Pharmacokinetics of cannabinoids

Iain J McGilveray PhD

IJ McGilveray. Pharmacokinetics of cannabinoids. Pain Res Manage 2005;10(Suppl A):15A-22A.

Delta-9-tetrahydrocannabinol (Δ-9-THC) is the main psychoactive ingredient of cannabis (marijuana). The present review focuses on the pharmacokinetics of THC, but also includes known information for cannabinol and cannabidiol, as well as the synthetic marketed cannabinoids, dronabinol (synthetic THC) and nabilone. The variability of THC in plant material (0.3% to 30%) leads to variability in tissue THC levels from smoking, which is, in itself, a highly individual process. THC bioavailability averages 30%. With a 3.55% THC cigarette, a peak plasma level of 152±86.3 ng/mL occured approximately 10 min after inhalation. Oral THC, on the other hand, is only 4% to 12% bioavailable and absorption is highly variable. THC is eliminated from plasma in a multiphasic manner, with low amounts detectable for over one week after dosing. A major active 11-hydroxy metabolite is formed after both inhalation and oral dosing (20% and 100% of parent, respectively). THC is widely distributed, particularly to fatty tissues, but less than 1% of an administered dose reaches the brain, while the spleen and body fat are long-term storage sites. The elimination of THC and its many metabolites (from all routes) occurs via the feces and urine. Metabolites persist in the urine and feces for several weeks. Nabilone is well absorbed and the pharmacokinetics, although variable, appear to be linear from oral doses of 1 mg to 4 mg (these doses show a plasma elimination half-life of approximately 2 h). As with THC, there is a high first-pass effect, and the feces to urine ratio of excretion is similar to other cannabinoids. Pharmacokinetic-pharmacodynamic modelling with plasma THC versus cardiac and psychotropic effects show that after equilibrium is reached, the intensity of effect is proportional to the plasma THC profile. Clinical trials have found that nabilone produces less tachycardia and less euphoria than THC for a similar antiemetic response.

Key Words: *Cannabinoids; Inhalation; Nabilone; Pharmacodynamics; Pharmacokinetics*

Pharmacocinétique des cannabinoïdes

Le delta-9-tétrahydrocannabinol (Δ-9-THC) est le principal ingrédient psychoactif du cannabis (marijuana). Le présent article de synthèse s'attarde à la pharmacocinétique du THC, mais inclut également des données sur le cannabinol et le cannabidiol, de même que sur les cannabinoïdes de synthèse sur le marché, soit le dronabinol (THC synthétique) et le nabilone. La variabilité des taux de THC dans la substance végétale (0,3 % à 30 %) donne lieu à des taux tissulaires variables de THC après l'inhalation, qui en soi, est déjà un processus hautement individuel. La biodisponibilité du THC est en moyenne de 30 %. Avec une cigarette dont la teneur en THC est de 3,55 % un pic plasmatique de 152 ± 86,3 ng/mL s'obtient environ 10 minutes après l'inhalation. D'autre part, le THC oral n'est biodisponible que dans une proportion de 4 à 12 % et son absorption est très variable. Le THC est éliminé du plasma de façon multiphasique, de faibles quantités étant décelables encore dans les sept jours suivant la consommation. Un important métabolite 11-hydroxy actif est formé après l'inhalation ou la prise orale (20 % et 100 % de la molécule-mère, respectivement). Le THC est très largement distribué, particulièrement dans les tissus gras, mais moins de 1 % d'une dose administrée atteint le cerveau, alors que la rate et les graisses corporelles en sont les sites de réserve à long terme. L'élimination du THC et ses nombreux métabolites (peu importe la voie d'administration) se fait par les selles et l'urine. Les métabolites persistent dans l'urine et les selles pendant plusieurs semaines. Le nabilone est bien absorbé et sa pharmacocinétique, bien que variable, semble être linéaire avec des doses orales de 1 à 4 mg (qui ont une demi-vie d'élimination plasmatique d'environ deux heures). Comme avec le THC, on note un effet de premier passage important et le ratio selles-urine de l'excrétion est semblable à celui d'autres cannabinoïdes. Par rapport à ses effets cardiaques et psychotropiques, le modèle pharmacocinétique-pharmacodynamique plasmatique du THC révèle qu'après l'atteinte de l'état d'équilibre, l'intensité de l'effet est proportionnelle à son profil plasmatique. Les essais cliniques ont montré que le nabilone entraîne moins de tachycardie et moins d'euphorie que le THC, pour une réponse antiémétique semblable.

CHEMISTRY

Marijuana is the common name for *Cannabis*, a hemp plant that grows throughout temperate and tropical climates in almost any soil condition. The plant yields cannabinoids such as delta-9-tetrahydrocannabinol (Δ-9-THC; referred to as THC), which is the main psychoactive ingredient of cannabis. The flowering tops and leaves of this plant are used to produce cannabis for smoking. Marijuana is most commonly smoked in hand-rolled cigarettes ('joints') containing the plant material. Recent work (1) has suggested that the restrictive phytochemical definition of cannabinoids be changed to a broader definition to include "all ligands of the cannabinoid receptor(s) and related compounds, including endogenous ligands of the receptors and a large number of synthetic analogues". The present review, however, will be restricted to the pharmacokinetics of the cannabinoids, including two synthetic compounds that have been subjected to extensive clinical studies.

Although the leaves and flowering tops of *Cannabis* plants yield more than 60 different cannabinoids, the major active components are THC (Figure 1), cannabinol (CBN) and cannabidiol (CBD) (Figure 2) (2).

