# Clinical Pharmacokinetics of Cannabinoids

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**ABSTRACT.** Absorption and metabolism of tetrahydrocannabinol (THC) vary as a function of route of administration. Pulmonary assimilation of inhaled THC causes a maximum plasma concentration within minutes, while psychotropic effects start within seconds to a few minutes, reach a maximum after 15 to 30 minutes, and taper off within 2 to 3 hours. Following oral ingestion, psychotropic effects set in with a delay of 30 to 90 minutes, reach their maximum after 2 to 3 hours, and last for about 4 to 12 hours, depending on dose and specific effect.

The initial volume of distribution of THC is small for a lipophilic drug, equivalent to the plasma volume of about 2.5-3 L, reflecting high protein binding of 95-99%. The steady state volume of distribution has been estimated to be about 100 times larger, in the range of about 3.5 L per kg of body weight. The lipophility of THC with high binding to tissue and in particular to fat, the major long-term storage site, causes a change of distribution pattern over time. Only about 1% of THC administered IV is found in the brain at the time of peak psychoactivity. THC crosses the placenta and small amounts penetrate into the breast milk.

Metabolism of THC occurs mainly in the liver by microsomal hydroxylation and oxidation catalyzed by enzymes of the cytochrome P-450 complex. In man, the C-11 carbon is the major site attacked. Hydroxylation results in 11-hydroxy-THC (11-OH-THC) and further oxidation to 11-nor-9-carboxy-THC (THC-COOH), which may be glucuronated to THC-COOH beta-glucuronide. Pharmacologically, 11-OH-THC shows a similar profile as THC while THC-COOH is devoid of psychotropic effects. With oral administration higher amounts of 11-OH-THC are formed than with inhalation, reaching similar plasma levels as its parent drug, and contributing significantly to the overall effects of THC.

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Metabolic interaction between THC and the non-psychotropic canna-bidiol (CBD) is based on inhibition of the cytochrome P-450-3A enzyme by CBD. Repeated administration of all cannabinoids causes induction of some cytochrome P-450 isoenzymes which may result in interactions with other medical and non-medical drugs that are using the same enzymes for metabolism. *[Article copies available for a fee from The Haworth Document Delivery Service: 1-800-HAWORTH. E-mail address: <getinfo@ haworthpressinc.com> Website: <http://www.HaworthPress.com> 2003 by The Haworth Press, Inc. All rights reserved.]*

## *INTRODUCTION*

Among the reasons for the decline of the medical use of cannabis in the first half of the 20th century were the pharmacokinetic properties of THC in oral preparations (tinctures, fatty extracts). With oral use cannabis effects commence in a delayed and erratic manner, making it difficult to titrate the required dose. Overdosing and underdosing of medicinal cannabis preparations of unknown THC content were the inevitable consequences often described by physicians of the 19th century (See 1890).

A basic understanding of the pharmacokinetic properties of cannabinoids is necessary to comprehend many issues in context with their medical use, e.g., interactions between cannabinoids and metabolic interactions of cannabinoids with other drugs, differences in onset of action and differences in systemic bioavailability between the oral, sublingual and rectal route of administration and inhalation.

Other questions of general interest, among them the possible effects of prenatal marijuana exposure and exposure to the nursing baby, possible health and legal consequences of passive smoking, forensic questions of drug detection and several other topics are easier to understand with some insight into absorption, tissue distribution and metabolism of THC.

The focus of this review will be on $\Delta^9$-THC (tetrahydrocannabinol). The pharmacokinetics of some other natural and synthetic cannabinoids will also be presented briefly.

### *Cannabinoids of the $^9$-THC Type*

Sixty-six phytocannabinoids have been detected, mainly belonging to one of 10 subclasses or types (ElSohly 2002), consisting of the

cannabigerol type (CBG), cannabichromene type (CBC), cannabidiol type (CBD), $\Delta^9$-THC type, $\Delta^8$-THC type, cannabicyclol type (CBL), cannabielsoin type (CBE), cannabinol type (CBN), cannabinodiol type (CBDL), or to the cannabitriol type (CBTL). It is unclear whether some types are artifacts, resulting from oxidation of the respective parent compounds: CBN from $\Delta^9$-THC, CBL from CBC, and CBE from CBD, or through migration of the double bond in $\Delta^9$-THC to the more thermodynamically stable position in $\Delta^8$-THC (ElSohly 2002).

The cannabinoid acids of $\Delta^9$-THC, cannabidiol (CBD), cannabichromene (CBC), and cannabigerol (CBG) are the quantitatively most important cannabinoids present in the plant (see Figures 1 and 2). Cannabinol (CBN), emerging from THC by oxidation, is also often found, particularly in older cannabis samples. Their relative concentrations vary, and plants have been described that mainly contain one of these cannabinoid types.

Nine cannabinoids belong to the $\Delta^9$-THC type with side chains of 1, 3, 4, and 5 carbons (see Table 1). The most abundant compounds are cannabinoids with a $C_5$ side-chain (Figure 3). Large quantities of propyl homologues ($C_3$ side-chain) have been found in some samples from the Indian subcontinent (Turner et al. 1980) and from Africa (Pitts et al. 1992), whereas the methyl ($C_1$ side chain) and butyl homologues ($C_4$ side chain) are always present in very low concentrations (Vree et al. 1972, Harvey 1976). The cannabinoid composition is determined by genetic and environmental factors. In one study Zambian seedstock plants presented with total tetrahydrocannabivarin (THCV, $C_3$ side chain) levels greater than tetrahydrocannabinol ($C_5$ side chain) but the ratio was progressively reversed in succeeding generations of plants grown in the UK (Pitts et al. 1992). In humans, $\Delta^9$-THCV is about one fourth as pharmacologically active as $\Delta^9$-THC (Hollister 1974).

The cannabinoid acids of $\Delta^9$-THC ($\Delta^9$-THCA) are devoid of psychotropic effects (Dewey 1986) and must be decarboxylated to the respective phenols to produce cannabis-like effects. The phenols are also responsible for most of the medicinal effects. More than 90% of the THC in cannabis plants grown in Europe is present as THC acids, while cannabis grown in hot climates of Africa and Asia contain considerable amounts of phenolic THC. The ratio of $\Delta^9$-THC acids to phenolic $\Delta^9$-THC in leaves and flowers of *Cannabis sativa* has been reported to range from 2:1 in Africa (Pitts 1992) to > 20:1 in Switzerland (Brenneisen 1984). In plants grown in the United Kingdom from Moroccan, Sri Lankan and Zambian seedstock, the

FIGURE 1. Average concentrations of the four cannabinoids THC, CBD, CBG, and CBN in confiscated marijuana and sinsemilla between 1980 and 1997 in the USA. Drawn according to data of ElSohly et al. (2000).

A.



B.
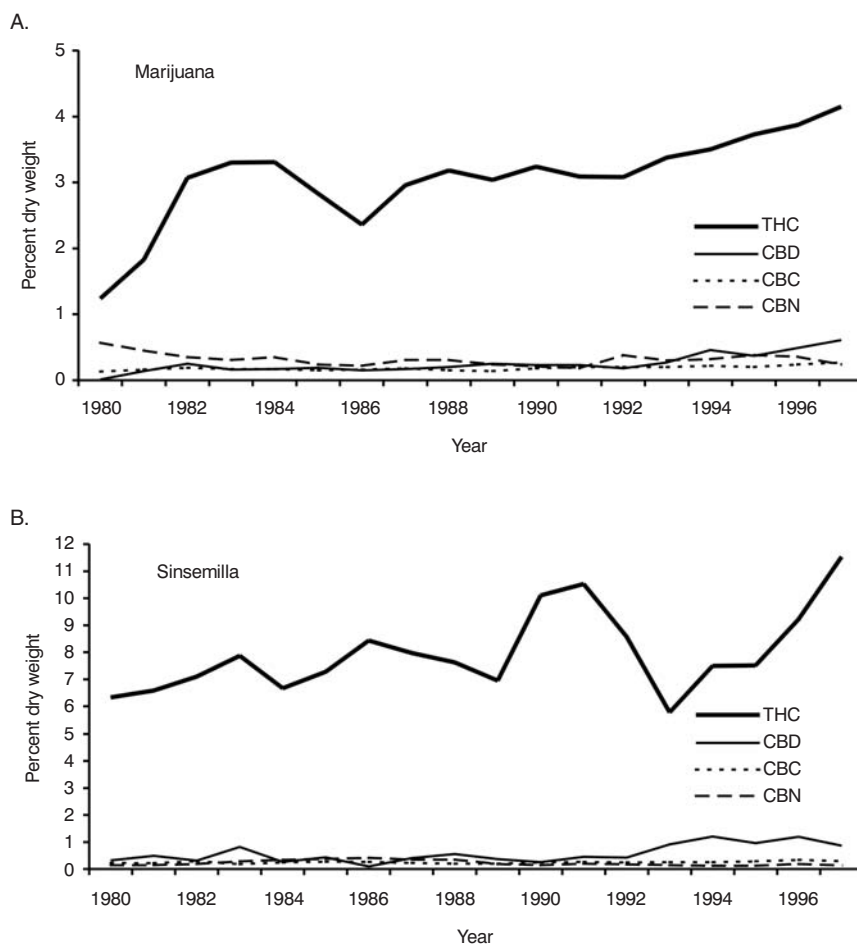


THCA/THC ratio was 17:1 compared with 2:1 in plants from the original areas (Pitts 1992). In several samples of cannabis resin (hashish) the THCA/THC ratio was reported to range between 6.1:1 and 0.5:1, the latter in hashish from India (Baker et al. 1981).

THC decarboxylation in cannabis occurs naturally over time, upon heating (Agurell and Leander 1971, Brenneisen 1984) or under alkaline conditions. Slow decarboxylation of $\Delta^9$-THC occurs at room temperature.
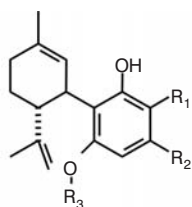
FIGURE 2. Some natural cannabinoids.
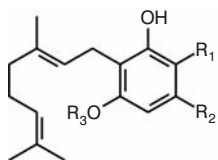
R$_1$ = H or COOH

R$_2$ = C$_3$ or C$_5$ side chain

R$_3$ = H or CH$_3$

**Cannabigerol type**

R$_1$ = H or COOH

R$_2$ = C$_3$ or C$_5$ side chain

**Cannabichromene type**

R$_1$ = H or COOH

R$_2$ = C$_1$, C$_3$, C$_4$ or C$_5$ side chain

R$_3$ = H or CH$_3$

**Cannabidiol type**
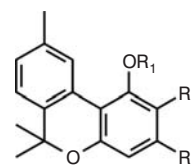
R$_1$ = H or C$_3$

R$_2$ = H or COOH

R$_3$ = C$_1$, C$_3$, C$_4$ or C$_5$ side chain

**Cannabinol type**

Five minutes of heating to 200-210°C have been reported to be optimal for this conversion (Brenneisen 1984), but a few seconds in the blaze of a cannabis cigarette are sufficient as well. Cannabis products with a high content of phenolic THC (e.g., hashish) may be very potent without heating, but usually the potency and medicinal efficacy of cannabis products is significantly increased with smoking the dried plant matter, or by cooking and baking the material.

