Chapter 10

Pediatric Dosing Considerations for Medical *Cannabis*

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Additional information is available at the end of the chapter

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Abstract

For patients who fail conventional therapies, ability to access medical *Cannabis* may offer a therapeutic alternative that addresses their unmet clinical need. However, a paucity of clinical trial evidence has led to ambiguous pediatric dosing guidelines for medical *Cannabis*, a situation further complicated by the impact of developmental maturation of the pharmacokinetic (PK) and pharmacodynamic (PD) processes governing drug effect and dosing requirements. The pediatric population is very heterogeneous, and dissimilar developmental trajectories result in important differences in the rate and extent of cannabinoid absorption, distribution, elimination, and response both between and within pediatric age group classifications. These developmental changes will require the prescribing caregiver to consider age-specific dosage regimens that may demand continual modification as the child ages. The chapter that follows emphasizes the impact of age-related changes in PK and PD processes as important considerations in pediatric dosing recommendations for medical *Cannabis*.

Keywords: medical *Cannabis*, dosing, pediatric, ontogeny, pharmacokinetics

1. Introduction

Optimal dose selection is fundamental to appropriate clinical care. A comprehensive understanding of drug pharmacokinetics (PK) and pharmacodynamics (PD) and the factors that can influence the drug exposure-response (PK-PD) relationship is important to facilitate the optimization of dosage regimens. In the pediatric patient, though, normal growth and maturation complicates dose selection and optimization. Experience has demonstrated that the usual practice of adjusting dose size according to body weight often results in inappropriate pediatric doses as this practice ignores the impact of developmental changes on drug PK and PD

processes. To ensure appropriate clinical care, then, dosing recommendations need to consider age-related changes in PK and PD. This becomes particularly important for new therapeutics, which have limited clinical trial data and experience of use in the pediatric population.

Medical *Cannabis* herbal extracts are being considered as new therapeutics for the management of pediatric conditions refractory to standard of care therapies. With no DIN (Drug Identification Number) designation, though, these herbal extracts have limited safety and efficacy data in the pediatric population. The small number of clinical pharmacology trials with pharmaceutical grade cannabinoid products as well as anecdotal use lends some support for medical *Cannabis* in such conditions, but no rational pediatric dosing recommendations are available for these products. The known age-related changes in drug PK and PD, differences further complicated by existing comorbidities and concurrent medications likely to influence drug PK and PD, have left treating caregivers uncertain and reluctant to recommend an appropriate medical *Cannabis* dosage regimen to their patient. A greater understanding of the developmental changes in cannabinoid PK and PD, though, may help to mitigate these uncertainties.

This chapter will mainly address issues of developmental maturation of PK and PD processes as key determinants of medical *Cannabis* herbal extract dosage regimens (henceforth referred to as *Cannabis* extracts). The chapter will first summarize the therapeutic applications for *Cannabis* extracts in pediatric populations. It then will highlight the key physiological determinants of PK and PD that undergo change with postnatal maturation and how such changes might lead to age-related cannabinoid PK and PD differences based on current understandings from adult populations. Superimposed with normal developmental programming, dose selection must also consider the influence of pharmacogenetics, disease, and drug-cannabinoid interactions, and these are briefly discussed. This chapter will underscore developmental maturation of PK and PD processes as paramount to considerations of medical *Cannabis* dosing of the pediatric patient.

2. Therapeutic applications

Many studies report the use of *Cannabis* to aid treatment of a diverse range of health conditions and symptoms. Although *Cannabis*' medical use dates back centuries with the first written records in China and India around 2900 BC and 900 BC, respectively, *Cannabis* was introduced to western medicine only in the nineteenth century [1, 2]. Today, potential indications for medical *Cannabis* include appetite stimulation, chronic pain, spasticity from multiple sclerosis or paraplegia, depression, anxiety, sleep problems, psychosis, glaucoma, Tourette's syndrome, epilepsy, dementia, cancer, post-traumatic stress disorder, and osteoarthritis [3]. Δ^9-Tetrahydrocannabinol (THC) and cannabidiol (CBD) are the most extensively studied cannabinoids for medical use. Individually, these cannabinoids have demonstrated therapeutic benefit and pharmaceutical grade products are available on the market today. However, CBD's ability to modulate THC's well-known intoxicating activity along with a growing body of evidence for an entourage effect among the many cannabinoids of the *Cannabis* plant may

extend therapeutic benefit beyond the purified cannabinoid leading to greater interest in the use of *Cannabis* herbal extract preparations [4]. Such entourage properties may explain the varied therapeutic applications of *Cannabis* over the centuries.

