (83%), Caucasian (72%), with some college education (94%). All of the participants were active cannabis users (median 5-6, range 3-10 cannabis cigarettes in the past 30 days). None had used the Volcano device, although one participant had previously experienced vaporized cannabis using a similar device.

Primary outcome measure

The vaporizer resulted in higher plasma concentrations of THC compared to smoked cannabis at 30 and 60 min at each strength. The two modalities were not significantly

different from one another at any of the three strengths in the 6-h area under the plasma THC concentration-time curve (AUC), or for the peak THC plasma concentrations measured at 2 min.

There was evidence of decreasing bioavailability and/or titration of THC intake with increasing strength of THC. The plasma THC AUC derived from the vaporizer normalized for the THC strength was highest at 1.7% THC (27.1 ng h/ml/%) and was progressively lower at higher THC strengths (3.4% THC: 20.5 ng h/ml/% and 6.8% THC: 14.3 ng h/ml/%), suggesting higher bioavailability and/or more intensive puffing at lower THC potency. This decline was statistically significant (ratio: 0.87; 95% CI: 0.84, 0.90; P<0.001 per 1% increase in THC strength) and did not appear to differ between vaporization and smoking (ratio for interaction: 0.92; 95% CI: 0.79, 1.05; P=0.25) in a mixed model which included fixed effects for randomization, a linear term for THC strength, and a term for the interaction between these effects.

There was also evidence of titration of intake of THC with increasing THC strength based on puffing behaviour. The number of puffs taken using smoked cannabis remained stable with increasing strength THC (mean puffs, 95% CI: 6.1 (4.8, 7.3), 5.9 (4.9, 6.8), and 6.4 (5.3, 7.6) for 1.7, 3.4, and 6.8% THC, respectively; mixed model analysis ratio: 1.01; 95% CI: 0.96, 1.05; P=0.81). The number of puffs taken using vaporized cannabis tended to decrease with increasing strength of THC, but the trend was not significant (mean puffs, 95% CI: 10.1 (8.8, 11.3), 9.2 (8.2, 10.1), and 8.6 (7.7, 9.4) for 1.7, 3.4, and 6.8% THC, respectively; mixed model ratio: 0.97; 0.92, 1.01; P=0.17).

Secondary outcome measures

The levels of exhaled CO increased very little after vaporization; mean= –1.9 p.p.m.; 95% CI: –4.4, 0.6 for 1.7% THC; mean= –1.8 p.p.m.; 95% CI: –3.7, 0.7 for 3.4% THC; and mean= –0.5 p.p.m.; 95% CI: –1.9, 0.9 for 6.8% THC), whereas there was a substantial increase after smoking cannabis (mean=15.5 p.p.m.; 95% CI: 11.0, 20.1 for 1.7% THC; mean=11.9 p.p.m.; 95% CI: 6.8, 17.1 for 3.4% THC; mean=7.0 p.p.m.; 95% CI: 4.0, 10.0 for 6.8% THC). This difference was statistically significant (P<0.001) at each THC strength. The increase in CO (AUC for CO) decreased during smoking (P=0.003 for trend), but not vaporization (P=0.25) with increasing THC strength. The expired CO AUC per puff is an indicator of how much smoke is inhaled per puff for the smoked cannabis. The CO AUC per puff decreased progressively (1.7% THC: [mean, 95% CI]: 2.8 (2.2, 3.3); 3.4% THC: 2.1 (1.1, 3.0); 6.8% THC: 1.2 (0.6, 1.9); P<0.001 for trend), consistent with taking smaller puffs with increasing THC content in the cannabis.

Subjective and safety observations

Self-reported high did not differ during vaporization compared to smoking overall (6-h AUC) or at any observation after consumption of cannabis. Self-reported high did increase significantly during both vaporization and smoking with increasing strength of

THC (P<0.001).

Although blinded with regard to dose, eight participants selected the day they received 3.4% THC (seven vaporized, one smoked) as their most preferred treatment day; four participants selected the day they received 6.8% THC via vaporization, and six participants had no treatment day preference. Overall, vaporization was the preferred method of administration by 14 participants, smoking was preferred by two, and two reported no preference. During the course of the study, no adverse events were reported.

4.1.5 Discussion

This study provides novel data on the absorption of THC from cannabis inhaled via the Volcano vaporizer system compared to smoking cannabis cigarettes. THC levels were generally similar over 6 h for the two types of delivery. The vaporizer was associated with higher plasma THC concentrations at 30 min and 1 h compared to smoking at each THC strength, suggesting that absorption was faster with the vaporizer.

This clinical study was conducted at a considerably lower temperature setting as the preclinical study by Gieringer et al. (2004), with a temperature setting of 6, which corresponds to a maximum temperature of about 190°C. It is expected that at this temperature, which seems to be enough to get a similar strong effect as with smoking a cannabis cigarette, even lower amounts of combustion products or no such products are generated than in the study by Gieringer et al. (2004), who found trace amounts of two combustion products.

Bioequivalence criteria developed for drugs require that the confidence intervals for the ratios of AUC for the test and reference products be between 80 and 125% to be judged bioequivalent. It was not possible to establish the bioequivalence of vaporization and smoking of cannabis. A much larger study would be needed to establish bioequivalence in this setting.

