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Clinical pharmacology of cannabidiol in refractory epilepsy

Farmacología clínica de cannabidiol en epilepsias refractarias

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Abstract

Objective: The aim of this article is to provide a systematic and updated review on the pharmacology of cannabidiol in the context of refractory epilepsy, with special emphasis on its pharmacokinetics, adverse drug reactions and drug-drug interactions.
Method: A review of the literature related to cannabidiol pharmacokinetics, adverse drug reactions and drug-drug interactions was carried out in the context of refractory epilepsy, through a search in PubMed and LILACS.
Results: Original studies that exhaustively describe the pharmacokinetics of cannabidiol are limited but informative. Cannabidiol is rapidly absorbed and its bioavailability increases when administered with high fat meals. Cannabidiol exhibits a linear pharmacokinetic profile for doses up to 3,000 mg/day and accumulates after multiple administrations. Elimination half-life has been reported between 14 h and 60 h depending on the sampling times of each study; changes in cannabidiol elimination due to continuous administration cannot be discarded. Of all reported drug-drug interactions with anticonvulsants or other co-administered drugs in patients with epilepsy, the strongest evidence is provided with clobazam. The most frequent cannabidiol-related adverse drug reactions were low to moderate and included somnolence, mainly related to concomitant administration of clobazam, and gastrointestinal alterations. Also, liver function abnormalities were reported during the use of cannabidiol and valproic acid.

Resumen

Objetivo: El objetivo del presente trabajo es brindar una revisión sistemática y actualizada acerca de la farmacología de cannabidiol, con especial énfasis en la farmacocinética, eventos adversos e interacciones, vinculada al uso de este fármaco en epilepsias refractarias.
Método: Se realizó una revisión de los trabajos publicados y relacionados con la farmacocinética y los eventos adversos e interacciones farmacológicas de cannabidiol utilizado para el tratamiento de las epilepsias refractarias mediante una búsqueda en PubMed y LILACS.
Resultados: Los estudios originales que describen la farmacocinética de cannabidiol de manera exhaustiva son limitados aunque informativos. La absorción de cannabidiol es rápida y se incrementa la biodisponibilidad por la ingesta conjunta de comidas ricas en grasas. El cannabidiol presenta farmacocinética lineal hasta dosis de 3.000 mg/día y se acumula por la administración continua. La semivida de eliminación se referencia entre 14 y 60 horas dependiendo de los tiempos de toma de muestra del estudio farmacocinético y no se descartan modificaciones en la eliminación por la administración en dosis múltiples. De las interacciones farmacológicas entre cannabidiol con otros fármacos antiepilépticos referenciadas hasta el momento, aquella con clobazam es la que presenta mayor evidencia científica. Los eventos adversos más frecuentes asociados al uso de cannabidiol fueron de gravedad leve o moderada e incluyeron somnolencia, principalmente por el uso conjunto de clobazam, y alteraciones gastroin-

Conclusions: Given the increased use of cannabidiol in refractory epilepsy, a comprehensive understanding of its pharmacological profile is essential for the clinical team. Specifically, clinical pharmacists play an important role in monitoring cannabidiol's safety and efficacy. This approach leads to treatment optimization, allowing to maximizing the pharmacological activity and minimizing the occurrence of adverse events as well as drug-to-drug interactions. Clinical follow-up is essential to avoid discontinuation of treatment or exacerbation of adverse events, which may impair the patients' quality of life.

testinales. Se evidenciaron asimismo anormalidades en la función hepática concomitantes con el uso de ácido valproico.

Conclusiones: Ante la creciente demanda de la utilización de cannabidiol en epilepsias refractarias, es fundamental el conocimiento de su farmacología por parte del equipo de salud. En especial, el farmacéutico clínico juega un papel primordial en la monitorización de su seguridad y eficacia. Esto permite la optimización del tratamiento clínico del cannabidiol administrado conjuntamente con otros fármacos antiepilépticos de mayor uso, lo que conduce a maximizar la actividad farmacológica y minimizar la aparición de eventos adversos al igual que de interacciones farmacológicas. El seguimiento clínico del paciente resulta fundamental para evitar la discontinuación del tratamiento o exacerbación de eventos adversos que afecten la calidad de vida del paciente.

Introduction

Cannabis sativa has been an important resource in the therapeutic arsenal of herb shops and medical pharmacopoeia for many centuries but it was only at the beginning of the 1990s that science provided a better understanding of its clinical potential[1,2]. Over the years, a significant increase has been observed in the number of reports (mainly pre-clinical studies) looking into the mechanism of action of cannabinoids (CBs). Nonetheless, few properly monitored case studies and clinical studies on the efficacy, effectiveness or safety of CBs have been published[3]. This means that healthcare professionals, including clinical pharmacists, play a very important role in promoting an appropriate use of CB-based formulations such as cannabidiol (CBD) and tetrahydrocannabinol (Δ9-THC)[4]. In this context, a significant expansion in the uses of CB is expected in the next few years. This will require healthcare professionals to be appropriately trained in CB pharmacology to provide clinical decision support[4].