Some reports mention the presence of Δ-8-THC, although this may be formed by the isomerization (2) of Δ-9-THC during isolation. Δ-9-THC is the principal psychoactive ingredient of cannabis, and the other components, such as CBN, CBD and Δ-8-THC, are present in smaller quantities and are not believed to make a significant contribution to the total effect of marijuana on behaviour or perception; however, CBD may have other pharmacological effects (3). THC is enantiomeric, with only the (–) enantiomers occuring in nature and the

McGilveray Pharmacon Inc, and University of Ottawa, Ottawa, Ontario
Correspondence and reprints: Dr McGilveray, 1 Stonehedge Park, Nepean, Ontario K2H 8Z1. Telephone 613-829-8551, fax 613-829-5175, e-mail mcgilver@magma.ca

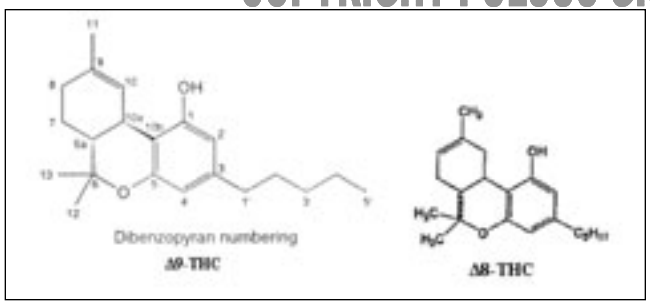

Figure 1) *The structure of delta-9-tetrahydrocannabinol (Δ-9-THC) using the common dibenzopyran numbering system. The Δ-9-THC analogue Δ-8-THC is also shown*

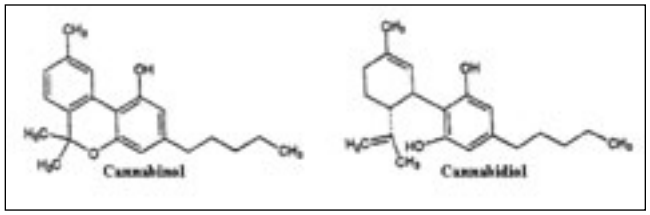

Figure 2) *The structure of cannabinol and cannabidiol*

synthetic (+) enantiomers being inactive. Δ-9-THC is sparingly soluble in water but has high lipid solubility (4). An oral form of synthetic Δ-9-THC ([–] enantiomer), dronabinol (2.5 mg, 5 mg or 10 mg capsules; dissolved in sesame oil), is marketed in the United States and Canada as Marinol (Solvay Pharma, Canada) (5).

Structure-activity relationships, comprising the effects of alteration in the cannabinoid molecule, were studied extensively in the 1960s and 1970s. This led to one synthetic drug, nabilone (6), being marketed as Cesamet capsules (Valeant Canada limitée/Limited) (7) (Figure 3). Nabilone is a sparingly water-soluble, racemic (±) mixture that is crystalline, unlike the resinous cannabinoid oils from the *Cannabis* plant.

Since the endogenous cannabinoid receptors were identified, there has been a resurgence in the study of the structure-activity relationship (8,9) of cannabinoids; however, while this research is promising, new receptor agonists are not yet in clinical use (10).

Cannabis also contains variable amounts of the carboxylic acid analogues of Δ-9-THC (tetrahydrocannabinolic acid [THCA]), in which the carboxyl groups can be positioned on carbon 2 or 4 of the molecule (according to the numbering in the structure shown in Figure 1). These substances are not pharmacologically active, although they may be released by gastric acid (1) and readily degrade on heating (eg, smoking) to yield THC (11,12). The decarboxylation is said to occur within 5 min at a temperature of 200°C to 210°C and within seconds in smoked marijuana cigarettes. This is important because according to Agurell et al (13), the total amount of THC and its corresponding acids is almost always considered in potency content. This is crucial information relating to activity because the ratio of inactive Δ-9-THCA to active Δ-9-THC is reported to range from 2:1 in areas where cannabis is grown in warmer climates to 17:1 in plants grown in cooler climates (14).

PHARMACOKINETICS

The present section will be restricted to human pharmacokinetics, mainly of smoked cannabis and with some comparisons of oral THC, including dronabinol (Marinol).

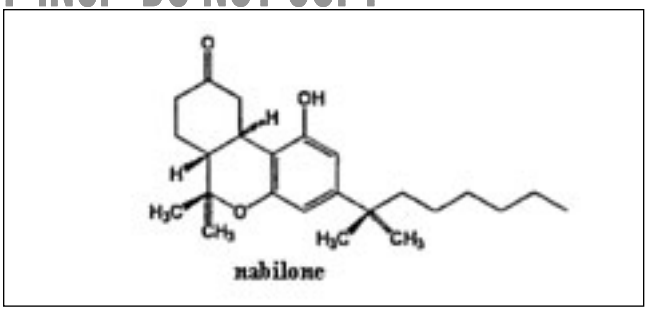

Figure 3) *The structure of nabilone*

ABSORPTION

Smoked cannabis

The estimation of the dose administered by the smoking route is a major variable in assessing the absorption of cannabinoids (mainly THC) in humans. The source of the plant material and the composition of the cigarette, together with the efficiency of smoking by the subject, are additional uncontrolled factors. It is reasonable to consider approximately 10% to 13% as the average THC content in Canadian marijuana (Health Canada information) (15).

Regarding smoking techniques, one research group (16) remarked, "it is incredible to see the variety of techniques marijuana users employ to smoke their cigarette". It appears that habitual heavy marijuana smokers can increase the amount absorbed and this is attributed to more efficient smoking techniques (12,13).

Table 1 indicates some of the variation found by various researchers (12,16-20) who investigated the amount of THC lost during smoking, with 69% regarded as the maximum available for absorption via mainstream smoke from a smoking machine (16). However, as much as 50% of the active drug in cigarettes can be lost due to pyrolysis. In one experiment, in which cigarettes containing approximately 19 mg of THC were smoked, it was reported that an average of 82% of the THC in the marijuana cigarette did not appear in the systemic circulation; an average of 6 mg (31%) was retained in the cigarette butts, with other losses due to pyrolysis and sidestream smoke during smoking (16,20). However, when the butt was smoked, it was estimated that 50% of the total THC dose was delivered. In experiments using a smoking machine, 16% to 19% of the THC was found in mainstream smoke, but when the cigarette was smoked in a single puff, avoiding sidestream smoke, 69% of the THC was in mainstream smoke (21); thus, approximately 30% of THC appears to be destroyed by pyrolysis (16). The United States National Institute of Drug Abuse (NIDA) group (16,20) reports that 20% to 37% of the THC is delivered in mainstream smoke, with pyrolytic destruction of 23% to 30% and sidestream losses of 40% to 50%. Less is known about the fate of smoked CBD and CBN, but it appears that the results are similar to THC, except that CBN plasma levels appear to be approximately twice as variable as other cannabinoids (13).

