1.6. Carbamazepine

Pharmacokinetic Parameters

Table 1.6-1. Carbamazepine Clearance in Adults

Adults (>15 years)	Clearance (L/hr/kg)[a]
Initial dosing (prior to autoinduction)	0.01–0.03
Chronic dosing	0.05–0.1

[a]Clearance relative to bioavailability (CL/F).

Select Drug–Drug Interactions

Carbamazepine (CBZ) Drug Interactions That Impact Concentrations of the Second Drug

CBZ increases concentration

Selegiline

Phenytoin

CBZ decreases concentration

Anticoagulants (warfarin, dicumarol)

Antifungal agents (e.g., ketoconazole)

Theophylline

Antipsychotics (aripiprazole, clozapine, fluphenazine, haloperidol, olanzapine, risperidone, ziprasidone)

Statins (atorvastatin, lovastatin, simvastatin)

Drug Interactions That Result in Changes in Carbamazepine (CBZ) Concentrations

Drug increases CBZ concentration

Acetazolamide

Antifungal agents (fluconazole, itraconazole, ketoconazole)

Antihistamines (loratadine)

Isoniazid

Non-dihydropyridine calcium channel blockers (diltiazem, verapamil)

Cimetidine

Valproic acid (CBZ-E[a])

Drug decreases CBZ concentration

Antineoplastic agents (cisplatin, doxorubicin)

Rifampin

Felbamate

Phenobarbital

Primidone

Phenytoin

Theophylline

Caffeine

[a]CBZ-E = 10,11-epoxide.

Dosing Strategy

Clearance relative to bioavailability (CL/F) predictors were developed using NONMEM* analysis and the following regression equations resulted for carbamazepine used alone or in combination with several other antiepileptic agents:[1]

1. CL/F (in L/hr) = [(0.0134 × ABW) + 3.58], *where ABW = actual body weight*
2. If the patient is also receiving phenytoin, the CL/F determined in (1) is multiplied by 1.42.
3. If the patient is receiving phenobarbital or felbamate in addition to carbamazepine, the CL/F determined in (1) is multiplied by 1.17.
4. If the patient is receiving phenytoin and phenobarbital or felbamate, the CL/F determined in (1) is multiplied by 1.62.
5. If the patient is ≥ 70 years of age, the CL/F determined in (1 to 4) is multiplied by 0.749.

*NONMEM (nonlinear mixed effects modeling) is a software package that has become the "gold standard."

Reference

1. Graves NM, Brundage RG, Wen Y, et al. Population pharmacokinetics of carbamazepine in adults with epilepsy. *Pharmacotherapy*. 1998;18(2):273–281.

Self-Assessment Problems

1. Determine the dosing of carbamazepine (CBZ) for a 60-year-old patient who weighs 80 kg to produce a predicted Css_{avg} of 7 mg/L. Use clearance values from **Table 1.6-1**.

   A. Predict the maintenance dose over a 24-hour period using oral suspension and using the midpoint and range of clearances for chronic dosing.

   B. What would be the anticipated impact of starting the full dose right away in a patient?

2. A. Determine the clearance predicted for the 60-year-old patient who weighs 80 kg from Problem 1 to that which would be determined from the dosing strategy described at the beginning of this section.

   B. If the patient was also receiving phenytoin, what is his predicted clearance using the dosing strategy?

   C. If the patient had been receiving carbamazepine and phenytoin with measured carbamazepine steady state trough concentrations averaging 6 mg/L, and the phenytoin were discontinued, what would be the prediction for the new steady state carbamazepine trough concentration after the drug–drug interaction abated?

3. The patient in Problem 1 needs to be switched to commercially available tablet doses. What would be the impact on predicted Css_{avg} if 200 mg were given every 6 hours or 300 mg every 8 hours? Assume the dose chosen for the midpoint of clearance (6 L/hr) would produce the Css_{avg} of 7 mg/L.

4. If a patient develops mild leukopenia, should carbamazepine be discontinued?

5. What would your concerns be relative to drug concentrations if a patient receiving carbamazepine were to be started on any of the following other drugs:

   Phenytoin, haloperidol, cimetidine, isoniazid, and theophylline?

6. What is the time period for autoinduction of carbamazepine clearance? Explain the reasons for the time it takes in terms of drug metabolism and dosing.