Limited information is available on the therapeutic use of *Cannabis* in pediatric patients. *Cannabis* is usually considered when the clinical condition becomes intractable to other types of treatments [5]. This is seen, for example, in treatment of children with refractory epileptic encephalopathy, in particular Lennox-Gastaut syndrome and Dravet syndrome [6]. However, studies supporting medical *Cannabis* suffer from small sample sizes and lack of dose standardization with variations in dose size, formulation, and frequency of administration. These limitations make it difficult to extrapolate data to the larger pediatric population [7]. Furthermore, *Cannabis* extract use has predated the usual pharmacology and toxicology testing applied to other marketed drugs. With virtually no toxicity and efficacy data, dose-plasma concentration-response data, and information on *Cannabis*-drug interactions, the prescribing caregiver is apprehensive to recommend a *Cannabis* extract dosage regimen to a pediatric patient. This inability to define age-appropriate dosage regimens has compromised the acceptability of medical *Cannabis* as a viable therapeutic for pediatric medical conditions.

3. Pediatric dosing considerations

3.1. Medical cannabis dosage forms

Commercially available medical *Cannabis* includes the purified pharmaceutical preparations and the herbal extracts. The extracts contain well-defined proportions of the major psychoactive cannabinoids, THC and CBD, and poorly documented quantities of other cannabinoids and terpenoids [4, 8, 9]. Nonmedical or recreational *Cannabis* have unknown contents of THC, CBD, and other components and should be avoided when used for medical benefit. Much of the anecdotal and observational human trial data usually correlates therapeutic benefit with content of THC or CBD or some ratio of THC to CBD [10]. Given the differences in the pharmacology of THC and CBD, different THC:CBD ratios are promoted within the range of possible clinical indications for medical *Cannabis*. For the pediatric patient, the choice of THC:CBD ratio, though, must acknowledge the known dose-related intoxicating effects of THC and the potential for adverse neurodevelopmental effects with cannabinoid exposure [11]. As well, the selection of *Cannabis* product should consider the presence of the secondary components that often contribute to the more unique characteristics of *Cannabis* extracts [4]. Little is known about the pharmacology of these secondary cannabinoids and terpenes and age-related differences in their PK and PD properties [4, 9]. With the current absence of product quality control on the composition of these other active *Cannabis* components, dose optimization of *Cannabis* extracts for different pediatric indications will need to principally focus on the specific THC:CBD ratio for now.

At present, age-appropriate formulations of *Cannabis* extracts are limited to oil-based oral products. Oral dosing is a challenging route of administration in the pediatric population as issues

with incomplete dose ingestion and product refusal negatively impact therapeutic outcomes [12, 13]. Often formulation development considers the adult patient and when used in the pediatric patient can be associated with reduced therapeutic efficacy and safety. For example, some excipients commonly used in adult formulations have well known safety concerns in the pediatric patient such as the common pharmaceutical formulation excipients propylene glycol, benzyl alcohol, and ethanol [14]. As well, factors such as ability to swallow, taste, texture, and smell that determine acceptability of an oral dosage formulation undergo developmental changes such that acceptable formulations in one pediatric age group may not be acceptable in another age group [12, 13]. Currently, medical *Cannabis* companies are actively pursuing product formulation development. Whether these efforts consider the unique requirements of the pediatric patient is uncertain, which will necessitate the treating caregiver to exercise caution when considering *Cannabis* product formulations for their pediatric patients.

3.2. Current dosing guidelines

Medical *Cannabis* dosing guidelines are largely unavailable for the pediatric patient. Such guidelines, though, should consider specific age strata since development and maturation result in age-dependent dosing requirements [15]. Recommended pediatric age strata are: pre-term newborn infants (born at less than 36 weeks of gestation), term newborn infants (age 0 to <28 days), infants and toddlers (age 28 days to 23 months; infants >28 days to 12 months and toddlers >12 months to 23 months), children (age 2–11 years; preschool children 2–5 years and school age children 6–11 years), and adolescents (12–18 years). As with other drugs, the safety and effectiveness of the cannabinoids likely will vary between the different age strata. Consequently, pediatric clinical trials that determine plasma cannabinoid concentration-effect relationships, efficacy, and safety within specific age strata will be required to develop optimal age-specific dosing recommendations.

In the absence of pediatric PK and clinical trial data, adult data become a starting point for pediatric dose selection. For simplicity, doses may be normalized to body weight and, in some cases, to body surface area. Dose scaling by body weight (or body surface area) requires dose adjustment according to the patient's clinical state and clinical response until a dose is titrated to appropriate effect. This process could take some time to identify an appropriate dosage regimen for the pediatric patient, if at all. Furthermore, given possible ceiling effects of the cannabinoids, where dosing beyond a certain amount per body weight may not yield further pharmacological benefit, this approach has risk of adverse therapeutic outcomes.