Of interest was that the systemic dose of THC, as estimated by the plasma AUC, normalized for the THC content of the cannabis, varied with THC strength. The dose of THC normalized for concentration of THC in the cannabis was greater at lower compared to higher THC strengths, both for vaporized and smoked cannabis. This observation suggests either dose-dependant bioavailability or self-titration of THC intake. Self-titration of drug intake means that smokers adapt their smoking behaviour to obtain desired levels of THC from the particular delivery system, taking more puffs and/or inhaling more efficiently at lower compared to higher THC strengths. Supporting the idea of titration was the trend to take more puffs at lower THC concentrations of vaporized cannabis and the higher CO per puff at lower THC concentrations of smoked cannabis. The phenomenon of self-titration of psychoactive drug intake from an inhaled delivery system is well documented for nicotine from cigarette smoking (Benowitz et al. 2006).

Whereas smoking cannabis increased CO levels as expected for inhalation of a

combustion product, there was little if any increase in CO after inhalation of THC from the vaporizer. This indicates little or no exposure to gaseous combustion toxins. Combustion products are harmful to health and reflect a major concern about the use of cannabis cigarettes for medical therapy. Although other combustion products such as polycyclic aromatic hydrocarbons and oxidant gases were not measured, the observation of little or no CO exposure suggests little or no exposure to these other compounds. The vaporizer was well tolerated, with no reported adverse effects. Most subjects preferred the vaporizer compared to cannabis smoking, supporting its potential for medical therapy. Thus, the Volcano is an acceptable system and may provide a safer way to deliver THC than smoking cannabis cigarettes.

In summary, this study by Abrams et al. (2007) provide data indicating that the availability of THC delivered by the Volcano vaporizer is comparable to that of cannabis cigarettes. Vaporization of cannabis does not result in exposure to combustion gases, and therefore is expected to be much safer than smoking cannabis cigarettes. The vaporizer was well tolerated and preferred by most subjects compared to cannabis cigarettes. The Volcano device was regarded as an "effective and apparently safe vehicle for THC delivery" by the authors.

4.2 Clinical study on the pharmacological effects of THC (dronabinol) administered by using the Volcano in healthy subjects (Zuurman et al. 2008)

The study by Zuurman et al. (2008) has been accepted for publication in the Journal of Psychopharmacology under the title "Effect of intrapulmonary THC administration in humans." The following texts on this study were taken from the manuscript of this publication provided by Dr. Zuurman and were partly rewritten by the author of this review of the clinical data on the Volcano.

4.2.1 Summary

Title: Effect of intrapulmonary THC administration in humans.

Identification of the medical device: Volcano® (Storz & Bickel GmbH & Co. KG, Tuttlingen, Germany, http://www.storz-bickel.com).

Name of sponsor: Sanofi-Aventis, Chilly-Mazarin Cedex, France

Objectives: The study was designed to investigate the pharmacological effects of increasing doses of inhaled THC using the Volcano device.

Subjects: 12 healthy male subjects between the ages of 21 and 27 years with a history of mild cannabis use for at least one year.

Methodology: This was a double blind, randomized, two-way balanced placebo-controlled, crossover study of inhaled rising doses of THC. On each study day, rising doses of THC (2, 4, 6 and 8 mg) or placebo were administered by inhalation at 90-

minute intervals using the Volcano vaporizer. Five to ten minutes before administration THC was vaporized at a temperature of about 225ºC. Subjects were instructed to inhale deeply and hold their breath for 10 seconds after each inhalation. The inhalation procedure was practiced at screening using the solvent as a placebo. Pharmacodynamic and pharmacokinetic measurements were performed frequently on both study days. Side effects were recorded.

Results: Typical THC pharmacological effects such as increase of heart rate were observed. Most adverse events were mild, transient and did not require medical intervention. The most frequently observed events were well-known THC effects like drowsiness, sleepiness, attention deficit and feeling high. During THC inhalation five subjects had to cough while subjects were required to hold their breath for 10 seconds. This was not reported after inhalation of the alcohol-vehicle during placebo occasions.

Conclusions: Authors of the study concluded, that their study showed a range of pharmacodynamic effects of THC, using a novel mode of intrapulmonary THC administration. Some of these effects were clearly dose- and concentration-related, and started with the lowest dose of 2 mg. The side effects (coughing) were not further mentioned in the discussion or conclusion part of the publication.

Authors of report: Lineke Zuurman, Christine Roy, Rik C. Schoemaker, Arno Hazekamp, Jan den Hartigh, Johan C.M.E. Bender, Rob Verpoorte, Jean-Louis Pinquier, Adam F. Cohen, Joop M.A. van Gerven

Publication date: accepted for publication in August 2007, not published until the end of 2007

4.2.2 Introduction

This study was conducted to measure pharmacological effects of THC after inhalation of different doses. In a pre-clinical study the performance of the Volcano vaporizer in terms of reproducible delivery of pure THC was evaluated and vaporization of THC was systematically improved by changing parameters such as temperature setting and balloon volume by the same group (Hazekamp et al. 2006, see chapter 3.2.).

In this subsequent clinical study, the pharmacodynamic effects of pure THC were measured using a battery of central nervous system (CNS) assessments that have been shown to be sensitive to a wide range of CNS-active agents (Steveninck et al. 1999, Visser et al. 2002). In addition, heart rate and blood pressure were measured frequently.

4.2.3 Materials and methods

Design

This was a double blind, randomized, two-way balanced placebo-controlled, crossover study of inhaled rising doses of THC. Informed consent was obtained in writing before any study-specific procedure was carried out. After a general health screen, eligible

subjects were enrolled in the study. Subjects were acquainted with the experimental methods and conditions, and with the inhalation procedure using alcohol-vehicle, in a training session within one week before the first study day. Pharmacodynamic and pharmacokinetic measurements were performed frequently on both study days. A follow-up visit (medical screening) was scheduled within two weeks after the second study day. The study protocol was approved by the Medical Ethics Review Board of Leiden University Medical Center and performed according to principles of ICH-GCP, the Helsinki declaration and Dutch regulations.