In a very recent abstract (22), it was reported that from plant material containing up to 18% of THC and its corresponding acid (THCA), approximately 50% was pyrolyzed and, of the recovered amount, 50% of the THCA was converted to THC. It also appeared that some of the acid (or THC) pyrolyzed was converted to CBD, CBN and smaller

TABLE 1
Estimates of the percentage of delta-9-tetrahydrocannabinol flow during smoking

	Delta-9-tetrahydrocannabinol flow (%)				
Reference	Undifferentiated stream	Sidestream	Pyrolyzed	Mainstream	Butt
Fehr and Kalant (17), Truitt (18)	50–60			40–50	
Agurell and Leander (12), Ohlsson et al (19)				20	
Huestis (16)		6–53	31–50	16–69*	10–21
Perez-Reyes (20)		40–50	23–30	20–37	

**'High' from single-puff smoking machine (20)*

TABLE 2
Relationship between cannabis potency and peak delta-9-tetrahydrocannabinol (THC) plasma concentrations

THC content in cannabis (%)	n	Plasma THC (ng/mL) ± SD	THC range (ng/mL)
1.00	6	90.4±20.2	45.6–187.8
1.32	6	100.0±10.1	62.8–125.3
1.97	6	119.8±10.6	44.5–180.9
2.40	18	63.0±8.6	11.7–137.0
2.54	6	162.6±18.7	107.4–204.7
4.84	12	124.2±16.2	44.8–218.0

**Data adapted from reference 20*

amounts of cannabichromene. Unexpectedly, for every sample analyzed, 50% of the THC was recovered compared with the original THCA content.

THC absorption by inhalation (with a bioavailability of 18% to 50% from cigarettes [16]) is extremely rapid, and is the main reason why this is the route of dosing preferred by many people (23). From experiments with deuterium-labelled THC given intravenously (5 mg) or smoked in cigarettes (10 mg), heavy smokers (n=14) were found to obtain higher overall bioavailability (23% to 27%) of THC (24) than light (n=13) marijuana smokers (10% to 14%) (25). In the two experiments, there was high intersubject variability (coefficient of variation 40% to 70%) with overlap between groups. A mean bioavailability of 20%, with a range of 10% to 30%, for THC is given by Iversen (23).

Standardized cigarettes have been developed by NIDA, and the relationships among cannabis (THC) content, dose administered and resultant plasma levels have been investigated. The inhalation from smoking cannabis, containing 1.64% THC (mean dose 13.0 mg THC), resulted in a mean peak THC plasma level of 77 ng/mL (19). In another experiment, controlled puffing of a 3.55% THC cigarette provided a maximum plasma level of 268.4 ng/mL (20). A comparison between cannabis 'joint' potency and resulting plasma THC concentrations from carefully controlled smoking experiments is shown in Table 2.

Even in these controlled experiments, there is clearly great variation in the amount absorbed among individuals and a poor relationship between the amount of THC in cigarettes (1% to 4.8%) and peak plasma THC concentrations. It is possibe that individuals control their own levels by limiting inhalation according to effect. It is noted that the total THC level of Health Canada medical marijuana is approximately 10%, although that estimate likely includes THCA. There does not appear to be any new pharmacokinetic information on this dose level.

Arguably, the most reliable information on absorption of marijuana is from work by Huestis et al (26), where a strict smoking protocol and an extremely rapid blood sampling technique were applied to six volunteers with cigarettes at two THC dose levels (1.75% and 3.55%). Concentrations of THC were detected in 2 min, just after the first puff, and peak concentrations occurred at 9 min, just before the last puff (which began at 9.8 min). Average peak plasma concentrations of 79±25.2 ng/mL and 152±86.3 ng/mL were obtained for the cigarettes containing 1.75% and 3.55% THC, respectively. Despite a rigorous smoking protocol, the variation displayed from the higher dose ranged from approximately 80 ng/mL to 260 ng/mL. Although the reported average maximum concentration occurred at 9 min, just before the final puff, the investigators noted that the time to peak concentration was influenced by the number of puffs, time between puffs, and the volume and length of inhalations; this was clear from other detailed studies (27,28). However, the effectiveness of breath-holding with 3.55% THC potency cigarettes appears to be limited. After puffing the cigarette, a 20 s hold did not increase plasma concentrations significantly over a 10 s hold (27).

There is little information for THC and other cannabinoids comparing pharmacokinetics in men and women. In a study with tritiated THC administered intravenously and orally to six young men and women, no differences in pharmacokinetics, including disposition and metabolism were noted (28). In another small study (29), three men and three women who were experienced marijuana smokers smoked two 1% THC cigarettes, with a 2 h interval between doses. They were asked to smoke at their usual rate. There was a difference between men and women in smoking rate, with men smoking more rapidly with more puffs (28 puffs versus 11 puffs for the women). There was a tendency for peak concentrations to be lower for the women, but there was no significant difference in the area under the concentration-time curve (AUC) (28,29). THC plasma levels decreased rapidly after cessation of smoking and, at 2 h after smoking, were below 5 ng/mL; 15 min after reaching the maximum, mean concentrations declined by approximately 50% (26,30).

Using modern sensitive analytical techniques, THC can be detected in the plasma for at least one day after a single dose, and for 13 days in chronic users (31). The decline of THC in plasma is multiphasic and, as Harvey (32) notes, estimates of the terminal half-life of THC in humans have increased as analytical methods have become more sensitive. Although there is still no consensus, it is probably safe to say that the terminal half-life of THC averages at least one week, but could be considerably longer. The half-life in plasma does not appear to be different between heavy and light users (33,34).

Oral THC

Information on oral THC was obtained mainly with dronabinol. THC is almost completely absorbed (90% to 95%) after single oral doses according to the recovery of ^{14}C-labelled dose (35), although these data include both THC and its degradation products. From an oral dose of 20 mg THC in a chocolate cookie, compared with an intravenous infusion of

5 mg, the systemic availability was only 4% to 12% (19), and is described as being slowly and unreliably absorbed (13). While most subjects had peak plasma THC concentrations between 1 h and 2 h, some of the 11 subjects only peaked at 6 h and many had more than one peak. When tritiated THC was administered in oil enclosed in capsules (total doses of 15 mg in women and 20 mg in men) 10% to 20% of the administered dose reached the systemic circulation. The peak THC concentrations observed ranged from 10 ng/mL to 15 ng/mL, approximately 10% of the levels attained by efficient smoking (28). Only 10% to 20% of synthetic THC (dronabinol) administered in capsules with sesame oil enters the systemic circulation, indicating extensive first-pass metabolism (5). The psychomotor effect or 'high' has been observed to occur more quickly by the smoking than by the oral route (13,19); Iversen (36) remarks this as the reason "smoking is the preferred route of cannabis for many people". As with the administration by smoking, the elimination phase from oral THC in plasma can be described using a two-compartment model with an initial (alpha) half-life of approximately 4 h and a beta half-life of 25 h to 36 h (37). However, as noted previously, the terminal half-life of THC can be much longer with considerable individual variability (31,32).

