# Harm Reduction Associated with Inhalation and Oral Administration of Cannabis and THC

Franjo Grotenhermen

**SUMMARY.** Inhalation of carcinogenic combustion products associated with smoking is generally regarded as the major health hazard in connection with the medical use of cannabis products. Strategies to reduce respiratory and other adverse events resulting from this common practice include relinquishment of inhalation and replacement by other routes of administration, the use of plants with a high THC content allowing reduction of the amount of smoked plant material, usage of inhalation devices that improve the ratio of THC and tar, and avoidance of the Valsalva maneuver that may cause spontaneous pneumothorax. The major risk associated with oral cannabis use is accidental overdosage, especially in inexperienced users that can be avoided by appropriate dosing procedures. A combination of oral use and inhalation may be meaningful in several indications, decreasing the specific risks of both routes. Preliminary studies using rectal, sublingual and transdermal routes indicate that these alternatives to the two most common forms of ingestion may be utilized medicinally in the future, further reducing the possible risks associated with the administration of cannabis or single cannabinoids. *[Article copies available for a fee from The Haworth Document Delivery Service: 1-800-342-9678. E-mail address: <getinfo@haworthpressinc.com> Website: <http://www.HaworthPress.com>* 

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**KEYWORDS.** Cannabis, marijuana, THC, cannabinoids, smoking, inhalation, oral use, rectal use, sublingual use, transdermal use, therapeutic use, side effects, health risk, harm reduction, cancer, spontaneous pneumothorax, dosing, overdose, opium, opiates, pharmacokinetics

## *INTRODUCTION*

Major objections to the use of crude cannabis products medicinally are often based not on properties of the natural herb itself, but on the possible adverse health effects resulting from the most prevalent form of application in recreational use: smoking a marijuana cigarette or pipe (Joy et al. 1999; Tashkin 2001). The major advantages of inhalation of cannabis or THC are rapid onset of action and flexible dose titration, making this route of administration very attractive to medical users. Dronabinol is a synonym for the natural (−)-trans isomer of delta-9-THC (the pharmacological most active isomer of delta-9-THC that is present in the cannabis plant) when synthesized and manufactured as Marinol . The oral route is more prone to improper dosing, resulting in unwanted side effects due to overdosage. However, this route may be advantageous if a long duration of drug action is desired. Harm reduction techniques are intended to minimize the health risks associated with different routes of application while maintaining the specific pharmacokinetic advantages.

## *PHARMACOKINETICS*

Depending on method of administration, there are significant differences in absorption and metabolism of THC, attendant effects, time until onset of action, and duration (Table 1).

Pulmonary absorption of cannabis results in maximum THC concentration within about five minutes. THC is detectable in plasma only seconds after the first inhalation. Psychotropic effects commence within seconds to minutes, are maximal after 30 min, and last about 2-3 h. Certain effects may last longer. Thus, Meinck et al. (1989) measured an improvement of some spasticity parameters for more than 12 hours after smoking a cannabis cigarette.

Agurell et al. (1986) noted that only about 20% of the THC present in a marijuana cigarette was absorbed via mainstream smoke when a group of cannabis users inhale in their customary fashion. Thus, most of the THC is lost in side-stream smoke. Effectiveness may be even lower in inexperienced users with a bioavailability below 10%. In experienced users the highest systemic bioavailability measured was 56% (Agurell et al. 1986). Davis et al. (1984) have analyzed smoking characteristics of marijuana cigarettes with a smoking

TABLE 1. Pharmacokinetic comparison of THC application to humans via intravenous, respiratory and oral routes. (Agurell et al. 1986, Azorlosa et al. 1992, Frytak et al. 1984, Wall et al. 1983, Ohlsson et al. 1980, Perez-Reyes et al. 1981, Perez-Reyes et al. 1973)

| Parameter | Intravenous | Inhaled | Oral (lipophilic vehicle) |
|---|---|---|---|
| Absorption | 100% | 10-30 (up to 50)% | > 95% |
| Systemic bioavailability | 100% | 10-30 (up to 50)% | 10-20% |
| Psychotropic threshold per kg body weight | 0.02 mg/kg | 0.06-0.1 mg/kg | 0.2-0.3 mg/kg |
| Psychotropic threshold per individual | 1 mg | 3-6 mg | ca. 10-20 mg |
| Maximum plasma concentration at the psychotropic threshold | 30-50 ng/ml | 30-50 ng/ml | 3-5 ng/ml |
| Dose producing marked intoxication* | 2-4 mg | 10-20 (up to 50) mg | 30-40 (up to 90) mg |
| Onset of action | within seconds | within seconds | 30-60 (up to 120) min |
| Duration of action** | 2-3 (up to 4) h | 2-3 (up to 4) h | 5-8 (up to 12) h |

* Doses producing a marked intoxication vary according to duration of therapy. Longer use may result in the development of tolerance, and higher doses are needed to achieve the similar effects.
** Duration of action varies according to examined effect and especially with oral use according to dose.

machine. When the whole cigarette was consumed in a single puff yielding little side stream smoke, 69% of the THC was preserved in the mainstream smoke, with about 30% lost due to pyrolysis. Smoking a pipe that produces little side stream smoke may also result in high effectiveness, with an average of 45% of THC transferred via the mainstream smoke (Agurell et al. 1986).

