3 Clinical Pharmacokinetics of Cannabinoids and Potential Drug-Drug Interactions

Marta Vázquez, Carlos García-Carnelli, Cecilia Maldonado, and Pietro Fagiolino

Abstract

Over the past few years, considerable attention has focused on cannabidiol (CBD) and Δ^9-tetrahydrocannabinol (THC), the two major constituents of *Cannabis sativa*, mainly due to the promising potential medical uses they have shown. However, more information on the fate of these cannabinoids in human subjects is still needed and there is limited research on the pharmacokinetic drug-drug interactions that can occur in the clinical setting and their prevalence. As the use of cannabinoids is substantially increasing for many indications and they are not the first-line therapy in any treatment, health care professionals must be aware of drug-drug interactions during their use as serious adverse events can happen related with toxic or ineffective outcomes. The present chapter overview summarizes our current knowledge on the pharmacokinetics and metabolic fate of CBD and THC in humans and discusses relevant drug-drug interactions, giving a plausible explanation to facilitate further research in the area.

Keywords

Δ^9-tetrahydrocannabinol · Cannabidiol · Pharmacokinetics · Drug-drug interactions

3.1 Introduction

Cannabis (*Cannabis sativa* L.) is an annual herbaceous plant originated from Central-West Asia and widely distributed in the world (Andre et al. 2016). It has been used for millennia in folk medicine and to produce fiber. Due to the psychoactive properties of the plant, it has also been used in religious rituals or for recreational purposes (Wills 1998). The vegetable extracts reached maximum popularity in the western world at the end of the nineteenth century, mainly in the form of tinctures or fluid-extracts (Fankhauser 2002). Subsequently, different reasons led to its prescription abandonment, falling into gradual disuse during the first half of the last century. In this way, this plant of ancient culture and a great use for human beings became well-known in the last decades of the previous century almost exclusively for its psychoactive properties and non-medicinal purposes. Thus, cannabis became the most consumed illicit drug in the world, and despite its potential therapeutic applications, there

M. Vázquez (✉) · C. Maldonado · P. Fagiolino
Pharmaceutical Sciences Department, Faculty of Chemistry, University of the Republic, Montevideo, Uruguay
e-mail: mvazquez@fq.edu.uy; cmaldonado@fq.edu.uy; pfagioli@fq.edu.uy

C. García-Carnelli
Pharmacognosy & Natural Products Laboratory, Organic Chemistry Department, Faculty of Chemistry, University of the Republic, Montevideo, Uruguay
e-mail: carlosga@fq.edu.uy

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was an obvious delay in basic and applied research on this plant concerning other drugs of vegetable origin.

The Cannabis plant (also referred to in many texts as Indian hemp, and commonly known as marijuana) belongs to the Cannabaceae family. The number of species within the Cannabis genus has been the product of a long controversy. Some authors recognize two or three species: *Cannabis sativa* L., *Cannabis indica* Lam., *and Cannabis ruderalis* Janisch., which can be distinguished by their way of growth, the characteristics of their fruits and the structure of their fibers (ElSohly et al. 1983). However, at present, it is considered as monospecific (*Cannabis sativa* L.), and it is classified into different varieties (Pollio 2016; Small 2017). These varieties often show clear morphological differences among themselves, but also remarkable phytochemical dissimilarities. Beyond that, different genotypes can be established (Hillig 2005) as well as different cannabis chemotypes according to the content of cannabinoids (de Meijer 2014) and terpenes (Fischedick 2017). The type and quantity of secondary metabolites not only vary according to the genotype but also to the plant organ, the age of the plant and the growing conditions (Hillig and Mahlberg 2004; Aizpurua-Olaizola et al. 2016). In this way, the effects on the biological systems of a cannabis extract will be potentially different depending on the factors mentioned above. Under controlled culture conditions, the pharmacological activity will depend on the chemotype used (Lewis et al. 2018).

Cannabis is predominantly dioecious (male and female flowers occur on separate plants). The sex of the plant is anatomically indistinguishable before the maturation and flowering phase. Virtually all aerial parts of the cannabis plant are covered with trichomes. But it is in the bracts of the female inflorescence where the highest density of glandular trichomes (rich in cannabinoids) is found (Potter 2014). Cannabinoids represent a group of secondary metabolic substances isolated only from the Cannabis plant. More than 120 different molecules of cannabinoids have been described so far (ElSohly et al. 2017). The main cannabinoids in the Cannabis plant include Δ^9-tetrahydrocannabinol (THC), cannabidiol (CBD), cannabinol (CBN) and cannabigerol (CBG). The molecular structures are shown in Fig. 3.1. THC, found at higher concentrations than CBD in the psychotropic ("drug-type") varieties for *Cannabis Sativa*, is the primary psychoactive compound, with CBD, a non-psychoactive