Other approaches exist to improve upon the simple extrapolation of body weight-adjusted adult doses. Allometric scaling approaches use body surface or body weight ratios and allometric models to extrapolate adult doses to the pediatric patient [16]. An important limitation of this approach is an assumption of a linear correlation between demographic covariates and the dose, which is not the case for the pediatric patient due to developmental maturation of PK and PD processes [16–18]. Children differ not only in body weight but also show changes in body composition, organ size, and maturation, which influence PK as well as result in differences in the therapeutic window (range of exposure concentrations that result in drug efficacy) due to PD changes with age. The use of exponential scaling factors adjusted by body

size (and age) to predict dosages in pediatric patients is also limited by the complexity of these modeling approaches that precludes general application to many drugs [16–18]. Hence, we seem left with the current self-titration dosing model where doses, based on weight adjusted adult doses, begin low to moderate and are increased slowly, along with adjustments in dosing interval, until the desired effect is achieved [19]. This empirical "trial-and-error" approach will not likely result in optimal dosing guidelines for the different pediatric age strata due to diverse developmental periods within this population [20, 21].

3.3. Accounting for growth and development in dosage selection

Changes in body size and maturation of the physiological and biochemical processes determining PK and PD must be considered during dosage selection. Normal growth results in a decreasing ratio of body weight to body surface area with age making it difficult to recommend dosing according to patient body weight or body surface area consistent with adult guidelines [22]. For example, in an analysis of pediatric patients, dosing adjustments of hydrophobic drugs (cannabinoids are hydrophobic) based on body weight provided better clinical outcomes in patients between 1 month and 1 year of age, while dosing based on body surface area was best in older children [18]. As well, within and between the age strata maturational changes in PK and PD processes occur at considerably different rates and patterns suggesting that dosage adjustments with long-term therapy may be necessary to ensure efficacy and avoid risk of adverse events [23, 24]. Other clinical and demographic variables such as puberty, which bring hormonal changes known to influence PK in adolescents, and the patient's clinical state, are known to influence dosing requirements [25]. Only with a greater understanding of the impact of such factors can we hope to rationally identify doses for different pediatric populations, particularly in the absence of robust clinical data. The following section addresses a key determinant of dosing requirements, the age-related changes in the PK processes acting upon a dose exposure.

4. Ontogeny of pharmacokinetic processes

4.1. Exposure and exposure route

For many drugs, dosage regimens are designed to attain and maintain drug concentrations within a therapeutic window, the range of concentrations that produce a desired effect. Pediatric therapeutic windows may be quite different from the adult due to PD differences, such as receptor ontogeny (maturation of receptor number and functionality), and organ specific distributional differences resulting in different tissue concentrations of drug to elicit pharmacological activity. Such differences can result in differences in efficacy and toxicity which brings into question use of pediatric therapeutic ranges based on adult clinical data. However, the absence of dose-concentration-response data in children results in a void of evidence that risks the development of arbitrary therapeutic ranges. This was evident with theophylline for neonatal apnea where the therapeutic range adopted in the early 1980s was inadequate and a considerable number of neonates were under-dosed [26]. Understanding the

therapeutic range of the cannabinoids for the different pediatric age-strata will be necessary to optimize dosing guidelines for *Cannabis* products. This will necessitate the use of population PK/PD modeling approaches with medical *Cannabis* extracts and a greater understanding of the age-related changes in PK and PD processes governing drug effect.

The attainment of plasma concentrations within the therapeutic window depends on route of administration, dosing frequency, size of dose, and the PK acting on the administered dose. Knowledge of the volume of distribution (V_d) is necessary in the design of a loading dose (the dose needed to quickly produce therapeutic concentrations, C_{Ther}), where V_d and the bioavailable dose (F × Dose) determine the plasma concentration (Eq. (1)). Following a chronic dosing regimen, the mean steady state therapeutic concentration ($C_{SS,Ther}$) is the result of the bioavailable dose, dosing interval (τ), and systemic clearance (Cl_S) (Eq. (2)).

$$C_{Ther} = \frac{F \times \text{Loading Dose}}{V_d} \tag{1}$$

$$C_{SS,Ther} = \frac{F \times {}^{\text{Dose}}/_{\tau}}{Cl_S} \tag{2}$$

With extravascular dosing (e.g., oral dosing), compounds must undergo absorption into the systemic circulation. Typically, less than 100% of the administered dose becomes available to the systemic circulation as presystemic mechanisms can limit the fraction of the oral dose that enters the systemic circulation as an unmodified compound (i.e., bioavailability (F)). Once absorbed into the blood supply, compounds distribute to the tissues of the body while systemic clearance mechanisms function to eliminate the compound. Hence, systemic exposure is determined by the extent of absorption (bioavailability) and by the efficiency of the systemic clearance mechanisms, while organ specific exposure additionally depends upon tissue distribution properties of the compound. Age-related changes occur with all these PK processes such that a standard dosage regimen will produce different systemic and tissue-specific exposure levels during pediatric development.

