

Review Article

The Pharmacotherapy of Carbamazepine in the Treatment of Epilepsy

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Abstract

Carbamazepine has been widely used as a primary pharmacotherapeutic for pain syndromes and epilepsy for decades, and its pharmacological profile has been extensively studied across a wide range of experimental and clinical settings. This review article outlines the significance and complexity of carbamazepine, with a focus on its anticonvulsant properties, and examines its pharmacodynamics, pharmacokinetics, efficacy, and adverse effects. This analysis is provided within the context of using suitable experimental models to adequately determine the validity, efficacy, and safety of existing and novel pharmacological agents.

ABBREVIATIONS

CBZ: carbamazepine; ACD: anticonvulsant drug; AD: afterdischarge; SS: seizure severity

INTRODUCTION

Carbamazepine (5H-dibenzo (b,f) azepine-5-carboxamide), is an iminostilbene derivative and is chemically related to the tricyclic antidepressants (Figure 1). It was initially synthesized in the early 1950s [1], in an attempt to discover new antidepressant medications, and subsequently used as pharmacotherapy for trigeminal neuralgia in the 1960s [2,3]. Carbamazepine (CBZ), was widely used outside of the United States as an anticonvulsant drug [4], and it wasn't approved by the Food and Drug Administration (FDA), until 1974 as an antiseizure compound. It has been promoted as an antimanic drug in bipolar disorder [5,6], and some reports of efficacy with psychosis [7]. There are more than 200 generic prescription products of CBZ, and over

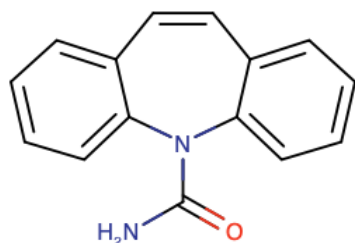


Figure 1 The structural formula of carbamazepine.

Keywords

- Epilepsy
- Antiepileptic drugs
- Anticonvulsant drugs
- Behavioral toxicity
- Kindling

150 international brands. Table 1 highlights some of these. Nowadays, CBZ is considered a primary drug of choice for partial and tonic-clonic seizures [8,9]. The focus in this paper is on CBZ's properties as an anticonvulsant drug (ACD).

PHARMACODYNAMICS

CBZ shares many similarities to phenytoin, another primary ACD, including its high lipid solubility, mechanisms of action, and clinical and experimental efficacy. At therapeutic doses carbamazepine appears to primarily exert its anticonvulsant effect, like phenytoin, by stabilizing voltage-gated sodium channels in the inactivated state, therefore limiting high-frequency discharge of neurons and ultimately resulting in depression of neuronal hyperexcitability [8,10]. Also similar to phenytoin, carbamazepine inhibits calcium entry into synaptic membranes [11,12]. Carbamazepine also depresses synaptic function via posttetanic potentiation reduction and inhibits catecholamine reuptake. However, these effects on synaptic function appear to occur only at supratherapeutic levels, suggesting that carbamazepine's anticonvulsant properties are not exerted through such mechanisms [13,14].

PHARMACOKINETICS

The pharmacokinetic profile of CBZ is complex, and ultimately variable due to its limited aqueous solubility, and the ability of CBZ to convert into active metabolites. It is absorbed slowly through the gastrointestinal tract, and has a bioavailability of 80-90%, which is similar across its range of formulations [15,16]. Peak plasma concentrations typically occur in 4-12 hours, but there is a wide range of 1.5-28 hours. The usual therapeutic range of CBZ is 3-12 µg/ml [8,17,18].

Table 1: A Sample of International Brand Names of Carbamazepine.

Brand Name	Manufacturer	Country
Actebral	Sanofi-Aventis	Ecuador
Anleptic	Square	Bangladesh
Biston	Zentiva	Czech Republic
Carbamat	Rontag	Argentina
Equetro	Validus	United States
Neurotop	Gerot	Lebanon
Tegretol Chewtabs	Novartis	United Kingdom
Tegretol-CR	Novartis	Belgium
Tegretol-XR	Novartis	United States
Teril	Taro	Israel
Timonil	Desitin	Germany
Versitol	Micro Synapse	India

CBZ is largely metabolized in the liver, with CYP3A4 being the major hepatic enzyme that metabolizes carbamazepine to its active metabolite, carbamazepine-10,11-epoxide. CBZ has an initial half-life range of 25-65 hours following acute doses, to 4-17 hours following repeated dosing [15-17]. The pharmacokinetic profile of CBZ appears to be similar in children and in adults, although the data shows a poor relationship between dosage and plasma levels in children [17].