After oral ingestion of cannabis, absorption is slow and erratic. Onset of effects is delayed for 30-90 min. Maximum plasma concentrations following 10-15 mg oral THC in sesame oil were noted after 1.75-7 h (Agurell et al. 1986; Brenneisen et al. 1996), usually peaking after about 2 hours. More than one plasma peak may also occur. Compared to inhalation, effects after oral ingestion last longer and fade away more slowly, over 5-8 h, or even longer with very high doses. Duration of action also depends on measured parameters.

Intestinal absorption of THC is increased by application in a lipophilic vehicle. Ohlsson et al. (1980) reported a systemic bioavailability of 6% ( 3%) after ingestion of THC in a chocolate cookie. Oral bioavailability was of the order of 10-20% after ingestion of THC in oil capsules (Wall et al. 1983). Therefore, cream or milk can be added to a marijuana tea, or a recipe with plenty of butter

may be used if the drug is baked in confections. $^{9}$-THC may be degraded by the acid of the stomach and in the gut. Several competing reactions occur at low pH, among them isomerization to $^{8}$-THC and protonation of the oxygen in the pyran ring, causing ring cleavage to substituted cannabidiols (Agurell et al. 1986). In lipophilic vehicles, such as in the case of Marinol capsules, where THC is dissolved in sesame oil, at least 95% of THC is absorbed from the gastrointestinal tract (Wall et al. 1983). Due to an extensive first-pass liver metabolism and pre-systemic elimination in the gut, with oral application systemic bioavailability is only 10-20% (Agurell et al. 1986).

In the cannabis plant, about 95% of $^{9}$-THC is present as one of two pharmacologically inactive acid forms, the $^{9}$-THC carboxylic acids (THCA) (Turner et al. 1980). Natural cannabinoids must be decarboxylated before ingestion, since the corresponding neutral phenolic forms of THC produce most biological effects. The simplest and fastest way to achieve this is through heating (smoking, baking, cooking). Neutral phenols are responsible for the known pharmacological effects of dronabinol. Five minutes of heating to 200-210°C has been determined as the optimal condition for complete decarboxylation of THCA without oxidation to cannabinol (Brenneisen 1984). In cannabis smoking, where temperatures of 600°C are achieved, only a few seconds of combustion are apparently sufficient for decarboxylation.

## *INHALATION OR ORAL APPLICATION*

Cannabis and THC can both be administered by various routes. Inhalation and oral use are the most frequent ways to ingest the drug, each demonstrating particular advantages and disadvantages. The advantage of oral intake is its more constant and prolonged activity, for example, in the prevention of nocturnal spasms in multiple sclerosis, or decreasing intraocular pressure for several hours. Its disadvantage is possible overdosage, especially with cannabis preparations of unknown THC content.

The major advantages of inhalation are fast onset of action and easy titration of dose. These are preferable in acute disorders that demand a fast effect, such as rapidly treating a migraine attack, or combating breakthrough pain. Inhalation is also superior to ingestion by mouth in nausea and vomiting, where it may be difficult to take pills or other oral preparations. The disadvantage of smoking is potential damage to the respiratory tract.

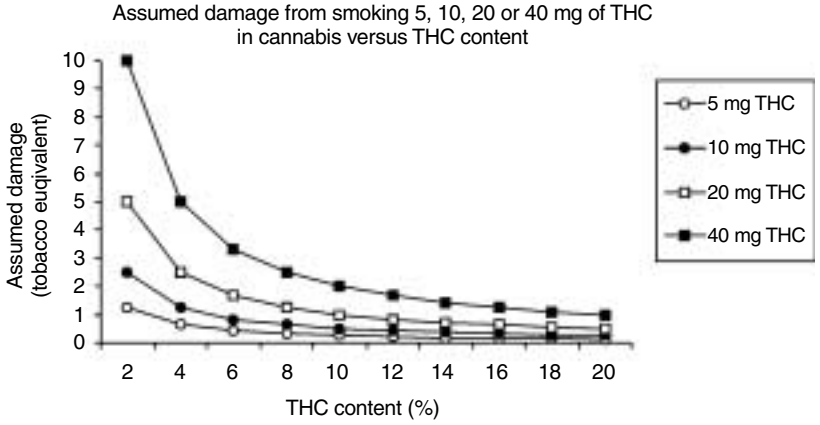
## *RISKS OF SMOKING*

More than 200 combustion products have been found in marijuana smoke (Sparacino et al. 1990), and many are known to be toxic to tissues of the respi-