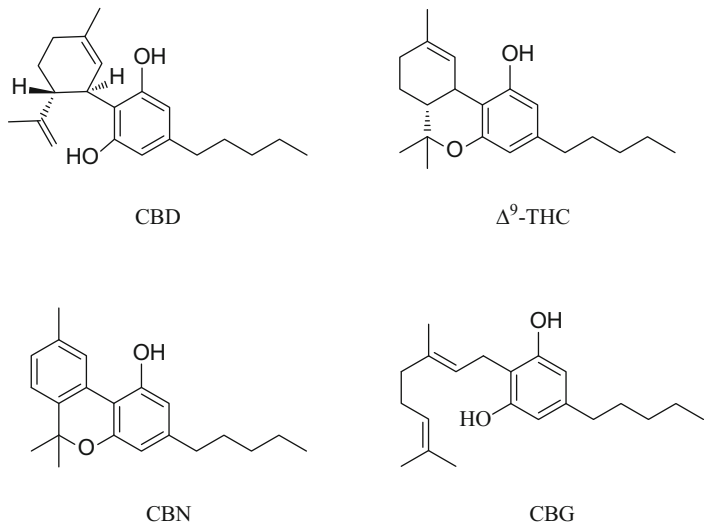

Fig. 3.1 Molecular structure of the main cannabinoids present in the cannabis resin

compound, ranking second. But the plant chemistry is far more complex than that of cannabinoids and different effects may be expected due to the presence of other chemicals. The number of other known compounds in the plant increased from approximately 400 to 650 (ElSohly and Gul 2014; Radwan et al. 2015,) so the chemical composition of *Cannabis sativa* is constantly changing. Apart from cannabinoids, the plant produces a large number of secondary metabolites such as terpenoids and flavonoids (ElSohly and Slade 2005). In recent years, terpenes have also been of interest, which, in addition to contributing to the organoleptic properties of the plant, they contribute to the pharmacological activity by modulating the effects of cannabinoids (Thomas and ElSohly 2016).

As a consequence of the development of synthetic cannabinoids and the discovery of endogenous ligands of the cannabinoid receptor (endocannabinoids) chemically different from plant cannabinoids, the term phytocannabinoids was proposed for these components of cannabis in particular (Russo 2007).

Phytocannabinoids in the plant are almost exclusively present as monocarboxylic acids and are practically not found as their neutral compounds (Flemming et al. 2007; Flores-Sanchez and Verpoorte 2008) but are formed upon decarboxylation of the acids (Fig. 3.2). The carboxyl group is not very stable and phytocannabinoids undergo spontaneous loss of this carboxyl moiety when subject to high temperature or direct sunlight. This occurs mainly in the harvest and post-harvest processes that is, when drying, heating, and storing are taking place, but also while smoking or in a hot oven when foods are prepared (Agurell and Leander 1971; Brenneisen 1984; De Backer et al. 2009).

Although the endocannabinoid system has been widely investigated and is considered an important neurotransmitter system, further investigation is needed to fully understand how this system works. Since the discovery of anandamide and 2-arachidonoylglycerol at the beginning of 1990, new molecular targets and biosynthetic and catabolic enzymes have been identified (Di Marzo 2018) and new research is being carried out as the complex functions of this novel system have created multiple new targets for drug action (Kerbrat et al. 2016; Navarro et al. 2016; van Esbroeck et al. 2017).

Cannabis and cannabinoid drugs have been increasingly accepted to treat several diseases or alleviate symptoms. Research into the medical use of cannabis and cannabinoids is constantly evolving but with differences in the available supporting data (Ware et al. 2010; Portenoy et al. 2012; Deshpande et al. 2015; Whiting et al. 2015; Devinsky et al. 2017; Meng et al. 2017; Nugent et al. 2017; Stevens and Higgins 2017; Thiele et al. 2018). An important fact to bear in mind is that the majority of the studies conclude on the use of cannabis as a third- or fourth-line therapy and the use of cannabis as monotherapy or first-line therapy is not supported for any indication. Mainly two major cannabinoids, CBD and THC have become the focus of clinical research. However, only THC and its metabolites: 11-hydroxytetrahydrocannabinol (11-OH-THC) and 11-nor-9-carboxytetrahydrocannabinol (THC-COOH) have been investigated more thoroughly.