Subjects

Twelve healthy males (21-27 years) with a history of mild cannabis use for at least one year were included in the study. Subjects were not allowed to use cannabis more than once a week (the average was calculated over the last six months), and had to be able to refrain from using cannabinoids during the study. Use of other drugs or any medication was not allowed. Subjects with a positive THC test at screening were tested again, and were required to be negative before the first study day. Subjects with a positive drug test on a study day were excluded. Subjects had to refrain from smoking and use of coffee and tea on study days. The subject had to maintain a normal day-night-rhythm in the week before each study day. Severe physical exercise shortly before the study days had to be avoided. Subjects were financially compensated for their participation.

Treatments

THC was purified according to GMP-compliant procedures (Farmalyse BV, Zaandam, The Netherlands) from the flowers of Cannabis sativa grown under Good Agricultural Practice (Bedrocan BV Medicinal Cannabis, Veendam, The Netherlands). Each dose (2, 4, 6 or 8 mg) of THC (>98% purity by HPLC/GC) was dissolved in 200 Jl 100 vol% alcohol. THC was stored in the dark at -20ºC in 1 ml amber glass vials containing a teflon screw-cap secured with Para film to minimize evaporation. The solvent was used as placebo. On each study day, rising doses of THC (2, 4, 6 and 8 mg) or placebo were administered by inhalation at 90-minute intervals using a Volcano® vaporizer (Storz & Bickel GmbH, Tuttlingen, Germany). Five to ten minutes before administration THC was vaporized at a temperature of about 225ºC and the vapour was stored in a transparent polythene bag equipped with a valved mouthpiece, preventing the loss of THC in between inhalations. The transparent bag was covered with a black plastic bag to prevent unblinding. Subjects were not allowed to speak, were instructed to inhale deeply and hold their breath for 10 seconds after each inhalation. Within 2-3 minutes the bag was to be fully emptied. The inhalation procedure was practiced at screening using the solvent as a placebo.

The inhalation schedule was predicted to cause incremental THC plasma concentrations and effects, with cumulative peak plasma levels corresponding to a single dose of

around 11 mg. The decision to proceed to the next highest THC dose was made by a physician, based on adverse events and physical signs. Because of the long half-live of THC study days were separated by a washout period of at least two weeks.

Pharmacokinetic measurements

For determination of the concentration of plasma THC and its two most important metabolites (11-OH-THC and 11-nor-9-carboxy-THC), venous blood was collected in aluminium foiled EDTA tubes of 4.5 ml. Blood samples were taken at baseline and at 10, 20 and 80 minutes after each THC administration. Additional samples were taken at 5, 35 and 55 minutes after administration of 6 mg THC and at 375, 425, 495, 545 and 1440 minutes after the first THC administration. After blood collection the tubes were put in ice water (0-4 ºC) and centrifuged within one hour for 10 minutes at 2000G at 4ºC. The THC samples were handled sheltered from light. Plasma samples were stored at a temperature of -20ºC for less than 3 months before laboratory analysis. Concentrations of THC and the metabolites were shown to be stable over this period.

Pharmacodynamic measurements

Pharmacodynamic assessment was performed in a quiet and temperature controlled room with standardised illumination with only one subject per session in the same room. All tests were measured twice pre-dose and obtained frequently at fixed time points after each consecutive THC dose.

Heart rate and blood pressure: Blood pressure and heart rate were measured in supine position after a rest of approximately 5 minutes, twice pre-dose and repeatedly post-dose on each of the two study days. All measurements were carried out with an automated sphygmomanometer (Nihon Kohden, Life Scope EC, Tokyo, Japan).

Pupil size: For pupil size (pupil/iris ratio) measurements, a picture of both eyes was taken using a Digital camera (Minolta DiMAGE) using a flashlight after at least five minutes adaptation in subdued lighting. For each eye, the diameters of the pupil and the iris in millimetres were determined. The pupil / iris ratio was subsequently calculated as a measure of pupil size.

Smooth pursuit and saccadic eye movement: Recording and analysis of saccadic and smooth pursuit eye movements was conducted with a personal computer using a validated Spike2 script (Cambridge Electronic Design Limited, Cambridge, UK). Disposable silver-silver chloride electrodes (Mediscore, VDP Medical, Nieuwegein, The Netherlands) were applied on the forehead and beside the lateral canthi of both eyes of the subject for registration of the electro-oculographic signals. Skin resistance was reduced to less than 5 kOhm before application of the electrodes. Head movements were restrained using a fixed head support. The equipment used for stimulus display was manufactured by Nihon Kohden (Nihon Kohden Corporation, Tokyo, Japan). For signal collection and amplification, a CED 1401 Power AD-converter (Cambridge

Electronics Design, Cambridge, UK), a Grass telefector (F-15EB/B1) and a 15LT series Amplifier Systems (Grass-Telefactor, Braintree, USA) was used.