ratory and upper intestinal tract. Aside from the nicotine content, cannabis smoke is qualitatively similar to that of tobacco (Tashkin 2001). Benzo[ ]anthracene and benzo[ ]pyrene, two highly procarcinogenic polycyclic aromatic hydrocarbons (PAHs) are present in 25-75% higher concentrations in the tar from cannabis as compared to tobacco (Lee et al. 1976). The deposition of PAHs is amplified approximately 4 times by a higher tar yield of unfiltered marijuana cigarettes compared to filter-tipped tobacco cigarettes, and a longer breathholding time with marijuana (Wu et al. 1988). A 4-fold longer breathholding results in a 40% greater deposition of tar in the respiratory tract (Wu et al. 1988).

Whether this higher tar yield from cannabis smoke leads to a fourfold stronger damage of the mucosa compared to smoking the same amount of tobacco is unclear. A fourfold increase may be regarded as the worst-case scenario, whereby smoking half a cannabis cigarette (about 0.4 grams of cannabis) would damage the mucosa to a similar degree as two tobacco cigarettes (see Figure 1). Histopathological alterations of the airways associated with smoking may lead to chronic bronchitis and, hypothetically, eventually to chronic

FIGURE 1. Assumed risk associated with smoking herbal cannabis vs. THC content (as % of the dried plant material) corresponding to that caused by tobacco cigarettes. The worst-case scenario is assumed, that smoking a certain amount of cannabis increases the risk of respiratory cancer and other damage 4 times higher than smoking the same amount of tobacco (see text). The risk of 0.2 grams of cannabis corresponded to 1 tobacco cigarette. Depending on THC content 0.2 grams of cannabis contain 4 mg (2% THC), 10 mg (5% THC), 20 mg (10% THC) or 40 mg THC (20% THC). About 4 puffs are needed to smoke 0.2 grams of cannabis (see Table 2).



obstructive pulmonary disease (COPD). Epidemiological and experimental data with regard to COPD are conflicting, however. Progressive airways narrowing in COPD can be detected by an accelerated decline in the forced expiratory volume in one second ($FEV_1$) and by a decreased ratio of $FEV_1$ to forced vital capacity (FVC). In a study by Bloom et al. (1987), marijuana smokers showed significant lower values for the $FEV_1$/ FVC ratio than nonsmokers and tobacco smokers. The prevalence of respiratory symptoms was increased. A 6-yr follow-up study with 1802 subjects demonstrated a significant reduction in $FEV_1$, and $FEV_1$/FVC in previous marijuana users but not in current users (Sherrill et al. 1991).

In contrast to these findings, a study by Tashkin et al. (1987) comparing marijuana smokers, tobacco smokers, smokers of both tobacco and marijuana, and nonsmokers, did not reveal any association between heavy use of marijuana for more than 15 years and resulting decrements in pulmonary function. None of the values of the applied sensitive measures was different from the average values observed in nonsmokers. In a second study, Tashkin et al. (1997) once more failed to find any association between marijuana use and lung function abnormality. $FEV_1$ was measured in 131 heavy, habitual smokers of marijuana alone, 112 smokers of marijuana plus tobacco, 65 regular smokers of tobacco alone, and 86 nonsmokers of either substance and in 255 subjects on up to six additional occasions over a period of 8 years. In neither men nor women was marijuana smoking associated with greater declines in $FEV_1$ than nonsmoking, nor was an additive effect of marijuana and tobacco noted, nor a significant relationship found between the number of marijuana cigarettes smoked per day and the rate of decline in $FEV_1$. In comparison, tobacco smoking was associated with greater annual rates of decline in lung function than nonsmoking. The authors concluded that "these findings do not support an association between regular marijuana smoking and chronic COPD but do not exclude the possibility of other adverse respiratory effects" (Tashkin et al. 1997, p. 141).

This conclusion is supported by experimental animal studies in which rats were exposed to progressively increasing doses of marijuana or tobacco smoke for six months (Huber et al. 1987, cited according to Tashkin 2001). After sacrifice, the lungs of the tobacco-exposed rats showed morphological and physiological evidence of emphysema, while the rats exposed to marijuana showed no detectable morphologic or physiologic abnormalities compared to unexposed control animals.

However, epidemiological studies suggest that marijuana smoking may increase the risk of respiratory cancer (Tashkin 2001). Bronchial wall biopsies in smokers of marijuana revealed extensive hyperplastic, metaplastic and dysplastic changes believed to be precursors of carcinoma (Fligiel et al. 1997). The damage was similar to that of regular smokers of tobacco, and the effects of marijuana and tobacco appeared to be additive. In a case-control study of

173 patients with newly diagnosed squamous cell carcinoma of the head and neck and 176 cancer-free matched controls, marijuana use was associated with a more than twofold increased risk of head and neck cancer and a dose-response relationship was found (Zhang et al. 1999).