Rectal THC

In a pilot study (38), a suppository containing 11.8 mg of the THC hemisuccinate ester (equivalent to 9 mg THC) was administered to three women (two of whom had previously exhibited low plasma THC levels with a 10 mg dose of the oral THC dronabinol [Marinol]) and it provided comparatively high plasma THC concentrations. The AUC for plasma THC was more than 30-fold higher than after oral dosing. In another pilot study (39), in two patients with spasticity, multiple 10 mg to 15 mg doses of oral THC (dronabinol [Marinol]) were compared with rectal THC hemisuccinate suppositories (2.5 mg to 5 mg) over 24 h. After oral doses, peak plasma levels from 2.1 ng/mL to 16.9 ng/mL THC and 74.5 ng/mL to 244.0 ng/mL metabolite were found and, after rectal doses, peak plasma levels from 1.1 ng/mL to 4.1 ng/mL THC and 6.1 ng/mL to 42.0 ng/mL metabolite were measured over 8 h. Corrected for dose, rectal THC was approximately twice as bioavailable as the oral form, and this is attributed both to lower absorption and higher first-pass metabolism from the oral versus rectal route.

DISTRIBUTION

Distribution of THC begins immediately and rapidly after absorption. The plasma protein binding of THC and its metabolites is approximately 97% (40,41). THC is mainly bound to low density lipoproteins, with up to 10% present in red blood cells (42), while the metabolite, 11-hydroxy-THC, is even more strongly bound, with only 1% found in the free fraction (43).

Because of its lipid solubility, THC has a large apparent volume of distribution, approximately 10 L/kg (13). Moreover, animal studies show that it is sequestered to the fat tissues, including the brain (32); however, considerably less than 1% of an administered dose reaches the brain (44).The highest concentrations are found in the heart and adipose tissue, with levels reaching 10- to 1000-fold that of plasma, respectively (18). THC readily crosses the blood-brain barrier and the slight delay in correlating peak plasma concentration to effects is assumed to reflect this distribution (19). In animal studies, while immediate distribution is high in the liver, the spleen and body fat are the major sites of distribution after 72 h and are the long-term THC storage sites (45).

There has been concern about the possible consequences of the long persistence of THC in fatty tissues. However, there is no evidence that the THC residues persist in the brain, and release from the fatty storage sites into blood is slow enough that the levels attained are not high enough to cause psychological effects. However, with regular use, THC will accumulate (32).

METABOLISM

The majority of the metabolism of cannabinoids occurs in the liver, and different metabolites predominate when different routes of administration are used. The complex metabolism of THC involves allylic oxidation, epoxidation, decarboxylation and conjugation (13). Cannabinoids are good substrates for cytochrome P_{450} (CYP) mixed-function oxidases and, in humans, the major site of hydroxylation is carbon 11, catalyzed by CYP 2CP (32). This is considered to be the enzyme that may influence potential drug interactions; however, the Marinol monograph (37) states, "in studies involving patients with AIDS and/or cancer, (dronabinol) capsules have been coadministered with a variety of medications (eg, cytotoxic agents, anti-infective agents, sedatives or opioid analgesics) without resulting in any clinically significant drug to drug interactions."

The major initial metabolites of THC are 11-hydroxy-THC and 11-nor-9-carboxy-THC. Over 80 other metabolites of THC, most of which are polar and acidic, have been identified and isolated by conducting in vivo experiments in humans or in vitro studies with human tissue (13). 11-hydroxy-THC is rapidly formed by the action of hepatic microsomal oxidases, and plasma levels parallel the duration of observable drug action. 11-hydroxy-THC has been found to have psychotomimetic properties equal to THC (46-48). After smoking 1.75% and 3.55% THC cigarettes, this metabolite appears rapidly and peaks shortly after THC, approximately 15 min after the start of smoking (16). 11-hydroxy-THC also exhibits peak plasma concentrations of approximately 7.5 ng/mL (approximately 5% of parent THC) and the AUC profile of this metabolite averages 20% of the parent. Similar results were obtained with intravenous administration (13).

The psychoinactive 11-nor-9-carboxy-THC is the primary acid metabolite of THC excreted in the urine (49), and it is the cannabinoid most often monitored in forensic analysis of body fluids (50). Peak plasma values of this metabolite occur 1.5 h to 2.5 h after smoking and are approximately one-third the concentration of parent THC. There are numerous oxidative products from the side chain and further oxidation of the alcohols yield carboxylic acid products (13). Following oxidation, the phase II metabolites of the free drug or hydroxy-THC appear to be glucuronide conjugates (13) that appear in the urine; however, they are not major or appreciably active.

There is limited information on the metabolism of CBD and CBN in humans. As with THC, the 11-hydroxy metabolites appear to be the major phase I products (51). For CBD, hydroxylation was found in all positions of the side chain, with several minor dihydroxylated metabolites being identified (52). For CBD, the amount of polar metabolites formed seems greater than for THC (13). For CBN, as well as the 11-hydroxy metabolite, dihydroxy-CBN, CBN-7-oic acid and more polar metabolites are formed after intravenous administration (53).

It is known that polyaromatic hydrocarbons found in tobacco and cannabis smoke induce the action of CYP 1A2. If it can be

shown that the metabolism of THC also involves this CYP, then repeated exposure to cannabis could cause the more rapid disappearance of THC via this specific enzyme. However, animal studies (54) suggest that there may be functional interactions between THC and nicotine, which might have addiction implications. Various other CYP enzymes are of interest for potential drug interactions. In human liver microsome preparations, CBD has been shown to inhibit formation of THC metabolites catalyzed by CYP 3A, with less effect on CYP 2C9 (32). However, others suggest that CBD decreases formation of 11-hydroxy-THC by inhibition of CYP 2C9 (55), but it does not appear to present as a clinical interaction (56).

After oral doses of THC, parent THC and its active metabolite, 11-hydroxy-THC, are present in approximately equal concentrations in the plasma (54,57). Concentrations of both parent drug and metabolite peak approximately 2 h to 4 h after oral dosing and decline over several days. Clearance averages approximately 0.2 L/kg•h, but is highly variable due to the complexity of cannabinoid distribution (37). The larger amount of 11-hydroxy-THC metabolite from first-pass metabolism by this route, which is similar in potency to THC, complicates the interpretation of potential effects. With oral THC dosing, absorption is slow and variable, and peak concentrations of THC may be only 10% of that from an efficiently smoked administration; however, the plasma levels of active 11-hydroxy metabolite are approximately threefold higher than that observed in the plasma from smoking (28,56).