A very important concept in pharmacology is pharmacokinetics. Pharmacokinetics, to put in simple words, is what the body does to a drug. A bit more technically, pharmacokinetics can be defined as the study of the time course of the

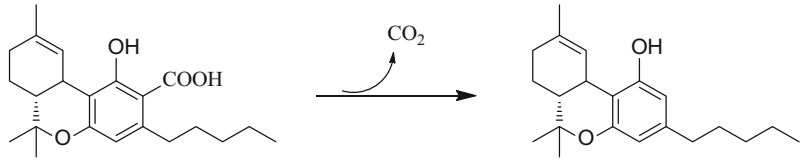

Fig. 3.2 Decarboxylation of delta-9-THC acid by heat action

absorption, distribution, metabolism, and excretion (ADME) of a drug. Dissolution is the first step in the oral absorption of solid drugs. The long and complex process of absorption culminates when the drug reaches the arteries of the great circulation. The stages of release and absorption are sequential, ie if the drug is not previously released from the pharmaceutical form, it cannot be absorbed. However, the distribution, metabolism, and excretion processes are simultaneous, and they are subsequent to the absorption. Once the drug reaches the aorta artery, it is available to be distributed to the different tissues and to undergo elimination (metabolism and/or excretion). Understanding the pharmacokinetics of a drug is essential to know the onset, magnitude, and duration of its pharmacodynamic responses and is critical in defining conditions for safe and effective use in patients.

The renewed interest in the therapeutic effects of cannabis makes cannabis available as a medicine to patients with a variety of conditions. As cannabinoids do not constitute first-line therapies as previously mentioned, health care professionals must be aware of drug-drug interactions during their use as sometimes serious or even fatal adverse events can happen either related to toxic or ineffective outcomes.

Little information on the pharmacokinetics of THC and CBD in humans and pharmacokinetic interactions of these cannabinoids with conventional medicine is available in the literature so this chapter will mainly focus on these issues. To facilitate further research in the clinical area, possible drug-drug pharmacokinetic interaction mechanisms will also be proposed and discussed in this chapter.

3.2 Pharmacokinetics of Cannabinoids

Extravascular cannabinoid pharmacokinetics encompasses absorption after diverse routes of administration and from different drug formulations, drug distribution throughout the body, and elimination (mostly by metabolism through the liver and extra-hepatic tissues, negligible by excretion). Studying the evolution and the fate of cannabinoids in the body has been a challenging task so far as the absorption and disposition of these compounds vary as a function of the route of administration. The most common methods of administration of cannabinoids are inhalation (smoking/vaporization), sublingual, and oral ingestion. Cannabinoids may be also taken by rectal administration, via transdermal delivery, eye drops, and aerosols. However, studies about the pharmacokinetics using these routes are scarce.

3.2.1 Absorption

3.2.1.1 Inhalation/Smoking

When smoked, the rapid delivery of cannabinoids compounds from the lungs to the central nervous system is observed. For this reason, smoking cannabis has high addictive potential (Grotenhermen 2007; Borgelt et al. 2013). Several studies revealed that plasma THC concentrations following inhalation are similar to those obtained after intravenous administration (Ohlsson et al. 1980). In these studies, high plasma concentrations were obtained within minutes and then concentrations dropped quickly. Due in part to intra- and inter-subject variability in smoking dynamics (number, duration, and spacing of puffs, inhalation volume, holding of breath after inhalation, etc), bioavailability following this route is highly variable: 2–56%. This is why this route contributes to uncertainty in dose delivery (Agurell and Leander 1971; Ohlsson et al. 1980; Ohlsson et al. 1982; Perez-Reyes et al. 1982; Ohlsson et al. 1985; Agurell et al. 1986).

Vaporization of cannabis has been proposed to avoid the formation of hazardous combustion products (tar, polycyclic aromatic hydrocarbons, carbon monoxide, and others) derived from smoked cannabis (Gieringer 2001; Gieringer et al. 2004; Hazekamp et al. 2006; Abrams et al. 2007). Vaporizers decarboxylate cannabinoid acids at about 200 °C and release the volatile cannabinoids entering, in this way, into the systemic circulation via pulmonary absorption from

the vapor. The onset of action is rapid but concentrations decrease very quickly and bioavailability is variable (Huestis 2007). Studies have been carried out (Abrams et al. 2007; Eisenberg et al. 2014; Lanz et al. 2016) to demonstrate the efficient administration of medicinal cannabis and cannabinoids using different vaporizers.

3.2.1.2 Oral

In comparison to the inhalation route, the onset of effects is delayed after oral ingestion. THC and CBD peak concentrations are lower attributed to the important first-pass metabolism of cannabinoids but the duration of the effect is prolonged: 4–12 hours (Huestis 2007; Borgelt et al. 2013). Bioavailability is low (approximately 5%) (Grotenhermen 2003).

First-pass metabolism is responsible for incomplete and variable bioavailability of an orally administered drug. THC and CBD do not escape from this and both of them are extensively metabolized in the intestine. The drug-metabolizing enzyme CYP3A4 is often implicated in this process as it is the most abundant P450 subfamily expressed in the small intestine and it functions there as a barrier against xenobiotics (Paine et al. 2006; Thummel 2007).