For recording and analysis of smooth pursuit eye movements the target moved sinusoidally at frequencies ranging from 0.3 to 1.1 Hz, increased by eight steps of 0.1 Hz. The amplitude of target displacement corresponded to 22.5 degrees eyeball rotations to both sides. Four cycles were recorded for each stimulus frequency. The average time during which the eyes were in smooth pursuit of the target, expressed as a percentage of stimulus duration, was used as the measurement parameter. The target for the saccadic eye movements consisted of an array of light emitting diodes on a bar, fixed at 50 cm in front of the head support. Saccadic eye movements were recorded for stimulus amplitudes of approximately 15 degrees to either side. Fifteen saccades were recorded with interstimulus intervals varying randomly between 3 and 6 seconds. Average values of latency (reaction time), saccadic peak velocity and inaccuracy of all artefact-free saccades were used as parameters. Saccadic inaccuracy was calculated as the absolute value of the difference between the stimulus angle and the corresponding saccade, expressed as a percentage of the stimulus angle.

Pharmaco-EEG: EEG recordings were made using silver chloride electrodes, fixed with collodion at Fz, Cz, Pz and Oz positions, with the same common ground electrode as for the eye movement registration (international 10/20 system). The electrode resistances was kept below 5 kOhm. EEG signals were obtained from leads Fz-Cz and Pz-Oz and a separate channel to record eye movements (for artefacts). The signals were amplified by use of a Grass telefector (F-15EB/B1) and a 15LT series Amplifier Systems (Grass-Telefactor, Braintree, USA) with a time constant of 0.3 seconds and a low pass filter at 100 Hz. Data collection and analysis were performed using a validated Spike2 script (Cambridge Electronics Design, Cambridge, UK). Per session eight consecutive blocks of eight seconds were recorded. The signal was AD-converted using a CED 1401 Power (Cambridge Electronics Design, Cambridge, UK) and stored on hard disk for subsequent analysis. Data blocks containing artefacts were identified by visual inspection and these were excluded from analysis. For each lead, fast Fourier transform analysis was performed to obtain the sum of amplitudes in the delta- (0.5- 3.5 Hz), theta- (3.5-7.5 Hz), alpha- (7.5-11.5 Hz) and beta- (11.5-30 Hz) frequency ranges. Outcome parameters were the square root of the total power in each band for each lead.

Body sway: The body sway meter allows measurement of body movements in a single plane, providing a measure of postural stability. Body sway was measured with an apparatus similar to the Wright ataxia meter (Wright 1971). With a string attached to the waist, all body movements in the antero-posterior direction over a period of 2 minutes were integrated and expressed as mm sway on a digital display. The contribution of vision to postural control was eliminated by asking subjects to close their eyes. Subjects were not allowed to talk during the measurement, and asked to wear the same comfortable low-heeled shoes at all measurements.

Adaptive tracking: The adaptive tracking test was performed as originally described by Borland and Nicholson (Borland et al. 1984), using customized equipment and software

(Hobbs 2000, Hertfordshire, UK). Adaptive tracking is a pursuit tracking task. A circle moved randomly about a screen. The subject had to try to keep a dot inside the moving circle by operating a joy stick. If this effort was successful, the speed of the moving circle increased. Conversely, the velocity was reduced if the test subject could not maintain the dot inside the circle. Average performance was scored after a 3 minute period. Each test was preceded by a run-in period. After 4 to 6 practice sessions, learning effects are limited. The adaptive tracking test is more sensitive to impairment of eye-hand coordination by drugs than compensatory pursuit tasks or other pursuit tracking tasks, such as the pursuit rotor. The adaptive tracking test has proved to be useful for measurement of CNS effects of alcohol, various psychoactive drugs and sleep deprivation (Steveninck et al. 1993, Steveninck et al. 1999).

Visual analogue scales (VAS): From the visual analogue scales as originally described by Norris (Norris 1971) (16 items), three factors can be derived, as described by Bond and Lader (Bond et al. 1974), corresponding to alertness, contendness and calmness. Increased scores of these scales indicate enhanced subjective feelings of alertness, contendness (in general) and calmness. Psychedelic effects were monitored by an adapted version of the visual analogue scales (13 items), originally described by Bowdle et. al. (Bowdle et al. 1998).

Analysis

Pharmacokinetic assay: Plasma samples for determination of THC, 11-OH-THC and 11-nor-9-carboxy-THC were stored at a temperature of -20ºC prior to bioanalysis. Analysis was performed using a validated high performance liquid chromatography with tandem mass spectrometric detection. Calibration range was for all compounds 1.00 – 500 ng/ml. Over this range the intra-assay coefficient of variation was between 4.0 and 6.5%. The inter-assay coefficient of variation was between 1.4 and 9.4%.

Statistics: All pharmacodynamic endpoints were summarized by treatment and time, and were presented graphically as mean over time, with standard deviation as error bars. The pharmacodynamic endpoints were analyzed separately by mixed model analyses of variance (using SAS PROC MIXED, SAS for Windows, V9.1.2, SAS Institute, Inc., Cary, NC, USA) with treatment, period, time and treatment by time as fixed effects, with subject, subject by time and subject by treatment as random effect, and with the (average) baseline value as covariate. Treatment effect was reported as the contrast between the placebo and THC treatment where the average of the measurements up to (and including) 10 hours was calculated within the statistical model. Additionally, the average response of the values obtained in the 90 minutes after the final administration of THC (identified as the ‘fourth dose effect’) was compared between treatments within the statistical model. Contrasts were reported along with 95% confidence intervals. EEG and body sway data were analysed after log-transformation and all other parameters were analysed without transformation except for VAS Bowdle. Log-transformed contrasts were back-transformed resulting in geometric mean ratios with associated confidence intervals. These were re-expressed as percentage change

from placebo.