Side effects associated with CBZ can be observed at about 9 µg/ml [8,9], to more obvious behavioral toxic effects at 11 µg/ml and over. In particular, disorientation and ataxia can be observed at levels of 11-15 µg/ml, aggression and hallucinations with levels of 15-25 µg/ml, and seizures and coma with levels above 25 µg/ml [19]. The toxicity related to CBZ will be further discussed below. A summary of the pharmacokinetic characteristics of CBZ is shown in Table 2.

CLINICAL EFFICACY

As previously indicated, carbamazepine has been established as one of the most important major ACDs and is one of the drugs of choice for complex partial and secondarily generalized seizures [9,20,21]. Additionally, tonic-clonic seizures associated with idiopathic generalized epilepsy are considered an indication for carbamazepine [22]. Carbamazepine is not recommended for absence or myoclonic seizures, and actually may exacerbate the condition [23]. Similarly, carbamazepine is usually not effective in infantile spasms, Lennox-Gastaut syndrome, or febrile seizures [21]. In addition to its anticonvulsant effects, carbamazepine has therapeutic effects in other indications such as psychiatric disorders [24-26], and various pain syndromes [9,17,27].

EXPERIMENTAL EFFICACY

An important consideration in the overall study of epilepsy and ACD development is the choice of an appropriate animal model for in vivo drug testing. Experimental testing of novel ACDs requires animal models that are predictive in anticonvulsant efficacy against specific seizure types and in terms of adverse or toxic effects at anticonvulsant doses. Models that mimic the symptoms, natural history, etiology and response to therapy of human epilepsy are crucial [28]. Valid models of partial seizures

should be used to test the anticonvulsant efficacy against partial epileptic activity [29-31]. Kindling [32,33], is generally considered to be the best available model of partial epilepsy and is particularly well suited for experimental study because precise control can be implemented over experimental conditions [34,35].

CBZ exerts relatively consistent anticonvulsant effects in the rat kindling model. CBZ has been shown to generally increase ADT [34,36,37], however, one exception reported a non-significant increase [38]. CBZ has also been shown to effectively decrease after discharge (AD) duration [38-40], and seizure severity [34,38-40]. Reductions in AD duration and seizure severity have also been reported in the cat [41,42], and in the baboon [42]. Further, in the guinea-pig kindling model of partial epilepsy, it was demonstrated that CBZ exhibited effective anticonvulsant properties by reducing both AD duration and seizure severity across acute drug administration [29] and repeated drug administration schedules [31].

ADVERSE EFFECTS

Acute toxicity with CBZ can result in disorientation and ataxia, aggression and hallucinations, and seizures and coma in a dose-dependent manner [19]. The most common side effects that accompany chronic CBZ treatment include drowsiness, dizziness, ataxia, dyskinesia, and visual disturbance. However, these neurologic effects occur most often at the beginning of carbamazepine therapy and are dose-related and reversible. More significant complications associated with CBZ treatment include serious dermatologic reactions, hypersensitivity reactions, aplastic anemia, and agranulocytosis. Of particular note, some retrospective case studies have indicated a strong association between a particular human leukocyte antigen, HLA-B*1502, and both Stevens-Johnson syndrome and toxic epidermal necrolysis [17,25]. It has been documented that this particular allele occurs almost exclusively with patients of Asian ancestry.

The use of CBZ, and ACDs in general, has significant implications for the overall health of women. Potential complications include interactions with oral contraceptives, possible teratogenic effects, and detrimental effects on vitamin metabolism in pregnant women [9,17]. With respect to teratogenicity, longitudinal research shows a significant risk for congenital malformations, including heart defects, neural tube defects, and cleft lip and palate.

Table 2: Pharmacokinetic Characteristics of Carbamazepine.