ABC transporters are a family of drug efflux pumps that utilize ATP hydrolysis to transport substrates across biological membranes. Apart from regulating drug absorption, they also play an important role in the disposition of many drugs in tissues because they are located in excretory organs such as the liver, intestine, and the blood-brain barrier (Fromm 2003). P-glycoprotein (Pgp), an ATP-dependent drug efflux transporter, plays a significant role in the absorption and disposition of many compounds (Fromm 2002). The Pgp is expressed in the apical membrane of the enterocyte and works in cooperation with intracellular enzymes such as CYP3A4, an enzyme with the highest content in the intestine as expressed before. Drug extrusion by Pgp is a way of improving enzymatic efficiency at the enterocyte and avoiding enzymatic saturation by high drug concentrations that reach the intestine from the stomach. This synergistic interaction between CYP3A4 and Pgp may enhance the first-pass loss of a drug as it was observed in many studies (Lown et al. 1997; Wacher et al. 1998).

The knowledge of this system working cooperatively was used in antiretroviral therapy combining two protease inhibitors: lopinavir and ritonavir. Ritonavir is a great inhibitor of both CYP3A4 and/or Pgp (Drewe et al. 1999) and, consequently, increases the coadministered protease inhibitor lopinavir (Boffito et al. 2004).

The enhancement of the expression of enzymes and efflux transporters leads to diminished oral drug bioavailability. An increase of Pgp expression, produced by inducers, reduces the amount of drug in the enterocyte effectively pumping drugs out of the gut wall and back into the intestinal lumen. Conversely, the inhibition of this coordinated system could improve drug bioavailability.

As both molecules, THC, and CBD, are poorly water-soluble and subjected to extensive first-pass metabolism in the gastrointestinal tract, leading to a limited oral bioavailability, several efforts have been made to avoid the loss of cannabinoids when given orally. Some researchers (Cherniakov et al. 2017) developed an advanced self-emulsifying oral drug delivery system with a natural absorption enhancer (piperine) and subsequently tested in rats. Several authors (Bhardwaj et al. 2002) showed that piperine inhibits both the drug transporter Pgp and the major drug-metabolizing enzyme CYP3A4. Because both proteins are expressed in enterocytes and hepatocytes and contribute to a major extent to the first-pass elimination of many drugs, their data indicate that dietary piperine could affect plasma concentrations of Pgp and CYP3A4 substrates in humans, in particular, if these drugs are administered orally. The results were promising as an increase in CBD and THC bioavailability was observed.

The same investigators (Atsmon et al. 2018; Atsmon et al. 2018) tested the new formulation based on pro-nano dispersion technology in healthy volunteers and compared it with similar doses from a marketed oromucosal spray. The new delivery system provided faster absorption

and improved bioavailability, compared to the oromucosal spray. Further, larger-scale clinical studies with this formulation are needed.

3.2.1.3 Sublingual

This route of administration bypasses the first-pass metabolism and goes directly into the bloodstream via the mouth. As there is a salivary gland under the tongue, sublingual formulations may stimulate the flow of saliva and it is difficult for patients to avoid swallowing leading this to a decreased bioavailability similar to that of oral delivery (Dev et al. 2016). After smoking/vaporizing, the sublingual method is the second fastest delivery method.

3.2.1.4 Buccal/Oromucosal

The medicine can be placed inside the cheeks or on the gums. The advantage over the sublingual application is that avoids the reflex of swallowing. Using this administration, a greater percentage of the active cannabinoids is absorbed compared to the sublingual method (Huestis 2007). Bioavailability following application on oral mucous membranes is around 13% (Karschner et al. 2011).

3.2.1.5 Rectal

When placed correctly (which means avoiding the superior rectal vein), the rectal route prevents first-pass metabolism (van Hoogdalem et al. 1991; Mattes et al. 1993). Unfortunately, there are very few scientific studies on the bioavailability of rectal administration. A study conducted with two patients (Brenneisen et al. 1996) deduced that the bioavailability was approximately twice that of oral ingestion.

3.2.1.6 Transcutaneous

This is another route of improving cannabinoid exposure as it avoids the first-pass metabolism. Some authors have demonstrated that CBD is more permeable than THC (Stinchcomb et al. 2004). The delivery to the brain when administered transcutaneous is much slower compared to smoking. Steady-state plasma concentrations were found to be maintained for at least 48 hours (Huestis 2007; Oberbarnscheidt and Miller 2017).