Examination of average graphs (and summary measures over time) indicated that the VAS measuring psychedelic effects demonstrated a very skewed frequency distribution. As zeroes can naturally occur for these data (response from 0 to 100), a 10log transformation was applied after first adding 2 to all values. The rationale for log(x+2) instead of the more common log(x+1) transformation was that, after examining scatter plots of the psychedelic variables, a clear gap was observed between the log(1) values and the remaining values. After implementing the log(x+2) transformation, the gap decreased and a more homogenous distribution was obtained. In order to reduce the number of VAS Bowdle scales and facilitate the interpretation of the results, cluster analysis and factor analysis was performed on the transformed psychedelic VAS scales. Two distinct clusters were found. VAS ‘feeling drowsy’ was removed from the first cluster because this was not really considered a psychedelic effect, and drowsiness is more properly assessed using Bond and Lader VAS alertness. The two resulting clusters can be interpreted as two modalities of psychedelic effects roughly corresponding to 'external perception’ and ’internal perception’. Changes in external perception reflect a misperception of an external stimulus or a change in the awareness of the subject’s surroundings. Internal perception reflects inner feelings that do not correspond with reality.

A subsequent factor analysis indicated that the factor loadings were more or less the same for factors in the two clusters. This means that the two new composite factors can be derived by simply averaging the (transformed) psychedelic VAS Bowdle scales. Since the log+2 transformation makes back-transformation problematic and the resulting scales have favourable statistical properties, it was decided to not backtransform the results. To avoid confusion, the unit “U” was used instead of ‘average (log+2 mm)’ in reporting the results.

PK/PD modelling: PD parameters demonstrating a significant treatment effect and clear concentration dependency were analysed using pharmacokinetic-pharmacodynamic (PK/PD) modelling. Nonlinear mixed effect modelling as implemented in the NONMEM program (Version 5, Globomax LLC, Ellicot City, MD, USA) was used. The PK/PD modelling is described in full detail by Strougo et al. (2008).

4.2.4 Results

Clinical and side effects

All 12 participants completed the study. Most adverse events (AEs) were mild, transient and did not require medical intervention, except for occasional use of paracetamol. The most frequently observed events were well-known THC effects like drowsiness, sleepiness, attention deficit and feeling high. In addition, also minor adverse events like headache and eye irritation were reported. During THC inhalation five subjects had to cough while subjects were required to hold their breath for 10 seconds. This was not reported after inhalation of the alcohol-vehicle during placebo occasions. Two out of 12

subjects experienced THC specific side effects severe enough to decide not to administer the last dose of 8 mg THC. One of these subject was too sleepy to perform any test, and the other subject vomited just after administration of the third dose.

Pharmacokinetics

THC plasma peak levels were reached within a few minutes. Plasma peak concentration was followed by a short distribution phase (approximately 25 minutes) and a longer elimination phase (roughly 250 minutes). Average plasma THC concentrations 10 min after the fourth dose (50.3 ± 14.4 ng/mL) exceeded the 11-OH-THC concentrations (6.8 ± 2.8 ng/mL) by 7.4-fold, and the 11-nor- 9-carboxy-THC concentrations (21.8 ± 4.8 ng/mL) by 2.3-fold. There was a very small between-subject variability in THC plasma concentrations as illustrated by the low standard deviations.

Heart rate and blood pressure

Heart rate increased in a dose-related manner compared to placebo. The average increase after the fourth dose of 8 mg was 19 beats per minute (95% CI 13.2, 25.5 bpm). After the initial increase, heart rate decreased rapidly after each dose, and hardly any accumulation was seen with repeated dosing. Blood pressure did not change after THC administration (fourth dose effect: systolic blood pressure: -1 mmHg: 95% CI -8, 6; diastolic blood pressure: -0.5 mmHg: 95% CI -8, 7).

Pupil size

Compared to placebo, slight increases were seen in pupil/iris ratio that were only significant after the fourth dose of 8 mg THC (0.025: 95% CI 0.003, 0.047).

Smooth pursuit and Saccadic eye movement

No changes in smooth pursuit eye movements occurred (fourth dose effect: -3%: 95% CI -9, 3). Compared to placebo, saccadic latency (20 msec: 95% CI 10, 30) and saccadic inaccuracy (3.1% : 95% CI 1, 5) increased only after the fourth dose of 8 mg THC. No changes were found in saccadic peak velocity (fourth dose effect: 14 deg/sec: 95%CI -4, 32).

Electro-encephalography (EEG)

After the highest dose of THC there were decreases in the power of Pz-Oz delta (-16%: 95% CI -24, -7), Pz-Oz theta (-15%: 95%CI -24, -5) and Pz-Oz beta activity (-12%: 95% CI -18, -4). No changes were found in alpha activity (-6%: 95% CI -17%, 5%). In the Fz-Cz region, changes in beta activity were predominant. No changes in delta and theta activity were seen in Fz-Cz region. Although EEG was affected significantly by active

treatment, the average time profiles did not indicate a clear dose and concentration dependency.

Body sway

After THC administration, dose-related increases were seen in body sway, which decreased only slowly after each dose and did not return to baseline between doses. Consequently, the effect accumulated with repeated dosing to a 109% increase over placebo: (95% CI 72, 152) after the highest dose.

Adaptive tracking

Compared to placebo no changes were observed in adaptive tracking performance (fourth dose effect: -1%: 95%CI -3, 1).

