CARBAMAZEPINE

01. Assay details

CH Labs Test Reference Guide

02. Therapeutic range

16-50 umol/L (4-12mg/L)

How well established:
Epilepsy: The upper limit of the therapeutic range is subject to debate, and it has been suggested that the dose be increased until either seizure control is achieved or side effects appear, without being concerned about the therapeutic range.

In one previous unblinded study, with higher carbamazepine doses in patients, a reduction of >50% in seizures was observed in 53% of patients, and 20% remained seizure free for 6 months.

In a recent (also unblinded) trial of patients with refractory seizures who initially had carbamazepine (CBZ) concentrations within the therapeutic range, doses were progressively increased until either a 50% reduction in seizures was sustained for 2 months or side effects appeared. 39% of patients improved, but this benefit was not long-lasting, and only 17% improved for >6 months. 78% of patients developed neurotoxic side effects, and toxicity was mainly encountered at concentrations >42 micromol/L (upper limit of usual therapeutic range). The conclusion was that this supported the strategy of increasing doses to either seizure control or appearance of side effects, but they noted that very few patients will improve for a long time without adverse effects.

In this study side effects were correlated with high CBZ plasma concentrations, but they did not correlate with carbamazepine-epoxide [CBZ-E]concentrations, although some studies have correlated side effects with high [CBZ-E], in the presence of normal [CBZ].

Patients should be observed closely for neurotoxic side effects if doses above the therapeutic range are to be used.

Pregnancy: A slight but significant decrease in total plasma CBZ concentration has been shown in pregnant women with generalised epilepsy. This appeared to be due largely to a decrease in protein binding, as no significant change was noted in the free concentration, and they did not demonstrate any relation between changes in antiepileptic plasma concentrations and clinical effects. They did not find any support for dosage adjustments in response to low or decreasing plasma concentrations unless there is a concomitant loss of seizure control.

Trigeminal neuralgia: Optimal relief of symptoms, with a minimum of side effects, has been observed at plasma concentrations of 5.7-10 mg/L (19-33 umol/L).

03. Pharmacokinetics

F: 0.85 (0.72-0.96)	**Vd** (L/kg): 1.4 (1-2)	**Cl** (L/h/kg): 0.08 (0.05-0.11)	**t½:** 15 hours (12-17) (single dose 30-40)
Fe: 0 (0-0.5)	**Elimination route:** Metabolism: epoxidation, hydroxylation, N-glucuronidation (active metabolite carbamazepine 10,11 epoxide)		
CYP: 3A4 (30-50%), 2C8, 1A2		**Protein binding:** 0.75 (0.7-0.78)	

F = Bioavailability, Vd = volume of distribution, Cl = clearance, t½ = terminal half-life of elimination, Fe = fraction excreted unchanged in the urine, CYP = cytochrome P450 enzyme/s

Other PK data:

- Food increases bioavailability
- Alcohol accelerates absorption
- Pregnancy increases clearance, and may result in a decrease in plasma concentration.
- Carbamazepine induces its own metabolism, so t1/2 decreases after multiple doses. The average steady state concentration is reduced by 50% after 3 weeks of therapy.
- Neonates: Vd is increased (1.5-2x), and Cl is increased, so t1/2 is reduced to 5-13 hours.
- Carbamazepine-epozide (CBZ-E) has a t1/2 of ~6 hours. Concentrations in plasma vary from 20-50% of those of CBZ. Several studies show plasma concentrations of CBZ and CBZ-E correlate only in patients on monotherapy, and not in patients on polytherapy.

04. Indications

1. Epilepsy; all forms except myoclonic and absence seizures
2. Bipolar affective disorder (mood stabilizer)
3. Trigeminal neuralgia, painful diabetic neuropathy and other chronic pain
4. Alcohol withdrawal

05. Loading dose

There is no specific loading dose.

06. Maintenance dose

Adults:

- Epilepsy: Initial dose is 200mg bd, increasing in increments of 200mg at weekly intervals. The usual maintenance dose is 17-25mg/kg (400-1200mg)/day in divided doses.
- Bipolar Affective Disorder: Initial dose as above. The maintenance dose is usually 600-1600mg/day. Occasionally doses of up to 2000mg/day have been used.
- Trigeminal neuralgia: Initial dose is 100mg bd, increasing by 100-200mg/day and titrating according to pain control. The maintenance dose is usually 400-800mg/day in divided doses.

Children:

- <6yr: Initial dose is 5-20 mg/kg/day in 2-3 divided doses (SR formulation), or QID (suspension). Maximum dose is 35mg/kg.
- 6-12yr: Initial dose is 10 mg/kg/day (usually100mg bd of SR formulation or 50mg QID suspension). Increase by 100mg/day on a weekly basis. Usual maintenance dose is 400-800mg/day, with a maximum dose of 1000mg/day (or 20-30mg/kg).
- >12yr: Dose as above for adults. Maximum doses are usually 1000mg/day (6-15yr), and 1200mg/day (>15yr)

07. Notes on administration

Take with meals, or at least at the same time each day.