TABLE 1. Cannabinoids of the $\Delta^9$-*trans*-tetrahydrocannabinol Type (Turner et al. 1980)

| Cannabinoid | Abbreviation | $R_1$ | $R_2$ | $R_3$ |
|---|---|---|---|---|
| $\Delta^9$-*trans*-tetrahydrocannabinolic acid A | $\Delta^9$-THCA | COOH | $C_5H_{11}$ | H |
| $\Delta^9$-*trans*-tetrahydrocannabinolic acid B | $\Delta^9$-THCA | H | $C_5H_{11}$ | COOH |
| $\Delta^9$-*trans*-tetrahydrocannabinol | $\Delta^9$-THC | H | $C_5H_{11}$ | H |
| $\Delta^9$-*trans*-tetrahydrocannabinolic acid-$C_4$ | | COOH or H | $C_4H_9$ | H or COOH |
| $\Delta^9$-*trans*-tetrahydrocannabinol-$C_4$ | $\Delta^9$-THC-$C_4$ | H | $C_4H_9$ | H |
| $\Delta^9$-*trans*-tetrahydrocannabivarinic acid | | COOH | $C_3H_7$ | H |
| $\Delta^9$-*trans*-tetrahydrocannabivarin | $\Delta^9$-THCV | H | $C_3H_7$ | H |
| $\Delta^9$-*trans*-tetrahydrocannabiorcolic acid | | COOH or H | $CH_3$ | H or COOH |
| $\Delta^9$-*trans*-tetrahydrocannabiorcol | $\Delta^9$-THC-$C_1$ | H | $CH_3$ | H |

FIGURE 3. Cannabinoids of the $\Delta^9$-THC type. The most widespread cannabinoids are the phenolic $\Delta^9$-THC with 21 carbon atoms and a $C_5$ side chain ($R_2 = C_5H_{11}$) and its two corresponding carboxylic acids A and B (see Table 1).
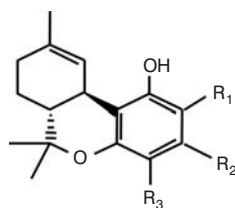


Natural $\Delta^9$-THC has two chiral centers at C-6a and C-10a in the trans configuration. Usually the acronym THC is applied for this naturally occurring $(-)$-*trans*-isomer of $\Delta^9$-THC.

## *Physicochemical Properties and Degradation of $^9$-THC*

$(-)$-$\Delta^9$-*trans*-tetrahydrocannabinol is defined as (6a*R*,10a*R*)-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b,d*]pyran-1-ol with the chemical short formula $C_{21}H_{30}O_2$ and a molecular weight of 314.47 Da. According to the German pharmaceutical monograph, dronabinol contains at least 95% of $\Delta^9$-THC, a maximum of 2% $\Delta^8$-THC and a maximum of 3% other substances, mostly cannabinol and cannabidiol (Kommission Deutscher Arzneimittel-Codex 2001). Dronabinol is avail-

able on prescription for medicinal use in several countries as Marinol™, among them in the USA, Canada, and in some European countries.

At room temperature, $\Delta^9$-THC is a light yellow, resinous sticky oil. $\Delta^9$-THC and many of its metabolites are highly lipophilic and essentially water-insoluble (Garrett and Hunt 1974). Solubility was found to be 2.8 mg/liter in water at 23°(Garrett and Hunt 1974). Calculations of the n-octanol/water partition coefficient ($K_{ow}$) of $\Delta^9$-THC at neutral pH vary between 6,000 using shake-flask methodology (Mechoulam et al. 1981) and 9,440,000 by reverse-phase high-pressure liquid chromatographic estimation (Thomas et al. 1990). The wide range for aqueous solubility and $K_{ow}$, may be attributed to the difficulty of uniformly dissolving this essentially water-insoluble substance and accurately measuring small amounts of it. The spectrophotometric pKa is 10.6 (Garrett and Hunt 1974).

$\Delta^9$-THC is thermolabile and photolabile. Storage leads to a decrease in cumulative THC content through oxidation of THC to CBN (Agurell and Leander 1971, Fairbairn et al. 1976). Within 47 weeks, the THC content of dried cannabis leaves and flowers decreased by 7% with dark and dry storage at 5°C, and by 13% at 20°C (Fairbairn et al. 1976). With additional light exposure, the loss increased threefold to 36%. Degradation in hashish occurs much more quickly (Agurell and Leander 1971) since the cannabinoids are no longer protected against oxidation by glandular trichomes. The manufacturer recommends that dronabinol be stored tightly closed, protected from light and in preferably completely filled containers (N. N. Monographs 2001). Stability of THC and two metabolites (11-OH-THC, THC-COOH) in blood and plasma was high for the first month of storage at $-10$°C, 4°C and room temperature (Johnson et al. 1984). Concentrations of THC stored at room temperature had decreased significantly at 2 months, but was unaltered at 4°C and $-10$°C for up to 4 months.

$\Delta^9$-THC rapidly degrades in acid solutions. The kinetics seems to be first order and specific hydrogen-ion catalyzed (Garrett and Hunt 1974), so that significant degradation of THC was assumed to occur in the normal stomach with a $t_{1/2}$ of 1 hr at pH 1.0 (Garrett and Hunt 1974). Thus, a long exposure of THC in the stomach may considerably decrease the potency of oral cannabis preparations, e.g., when taken together with meals that are difficult to digest.

### PHARMACOKINETICS OF $\Delta^9$-THC

Most available information on the pharmacokinetics of cannabinoids pertains to $\Delta^9$-THC (Figure 4). Other cannabinoids, among them the phytocannabinoids cannabidiol (Samara et al. 1988) and cannabinol (Johansson et al. 1987) and the synthetic derivative dexanabinol (HU-211) (Brewster et al. 1997), show similar kinetic profiles as the major psychotropic constituent of cannabis. Kinetics of cannabinoids are basically much the same for female and male humans (Wall et al. 1983).

Cannabis products are commonly either inhaled by smoking a cannabis cigarette, taken orally as dronabinol capsules (Marinol™), or in baked foods or liquids (see Figure 4), doses ranging in the order of 2.5-40 mg THC. Various other routes of administration and delivery forms have been tested for therapeutic purposes. The rectal route with suppositories has been applied in some patients (Brenneisen et al. 1996), while dermal (Stinchcomb et al. 2001) and sublingual (Guy and Flint 2000) applications are under investigation. Other methods include eye drops to decrease intraocular pressure (Merritt et al. 1981), as well as aerosols and inhalation with vaporizers to avoid the harm associated with smoking (Williams et al. 1976, Lichtman 2000). In February 2002, Unimed Pharmaceuticals, the marketer of Marinol™ capsules, announced its intention to develop a

FIGURE 4. Pharmacokinetic properties of $\Delta^9$-THC. Modified according to Brenneisen (2002).
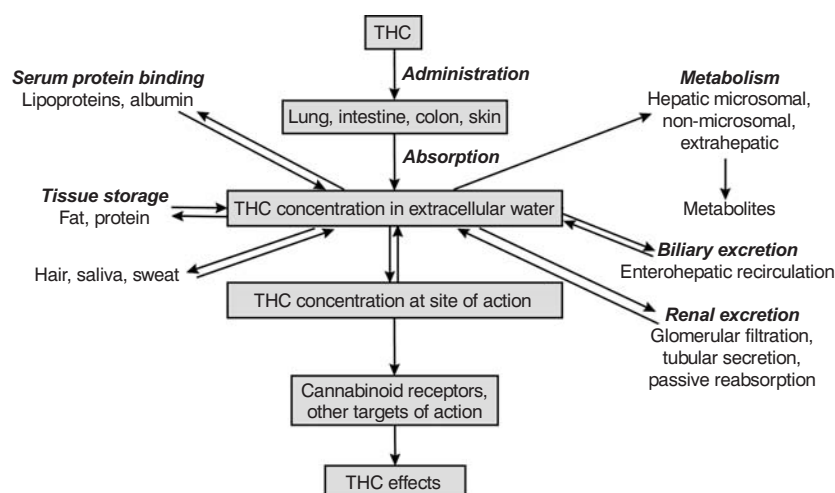
metered dose inhaler (MDI) of dronabinol (IACM Bulletin of 3 March 2002).

## ABSORPTION

Absorption and metabolism of THC varies according to route of administration. The course of plasma concentration following inhalation is similar to that with intravenous administration with a high peak plasma concentration developing within minutes, which then drops quickly (Wall et al. 1983, Ohlsson et al. 1980a). Oral ingestion results in delayed absorption with a flat plasma course achieving its maximum usually after one to two hours (Ohlsson et al. 1980a, Wall et al. 1983, Frytak et al. 1984) (see Table 2).

### Inhalation

Rapid absorption of THC occurs with smoking. THC is detectable in plasma only seconds after the first puff of a cannabis cigarette (Huestis et al. 1992a), with peak plasma concentrations occurring 3 to 10 minutes after onset of smoking (Hollister et al. 1981, Lindgren et al. 1981, Ohlsson

TABLE 2. Systemic Bioavailability of $\Delta^9$-THC Following Inhalation, Oral and Rectal Administration

| Route | Subjects | Systemic bioavailability (%) | | Formulation | References |
|-------|----------|---------|-------|-------------|------------|
| | | Average | Range | | |
| *Oral* | | | | | |
| | 11 frequent or infrequent users | 6 ± 3 | 4-12 | THC in chocolate cookie | Ohlsson et al. 1980 |
| | 6 men, 6 women | 10-20 | | THC in sesame oil | Wall et al. 1983 |
| | 7 men, 10 women | 7 ± 3 | 2-14 | THC in sesame oil | Sporkert et al. 1982 |
| *Inhalation* | | | | | |
| | 9 heavy users | 23 ± 6 | 6-56 | Marihuana cigarette | Lindgren et al. 1981 |
| | 9 light users | 10 ± 7 | 2-22 | Marihuana cigarette | Lindgren et al. 1981 |
| | 5 heavy users | 27 ± 10 | 16-39 | Marijuana cigarette | Ohlsson et al. 1982 |
| | 4 light users | 14 ± 1 | 13-14 | Marijuana cigarette | Ohlsson et al. 1982 |
| | 11 frequent or infrequent users | 18 ± 6 | 8-24 | THC in cigarette | Ohlsson et al. 1980 |
| *Rectal* | | | | | |
| | 2 patients with spasticity | 190-220% of oral bioavailability | | THC-hemisuccinate | Brenneisen et al. 1996 |

et al. 1980a, Chiang and Barnett 1984, Perez-Reyes et al. 1982b, Huestis et al. 1992a) (see Figure 5).

Systemic bioavailability in several studies ranged between 2 and 56% after smoking a marijuana cigarette, generally between about 10 and 35%, with regular users more efficient (see Table 2). Bioavailability varies according to depth of inhalation, puff and breathholding duration. About 30% of THC in a cannabis cigarette is assumed to be destroyed by pyrolysis. With normal smoking behavior, additional THC is lost in the butt, by side-stream smoke, and by incomplete absorption in the lungs.