Visual analogue scales (VAS)

VAS Bond & Lader. The VAS 'alertness' was affected by THC in a dose related manner. The decrease accumulated to -34 mm: 95% CI -42, -26 after the fourth dose. A decrease was seen in VAS 'contendness' after the fourth dose (-7 mm 95%CI -13, -1) but no change was seen in VAS 'calmness' (-3 mm: 95% CI -10, 4).

VAS Bowdle – internal and external perception. Many of the individual visual analogue scales measuring psychedelic effects demonstrated treatment effects, with VAS 'feeling high' as one of the most responsive scales (1.1 U: 95% CI 0.9, 1.3). The composite score of 'external perception' showed a dose response effect of THC and an increase of 0.6 U after the fourth dose (95% CI 0.4, 0.7). Although a significant treatment effect was also demonstrated for the 'internal perception' composite scale (0.2 U: 95% CI 0.1, 0.4 after the fourth dose), concentration- and dose-dependency were much less pronounced than the effect for 'external perception' and seemed to be associated with an 'on/off effect' or at least a very steep dose-response curve (no response after 2 mg, maximum response at doses of 4 mg and higher).

PK/PD modelling

The effects of THC lagged behind the THC plasma concentration, revealing hysteresis. Equilibration half-lives that quantify hysteresis varied from 7.68 minutes for heart rate and from 39.2 to 84.8 minutes for the effects on the central nervous system. The PK/PD modelling is described in full detail by Strougo et. al. (2008).

4.2.5 Discussion

This study was designed to investigate the acceptability and usefulness of THC

administration using the Volcano vaporizer. In this study the average plasma THC profiles indicate very limited inter-individual variability, characterising the Volcano vaporizer as a suitable method for the administration of pure THC.

The effect of THC on different CNS and non-CNS tests was investigated. Many of the THC-effects were dose-dependent after administration of repeated doses of 2, 4, 6 and 8 mg. Feelings of unreality, hallucinations, paranoia and anxiety have been observed after use of high doses of cannabis and in cannabis naïve subjects (Dittrich & Woggon 1974; D'Souza et al. 2004). In this study subjects familiar with the effects of cannabis were included and possibly the doses in our study were not high enough to elicit such effects. Interestingly, all observed CNS effects showed accumulation of the effects since the effect of the previous dose had not faded before the next dose was administered.

The literature reports conflicting results on tracking tests, which is probably due to differences in tasks (Roth et al. 1973). The critical tracker task employed by Stoller et al. resembles the tracker test used in this study. They reported a statistically significant effect on the critical tracking test after the oral administration of 22.5 mg THC (Stoller et al. 1976). Since the pulmonary administration of THC is on average approximately 2.6-3 times more potent than oral administration (Isbell et al. 1967), this result should resemble the cumulative effect after the fourth dose in this study. However, we did not observe significant changes.

CB1 receptors are sparsely found in the brainstem (Herkenham et al. 1990; Mackie 2005) which may explain why few changes in smooth pursuit and saccadic eye movements were seen. Smooth pursuit eye movements are primarily steered by the paramedian pontine reticular formation, and saccadic eye movements by the superior colliculus (Leigh et al. 1991). The lower brain stem areas also control cardiovascular function. Orthostatic hypotension has been reported in literature (Hall et al. 1998; Sidney 2002). In this study no changes in blood pressure have been seen, which may be due to the supine blood pressure measurements. In this respect, the sharp dose dependent increase in heart rate could be considered as a compensatory mechanism for a loss of vascular tone.

The increase in heart rate was clearly dose dependent and closely associated with THC plasma concentrations. Tachycardia was significant, with an average increase of 19 beats per minute after the fourth dose, without any indications for blood pressure reductions. In contrast with different CNS parameters hardly any accumulation was seen in heart rate after rising doses of THC. These results correspond to data found in literature (Hall et al. 1998; Sidney 2002). The faster response in heart rate prior to the onset of subjective effects has also been observed after oral administration of 15 mg THC (Zeidenberg et al. 1973). Literature also reported that THC plasma concentration already dropped significantly before maximum psychotropic effects were achieved (Ohlsson et al. 1980; Chiang et al. 1984). These observations make it likely that a peripheral mechanism is involved in the increase in heart rate. This is supported by PK/PD modelling of the current study, which showed a relatively short equilibration half-live for heart rate of 7.68 minutes (Strougo et al. 2008). This is much shorter than the

equilibration half-lives found on central nervous system effects, which varied from 39.2 to 84.8 minutes. In addition, CB1 receptors are present in human atrial muscle (Bonz et al. 2003).

Lipophilic compounds like THC that cross the blood-brain barrier tend to accumulate in the brain, which explains the prolongation of the CNS effects, in contrast to the much faster response of heart rate. The equilibration half-lives that quantify hysteresis varied from 39.2 to 84.8 minutes for the effects on the central nervous system. This range may reflect various mechanisms of action, in which receptor density and receptor distribution between different brain regions, activation of secondary neurotransmitters systems, or perhaps yet unidentified CB-receptors may play a role. Only limited and transient side effects were seen. The authors therefore consider administration of rising doses up to 6 or 8 mg pure THC using the Volcano vaporizer a safe method of THC administration. Two out of 12 subjects experienced side effects severe enough to decide not to administer the last dose of 8 mg THC. These side effects were all THC related and not related to the Volcano device.