08. When to monitor

Trough concentrations should be measured, preferably just prior to the next dose.

NB: Full blood count should also be monitored before therapy, then two weekly for three months and periodically thereafter; liver function tests should be measured once before therapy and then periodically. NB. Enzyme inducing agents such as carbamazepine may moderately increase [ALP] or [GGT] due to autoinduction.

09. Dose individualisation

Renal impairment: no dosage adjustment required, because Fe = 0.01.
Hepatic insufficiency: Avoid in active liver disease. Dose may need to be halved with severe liver dysfunction.
Elderly: Lower doses are generally required.

10. Adverse effects

>10%

CNS: eye muscle incoordination, dizziness, limb and gait ataxia, sedation, fatigue, slurred speech, clumsiness, confusion, nystagmus
GI: nausea and vomiting (brainstem neurotoxicity)

1-10%

ENDO: SIADH causing hyponatraemia, peripheral oedema, exacerbation of heart failure
LIVER: abnormal liver enzymes, in particular transaminase elevation

<1%

CNS: agitation, restlessness, irritability, insomnia, seizures, coma (with very high doses), cognitive disturbances.
CVS: autonomic instability, bradycardia, atrioventricular block.

MISC: diarrhoea, hypocalcaemia, hypotension, hypertension, urinary retention, impotence, neutropenia, aplastic anaemia, agranulocytopenia, eosinophilia, leukopenia, pancytopenia, thrombocytopenia, bone marrow depression, hepatitis, hypersensitivity reactions, altered thyroid function tests, neuroleptic malignant syndrome

11. Drug Interactions

Drugs that increase carbamazepine concentrations:

(via enzyme inhibition, predominantly CYP3A4)
Ketoconazole, itraconazole, isoniazid, cimetidine,
Macrolide antibiotics: erythromycin, clarithromycin, (NB: not azithromycin)
Metronidazole, propoxyphene, danazol, nicotinamide
Verapamil, diltiazem (NB: not nifedipine)
Possible: Fluoxetine, sertraline, (NB: not paroxetine)
Case reports: Acetazolamide, clobazam
Inhibition of epoxide hydrolase, causing increased concentrations of carbamazepine-epoxide (active metabolite) despite normal carbamazepine concentrations: valproate, lamotrigine

Drugs that decrease carbamazepine concentrations

NB: Carbamazepine induces its own metabolism (this begins after 3-5 days and takes 2-4 weeks for full induction)
Enzyme induction: Phenytoin, phenobarbitone, primidone,
Reduced oral bioavailability: activated charcoal, doxorubicin, cisplatin

Pharmacodynamic Interactions:

Carbamazepine induces CYP3A4, and may also induce other enzymes, including CYP3A, 2B, 2C, 2E and glucuronyl transferase, causing reduced concentrations of the following drugs:

- Benzodiazepines: clonazepam, midazolam, ?alprazolam (NB clobazam and diazepam have active metabolites, so this is less significant clinically).
- Antidepressants: imipramine, amitriptyline, desipramine, nortriptyline, desmethylchlomipramine, mianserin, paroxetine
- Antipsychotics: haloperidol, chlorpromazine, flupenthixol, clozapine, clopenthixol
- Anticonvulsants: ethosuximide, valproate, lamotrigine, topiramate, primidone (causing increased phenobarbital concentration) NB no effect on vigabatrin or gabapentin.
- Oral anticoagulants
- Glucocorticoids, oral contraceptive
- Ciclosporin
- Neuromuscular blocking agents: atracurium, pancuronium, vecuronium, pipecuronium, rocuronium
- Other: reports for theophylline, thyroid hormones, doxycycline, and other drugs -see references
- Phenytoin: The effect of carbamazepine on phenytoin is inconsistent, with reports of both shortening and prolongation of the t1/2 of phenytoin.
- Other interactions:
- MAOI - increased incidence of cardiac arrhythmias
- Alcohol - increased effects of alcohol
- Lithium - reports of increased neurotoxicity

12. Factors that may give a false assay result

Nil known

13. Overdose

TOXINZ

14. Dialysability

Haemodialysis and peritoneal dialysis are generally ineffective at removing carbamazepine, though one report describes clearance of 40-64 ml/min, and a calculated drug removal of 40-53 mg over 4 hours with haemodialysis.

15. Comments

Nil.

16. Key references

1. Spina E, et al. Clinically significant drug interactions with carbamazepine. Clinical Pharmacokinetics 1996; 31(3): 198-214.
2. Yukawa E. Optimization of antiepileptic drug therapy. Clinical Pharmacokinetics 1996; 31(2): 120-130.
3. Troupin A. Dose related adverse effects of anticonvulsants. Drug Safety 1996; 14(5): 299-328.
4. Semah F, et al. Carbamazepine and its epoxide: an open study of efficacy and side effects after carbamazepine dose increment in refractory partial epilepsy. Therapeutic Drug Monitoring 1994; 16(6): 537-540:
5. Seymour J. Carbamazepine overdose. Drug Safety 1993; 8(1):81-88.

17. Last updated

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