A systemic bioavailability of 23 ± 16% (Lindgren et al. 1981) and 27 ± 10% for heavy users (Ohlsson et al. 1982) versus 10 ± 7% and 14 ± 1% for occasional users of the drug was reported. In a study with a smoking machine, patterns of cannabis smoking were simulated with regard to puff duration and volume (Davis et al. 1984), resulting in a figure of 16 to 19%

FIGURE 5. Mean plasma levels of THC, 11-OH-THC, and THC-COOH of six subjects during and after smoking a cannabis cigarette containing about 34 mg THC (drawn from a table of Huestis et al. 1992a).
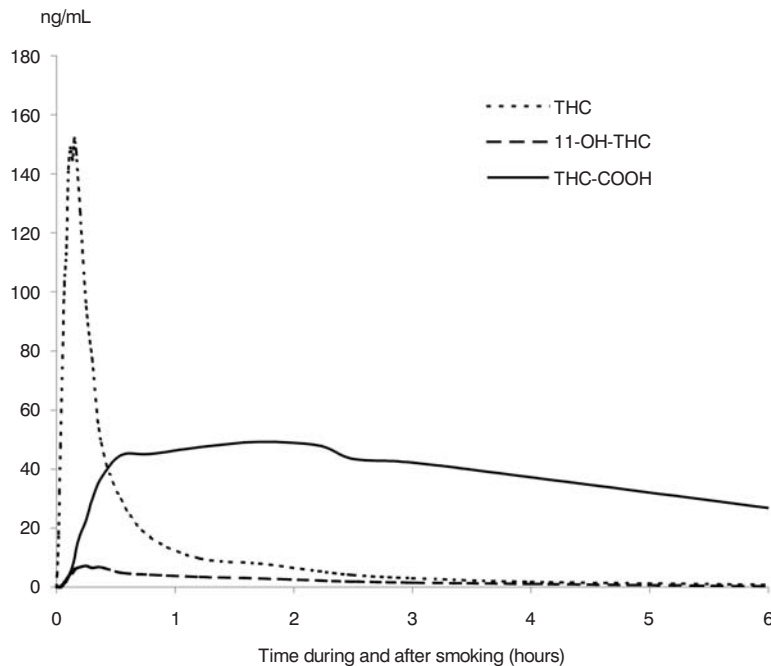
of THC retention in the mainstream smoke. If the whole cigarette was smoked in one puff, the percentage of THC in the mainstream increased to 69%. Smoking a pipe that produces little side stream smoke may also result in high effectiveness with 45% of THC transferred via the mainstream smoke in one smoker tested (Agurell et al. 1971).

Passive smoking has been shown to result in measurable THC plasma concentrations (Cone and Johnson 1986, Perez-Reyes et al. 1983) and subsequent detection of THC metabolites in the urine (Magerl et al. 1987, Cone et al. 1987, Perez-Reyes et al. 1983). Passive exposure of five drug-free volunteers for one hour to 16 marijuana cigarettes in a small unventilated room on six consecutive days resulted in maximal plasma concentrations of 18.8 ng/ml in one participant and several urine positives with the EMIT cannabinoid assay using a cut-off of 20 ng/ml (Cone and Johnson 1986). However, passive inhalation experiments under conditions likely to reflect realistic exposure consistently resulted in values less than 10 ng/ml of cannabinoids in urine (Mule et al. 1988).

### *Oral Administration*

With oral cannabis use, absorption is slow and erratic, resulting in maximal plasma concentrations usually after 60-120 minutes (Ohlsson et al. 1980a, Wall et al. 1983, Timpone et al. 1997) (see Figure 6). In several studies maximal plasma levels were observed as late as 4 hours (Law et al. 1984), and even 6 hours in some cases (Ohlsson et al. 1980a, Frytak et al. 1984). Several subjects showed more than one plasma peak (Ohlsson et al. 1980a, Hollister et al. 1981). Three daily doses of 15 mg of oral THC did not result in significantly higher THC plasma levels than a single dose (Frytak et al. 1984).

$\Delta^9$-THC is expected to be degraded by the acid of the stomach and in the gut (Garrett and Hunt 1974). At low pH, isomerization to $\Delta^8$-THC and protonation of the oxygen in the pyran ring may occur with cleavage to substituted CBDs (Garrett and Hunt 1974). It has been suggested that a somewhat higher bioavailability is obtained in an oil formulation (Harvey and Brown 1991); however, absorption seems to be nearly complete in different vehicles. Ninety-five percent of total radioactivity of radiolabeled THC was absorbed from the gastrointestinal tract in an oil vehicle (Wall et al. 1983) and 90-95% if taken in a cherry syrup vehicle (Lemberger et al. 1972), but it is unclear from these data how much of this radioactivity was attributable to unchanged THC as opposed to its breakdown products.

FIGURE 6. Mean plasma levels of THC, 11-OH-THC, and THC-COOH of six cancer patients after ingestion of one oral dose of 15 mg THC (estimated from single graphs for each patient of Frytak et al. 1984, with permission). The plasma courses of THC showed considerable interindividual variation (see Figure 8 for the courses of THC plasma concentrations of three patients).
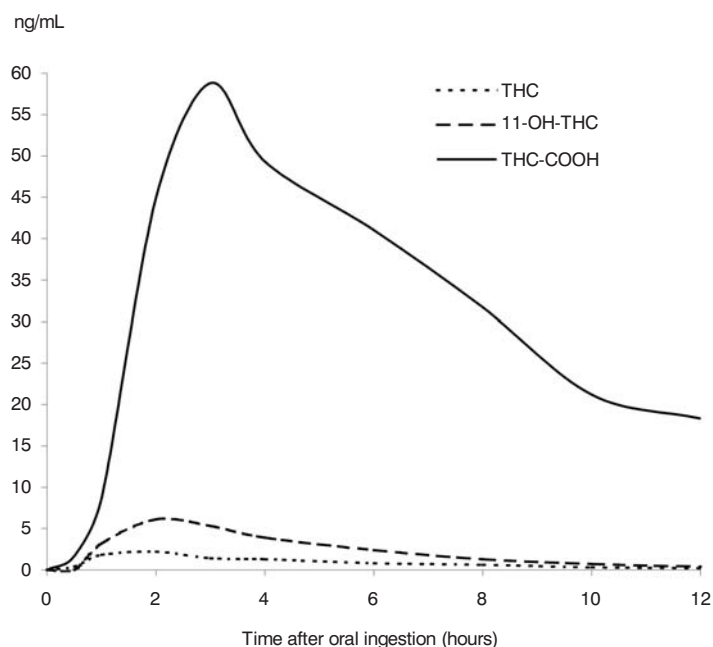


An extensive first pass liver metabolism further reduces oral bioavailability of THC, i.e., much of the THC is initially metabolized in the liver before it reaches the sites of action. Ingestion of 20 mg THC in a chocolate cookie (Ohlsson et al. 1980a) and administration of 10 mg dronabinol (Sporkert et al. 2001) resulted in a systemic bioavailability of 6 ± 3% (range: 4-12%) or 7 ± 3% (range: 2-14%) with a high inter-individual variation (see Table 2).

## Ophthalmic Administration

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

### Rectal Administration

With rectal application, systemic bioavailability strongly differed depending on suppository formulations. Among formulations containing several polar esters of THC in various suppository bases, THC-hemisuccinate in Witepsol H15 showed the highest bioavailability in monkeys and was calculated to be 13.5% (ElSohly et al. 1991). The rectal bioavailability of this formulation in man was calculated to be about as twice as high (190-220%) as oral bioavailability in a small clinical study (Brenneisen et al. 1996).

### Sublingual Administration

Clinical studies are under way using a liquid cannabis extract applied under the tongue. A phase 1 study in six healthy volunteers receiving up to 20 mg THC was reported to result in "relatively fast" effects (Guy et al. 2000). In phase 2 studies, THC plasma concentrations of up to 14 ng/ml were noted (Notcutt et al. 2001).

### Dermal Administration

A few experimental studies have investigated the skin permeation behavior of THC (Touitou and Fabin 1988a, Touitou et al. 1988b, Stinchcomb et al. 2001). In a study using the more stable $\Delta^8$-THC isomer the permeability coefficient of THC was significantly enhanced by water and by oleic acid in propylene glycol and ethanol (Touitou et al. 1988a). Significant THC concentrations in the blood of rats treated with formulations containing 26.5 mg/g THC were measured. Recent studies designed to develop transdermal delivery of cannabinoids found a mean effective permeability coefficient for $\Delta^9$-THC in propylene glycol of $6.3 \times 10^{-6}$ cm/h (Stinchcomb et al. 2001).

## DISTRIBUTION

Tissue distribution of THC and its metabolites are assumed to be governed only by their physicochemical properties, with no specific transport processes or barriers affecting the concentration of the drug in the tissues (Leuschner et al. 1986).

About 90% of THC in the blood is distributed to the plasma, another 10% to red blood cells (Widman et al. 1974); 95-99% of plasma THC is bound to plasma proteins, mainly to lipoproteins (Widman et al. 1974, Hunt and Jones 1980, Wahlqvist et al. 1970, Fehr and Kalant 1974) and less to albumen. Only 5% or less of THC is free for pharmacological activity. The metabolite 11-OH-THC appears to be even more strongly bound than the parent molecule (Harvey 1984). Protein binding of THC metabolites was lower in early phases, with values of 88-93% after 21 and 70 min of intravenous THC application, compared to 92-99% after 240-1,500 min (Hunt and Jones 1980).

The course of plasma concentrations of cannabinoids has been described to correspond to an open two (Wall et al. 1983, Lemberger et al. 1971), three (Barnett et al. 1982, Timpone et al. 1997, Brewster et al. 1995) or four (Hunt and Jones 1980) compartment model. Even five and six compartment concepts have been found in computer models to best fit the THC plasma course in animals (Leuschner et al. 1986). Following an absorption phase, a distribution phase is distinguished from a plasma elimination phase (two compartment model), that may be distinguished from one or more intermediate phases.

The apparent (initial) volume of distribution of THC is small for a lipophilic drug, equivalent to the plasma volume of about 2.5-3 L, reflecting high protein binding that complicates initial disposition. It was reported to be 2.55 ± 1.93 L in drug free users (Hunt and Jones 1980) and 6.38 ± 4.1 in chronic user (Hunt and Jones 1980). The steady state volume of distribution has been estimated to be more than 100 times larger, in the range of about 10 L/kg (Lemberger et al. 1971, Hunt and Jones 1980, Wall et al. 1983). These early data have been questioned because of possible inaccuracy of the quantification methods used. With the use of radiolabeled THC, some metabolites might have been considered to be THC. Based on pharmacokinetic data of two studies (Hollister et al. 1981, Lindgren et al. 1981) that applied gas chromatography/mass spectrometry (GC/MS) for analysis of THC concentration an average volume of distribution of 236 L or 3.4 L/kg (assuming a 70kg body weight) has been calculated (Sticht and Käferstein 1998). Even smaller steady state volumes of distribution of about 1 L/kg have been reported with GC/MS (Kelly and Jones 1992). This volume is still about 20 times the plasma volume since the majority of the lipophilic drug is in the tissues.

### *Distribution to Tissues and Redistribution*

The lipophility of THC with high binding to tissue, and in particular to fat, causes a change of distribution pattern over time (Ryrfeldt et al. 1973). THC distribution may be divided into several phases representing several pharmacokinetic compartments (Leuschner et al. 1986) or different composites of tissues into which the cannabinoid is distributed (Chiang and Rapaka 1987). Hunt and Jones (1980) estimated that 70% of THC initially leaving the central compartment is taken up by tissues and 30% is converted via metabolism. THC rapidly penetrates highly vascularized tissues, among them liver, heart, fat, lung, jejunum, kidney, spleen, mammary gland, placenta, adrenal cortex, muscle, thyroid, and pituitary gland, resulting in a rapid decrease in plasma concentration (Ho et al. 1970). Low concentrations were found in the brain, testis and the fetus (Hutchings et al. 1989, Bailey et al. 1987, Ho et al. 1970). Only about 1% of THC administered IV is found in the brain at the time of peak psychoactivity (Gill and Jones 1972). Penetration of the major THC metabolite 11-OH-THC into the brain seems to be faster and higher than that of the parent compound (Perez-Reyes et al. 1976). A ratio of 6:1 has been reported by Gill and Jones (1972). In humans, 11-OH-THC has a similar kinetic profile (Wall et al. 1976) and is as potent as THC in eliciting psychoactive and other effects (e.g., decrease of intraocular pressure) (Perez-Reyes et al. 1972). Thus, it can be expected that the metabolite will significantly contribute to the overall central effects of THC, especially with oral use, but also with inhalation to a lesser degree.