Regarding CBD, refractory or drug-resistant epilepsy is the physiopathological condition for which it is most frequently prescribed. Several clinical studies demonstrate the effectiveness and safety of the treatment, particularly in children suffering from the disease[5-10]. Nevertheless, data on the potential adverse events associated to CBD are limited. Thus, a pharmacologically effective treatment may eventually be discontinued. Gaining such knowledge is essential for appropriate clinical management[4]. In addition, CBD is routinely administered in patients who also receive other drugs and/or nutrients that could interact with it, limiting the efficacy and increasing the toxicity of CBs or the concomitant drugs[3].

Cannabis sativa contains over 500 different compounds including flavonoids, terpenes and CBs, in addition to carbohydrates, fatty acids and their esters, amides, amines and phytosterols[11]. At least one-hundred of the CBs compounds are pharmacologically active[3,12,13]. According to the demonstrated pharmacological activity and the quantity, CBD and THC are the main compounds in *C. sativa* (Figure 1). CB acids are present as primary

metabolites in *C. sativa* but do not produce any significant psychotropic effects. However, they do exhibit some pharmacological activity. Cannabidiolic acid (CBDA) and tetrahydrocannabinolic acid (THCA) are the natural precursors of CBD and Δ9-THC, which convert to them through exposure to UV radiation, heat, and long-term storage[2,13].

The discovery of the endocannabinoid system, including endogenous CBs or endocannabinoids such as anandamide, CB receptors and their regulatory enzymes, made a decisive contribution to the understanding of the pharmacological profile of CBs[14]. The endocannabinoid system plays an hemostasis-regulating role in the brain, the skin, the digestive tract, the liver, the cardiovascular system, the genitourinary system and even the bones.

G protein-coupled receptors, nowadays known as CB1 and CB2, differ in the biological processes they are involved and in their anatomic distribution. CB1 receptors predominate in the central and peripheral nervous systems and are less active in other tissues such as the spleen, the tonsils, the gastrointestinal tract, the uterus, the prostate and the adrenal glands. In contrast, CB2 receptors are found mainly in the immune system and are less represented in the central and peripheral nervous systems and the gastrointestinal tract[13-15]. The roles of these receptors are also different: while CB1 receptors are involved in the central regulation of food intake, response to novelty and stress, addictive behavior, regulation of hepatic and gastrointestinal activity, smell and cardiovascular activity, CB2 receptors play a role in immune regulation, neurodegeneration and, to a lesser extent, in the processing of reward and addictive behavior[16]. THC exerts its main psychoactive effects mediated by CB1 receptors[1].

Noticeably, not all CB activity is mediated by CB1 or CB2 receptors. G protein coupled receptors 18 and 55 (GPR18 and GPR55), the transient receptor potential vanilloid type 1 (TRPV1) and peroxysome proliferator-activated receptors alpha and gamma (PPARα and PPARγ) also play an important role[13,15,17-19]. This means that CBD is a non-psychoactive substance involved in modulating different receptors outside the endocannabinoid system, which explains its antiepileptic, anti-inflammatory, analgesic and anxiolytic properties[19-22].

The mechanism of action of CBD in the setting of epilepsy is not yet fully understood. CBD has demonstrated significant activity against the disease and has been found to bind to more than 65 different molecular targets. However, the concentrations required for binding do not seem to be achievable in the human brain[22]. Moreover, the idea that THC could contribute to the anti-seizure activity of CBD through the CB1 receptor should not be ruled out[19,23]. The main molecular targets of CBD include voltage-dependent calcium channels, which are involved in regulating neuronal excitability. The interaction of these channels with CBD results in their inhibition, which could explain their anti-seizure activity[24]. The agonistic activity of CBD on TRPV1 leads to a desensitization of voltage-dependent calcium channels and normalization of intracellular calcium levels[24]. Regarding serotonin receptors, subtypes 5-HT1A and 5-HT2A could constitute a valid therapeutic target for CBD[19,24]. Other receptors related with the activity of CBD in epilepsy include glycine-activated ion channels, GPR55, the γ-aminobutyric acid type A (GABA$_A$) receptor, modulation of adenosine, the voltage-dependent anion-selective protein (VDAC1) and the release of tumor necrosis factor-alpha (TNFα)[21,25-27]. In addition, CBD appears to exert an anti-seizure effect by inhibiting the μ and δ opioid receptors[24]. CBD also seems to reduce inflammation of the nervous system by downregulating its proinflammatory

Figure 1. *Molecular structure of cannabidiol and Δ9- tetrahydrocannabinol.*

Δ9-tetrahydrocannabinol (Δ9-THC)