3.2.2 Distribution

The distribution of THC is governed by the high lipophilicity of this substance. The compound rapidly penetrates highly vascularized tissues resulting in a quick decrease in plasma concentrations. Subsequently, accumulation occurs in less vascularized tissues and finally in body fat, being the latter a long-term storage site. With prolonged drug exposure, for example, THC can be retained in body fat for extended periods (Huestis 2007). The steady-state volume of distribution is about 10 L/kg.

CBD is rapidly distributed into the tissues with also a high volume of distribution (more than 10 L/kg). Like THC, CBD may preferentially accumulate in adipose tissues due to its high lipophilicity (Fasinu et al. 2016).

Experimental data show that THC rapidly crosses the placenta, although concentrations are lower in fetal blood and tissues than in maternal plasma and tissues (Huestis 2007). THC also concentrates on breast milk from maternal plasma due to its high lipophilicity. Due to similar lipophilicity, CBD could follow the same behavior (Grant et al. 2018).

THC and CBD are highly protein-bound in blood and as stated in the literature (Wahlqvist et al. 1970; Widman et al. 1974; Klausner et al. 1975; Hunt and Jones 1980; Devinsky et al. 2014) are mainly bound to low-density lipoproteins, with up to 10% present in red blood cells and only 2–3% as free drug.

3.2.3 Elimination

Elimination of THC and CBD is mainly by metabolism in the liver and the intestine. To a much lesser degree, other extrahepatic organs and/or tissues such as the heart, the brain, and the lungs also contribute to the metabolism of cannabinoids (Krishna and Klotz 1994; Huestis 2007; Stout and Cimino 2014).

Cannabinoids are substrates of cytochrome P450 monooxygenases (CYP450). The enzymes CYP2C9, CYP2C19, and CYP3A4 catalyze the majority of hydroxylations that take place in their metabolism. *In vitro* data showed that hepatic isoenzymes 2C9 and 3A4 play a significant role in the primary metabolism of THC (Yamamoto et al. 2003), whereas 2C19 and 3A4 may be responsible for the metabolism of CBD (Stout and Cimino 2014). Other CYP enzymes may be involved in CBD metabolisms such as CYP1A1, CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5 (Jiang et al. 2011). One metabolite of THC: 11-hydroxy-THC (11-OH-THC) exhibits similar activity and disposition to THC (Grotenhermen 2003).

The implication of CYP3A4 and CYP2C19 was evaluated in human beings. Increases in THC, CBD and 11-OH-THC concentrations seen when ketoconazole, a well-known CYP3A4 inhibitor (Greenblatt et al. 2011), or decreases of these compounds when rifampicin, a well-recognized inducer (Mahatthanatrakul et al. 2007), were coadministered with oromucosal cannabis extract support the implication of CYP3A4 as an important contributor to the metabolism of these compounds (Stott et al. 2013). The significance of CYP2C19 contribution to CBD metabolism, in contrast, was not supported by the clinical study with omeprazole, a CYP2C19 inhibitor (Shirasaka et al. 2013). So this enzyme perhaps is not so involved in *in vivo* metabolism of CBD, THC, and 11-OH-THC at the dose of THC/CBD spray investigated or plays a less significant role in CBD metabolism. Pharmacogenetic data support CYP2C9 as a significant contributor to THC metabolism (Sachse-Seeboth et al. 2009).

Cannabinoids are the subject of UDP-glucuronosyltransferase (UGT)-dependent glucuronidation. UGTs have been identified as capable of catalyzing both primary (CBD and CBN) and secondary (Δ^{9} THC) cannabinoids metabolism (Stout and Cimino 2014).

The true elimination half-lives of THC and CBD are difficult to calculate from plasma as the equilibrium plasma/fatty tissue is slowly reached. So highly variable elimination half-lives are reported in the literature for THC, ranging from 20–30 hours for THC (Lemberger et al. 1971) to 4–6 days when plasma levels were determined for 2 weeks and 9–13 days when they were followed-up for 1 month (Johansson et al. 1989).

3.3 Pharmacokinetic Interactions

Potential drug-drug interactions are preventable and are common causes of adverse drug effects (Namazi et al. 2014). Since CBD and/or THC are often administered concomitantly with other medicines as add-on therapy, drug-drug interactions should be taken into account**.** Many studies have demonstrated (Hawksworth and McArdle 2004; Yamaori et al. 2011; Yamaori et al. 2011; Jiang et al. 2013; Zendulka et al. 2016) that CBD is not only a substrate but also an inhibitor of CYP450 enzymes, and thus, it could interfere with the metabolism of other xenobiotics. All these studies were *in vitro.* Furthermore, *in vitro* studies have shown that CBD and THC interact in some way with ABC transporters. CBD inhibits the ABC transporters Pgp (Zhu et al. 2006) and Bcrp (Breast Cancer Resistance Protein) (Spiro et al. 2012; Feinshtein et al. 2013), and thus, it may affect the pharmacokinetics of many drugs that are substrates of these transporters. Interestingly, it was proved by some authors (Brzozowska et al. 2016) that CBD was a not a substrate of efflux transporter but an inhibitor of these proteins The inhibition CBD exerts on ABC transporters might be of importance on THC pharmacokinetic as THC is a dual Pgp and Bcrp substrate (Todd and Arnold 2016), and CBD can potentiate some of THC effects via increasing its brain concentrations.