In conclusion, this study showed a range of pharmacodynamic effects of THC, using intrapulmonary THC administration by the Volcano vaporizer. Some of these effects were clearly dose- and concentration-related, and started with the lowest dose of 2 mg. These dose-related effects include impairments of subjective alertness and postural stability, feeling ‘high’ and psychedelic effects, and an increase in heart rate. The most sensitive effects seem to correspond to brain regions that have the highest densities of cannabinoid receptor localization. These results can be useful in the development of therapeutically beneficial cannabinoid agonists and antagonists, and in studies of the pharmacology and physiology of cannabinoid systems in humans.

5 Summary and conclusions

Intrapulmonary administration of cannabinoids is regarded as an effective mode of delivery since it results in fast onset of action and high systemic bioavailability (Grotenhermen 2003). Since the 1970s attempts have been made for intrapulmonary administration of cannabis compounds without the risks associated with combustion of the material. Vaporization is suggested as one of these means, where cannabinoids and terpenoids of the plant are vaporized below a temperature at which combustion of the dried plant matter commences. Another alternative to smoking is the administration of THC by aerosol. Several studies have been performed using an aerosol for the administration of THC, resulting in the well-known pharmacological effects (Wilson et al. 2002, Naef et al. 2004, Lichtman et al. 2000, Hartley et al. 1978). But administration of cannabinoids by this way is associated with new problems. Since cannabinoids are almost completely insoluble in water it requires the use of solubilizers that are to be inhaled together with THC, which frequently results in irritation of the lungs and coughing. Moreover, part of an administered aerosol can be swallowed and thereby administered orally, complicating the effect, kinetics, and metabolism of the administered compound. This has already been shown for aerosol administration of radiolabeled

isoproterenol (Lyons et al. 1973). The Volcano vaporizer seems to eliminate at least part of the problems associated with the use of an aerosol for the delivery of THC or other cannabinoids. It is likely that the Volcano also produces an aerosol, that is, droplets of various sizes in a gas phase made up of vapour and air. But this aerosol is inhaled without need of a solubilizer.

For the recreational use of cannabis the drug is usually smoked, which is not regarded as an acceptable way of delivery for medicinal use by many since carcinogenic combustion products qualitatively similar to the smoke of tobacco (Moir et al. 2007) are formed and inhaled, which may cause severe health problems (Grotenhermen 2004). Combustion of dried plant matter needs higher temperatures than needed for the vaporization of cannabinoids. The main compound of dried plant material is cellulose, for which no data on auto-ignition temperature is available (see the material safety data sheet for cellulose at http://www.sciencelab.com/xMSDS-Cellulose-9927490).

Temperatures on the central axis of the coal of a tobacco cigarette have been reported to be in the range of between 800° and 900°C during a puff and 700-800°C during the natural smoulder between puffs (Baker 1974). It was reported to be 300°C at the periphery of the coal (Baker 1974). White et al. (2001) investigated the mutagenicity of tobacco smoke aerosol of different temperatures. Tobacco smoke aerosol was generated under precisely controlled temperature conditions from 250 to 550°C by heating compressed tobacco tablets in air. Tobacco smoke condensates were not mutagenic in the Ames *Salmonella* microsome test when the tobacco smoke aerosol was generated at temperatures below 400°C. It can be expected that cannabis behaves similar as tobacco in this respect. In their study Gieringer et al. (2004) found only trace amounts of combustion products of dried cannabis at the maximum temperature setting of 9 of the Volcano device, which resulted in a maximum temperature of 218°C.

Two preclinical and two clinical studies have been conducted so far to investigate the feasibility and safety of the Volcano vaporizer for the delivery of THC (dronabinol) and other compounds of the cannabis plant to humans for therapeutic and other purposes. Two of these studies (one preclinical and one clinical) used dried cannabis plant material (Gieringer et al. 2004, Abrams et al. 2007) and were conducted in the USA, the two others conducted by a group in the Netherlands used isolated THC (dronabinol) (Hazekamp et al. 2006, Zuurman et al. 2008) which is regarded as the main compound of the cannabis plant with regard to pharmacological activity. With the exception of providing the Volcano vaporizers the company Storz & Bickel GmbH & Co. gave no financial support to the studies. The sponsors of the two clinical studies were the University of California Center for Medicinal Cannabis and the US National Institutes of Health (Abrams et al. 2007) and Sanofi-Aventis, France, (Zuurman et al. 2008), respectively. In this report these four studies were presented in brief in the chapters 3 (preclinical studies) and 4 (clinical studies).

The preclinical study by Gieringer et al.(2004) demonstrated that at the highest temperature setting of the Volcano samples of dried cannabis are heated to temperatures of between 155°C (on the top surface of the sample) and 218°C (on the

screen closest to the heater). The highest temperature setting is 9 on a scale between 1 and 9. At this temperature the dried plant material did not turn to ash. The vapour generated consisted overwhelmingly of cannabinoids with trace amounts of three other compounds. The three were caryophyllene (a terpene) plus two other compounds of undetermined origin (2-Methyl-2, 4 (2H-1-benzopyran-5-ol), 5-[(Acetyl benz [e] azulene-3,8-dione). In contrast, in the smoke of cannabis cigarettes, which were used for comparison in this study, cannabinoids represented only 12% of the inferred recovered mass; the remaining 88% consisted of extraneous products of combustion. The authors summarized: "The major finding of this study was a drastic quantitative reduction in non-cannabinoid compounds in the vapour from the Volcano. This strongly suggests that vaporization is an effective method for delivering medically active cannabinoids while effectively suppressing other potentially deleterious compounds that are a byproduct of combustion." Data from this study have been submitted to the US Food and Drug Administration (FDA) in support of an application for an investigational device exemption (IDE) to permit the Volcano to be used in the study by Abrams et al. (2007).