Cannabidiol (CBD)
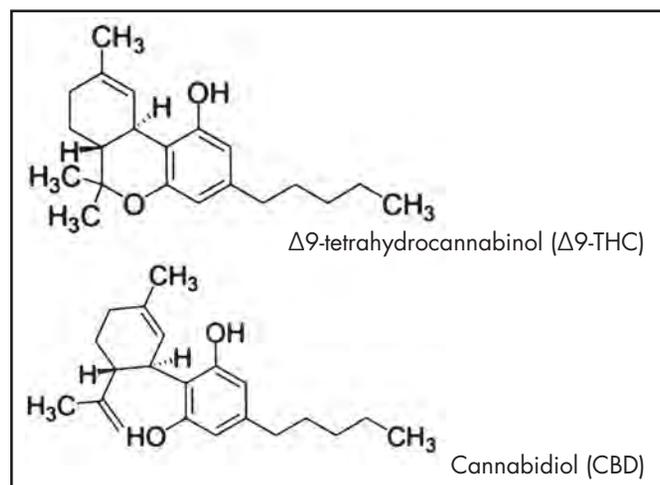
functions and inhibiting astrocyte signaling, which has shown to prevent proliferation of inflammatory cytokines (IL-6) in animal models. However, the role played by neuroinflammation in the onset and progression of seizures is still under research[19]. Moreover, other kinds of CB such as cannabichromene, Δ9-THC and CBD propyl analogs (Δ9-tetrahydrocannabivarin and cannabidivarin, respectively) were also found to be active in the central nervous system, although their molecular pharmacology and mechanisms of action are less understood[20].

CBD is able to modulate some of the effects of Δ9-THC as it decreases the psychoactive effects of Δ9-THC, boosting its tolerability and potentiating its therapeutic range. Besides, CBD may counteract some of the psychoactive effects of CB1 activation on the brain, possibly through an indirect enhancement of the activity of adenosine A1 receptors. This may explain, at least in part, why users of cannabis preparations with a high CBD/Δ9-THC ratio are less likely to develop psychotic symptoms than those using preparations using preparations for which this ratio is low. These and other mechanisms of action of CBD may contribute to the so-called "entourage effect" between CBD and THC and to the ability of CBD to reduce THC's psychoactive side effects[16,20]. At the same time, CBD may reinforce the antiseizure effects of Δ9-THC[20].

Treatment with CBD involves regular and continuous administration of the drug over time. The pharmacokinetic profile of CBD depends on several factors including the administration route, the type of product, the concomitant administered drugs, the pathological status of the patient, and even the type of diet. For that reason, the present study focuses only on the pharmacokinetic and pharmacodynamic profile of CBD contained in products approved by health authorities. As these products are manufactured under good manufacturing practices, the composition is well established, the potential variability in CBD pharmacokinetics or safety will not depend on the pharmacotechnical characteristics of the drug product.

Furthermore, it is worth mentioning that CBD pharmacokinetic profile varies across different animal species. This fact must be taken into consideration when performing clinical studies, so as not to make incorrect extrapolations and draw erroneous conclusions[28].

The present paper reviews the state of the art of CBD pharmacology, with special emphasis on the pharmacokinetics, drug-drug interactions and adverse drug reactions related to CBD in the context of refractory epilepsy. It also provides key tools to assist clinicians in daily practice.

Methods

The present review included preclinical and cohort studies of pediatric and adult patients published in PubMed and LILACS up to December 2019. The search included the following MeSH terms: "cannabidiol", "pharmacokinetics", "bioavailability", "adverse drug reactions", "drug-drug reactions" and free-text terms in Spanish. The following filters were applied in a sequential, additive and alternative manner: "Other animals", "Humans", "Clinical trials", "Adults: +19 years" and "Child: birth-18 years". In order to analyze the pharmacokinetic and pharmacodynamic parameters of CBD and their mutual association, only original *in vitro* studies were considered, as well as studies performed in animal models or pediatric or adult human subjects, as appropriate for each variable under study, provided that the manuscripts were available in their full text format.

Results

In total, 2,783 articles were identified, of which 61 met the extended selection criteria. Of these, 31 articles were included, which were original *in vitro* studies as well as original studies performed in humans or animals.

Pharmacokinetics

Absorption of CBD was found to be fast, with maximum plasma concentrations (Cmax) being reached at 0.5-6 h following administration in children and adults[29-34]. A study on adult volunteers analyzed the behavior of CBD following single and increasing doses between 1,500 and 6,000 mg, with maximum plasma concentration (Cmax) being attained at 3-5 h (Tmax) from administration, regardless of dose[30]. It was also found that for doses of CBD equal or higher than 4,500 mg (approximately 64 mg/kg/day, considering an average weight of 70 kg for an adult), CBD presents a non-linear pharmacokinetics, i.e. as both Cmax and the area under

the curve defined by the concentration over time (AUC) showed disproportional increases relative to the change in dose. Furthermore, no differences were observed in the elimination half-life with the increasing CBD doses. Therefore these results suggest bioavailability decreases with higher CBD doses[30]. Nevertheless, children showed a linear increase in systemic CBD exposure between 10 and 40 mg/kg/day doses[7].