Subsequently intensive accumulation occurs in less vascularized tissues, and finally in body fat (Agurell et al. 1970, Johansson et al. 1989b, Kreuz and Axelrod 1973), the major long-term storage site, resulting in concentration ratios between fat and plasma of up to $10^4$:1 (Harvey et al. 1982), while the concentration in the brain was reported to be only three to ten times higher than in plasma (Harvey 1984). Studies with tritium labeled THC determined maximal levels of radioactivity in kidneys and lung after 2 h, whereas after 72 h highest levels were found in spleen and body fat (Agurell et al. 1970), levels in body fat still increasing after 28 days of chronic administration (Kreuz and Axelrod 1973). In humans, up to 193 ng/g of wet tissue were found in fat tissues four weeks after smoking radiolabeled THC (Johansson et al. 1989b). The relatively low concentration in brain is supposed to be due to the fact that the brain is well perfused, moving THC in and out of the brain quickly (Chiang and Rapaka 1987).

The exact composition of the material accumulated in fat is unknown (Harvey 1991), among the possibilities being unaltered THC and its hydroxy metabolites (Kreuz and Axelrod 1973). A substantial proportion of the deposits in fat seems to consist of fatty acid conjugates of 11-OH-THC (11-palmityloxy-THC, 11-stearyloxy-THC, 11-oleyloxy-THC, 11-linoleyloxy-THC) (Haggerty et al. 1986, Leighty et al. 1976). These conjugates have a more lipophilic character than THC itself (Leighty et al. 1976).

### Distribution to Fetus and Breast Milk

In animal and man $\Delta^9$-THC rapidly crosses the placenta (Blackard and Tennes 1984). The course of THC levels in fetal blood fairly coincides with that in the maternal blood, though fetal plasma concentrations were found to be lower compared to the maternal level in rats (Hutchings et al. 1989), sheep (Abrams et al. 1985-1986), dogs (Martin et al. 1977), and monkeys (Bailey et al. 1987). The metabolites 11-OH-THC and THC-COOH cross the placenta much less efficiently than THC (Bailey et al. 1987, Martin et al. 1977).

Following oral intake, THC plasma concentrations in the fetus seem to be much lower, about one tenth of the maternal plasma concentration (Hutchings et al. 1989), compared to intravenous and inhalation THC intake, with about one third of the maternal plasma concentration (Martin et al. 1977, Abrams et al. 1985-1986), reflecting differences in metabolism. In humans, THC in cord blood was found to be 3 to 6 times lower than concentrations in maternal blood (Blackard and Tennes, 1984). Thus, oral intake may be less toxic for the fetus compared to inhalation. Additionally, there seems to be a considerable variation in fetal exposure to maternal THC in dependency of placenta function. In a twin study with six dizygotic pairs (where each of the twins has an individual placenta) there were large differences between the pairs in cannabinoid concentrations in hair and meconium (Boskovic et al. 2001). Given that twins are theoretically exposed to similar maternal drug levels, these findings suggest that the placenta may have a major role in modulating the amounts of THC reaching the fetus. The ratio of concentrations in maternal and fetal plasma was maintained with multiple administrations (Martin et al. 1977, Hutchings et al. 1989), indicating that the maternal plasma THC and not the fetal tissue is the actual source for the fetal plasma THC.

THC passes into the breast milk. In monkeys 0.2% of the THC ingested by the mother appeared in the milk (Chao et al. 1976). Chronic adminis-

tration leads to accumulation (Perez-Reyes and Wall 1982a). In a human female the THC concentration in milk was 8.4 times higher than in plasma (Perez-Reyes and Wall 1982a). Thus, the nursing infant might ingest daily THC amounts in the range of about 0.01-0.1 mg from the milk of her mother who is consuming 1-2 cannabis cigarettes a day, assuming an average daily ingestion of 700 ml milk.

### *Distribution to Saliva and Sweat*

THC has been detected in oral fluid (saliva) and forehead wipes (sweat) in 16 of 198 injured drivers admitted to an emergency hospital (Kintz et al. 2000). Concentrations varied between 1 and 103 ng/salivette in oral fluid and between 4 and 152 ng/pad in sweat of the forehead applying GC/MS technology. In a study by Niedbala et al. (2001) with ten volunteers who had been administered single doses of marijuana by smoked and oral routes, THC was detectable in oral fluid for an average of 34 h with a high interindividual variability (range: 1-72), and THC-COOH for 13 h (range: 1-24) by gas chromatography-tandem mass spectrometry (GC-MS-MS) with a 0.5-ng/ml cutoff concentration.

Results of roadside studies using screening devices (immunoassays) for saliva and sweat have provided conflicting results with regard to sensitivity. While screening methods show high sensitivity and specifity for the hydrophilic amphetamines and opiates, they are less sensitive for the lipophilic cannabinoids (Gronholm and Lillsunde 2001). High rates of false negative and false positives have been observed (Samyn and van Haeren 2000, Mura et al. 1999), while others reported good correlation of screening results with later GC/MS analysis of the blood; at least positive results in the screening could mostly be confirmed by GC/MS (Steinmeyer et al. 2001).

### *METABOLISM*

Metabolism of THC occurs mainly in the liver by microsomal hydroxylation and oxidation catalyzed by enzymes of the cytochrome P-450 complex (Matsunaga et al. 1995, Narimatsu et al. 1992), a member of the CYP2C subfamily of isoenzymes playing the major role in humans (Watanabe et al. 1995). Because of its high lipophility, THC needs considerable structural modification to ease excretion. Metabolism of THC occurs fats. In rats more than 80% of intravenous THC was metabolized within 5 minutes (Alozie et al. 1980).

Metabolic rates show relevant interspecies differences that may be in part responsible for some problems of interspecies extrapolation of pharmacological and toxicological effects (Grotenhermen 2002b). Borys and Karler (1979) found three times higher metabolic rates in mice than in rats. Differences in composition of metabolic compounds may be attributed to different profiles of cytochrome P-450 isoenzymes (Harvey and Brown 1991). In humans, allylic oxidation, epoxidation, alphatic oxidation, decarboxylation and conjugation have been described (Chiang and Rapaka 1987) (see Figures 7 and 8).

Besides the liver, other tissues are able to metabolize cannabinoids, but to a much lesser degree, among them the heart and the lung (Nakazawa and Costa 1971, Widman et al. 1975, Harvey and Paton 1976). Nearly 100 metabolites have been identified for THC (Harvey and Brown 1991). Biotransformation of THC produces mono-, di-, and tri-hydroxy metabolites (Wall et al. 1972, Lemberger et al. 1970, Lemberger et al. 1971). Further oxidation results in a series of carboxylic acids and their hydroxy derivatives (Wall et al. 1981).

Major metabolites are monohydroxylated compounds, but the pattern of hydroxylation varies considerably between species (Harvey and Brown 1991). In man (Widman et al. 1978, Halldin et al. 1982, Wall 1971) and many other species, among them mouse, rat, guinea pig, rabbit and gerbil (Harvey and Paton 1976, Harvey and Brown 1991) C-11 is the major site attacked (see Figure 7). Hydroxylation results in 11-hydroxy-THC (11-OH-THC), and further oxidation in 11-nor-9-carboxy-THC (THC-COOH). THC-COOH may be glucuronated to 11-nor-9-carboxy-THC beta-glucuronide. Long-chain fatty acid conjugates of 11-OH-THC are proposed to be a form in which THC may be stored within tissues (Leighty 1973). The C-8 position is also attacked in humans but to a much lesser degree than C-11 (Widman et al. 1978, Halldin et al. 1982a).

Average plasma clearance rates have been reported to be 197 ± 50 ml/min for females and 248 ± 62 ml/min for males (Wall et al. 1983) while others reported higher clearance rates of 760-1190 ml/min (Ohlsson et al. 1982) or 605 ± 149 ml/min for naive THC users and 977 ± 304 ml/min for chronic users (Hunt and Jones 1980) (Table 3). The higher values are similar to the volume of hepatic blood flow, indicating that it is the limiting step of the metabolic rate. These high clearance rates explain the high degree of first pass metabolism, the low systemic bioavailability of THC after oral use and the much higher concentration of 11-OH-THC after oral administration compared to inhalation.

FIGURE 7. Main metabolic pathways of THC.

Fatty acid conjugate

$11\ CH_3 \rightarrow CH_2OH \rightarrow COOH \rightarrow CO\text{-}O\text{-}Glucuronide$
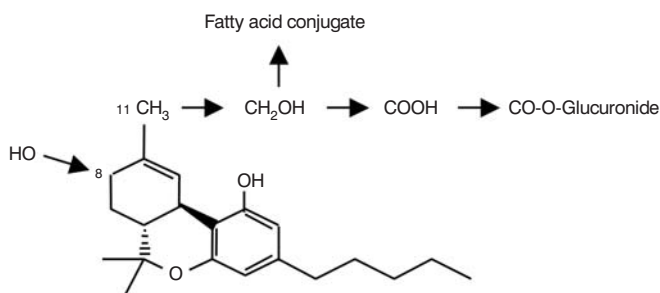
FIGURE 8. Summary of metabolic pathways of THC (modified according to Harvey 1991).
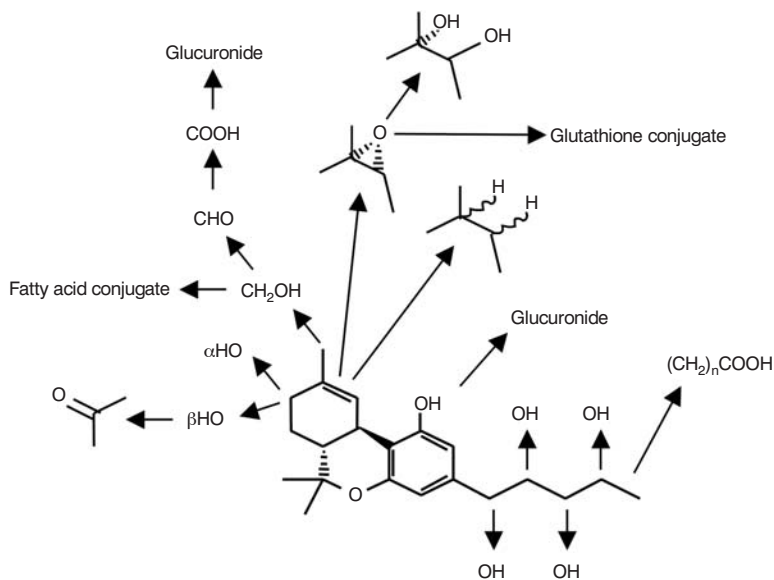
Only slight differences in pharmacokinetic parameters were observed after single and repeat dosing, indicating that the tolerance after chronic THC administration is not or only slightly due to altered metabolism or excretion after repeated dosing (Hunt and Jones 1980). Neither enzyme induction nor enzyme inhibition appear to have much effect on metabolic clearance of THC.

