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.
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 μmol/L). The upper boundary of the reference range for carbamazepine-10,11-epoxide is 9 μmol/L. The conversion factor from mg/L to μmol/L for carbamazepine is 4.23 (i.e., 1 mg/L = 4.23 μmol/L) while that of carbamazepine-10,11-epoxide, it is 3.96 (i.e., 1 mg/L = 3.96 μmol/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

<table>
<thead>
<tr>
<th>AED</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acetazolamide</strong></td>
<td>Affects the pharmacokinetics of carbamazepine.</td>
</tr>
<tr>
<td><strong>Consequence</strong></td>
<td>Increases carbamazepine plasma levels via an unknown mechanism [1].</td>
</tr>
<tr>
<td><strong>Clobazam</strong></td>
<td>Inhibits the metabolism of carbamazepine.</td>
</tr>
<tr>
<td><strong>Consequence</strong></td>
<td>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].</td>
</tr>
<tr>
<td><strong>Clonazepam</strong></td>
<td>Does not affect the pharmacokinetics of carbamazepine [3].</td>
</tr>
<tr>
<td><strong>Eslicarbazepine acetate</strong></td>
<td>Does not affect the pharmacokinetics of carbamazepine [4].</td>
</tr>
<tr>
<td></td>
<td>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].</td>
</tr>
<tr>
<td><strong>Ethosuximide</strong></td>
<td>Does not affect the pharmacokinetics of carbamazepine [6].</td>
</tr>
<tr>
<td><strong>Felbamate</strong></td>
<td>Enhances the metabolism of carbamazepine.</td>
</tr>
<tr>
<td><strong>Consequence</strong></td>
<td>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].</td>
</tr>
<tr>
<td>AED</td>
<td>Effect on Pharmacokinetics of Carbamazepine</td>
</tr>
<tr>
<td>-------------------</td>
<td>--------------------------------------------</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Does not affect the pharmacokinetics of carbamazepine [8].</td>
</tr>
<tr>
<td>Lacosamide</td>
<td>Does not affect the pharmacokinetics of carbamazepine [9].</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Does not affect the pharmacokinetics of carbamazepine [11].</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Does not affect the pharmacokinetics of carbamazepine [13].</td>
</tr>
<tr>
<td>Methsuximide</td>
<td>Enhances the metabolism of carbamazepine.</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Enhances the metabolism of carbamazepine.</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 pharmacologically 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


Antiepileptic Drug Interactions
A Clinical Guide
Patsalos, P.N.
2013, LXV, 437 p. 29 illus., Softcover
ISBN: 978-1-4471-2433-7