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Pharmacology and drug interactions of cannabinoids

Cecilie Johannessen Landmark [1], Ulrich Brandl [2]

[1] Programme for Pharmacy, Faculty of Health Sciences, Oslo Metropolitan University, and The National center for epilepsy and Dpt of Pharmacology, Oslo University Hospital, Norway

[2] Department of Neuropediatrics, University Hospital Jena, Jena, Germany

ABSTRACT – Cannabinoids include a variety of substances, of which cannabidiol (CBD) is the main substance investigated for the treatment of epilepsy, and this will be the focus in the present review. CBD preparations exist in various forms. There are significant differences in quality control regarding content and reproducibility for an approved drug versus herbal preparations. Cannabidiol has challenging pharmacological properties, and pharmaceutical and pharmacokinetic aspects will depend on the formulation or preparation of a certain product. This article will focus on the characteristics, pharmacokinetic challenges, and interactions of standardised CBD-containing drugs based on evidence from clinical and pharmacokinetic studies.

Key words: cannabidiol, CBD, epilepsy, treatment, pharmacology, interaction, Dravet syndrome, Lennox-Gastaut syndrome

Pharmacokinetic properties of CBD

CBD has challenging pharmacokinetic properties that differ from most other antiepileptic drugs (AEDs). An ideal drug would have near absolute bioavailability, distribution with low protein binding, and non-CYP mediated metabolism such that elimination would be predictable. In contrast, CBD has limited and variable bioavailability for oral oil formulations (<6%), due to extensive first pass metabolism in the liver (Bialer *et al*., 2017, 2018). It was recently demonstrated that the absorption is increased 4-5-fold when ingested with a fat-rich meal (Taylor *et al*., 2018). With new nanotechnology (PTL401 capsules), the relative oral bioavailability of cannabinoids, CBD and tetrahydrocannabidiol (THC), was increased by 31% and 16%, respectively, when compared to oromucosal spray in 14 volunteers (Atsmon *et al*., 2018).

CBD has a 99% protein binding capability, leaving only 1% accessible to be distributed across the blood-brain barrier for pharmacological action (*table 1*). Changes in protein binding due to low albumin or interactions with other highly bound drugs could then affect this parameter. The volume of distribution of such drugs is extremely large, and clearance could be affected if the drug is a low extraction drug in the liver. CBD is metabolised through CYP2C19 to the active metabolite, 7-hydroxy-CBD, and further to inactive metabolites as a carboxylic acid and glucuronoids through CYP3A4 and UGTs (*figure 1*). The inactive metabolites are excreted in the faeces and urine (*figure 1, table 1*).

Correspondence:
Pr. Cecilie Johannessen Landmark
Faculty of Health Sciences, Oslo Metropolitan University,
and The National center for epilepsy and Dept of Pharmacology,
Oslo University Hospital, Pilestredet 50, N-0167 Oslo, Norway
<cecilie.landmark@oslomet.no>

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Table 1. Pharmacokinetic characteristics of CBD.

Pharmacokinetic properties	Comments
Absorption Bioavailability ≈6 %, T_{max} 90-120 min, oral oil formulation	Minimal absorption Extensive first-pass metabolism through CYP3A4 Substantial variability between patients, >4-5-fold with a fat-rich meal
Distribution Protein binding 94-99 %, V_d 20-40.000 L!	Variability in free fraction? Displacement interactions?
Metabolism CYP3A4, 2C19, UGT1A7,1A9,2B7, $t_{1/2}$ 24-60 h	Strong enzyme-inhibiting properties, PGP?, active metabolite, 7-OH-CBD
Excretion Faeces, urine unchanged 12%	

Despite the publication of almost 800 articles, revealed in a recent update on the pharmacokinetics of cannabidiol in humans, appropriate data to draw quantitative comparisons was only available from 24 studies (Millar *et al.*, 2018). This highlights the need for more research and documentation.