EXCRETION

Elimination of inhaled THC and its metabolites occurs via the feces (65%) and urine (20%). After five days, 80% to 90% of the total dose is excreted (28,34). Metabolites in the urine (of which there are 20) are mainly acidic, such as 11-nor-9-carboxy-THC. Those in the feces are both acidic and neutral, the most abundant metabolites being 9-carboxy-THC (29%) and 11-hydroxy-THC (21%) (28,32).

Similarly, following oral doses, THC and its biotransformation products are excreted in both feces and urine (37). Biliary excretion (complicated with enterohepatic recycling) is the major route of elimination, with approximately one-half of a radiolabelled oral dose being recovered from the feces within 72 h, compared with 10% to 15% recovered from urine (58). Less than 5% of an oral dose is recovered unchanged in the feces (37). Following administration of a single oral dose, low levels of THC metabolites have been detected for more than five weeks in the urine and feces (37,59).

In forensic or employment situations when such testing may be applied, it is important for patients (or recreational users) to be aware that traces of marijuana can be detected in urine even weeks after dosing (50).

NABILONE

As previously stated, dronabinol is identical to THC from the marijuana plant. However, nabilone was developed from structure-action evaluation by industry (7) and has been marketed in Europe and Canada for over 20 years for the management of severe nausea and vomiting associated with cancer chemotherapy (8). It has also been studied for the treatment of chronic pain of various etiologies, with some patients experiencing useful benefits; however, there remains a need for more clinical trials on this aspect (60).

Absorption

In radiotracer studies with ^{14}C-nabilone administered intravenously and orally, 95.8% was absorbed (61) from oral administration (the disappearance from plasma was rapid due to extensive distribution and rapid metabolism). Additionally, for both the intravenous and the oral routes, the total radioactivity exhibited half-lives of 20.6 h and 35 h, respectively, and the parent nabilone had a plasma elimination half-life of approximately 2 h (62). As with THC, there is a high first-pass effect, but it is well absorbed and the pharmacokinetics appear to be linear (but variable) from oral doses of 1 mg to 4 mg (62).

Distribution

Information on the protein binding of nabilone is lacking. However, after intravenous tracer administration, the disappearance of total radioactivity, parent nabilone and the alcohol metabolite was biphasic, with the first phase (half-life approximately 10 min) attributed to distribution into tissue and the slower phase to elimination (61,63).

Metabolism

The metabolism of nabilone has not yet been fully elucidated. The major metabolites of nabilone in plasma are a mixture of isomeric alcohols yielded from the reduction of the ketone group on carbon 9 (61,62). These metabolites are excreted in feces, but not urine. The metabolites in urine are uncharacterized, and are highly polar and acidic, although there is no evidence of sulfate or glucuronide conjugates (62). It is speculated that, like THC, there is hydroxylation of various sites on the dimethylheptyl side chain (61) and one nabilone diol has been recovered from feces with one alcohol on the carbon 9 and the other on the side chain (64). There is virtually no information on drug interactions for this agent.

Excretion

From both oral and intravenous tracer doses, over 90% of the dose was recovered over seven days, with approximately 67% in feces and 23% in urine (61,62). These values are similar to the feces to urine ratio of excretion found with other cannabinoids (62).

PHARMACOKINETIC-PHARMACODYNAMIC RELATIONSHIPS

Most studies (65) of plasma concentration and effect relationships for marijuana have been directed at the psychotropic effect ('high') and the temporal relationship between this effect and plasma levels, as well as at intoxication; impairment of cognitive or motor function is not yet clear but is of major forensic interest (66). The acute effect on heart rate has also been used for such modelling (30). Dose and plasma concentration versus response for possible therapeutic applications are ill-defined, except for some information obtained for oral dosing with dronabinol for its limited indications (19). Such correlations of THC pharmacokinetics are complicated by the emergence of active metabolites, particularly 11-hydroxy-THC (47,49), which attains higher plasma concentrations after oral than inhalation doses.

In one study (30), six volunteers smoked 1% by weight cigarettes with an average weight of 894 mg (total THC dose 8.9 mg), and then smoked a second cigarette after 2 h. Plasma THC concentrations, heart rate and self-reported 'high' profiles were documented. Similar psychological 'highs' occurred after both cigarettes, but less heart rate acceleration was found for the second cigarette. The heart rate for the first cigarette peaked at an

average of 11 min after the start of smoking and was maintained until approximately 30 min after smoking. Thus, the effect was observed to begin at approximately 5 min after peak plasma concentration (mean 45 ng/mL) was reached – it exhibited a lag time – and it returned to baseline at approximately 30 min, when the plasma concentration was approximately 7 ng/mL. Although the heart rate increase was much smaller with the second cigarette, the lag time was similar. For the psychotropic effect, there was a different pattern with a gradual emergence of effect at 10 min (concentration of 30 ng/mL, post-peak), peaking at 30 min after smoking (concentration of approximately 7 ng/mL) and diminishing rapidly 45 min after smoking (concentration of 4.5 ng/mL). The second dose showed very similar pharmacokinetic and response profiles to the first cigarette. The data were fitted with a lag time model because the effect emerged approximately 20 min after the peak plasma concentration. In another experiment (67), the relationship between THC plasma concentrations and self-reported 'highs' with single cigarettes of three different potencies were examined. The cigarettes were 1.3%, 2.0% and 2.5% in THC potency. Because NIDA cigarettes average 900 mg, the total dose available ranged from 11.7 mg to 22.5 mg. The results indicated a proportional dose response, with the intensity and duration greatest for the 2.5% cigarette. As with the experiment above, there was a lag time from the peak plasma concentration until the 'high' and, for the highest dose, the feeling commenced at 5 min after smoking, when the plasma concentration was approximately 140 ng/mL. However, with the lowest dose, a similar intensity was noted at 5 min at a concentration of 90 ng/mL (which appears near the peak concentration for this dose). For the low dose, the intensity of the 'high' reached 50% of its maximum at 30 min and then gradually declined over 2 h, whereas, for the high dose, the 'high' almost plateaued at 20 min for 60 min to 75 min at 70% intensity, before declining. Modelling this data suggests that the steady-state plasma concentration at 50% of the maximum high-effect ($C_{ss[50]}$) would be 25 ng/mL to 29 ng/mL (67).

