GENERAL REVIEW

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Genetic polymorphism and pharmacokinetics/toxicokinetics of carbamazepine: a general review

Genetički polimorfizam i farmakokinetika/toksikokinetika karbamazepina: opšti pregled

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Abstract

Carbamazepine (CBZ) is a widely used medication in treating epilepsy, bipolar disorder, and neuropathic pain. Its pharmacokinetic profile is highly variable due to slow absorption, extensive metabolism, and auto-induction. Genetic polymorphisms affect transporters and metabolic enzymes, additionally modifying therapeutic response, and lead to nonlinear and unpredictable toxicokinetics in overdose. CBZ is primarily metabolized by cytochrome P450 (CYP) enzymes CYP3A4, CYP3A5, and CYP2C8 to the active metabolite CBZ-10, 11-epoxide (CBZ-E), with subsequent hydrolysis by epoxide hydrolase 1 (EPHX1) and glucuronidation by uridine diphosphate glucuronosyltransferase 2B7 (UGT2B7), with other CYPs additionally contributing to the formation of reactive intermediates and inactive CBZ metabolites. Polymorphisms in genes encoding enzymes (EPHX1, CYP3A4/5, and UGT2B7) and transporters (ABCB1, ABCC2, RALBP1) can affect CBZ and CBZ-E exposure, maintenance dose, and the risk of adverse drug reactions. In overdose cases, CBZ exhibits saturable epoxidation, which leads to the accumulation of the drug and its active metabolite, prolonged elimination, and neurotoxicity, while serum concentrations correlate poorly with clinical findings. Therapeutic monitoring of the drug and its active metabolite in patients' blood, together with pharmacogenetic testing, could improve both the individualization of therapy and the management of overdose.

Keywords:
carbamazepine; cytochrome p-450 enzyme system; drug monitoring; metabolism; pharmacokinetics; poisoning; polymorphism, genetic; toxicokinetics.

Apstrakt

Karbamazepin (KBZ) je široko korišćen lek u terapiji epilepsije, bipolarnog poremećaja i neuropatskog bola. Njegov farmakokinetički profil je veoma varijabilan zbog spore resorpcije, ekstenzivnog metabolizma i autoindukcije. Genetički polimorfizmi utiču na transportere i metaboličke enzime, dodatno modifikujući terapijski odgovor i dovode do nelinearne i nepredvidive toksikokinetike u slučaju predoziranja. KBZ se prvenstveno metaboliše putem citohrom P450 (CYP) enzima CYP3A4, CYP3A5 i CYP2C8 do aktivnog metabolita KBZ-10, 11-epoksida (KBZ-E), nakon čega sledi hidroliza pomoću epoksid hidrolaze 1 (EPHX1) i glukuronidacija pomoću uridin difosfat glukuronil transferaze 2B7 (UGT2B7). Drugi CYP enzimi dodatno doprinose stvaranju reaktivnih intermedijera i neaktivnih metabolita KBZ. Polimorfizmi u genima koji kodiraju enzime (EPHX1, CYP3A4/5 i UGT2B7) i transportere (ABCB1, ABCC2, RALBP1) mogu uticati na izloženost organizma KBZ i KBZ-E, dozu održavanja i rizik od neželjenih reakcija na lek. U slučajevima predoziranja lekom dolazi do zasićenja procesa epoksidacije, što dovodi do akumulacije leka i njegovog aktivnog metabolita, produžene eliminacije i neurotoksičnosti, dok serumske koncentracije slabo koreliraju sa kliničkim nalazima. Praćenje koncentracije leka i njegovog aktivnog metabolita u krvi bolesnika, zajedno sa farmakogenetičkim testiranjem, moglo bi poboljšati i individualizaciju terapije i lečenje predoziranja.

Ključne reči:
karbamazepin; citohrom p-450; lekovi, monitoring; metabolizam; farmakokinetika; trovanje; polimorfizam, genetički; toksikokinetika.

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Introduction

Carbamazepine (CBZ) is a medication chemically related to tricyclic antidepressants that has been used for decades as an anticonvulsant in monotherapy for partial and generalized tonic-clonic seizures. Its use in combination regimens is generally reserved for patients who cannot be adequately controlled with previous monotherapy, and it is usually ineffective in the myoclonic and absence seizures [1–3]. Additionally, the established indications include the treatment of bipolar disorders and trigeminal neuralgia. Regarding its mechanism of action, it stabilizes hyperexcitable neuronal membranes by blocking voltage-gated sodium channels, inhibiting repetitive neuronal firing, and reducing the propagation of synaptic excitatory impulses. Its action also involves calcium channel inhibition, inhibition of excitatory amines, and gamma-aminobutyric acid agonism. By modulating inhibitory and excitatory neurotransmission, CBZ exerts a mood-stabilizing effect and exhibits an antineuralgic effect. It also has anticholinergic, antidiuretic, muscle-relaxant, and antiarrhythmic properties [3-6].