TABLE 3. Pharmacokinetic Data for $\Delta^9$-THC

| | Subjects | Dosage (mg) | AUC (ng/ml) × min | $C_{max}$ (ng/ml) | $t_{1/2\beta}$ (h) | $V_D$ (L) | $Cl_T$ (ml/min) | References |
|---|---|---|---|---|---|---|---|---|
| *Intravenous* | | | | | | | | |
| | 4 non-users | 0.5 | | | 57 ± 4 | 658 ± 174 | | Lemberger et al. 1971 |
| | 5 regular users | 0.5 | | | 27 ± 1 | 597 ± 76 | | Lemberger et al. 1971 |
| | 6 males (drug free) | 2 | | | 19.6 ± 4.1 | 626 ± 296 | 605 ± 149 | Hunt and Jones 1980 |
| | 6 males (chronic) | 2 | | | 18.7 ± 4.2 | 742 ± 331 | 977 ± 304 | Hunt and Jones 1980 |
| | 6 males | 4 | | 70 ± 30 | 36 | 734 ± 444 | 248 ± 62 | Wall et al. 1983 |
| | 6 females | 2.2 | | 85 ± 26 | 29 | 523 ± 217 | 197 ± 50 | Wall et al. 1983 |
| | 11 males | 5 | 4330 ± 620 | 161-316 | | | | Hollister et al. 1981, Ohlsson et al. 1980 |
| | 9 heavy users | 5 | 4300 ± 1670 | 288 ± 119 | | | | Lindgren et al. 1981 |
| | 9 light users | 5 | 6040 ± 2.21 | 302 ± 95 | | | | Lindgren et al. 1981 |
| | 5 heavy users | 5 | 5180 ± 830 | | > 20 | | 980 ±150 | Ohlsson et al. 1982 |
| | 4 light users | 5 | 5460 ± 1180 | | > 20 | | 950 ± 200 | Ohlsson et al. 1982 |
| | 4 heavy users | 5 | 9908 ± 3785 | 438 ± 36 | 1.9 ± 0.3 | 75 ± 16 | 777 ± 690 | Kelly and Jones 1992 |
| | 4 light users | 5 | 7094 ± 2248 | 386 ± 29 | 1.6 ± 0.5 | 74 ± 35 | 771 ± 287 | Kelly and Jones 1992 |
| *Oral* | | | | | | | | |
| | 6 males | 20 | | 14.5 ± 9.7 | 25 | | | Wall et al. 1983 |
| | 6 females | 15 | | 9.4 ± 4.5 | 25 | | | Wall et al. 1983 |
| | 11 males | 20 | 1020 ± 320 | 4.4-11 | | | | Hollister et al. 1981, Ohlsson et al. 1980 |
| | 3 males | 3 × 15 | | 4-6 | | | | Frytak et al. 1984 |
| | 3 males, 3 females | 15 | | 3-5 | | | | Frytak et al. 1984 |
| | 20 AIDS patients | 2 × 2.5 | | 2.01 (0.58-12.48) | | | | Timpone et al. 1997 |
| | 7 men, 10 women | 10 | 610 ± 310 | 4.7 ± 3.0 | | | | Sporkert et al. 2001 |

|  | Subjects | Dosage (mg) | AUC (ng/ml) × min | $C_{max}$ (ng/ml) | $t_{1/2\beta}$ (h) | $V_D$ (L) | $Cl_T$ (ml/min) | References |
|---|---|---|---|---|---|---|---|---|
| *Inhalation* | | | | | | | | |
|  | 11 males | 19 | 1960 ± 650 | 33-118 | | | | Hollister et al. 1981, Ohlsson et al. 1980 |
|  | 9 heavy users | 19 | 2160 ± 1030 | 98 ± 44 | | | | Lindgren et al. 1981 |
|  | 9 light users | 19 | 1420 ± 740 | 67 ± 38 | | | | Lindgren et al. 1981 |
|  | 5 heavy users | 10 | 2450 ± 530 | | | | | Ohlsson et al. 1982 |
|  | 4 light users | 10 | 1420 ± 340 | | | | | Ohlsson et al. 1982 |
|  | 6 males | 15.8 | | 84 (50-129) | | | | Huestis et al. 1992a |
|  | 6 males | 33.8 | | 162 (76-267) | | | | Huestis et al. 1992a |

AUC = Area under the curve; $C_{max}$ = Maximum plasma concentration; $t_{1/2\beta}$ = plasma elimination half-life; $Cl_T$ = total clearance; $V_D$ = volume of distribution

## COURSE OF PLASMA CONCENTRATION OF THC AND METABOLITES

Intravenous infusion of 5 mg THC over 2 min caused average plasma levels within 2 min after the end of infusion of 438 ng/ml in frequent and of 386 ng/ml in infrequent users, that fell rapidly to an average of 25 and 20 ng/ml at 90 min (Kelly and Jones 1992).

The course of plasma THC levels after inhalation resembles that after iv administration (Perez-Reyes et al. 1982b, Huestis et al. 1992a). Smoking a single cannabis cigarette containing 16 or 34 mg THC caused average peak levels of 84.3 ng/ml (range: 50.0-129.0) for the lower dose and 162.2 ng/ml (range: 76.0-267.0) for the higher dose, than rapidly decreased to low levels of about 1-4 ng/ml within 3-4 h (Huestis et al. 1992a) (see Figure 5).

The maximal THC plasma level after smoking a marijuana cigarette (3.55% THC) was reported to exceed the maximal THC-COOH level by threefold and 11-OH-THC by twentyfold (Huestis et al. 1992a). However, THC/11-OH-THC ratios declined and reached a ratio of about 2:1 after 2-3 h (Huestis et al. 1992a). Peak concentrations for THC were observed 8 min (range: 6-10) after onset of smoking. After onset of smoking, 11-OH-THC peaked 15 min (range: 9-23) and THC-COOH peaked 81 min (range: 32-133) (Huestis et al. 1992a).

After oral application the THC plasma concentration shows a flat course with peaks ranging from 4.4-11 ng/ml following 20 mg THC (Ohlsson et al. 1980a), from 2.7-6.3 ng/ml with 15 mg THC (Frytak et al. 1984) and from 0.58-12.48 ng/ml with 2.5 mg THC (Timpone et al. 1997). The plasma course of THC and 11-OH-THC is much more variable than after smoking (see Figure 9). Much higher amounts of 11-OH-THC are formed as with inhalative or intravenous application (Wall et al. 1983, Frytak et al. 1984, Brenneisen 1996). In a study by Wall et al. (1983) the ratio of THC and 11-OH-THC plasma levels in men and women was about 2:1 to 1:1. In several clinical studies (Frytak et al. 1984, Timpone et al. 1997) 11-OH-THC levels even exceeded the THC levels in patients. In a clinical study with 2.5 mg dronabinol daily medium maximal THC levels were 2.01 ng/ml compared to 4.61 ng/ml 11-OH-THC (Timpone et al. 1997).

FIGURE 9. Mean plasma levels of THC, 11-OH-THC, and THC-COOH of three of the six cancer patients of Figure 6 after ingestion of one oral dose of 15 mg THC (estimated from graphs of Figure 2 of Frytak et al. 1984).
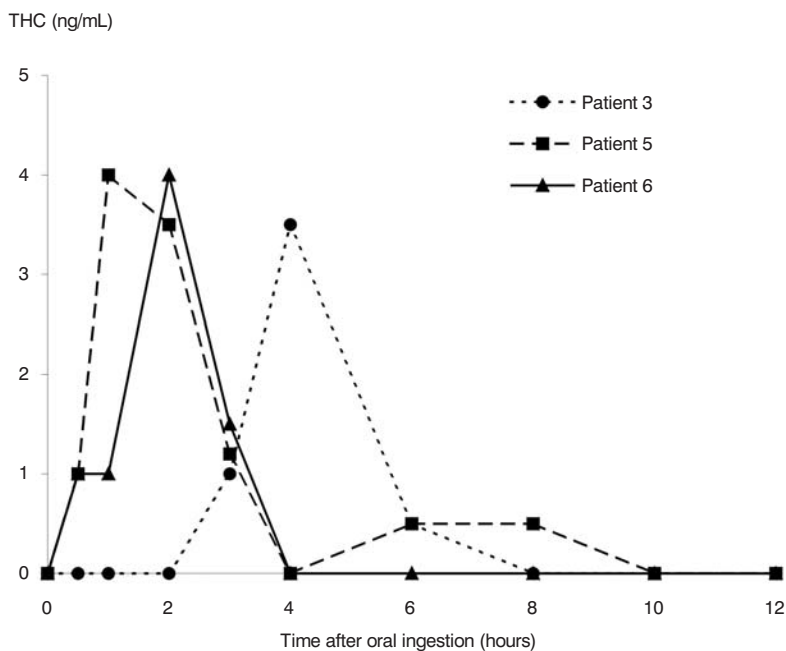
## ELIMINATION

### Elimination from Plasma

About 6 hours after intravenous dosing of THC a pseudoequilibrium is reached between plasma and tissues (Chiang and Rapaka 1987). Concentration in plasma usually has dropped below 2 ng/ml at this time and then decreases more slowly with increasing time from use (Perez-Reyes et al. 1982b, Huestis 1992a). Residual THC plasma levels may persist in frequent cannabis users for several days after last use and may cause difficulties in predicting time of inhalation from THC plasma levels (Huestis et al. 1992b).

After smoking a low dose cannabis cigarette (1.75% THC, about 16 mg) the detection limit of 0.5 ng/ml THC in plasma was reached after 7.2 h (range: 3-12 h) and following a high dose cigarette (3.55% THC, about 34 mg) a plasma concentration of 0.5 ng/ml THC was reached within 12.5 h (range: 6-27 h). Metabolites disappear more slowly. THC-COOH was detectable for 3.5 days (range: 2-7 d) after the low dose and for 6.3 days (range 3-7 days) after smoking the high dose cigarette (Huestis 1992a). After a single oral dose of 20 mg overall $\Delta^9$-THC metabolites reached the detection limit of 0.4 ng/ml in plasma after five days (Law et al. 1984).

The major reason for the slow elimination of THC from the plasma is the slow rediffusion of THC from body fat and other tissues into the blood (Leuschner et al. 1986).

The true elimination half-life of THC from the plasma is difficult to calculate, as the concentration equilibrium ratio plasma/fatty tissue is only slowly reached, resulting in very low plasma levels that are difficult to analyze. In a study by Wall et al. (1983) the terminal phase $t_{1/2\beta}$ ranged from 25-36 h for THC, from 12-36 h for 11-OH-THC and from 25-55 h for THC-COOH after oral or intravenous dosing in man and women. The plasma concentration was followed for 72 h in this study, not long enough to determine the half life accurately. Similar elimination half lives for THC in the range of 20-30 h covering similar periods have been reported by others (Lemberger et al. 1971, Hunt and Jones 1980, Ohlsson et al. 1982).

Longer half-lives of THC plasma elimination have been determined after higher doses and longer periods of measurement in animals (Harvey et al. 1982) and humans (Johansson et al. 1989a). In a study by Johansson et al. (1989a), regular users of cannabis were asked to smoke 56 mg radiolabeled THC during two days and then abstain from all cannabis use.