Other reports (16,66) showed similar results using a 3.55% THC cigarette (which can yield an available dose of 32 mg of THC). In this case, the effect was perceptible within 2 min to 3 min and exhibited a plateau that commenced at 9 min and continued for 1.5 h before diminishing over 3 h to 4 h. A simultaneous average plasma concentration profile showed that at 1.5 h, the THC level is approximately 10 ng/mL and the 11-hydroxy-THC level is somewhat less. It was noted that the lack of correspondence between the plasma profile and the subjective 'high' response can be fitted with a more complex pharmacodynamic mode. This includes an 'effect compartment', which, after a lag time, reaches equilibrium with an effect curve. After equilibrium is reached, the intensity of the effect is proportional to the plasma THC profile. This concentration-effect response demonstrates a counterclockwise hysteresis.

This type of modelling (66) supports a 10 ng/mL cutoff as evidence of functional impairment, which agrees with the above $C_{ss(50)}$ estimate (67). In addition, the model was used to simulate multiple dosing with a 1% cigarette containing 9 mg THC (68). The duration of the maximal 'high' for this dose was estimated at approximately 45 min after dosing and declined to 50% of this peak effect at approximately 100 min after smoking. At this dose, a dosing interval of 1 h gave a 'continuous high' and the recovery after the last dose occurred at 150 min. The peak plasma concentration during this dosage was estimated at approximately 70 ng/mL and the $C_{ss(50)}$ at approximately 30 ng/mL THC.

The data relating concentration and response were limited to the cardiac and subjective 'high' responses, and these show dissimilarities in profile. The information obtained from oral dosing with dronabinol was complicated because there is a greater amount of psychoactive 11-hydroxy-THC metabolite formed by this route of administration (49). Thus, the target THC plasma concentrations derived actually depend on the subjective 'high' response that may or may not be related to the potential therapeutic applications. However, it is likely that the psychoactivity that elicits this response from the central nervous system is receptor-derived and the concentrations are useful for suggesting doses from smoking.

There are no formal pharmacokinetic-pharmacodynamic correlations with nabilone; however, there have only been a limited number of dose-response studies performed using doses between 1 mg and 5 mg (69). The responses examined were heart rate, blood pressure and subjective signs and symptoms, particularly euphoria. There was a decrease in pulse rate with the 1 mg dose and a slight increase of 7 beats/min to 8 beats/min with the 2.5 mg and 5 mg doses. There was no change in blood pressure when the subjects were recumbent but, with the 5 mg dose, blood pressure dropped significantly on standing and this was associated with dizziness (68). Subjective signs and symptoms, including euphoria and relaxation, were also more marked after the 5 mg dose. In experiments examining tolerance to these effects, a 2 mg dose was administered twice daily for seven days, and subjects were challenged with a 5 mg dose on the eighth day and again after a week of washout. After six days on the 2 mg dose, postural hypotension and euphoria were absent and did not recur with an immediate higher dose. However, after the washout, there was a change in blood pressure and subjective responses, although this was not as marked as in naïve subjects. It is important to note that tolerance did not develop to the relaxant and antiemetic effects of nabilone, as has been confirmed by clinical trials (6,7,61). These trials have also found that compared with THC, nabilone produces less tachycardia and less euphoria for a similar antiemetic response (70).

CONCLUSIONS

The chemistry of cannabinoids is complex (for a more detailed description, see Grotenhermen [1], Mechoulam et al [2] and Mechoulam [70]) and the information on pharmacokinetics is limited, except for the THC component. Absorption from smoked cannabis is rapid and highly variable, with fast effects on heart rate and a quick attainment of the marijuana 'high'; these effects may be somewhat controlled by the smoker's uptake. Absorption from oral dosing is also variable; however, it is much slower and the production of active THC metabolites (first-pass metabolism) leads to some prolonged activity. The synthetic derivative nabilone is rapidly well absorbed from the oral route and also appears to have active metabolites, being more than 90% eliminated in seven days. Less is known about the pharmacokinetics of other cannabis components, and the absorption and fate by other routes, such as rectal or dermal. There is very recent information on dermal uptake of Δ-8-THC (71) indicating that a constant plasma concentration can be maintained for 48 h. While there have been concerns about possible drug interactions of marijuana or THC (particularly with other central nervous system drugs), and concerns in the treatment of frail patients on many other treatments (eg, AIDS), there is no substantive literature to indicate that these are clinically significant (72).