Pharmacokinetic interactions

CBD exhibits numerous interactions with AEDs, both pharmacodynamic and pharmacokinetic (Johannessen Landmark and Patsalos, 2010; Johannessen and Johannessen Landmark, 2010; Johannessen Landmark *et al.*, 2012, 2016; Patsalos, 2013a, 2013b). Pharmacokinetic interactions are easier to evaluate, as the consequence of such interactions includes a change in the serum concentration of the affected drug. Pharmacokinetic interactions may affect the processes of absorption, distribution (protein binding), metabolism, and excretion; the most important step being metabolism by enzyme induction or enzyme inhibition. Commonly used AEDs that interact with CBD include both potent enzyme inducers, such as carbamazepine and phenytoin, and inhibitors, such as stiripentol, felbamate, and valproate (Johannessen and Johannessen Landmark, 2010; Johannessen Landmark *et al.*, 2012, 2016; Patsalos, 2013a, 2013b). CBD is also included among the enzyme inhibitors, as illustrated in *figure 2*. The clinical impact of such interactions in the individual patient is difficult to predict and may have no, moderate, or serious consequences. The measurement of unbound CBD concentration in patients would improve our understanding of drug exposure in the body. Patients should be systematically questioned regarding efficacy, tolerability, and adherence, and serum concentrations should be measured and dosages adjusted accordingly, in order to optimize treatment in each patient.

What do we know so far?

A few studies have characterized the pharmacokinetic interactions between CBD and other concomitantly used drugs, based on the results from clinical trials. Enzyme inhibition by CBD, causing higher levels of various other AEDs, has been shown. Interactions caused by other cannabinoids are less described. The best characterized interaction is the combination of CBD and clobazam, which was a common combination in the clinical studies of CBD. High levels, with up to a five-fold increase in desmethylclobazam, caused an increased risk of toxicity, although there was extensive variability between patients (Geffrey *et al.*, 2015). Sedation was more frequently reported in patients who had high levels of desmethylclobazam (Gaston *et al.*, 2017). This interaction could also contribute to improved seizure control as measured in the studies, however, no comparison of CBD without concomitant use of clobazam has been performed.

Furthermore, serum levels of topiramate, rufinamide, and desmethylclobazam increased moderately in children and adults, and zonisamide and eslicarbazepine levels were found to increase in adults with increasing dose of CBD (Gaston *et al.*, 2017) (*figure 3*). This has to be studied more closely (Franco and Perucca, 2019). The concentration/dose ratio of topiramate increased by 25% in one of our patients in combination with CBD at 20 mg/kg. In addition, we observed a 70% increase in the concentration/dose (C/D) ratio of desmethylclobazam following CBD initiation even at a very low exposure of 1 mg/kg/day (Johannessen Landmark, unpublished observations).

It is likely that other AEDs would be affected based on their metabolic pathways, and CBD may inhibit drugs such as lamotrigine which is mainly metabolised through UGT1A4 and is highly susceptible to enzyme inducers and inhibitors (Johannessen Landmark and Patsalos, 2010; Johannessen Landmark *et al.*, 2016). Furthermore, anecdotal reports indicate that CBD may influence perampanel, metabolised through CYP3A4, via enzyme inhibition, as increased sleepiness was reported in patients following initiation of CBD.