Damage to the mucosa by cannabis smoking, and the presence of pathogens in the plant material may increase the risk of infections, and are of special concern in immunocompromised patients. Cannabis smoke may harbor bacteria and fungi such as *Aspergillus, Mucor* and *Fusarium* species, *Klebsiella pneumoniae, Enterobacter cloacae*, group D *Streptococcus*, some *Bacillus* species and others (for a review see: McPartland 2001).

Performance of the Valsalva maneuver may cause barotrauma to the lung and increase the risk for spontaneous pneumothorax and pneumomediastinum (Feldmann et al. 1993; Miller et al. 1972). Cannabis smokers may typically perform the Valsalva maneuver against a closed glottis after deep inhalation to increase intrathoracic pressure and absorption rate of THC.

## *HARM REDUCTION WITH INHALATION*

The major strategies to reduce the risks of smoking are:

- *The use of cannabis strains with high THC content*. The average concentration of $^{9}$-THC in marijuana confiscated in the USA was 4.2% in 1997 (ElSohly et al. 2000). Currently, high-grade cannabis with THC concentrations of 10-20% in the dried flowers is available, reducing the amount necessary for medicinal use and potential damage to the mucosa (see Figure 1). If a strain with a THC content of 10% is used, one puff provides about 5 mg THC (see Table 2). In studies with HIV/AIDS patients, daily doses of 2.5-20 mg have been used to treat anorexia and cachexia, or nausea and vomiting. In a long-term study by Beal et al. (1997) patients received dronabinol orally 2.5 mg once or twice daily to effectively treat anorexia and cachexia in HIV/AIDS. Conant et al. (1991) applied between 2.5 mg dronabinol twice daily and 5 mg three times a day. In a small study by Gorter et al. (1992) participants received between 2 $\times$ 2.5 mg and 4 $\times$ 5 mg dronabinol. Abrams et al. (2000) used smoked cannabis (3.95% THC) and oral dronabinol (3 $\times$ 2.5 mg). Due to the development of some tolerance doses are often increased up to 20 mg with long duration of therapy (personal communications from several physicians), equivalent to one quarter of a marijuana cigarette containing 800 mg of cannabis of 10% THC.
- *The use of pure cannabis*. Sometimes cannabis is smoked together with tobacco or other dried herbs. This procedure should be avoided to minimize the inhalation of smoke from burnt plant material.

- *The use of pipes*. Pipes are superior to cigarettes in some situations in that they easily allow the patient to smoke small amounts of pure high-grade cannabis. The percentage of tars in the smoke is reduced by condensation on the pipe walls. Pipes should be cleaned frequently. Water pipes are inferior to cigarettes and should be avoided (see below).
- *The use of cannabis that is free of natural contaminants and adulterants*. Only disease-free cannabis should be harvested and air-dried. Gross infection with pathogens is easily detectable. Ungerleider et al. (1982) proposed two methods of sterilization: gas-sterilization in a mix of 12% ethylene oxide and 88% dichlorodifluoromethane, and sterilization with Cobalt 60 irradiation. Neither method reduced THC content. Baking plant material in home ovens at 150°C for five minutes kills spores of *Aspergillus fumigatus, A. flavus* and *A. niger* without reducing THC content (McPartland 2001).
- *The use of inhalation devices that reduce output of tars*. Gieringer tested vaporizers that heat marijuana to 180-190°C vaporizing THC below the burning point of cellulose and other plant material. The production of polycyclic hydrocarbons was reduced. The best vaporizer delivered 10 parts of tar to one part of cannabinoids, while in contrast, cannabis cigarettes yielded a ratio of 13:1 (average), and water pipes an average of 27:1 (cited in McPartland 2001). Thus, the best vaporizers achieved a performance ratio about 25% higher than the unfiltered cannabis cigarette, while water pipes were less favorable than cigarettes. The use of a filter in a cannabis cigarette was not advantageous since it not only filtered the tars, but also the cannabinoids. Indeed, the performance ratio was decreased by about 30% compared to the unfiltered cigarette (Gieringer 2000). In a new study Gieringer (2001) was able to demonstrate that combustion products were substantially reduced with another vaporizer. The device used produced THC at a temperature of 185°C while completely eliminating benzene, toluene and naphthalene. Significant amounts of benzene began to appear at temperatures of 200°C, while combustion occurred around 230°C or above. Traces of THC were in evidence as low as 140°C. Carbon monoxide and tars were both qualitatively reduced by the vaporizer, but were not quantified in this study. However, a significant reduction of polycyclic aromatic hydrocarbons was assumed since vaporized cannabis emitted a thin gray vapor and the plant material was left with a green to greenish-brown "toasted" appearance, whereas the combusted sample produced thick smoke and turned to ash.
- *Omission of the Valsalva maneuver and prolonged breathholding*. Several techniques are used to enhance THC absorption in the lungs including the Valsalva maneuver and prolonged breathholding. The first may cause barotrauma to the lung, while the second increases the deposition