A terminal half-life of 4.3 ± 1.6 days has been determined in five subjects whose plasma levels were followed for 2 weeks. In two subjects followed for four weeks terminal half-lives of 9.6 and 12.6 d were noted. However, it is unclear whether THC could be reliably distinguished from its metabolites in this study, thus overestimating the length of the half live (Kelly and Jones 1992). Studies using sensitive GC/MC that follow THC plasma concentrations for long periods are needed to determine the elimination half life of THC from plasma. Kelly and Jones (1992) measured a terminal half life for THC of only 117 min for frequent and 93 min for infrequent users, applying GC/MS technology.

The elimination half life for THC metabolites from plasma is longer than the elimination half life of the parent molecule. In a study by Hunt and Jones (1980), the terminal half life of THC for chronic users was 18.7 ± 4.2 h and of the overall metabolites 52.9 ± 3.7 h. In the study by Kelly and Jones (1992), the plasma elimination half life for THC-COOH was 5.2 ± 0.8 days for frequent and 6.2 ± 6.7 days for infrequent cannabis users.

Studies in humans have found no difference in elimination kinetics between heavy and light users (Ohlsson et al. 1982, Hunt and Jones 1980). Differences between regular and casual users in an earlier study (Lemberger et al. 1971) may be attributed to insufficiencies of the detection method (Cone and Huestis 1993). No relevant differences between men and women have been noted (Wall et al. 1981).

### *Excretion with Urine and Feces*

THC is excreted within days and weeks, mainly as metabolites, about 20-35% in urine and 65-80% in feces, less than 5% of an oral dose as unchanged drug in the feces (Wall et al. 1983, Hunt and Jones 1980). After three days overall excretion rates were about 65% following oral, and about 45% with intravenous administration (Wall et al. 1983) (see Table 4). Excretion rates for urine were similar with both routes of application, but excretion rate in feces were substantially higher after oral use.

After smoking cannabis, the urine started to test positive for THC-COOH by GC/MS after an average time of 4 hours (range: 2-8 h) (Niedbala et al. 2001). A single dose of THC may result in detectable metabolites in urine for up to 12 days (Law et al. 1984), usually for 3-5 days (Schwartz et al. 1985). In one study, the average time to the first negative result in urine screening for THC metabolites (enzyme immunoassay with a cutoff calibration of 20 ng/ml) was 8.5 days (range: 3-18 d) for infrequent users and 19.1 days (range: 3-46 d) for regular users (Ellis et al. 1985).

TABLE 4. Mean Cumulative Cannabinoid Excretion According to Wall et al. (1983)

| Subjects | Urine (%) | | Faeces (%) | | Total (%) | % of Total in Urine |
|---|---|---|---|---|---|---|
| | 24 h | 72 h | 24 h | 72 h | 72 h | 72 h |
| Women Intravenous | 11 ± 2 | 16 ± 3 | 9 ± 11 | 26 ± 19 | 42 | 38.1 |
| Men Intravenous | 10 ± 5 | 15 ± 4 | 14 ± 11 | 35 ± 11 | 50 | 30.0 |
| Women Oral | 12.5 ± 3.0 | 15.9 ± 3.6 | 9 ± 11 | 48 ± 6 | 63.9 | 24.9 |
| Men Oral | 10.3 ± 2.1 | 13.4 ± 2.0 | 24 ± 42 | 53 ± 18 | 66.4 | 20.2 |

Since urine excretion of metabolites does not monotonously decrease, urine screenings may fluctuate between positive and negative results for several days (see Figure 10). The average time until the latest positive result was 12.9 d (3-29 d) for light users and 31.5 d (4-77 d) for heavy users (Ellis et al. 1985). Similar results with detection times of up to 1-2 months for regular cannabis users and even longer in single cases were reported by others (Daldrup et al. 1988).

An average urinary excretion half life for THC-COOH of about 30 h was observed with a 7-day monitoring period and of 44-60 h with a 14-day period (Huestis et al. 1998). Other groups calculated similar average values of 1.9 and 2 days for frequent and infrequent cannabis users with a 12-day monitoring period (Kelly and Jones 1992) and of about 3 days (range: 0.9-9.8 days) when THC-COOH was measured for 25 days (Johansson and Halldin 1989).

Mainly acids are excreted with the urine of which 18 have been identified (Halldin et al. 1982a, 1982b), the main metabolite being the acid glucuronide of THC-COOH (Williams and Moffat 1980). Free THC-COOH is not excreted in the urine in significant concentration (Law et al. 1984). It was proposed that unconjugated THC-COOH cannot be detected in urine of infrequent users (Alburges and Peat 1986), while others found free THC-COOH concentrations of 1 ± 1.5 ng/ml one day after intravenous administration of THC in casual cannabis smokers (Kelly and Jones 1992). In regular users, free THC-COOH is usually found and was present in concentrations of 2.8 ± 2.7 ng/ml one day after intravenous administration of THC (Kelly und Jones 1992). The detection of 8β,11-dihydroxy-THC above levels of 15-20 ng/ml was proposed to be indicative of use within the previous 4 to 6 hr (McBurney et al. 1986).

Several authors reported that the concentrations of THC and 11-OH-THC in urine were insignificant (Garrett and Hunt 1974, Wall and

FIGURE 10. Course of urine concentration of THC-COOH in one infrequent and two frequent users who abstained from cannabis use at day 0, measured with enzyme immunoassay (EMIT) (drawn according to data of Ellis et al. 1985).
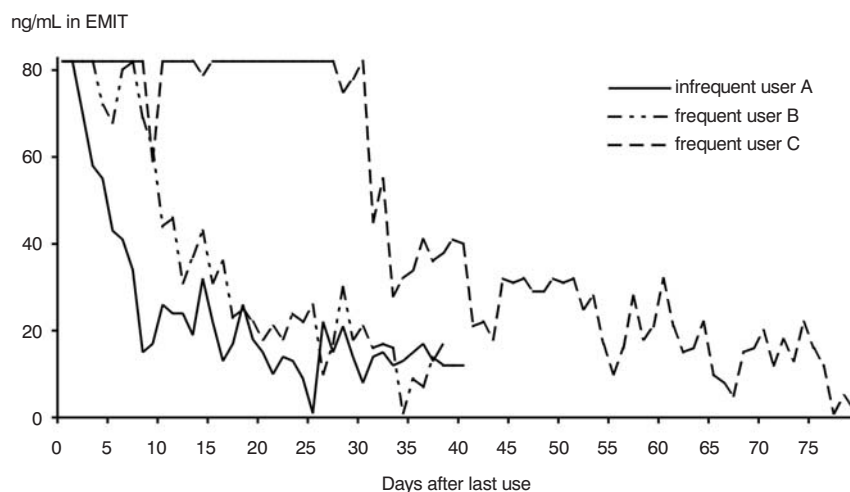


Perez-Reyes 1981), but a recent study found significant concentrations of these neutral cannabinoids using an enzymatic hydrolysis step in the extraction protocol, with THC concentrations peaking at 21.5 ng/ml (range: 3.2-53.3) after 2 h of smoking 27 mg THC in cannabis cigarettes, 11-OH-THC peaking at 77.3 ± 29.7 ng/ml after 3 h and THC-COOH peaking at 179.4 ± 146.9 ng/ml after 4 h (Manno et al. 2001) (see Figure 11).

Renal clearance is not constant, and has been reported to decrease from a maximum of 20 ml/min at approximately 100 min to 1 ml/min after 4 days of THC administration (Hunt and Jones 1980). The high lipophilicity of THC resulting in complete tubular reabsorption explains the lack of significant renal excretion of the unchanged drug (Garrett and Hunt 1974).

The marked enterohepatic recirculation of metabolites and the high protein binding explains the dominance of fecal excretion. The metabolites in the feces are only present in the non-conjugated form (Wall et al. 1983). Acids metabolites, among them THC-COOH, and neutral metabolites, in particular 11-OH-THC, have been found (Mikes et al. 1971, Wall et al. 1983). Differences in metabolite composition have been reported in

FIGURE 11. Mean urine concentrations of unchanged THC and its major metab-olites after smoking a cannabis cigarette containing about 27 mg THC by eight subjects with self-reported history of light marijuana use (1-3 cigarettes per week or less). One subject later admitted regular use and presented with high baseline concentrations of 11-OH-THC and THC-COOH (drawn from a table of Manno et al. 2001).

ng/mL (mean)



Time after smoking (hours)
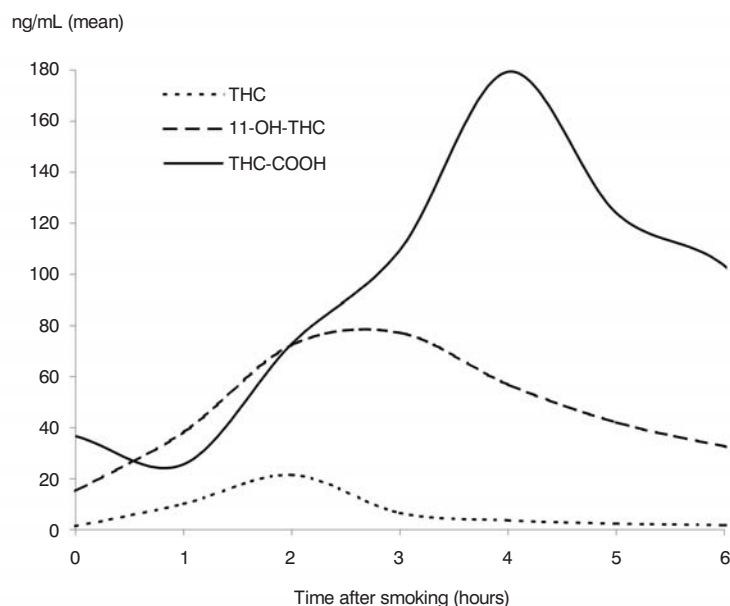
dependency of route of administration for excretion in both urine and fe-ces. More unaltered THC, less of the hydroxy metabolite and more THC-COOH is excreted in feces after oral compared to intravenous dos-ing (Wall et al. 1983).

## *TIME EFFECT RELATIONSHIP*

The peak psychotropic effects ("high") after intravenous and inhalative THC application were noted after 20-30 min and decreased to low-level after 3 h and to baseline after 4 h (Hollister et al. 1981, Lindgren et al. 1981, Chiang and Barnett 1984) (see Figure 12). Maximum increase of heart rate was noted within a few minutes (1-5 min), decreasing to base-line after 3 h (Lindgren et al. 1981). Conjunctival injection was noted

within a few minutes and subsided in some participants by 3 h after smoking (Ohlsson et al. 1980a). Duration of maximal effects is dose dependent and was found to be 45 min after 9 mg THC (Harder and Rietbrock 1997) and more than 60 min with higher doses (Robbe 1994).

Following inhalation, THC plasma concentrations have already dropped significantly before maximal psychotropic effects are achieved (Chiang and Barnett 1984, Ohlsson et al. 1980a). A plot of THC plasma levels versus THC effects shows a counterclockwise hysteresis (Chiang and Barnett 1984). During the first 15 minutes the intensity of psychic effects is still rising while plasma levels are falling (Ohlsson et al. 1980a). It has been proposed that the first hour represents the distribution phase (Sticht and Käferstein 1998) and that after 1 h the central compartment has reached equilibrium with effect compartment (Chiang and Barnett 1984). Hence, about 1-4 h after smoking there is a good correlation between plasma level and effects (Chiang and Barnett 1984). There was also a good correlation between THC plasma level and other effects in this phase, with heart rate (Cocchetto et al. 1981) and with psychomotor impairment (Barnett et al. 1985). Overall correlations between log plasma concentrations and ratings of "high" were reported to be moderately positive (r = 0.53) (Ohlsson et al. 1980a), with better correlations at lower THC levels.