CBZ has a complex and variable pharmacokinetic profile, characterized by slow absorption, extensive protein binding, liver enzyme-mediated metabolism, and autoinduction, which necessitates careful monitoring to minimize the risk of adverse reactions [2, 5, 7]. In overdose cases, the elimination of CBZ follows zero-order kinetics, leading to symptoms of prolonged toxicity coinciding with the peak serum levels of CBZ and its active metabolites [8–10].

Scope and methodology approach

The aim of this manuscript was to synthesize current knowledge on how genetic variations influence the pharmacokinetics of CBZ at therapeutic doses and the risk of adverse drug reactions (ADRs), with a focus on clinical interpretation rather than quantitative analysis. Additionally, the toxicokinetics of CBZ in overdose patients differ from its behavior within the therapeutic range, focusing on how the body influences CBZ and its metabolites at concentrations exceeding the therapeutic level.

For this general review, a literature search was conducted from September to December 2025 to obtain newly available clinical data and regulatory information. The literature search was performed in PubMed and EBSCO databases, with Google Scholar used as a complementary tool for cross-checking and identification of supplementary publications. The following criteria were applied to identify English-language publications published up to 2025: (“carbamazepine“ OR “anticonvulsants“ OR „antiepileptic drugs” OR “carbamazepine metabolites” OR “carbamazepine-10,11-epoxide”) AND (“pharmacokinetics” OR “population pharmacokinetics” OR “toxicokinetics” OR “CYP450” OR “poisoning” OR “overdosage” OR “genetic polymorphism” OR “metabolism” OR “elimination kinetics”). We also included reference lists from recent systematic reviews, meta-analyses, and clinical guidelines as additional sources. Only relevant full texts were evaluated. Furthermore, we reviewed regulatory databases from the United States Food and Drug Administration and the European Medicines Agency, as well as authoritative drug information sources (drugs.com and the Electronic Medicines Compendium). Commentaries, opinion articles, editorials, and conference abstracts were excluded.

Pharmacokinetics of carbamazepine

Absorption, distribution, and transport protein genetic polymorphisms

CBZ is a lipophilic molecule that shows slow and variable but almost complete absorption [2, 5, 7]. After oral administration, peak plasma concentrations occur 2–8 hrs after ingestion of immediate-release formulations and 12–24 hrs after ingestion of CBZ sustained-release formulations (single dose) and 4–8 hrs after multiple doses [9]. The absorption of CBZ could additionally be delayed due to its weak anticholinergic properties and decreased gastrointestinal motility [5, 11]. Its bioavailability ranges from 75% to 85% for sustained-release formulations and up to 90% for immediate-release formulations [7, 12, 13].

Due to the moderate to high lipid solubility of CBZ, the apparent volume of distribution in adults and older children generally ranges between 0.59 and 2 L/kg [4, 7, 14]. The drug binds to plasma proteins at 70–80%, primarily to albumin and α1-acid glycoprotein. In neonates, the free fraction is higher, ranging from 30 to 35%, due to lower plasma protein concentrations [4, 15].

The transport of CBZ across biological membranes occurs *via* adenosine triphosphate (ATP)-binding cassette sub-family B member 1 (ABCB1), ATP-binding cassette sub-family C member 2 (ABCC2), and Ral-binding protein 1 (RALBP1) transport proteins, which significantly contribute to the pharmacokinetic variability of many drugs and play a crucial role in the efflux of CBZ [16, 17]. These proteins participate in the transport of CBZ across the intestinal barrier and the blood-brain barrier. They are also expressed in the liver, where they are involved in ATP-dependent efflux of CBZ and its metabolites from hepatocytes. Transporters substantially influence intracellular drug availability and contribute to interindividual variability in therapeutic response [16]. ABCB1 is a major efflux transporter at the intestinal and blood-brain barrier surfaces. The ABCC2 transporter contributes to the efflux of xenobiotics and metabolites [18]. RALBP1 is also an ATP-dependent transporter implicated in the removal of CBZ conjugates. Boughrara and Chentouf [16] concluded that genetic variability in *ABCB1*, *ABCC2*, and *RALBP1* contributes to interindividual differences in CBZ response, but the overall evidence is still inconsistent across populations. Djordjevic et al. [19] also discussed *ABCB1* polymorphisms, the most extensively studied efflux transporter, which showed that haplotypes like c.3435C>T (cytosine replaced by thymine), c.2677G>T/A (guanine replaced by thymine or adenine), and c.1236C>T (cytosine replaced by thymine) are associated with altered CBZ transport and treatment outcomes.