Moreover, it was demonstrated that THC exposure increased Pgp expression in various important brain regions (Brzozowska et al. 2017). This could affect many drugs that are substrates of these transporters.

So a summary of possible interactions with relevance in the clinical use of CBD and/or THC is going to be exposed so that the reader can have tools to act in the clinical setting.

3.3.1 Cannabinoids-Statins

Statins exert a competitive inhibition of the 3-hydroxy-3-methylglutaryl CoA (HMG-CoA) reductase to impair endogenous cholesterol synthesis. This decrease in intracellular cholesterol concentration induces the upregulation of low-density lipoprotein (LDL) receptor expression on the hepatocyte cell surface, which increases LDL-cholesterol extraction from the blood and thus decreased levels of circulation LDL-cholesterol (Schachter 2005).

As previously mentioned, both CBD and THC primarily bind to lipoproteins, mainly LDL. The unbound fractions of THC and CBD in plasma are low. Therefore, the disposition of these two compounds depends not only on physicochemical characteristics but also on lipoproteins. CBD-LDL and THC-LDL can reach the intracellular space of the hepatocyte via the LDL membrane receptor as cholesterol does. When cannabinoids are coadministered with statins, an increase in the clearance of the former may be observed as statins reduce plasma LDL and in this way, they increase the free fraction of CBD and THC. Moreover, statins upregulate LDL receptors in the liver, so THC and CBD biotransformation increases. Both factors might cause a decrease in free and total THC and CBD plasma concentrations. So cannabinoids could become less effective in patients taking statins (Fig. 3.3).

A case was reported by our research group (Eiraldi et al. 2004) with cyclosporine (CYA) and atorvastatin. CYA exhibits the same binding characteristics as cannabinoids, primarily binding to LDL. In the interaction reported, the combination of the two drugs resulted in an acute rejection episode as CYA clearance increases yielding lower concentrations.

Another factor must be taken into consideration; some statins (simvastatin and atorvastatin) are metabolized by CYP3A4 and are substrates of

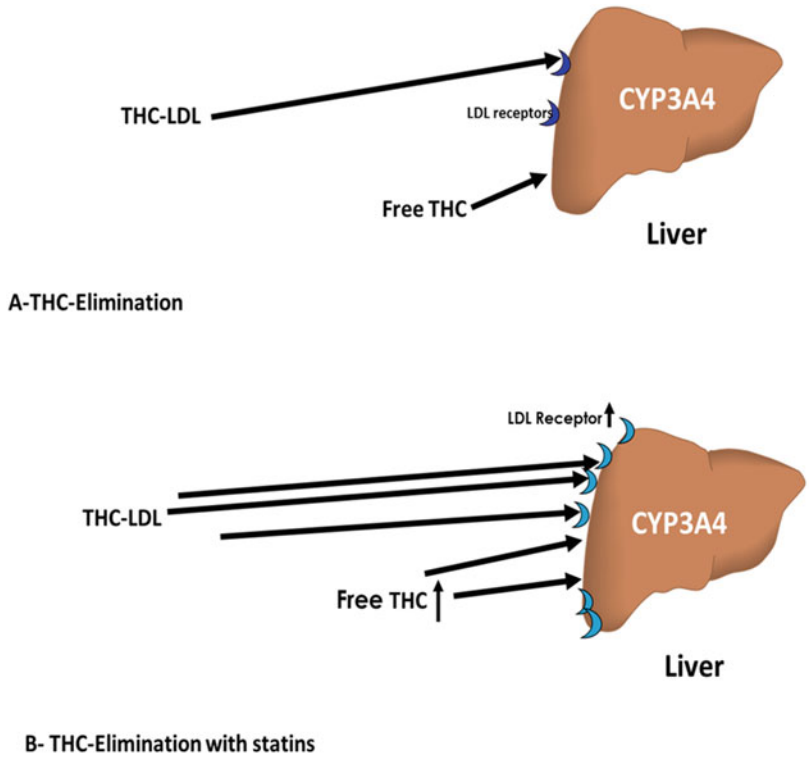

Fig. 3.3 Illustration of THC elimination given alone (**a**) or in combination with statins (**b**)

Pgp (Holtzman et al. 2006; Neuvonen et al. 2006). CYP3A4 and/or Pgp inhibitors such as CBD may increase the plasma concentration of these statins, increasing the risk of adverse reactions such as myopathy and/or rhabdomyolysis. However, as the same authors stated, the role of Pgp in these specific drug interactions remains unclear so further studies are necessary to conclude on this issue. If the interaction were important, on the one hand, CBD would increase simvastatin and atorvastatin levels inhibiting CYP3A4 and/or Pgp, but on the other hand, statins would increase cannabinoids clearance decreasing their effects. In the end, no clinical effect would be observed.