FIGURE 12. Time course of subjective effects following three modes of administration. A rating of the degree of "high" was made by subjects on a 0 to 10 scale (estimated from figures of Hollister et al. 1981 and Ohlsson et al. 1980).
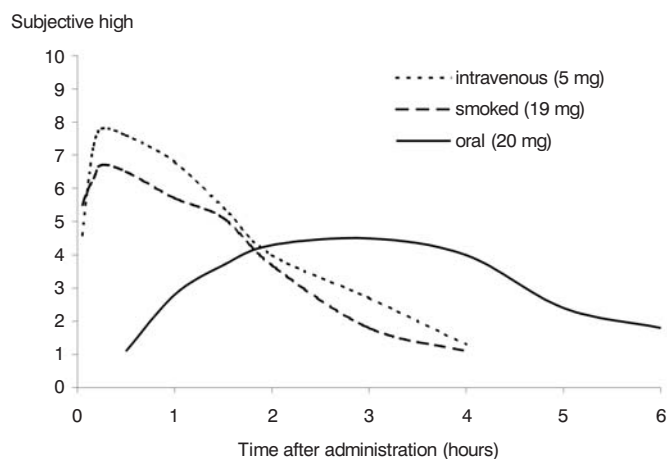
After oral use (20 mg THC in a cookie), reddening of the conjunctivae occurred within 30-60 min and was maximal from 60-180 min, gradually lessening thereafter (Ohlsson et al. 1980a). As with inhalation the pulse rate often returned to baseline or below even while the participants felt "high" (Ohlsson et al. 1980a). Psychotropic effects after oral use set in after 30-90 minutes (Wall et al. 1983, Hollister et al. 1981), were maximal between 2 to 4 h, and declined to low levels after 6 h (Hollister et al. 1981). Maximal psychotropic effects usually were delayed for 1-3 h when the plasma levels started to fall (Hollister et al. 1981) (see Figure 13). Correlations between log plasma concentrations and ratings of "high" were reported to be slightly lower compared to inhalation (r = 0.42) (Ohlsson et al. 1980a).

### *Pharmacokinetic Pharmacodynamic Modeling*

With both inhalation and oral use the association between THC levels in the plasma and subsequent psychotropic effects describes a hysteresis over time (see Figure 13). Intensity of THC effects depends on concentration in the effect compartment. THC quickly crosses the blood brain barrier (Nyoni et al. 1996). The short delay in psychotropic THC effects compared to plasma levels is attributed to the time needed to penetrate the barrier and bind the cannabinoid receptors. While plasma levels are already falling, the brain concentrations are still rising (Ohlsson et al. 1980b, Nyoni et al. 1996). In monkeys an IV dose of radiolabelled THC resulted in peak radioactivity levels in the brain after 15-60 minutes in accordance with the time of maximal effect after intravenous and inhalative administration in man (McIsaac et al. 1971). The equilibrium half-life with the effect compartment was calculated to be 29 minutes after smoking a cannabis cigarette (Harder and Rietbrock 1997). Chiang and Barnett (1984) have proposed a kinetic and dynamic model based on an open two compartment model (see Figure 14). Similar kinetic models have been proposed by others (Harder and Rietbrock 1997).

According to the Hill equation there is an association between the intensity of the high effects (E) and the amount of THC in the effect compartment.

$$E = \frac{\left( k_{e0} * A_e / k_{e1} * V_1 \right)^{\gamma}}{\left( k_{e0} * A_e / k_{e1} * V_1 \right)^{\gamma} + C_{ss}\left(50\right)}$$

FIGURE 13. Phase plots of subjective high/plasma THC levels after oral ingestion of 15 mg THC in a choccolate cookie from 0 to 360 minutes (estimated from figures by Hollister et al. 1981 with some extrapolated data). Every thick point in the figure marks 30 minutes of the whole time. The maximum THC plasma concentration (5.7 ng/ml) was reached after 60 minutes, while the maximum subjective high (on a 0 to 10 scale, see Figure 12) was noted 2-4 hours after intake of the cannabinoid.
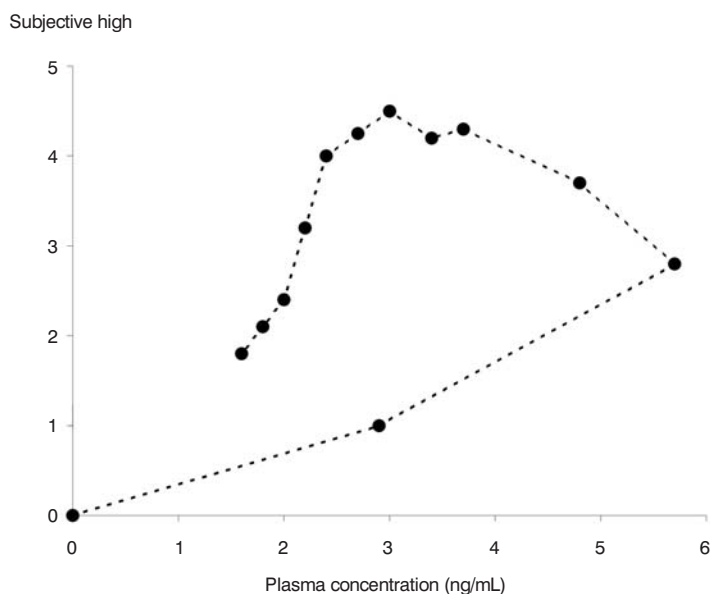


The steady-state plasma concentration at the 50% of maximum high effect $C_{ss}(50)$ was ascertained to be 25-29 (ng/ml) by using cannabis cigarettes of three different potencies (Chiang and Barnett 1984). The elimination rate constant from the effect compartment ($k_{e0}$) ranged from 0.03 to 0.04 $min^{-1}$, the sigmoid parameter $\gamma$ (the degree of sigmoidicity of the effect/amount relationship) was 1.5-2.0. The transfer rate constant $k_{21}$ from the tissue compartment was much smaller (0.0078-0.012 $min^{-1}$) than the elimination rate constant. Thus, the time course of effect must precede the time course of the THC amount in the tissue compartment. The rate constant $k_{10}$ is probably consisting of a mixture of constants for metabolism and distribution between the central and deep tissue compartments (Chiang and Barnett 1984).

FIGURE 14. Kinetic and dynamic model for THC (modified according to Chiang and Barnett 1984). $K_a$, $k_{12}$, $k_{21}$, and $k_{10}$ describe THC kinetics in the empiric two compartment model. The rate constants $k_{1e}$ and $k_{e0}$ characterize the effect compartment.
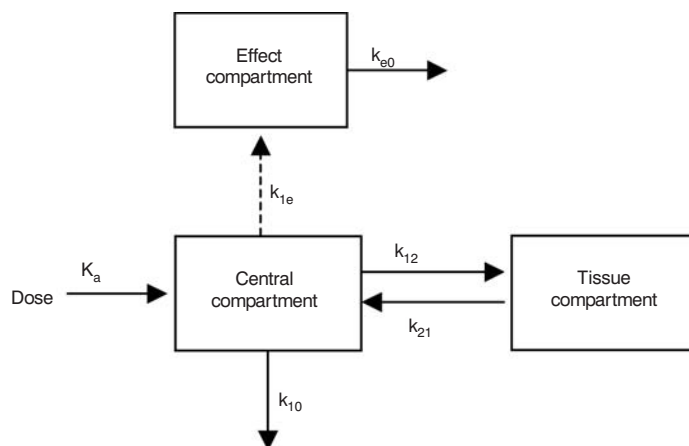


## Predicting Time of Administration

Several models have been applied to predict time of cannabis use from blood concentrations. Recent cannabis use and possible significant impairment was assumed with THC plasma levels of more than 2-3 ng/mL (McBurney et al. 1986) or more than 10 ng/mL (Law and Moffat 1985).

Hanson et al. (1983) were the first to propose the ratio of metabolites to parent molecule for time estimation of last use. Law et al. (1984) stated that a ratio of overall metabolites and THC of < 20 was indicative of recent use, although the ratio could be > 30 in regular users due to accumulation of THC-COOH. Other authors assumed that a THC-COOH/THC ratio < 1 was indicative for use within the past 30 min, a ratio of 2 within one h, a ratio of 3 within two, of 4 within three and a ratio of 7 within 24 h (Garriott et al. 1986).

Huestis et al. (1992b) proposed two mathematical models, derived from linear regression analysis of plasma THC concentration and elapsed time after cannabis use (Model I, r = 0.949), and from linear regression analysis of plasma THC-COOH/THC ratios versus elapsed time after use (Model II, r = 0.919):

*Model I:* Log (time in h) = $-0.698$ log [THC] + 0.687

*Model II:* Log (time in h) = (0.576 * [THC-COOH]/[THC]) − 0.176

Medium deviation from the correct time of use was about 1-2 h two to four hours after use and about 2.5-4 h four to eight hours after use (Huestis et al. 1992b). Model I was more accurate following inhalation in infrequent and frequent users, but less reliable with oral use of cannabis, while model II was more accurate for infrequent inhalation and oral ingestion, but tended to overestimate time of usage in frequent users.

Daldrup (1996) proposed a CIF factor (cannabis influence factor) consisting of a ratio of THC together with 11-OH-THC and THC-COOH weighted with constants.

$$CIF = \frac{\dfrac{[THC]}{314.5} + \dfrac{[11\text{-}OH\text{-}THC]}{330.5}}{\dfrac{[THC\text{-}COOH] * 0.01}{344.5}}$$

Individuals with a CIF > 10 were classified as being severely impaired with regard to driving abilities. This author applied Daldrup's equation to data of a paper by Huestis et al. (1992a). A CIF of > 10 was usually reached 2.5-4 h after smoking a marijuana cigarette with great inter-individual variability (Grotenhermen 2001).

## PHARMACOKINETICS OF OTHER CANNABINOIDS

The pharmacokinetics of other cannabinoids resembles the kinetics of THC with regard to plasma course, terminal half-lives and other parameters. These will be reviewed briefly for the natural cannabinoids CBD and CBN, for nabilone, a synthetic 9-ketocannabinoid and psychotropic derivative of cannabinol available on prescription in several countries, and for dexanabinol, a non-psychotropic analog of $\Delta^8$-THC under clinical investigation.

### Cannabidiol (CBD)

Average systemic bioavailability of inhaled CBD in a group of cannabis users was 31% (range: 11-45%) (Ohlsson et al. 1984). The plasma pattern was similar to that of THC with high levels of about 100 ng/ml within minutes after smoking, and a fast decrease to a concentration of about 10

ng/ml after one hour. After oral administration of 40 mg CBD, the plasma course over 6 h was in the same range as the course after 20 mg THC (Agurell et al. 1981). Daily oral doses of 10 mg/kg CBD per day for 6 weeks in patients with Huntington's disease resulted in mean weekly plasma levels of 5.9-11.2 ng/ml (Consroe et al. 1991). The distribution volume was about 30 L/kg, greater than for THC (Ohlsson et al. 1984). In rats receiving intravenous THC and CBD (1 mg/kg body weight each), brain concentrations of unchanged CBD were higher than that of THC 5 minutes after administration (Alozie et al. 1980).

The plasma clearance ranged from 960 to 1560 ml/min (Ohlsson et al. 1984). An average terminal half-life of 24 h (range: 18-33 h) was determined after intravenous injection of 20 mg during an observation period of 72 h (Ohlsson et al. 1984).