Additionally, the 1236T–2677T–3435T haplotype is associated with increased clearance in pediatric patients, therefore showing more efficient efflux and lower systemic exposure [19]. Wang et al. [20] have concluded that the *ABCB1* rs2032582, rs10234411, and rs2032582-rs10234411 AT, CA haplotype is significantly associated with the ratio of CBZ-10,11-epoxide (CBZ-E) to CBZ when CBZ is used in therapy in combination with other anticonvulsants, such as phenobarbitone or phenytoin. In addition, several authors suggested that the *ABCB1* gene polymorphism increases the risk of poor treatment response [21], particularly the rs1128503 polymorphism, which was significantly associated with CBZ pharmacoresistance [22]. *ABCC2* polymorphisms included c.-24C>T, c.1249G>A, and c.3972C>A, and several *RALBP1* variants were examined for their potential association with drug resistance [16]. RALBP1 is a multifunctional protein, a non-ATP-binding cassette important transporter for CBZ at the human blood-brain barrier, where its expression is increased in patients with drug-resistant epilepsy [23]. On the contrary, other authors have not found an association between *RALBP1* expression and resistance to antiepileptic drugs [24].

Metabolism and genetic polymorphism of metabolic enzymes

CBZ is extensively metabolized in the liver by microsomal cytochrome P450 (CYP) enzymes – CYP450, and excreted in feces (28%), with only 1–3% of the dose excreted as unchanged drug in urine, while the rest, about 70%, is excreted as metabolites [2, 7, 17, 25]. The major pathway of CBZ metabolism is oxidation mediated by CYP3A4, with involvement of CYP2C8 and CYP3A5, forming the pharmacologically active metabolite CBZ-E, which contributes to both its efficacy and toxicity. CBZ-E undergoes further metabolism *via* microsomal epoxide hydrolase 1 (EPHX1) to trans-10,11-dihydro-10,11-dihydroxycarbamazepine, CBZ-diol, a pharmacologically inactive metabolite. After oxidative metabolism and further hydrolysis by EPHX1, phase II metabolism involves the glucuronidation of CBZ and CBZ-E by uridine diphosphate glucuronosyltransferases (UGTs), particularly UGT2B7, which facilitates renal excretion of both CBZ and CBZ-E [26].

Several reactive intermediates are formed during the minor oxidative pathways of CBZ. One branch involves the generation of an epoxide intermediate, CBZ-2,3-epoxide, which is further oxidized by multiple CYP isoenzymes to 2-hydroxycarbamazepine (2-OH-CBZ) and by CYP3A4 and CYP2B6 to 3-hydroxycarbamazepine (3-OH-CBZ). The 2-OH-CBZ undergoes secondary oxidation *via* CYP3A4 to form 2-hydroxyiminostilbene, which is further converted to iminoquinone, a highly reactive electrophilic species capable of forming covalent adducts with protein residues, including CYP450 enzymes. The formation of such adducts may inactivate enzymes and contribute to immune-mediated hypersensitivity reactions, such as Stevens-Johnson syndrome [27]. The 3-OH-CBZ metabolite is further oxidized by CYP2C19, CYP3A4, and CYP3A5 to CBZ catechol and subsequently to CBZ o-quinone. In parallel, through myeloperoxidase-mediated oxidation, 3-OH-CBZ can generate free radicals and reactive oxygen species, which enhance oxidative stress and promote tissue injury [28] (Figure 1). Lukic et al. [10] supposed that CYP3A activity decreased, while CYP2B6 activity increased, accompanied by increased free radicals and reactive oxygen species, leading to increased markers of inflammation in patients with acute self-poisoning with CBZ.

