Carbamazepine (Fig. 1) corresponds chemically to 5H-dibenz[b,f]azepine-5-carboxamide with an empirical formula of $\text{C}_{15}\text{H}_{12}\text{N}_2\text{O}$ and a molecular weight of 236.27.

\[ \text{Figure 1 Carbamazepine} \]
Pharmacokinetic Characteristics

Absorption and Distribution

After oral ingestion, carbamazepine is rapidly absorbed ($T_{\text{max}}$ is formulation-dependent) with a bioavailability of 75–85 %. Its volume of distribution is 0.8–2.0 L/kg, and plasma protein binding is 75 %. The protein binding of the pharmacologically active metabolite, carbamazepine-10,11-epoxide, is 50 %.

Biotransformation

Carbamazepine is extensively metabolized in the liver, primarily by CYP3A4, to carbamazepine-10,11-epoxide which is pharmacologically active. Additional isoenzymes that contribute to the metabolism of carbamazepine include CYP2C8, CYP2B6, CYP2E1, CYP1A2, and CYP2A6. Carbamazepine-10,11-epoxide is in turn metabolized, via epoxide hydrolase, to an inactive trans-carbamazepine diol. Carbamazepine is an enzyme inducer, and additionally, carbamazepine undergoes autoinduction so that its clearance can increase 3-fold within several weeks of starting therapy and this often requires an upward dosage adjustment.

Renal Excretion

Less than 2 % of an administered dose is excreted as unchanged carbamazepine in urine.

Elimination

Following a single dose, plasma elimination half-life values in adults and children are 18–55 h and 3–32 h, respectively. During
maintenance carbamazepine monotherapy, half-life values in adults and children are 8–20 h and 10–13 h, respectively, while in the elderly, carbamazepine half-life values are 30–50 h. The half-life of carbamazepine-10,11-epoxide is \(~34\) h.

Time to new steady-state blood levels consequent to an inhibition of metabolism interaction:

- Carbamazepine = 2–5 days later
- Carbamazepine-10,11-epoxide = 7 days later

**Effects on Isoenzymes**

No in vitro data on the induction or inhibition potential of carbamazepine on human CYP or UGT isoenzymes have been published.

**Therapeutic Drug Monitoring**

Optimum seizure control in patients on carbamazepine monotherapy is most likely to occur at plasma carbamazepine levels of 4–12 mg/L (17–51 \(\mu\)mol/L). The upper boundary of the reference range for carbamazepine-10,11-epoxide is 9 \(\mu\)mol/L. The conversion factor from mg/L to \(\mu\)mol/L for carbamazepine is 4.23 (i.e., 1 mg/L = 4.23 \(\mu\)mol/L) while that of carbamazepine-10,11-epoxide, it is 3.96 (i.e., 1 mg/L = 3.96 \(\mu\)mol/L).

**Propensity to Be Associated with Pharmacokinetic Interactions**

- Carbamazepine affects the pharmacokinetics of other drugs – substantial.
- Other drugs affect the pharmacokinetics of carbamazepine – substantial.
Interactions with AEDs

**Acetazolamide**
Affects the pharmacokinetics of carbamazepine.
Consequence Increases carbamazepine plasma levels via an unknown mechanism [1].

**Clobazam**
Inhibits the metabolism of carbamazepine.
Consequence Carbamazepine plasma levels can increase by 15 %, and carbamazepine-10,11-epoxide plasma levels (the pharmacologically active metabolite of carbamazepine) can increase by 87 % [2].

**Clonazepam**
Does not affect the pharmacokinetics of carbamazepine [3].

**Eslicarbazepine acetate**
Does not affect the pharmacokinetics of carbamazepine [4].
During combination therapy, carbamazepine enhances eslicarbazepine adverse effects including diplopia, abnormal coordination, and dizziness. These effects are probably the consequence of a pharmacodynamic interaction [5].

**Ethosuximide**
Does not affect the pharmacokinetics of carbamazepine [6].

**Felbamate**
Enhances the metabolism of carbamazepine.
Consequence Mean carbamazepine plasma levels can decrease by 19 %, and mean carbamazepine-10,11-epoxide plasma levels (the pharmacologically active metabolite of carbamazepine) can increase by 33 %. The interaction is the consequence of induction of carbamazepine metabolism through CYP3A4 and inhibition of the metabolism of carbamazepine-10,11-epoxide via an action on epoxide hydro-lase [7].
<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect on Carbamazepine Pharmacokinetics</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin</td>
<td>Does not affect the pharmacokinetics of carbamazepine [8].</td>
<td></td>
</tr>
<tr>
<td>Lacosamide</td>
<td>Does not affect the pharmacokinetics of carbamazepine [9].</td>
<td>Neurotoxicity may occur in combination with carbamazepine, and other voltage-gated sodium channel blocking antiepileptic drugs, consequent to a pharmacodynamic interaction [10].</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Does not affect the pharmacokinetics of carbamazepine [11].</td>
<td>The high frequency of neurotoxicity observed with this drug combination represents a pharmacodynamic rather than pharmacokinetic interaction [12].</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Does not affect the pharmacokinetics of carbamazepine [13].</td>
<td>A pharmacodynamic interaction may occur whereby symptoms of carbamazepine toxicity present [14].</td>
</tr>
<tr>
<td>Methsuximide</td>
<td>Enhances the metabolism of carbamazepine.</td>
<td>Plasma levels of carbamazepine can decrease by 23%. The interaction is the consequence of induction of carbamazepine metabolism through CYP3A4 [15].</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Enhances the metabolism of carbamazepine.</td>
<td>Median carbamazepine plasma AUC values can decrease by 9%, and median carbamazepine-10,11-epoxide plasma AUC values (pharmacologically active metabolite of carbamazepine) can increase by 33%. The interaction is the consequence of induction of carbamazepine metabolism through CYP3A4 and inhibition of the metabolism of</td>
</tr>
</tbody>
</table>
carbamazepine-10,11-epoxide via an action on epoxide hydrolase [16].