4.2. Oral absorption

The most common route of administration for pediatric patients is the oral route. The rate and extent of oral absorption is determined by the interaction of the physicochemical properties of the cannabinoid and its formulation with the physiological processes governing absorption. With oral ingestion of cannabinoids, time (T_{max}) to maximum concentrations (C_{max}) varies on average from 1 to 6 h, and bioavailability is low and quite variable (4–12%) in adults due to extensive first pass effects [27, 28]. As well, first-pass metabolism following an oral administration results in production of active metabolites (e.g., 11-hydroxy-THC, 7-hydroxy-CBD) with potent psychoactive effects that contribute to the pharmacology of the cannabinoids [27]. Age-related differences in T_{max}, C_{max}, and F may cause important differences in the onset and intensity of effect of an oral cannabinoid dose.

Growth and maturation of gastrointestinal absorption processes variably influence both absorption rate and extent (i.e., bioavailability), a key determinant of the effective dose.

pH dependent passive diffusion, biliary excretion, and gastrointestinal (GIT) transit times undergo considerable change with maturation [29]. Gastric pH is high at birth, becomes acidic in the first 24 h, returns to neutral pH values within the first 10 days of life, and subsequently decreases to adult pH levels within the first year or two of life [16]. Intestinal tract pH tends to be similar with the adult at all pediatric age groups [30]. Although impact of pH is likely limited on cannabinoid bioavailability (as these are neutral compounds), the higher gastric pH might reduce the extent of THC degradation [31]. Biliary excretion, though, is lower in the neonate (2–4 mM) than the adult (5–6 mM) in the first weeks of life, which is due to immaturity of the hepatic transporters responsible for their biliary excretion rather than ability to synthesize bile salts [32, 33]. As hydrophobic molecules, this may reduce cannabinoid bioavailability due to lower GIT solubilization in the first months of life. Gastrointestinal motility is also reduced at birth and gastric emptying and intestinal peristaltic function likely become similar to adults in the first weeks of life [34, 35]. This suggests T_{max} is likely to be similar with adults within a month of birth, although differences in motility may not influence C_{max}.

Other gastrointestinal physiological factors that have importance on the extent of absorption (i.e., bioavailability) include gastrointestinal permeability and first pass effects. All cannabinoids undergo passive permeation across the gastrointestinal epithelium. Intestinal permeability is initially high at birth given the leakiness of the epithelial tight junctions, but with junction closure within the first week of birth overall permeability becomes lower than adult due to a smaller intestinal absorptive surface area [36]. Passive transport mechanisms likely reach adult values within 4 months of birth. First-pass effects have a longer maturational trajectory. First pass effects include the activity of microbiota and gut luminal enzymes, enzymes and transporters of the gastrointestinal epithelia and liver. In adults, the low and variable bioavailability of CBD and THC is due to pre-systemic elimination by cytochrome P450 enzymes, principally CYP3A4 and CYP2C's, expressed in the intestinal and hepatic epithelium [37]. Intestinal and hepatic CYP3A4 expression and hepatic CYP2C expression principally contribute to considerable first-pass metabolism and the low oral bioavailability of cannabinoids [38]. With development, hepatic CYP2C expression reaches adult levels by 6 months, exceeds adult levels in childhood, and returns to adult levels after puberty [39]. CYP3A4 undergoes a slower maturation with considerable increases in the first 6 months but does not reach adult levels until after 2 years of age [40, 41]. CYP3A4 activity also exceeds the adult in early childhood and returns to adult levels after puberty. Their developmental maturation suggests bioavailability is likely to be higher in neonates and infants until these enzymes reach adult expression levels. The xenobiotic transporters also contribute to first-pass effects. THC is a substrate of efflux transporters including p-glycoprotein (MDR1) and BCRP, while CBD only inhibits these efflux transporters. These transporters undergo rapid ontogeny in the first 6 months of life to reach adult values by 2 years of age, but may not contribute to age-related differences in bioavailability beyond 6 months of age [42]. The immaturity of these transporters can further enhance THC bioavailability relative to the adult.

Bacterial activity within the gastrointestinal tract lumen may influence first pass metabolism. Whether cannabinoids undergo bacterial metabolism is unknown, but glucuronide metabolites may undergo deconjugation in the gut lumen. Children from 3 to 15 years of age showed no differences in activity of bacterial enzymes such as beta-glucuronidase, beta-glucosidase,

and other enzymes and intestinal bacterial colonies approach adult characteristics by 1–4 years of age [43]. The gastrointestinal microbiome also influences the regulation of drug metabolizing enzymes and transporters, but information in the pediatric patient is lacking. A multitude of factors can influence the microbiome including age, disease, diet, and drug exposure, and our understanding of their impact during development is limited.