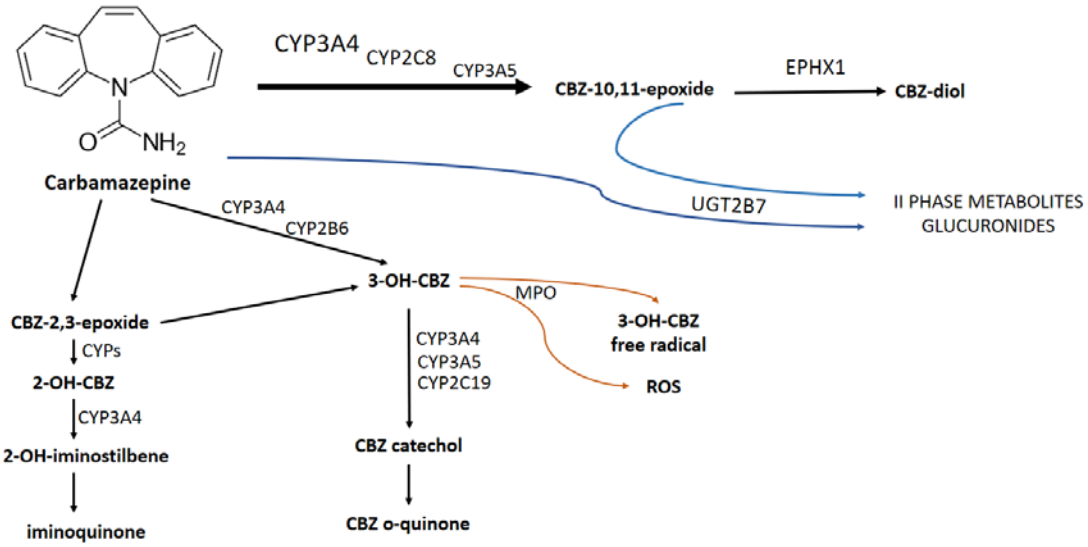

Fig. 1 – **Hepatic biotransformation pathways of CBZ and associated enzymes. Adapted from the ClinPGx CBZ pathway, pharmacokinetics [28].**
CBZ – carbamazepine; CYP – cytochrome P450 enzymes; EPHX1 – epoxide hydrolase 1; 2-OH-CBZ – 2-hydroxycarbamazepine; 3-OH-CBZ – 3-hydroxycarbamazepine; 2-OH-iminostilbene – 2-hydroxyiminostilbene, UGT2B7 – uridine diphosphate glucuronosyltransferase-2B7; MPO – myeloperoxidase; ROS – reactive oxygen species.
***Note*: CYP3A4, CYP3A5, CYP2C8, CYP2C19, CYP2B6 – specific CYP450 isoenzymes involved in the CBZ metabolism.**

CBZ exhibits autoinduction within the first few weeks of therapy, accelerating its own metabolism and decreasing its elimination half-life over time [7, 29]. This process corresponds to CBZ binding to nuclear receptors NR1|2 and NR1|3, which upregulate CYP1A2 during autoinduction. The −163C>A polymorphism alters CYP1A2 inducibility and contributes to interindividual differences in CBZ metabolism [30]. Although CYP1A2 is not directly involved in the biotransformation of CBZ, its induction amplifies the broader hepatic autoinduction response, contributing to increased expression and activity of both CYP3A4 and CYP2B6, two primary enzymes responsible for CBZ metabolism and several co-administered drugs [15, 25, 31].

Investigating the genetic polymorphisms of CBZ-metabolizing enzymes and transport pathways can significantly impact individual drug responses, leading to safer and more effective personalized dosing [32]. In the previous section, it was shown that three main groups of enzymes are involved in CBZ elimination: oxidative metabolism and hydrolysis enzymes of phase I *via* CYP3A4, CYP3A5, CYP2C8, and EPHX1, and phase II glucuronidation *via* UGT2B7 (Figure 1). Therefore, the influence of genetic polymorphisms as predictors of responsiveness to CBZ therapy is exerted by genes that affect CYP3A4, CYP3A5, CYP2C19, and CYP2C8 activity, as well as the *EPHX1* gene [33].

The most significant association exists between the *EPHX1* gene polymorphism and the maintenance dose of CBZ [33, 34]. Two common polymorphic sites in the gene affect EPHX1 activity and, subsequently, CBZ and CBZ-E plasma levels. The presence of the 337C allele instead of 337T (when the amino acid tyrosine is replaced by histidine) is associated with decreased microsomal epoxide hydrolytic activity. Lower EPHX1 activity leads to increased CBZ-E (less conversion to CBZ-diol), while variability in the CBZ-diol/CBZ-E ratio could be a good indicator of hydrolase catalytic activity. Furthermore, increased concentrations of CBZ-E in patients with epilepsy may lead to more frequent skin reactions and severe ADRs, such as Stevens–Johnson syndrome and toxic epidermal necrolysis [35].

An increased enzymatic activity is observed in the presence of the 416G allele, rather than the 416A, when histidine is replaced by arginine, which accelerates CBZ-E hydrolysis, resulting in reduced CBZ-E levels and a lower CBZ-diol/CBZ-E ratio as CBZ-diol declines much faster due to glucuronidation and renal excretion [33, 34, 36]. On the contrary, population pharmacokinetic modeling by Yip et al. [37] showed that the *EPHX1* 416G/G genotype was associated with a 50% decrease in the overall clearance of CBZ-E, reflecting the influence of conversion rate, downstream glucuronidation, and systemic elimination processes. CBZ-E retains anticonvulsant activity, but elevated plasma concentrations have been associated with reduced tolerability to CBZ treatment and increased adverse events, such as blurred vision, dizziness, and fatigue.