of tars (see above). According to two quantitative studies (Tashkin et al. 1991; Azorlosa et al. 1995) that correlated breathholding and resulting effects, longer breathholding enhanced THC effects, thus, confirming in part a common behavior of cannabis smokers. However, extended breathholding did not seem to further maximize absorption. Azorlosa et al. (1995) compared breathholding of 0, 10 and 20 seconds in seven subjects who took 10 puffs of cannabis containing 1.75 or 3.55% THC (Figure 2). Maximum THC plasma concentrations after smoking were 61.2, 146.6, and 130.6 ng/ml with the more potent cigarettes. While THC concentrations significantly increased between the 0 sec and the 10 sec conditions, there was no further increase in plasma concentrations by prolonging breathholding from 10 to 20 sec. Thus, prolonged breathholding may increase the amount of deposited tar without increasing THC absorption.

- *Combination of oral use and inhalation*. In several indications, a combined regime of a basic oral medication with cannabis or THC and a demand inhaled medication may be useful to reduce risks from smoking and overdosage with oral administration. Similar regimes are routine with opiates to treat chronic and breakthrough pain (Stevens and Ghazi 2000).

## *RISKS OF ORAL USAGE*

Responsiveness to the action of THC shows a high inter-individual variation. 10 mg of oral THC will not consistently result in psychic alterations, but in some persons even 2.5 mg produce recognizable effects. In a study by Chesher et al. (1990) of a healthy population dosed orally with 5 mg THC, no difference was found to placebo controls as to the subjective level of intoxication. Doses of 10 and 15 mg THC caused slight differences compared to the placebo, and a dose of 20 mg, finally, caused marked differences in subjective perception. In a clinical study by Beal et al. (1995) in AIDS patients some patients experienced mostly mild to moderate side effects (euphoria, dizziness) with 2.5 mg dronabinol twice daily. Lucas and Laszlo (1980) found pronounced psychotropic reactions (anxiety, marked visual distortions) in patients undergoing cancer chemotherapy that had received 15 mg THC/$m^2$ (square meter of body surface), which corresponds to about 25 mg THC in an average adult person of 1.7 $m^2$ body surface area. A reduction to 5 mg THC/$m^2$, about 7.5-10 mg THC, produced only mild reactions. In a study by Frytak et al. (1979) in cancer patients receiving 15 mg dronabinol three times a day as an antiemetic, 52% reported a "high." Brenneisen et al. (1996) administered single oral doses of 10 or 15 mg THC to two patients. Physiologic parameters (heart rate) and psychological parameters (concentration, mood) were not modified by the administration.

TABLE 2. Dosing-scheme for cannabis taken orally and smoked

| Amount of cannabis taken | THC content in herbal cannabis | | |
|---|---|---|---|
| | 2% THC | 5% THC | 10% THC |
| **oral** | | | |
| 0.05 g | 1 mg THC | 2.5 mg THC | 5 mg THC |
| 0.1 g | 2 mg THC | 5 mg THC | 10 mg THC |
| 0.2 g | 4 mg THC | 10 mg THC | 20 mg THC |
| 0.5 g | 10 mg THC | 25 mg THC | 50 mg THC |
| **smoking*** | | | |
| 1 puff (0.05 g) | 1 mg THC | 2.5 mg THC | 5 mg THC |
| 2 puffs (0.10 g) | 2 mg THC | 5 mg THC | 10 mg THC |
| 4 puffs (0.20 g) | 4 mg THC | 10 mg THC | 20 mg THC |
| 8 puffs (0.40 g) | 8 mg THC | 20 mg THC | 40 mg THC |
| 16 puffs (0.80 g) | 16 mg THC | 40 mg THC | 80 mg THC |

* Ingested THC was calculated according to the formula: x = amount of cannabis/100 by THC content. It was assumed that an average of 50 mg of cannabis are smoked with one puff, calculated from the following data. Marijuana cigarettes provided by the U.S. National Institute of Drug Abuse (NIDA) weigh about 800 mg (Azorlosa et al. 1992, Azorlosa et al. 1995). Perez-Reyes et al. (1981) noticed that about 24 puffs were necessary to smoke a low-dose NIDA marijuana cigarette, corresponding to 33 mg of cannabis per puff. Liguori et al. (1998) used a smoking regime with 64 mg marijuana per puff. It should be noted that THC becomes concentrated in the uncombusted parts of a cigarette so that the first puffs yield a little less THC than the later (Tashkin et al. 1991).