REFERENCES

1. Grotenhermen F. Pharmacokinetics and pharmacodynamics of cannabinoids. Clin Pharmacokinet 2003;42:327-60.
2. Mechoulam R, Devane WA, Glaser R. Cannabinoid geometry and biological activity. In: Nahas GG, Sutin KM, Harvey D, Agurell S, eds. Marihuana and Medicine. Totowa, New Jersey: Humana Press, 1999:65-90.
3. Joy JE, Watson SJ Jr, Benson JA Jr. Marijuana and medicine: Assessing the science base. <www.nap.edu/books/0309071550/html/> (Version current at June 20, 2005).
4. Garrett ER, Hunt CA. Physiochemical properties, solubility, and protein binding of delta9-tetrahydrocannabinol. J Pharm Sci 1974;63:1056-64.
5. Marinol® monograph. Compendium of Pharmaceuticals and Specialties (CPS), Canadian Pharmacists Association, Ottawa, 2003:949.
6. Lemberger L. Nabilone, a synthetic cannabinoid of medical utility. In: Nahas GG, Sutin KM, Harvey D, Agurell S, eds. Marihuana and Medicine. Totowa, New Jersey: Humana Press, 1999:561-66.
7. Cesamet® monograph. Compendium of Pharmaceuticals and Specialties (CPS), Canadian Pharmacists Association, Ottawa, 2003:332.
8. Razdan RK. Structure-activity relationships in cannabinoids. Pharmacol Rev 1986;38:75-149.
9. Martin BR, Mechoulam R, Razdan RK. Discovery and characterization of endogenous cannabinoids. Life Sci 1999;65:573-95.
10. Martin BR, Jefferson R, Winckler R, et al. Manipulation of the tetrahydrocannabinol side chain delineates agonists, partial agonists, and antagonists. J Pharmacol Exp Ther 1999;290:1065-79.
11. Brenneisen R. [Psychotropic drugs. II. Determination of cannabinoids in *Cannabis sativa L.* and in cannabis products with high pressure liquid chromatography (HPLC)]. Pharm Acta Helv 1984;59:247-59.
12. Agurell S, Leander K. Stability, transfer and absorption of cannabinoid constituents of cannabis (hashish) during smoking. Acta Pharm Suec 1971;8:391-402.
13. Agurell S, Halldin M, Lindgren JE, et al. Pharmacokinetics and metabolism of delta 1-tetrahydrocannabinol and other cannabinoids with emphasis on man. Pharmacol Rev 1986;38:21-43.
14. Pitts JE, Neal JD, Gough TA. Some features of *Cannabis* plants grown in the United Kingdom from seeds of known origin. J Pharm Pharmacol 1992;44:947-51.
15. Health Canada. http://www.hc-sc.gc.ca/hecs-sesc/marihuana/pdf/qc-result-cq_e.pdf> (Version current at August 3, 2005).
16. Huestis M. Pharmacokinetics of THC in inhaled and oral preparations. In: Nahas GG, Sutin KM, Harvey D, Agurell S, eds. Marihuana and Medicine. Totowa, New Jersey: Humana Press, 1999:105-16.
17. Fehr KO, Kalant H. Analysis of cannabis smoke obtained under different combustion conditions. Can J Physiol Pharmacol 1972;50:761-7.
18. Truitt EB Jr. Biological disposition of tetrahydrocannabinols. Pharmacol Rev 1971;23:273-8.
19. Ohlsson A, Lindgren JE, Wahlen A, Agurell S, Hollister LE, Gillespie HK. Plasma delta-9 tetrahydrocannabinol concentrations and clinical effects after oral and intravenous administration and smoking. Clin Pharmacol Ther 1980;28:409-16.
20. Perez-Reyes M. Marijuana smoking: Factors that influence the bioavailability of tetrahydrocannabinol. NIDA Res Monogr 1990;99:42-62.
21. Davis KH Jr, McDaniel IA Jr, Caldwell LW, Moody P. Some smoking characteristics of marijuana cigarettes. In: Agurell S, Dewey WL, Willette RE, eds. The Cannabinoids: Chemical, Pharmacologic and Therapeutic Aspects. New York: Academic Press, 1984:97-109.
22. Jack A, McKay G. Qualitative and quantitative analysis of the cannabinoid content of combusted plant tissue. Abstract no 36, Canadian Society for Pharmaceutical Sciences, 7th annual symposium, Vancouver, British Columbia, June 9-12, 2004.
23. Iversen LL. The Science of Marijuana. Oxford: Oxford University Press, 2000:37.
24. Lindgren JE, Ohlsson A, Agurell S, Hollister L, Gillespie H. Clinical effects and plasma levels of delta 9-tetrahydrocannabinol (delta 9-THC) in heavy and light users of cannabis. Psychopharmacology (Berl) 1981;74:208-12.
25. Azorlosa JL, Heishman SJ, Stitzer ML, Mahaffey JM. Marijuana smoking: Effect of varying delta 9-tetrahydrocannabinol content and number of puffs. J Pharmacol Exp Ther 1992;261:114-22.
26. Huestis MA, Sampson AH, Holicky BJ, Henningfield JE, Cone EJ. Characterization of the absorption phase of marijuana smoking. Clin Pharmacol Ther 1992;52:31-41.
27. Azorlosa JL, Greenwald MK, Stitzer ML. Marijuana smoking: Effects of varying puff volume and breathhold duration. J Pharmacol Exp Ther 1995;272:560-9.
28. Wall ME, Sadler BM, Brine D, Taylor H, Perez-Reyes M. Metabolism, disposition, and kinetics of delta-9-tetrahydrocannabinol in men and women. Clin Pharmacol Ther 1983;34:352-63.
29. Perez-Reyes M, Owens SM, Di Guiseppi S. The clinical pharmacology and dynamics of marihuana cigarette smoking. J Clin Pharmacol 1981;21(Suppl 8-9):201S-7S.
30. Barnett G, Chiang CW, Perez-Reyes M, Owens SM. Kinetic study of smoking marijuana. J Pharmacokinet Biopharm 1982;10:495-506.
31. Johansson E, Agurell S, Hollister LE, Halldin MM. Prolonged apparent half-life of delta 1-tetrahydrocannabinol in plasma of chronic marijuana users. J Pharm Pharmacol 1988;40:374-5.
32. Harvey DJ. Absorption, distribution and biotransformation of the cannabinoids. In: Nahas GG, Sutin KM, Harvey D, Agurell S, eds. Marihuana and Medicine. Totowa, New Jersey: Humana Press, 1999:91-103.
33. Ohlsson A, Lindgren JE, Wahlen A, Agurell S, Hollister LE, Gillespie HK. Single dose kinetics of deuterium labelled delta 1-tetrahydrocannabinol in heavy and light cannabis users. Biomed Mass Spectrom 1982;9:6-10.
34. Hunt CA, Jones RT. Tolerance and disposition of tetrahydrocannabinol in man. J Pharmacol Exp Ther 1980;215:35-44.
35. Lemberger L, Weiss JL, Watanabe AM, Galanter IM, Wyatt RJ, Cardon PV. Delta-9-tetrahydrocannabinol. Temporal correlation of the psychologic effects and blood levels after various routes of administration. N Engl J Med 1972;286:685-8.
36. Iversen LL. The Science of Marijuana. Oxford: Oxford University Press, 2000:46-7.
37. Unimed Pharmaceuticals Inc. Marinol® US monograph. <http://www.unimed.com/proddisc3.html> (Version current at June 20, 2005).
38. Mattes RD, Shaw LM, Edling-Owens J, Engelman K, Elsohly MA. Bypassing the first-pass effect for the therapeutic use of cannabinoids. Pharmacol Biochem Behav 1993;44:745-7.
39. Brenneisen R, Egli A, Elsohly MA, Henn V, Spiess Y. The effect of orally and rectally administered delta 9-tetrahydrocannabinol on spasticity: A pilot study with 2 patients. Int J Clin Pharmacol Ther 1996;34:446-52.
40. Garrett ER, Hunt CA. Pharmacokinetics of delta-9-tetrahydrocannabinol in dogs. J Pharm Sci 1977;66:395-407.
41. Widman M, Agurell S, Ehrnebo M, Jones G. Binding of (+)- and (minus)-delta-1-tetrahydrocannabinols and (minus)-7-hydroxy-delta-1-tetrahydrocannabinol to blood cells and plasma proteins in man. J Pharm Pharmacol 1974;26:914-6.
42. Wahlqvist M, Nilsson IM, Sandberg F, Agurell S. Binding of delta-1-tetrahydrocannabinol to human plasma proteins. Biochem Pharmacol 1970;19:2579-84.
43. Widman M, Nilsson IM, Agurell S, Borg H, Granstrand B. Plasma protein binding of 7-hydroxy-1-tetrahydrocannabinol: An active 1-tetrahydrocannabinol metabolite. J Pharm Pharmacol 1973;25:453-7.
44. Nahas G, Leger C, Tocque B, Hoellinger H. The kinetics of cannabinoid distribution and storage with special reference to the brain and testis. J Clin Pharmacol 1981;21(8-9 Suppl):208S-214S.
45. Nahas GG, Frick HC, Lattimer JK, Latour C, Harvey D. Pharmacokinetics of THC in brain and testis, male gametotoxicity and premature apoptosis of spermatozoa. Hum Psychopharmacol 2002;17:103-13.
46. Iversen LL. The Science of Marijuana. Oxford: Oxford University Press, 2000:51.
47. Perez-Reyes M, Timmons MC, Lipton MA, Davis KH, Wall ME. Intravenous injection in man of 9-tetrahydrocannabinol and 11-OH-9-tetrahydrocannabinol. Science 1972;177:633-5.
48. Christensen HD, Freudenthal RI, Gidley JT, et al. Activity of delta8- and delta9-tetrahydrocannabinol and related compounds in the mouse. Science 1971;172:165-7.