CYP3A4 is essential for the oxidation of CBZ to active metabolites such as CBZ-E, which is then deactivated by other enzymes [2, 7, 15, 25, 38]. Several *CYP3A4* polymorphisms, such as *CYP3A4*1G* (rs2242480) and rs4646440, modify enzyme activity and may accelerate CBZ clearance, although studies have shown an inconsistent causal relationship with steady-state plasma concentrations. Some studies report that carriers of *CYP3A4*1G* variant alleles exhibit higher metabolic activity and lower adjusted CBZ levels. However, overall, the effect of *CYP3A4* genetic variation on CBZ efficacy appears to be modest [39]. Other authors have noted that *CYP3A4* has limited polymorphism, and its inducibility outweighs genetic effects on enzyme activity. Therefore, genetic variations in *CYP3A4* have less influence than those in other CYP enzymes, such as *CYP3A5*, which shows higher genetic variability [40]. A meta-analysis by Zhao et al. [41] regarding the *CYP3A4* rs2242480 polymorphism revealed that carriers of the AG genotype had significantly lower plasma CBZ concentrations than those with the GG genotype, indicating a genotype-dependent effect on drug exposure. Overall, the data suggest that the G allele of this single-nucleotide polymorphism (SNP) could reduce plasma CBZ levels. At the same time, individuals with the AA genotype display a lower CBZ-E/CBZ ratio than GG or AG+GG carriers, without any influence on CBZ-E. Wang et al. [20] investigated *CYP3A4* gene polymorphisms in the Chinese population, focusing on rs2242480 and rs4646440, which are common SNPs and may affect CYP3A4 catalytic activity. Authors have concluded that the examined *CYP3A4* genotypes were not associated with CBZ plasma concentrations, neither in the monotherapy group nor in the polytherapy group. On the other hand, *CYP3A5* rs776746 and rs15524 might affect CBZ metabolism and were significantly associated with CBZ plasma concentrations [20]. In the research by Jamil et al. [42], which assessed *CYP3A5* rs15524 rather than specific *CYP3A4* SNPs, it was concluded that *CYP3A5* polymorphisms are an important genetic factor influencing CBZ serum concentrations and the need for dose adjustments. In White populations, the failure of *CYP3A* polymorphisms to predict the maintenance dose due to low activity of the *CYP3A4*-392 G allele may be compensated by functional *CYP3A5* in individuals carrying at least one copy of the 6986A allele. Such influence is not expected in Japanese individuals, who generally lack the *CYP3A4*-392 G allele, and in whom *CYP3A5* c. 6986A>G polymorphism is a major contributor to interindividual variability in CBZ pharmacokinetics [34]. While investigating *CYP3A5* genetic polymorphism, Ganesapandian et al. [43] concluded that the impact of this polymorphism on CBZ metabolism showed discrepant results in different populations. According to their results, the *CYP3A5*3* polymorphism significantly influenced CBZ metabolism in Indian epileptic patients, consistent with studies performed in Serbian, Chinese, and Korean populations. Additionally, Seo et al. [44] concluded, based on a study with Japanese patients with epilepsy, that the *CYP3A5*3* genotype increased CBZ oral clearance by only about 8% compared with *CYP3A5*1* carriers, indicating a minimal effect on overall CBZ pharmacokinetics. Some other authors have concluded that genetic variability in *CYP3A5* and *EPHX1* moderately influences plasma

concentrations, which are usually insufficient to cause significant clinical effects [26]. Ragia et al. [45] suggested that, despite the lack of definitive conclusions on whether the CYP3A5 enzyme has similar affinity and metabolic capacity to CYP3A4 for psychiatric drugs, the role of CYP3A5 should be more thoroughly investigated in the future due to its potential to catalyze alternative metabolic pathways and form intermediate metabolites with unknown pharmacological properties that influence CBZ bioavailability. Additionally, studies of CBZ epoxidation and the influence of *CYP3A5*3* on pharmacokinetic parameters were examined. Wild-type *CYP3A5*1/*1* liver microsomes have the highest maximum velocity (V_{max}) and maximum clearance (CL_{max}), meaning strong catalytic activity. Heterozygous *CYP3A5*1/*3* microsomes show markedly reduced activity, less than half of the wild-type, and homozygous *CYP3A5*3/*3* microsomes show activities similar to wild-type. These results suggest that the *CYP3A5*3* polymorphism has a negligible effect on CBZ epoxidation in an *in vitro* system using human liver microsomes, primarily because *in vivo* CYP3A4 is the dominant enzyme for epoxidation processes [46].