Overall, postnatal development of pH, gastrointestinal motility, and first-pass mechanisms should reach maturity by 5 years of age [17] at which time the rate and extent of oral absorption should have similarity to adult estimates. The variable rate and pattern of maturation, though, will lead to large ranges in T_{max}, C_{max}, and bioavailability estimates between the different pediatric age classes. Since variability in blood concentrations is principally inversely proportional to oral bioavailability, we may expect important differences in the oral dose requirements needed to attain equivalent plasma concentrations and therapeutic responses. Variable bioavailability will challenge treating caregivers on advising doses indicated by age, and individualization of dosage regimens will remain necessary. This expectation, though, creates opportunity for development of pediatric dosage formulations that considers both the potential age influences on cannabinoid liberation from the dosage formulation and the need to provide higher and more consistent oral bioavailability. Effective oral formulations promise more consistent dosage recommendations and reductions in the risk of under- or overdosing.

4.3. Distribution

Age-related differences in the extent of tissue distribution (i.e., volume of distribution, V_d) will impact intensity and duration of cannabinoid activity. In adults, the high plasma protein binding characteristics (>97% bound in the adult) [44] of the cannabinoids result in a small central V_d (2.5–3 L). The cannabinoids undergo rapid and extensive distribution into lipophilic tissues (e.g., brain and adipose) and the highly perfused tissues (e.g., heart, lung, and liver) resulting in a large steady state V_d with reports ranging from 2.5–3 to 10 L/kg [27, 45]. The slow redistribution of cannabinoids from tissues, in particular adipose, as well as enterohepatic recirculation lead to long half-lives ranging from 1.5 to 5 days or longer for THC and 1–2 days for CBD, and even longer for the metabolites [27, 45]. Since the V_d is an important determinant of half-life, which, in turn, is used to guide the dosing interval, the expected age-related differences in cannabinoid V_d are likely to lead to differences in half-lives between the pediatric age strata and a possible need to consider such differences in the dosing interval.

Body composition, plasma and tissue protein binding, and physicochemical characteristics of the cannabinoids will influence the extent of their distribution (i.e., V_d). For many compounds, V_d demonstrates a linear relationship with body size. In the pediatric population, body size can change from less than 1 kg to up to 100 kg or more with development. Consequently, V_d expressed on a per body weight basis will show tremendous variability in the pediatric population. Ratio of fat, muscle, and intracellular and extracellular water also changes with maturation. At birth, total body water is 75%, and total body water-to-fat ratio is the highest in neonates and young infants with total body water reaching adult values by 6 months [46]. However, older infants and toddlers tend to have the highest fat-to-body water ratio only to reach adult ratios in later childhood [46]. Although higher body fat to water ratio may suggest

higher V_d for the hydrophobic cannabinoids in these age groups, studies with other highly lipophilic drugs suggest that the V_d was not different between adults and infants [47]. Past infancy, then, the V_d might be similar between children and adults for the cannabinoids [47]. The lipophilic nature of the cannabinoids, though, raise concerns with childhood obesity and whether obese children should be dosed based on actual or ideal body weights [48].

Plasma protein binding is an important physiological determinant of V_d and the unbound fraction in the blood. In adults, cannabinoids bind extensively to lipoproteins and albumin where the unbound fraction can range from 1 to 5% [44, 45]. In the pediatric population, the plasma levels of albumin and alpha$_1$-acid glycoprotein, the two major plasma binding proteins, are lower at birth and increase gradually to reach adult values by 1–3 years of age [49]. Lipoprotein and triglyceride levels also rise gradually during the first year of life, with further increases in childhood and adolescence [50]. Consequently, neonates and infants might exhibit lower bound fractions of the cannabinoids due to lower lipoprotein and albumin concentrations. These age dependent increases in plasma proteins might also mean higher distribution volumes in the neonate and infant and a lower C_{max}.

With high binding characteristics, seemingly small differences in binding, though, may result in large differences in the availability of cannabinoids to bind to their therapeutic targets. The unbound concentration is known to better reflect the pharmacodynamics of highly bound drugs [51], and a greater unbound fraction coupled with a lower elimination capacity for the cannabinoids (see section below) would enhance the availability of cannabinoids at their pharmacological sites of action. This can result in more intense pharmacological or toxicological responses and possibly a need to adjust doses to ensure equivalent PD responses. In addition to the amount of protein available for binding, binding affinity shows age-related changes. The presence of endogenous competitors for plasma protein binding sites, such as bilirubin and free fatty acids, is higher in the neonate [52], and along with exogenous competitors (e.g., co-administered drugs) may further increase the unbound cannabinoid concentration with subsequent enhancements in their pharmacological or adverse effects. Either way this might necessitate a dose reduction.