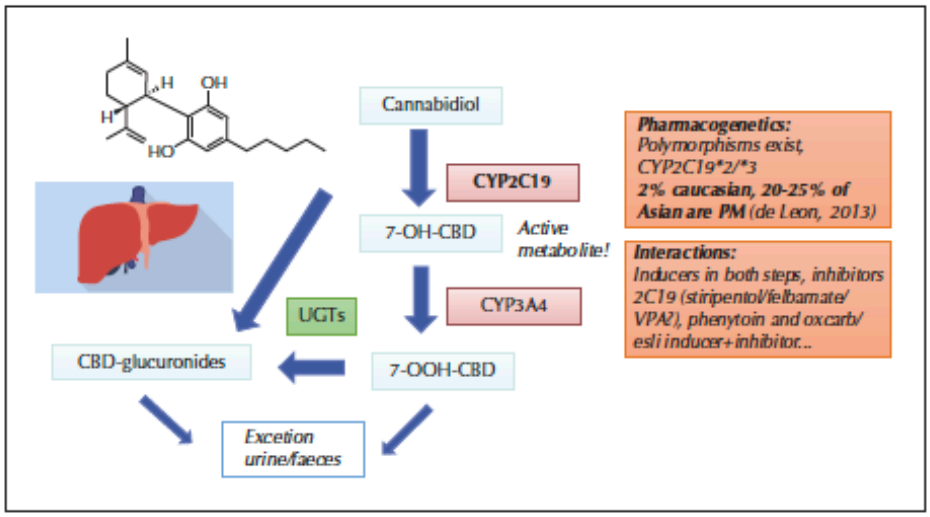

Figure 1. Metabolism of CBD. The metabolism of CBD via CYP and UGT enzymes is illustrated; 7-hydroxy-CBD (7-OH-CBD) is an active metabolite, while the carboxylic acid (7-OOH-CBD) is regarded as an inactive metabolite.

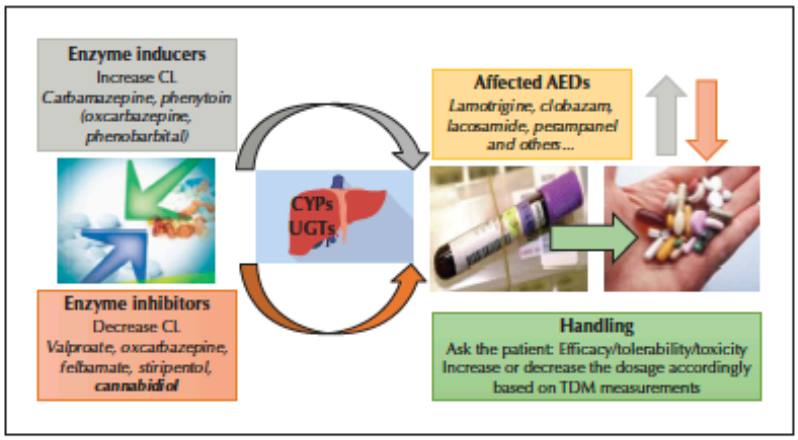

Figure 2. Pharmacokinetic interactions with AEDs. Pharmacokinetic interactions with AEDs in the liver involve enzyme induction; an inducer such as carbamazepine or phenytoin speeds up the metabolism of other drugs (such as lamotrigine) by inducing the synthesis of more enzymes. This process often takes a couple of weeks. The result is that the serum concentration of the affected drug is decreased and a dosage adjustment may be needed. The opposite occurs with an enzyme inhibitor, but this process is more rapid as it is only dependent on the half-life of the drugs involved. The serum concentration of the affected drug is increased, and the dosage may then be decreased accordingly, dependent on the serum concentration achieved through therapeutic drug monitoring (TDM). CL: clearance.

What we do not know?

Possible pharmacokinetic interactions with other AEDs that affect the metabolism of CBD are not yet documented but might be of clinical relevance, such as clobazam. The combination of CBD and stiripentol or valproate is being studied in a Phase 2 trial which may provide answers regarding possible interactions at the level of metabolism as well as protein binding.

Since CBD is metabolised through common pathways that might be affected by other enzyme inducers and inhibitors, conversely, the potential effect of CBD metabolism on other enzyme inducers and