Glucuronidation plays an important role in the elimination of CBZ [3, 26]. The enzyme UGT2B7 is responsible for the glucuronidation of both CBZ and CBZ-E. The *UGT2B7*2* (802C>T) variant has been shown to influence CBZ clearance, as demonstrated in a study of 62 patients on CBZ monotherapy, in which carriers of the *1/*2 and *2/2 genotypes exhibited lower steady-state CBZ concentrations and required higher maintenance doses than wild-type individuals [33, 47]. In contrast, the *UGT2B7*3* (211G>T) polymorphism did not affect steady-state levels nor dosing adjustments. On the other hand, other studies have not reported a significant association between *UGT2B7* variants and CBZ pharmacokinetics [33, 47, 48]. Population pharmacokinetic modeling allows clinicians to predict drug clearance in patients using only a few clinical characteristics [49]. It is a helpful tool for optimizing dosing regimens of drugs with high variability, autoinduction, and a narrow therapeutic window, like CBZ [25]. Jankovic et al. [25] demonstrated in their study that physiological covariates, such as age and weight, as well as drug–drug interactions (DDI) in polytherapy with valproate, are the primary drivers of CBZ clearance in Serbian patients. The low residual variability suggests that many unexplained differences could originate from genetic polymorphisms, highlighting the need for future pharmacogenomic work in this population. A systematic review of the population pharmacokinetics of CBZ by Methaneethorn et al. [11] highlights that the most frequently identified covariates, such as age, weight, CBZ dose, and concomitant therapy with other anticonvulsants (phenytoin, phenobarbitone, valproate), influence the clearance of CBZ. Only two studies evaluated genetic predictors, and the *CYP1A2*-163A/A variant had a small but statistically significant influence on clearance, while the *CYP2C8*3* variant showed no clinically significant effect. The authors highlight that although the pharmacokinetic determinants of CBZ disposition are well defined, the relationship between pharmacokinetic variability and pharmacodynamic outcomes remains largely inconclusive and highly dependent on the target population [11].

According to Kanojia et al. [50], CBZ can induce *CYP1A1 via* aryl hydrocarbon receptor-dependent transcriptional regulation, which contributes to the clinically relevant interindividual variability in response to CBZ therapy.

In a systematic review, Zhang et al. [51] found that the *ABCB1* c.3435C>T and *EPHX1* c.416A>G gene polymorphisms significantly affected CBZ concentrations, indicating their critical role in CBZ pharmacokinetics and pharmacodynamics. Various confounding factors, such as ethnicity, age, and differences in dosing and treatment duration, could explain the observed inconsistencies across studies, suggesting that considerable caution is needed when transferring to other populations.

Therapeutic drug monitoring

CBZ reaches steady state very slowly, typically within 4 to 30 days. Its half-life at steady state ranges from 20 to 36 hrs in adults and 8 to 14 hrs in children, again reinforcing the need for individualised dose titration [4, 7]. The initial half-life of the epoxide metabolite is 25–43 hrs [4]. Due to its narrow therapeutic window and non-linear pharmacokinetics, therapeutic drug monitoring (TDM) is essential for achieving safe and effective dosing of CBZ [11, 52]. The most commonly applied methods for routine CBZ determination in biological materials are high-performance liquid chromatography with ultraviolet or photodiode detection [high-performance liquid chromatography-ultraviolet (HPLC-UV) and high-performance liquid chromatography–photodiode array (HPLC-PDA)] and immunoassay [fluorescence polarization immunoassay (FPIA)] [53]. The therapeutic CBZ reference range is 4–12 mg/L, although individual variation exists, with the minimum toxic level of 10 mg/L [4, 54, 55]. The usual plasma concentration range of CBZ-E, 0.2–2 mg/L, should be considered in case of intoxication [55]. When CBZ is prescribed with other anticonvulsants, the therapeutic range is from 4 to 8 mg/L. Therefore, TDM is also critical for assessing the effect of co-administration of other drugs, since CBZ can induce CYP3A4 or other oxidative enzymes and enhance glucuronyltransferase activity, and, as a result, accelerate metabolism of these drugs and decrease their concentrations in the body (like warfarin, oral contraceptives, tricyclic antidepressants, antipsychotics) [3, 56, 57]. In contrast, felbamate, oxcarbazepine, phenobarbital, phenytoin, primidone, and rufinamide induce its clearance, resulting in lower CBZ concentrations [56, 57].

Moreover, there are suggestions related to genotyping patients in order to evaluate its effects on CBZ TDM. Belhekar et al. [58] conducted a study demonstrating that adding *CYP3A5* genotyping to TDM did not improve the prediction of CBZ plasma levels or reduce ADRs compared with TDM alone. They observed substantial interindividual variability in CBZ plasma concentrations and CYP3A5 status, but no significant associations were noticed with trough plasma levels at 1, 3, 6, or 12 months of therapy, nor

with the occurrence of CBZ-related adverse effects. Their findings indicate that *CYP3A5* polymorphism, although biologically relevant to CBZ metabolism, does not substantially influence TDM outcomes in epileptic patients. They suggest routine genotyping for patients who develop unexpected toxicity of CBZ.

The complex pharmacokinetic CBZ behavior increases the potential for ADRs. Hypersensitivity reactions may occur in approximately 10% of patients [37]. The primary cause of ADRs may be metabolism *via* CYP3A4, as it is highly prone to auto- and hetero-induction or inhibition, making CBZ susceptible to a wide range of DDI that may increase or decrease its serum levels. Anticonvulsants such as clobazam and stiripentol inhibit CBZ metabolism, thereby increasing its plasma concentration and potentially leading to ADRs [3, 56, 57].