Relevant to the cannabinoids is the possible influence of age-related differences in the volume of the brain and the permeability of the blood-brain-barrier. Brain volume is larger in younger children and approaches adult values at 4–6 years of age [53]. THC but not CBD is a substrate for P-glycoprotein (P-gp, ABCB1) and breast cancer resistance protein (BCRP, ABCG2) [54], while both cannabinoids inhibit P-gp and BCRP activity [55, 56]. These transporters function to limit permeation of THC and other drug substrates across the blood-brain-barrier and expedite their elimination from the brain, while CBD brain uptake and removal is not influenced by these transporters [54]. This might suggest a longer residence time of CBD in brain tissue relative to THC and a potential disconnect between plasma levels and the psychoactive effects of these compounds. As an inhibitor of efflux transporters, CBD might also modulate brain disposition of THC, which could explain, in part, its known ability to modulate THC psychoactive effects [57]. Important cannabinoid-drug interactions might ensue with co-administration of other efflux transporter substrates with a concomitant risk for brain accumulation of these drugs and potential adverse effects. Finally, known pharmacogenetic

polymorphisms in these transporters result in reduced activity, which may enhance brain penetration and residence, increase the psychoactive effects, and, in turn, risk *Cannabis* dependence or possibly brain disorders [58]. Although ontogeny of these transporters at the blood-brain-barrier is unknown, developmental maturation of the efflux transporters may result in a developmental vulnerability to THC use.

4.4. Elimination

The lipophilic cannabinoids are eliminated primarily through hepatic metabolic clearance. Hepatic clearance depends on three physiological determinants, plasma protein binding, hepatic blood flow, and intrinsic clearance (the overall ability of the liver to metabolize a compound). The cannabinoids appear to fall within the class of intermediate to high extraction ratio compounds (systemic clearance ranging from 600 to 1190 mL/min for THC and 960 to 1560 mL/min for CBD) [59, 60], suggesting that hepatic clearance is influenced variably by hepatic blood flow, intrinsic clearance, and plasma protein binding or predominantly by the hepatic blood flow at the highest hepatic clearance values. All determinants undergo developmental maturation. Hepatic metabolic clearance of the cannabinoids principally involves cytochrome P450 enzyme-mediated metabolism. The metabolites generated from P450 enzyme reactions may undergo further phase II enzyme conjugation reactions for their subsequent renal or biliary excretion. An understanding of the contribution of Phase I and II enzymes is important as the rate and pattern of their maturation tend to follow different developmental trajectories.

Cannabinoids are principally metabolized by CYP3A4, CYP2C9, and CYP2C19 [45, 61]. As a superfamily of enzymes, the developmental trajectories of P450 enzymes are grouped into three characteristic classes [62]. CYP3A4 and CYP2C enzymes are class II enzymes, where enzymes are expressed at low levels at birth and gradually increase postnatally to achieve adult values within a year or two of age [62]. For instance, CYP2C19 activity is less than one-third adult values at birth, surges to 50% of adult activity in the first month of postnatal life, and reaches adult values at 1 year of age [39]. After 1 year, the hepatic clearance of CYP2C19 substrates show similarity to adult values [62]. Although CYP3A4 is the most abundant hepatic P450 enzyme in the adult, the predominant CYP3A isoform at birth is CYP3A7, while CYP3A4 expression is only 10% of adult levels [62, 63]. A developmental switch is observed such that CYP3A4 activity increases concomitantly with reductions in CYP3A7 activity. By 1 year of age, CYP3A4 activity is 75% adult levels, while CYP3A7 activity is considerably reduced [62, 63]. Although the two isoforms share 95% identity in their nucleotide sequence, differences in substrate specificities are noted for the two isoforms as well as a lower metabolism rate by CYP3A7 [64]. No study has evaluated the metabolic activity of CYP3A7 against CBD and THC, but CBD was identified as an inhibitor of this CYP3A isoform [65].

CBD, THC, and their respective metabolites also undergo phase II metabolism principally by the UDP-glucuronosyltransferase (UGT) enzymes. UGT1 and UGT2 families are involved in drug metabolism and typically more than one isoform contributes to the metabolism of a single compound [66]. Generally, the UGT enzymes have 25% activity in young infants relative to adult levels with adult levels achieved within 6–30 months of birth [66]. However,

individual UGT enzymes undergo different maturation patterns leading to considerable variability reported in the glucuronidation capacity of newborns and infants.

The developmental pattern of the major cannabinoid metabolizing enzymes suggests that systemic clearance and oral bioavailability may change throughout the pediatric period. Neonates and infants may demonstrate lower systemic clearance and higher oral bioavailability due to reductions in hepatic metabolism, but adolescents may have similar values to the adult. Interesting children ages 2–12 may require larger weight adjusted doses. In a mechanistic-based analysis, for drugs almost solely eliminated by CYP3A4 children required higher (~2 times) doses corrected for body weight relative to the younger child and adult, although similar weight-corrected doses between children and adults were required for drugs eliminated solely by CYP2C19 or UGT isoforms to achieve equivalent plasma concentrations [17]. Given the contribution of both P450 enzymes to the elimination of cannabinoids, higher weight adjusted doses may be required in children relative to the adult due to higher systemic clearance or first-pass metabolism.