3.3.2 Cannabinoids-Warfarin

Warfarin is one of the most widely used oral anticoagulant (Pengo et al. 2006). It is administered as a racemic mixture of the R- and S- stereoisomers, being S-warfarin 3–5 times more potent than R-warfarin. S-warfarin is metabolized predominantly via CYP2C9 whereas the R-stereoisomer is utilizing the CYP3A4 isoenzyme (Ansell et al. 2008). Frequent monitoring of the INR is required to both achieve and subsequently maintain appropriate anticoagulant effects; this is mainly due to the narrow therapeutic index warfarin has. Concomitant medications, diet, alcohol intake, and genetic polymorphisms in the genes encoding CYP2C9, must also be taken into consideration. Drugs that inhibit the isoenzymes implied in warfarin metabolism may increase its plasma concentrations and INR, and thus potentially increase the risk of bleeding. CBD has been demonstrated to act as a potent competitive inhibitor of CYP enzymes, mainly CYP2C9 and CYP3A4 to a lesser extent and as such could further impair the degradation of warfarin (Yamaori et al. 2011; Yamaori et al. 2012). Some researchers (Grayson et al. 2017) observed a rise in INR values with increasing CBD doses suggesting an interaction between warfarin and cannabidiol. The situation was reversed once the warfarin dose was decreased.

3.3.3 Cannabinoids-Anticonvulsants

About one-third of patients with epilepsy suffer from drug-resistant disease and the efficacy of the medication available in the market is limited (Kwan and Brodie 2000; Kwan et al. 2010). So interest has arisen to develop new medications with anticonvulsant properties acting on novel receptors. CBD has been studied for a long time to be effective in animal models of epilepsy (Carlini et al. 1973; Rosenberg et al. 2017). The use of CBD in the treatment of refractory epilepsy in children has been increasing but only in the last few years, data from randomized trials with CBD is available (Devinsky et al. 2016; Devinsky et al. 2017; O'Connell et al. 2017; Thiele et al. 2018). These trials as well as studying safety, have also explored the potential efficacy of CBD use in children with Dravet and Lennox-Gastaut syndromes.

As CBD is used as an add-on therapy to other antiepileptic drugs (AEDs), it is important to understand how CBD can interact with them to predict or prevent drug-drug interactions.

Based on what is known about CBD metabolism and the metabolism of other AEDs, one could speculate that there could be many interactions given the involvement of CYP enzymes in the metabolism of AEDs and the inhibition or induction several of these drugs exhibit. To date, there are few data on CBD interactions with other AEDs and the studies found in the literature (Geffrey et al. 2015; Gaston et al. 2017; Perucca 2017) focus on what CBD can do to other plasma AEDs concentrations but the information is lacking about the influence of concomitant AEDs on plasma CBD levels.

3.3.3.1 With Clobazam, Clonazepam

Clobazam is a benzodiazepine that has been approved for use in the treatment of Lennox-Gastaut Syndrome and other epileptic syndromes and anxiety (Giarratano et al. 2012). The main enzyme involved in the process of N-demethylation of clobazam to form norclobazam (an active metabolite) is CYP3A4 and to a lesser extent CYP2C19 and CYP2B6.

Norclobazam itself is also metabolized via hydroxylation, primarily by CYP2C19 (Walzer et al. 2012).

The interaction with clobazam and its metabolite has been reported (Geffrey et al. 2015; Gaston et al. 2017). Some authors (Geffrey et al. 2015) reported elevated clobazam and norclobazam levels in children with refractory epilepsy by 60 and 500% respectively when CBD was introduced in their therapy. Side effects were reported in 10 of the 13 children, but once clobazam dose was reduced, side effects also decreased. The interaction appears to be more important between CBD and norclobazam than with clobazam. This is due, perhaps, to more potent inhibition of CYP2C19 by CBD than that of the isoenzyme CYP3A4. Some pharmacokinetic studies (Kosel et al. 2002) suggest a low clinical impact of CBD on the CYP3A4 function. CBD's ability to inhibit ABC transporters alters the pharmacokinetics of co-administered drugs that are ABC transporter substrates. Interestingly, clobazam is a P-gp/Bcrp substrate, opening the possibility that these transporters may contribute to this drug interaction (Nakanishi et al. 2013). If norclobazam is an efflux transporter substrate is still unknown.