After repeated administration of 750 or 1,500 mg of CBD every 12 h, the steady state was reached after 2-4 days. CBD and its metabolites Tmax were attained at 3 h, regardless of the dose. In this cohort of volunteers taking multiple doses between 750 and 1,500 mg, a 2 to 3-fold accumulation of CBD was observed. Also, CBD systemic exposure doubled by twice increasing the dose, which corresponds to linear pharmacokinetics in the evaluated dose range[30]. Another interesting finding in this study was that systemic exposure to CBD administered during the night was 2- to 6-fold higher than that recorded during daytime administration (following an 8-12 h fasting period). This may be explained as a result of a postprandial and chronopharmacokinetic effect.

Although no reports exist regarding CBD oral bioavailability, it is estimated to be low (6-10%) given the first pass effect mainly mediated by the CYP3A4 enzyme, a member of the most abundantly expressed P450 subfamily in the small intestine, which acts as a barrier against xenobiotics[35-37]. Moreover, the highly hydrophobic nature of CBD, and its low solubility in gastrointestinal fluids, explain CBD's low oral bioavailability[37].

Recent studies shed some light into the food effect on the bioavailability of CBD. Zgair *et al.* found an increase in CBD oral bioavailability in an animal model when they administered it together with a following a high-fat/calorie meal. This increase probably occurred because the lipid-rich meals favored absorption of CBD, mediated by the lymphatic system of the gut[38]. Several studies on healthy adults have shown that administration of a low dose (300, 750 or 1,500 mg) of CBD following with a high-fat/calorie meal meal results in a four-fold increase in the CBD systemic exposure compared with its administration on an empty stomach[30,32,33]. Some authors report that the variability of CBD plasma concentrations was lower after it was administered with a meal[30]. In addition, administration of 750 mg of CBD accompanied by a low-fat/calorie meal or by milk also led to a 3 to 4-fold increase in the bioavailability of the CB given the reduction in the apparent volume of distribution (Vd/F) and the apparent clearance (Cl/F), but not in the elimination half-life (t$_{1/2}$)[33]. These results means that administration of CBD with food leads to increased bioavailability. This effect may be due to the fact that lipid-rich foods increase gastrointestinal transit time and stimulate the secretion of bile acids that emulsify lipids and hydrophobic compounds, promoting dissolution and absorption of CBD. On the other hand, preclinical studies have suggested that hypercaloric meals favor absorption of CBD, mediated by the gut's lymphatic transport system[38]. Nevertheless, it would be interesting to determine whether this increased bioavailability results in an improvement in the control of seizures, and if so, without affecting the incidence of adverse drug reactions.

Importantly, efflux pumps such as ATP-dependent transporters may play a very significant role in the bioavailability of drugs[39].

As CBD is poorly water-soluble and is subject to an extensive first-pass metabolism in the gastrointestinal tract, an alternative way to increase its absorption and improve its bioavailability is sublingual administration[40,41]. This route of administration bypasses the first-pass metabolism, with the active ingredient reaching directly into the systemic circulation. However, this route of drug administration may lead to a decrease in bioavailability given the existence of a salivary gland below the tongue that is stimulated by sublingual formulations, being difficult for the patient to avoid swallowing[42].

Regarding distribution, both CBD and its metabolites bind strongly to plasma proteins (>95%), mainly low-density lipoproteins. Around 10% of CBD is bound to circulating red blood cells and only 2-3% is unbound[20,43-46]. Given its lipophilic nature, CBs are widely distributed in the body; firstly in highly vascularized organs, then in less vascularized tissues and finally in fatty tissues, where it is stored on a long-term basis. The affinity of CBD to fatty tissue prompts its deposit after chronic aadministration particularly in obese patients. CBs cross the placenta and are excreted through breast milk during lactation. Studies on pregnant animals

found that fetal plasma concentrations of CB were 10% of maternal concentrations[48,49].

In healthy adults who received a dose between 1,500 and 6,000 mg of CBD, Vd/F reached values between 1,111 and 1,909 L, in line with reports describing CBD's high volume of distribution[30]. Although there are no data on the concentration of CBD in different types of human tissues, studies performed in rats showed that CBD concentrations in the brain was 30% of that observed in the plasma, with a homogeneous distribution across all cerebral regions[50,51].