Quantitatively and qualitatively P450 and UGT enzymes show considerable variation in their developmental maturation both within and between the age strata. A consequence of this variation may be altered cannabinoid metabolite profiles relative to the adult. After oral administration in the adult, extensive first-pass metabolism results in the production of high circulating levels of bioactive hydroxylated metabolites of CBD and THC [27]. These active metabolites contribute to the pharmacology of *Cannabis* herbal extracts. A further consideration is the genetic polymorphism of P450 and UGT enzymes which divides the population into poor metabolizers and fast metabolizers (e.g., CYP2C's) or results in extensive variability in metabolic rates (e.g., CYP3A4) [67]. The impact of genetic polymorphism in the different pediatric age classifications is unknown. A few drugs with available data suggest that phenotype does not relate to genotype at birth, but enzyme maturation will eventually result in phenotype-genotype relationships similar to the adult. Hence, postnatal maturation of P450 and UGT enzymes has considerable influence on therapeutic efficacy and toxicity because metabolism determines oral bioavailability, hepatic metabolic clearance, and the active metabolite profile.

Renal and biliary excretion mediates the elimination of the cannabinoid phase I and II enzyme metabolites. Elimination by the kidney occurs by glomerular filtration and tubular secretion. Neonates are born with reduced glomerular and tubular function, which is further compromised in the preterm neonate due to incomplete nephrogenesis [68]. Profound anatomical and functional changes in the kidney occur following birth that include enhancements in renal blood flow, redistribution of blood flow in the kidney, improvements in glomerular filtration efficiency, and the growth and maturation of renal tubules and tubular processes. These changes result in rapid attainment of renal elimination function within the first year of age [68]. Maturation of glomerular filtration processes precedes tubular processes, such that glomerular filtration rate reaches adult levels by 6 months of age and tubular reabsorption and excretion processes mature to adult levels by 1 year of age [68]. The excretion rate in toddlers and preschool children, though, can exceed adult levels but subsequently returns to adult levels in childhood [68]. The anatomical and functional immaturity of the kidney and the discordance in the maturation of glomerular and tubule function can contribute to considerable interindividual variability in renal elimination in pediatric patients.

4.5. Transporters

Transporters are categorized into ATP-Binding Cassette (ABC) and Solute Carrier (SLC) families. ABC proteins are efflux transporters expressed apically at tissue-blood interfaces and function to limit penetration of compounds into these tissues. Maturation of ABC transporters can result in a developmental vulnerability to THC use. ABC transporter ontogeny as well as genetic variation (polymorphisms) is known to influence treatment response to drugs and increase risk for psychiatric disorders in pediatric populations as a result of altered disposition to the brain [69]. For example, the common P-glycoprotein (ABCB1) genetic variant C3435T, which results in altered p-glycoprotein expression, was associated with increased risk of *Cannabis* dependence [58]. As well, transporter ontogeny and genetic polymorphisms can contribute to the interindividual variability in response to *Cannabis*. In general, the ontogeny of ABC and SLC transporters is poorly known.

5. Ontogeny of pharmacodynamic processes

Dosing considerations of the pediatric patient not only need to acknowledge the impact of age-related changes in PK processes, but also the maturation of the endocannabinoid system and how this will influence PD and the relationship between exposure and response. Very little data, though, are available from human clinical studies on the developmental maturation of the endocannabinoid system and how these may influence cannabinoid pharmacology. What is known is that the endocannabinoid system is expressed early in fetal life and plays a critical role in normal neurological development. Cannabinoid receptor populations and levels of the enzyme systems and endocannabinoids are dynamic in pediatric development particularly during adolescence [70]. Some data suggest daily high dose exposure to THC may pose a risk to normal neurological development, although the data are not available for CBD [71].

The lack of data on PD ontogeny and age-specific exposure-response relationships risks development of inappropriate therapeutic ranges. In the absence of any data, the treating caregiver may apply therapeutic ranges in adults or older pediatric age groups to younger pediatric age classes on the assumption of a similar exposure-response relationship to help inform dose selection [72]. Yet drawing from examples with other drugs, changes in receptor density expression with maturation have altered the efficacy and safety of drugs in children, such as reduced PD sensitivity to propofol resulting in overdosing and subsequently myocardial failure, metabolic acidosis, multiorgan failure, and death [73]. Given that the endocannabinoid system undergoes continued development, therapeutic windows are likely to be different among the different pediatric age strata.