**Phenobarbital**  
Enhances the metabolism of carbamazepine.  
**Consequence** Mean carbamazepine plasma levels can decrease by 33 %, and mean carbamazepine-10, 11-epoxide plasma levels (the pharmacologically active metabolite of carbamazepine) can increase by 24 %. The interaction is the consequence of induction of carbamazepine metabolism through CYP3A4 and inhibition of the metabolism of carbamazepine-10,11-epoxide via an action on epoxide hydrolase [17].

**Phenytoin**  
Enhances the metabolism of carbamazepine.  
**Consequence** Mean carbamazepine plasma levels can decrease by 44 %. However, carbamazepine-10, 11-epoxide levels (the pharmacologically active metabolite of carbamazepine) are unaffected. The interaction is the consequence of induction of carbamazepine metabolism through CYP3A4 [17].

**Piracetam**  
The interaction has not been investigated. Theoretically, a pharmacokinetic interaction would not be anticipated.

**Pregabalin**  
Does not affect the pharmacokinetics of carbamazepine [18].

**Primidone**  
Enhances the metabolism of carbamazepine.  
**Consequence** Mean carbamazepine plasma levels can decrease by 25 %, and mean carbamazepine-10,11-epoxide levels (the pharmacologically active metabolite of carbamazepine) can increase by 75 %.
The interaction is the consequence of induction of carbamazepine metabolism through CYP3A4 and inhibition of the metabolism of carbamazepine-10,11-epoxide via an action on epoxide hydrolase [17].

**Retigabine**

Does not affect the pharmacokinetics of carbamazepine [19].

**Rufinamide**

Increases the clearance of carbamazepine.

**Consequence**

The clearance of carbamazepine is increased by 8–15 % so that plasma carbamazepine levels are decreased by 7–13 %. The action is probably the consequence of induction of CYP3A4 [20].

**Stiripentol**

Inhibits the metabolism of carbamazepine.

**Consequence**

The clearance of carbamazepine is decreased by 27–70 % so that plasma carbamazepine levels are increased while plasma levels of carbamazepine-10,11-epoxide (the pharmacologically active metabolite carbamazepine) are decreased. The action is the consequence of inhibition, primarily of CYP3A4, but with a minor effect on CYP2C8. Epoxide hydrolase, the enzyme responsible for the metabolism of carbamazepine-10,11-epoxide, is unaffected [21].

**Sulthiame**

The interaction has not been investigated. Theoretically, a pharmacokinetic interaction could occur.

**Tiagabine**

Does not affect the pharmacokinetics of carbamazepine [22].

**Topiramate**

Does not affect the pharmacokinetics of carbamazepine [23].
Carbamazepine toxicity has been described in patients co-prescribed with topiramate, and this is considered to be the consequence of a pharmacodynamic interaction [24].

**Valproic acid**

Inhibits the metabolism of the pharmacologically active metabolite carbamazepine-10,11-epoxide.

**Consequence**

Mean plasma levels of carbamazepine-10,11-epoxide (the pharmacologically active metabolite carbamazepine), with either no change or a small decrease in plasma carbamazepine levels, can increase by 25 %. This interaction is related to valproic acid inhibition of epoxide hydrolase, the enzyme responsible for the metabolism of the epoxide metabolite [25, 26].

During combination therapy, valproic acid can synergistically enhance the antiepileptic efficacy (partial seizures) of carbamazepine. This effect is the consequence of a pharmacodynamic interaction [27].

**Vigabatrin**

The effect of vigabatrin on the pharmacokinetics of carbamazepine is controversial.

**Consequence**

There is a suggestion that in patients with low carbamazepine levels (<9 mg/L), the plasma carbamazepine levels can be significantly increased (20–132 %), through an unknown mechanism, during concomitant administration with vigabatrin. Another study reports that mean carbamazepine levels are decreased by 18 % and that mean carbamazepine clearance increases by 35 % [28, 29].
During combination therapy, vigabatrin may synergistically enhance the antiepileptic efficacy (partial seizures) of carbamazepine. This effect is probably the consequence of a pharmacodynamic interaction [27].

**Zonisamide**

Inhibits the metabolism of the pharmaco-logically active metabolite carbamazepine-10,11-epoxide.

**Consequence**

Mean plasma carbamazepine-10,11-epoxide $C_{\text{max}}$ and AUC values can increase by 38 and 17 %, respectively. Carbamazepine is not affected. The interaction is the consequence of a decrease in the renal clearance of carbamazepine-10,11-epoxide [30].

**References**

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