Bioavailability	75 - 89 (%)
Peak Plasma Concentration	1.5 - 28 (hr)
Volume of Distribution	0.7 - 1.9 (L/kg)
Protein Binding	70 - 80 (%)
Half-life (initial)	25 - 65 (hr)
Half-life (chronic)	4 - 17 (hr)
Time to Steady State	20 - 35 (d)
Therapeutic Range	3 - 12 (µg/ml)
Dose	10 - 30 (mg/kg/d)
Behavioral Toxicity	9 - 25+ (µg/ml)

As indicated above, the therapeutic dose of carbamazepine in humans is between 3 and 12 µg/ml in free plasma [8,17,18]. An overview of findings from the laboratory reveals an interesting comparative to gain a more complete understanding of CBZ's pharmacological profile. After a single i.p. dose of 30 mg/kg carbamazepine to female rats, a peak concentration of 16.3 µg/ml was reached 30 min following administration [43]. The concentrations declined thereafter, with drug concentrations considered to be within the therapeutic window between 2 and 6 hours post administration. In another study, plasma levels of carbamazepine in the rat were measured at one hour after a single i.p. administration and found a linear relationship with 20 mg/kg resulting in 5.5 µg/ml, while 60 mg/kg resulted in 18 µg/ml [39]. Similar pharmacokinetics were also reported for the cat [42,44].

In guinea-pigs, CBZ was adequately absorbed and yielded plasma levels associated with anticonvulsant efficacy comparable to those observed in humans [29]. A range of single i.p. doses of 10 to 40 mg/kg CBZ resulted in 4 to 20 µg/ml 1 to 2 hours post administration. It was shown that when plasma levels of CBZ were within the human therapeutic range, significant adverse effects were not observed in guinea-pigs [29].

Following chronic administration of carbamazepine in many species, including humans, metabolic tolerance has been observed, due to the fact that carbamazepine induces its own metabolism [8,45]. During prolonged administration of carbamazepine the elimination half-life is reduced to about half the time [45]. This is obviously an important factor to understand when considering the therapeutic concentration in plasma because it may reflect the tolerant state of the animal or human.

In the rat kindling model, Hönack and Löscher [46], reported that at 15 min following administration, the median minimal neurotoxic dose of carbamazepine was approximately 32 mg/kg i.p. in both non-kindled and kindled rats. They used the rotarod test as a measure of behavioural impairment. After 30 mg/kg carbamazepine, female rats displayed ataxia, temperature drop, and abdominal muscle relaxation, but almost no sedation [43]. Silver et al. [38], observed that carbamazepine at 25 mg/kg i.p. resulted in minimal ataxia, while Voits and Frey [39], reported that at 20 and 40 mg/kg, the animals showed slight sedation effects. After chronic administration of the drug, the degree of ataxia and muscle relaxation was markedly reduced, indicating the development of tolerance, but the temperature reducing effect of carbamazepine did not change [43].

In the guinea-pig kindling model, Gilbert and Teskey [29,31], used a battery of behavioral tests (bracing, righting and swimming) and open-field measures of sedation and muscle relaxation to investigate potential adverse effects of CBZ. Overall, they found non-significant differences across the quantitative measures following doses of 10, 25, and 40 mg/kg CBZ, but they did observe minimal to moderate adverse effects based on sedation, muscle relaxation, and body weight scores.

DISCUSSION

Carbamazepine has been around for almost 70 years serving in various pharmacotherapeutic capacity, and it remains a primary drug of choice for complex partial epilepsy. Although CBZ

can produce a diverse range of adverse effects, it can be effective with careful monitoring in eligible patients. CBZ has solidified its standing as a beneficial ACD, and research continues to be prolific in expanding its profile in the treatment of the epilepsies, as well as its therapeutic efficacy across other human conditions. Considering the reality of polypharmacy in treating general medical, neurological, and neuropsychiatric disorders, metabolic complexities associated with drug interactions becomes a formidable challenge. Accordingly, further investigation into such scenarios is warranted. As has been with the study of CBZ, it is important that appropriate experimental models be used for screening in order to obtain a complete analysis of the efficacy and safety of existing and novel pharmacological agents.

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