6. Other factors

6.1. Safety and adverse effects

The toxicity of cannabinoids is generally considered quite low. In adults, cannabinoids have a number of central nervous system effects that include intoxication, appetite stimulation,

disruption of psychomotor behavior, short-term memory impairment, antinociceptive actions, and anti-emesis. Lethal doses are unknown, but the size of a single lethal dose is likely to be very high. The apparent low toxicity in adults, though, cannot necessarily translate to a low adverse effect potential in pediatric patients. Very little information exists on the pediatric specific adverse effects of *Cannabis.* Further, its use as an adjunct therapy in conditions such as pediatric seizure creates uncertainty—are the reported adverse effects the result of the cannabinoid or due to a cannabinoid-drug interaction? Experience with other drugs suggests that the immature physiological system predisposes pediatric patients to an increased risk for adverse effects [74]. It is these examples that highlight the concern among the treating caregiver of the safety of *Cannabis* use in pediatric patients. Unfortunately, the typical short-term clinical trial is inadequate to determine safety of medical *Cannabis* on growth and maturation. Pharmacovigilance over the long-term will be necessary, and this will require reevaluation of the original cohort of patients in clinical trials years after termination of the trial.

6.2. Pharmacokinetic and pharmacodynamic interactions

In pediatric patients, medical *Cannabis* is typically administered as an add-on to standard of care therapies. This practice can result in clinically relevant competitive interactions involving metabolic enzymes, transporters, or plasma protein binding sites, and at times pharmacological receptors. Cannabinoids are known to inhibit the metabolism of drugs that share the same P450 enzymes, with inhibition constants in the low micromolar range [37]. Conversely, drug substrates of CYP2C and CYP3A4 can slow the metabolism of the cannabinoids. A well-known interaction is the co-administration of CBD with clobazam in refractory pediatric epilepsy where CBD is reported to increase clobazam and norclobazam (active metabolite) circulating concentrations due to inhibition of CYP2C19 [75]. Interactions between CBD and THC are also possible. CBD is known to competitively decrease the metabolism of THC resulting in its persistence in the body [76]. Higher ratios of CBD:THC can attenuate THC-induced effects and can produce more THC active metabolites [77]. P450 enzyme induction is possible in all pediatric age classes and can result in clinically significant enhancements in the elimination of cannabinoids and shorter half-lives. Without dosage regimen adjustments, enzyme induction and inhibition can result in concentrations outside the therapeutic window.

Other PK and PD interactions of concern include interactions at efflux transporters and impact of disease. The exposure-response relationship can be affected by clinically relevant interactions at the efflux transporters expressed at the blood brain barrier. Such interactions can alter the brain distribution of the pharmacologically active cannabinoid fraction to enhance cannabinoid response at a given *Cannabis* dose. Although our understanding of the impact of disease on cannabinoid PK and PD is very limited, clear examples exist where dosing recommendations depend upon the specific comorbidity under treatment. As well, some childhood diseases result in unique pathophysiological changes not present in the adult precluding a simple extrapolation of dose from adult experience. In the absence of data, pediatric patients will need close monitoring to ensure effective, safe therapy in the presence of disease and other comorbidities.

6.3. Perspectives on the use of medical cannabis in pediatric populations

We face a clinical and ethical dilemma in the use of medical *Cannabis* in pediatric populations. Product quality, limited age-appropriate formulations, the lack of PK and efficacy data spanning the specific pediatric age categories, the possible adverse effects of *Cannabis* on normal growth and development, and limited pediatric-specific safety data cause considerable uncertainty regarding the use of medical *Cannabis* and identification of an appropriate dosage regimen. It is not surprising that treating caregivers hesitate to give medical authority for use. Just as the regulatory agencies have identified a critical need for pediatric data in new drug development, so must the medical *Cannabis* field recognize the danger of inadequate safety and efficacy data and inadequate regulation of *Cannabis* product quality. To realize the full advantages of medical *Cannabis*, well-powered and rigorous clinical trials will be needed. Ethical justification for such studies should weigh toward benefit of the need to understand its safety and effectiveness in different pediatric age strata. Such studies must acknowledge the impact of physiological maturation and clinical variables on dose requirements and have sufficient power to enable evaluation of these factors on cannabinoid PK and PD. In fact, our current knowledge of the impact of maturation on PK and exposure-response relationships invalidates the practice of empirical methods for dose selection despite their simplicity for treating caregivers. Pediatric clinical trials for medical *Cannabis* should be considered mandatory and such trials should focus on both PK and the target PD outcome. Finally, a framework for assessing and reporting adverse effects and benefits should accompany the use of medical *Cannabis* in the pediatric population. Eventually, these studies will make possible the development of pediatric dosage regimens that are safe and precisely address the therapeutic need. Until then, the treating caregiver can rationally approach dose selection in different pediatric age groups with an understanding of the impact of growth and maturation on cannabinoid PK and PD.

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