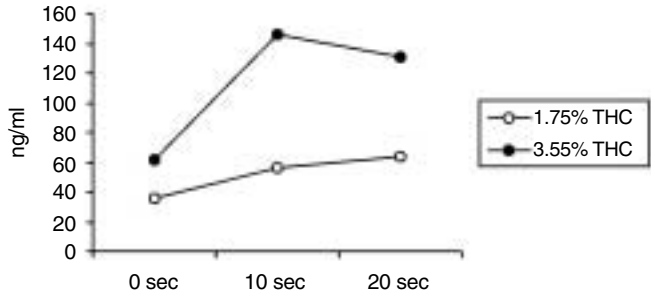
Additionally, there may be an intra-individual variance of THC absorption, especially if the drug is taken under different conditions. Intestinal absorption and degradation of THC may depend on several factors. As with opioids, onset of action might depend on the presence or absence of food. Immediate release oral opioid preparations are known to require about 30 minutes to onset of analgesic action taken on an empty stomach, but onset of action may be delayed when taken on a full stomach (Stevens and Ghazi 2000).

Due to the delayed onset of action, oral cannabis products may be difficult to dose precisely, resulting in either overdosage or underdosage, an observation often reported by physicians of the nineteenth century (Fankhauser 2001).

## *HARM REDUCTION WITH ORAL USE*

The major risk associated with oral cannabis use is overdosing. To achieve appropriate dosing two principles should be followed:

FIGURE 2. Average plasma THC levels (ng/ml) in seven healthy young males following ten puffs from a cannabis cigarette containing 1.75 or 3.55% THC with a breathholding duration of 0, 10, and 20 seconds immediately after smoking (drawn according to data from Azorlosa et al. 1995).




- Ascertainment of optimal individual dose by slowly increasing doses.
- Intake of the medication under the consistent conditions, especially with regard to vehicle and filling of the stomach.
- Subsequent administration of supplemental doses by inhalation.

If possible, slowly increasing doses should be applied in a titrated fashion to avoid undesirable side effects on psyche and circulation. Starting doses are $2 \times 2.5$ mg or $2 \times 5.0$ mg of dronabinol per day. Dosages may be increased up to several units of 10 mg daily. In AIDS wasting and HIV related nausea and vomiting 5-20 mg THC daily are usually sufficient (Beal et al. 1995; Beal et al. 1997; Gorter et al. 1992; Abrams et al. 2000). If natural cannabis products of unknown THC content are used orally, the patient should begin with about 0.05-0.1 g of the drug (for cannabis with an average THC content of 5% this corresponds to 2.5-5 mg THC, see Table 2).

If possible, the THC content should be determined in a laboratory. If this is not possible, a store of cannabis sufficient for several weeks should be secured so that a constant quality is ensured. In a study by Fairbairn et al. (1976) the THC content of marijuana only decreased by 7% within 47 weeks with dry storage in the dark at 5°C, and by 13% at a temperature of 20°C.

To achieve reproducible effects, cannabis or THC should always be ingested under similar conditions with regard to food intake, e.g., one hour before a meal. If natural cannabis preparations are used, doses should be weighed carefully and taken with the same carrier, e.g., tea with half a gram of dried cannabis flowers in half a liter of water and some cream.

As with opiates, some side effects may decrease within a period of days or weeks, thereby increasing the acceptance of the drug. Prolonged THC inges-

tion causes tolerance to orthostatic hypotension, tachycardia and psychological effects (Benowitz and Jones, 1975), so that daily doses of more than 50 mg THC may sometimes be taken without significant undesirable psychic or physical side effects (Holdcroft et al. 1997). Heavy chronic users in western societies may smoke five to ten cannabis cigarettes per day, thus well tolerating daily doses of 100 mg THC and more. In a sample analyzed by Solowij (1991) mean weekly consumption was 766 mg of THC, with a range from 30-2400 mg THC.

Tolerance may also arise with respect to therapeutically desired effects (e.g., decrease of intraocular pressure, analgesia), and require increased doses (Jones et al. 1981). O'Shaughnessy (1839) reported development of tolerance in connection with the medical use of a cannabis tincture in rheumatism: Two of three treated patients showed good improvement, while the third patient did not respond to the drug. He finally admitted to being a habitual user.

Duration of tolerance to THC differs depending on effect. In mice hypothermia, depression of intestinal motility and spontaneous locomotor activity were investigated (Anderson et al. 1975). Normal hypothermic responses returned after 12 dose-free days and baseline locomotor activity returned within 4 days. Tolerance to the depressant effect on intestinal motility still persisted after 19 dose-free days. According to self-reports of patients to the author, tolerance may remain for some weeks to months after stopping the drug.

## *TREATMENT OF ACCIDENTAL OVERDOSE*

Ingestion of cannabis and THC may result in unwanted effects on the circulatory system (increased heart rate, changes of blood pressure) and psychological effects such as an acute panic reaction and hallucinatory experiences (Hall and Solowij, 1998).