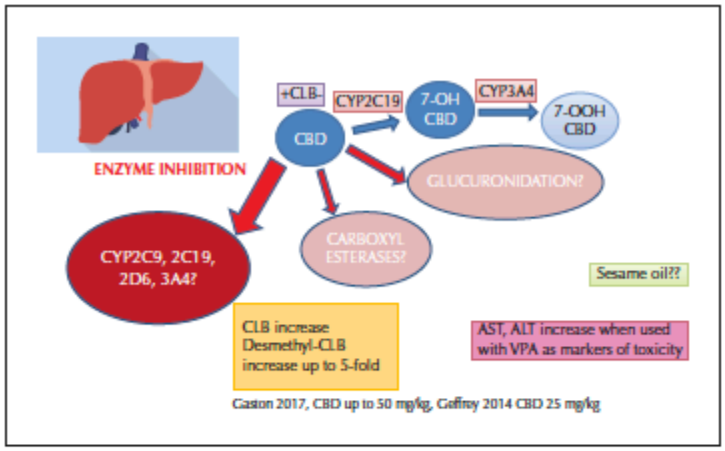

Figure 3. Pharmacokinetic interactions with CBD. The pharmacokinetic interactions that have been documented so far are related to metabolism; enzyme inhibition of various CYP and UGT enzymes (Geffrey *et al.*, 2015; Gaston *et al.*, 2017; Bialer *et al.*, 2018; Franco and Perucca, 2019). No interactions regarding protein binding have been identified, however, such interactions are possible based on the high degree of protein binding of CBD as well as other AEDs (valproate, stiripentol).

inhibitors has not yet been studied. Inducers act at various steps during the metabolism of CBD, CYP3A4, 2C19 and UGTs (carbamazepine, phenytoin), and inhibitors during the metabolism of CYP2C19 and UGTs (stiripentol, felbamate, valproate, and the mixed inducer/inhibitor oxcarbazepine) (Johannessen and Johannessen Landmark, 2010; Patsalos, 2013a; Burns *et al.*, 2016).

Since CBD is 99% protein bound, possible displacement interactions with other highly bound AEDs may occur, such as those commonly used for Dravet syndrome which include stiripentol and valproate. Other candidates might also include clobazam and perampanel based on a recent review of the use of therapeutic drug monitoring (TDM) and measurements of unbound concentrations of all AEDs (Patsalos *et al.*, 2017; Patsalos *et al.*, 2018).

There are therefore still a number of unanswered questions regarding the pharmacology of CBD due to its challenging pharmacokinetics, including absorption and interactions, as also pointed out in a recent expert review (Brodie and Ben-Menachem, 2018).

Recommendations for handling of CBD

Clinical experience has shown that CBD is effective in controlled randomized trials for Dravet and Lennox-Gastaut syndrome. Open drug trials have shown a similar effectiveness in children with CDKL-5, Aicardi syndrome, Dup15q and Doose syndrome (Devinsky *et al.*, 2018a). Many case reports also show successful treatments for other epilepsy syndromes (Arzimanoglou *et al.*, 2020).

CBD is administered orally as an oily solution. In the controlled studies, doses up to 20 mg/kg/day were used and in open-label studies even higher doses, mostly up to 25 mg/kg, were used. Safety data from the controlled trials show a clear dose dependency of adverse effects such as somnolence, diarrhoea and appetite loss (Devinsky *et al.*, 2018a; Thiele *et al.*, 2018) (*figure 4*). Most other adverse effects were not significant relative to the placebo groups. The odds ratio for discontinuation due to adverse effects was 1.45 (95% CI: 0.28-7.41; $p = 0.657$) and 4.20 (95% CI: 1.82-9.68; $p = 0.001$) for CBD at the doses of 10 and 20 mg/kg/day, respectively, in comparison to placebo based on a meta-analysis from the available controlled studies (Lattanzi *et al.*, 2018). Efficacy data, however, show that a significant proportion of children already respond to doses of 10 mg/kg/day (*figure 4*) in studies on Lennox-Gastaut syndrome. Therefore a "start slow" and "increase individually" strategy is recommended. A starting dose of 5 mg/kg/day, given in two doses, appears to be adequate. This dose should be increased to 10 mg/kg/day after two weeks of treatment. Thereafter, the individual response should be carefully observed. The observation time needed strictly depends on baseline seizure frequency before administration of CBD. If the drug is well tolerated but not sufficiently effective, the dose should be slowly increased in increments of 5 mg/kg/day, as long as it is tolerated, up to a maximum of 20-25 mg/kg/day (*box 1*).