A series of *in vitro* studies on human liver models suggested that enzyme-catalyzed processes responsible for CBD metabolism comprise oxidation, mediated by cytochrome P450 (CYP) isoenzymes CYP2C19, CYP3A4 and, to a lesser extent, CYP1A1, CYP1A2, CYP2C9, CYP2D6 and CYP3A5, as well as the glucuronyl-transferase activity of uridine-diphosphate glucuronidase (UGT) UGT1A7, UGT1A9 and UGT2B7[52,53]. These reactions involve oxidation of the molecule to form 7-OH-CBD, and subsequent modifications that result in the formation of over 100 metabolites identified in different organisms[54]. The CYP2C19 enzyme mediates the formation of the pharmacologically active metabolite 7-OH-CBD, which is in turn transformed by CYP3A4 to 7-COOH-CBD, an inactive and main compound found in human blood[30-33,52-54]. CBD also metabolizes, to a lesser extent, to 6-OH-CBD through the CYP2C19 and CYP3A enzymes, as well as to other inactive metabolites, through the CYP1A and CYP3A enzymes[54,58]. Noticeably, even if the predominant metabolites are 6-OH, 7-OH and 7-COOH-CBD, the metabolite profile differs across different animal species, so extrapolation to humans of the results obtained in animals should be done with caution.

Clearance of intact CBD, CBD-glucoronide and free or conjugated metabolites occurs mainly through the feces. Renal excretion plays a minor role[57]. More than thirty years ago, in a study on healthy adult volunteers administered with 20 mg of deuterated intravenous CBD, the clearance reported was 960-1,560 ml/min and the elimination half-life was 24 h[58,59]. Sixteen percent of all cleared CBD was excreted in the urine, most of it as unchanged drug and, in a smaller proportion, as CBD conjugates. The feces contained 33% of the eliminated products, mainly as unchanged CBD and also, in a smaller proportion, as mono- and dihydroxylated metabolites, carboxylic derivatives and glucuronid acid conjugates[59].

Several studies on adults obtained CL/F values between 6 and 20 L/h/kg following oral administration of CBD regardless of the dose, which represents a substantial elimination of the drug from the body[30-33]. In pediatric populations, to date, only one study has been published on this subject reporting CL/F of CBD oil. Cl/F values ranged between 24 to 38 L/h/kg in all patients, regardless of whether they received CBD alone or CBD with clobazam[7]. Noticeably, in adults with severe hepatic impairment, Cl/F was 0.3 L/h/kg[60]. This will be discussed below.

Drugs like CBD that exhibits a wide distribution in the adipose tissue leading to a multi-exponential decrease in their plasma concentration. Therefore, the $t_{1/2}$ value may be misleading as the balance between plasma and adipose tissue concentrations is gradually reached. This explains the dissimilar $t_{1/2}$ values reported in the literature for CBD in children and in adults, after a single or multiple doses, ranging between 14 and 60 h[7,30-33].

Pharmacokinetics in liver dysfunction

As mentioned above, CBD undergoes a predominantly hepatic metabolism, which means that any functional alteration in the liver is likely to affect CBD pharmacokinetics. A recent study reported at the effect of liver dysfunction on CBD pharmacokinetics in adults with a normally functioning liver or with mild, moderate or severe hepatic alterations[60]. Systemic CBD exposure increased two to five times, correlated with the degree of liver dysfunction. Besides, an increase in $t_{1/2}$ and a reduction of Cl/F was observed in patients with severe hepatic impairment. Regarding metabolites, high systemic exposure to 6-OH and 7-OH-CBD was found in severe cases of liver dysfunction. On the contrary, systemic exposure to 7-COOH-CBD decreased in patients with severe liver dysfunction, probably as a result of a decreased metabolic rate. Furthermore, the manufacturer of Epidiolex®, a product that contains CBD as an active ingredient, recommends titrating the dose in patients with moderate or severe liver dysfunction[43]. These re-

sults highlight the need of close therapeutic monitoring in patients with liver dysfunction.

Pharmacokinetics in the pediatric setting

After the administration of 1.25 mg/kg/day of CBD in pediatric patients with refractory epilepsy, Cmax was approximately 30 ng/mL and Tmax was 2.5 h[5]. In the same study, repeated administration of 5, 10 or 20 mg/kg/day of CBD resulted in a mean Cmax of 130, 242 and 380 ng/mL, respectively. This demonstrates a linear increase in CBD systemic exposure according to the dose in the study range. Nonetheless, the authors reported an AUC variability between 20 and 120%. The main metabolite was 7-COOH-CBD with an exposure between 12 and 17 times higher than that of CBD. Systemic exposure to 6-OH-CBD was lower than 6%. The ratio between 6-OH-CBD and CBD exposure remained constant throughout the three dosing levels. This was not the case for the ratio between 7-COOH-CBD and CBD AUC. This highlights the importance of the metabolic pathway of CBD towards 7-COOH-CBD and the accumulation of this metabolite.