Some authors have highlighted clear benefits of combining TDM with genotyping to reduce ADRs. CBZ TDM is routinely done to optimize dosing, but genetic polymorphisms significantly influence patients' risk of CBZ toxicity or CBZ-induced hypersensitivity [58]. In a systematic review, Jaramillo et al. [59] noted that *HLA-B**15:02 and *HLA-A**31:01 are strongly linked to severe skin-related ADRs. They recommend *HLA-B**15:02 genotyping for Asian patients to prevent severe ADRs. Relying only on TDM is insufficient because it cannot predict the CBZ immune-mediated reactions.

CBZ has an established role in epilepsy treatment, but up to 40% of patients may still demonstrate pharmacoresistance [60]. A study by Puranik et al. [61] showed that genetic variation in *CYP3A4*, *CYP3A5*, *EPHX1*, *UGT2B7*, *ABCB1*, and *ABCC2* significantly contributes to interindividual differences in CBZ pharmacokinetics, emphasizing a clear genotype-dependent covariate in population pharmacokinetics. These factors also contributed to altered CBZ-E/CBZ and CBZ-diol/CBZ-E ratios. Transporter polymorphisms were associated with decreased central nervous system penetration and inadequate seizure control.

A study by Kang et al. [27] did not directly determine the genetic polymorphisms of *CYP3A4*; however, it demonstrated that functional variability in the activity of this enzyme could have a substantial influence on patients' susceptibility to form reactive covalent adducts and develop severe idiosyncratic ADRs.

Fuhr et al. [62] developed a physiologically based pharmacokinetic model of CBZ and CBZ-E that included autoinduction of CYP3A4, CYP2C8, CYP2B6, and UGT2B7, which could predict plasma and saliva concentration-time profiles and DDI predictions. As CBZ is a known inducer of various enzymes and transporters, modelling methods for sensitive substrates could have future clinical implications.

Toxicokinetics of carbamazepine

In acute CBZ poisoning, the risk of severe outcomes depends on the ingested dose and the plasma concentrations of CBZ and its metabolite CBZ-E [63].

When doses of CBZ exceed 24 g in adults, it is correlated with fatal outcomes. Signs and symptoms of toxicity appear up to 3 hrs after ingestion, starting with neuromuscular disturbances, followed by impaired consciousness, which leads to coma, tremor, restlessness, psychomotor disturbances, dizziness, and drowsiness. Initial hyperreflexia is progressing to hyporeflexia, and ingested doses higher than 60 g led to severe cardiac dysfunction. Additionally, the presence of respiratory depression, abnormalities in the electrocardiogram, shock, and urinary retention demands intensive patient monitoring. The measures for overdose treatment are focused on the elimination of CBZ and include vomiting, gastric lavage, therapy with activated charcoal, forced diuresis, and extracorporeal therapy, such as hemodialysis or plasmapheresis. If seizures occurred, then treatment with benzodiazepines is recommended [4, 5, 64–66].

However, there are insufficient data on the relationship between CBZ dose, its pharmacokinetic behavior, and the severity of clinical manifestations [8, 9, 67]. CBZ pharmacokinetics is complex and variable even at therapeutic doses. In cases of large CBZ ingestions, it is additionally unpredictable, characterized by slow absorption, delayed peak concentrations, and prolonged elimination, resulting in zero-order kinetics [68, 69]. Serum levels of CBZ may increase up to 72–96 hrs, depending on the formulation used, due to impaired gastrointestinal motility, as a result of its anticholinergic effect, and poorly soluble mass of drug, whose dissolution rate is a limiting factor in the absorption process, since CBZ is a poorly water-soluble drug [70–72]. Compared with solid-dose CBZ formulations, which exhibit slow and variable absorption, the CBZ suspension for children and adults demonstrates predictable, rapid absorption, with a short time to reach peak drug levels [73]. Liquid formulations can cause severe clinical manifestations in cases of acute overdose due to rapid absorption and distribution. Based on the elimination rate of these patients, they recover much faster than others with CBZ solid formulation overdoses. However, although the toxic CBZ concentrations in patients are not entirely consistent with clinical manifestations, measuring serum CBZ concentrations is a standard method used to confirm drug exposure, and the minimum toxic level is 10 mg/L, while severe intoxication occurs at serum levels > 20 mg/L [4, 54, 55]. In children, the toxicity range is much lower. Monitoring of serum CBZ concentration in acute poisoning is a routine clinical procedure. Djordjević et al. [67] have demonstrated that salivary CBZ levels correlate well with serum concentrations in cases of overdosing, suggesting the possibility of extrapolating concentrations to their corresponding serum values. Clinical data from a study that analyzed acute mood stabilizer poisonings indicate that CBZ is associated with variable toxicity severity and clinical outcomes, emphasizing significant interindividual differences in the toxicokinetic behavior of CBZ that are not entirely predictable from dose alone [74].