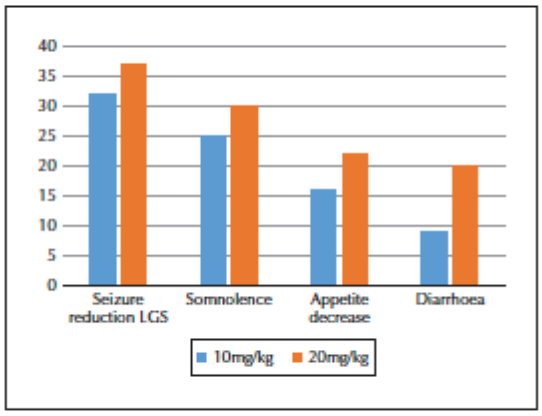

Figure 4. Dose dependency of efficacy (percentage of seizure reduction; Data pooled from the two controlled Lennox-Gastaut trials 1414 and 1423) and common adverse effects (percentage) at 10 mg/kg and 20 mg/kg CBD. A significant number of patients responded to 10 mg/kg CBD. Adverse effects are clearly dose-dependent. (No efficacy data are available for Dravet syndrome patients treated with 10 mg/kg CBD).

Handling CBD in combination with clobazam and/or stiripentol

Special care should be taken if CBD is added to clobazam treatment. In some cases, extreme increases in clobazam/desmethylclobazam levels were observed (Devinsky *et al.*, 2018a, 2018b, 2018c). Adverse effects such as fatigue, somnolence, ataxia, a decrease in cognitive function or behavioural changes might indicate toxic benzodiazepine levels. Clinically, this is difficult to distinguish from possible adverse effects of CBD itself. Therefore, monitoring of clobazam/desmethylclobazam levels is strictly recommended. Baseline TDM should be performed in these patients before administration of CBD and then after each increase. If a significant increase in benzodiazepine levels is observed, an adequate decrease in clobazam dose is recommended. Regarding the extent of decrease in dose, an estimate based on linear kinetics is adequate (benzodiazepine levels should be rechecked after dose reduction).

Stiripentol, like CBD, inhibits the same CYP P450 subtype 2C19. Therefore, a further increase in benzodiazepine levels will be uncommon if the patient is already on stiripentol. As the number of available data on these combinations is still limited, it cannot be fully excluded that some patients still might react with a further benzodiazepine increase. This might be the case particularly in patients receiving lower than recommended (50 mg/kg/day) doses of stiripentol. Therefore, a baseline clobazam/desmethylclobazam level should also be measured in this patient group. The levels should be re-checked in the event of one of the above-mentioned adverse effects.

Box 1. Clinical handling of CBD.

- Start low (2.5 or 5 mg/kg/day), increase to 10 mg/kg/day after two weeks
- Review clinical response and adverse effects on 10 mg/kg/day
- Remain on this dose if effective
- Otherwise increase dose in steps of 5 mg/kg/day if CBD is well tolerated
- Stop at 20-25 mg/kg/day - withdraw CBD if ineffective

Recommendations for drug level and safety monitoring

Regarding safety aspects and risks, the levels of liver enzymes, AST and ALT (markers of toxicity), increased up to more than three-fold in patients who used valproate concomitantly, causing withdrawal of CBD in some cases (Gaston *et al.*, 2017; Devinsky *et al.*, 2018b). In addition to TDM, biochemical markers of toxicity may be measured, such as liver enzymes, for improved knowledge and patient safety (Johannessen Landmark and Johannessen, 2012).

CBD is initially metabolised by CYP2C19, an enzyme that exerts pharmacogenetic variability, and some patients are poor or extra-rapid metabolisers (de Leon *et al.*, 2013; Johannessen Landmark *et al.*, 2016). Polymorphisms (*1,2,3) exist and are present at different frequencies according to ethnic group; *e.g.* 2% in Caucasians but 20-25% in the Asian population (de Leon *et al.*, 2013). Thus, pharmacogenetic variability and the possibility that some patients may experience adverse effects at low exposures should be considered. In this regard, previous observations of unexpected high levels of desmethylclobazam should be noted.