Thirty-three metabolites were identified in the urine of a patient treated with CBD and further four metabolites were partially characterized (Harvey and Mechoulam 1990). The metabolic pattern is similar to THC (Wall et al. 1976). The widely used dibenzopyran system for the numbering of cannabinoids cannot be applied to CBD. Metabolites of CBD have to be numbered according to the monoterpene system which can cause some confusion, since the main attacked carbon is numbered C-7 instead of C-11 (see Figure 15), resulting in the hydroxy metabolite 7-OH-THC. Several cyclicized cannabinoids were identified as well, among them $\Delta^9$-THC, $\Delta^8$-THC and cannabinol (Harvey and Mechoulam 1990). The excretion rate of metabolites in humans in urine (16% in 72 h) is similar to that of THC (Wall et al. 1976). Unlike THC, unchanged CBD is excreted in large percentages in the feces (Wall et al. 1976).

### *Cannabinol (CBN)*

Average systemic bioavailability after smoking 19 mg CBN was 26% (range: 8-65%), similar or somewhat higher than the values for THC (Johansson et al. 1987). The plasma course following oral ingestion (Agurell et al. 1981), inhalation (Ohlsson et al. 1985, Johansson et al. 1987) and intravenous administration (Ohlsson et al. 1985, Johansson et al. 1987) was similar to that of CBD. The volume of distribution was determined to 23 L/kg (Johansson et al. 1987). The apparent terminal half lives for CBN were 17 h and 29 h after intravenous administration and smoking, respectively (Johansson et al. 1987). Metabolic patterns in humans were similar to THC with a main attack at C-11 (Wall et al. 1976). Excre-

FIGURE 15. Numbering of cannabinoids. Chemical structure of THC, according to the monoterpenoid system ($\Delta^1$-THC) and dibenzopyran system ($\Delta^9$-THC).



Monoterpenoid numbering          Dibenzopyran numbering
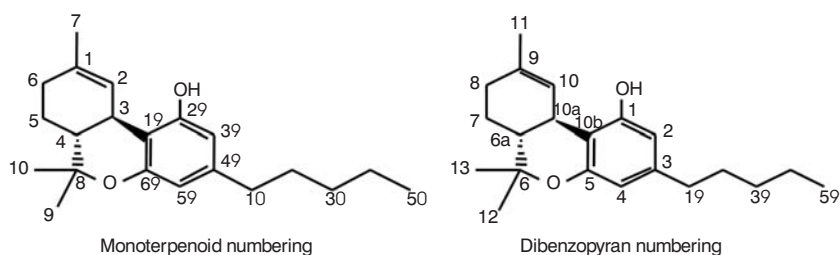
tion was slower with about 8% eliminated with urine and 35% excreted in feces within 72 h (Wall et al. 1976).

### Nabilone

The absorption of oral nabilone (Figure 16) (as a polyvinylpyrrolidone coprecipitate) is nearly complete (Lemberger et al. 1982) with plasma levels peaking at 1-4 h. Nabilone was reported to disappear from plasma relatively fast, with a half life of about 2 h (Rubin et al. 1977, Lemberger et al. 1982), while total radioactivity disappeared slowly with a half life of 30 h (Lemberger et al. 1982). Circulating metabolites in plasma include isomeric carbinols with long half lives formed by reduction of the ketone at C-9 (Rubin et al. 1977, Sullivan et al. 1978, Sullivan et al. 1987). About 91% of nabilone was excreted within 7 days, 23% in urine and 67% in the feces (Lemberger et al. 1982).

### Dexanabinol (HU-211)

The pharmacokinetics of the synthetic non-psychotropic cannabinoid dexanabinol (HU-211) (Figure 17) was evaluated with doses of 48 mg, 100 mg, and 200 mg as short iv infusions in healthy volunteers. The plasma course best corresponded to a 3-compartment model with a terminal elimination half-life of approximately 9 h (Brewster et al. 1997). The plasma clearance of the drug (about 1,700 ml/min) and the volume of distribution (about 15 L/kg) were somewhat higher than seen with THC.

## *METABOLIC INTERACTIONS*

Interactions of cannabinoids with other drugs may depend on activity on similar effector systems or metabolic interactions (Pryor et al. 1974). Since cannabinoids are strongly bound to proteins, interactions with other protein bound drugs may also occur. However, the latter effect has never been reported.

### *Metabolic Interactions Between Cannabinoids*

Metabolic interaction between cannabinoids has been observed, but only cannabidiol seems to have a significant effect on THC by inhibiting hepatic microsomal THC metabolism through inactivation of the cytochrome P-450 oxidative system (Watanabe et al. 1987, Bornheim et al. 1998, Jaeger et al. 1996, Yamamoto et al. 1995). Preincubation of human liver microsomes with cannabidiol selectively decreased the formation of tetrahydrocannabinol metabolites catalyzed by cytochrome P450-3A but had no effect on P450-2C9-catalyzed metabolites (Jaeger 1996).

Treatment of mice with high doses of CBD (120 mg/kg) resulted in changes of metabolism of 12 mg/kg THC and modest elevation of THC blood levels (Bornheim et al. 1995). The plasma area under the curve
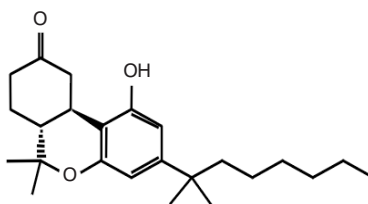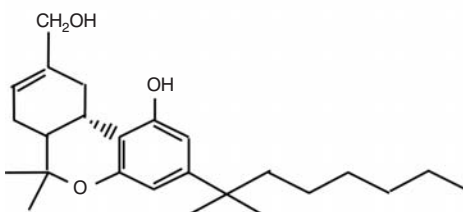
FIGURE 16. Nabilone.



FIGURE 17. Dexanabinol (HU-211).

(AUC) of THC was increased by 50% as a function of decreased clearance, while brain levels of THC increased by nearly 3-fold and brain AUC by 7- to 15-fold (Bornheim et al. 1995). The inhibition of cytochrome P-450 isoenzymes by CBD has been proposed to be a reason for recreational use of cannabis together with other drugs that need cytochrome P-450 for metabolism (cocaine, phencyclidine) (Reid and Bornheim 2001); however, THC and THC metabolites (Bornheim et al. 1994, Watanabe et al. 1986), other cannabinoid receptor agonists (Costa et al. 1996) and even CBD (Bornheim et al. 1994) seem to increase the activity of cytochrome P450 with repeated administration through enzyme induction.

In humans, *pretreatment* with 40 mg oral CBD resulted in a delayed, longer and only slightly reinforced action of 20 mg oral THC (Hollister 1975), while *simultaneous* administration of CBD and THC resulted in a significant block of several THC effects, among them anxiety and other subjective alterations caused by THC (Zuardi et al. 1982), and tachycardia (Karniol 1974), if CBD and THC were given in a ratio of 1:1 or higher, presumably due to antagonistic interaction of CBD at the cannabinoid-1 receptor (Petitet et al. 1998). There were no or only minimal effects of CBD on plasma levels of THC in man (Agurell 1981, Hunt et al. 1981), and there may be a minimal effect on the formation and excretion of metabolites (Hunt et al. 1981).

### Metabolic Interactions with Other Drugs

Metabolic interactions of THC with other drugs may occur if these drugs are metabolized by the same isoenzymes of the cytochrome P-450 complex.

A Swiss study found lower plasma levels of the antipsychotic drugs clozapine and olanzapine in smokers of tobacco and cannabis, which was attributed to induction of CYP1A2 of the cytochrome P-450 complex by some smoke constituents (Zullino et al. 2002). Two patients treated with these antipsychotics who stopped smoking experienced adverse drug effects due to increased plasma levels of the drugs, which made dose adjustment necessary (Zullino et al. 2002).

Authors of a case report of a young man who presented with myocardial infarction after taking Viagra® (sildenafil citrate, that is metabolized predominantly by the cytochrome P450 3A4 enzyme) in combination with cannabis supposed that the harmfulness of this combination was mainly due to the inhibition of the cytochrome P450 3A4 isoenzyme by cannabinoids (McLeod et al. 2002). However, it seems more likely that

the combination of the cardiovascular effects of both drugs were the main reason (see Mittleman et al. 2001), since a relevant inhibition of this enzyme by natural cannabinoids would have only been expected with high doses of CBD.

In a clinical study with AIDS patients, there was only a minor influence of cannabis smoking and oral dronabinol on pharmacokinetic parameters of antiretroviral medication used in HIV infection and metabolized by cytochrome P-450 enzymes, and the use of cannabinoids was regarded as unlikely to impact antiretroviral efficacy (Kosel et al. 2002).

Most interactions of cannabinoids with other drugs are not based on metabolic interactions, but on their activity on similar effector systems (Grotenhermen 2002a).

## *CONCLUSION*

With regard to the absorption of cannabinoids efforts are made to compensate the special disadvantages of oral use and inhalation. Sublingual administration of cannabis-based medicines is used in current clinical studies to accelerate the onset of action which is slow and erratic with dronabinol capsules or cannabis confections. The use of vaporizers and the development of inhalers are intended to avoid the harm caused by combustion products inhaled with the smoke of herbal material. Further promising alternatives to the most common routes of administration of today are rectal and transdermal administration, increasing either bioavailability or duration of action.

With regard to distribution and redistribution, cannabinoids cause several problems in forensic science. It is difficult or impossible to assess the actual degree of impairment of drivers from cannabinoid levels in body fluids or to estimate the time of the last consumption. In contrast to the hydrophilic alcohol, cannabinoids are lipophilic and there is only weak correlation between THC levels in the effect compartment (central nervous system) and THC levels in blood or other body fluids. Therefore, it seems reasonable to assess actual impairment with other means, e.g., reactions of the eye pupils to light. Amplitude, contraction speed and dilation speed of the pupils following a defined light stimulus show a dose dependent behavior with maximal effects in the first hour after smoking cannabis and a gradual decline thereafter (Kelly et al. 1993).

Questions of interest with regard to metabolism include different patterns of metabolism in dependency of administration route, and interactions between natural cannabinoids and with other drugs. Since

cannabinoids are metabolized by enzymes of the cytochrome P-450 complex, both decreased (through inhibition by CBD) and increased (through enzyme induction by all cannabinoids) activity of these enzymes may occur. This complex metabolic interaction may be further complicated by other forms of interaction (e.g., interactions at the receptor site). Thus, CBD may reinforce the activity of THC by reducing its metabolic rate and antagonize its activity at the $CB_1$ receptor site, which may explain contradictory results in studies investigating the interaction of the two phytocannabinoids. In general, it can be expected that metabolic interactions of cannabis products (that usually contain only low amounts of CBD) with other drugs are based more on enzyme induction than on inhibition, but this topic needs further investigation.

The increased formation of 11-OH-THC with oral use compared to inhalation is often made responsible for stronger psychotropic effects of oral cannabinoids. But it seems that this metabolite has a similar pharmacological profile as THC in man and binds to the $CB_1$ receptor, making it unclear how this metabolic difference may cause differences in effects. There seems to be no relevant difference between single THC and whole plant cannabis taken both orally and inhaled with regard to psychotropic and other subjective effects (Wachtel et al. 2002), supporting the view that the differences in scheduling cannabis and THC (dronabinol) in the narcotics acts of many countries are based more on political than on pharmacological grounds.

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