Of interest is the finding that clonazepam, mainly metabolized by CYP3A4 (Anderson and Miller 2002) did not show an interaction with CBD (Gaston et al. 2017). Moreover, this drug might not be an efflux transporter substrate.

So, the dose of clobazam may need to be adjusted when starting CBD as high levels of the metabolite were associated with increases in sedation or clonazepam can be used instead.

3.3.3.2 With Valproic Acid

Valproic acid (VPA), a branched short-chain fatty acid is mainly metabolized by three routes: glucuronidation, β-oxidation in the mitochondria (major routes accounting for 50% and 40% of dose respectively) and ω-oxidation (considered a minor route, 10%), resulting, the latter, in the formation of a hepatotoxic metabolite (4-en-VPA) (Siemes et al. 1993; Ghodke-Puranik et al. 2013). It is frequently used in the management of epilepsy and bipolar disorder. Other indications include neuropathic pain and prophylactic treatment of migraine headaches (Loscher 1999).

Glucuronidation is also involved in CBD metabolism (Mazur et al. 2009; Ujváry and Hanuš 2016). Some authors (Al Saabi et al. 2013) have revealed that CBD significantly inhibited ethanol glucuronidation in a non-competitive manner. If CBD also impairs VPA glucuronidation, more formation of 4-en VPA can be the cause of elevated liver function test results observed by some researchers (Gaston et al. 2017) when VPA was coadministered with CBD. These liver abnormalities were not seen in patients taking CBD and other anticonvulsants indicating that perhaps CBD enhances the negative effects of VPA on liver functions. Once CBD and VPA were discontinued, liver enzymes levels normalized quickly. Interestingly, the patients were rechallenged on CBD alone and did not experience these abnormalities again.

Moreover, if VPA clearance is reduced by CBD administration, higher levels of VPA will be found resulting in an increase in seizures due to hyperammonemia formation (Vázquez et al. 2013; Vázquez et al. 2014; Maldonado et al. 2016).

3.3.4 Cannabinoids and Substrates of Efflux Transporters

The distribution across the blood-brain barrier of the antipsychotic drug risperidone and its active metabolite 9-hydroxy-risperidone is profoundly limited by Pgp. Some animal studies carried out by some authors (Holthoewer et al. 2010; Schmitt et al. 2016) revealed that induction of Pgp affects the disposition of such drugs increasing blood levels and decreasing brain concentrations. THC and CBD can have opposite effects on risperidone and its metabolite in the brain as it was previously mentioned, THC can upregulate those transporters and CBD may inhibit them.

According to *in vitro* studies (Boulton et al. 2002), clozapine (a weak Pgp substrate antipsychotic drug) may be a better first-line treatment for patients with schizophrenia and with a history

of cannabis use. Quetiapine as well as risperidone are good Pgp substrates and olanzapine showed intermediate affinity. *In vivo* studies are needed to confirm these findings.

Similarly, many anticonvulsant drugs such as phenytoin, phenobarbital, and clobazam are also ABC transporter substrates and subject to poor brain uptake (Nakanishi et al. 2013).

3.3.5 Drug Effects on Cannabinoids Levels

CBD and THC are metabolized, among others, via the CYP3A4 enzyme. Various drugs such as ketoconazole, itraconazole, ritonavir, and clarithromycin inhibit this enzyme resulting in higher CBD and THC concentrations because of increased bioavailability and/or reduced clearance (Stott et al. 2013). On the other hand, phenobarbital, rifampicin, carbamazepine, and phenytoin induce CYP3A4, leading to decreased levels of cannabinoids (Flockhart 2007; Stott et al. 2013).

3.4 Conclusions

Considering the absorption of cannabinoids, several efforts have been made to compensate for the disadvantages of oral use and inhalation. On the one hand, research is focusing on increasing the low bioavailability of THC and CBD after oral ingestion; on the other hand, several vaporizers are being tested to avoid the harm that combustion products can provoke. Sublingual administration of cannabis-based medicines is used nowadays to accelerate the onset of action which is slow and erratic after oral ingestion. Other alternatives such as rectal and transdermal administration are promising as they can increase either bioavailability or duration of action.

Cannabinoids are metabolized by enzymes of the cytochrome P-450 and either increasing or decreasing the activities of these enzymes could result in a lack or exacerbation of their effects respectively. Furthermore, efflux transporters can affect both absorption and disposition of THC and CBD and these transporters are plausible for being involved in interactions.

Despite the discussions of the potential drug-drug interactions studied in this chapter when drugs were administered concomitantly with THC and/or CBD, the full understanding of their relevance awaits further investigation.

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