In another pharmacokinetic study in pediatric patients[7] subjects received a synthetic formulation of CBD (different from that used in the previously cited study) during 10 days at doses of 10, 20 and 40 mg/kg/day BID. This report showed that CB exposure increased proportionally with the administered dose. Mean Cmax values for each dose were 120, 220 and 427 ng/mL, respectively, which supports the hypothesis that CBD has a linear pharmacokinetic profile. However, these Cmax values double those reported by Devinsky *et al.*[5], which may be attributed to the number of samples obtained to characterize the pharmacokinetic profile and to the different CBD formulations. Moreover, the authors reported a CBD $t_{1/2}$ between 20 and 30 h regardless of the dose administered, which supports the lineal pharmacokinetics hypothesis. Importantly, authors reported high interindividual variability in CBD pharmacokinetics and lower CBD concentrations in children younger than 2 years old compared to other groups of pediatric patients. These findings emphasize the need of characterizing CBD pharmacokinetics for each available product on the market and adapting the CBD dose to the individual requirements according to the age.

Drug-drug interactions

Drug-drug interactions may be additive, synergistic or antagonistic and may result in an altered therapeutic response (therapeutic failure or toxicity). Pharmacokinetic interactions develop as CBD is predominantly metabolized by CYP450 enzymes. This means that concomitant administration of drugs that induce or inhibit the isoenzymes that play a role in the transformation of CBD will modify its systemic exposure. It should be emphasized that there may be different types and degrees of interaction between the co-administered drug and CBD according to the available products on the market. Particularly, these formulations are not always approved by the health authorities and their composition and degree of purity often remain unknown. This means that if the concentration of CBD in the product is lower or higher than the one informed on the label, the interaction may not occur or, conversely, may be substantially higher than that recorded for pharmaceutical grade CBD products. For that reason, this study only addresses interactions observed in studies using pharmaceutical grade CBD products.

Interactions between Sativex® (composed of CBD and THC in a 1:1 ratio) and rifampicin, ketoconazole and omeprazole were evaluated in adult volunteers. Co-administration of repeated doses of rifampicin, a well-known CYP3A4 and CYP2C19 inducer, resulted in a 50% reduction of CBD (and THC) systemic exposure and an increase in Cl/F, whereas concomitant administration of ketoconazole (a CYP3A4 inhibitor) led to a 100% increase in CBD systemic exposure. Moderate CYP2C19 inhibitors such as omeprazole were not found to have any effect on CBD pharmacokinetics[61].

The *in vitro* inhibitory activity of CBD on CYP2C19 can also be observed in clinical practice, specifically in patients with epileptic encephalopahy, who are often treated with a combination of CBD and clobazam (CLB). Biotransformation of CLB through demethylation, gives rise to the active metabolite N-desmethyl-clobazam (N-CLB), which is metabolized by CYP3A4, CYP2C19 and CYP2B6. Subsequently, N-CLB becomes hydroxylated to

form an inactive metabolite 4′-OH-N-CLB through the action of CYP2C19[63]. Foe this reason, co-administration of CLB and CBD (which inhibits CYP2C19 and CYP3A4) results in the inhibition of N-CLB metabolism and the accumulation of N-CLB with development of adverse events such as somnolence[64-67].

In pediatric epileptic patients, combined treatment with CBD and CLB did not affect CLB systemic exposure but did result in a 500% increase in N-CLB concentrations after 21 days. Also, the ratio between N-CLB and CLB concentrations, increased up to 660% compared to the first day of treatment with CBD, which exhibit the metabolic inhibition of N-CLB and the accumulation of that metabolite[66]. In line with these findings, a study by Geoffrey *et al.* in pediatric patients who received CBD (at a dose that increased from 5 mg/kg to 25 mg/kg/day) and CLB, demonstrated a 500% increase in N-CLB levels as a result of the combined treatment. The increase in N-CLB levels led to the appearance of somnolence, which resolved when the dose of CLB was reduced[67]. CBD concentrations may also be affected. A two-fold increase in CBD exposure was observed in patients receiving 40 mg/kg/day doses of CBD simultaneously with CLB[7]. In these pediatric patients, CLB and N-CLB concentrations were twice as high as those found in patients receiving lower doses of CBD. Lastly, in pediatric and adult epileptic patients who received CBD (initial dose: 5 mg/kg/day inclreasing to a maximum of 50 mg/kg/day)[66], an increase in serum concentrations of N-CLB, topiramate and zonisamide was observed when higher doses of CBD were administered. This may be explained by the competition for the CYP2C9, CYP2C19 and CYP3A4-metabolic pathways.