Tachycardia may be undesirable in persons suffering from coronary heart disease. It seems to be caused by sympathetic stimulation and can be treated by beta-blockers. Perez-Reyes et al. (1973) used propranolol infused at a rate of 0.5 mg per minute for 6 minutes to block the acceleration of heart rate following oral administration of 35 mg THC in different vehicles. The psychological effect was not altered. Thus, it may be also possible to use beta-blockers as prophylactic agents in individuals with heart disease without influencing other specific effects of THC, including therapeutic actions. In case of orthostatic hypotension or syncope, the patient should lie down with the legs elevated.

"Talking the patient down" may treat dysphoric states. If this proves insufficient, intravenous diazepam (5-10 mg) may be administered (Perez-Reyes et al. 1973).

## *ALTERNATIVE FORMS OF DELIVERY*

Many other forms of application have been tested experimentally, decreasing the time until onset of action compared to oral use and leading to more reliable reproduction of effects. Some routes may be promising in the future.

*Sublingual:* At the 2000 Meeting of the International Cannabinoid Research Society a British group presented data on studies performed with three different sublingual cannabis extracts (Guy et al. 2000). They had been administered to six healthy volunteers receiving up to 20 mg THC. The group reported that sublingual administration of cannabis extract resulted in relatively fast effects and was well tolerated. No quantitative data on bioavailability are yet available.

*Rectal:* A few studies have been conducted with rectal THC preparations (Mattes et al. 1994; Brenneisen et al. 1996). Bioavailability strongly differed depending on suppository formulations. Among the formulations containing several polar esters of $^{9}$-THC in various suppository bases, $^{9}$-THC-hemisuccinate in Witepsol H15 showed the highest bioavailability (ElSohly et al. 1991), about as twice as high as with oral administration in man (Brenneisen et al. 1996).

The author of this article is aware of experiments by several cannabis users, who rectally self-administered natural cannabis preparations. In one example, dried milled cannabis flowers were cooked in cocoa butter for one hour. After cooling, suppositories were formed. The effect was noticeable within about ten minutes. No scientific data are available in this regard. These personal experiences contrast with experimental data according to which unchanged delta-9-THC is not bioavailable by the rectal route (Perlin et al. 1985; ElSohly et al. 1991).

In a study by ElSohly et al. (1991) with various esters of THC in both lipophilic and hydrophilic suppository bases (Witepsol H15 and polyethylene glycol), no delta 9-THC or its metabolites were detected in the blood samples using the Witepsol H15 with the exception of the hemisuccinate ester. Using polyethylene glycol, only low levels of delta 9-THC and its metabolites were detected in blood for all esters tested.

*Transdermal:* The scientific literature provides little specific information on the transdermal uptake of THC from topically applied preparations. There are only two experimental studies investigating the skin permeation behavior of THC (Touitou and Fabin 1988; Touitou et al. 1988). These investigations were designed to develop an effective transdermal delivery system for THC, an antiemetic in patients receiving cancer chemotherapy. Researchers in this study used $^{8}$-THC since this molecule is more stable than the $^{9}$-THC.

Generally, the human skin is well protected against penetration by external substances. Many topically applied substances attain a systemic bioavailability of only a few percent (Hadgraft 1996). The main barrier to penetration

is the cornified layer of the stratum corneum. There is evidence that only a small fraction of strongly lipophilic substances, such as THC, overcome the hydrophilic phases of the intercellular space between the cells of the stratum corneum (Bast 1997).

However, the uptake of compounds via the skin can be influenced by the presence of other compounds in the matrix. Penetration enhancers may disrupt the stratum corneum lipids, interact with intercellular proteins, or improve the partitioning of a compound. These may include synthetic chemicals such as dimethylsulfoxide (DMSO), surfactants, and certain unsaturated fatty acids, e.g., oleic acid.

The research by Touitou et al. (1988) showed that the permeability coefficient of $^{8}$-THC was significantly enhanced by water and by oleic acid in propylene glycol and ethanol (PG-EtOH). Significant THC concentrations in the blood of rats treated with formulations containing 26.5 mg/g THC on the skin were measured. The permeability coefficient of THC was increased 6 times by 3% oleic acid in PG-EtOH solutions and 14 times by 3% oleic acid in PG-EtOH-$H_2O$ solutions (Touitou and Fabin 1988).

An Albany College of Pharmacy research team was awarded a $361,000 three-year grant in January 2000 by the American Cancer Society to study whether cannabinoids can be absorbed effectively through the skin (Gormeley 2000). The research is intended to develop a cannabinoid patch for therapeutic use and is expected to require several years for completion.

The US Patent and Trademark Office granted a patent for a "Cannabinoid patch and method for cannabis transdermal delivery" on September 5, 2000 (United States Patent 6,113,940). The patent describes a trial in two subjects who received 0.2 g of cannabis oil in a carrier (DMSO). The patch was applied to the underside of the wrist of two human subjects. According to the patents, subjective THC effects were noted within ten minutes and lasted four to six hours.