The metabolism of CBD has been hypothesised to account for possible CBD-related hepatotoxic effects. In one study, it was shown that 50% of CBD metabolism gave rise to the metabolite, 7-OOH-CBD, which exhibits, in part, the chemical structure of the fatty acid valproate, 2-n-VPA, and this valproate metabolite has been associated with hepatotoxicity as well as teratotogenic effects (Ujvary and Hanus, 2016). One may therefore speculate whether this metabolite of CBD causes the hepatoxic effects by the same mechanism as that involved in valproate-induced hepatotoxicity, however, this remains to be investigated.

Attention to clinical pharmacology and AED interactions, as well as TDM, should reveal these effects and it is highly recommended to follow changes in serum concentrations of all drugs in use for all patients initiating CBD as a basis for appropriate dosage adjustment in order to take this safety aspect into account. TDM should always be requested on clinical grounds and should form the basis for establishing an individual reference range where the patient has achieved an optimal balance between efficacy and tolerability. This concentration would then serve as a reference for further follow-up, dosage adjustments, and initiation and withdrawal of various comedications (Patsalos *et al*., 2008; Johannessen Landmark *et al*., 2016; Patsalos *et al*., 2018). The serum concentrations of other concomitantly used AEDs as well as other relevant drugs in use, such as psychotropic drugs (mood stabilisers, antidepressants, and antipsychotics), should also be followed to reveal possible pharmacokinetic interactions or reasons for poor clinical effects or observed adverse effects.

Pharmacogenetic testing of CYP2C19 could be performed if a poor metabolizer (PM) genotype is suspected based on unexpectedly high levels of CBD relative to the dose.

Safety monitoring of liver enzymes is highly recommended. In the controlled trials, 8% of the patients showed significantly increased liver enzymes at 10 mg/kg/day and 16% at 20 mg/kg/day in combination with valproate (Devinsky *et al*., 2018b). This condition led to withdrawal of CBD if AST or ALT showed a three-fold increase over baseline in the presence of any symptoms (fever, rash, nausea, abdominal pain, or increased bilirubin) or an eight-fold increase in the absence of such symptoms. In rare cases, an increase in ALT/AST was observed with 20 mg/kg/day CBD without concomitant use of valproate, but not with lower doses of CBD. The increase in liver enzymes was reversible in about half the cases, without taking any action; in the remaining cases, CBD was withdrawn, leading to normalization of AST/ALT (Devinsky *et al*., 2018b).

With the exception of clinical trials, significantly increased liver enzymes should lead to at least withdrawal or a reduction of CBD or valproate. A decrease in valproate should be considered first if the patient's history does not indicate a significant benefit with valproate but a favourable effect with the addition of CBD. In all other cases, CBD should be withdrawn or reduced to 10 mg/kg. A mild increase in ALT/AST can be observed for a few weeks before taking any action.

Summary

AEDs exhibit extensive pharmacological variability with numerous interactions with CBD. CBD demonstrates a challenging pharmacokinetic profile with low bioavailability, significant protein binding, and interactions with various metabolic pathways in the liver, including CYPs that are susceptible to pharmacogenetic variability and drug interactions.

More pharmacokinetic studies are needed, as many AEDs are affected, causing increased concentrations and risk of toxicity. The interaction with clobazam has been best characterised, giving rise to a several-fold increase in the active metabolite desmethylclobazam, with risk of excessive adverse effects. Serum concentration measurements and the use of TDM and biochemical markers of toxicity, such as liver enzymes, are important for improved knowledge and patient safety. This is recommended for all patients initiating CBD treatment in order to follow changes in serum concentration of all drugs as a basis for appropriate dosage adjustment.

Since the pharmacokinetics of CBD is highly variable and unpredictive, CBD is used as polytherapy in patients with refractory epilepsy, often with a high drug burden. As there are numerous possible pharmacokinetic interactions resulting in possible toxicity, TDM should be implemented to individualise treatment with CBD, thus pharmacological observations may be documented and related to clinical outcome of CBD treatment in a safe way. □

Supplementary data.
Summary didactic slides are available on the www.epilepticdisorders.com website.

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