Additionally, in overdose situations, CBZ reached markedly high serum concentrations due to saturation

kinetics in the epoxidation [75]. Namely, it is well known that processes which depend on specific proteins are capacity-limited, and due to that, metabolism in drug overdose is saturable in a dose-dependent manner [8]. According to Vree et al. [75], serum concentrations of CBZ in acute poisoning are consistently plateau-like, with delayed decreases and extended half-lives of CBZ and its metabolite, CBZ-E. Moreover, prolonged serum CBZ monitoring in severe overdose is necessary due to the possible clinical deterioration as a result of delayed toxicity caused by the rebound phenomenon due to redistribution of the drug from the tissue to the serum after some therapeutic measures, such as hemoperfusion [65, 75]. Nevertheless, it is necessary to monitor CBZ and CBZ-E serum concentrations serially, as prolonged absorption and enterohepatic recirculation may lead to late rises [76].

It was noted that there was an apparent lack of correlation between CBZ serum concentrations and clinical manifestations of toxicity, which could be partially attributed to the formation of active metabolites [65, 77]. Nonetheless, Winnicka et al. [9] have not found a statistically significant influence of CBZ-E levels on the duration of coma in poisoned patients. Perhaps the CBZ metabolites cannot be excluded as contributing factors to toxicity, since their protein binding is lower, and at high concentrations, they could have a significant impact. The study of Hundt et al. [8] suggests that CBZ metabolites are not more potent than the parent drug, but their additive effects can prolong or intensify clinical manifestations during overdose. In accordance with such findings, a case report was published describing the additional influence of CBZ-E in a case of fatal CBZ ingestion, and a dramatically higher ratio of CBZ-E/CBZ was observed, pointing to a significant contribution of CBZ-E serum concentrations quantification in overdose cases [63]. Therefore, the active metabolite CBZ-E accumulates alongside the parent drug and additionally contributes to neurotoxicity. In order to determine patients at risk for moderate to severe toxicity according to available clinical data at the time of initial admittance to the poison control center, Montgomery et al. [78] conducted a six-year study on patients with CBZ overdose. The most important finding regarding CBZ toxicokinetics was a confirmation of a weak but significant correlation between outcome and peak CBZ level for each observed age group, with severe toxicity exhibited in children at slightly lower CBZ levels than in adults. Clinical pharmacokinetic study of CBZ and its metabolites after an acute drug overdose indicated that CBZ and CBZ-E clearance values were low, and their dependency on urine flow supported the assumption that both were excreted by glomerular filtration minus tubular reabsorption [75]. Further population toxicokinetics research focused on estimating the clearance and volume of distribution of CBZ, CBZ-E concentrations, and the sum of these values. Lukic et al. [10] discussed the factors influencing the elimination of CBZ and CBZ-E in adult patients after acute poisoning with this drug. They concluded that elimination kinetics is strongly associated with high C-reactive protein and aspartate aminotransferase levels, as well as with treatment with sedating agents. Additionally, the elevated aspartate aminotransferase was not only an indicator of hepatic impairment, but also a consequence of possible rhabdomyolysis in patients with seizures or prolonged coma. Creatine kinase values in poisoned patients were significantly higher than in the healthy population.

When an overdose occurs after long-term exposure to CBZ, the toxicokinetic profile is very different from that of an acute overdose. Chronic use induces the liver CYP system continuously, so concentrations of CBZ may remain within the therapeutic range even when toxicity develops [76].

Conclusion

Carbamazepine exhibits significant pharmacokinetic and toxicokinetic variability due to its slow and variable absorption, extensive and complex hepatic metabolism, and pronounced autoinduction of the enzymes involved in its metabolism. Additionally, there is wide interindividual variability influenced by genetic polymorphisms in genes encoding the most important carbamazepine metabolic proteins, such as CYP3A4, CYP3A5, CYP2C8, EPHX1, UGT2B7, and transporters like ABCB1, ABCC2, and RALBP1, which influence carbamazepine absorption, distribution, metabolism, and excretion. The combination of routine therapeutic drug monitoring and pharmacogenetic testing could improve the safety and personalization of therapy. However, therapeutic drug monitoring remains the central tool in routine clinical practice, while the routine implementation of pharmacogenetic testing is currently limited to specific clinical situations and selected patient populations. After an overdose, the toxicokinetics of carbamazepine exhibit prominent nonlinearity due to prolonged absorption, saturable epoxidation in the liver, delayed clearance, and extended toxicity, as a result of accumulation of both parent compound and active metabolites. All of these lead to unpredictable elimination kinetics. Further well-designed prospective studies are needed to clarify genotype-phenotype relationships and their contribution to the precision of dosing strategies, both for therapeutic use and overdose treatment.

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Conflict of interest

The authors declare no conflict of interest.

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