In the clinical study by Abrams et al. (2007) with 18 healthy subjects intrapulmonary administration of cannabis compounds using the Volcano was compared to the inhalation of cannabis by smoking. Temperature setting 6 was used, which corresponds to about 190°C and is considerably lower than the setting in the preclinical study by Gieringer et al. (2004). Results of the study by Abrams et al. show that even at this lower temperature setting peak plasma concentrations and area under the plasma concentration-time curve of THC were similar under both conditions, while CO levels were reduced with vaporization. Authors noted no adverse events related to the Volcano device.

In contrast to the US studies, the two Dutch studies presented in this report were not conducted with dried cannabis but with pure THC (Hazekamp et al. 2006, Zuurman et al. 2008). In the preclinical study parameters such as temperature setting, type of evaporation sample and balloon volume, the vaporation of THC by the Volcano was systematically improved to its maximum and inter- and intra-device variability was tested (Hazekamp et al. 2006). Authors concluded that variability was low and that THC can be delivered in a reproducible manner.

In the clinical study with THC by Zuurman et al. (2008) typical THC effects were observed after the administration of increasing doses of THC (2, 4, 6 and 8 mg) by the Volcano to 12 healthy subjects, including increase of heart rate, feeling high, drowsiness and sleepiness. This is the only study reporting side effects caused by the mode of delivery. During THC inhalation 5 of the 12 subjects had to cough while holding their breath for ten seconds. This was not reported following inhalation of the alcohol-vehicle during placebo occasions. Apparently, authors did not regard this side effect as a major problem, since they did not even discuss this issue in their discussion part of their article.

In summary, preclinical and clinical research with the Volcano has demonstrated that cannabinoids from dried cannabis and isolated cannabinoids can safely and in a

reproducible manner be administered with this device to humans. Side effects are usually due to the typical pharmacological effects of the inhaled substances. Side effects associated with the mode of administration were coughing observed in some participants of a clinical study, apparently due to an irritation of the respiratory tract. Trace amounts of combustion products observed in the preclinical study by Gieringer et al. (2004) may be further reduced or completely avoided by reducing the maximum temperature setting of the device. All authors of the four articles on research with the Volcano regarded the device as being promising for the medical use or pharmacological research in humans.

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7 About the author of this review

Franjo Grotenhermen, MD, born in 1957, has devoted the last 15 years of his career to the investigation of scientific and policy issues related to the medicinal and recreational use of cannabis and cannabinoids. Dr. Grotenhermen is founder and chairman of the Association for Cannabis as Medicine (ACM) and founder and executive director of the International Association for Cannabis as Medicine (IACM) (www.cannabis-med.org). The ACM was founded in 1997 by physicians, patients and others advocating the medical use of cannabis. Its members are from the German speaking countries. The ACM formed the basis of the International Association for Cannabis as Medicine (IACM), a scientific association, which serves as a global clearinghouse for science-based information on the medicinal uses of cannabis and continues to provide information to other researchers, patients, pharmaceutical firms, policy makers, and the media. He is editor of the IACM-Bulletin, which is published bi-weekly in six languages (English, German, French, Spanish, Dutch and Italian) and editor of the internet journal CANNABINOIDS, published on the website of the IACM. He is a principal of the nova-Institute based near Cologne and author of many articles, books and book chapters on the therapeutic potential, pharmacology and toxicology of the cannabinoids. He is an expert and consultant on these issues for private persons, companies, courts and institutions, including the World Health Organization.

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Addition to Evaluation of Clinical Data concerning transferability of the results of the two clinical studies with the Volcano with healthy subjects to patient populations in response to the letter of TÜV SÜD Product Service GmbH of 26 March 2008

by Franjo Grotenhermen, nova-Institut, Hürth, Germany

No clinical studies have been conducted so far with the Volcano device in people suffering from specific diseases. However, it is well-known from several clinical studies with different patient populations that dronabinol (THC) is well absorbed by the respiratory tract, when cannabis is inhaled by smoking, and that this absorption results in pharmacological effects with an intensity similar to the intensity of effects in healthy subjects. Smoked cannabis was effective in patients with a disease of the respiratory tract (asthma) as well as in patients supposed to have no altered lung function.

Oral dronabinol and smoked cannabis resulted in a dose-dependent increase of food intake in HIV-positive subjects (Haney et al. 2007). Smoked cannabis caused a significant pain reduction in a placebo-controlled study in patients with HIV-associated sensory neuropathy (Abrams et al. 2007a). Smoked cannabis improved spasticity and ataxia in a patient with multiple sclerosis (Meinck et al. 1989). Smoked cannabis improved nausea and vomiting in patients undergoing cancer chemotherapy (Vinciguerra et al. 1988). Oral dronabinol and smoked cannabis were similar effective in reducing side effects of cancer chemotherapy in a controlled study with placebo dummies of dronabinol and cannabis cigarettes (without THC) (Levitt et al. 1984). Smoked cannabis reduced intra-ocular pressure in patients suffering from glaucoma (Merritt et al. 1980). Oral dronabinol and smoked cannabis caused significant bronchodilation of at least 2 hours duration in asthmatic patients (Tashkin et al. 1974).

Since the study by Abrams et al. (2007b) showed that the administration of cannabis with the Volcano device and smoking of cannabis resulted in similar peak plasma concentrations and 6-h area under the plasma concentration-time curve of THC, it can be expected that dronabinol (THC) can also effectively be administered to different patient populations with similar effects well-known from smoking cannabis.

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