## *SOME COMPARISONS TO OPIUM OPIATES*

There are some parallels between opiates and cannabinoids with regard to mechanism of action and indications (Vaughan and Christie 2001), which shall be discussed in brief, mainly with regard to side effects and routes of administration.

Cannabis (*Cannabis sativa* L.) and opium (*Papaver somniferum* L.) are used recreationally, most often by inhaling the smoke of the burnt plant material. In contrast to cannabis, the illegal use of single opium compounds (natural opiates and their derivatives) are more common today than the use of whole plant preparations. As with cannabis, the specific chronic health effects associ-

ated with the use of illegal opiates and opioids largely depend on the route of application.

While smoking is the major route of application for cannabis, it is injection into the blood vessels for opiates. Injection may result in local injury and inflammation, and in the transmission of hepatitis C and HIV through contaminated needles. The chronic use of non-injected opiates seems to cause only minor health effects (Hall et al. 1999). It is remarkable to note that smoking is generally regarded as a minor health hazard in context with opiates (Hall et al. 1999) but seems to be of greater concern in context with cannabis (Joy et al. 1999).

Opium contains about 25 alkaloids. As with cannabis there is one most prominent ingredient. Morphine is present in the plant with 10-15% of dry plant weight. However, there are other pharmacologically potent alkaloids in relevant concentrations, particularly codeine (1%-3%), noscapine (4%-8%), and papaverine (1%-3%).

In addition to the medical use of single natural constituents of opium (morphine, codeine, noscapine), doctors in many countries (e.g., Germany) may also prescribe whole opium preparations. The effects of opium differ qualitatively from that of morphine. Due to the presence of other alkaloids, especially papaverine, opium causes an atonic constipation, in contrast to a spastic constipation with morphine (Mutschler 1996). The difference between whole cannabis and single dronabinol remains to be elucidated, and it is unclear whether this difference is less prominent than between opium and morphine (see McPartland and Russo 2001 in this issue).

There are major differences between the pharmacokinetics of opiates and cannabinoids. To achieve a fast onset of action, hydrophilic opiates may be given intravenously. But the intravenous application of THC is complicated by its lipophilic properties. Even oral opiates have a faster onset than oral cannabinoids (30 min versus 30-90 min) and show a more constant and reliable absorption (Cleary 1997). In contrast to the situation with opiates, there is currently no good available alternative to the inhalation of cannabis or cannabinoids if a fast onset of action is required. The sublingual application of cannabis preparations currently under investigation in clinical studies in the United Kingdom seems to be a promising route.

## *PRINCIPLES OF HARM REDUCTION WITH CANNABIS*

Natural cannabis is usually inhaled. However, this route of administration is often used even if the advantages over oral application are not really of relevance to achieve optimal therapeutic benefits. In cases where inhalation is the best way to administer cannabis or single cannabinoids, techniques designed

to reduce risks to the mucosa should be applied. Harm reduction with regard to the medical use of cannabis may include the following strategies:

- Relinquishment of inhalation and replacement by other routes of administration if possible, or combination of several routes.
- Minimization of damage to the respiratory tract with appropriate techniques including the use of cannabis with high THC content, inhalation with vaporizers, avoidance of the Valsalva maneuver and prolonged breath holding over 10 sec.
- Avoidance of accidental over-dosing through thorough dosing procedures with oral ingestion.
- Development and improvement of non-smoked, parenteral application forms, including the rectal, sublingual, and transdermal route.

Taken together these maxims allow reduction in the risks associated with the oral and inhalation routes of administration to a tolerable degree.

Since many physicians reject the concept of smoking medication on principle, it may be helpful to look at this controversial topic in a broader context. To ingest 20 mg of THC, 0.2 g of cannabis (or a quarter of a cigarette) with a THC content of 10% has to be smoked (see Figure 1). Even if a 4-fold health risk potential for cannabis smoke compared to tobacco smoke is assumed, this would result in an equivalent of the respiratory risks associated with smoking one tobacco cigarette a day.

The principle *nihil nocere* ("do no harm"), and the association with recreational usage of cannabis may be regarded as the two major reasons for dismissing smoking. This rejection may evoke a more emotional than scientific attitude towards this question. It should be noted that other accepted routes of administration for many drugs designed to achieve a rapid onset of action are associated with multiple risks, even fatal ones, and various drugs also damage the mucosa. Intravenous or intramuscular application of a drug may harm surrounding tissues and in some cases may produce severe damage. Oral administration of various drugs adversely affects the mucosa of the intestinal tract, among them widely used non-steroidal anti-inflammatory drugs (NSAIDs), such as indomethacin and acetylsalicylic acid. We customarily accept relatively high medical risks, as with intrathecal administration of opioids, if the anticipated benefits outweigh those drawbacks. The inhalation of a limited amount of combustion products with smoked cannabis may be regarded as a rather low and acceptable risk as well, if the benefit for a patient is high.

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