The only study on healthy adult volunteers designed to quantify the interaction between clobazam, striripentol or valproate with CBD and its metabolites demonstrated a notable increase in N-CLB exposure without alteration of the pharmacokinetic profile of striripentol, valproate or valproate metabolite after concomitant administration with CBD[64]. Furthermore, repeated administration of clobazam led to an increased in 7-OH-CBD exposure without modification of CBD or 7-COOH-CBD. Striripentol, in turn, led to a slight but significant decrease in 7-OH-CBD and 7-COOH-CBD exposure. Once again, valproate did not affect CBD pharmacokinetics.

Other drugs are subject to interactions with CBD given its inhibitory effect on the activity of CYP2C19 and CYP3A4, and to a lesser extent on CYP1A1, CYP1A2, CYP1B1, CYP2A6, CYP2B6, CYP3A5, CYP2D6 and CYP2C9, and on glucuronidation enzymes UGT1A9 and UGT2B7[53,55,57,68,69]. Therefore, dose adjustments of drugs subject to metabolism by these enzymes, such as valproic acid, are recommended. Also, phenobarbital, carbamazepine and phenytoin are enzymatic inducers which, according to data obtained from *in vitro* studies, could promote a decrease in CBD levels[53]. Furthermore, CBD may induce an increase in antiepileptic drug concentrations through enzyme inhibition or disrupt the activity of P-glycoprotein (Pgp).

Some *in vitro* and animal studies have demonstrated that CBD interacts with ATP-dependent transporters such as the breast cancer resistance protein (Bcrp) and Pgp. For this reason, modulation of these efflux transporters by CBD could also have an impact on the absorption and bioavailability of other concomitantly administered drugs. According to some preclinical studies, CBD inhibits Pgp and Bcrp and could therefore lead to pharmacokinetic changes in other drugs that are substrates of these transporters[70-73]. Although cytochrome P450 enzymes inhibitors are often substrates, *in vitro* studies with Madin-Darby Canine Kidney (MDCK) cells and *in vivo* studies on murine models demonstrated that CBD is not a Pgp substrate but induces a negative regulation in Pgp expression[74,75]. Thus, given that overexpression of these transporters has been described in refractory epilepsy, the concomitant use of CBD and antiepileptic drugs substrates of these transporters such as phenytoin, would be beneficial since it would lead to higher concentrations of the antiepiletic drugs at the site of action.

In summary, therapeutic drug monitoring of antiepileptic drugs, including CBD, is essential to optimize the treatment as drug-drug interactions may result in adverse events or therapeutic failure.

CBD adverse drug reactions

Different studies conducted in pediatric patients with Dravet syndrome and refractory seizures who received CBD 5 to 20 mg/kg/day BID in combination with other antiepileptic drugs, reported that at least 90% of patients developed adverse drug reactions (ADRs)[5,6]. Most frequent ADRs included somnolence, diarrhea, decreased appetite, fatigue, vomiting, fever, seizures and upper respiratory tract infections. Liver function tests yielded normal results[5,6,7,34]. Eighty-four percent of ADRs were mild to moderate in the CBD group, and were related to the administration of the compound. Severe ADRs comprised fever, seizures, thrombophlebitis, apnea and skin rash[6,7]. Although some studies indicate that ADRs occurred regardless of the administered dose, others confirm the existence of a relationship between CBD dose and certain ADRs such as decreased appetite, diarrhea, weight gain, somnolence and psychomotor agitation[5,7]. In patients with clinically significant weight loss, dose reduction or suppression of CBD generally led to stabilization and weight gain[8]. Noticeably, 80% of patients who developed somnolence, were also receiving CLB. In most patients, the event was reversed by decreasing the CLB dose. Importantly, patients treated with valproic acid presented abnormal liver function tests[5,6,34]. In some cases these values normalized after reduction of the valproate dose or discontinuation of CBD[5,6,8].

In a retrospective study, which analyzed 70 children, adolescents and young adults suffering from refractory epilepsy, ADRs were evaluated after administration of CBD oil solution at a CBD dose of 1-3 mg/kg/day to 16 mg/kg/day BID. The most commonly used concomitant antiepileptic drugs included valproic acid, clobazam, vigabatrin, lamotrigine and phenobarbital, followed by levetiracetam, topiramate, rufinamide and oxcarbazepine. AEs were observed in five children. One patient developed reduced motility at a dose of 20 mg/kg/day, which reversed by reducing the dose to 10 mg/kg/day. A morbidly obese patient receiving high doses of CBD (1,000 mg/day), developed nocturnal enuresis which reversed by reducing the dose to 800 mg/day. In one patient, development of eosinophilia caused the discontinuation of CBD treatment, although the association between the adverse events and CBD was unclear. Stomachache in one patient was associated with slightly elevated liver enzymes, which normalized after reduction of CBD doses[9].

Table 1 provides a description of the most frequent and the most severe adverse drug reactions associated to CBD.