49. Huestis MA, Henningfield JE, Cone EJ. Blood cannabinoids. I. Absorption of THC and formation of 11-OH-THC and THCCOOH during and after smoking marijuana. J Anal Toxicol 1992;16:276-82.
50. Huestis MA, Mitchell JM, Cone EJ. Urinary excretion profiles of 11-nor-9-carboxy-delta 9-tetrahydrocannabinol in humans after single smoked doses of marijuana. J Anal Toxicol 1996;20:441-52.
51. Martin BR, Cone EJ. Chemistry and pharmacology of cannabis. In: Kalant H, Corrigall W, Hall W, Smart R, eds. The Health Effects of Cannabis. Toronto: Centre for Addiction and Mental Health, 1999:21-68.
52. Martin B, Nordqvist M, Agurell S, Lindgren JE, Leander K, Binder M. Identification of monohydroxylated metabolites of cannabidiol formed by rat liver. J Pharm Pharmacol 1976;28:275-9.
53. Martin B, Agurell S, Nordqvist M, Lindgren JE. Dioxygenated metabolites of cannabidiol formed by rat liver. J Pharm Pharmacol 1976;28:603-8.
54. Valjent E, Mitchell JM, Besson MJ, Caboche J, Maldonado R. Behavioural and biochemical evidence for interactions between Delta 9-tetrahydrocannabinol and nicotine. Br J Pharmacol 2002;135:564-78.
55. Bornheim LM, Everhart ET, Li J, Correia MA. Characterization of cannabidiol-mediated cytochrome P450 inactivation. Biochem Pharmacol 1993;45:1323-31.
56. Wall ME, Brine DR, Perez-Reyes M. Metabolism of cannabinoids in man. In: Braude MC, Szara S, eds. Pharmacology of Marihuana. New York: Raven Press, 1976:93-113.
57. Hollister LE, Gillespie H. Interactions in man of delta-9-tetrahydrocannabinol. II. Cannabinol and cannabidiol. Clin Pharmacol Ther 1975;18:80-3.
58. Hawks RL. The constituents of cannabis and the disposition and metabolism of cannabinoids. NIDA Res Monogr 1982;42:125-37.
59. Ellis GM Jr, Mann MA, Judson BA, Schramm NT, Tashchian A. Excretion patterns of cannabinoid metabolites after last use in a group of chronic users. Clin Pharmacol Ther 1985;38:572-8.
60. Notcutt W, Price M, Blossfeldt P, Chapman G. Clinical experience of the synthetic cannabinoid nabilone for chronic pain. In: Nahas GG, Sutin KM, Harvey D, Agurell S, eds. Marijuana and Medicine. Totowa, New Jersey: Humana Press, 1999:561-6.
61. Ward A, Holmes B. Nabilone. A preliminary review of its pharmacological properties and therapeutic use. Drugs 1985;30:127-44.
62. Rubin A, Lemberger L, Warrick P, et al. Physiologic disposition of nabilone, a cannabinol derivative, in man. Clin Pharmacol Ther 1977;22:85-91.
63. Lemberger L, Rubin A, Wolen R, et al. Pharmacokinetics, metabolism and drug-abuse potential of nabilone. Cancer Treat Rev 1982;9(Suppl B):17-23.
64. Sullivan HR, Hanasono GK, Miller WM, Wood PG. Species specificity in the metabolism of nabilone. Relationship between toxicity and metabolic routes. Xenobiotica 1987;17:459-68.
65. Harder S, Rietbrock S. Concentration-effect relationship of delta-9-tetrahydrocannabiol and prediction of psychotropic effects after smoking marijuana. Int J Clin Pharmacol Ther 1997;35:155-9.
66. Cone EJ, Huestis MA. Relating blood concentrations of tetrahydrocannabinol and metabolites to pharmacologic effects and time of marijuana usage. Ther Drug Monit 1993;15:527-32.
67. Chiang CW, Barnett G. Marijuana effect and delta-9-tetrahydrocannabinol plasma level. Clin Pharmacol Ther 1984;36:234-8.
68. Huestis MA, Henningfield JE, Cone EJ. Blood cannabinoids. II. Models for the prediction of time of marijuana exposure from plasma concentrations of delta 9-tetrahydrocannabinol (THC) and 11-nor-9-carboxy-delta 9-tetrahydrocannabinol (THCCOOH). J Anal Toxicol 1992;16:283-90.
69. Lemberger L, Rowe H. Clinical pharmacology of nabilone, a cannabinol derivative. Clin Pharmacol Ther 1975;18:720-6.
70. Mechoulam R. Chemistry of cannabis. Handbook Exp Pharmacol 1981;55:119-34.
71. Valiveti S, Hammell DC, Earles DC, Stinchcomb AL. In vitro/in vivo correlation studies for transdermal delta 8-THC development. J Pharm Sci 2004;93:1154-64.
72. Hollister L. Interactions of marihuana and THC: What we don't but should know. In: Nahas GG, Sutin KM, Harvey D, Agurell S, eds. Marijuana and Medicine. Totowa, New Jersey: Humana Press, 1999:273-8.