Table 1. Adverse drug reactions to cannabidiol

Classification	Adverse drug reactions
Common adverse events	– **Dermatologic:** Skin rash. – **Gastrointestinal:** Decreased appetite, diarrhea and vomiting. – **Immunologic:** Infection (upper respiratory tract). – **Neurologic:** Asthenia, insomnia (sleeping difficulty or sleeping disorders), somnolence (in general associated to clobazam), sedation, dizziness, seizures, catatonia. – **Others:** Fatigue, anemia, general discomfort, changes in normal behavior, ataxia, weight loss and fever.
Severe adverse events	– **Hepatic:** Higher liver aminotransferase levels. – **Psychiatric:** Suicidal ideation and behavior. – **Respiratory:** Hypoxia and respiratory failure. – **Others:** Weight loss.

Discussion

The increasing use of CBD in the treatment of refractory epilepsy has attracted the interest of the scientific and clinical community as well as the general population using the drug. For that reason, it is extremely important that health care professionals, specially pharmacists, are informed regarding the approved uses of CBD, its mechanism of action, pharmacokinetic characteristics, effectiveness and safety profile. This is crucial as CBD is included in the therapeutic arsenal against epilepsy. It is also important to consider the potential drug-drug interactions when combining CBD with other drugs as this may increase the risk of ADRs. Understanding potential AEs resulting from CBD and their appropriate clinical management is extremely important to maximize treatment outcomes, and to avoid discontinuation and enhance quality of life in patients with refractory epilepsy. Data provided by this study may impact and support clinical decisions in the optimization of CBD treatments in refractory epilepsy.

The original studies discussed in this review provide information on CBD pharmacokinetics obtained from preclinical models as well as different patient cohorts, including subjects from different age groups and different health conditions.

CBD presents fast absorption, with a Tmax value between 0.5 and 4 h, which may extend to 6 h[5,7,30,32,33]. Systemic concentrations of CBD presented a 4-fold increase after its administration with lipid-rich foods compared to the fasting state[30,32,33]. Fluctuations in CBD bioavailability according to the type of ingested food are significant. Thus, healthcare professionals are required to issue clear recommendations to patients regarding the administration of CBD on an empty stomach or with food and the need to follow those suggestions throughout the treatment. Future research into this area should be focused in determining whether the increased bioavailability of CBD when co-administered with lipid-rich food is associated (or not) with a higher incidence of CBD-related ADRs or differences in CBD effectiveness.

Prolonged administration of CBD results in the accumulation of the drug. Doses up to 4,500 mg/day in adults (approximately 40 mg/kg/day considering a mean weight of 70 kg) and 40 mg/kg in children exhibit a linear pharmacokinetic behavior[5,7,30]. Higher doses presented a lack of pharmacokinetic linearity, probably due to a reduced absorption of this lipophilic drug.

CBD is mainly eliminated from the body by liver and intestinal metabolism and hald-life values after oral ingestion are within the 14-40h range[7,30,32,33]. This large variation may be attributed to the delay in the equilibrium between CBD concentrations in plasma and in peripheral tissues (particularly adipose tissue). For that reason, pharmacokinetic analyses should include long sampling times. However, this was not the case in all examined studies. Further research regarding the impact of single or multiple doses of CBD on its pharmacokinetics is required. In cases of severe hepatic impairment, adjustment of CBD dose is highly recommended given the decreased clearance of the drug observed in such cases[60].

Patients with refractory epilepsy often receive multiple drugs, which often leads to the development of several drug-drug interactions. Also, given that CBD is a substrate and inhibitor of several cytochrome P450 enzymes, the occurrence of drug-drug interactions is expected[53-58]. Until now, the interaction of CBD with CLB presents the highest evidence in *in vitro* and *in vivo* studies[64,65,67]. Such pharmacokinetic interactions results in increased CLB metabolite levels. The most frequent ADRs associated to CBD were either mild or moderate, and included somnolence, mainly due to concomitant administration of CLB, and gastrointestinal disturbances. In addition, liver function abnormalities were observed in association with the use of valproic acid. Severe ADRs were scarce[5,6,8,9].

One of the most significant limitations of the present study is related to the fact that it focuses its attention mainly on the pharmacokinetic and pharmacodynamic profile of CBD applied to the treatment of refractory epilepsy. This means that other studies might have been excluded that could have provided more comprehensive information. Another limitation is related with the lack of statistical analysis of the data, which is presented qualitatively. One final limitation is related to the scarcity of data provided, which is attributed to the limited available reports in the literature.

In conclusion, the present review provides an update on the knowledge of the pharmacokinetics and pharmacodynamics of CBD to reinforce the role of the clinical pharmacist in the management of patients with refractory epilepsies treated with CBD.

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Conflict of interest

No conflict of interest to declare.

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