Clinical Pharmacokinetics and Pharmacological Effects of Carbamazepine and Carbamazepine-10,11-Epoxide
An update

Leif Bertilsson and Torbjörn Tomson

Department of Clinical Pharmacology, Karolinska Institute, Huddinge Hospital, Huddinge, and Department of Neurology, Karolinska Institute, Söder Hospital, Stockholm

Summary

Carbamazepine is a first-line drug in the treatment of most forms of epilepsy and also the drug of first choice in trigeminal neuralgia. Furthermore, it is now frequently used in bipolar depression.

Most oral formulations of carbamazepine are well absorbed with high bioavailability. The drug is 75% bound to plasma proteins. The degree of protein binding shows little variation between different subjects, and there is no need to monitor free rather than total plasma concentrations.

Carbamazepine is metabolised in the liver by oxidation before excretion in the urine. A major metabolite is carbamazepine-10,11-epoxide which is further metabolised by hydration before excretion. This epoxide-diol pathway is induced during long term treatment with carbamazepine. Co-medication with phenytoin or phenobarbitone further induces this metabolic pathway. Some but not all studies indicate an increased metabolism of carbamazepine during pregnancy. The drug crosses the placenta, and the newborns who are exposed to the drug during fetal life eliminate the drug readily after birth. There seems to be no problem to nurse children during treatment with carbamazepine. Metabolism of carbamazepine is comparable in children and adults.

Several studies have tried to establish a relationship between plasma carbamazepine and clinical effect in epilepsy, but very few of these are controlled. The best anticonvulsant effect seems to be obtained at plasma concentrations of 15 to 40 μmol/L and a similar optimal plasma concentration range was found in a controlled study in trigeminal neuralgia. Side effects are more frequent at higher plasma concentrations but are also seen within that range. In some patients, with pronounced fluctuation of plasma concentrations during the dosage interval, side effects may be avoided by more frequent dosing.

Carbamazepine-10,11-epoxide is a potent anticonvulsant in animal models. During treatment with carbamazepine the plasma concentrations of this metabolite are usually 10 to 50% of those of the parent drug. It has not been possible to establish the relative contribution of the two compounds to the pharmacological effects. The epoxide has therefore been given to humans with the aim of determining the relative potency of the parent drug and its metabolite. After single oral doses of carbamazepine-10,11-epoxide to healthy subjects, the compound was rapidly absorbed. As a mean of 90% of the given dose was recovered in urine as trans-10,11-dihydroxy-10,11-dihydro-carbamazepine, a complete absorption of unchanged epoxide was shown. The mean plasma half-life of unchanged epoxide was 6.1 hours with a mean volume of distribution of 0.74 L/kg.
Six patients with trigeminal neuralgia had their optimal carbamazepine dose replaced with carbamazepine-10,11-epoxide for 3 to 6 days. The study was single-blind and placebo controlled. When carbamazepine and the epoxide were given in similar doses, the pain control was comparable. The results show that during carbamazepine therapy, the contribution of the epoxide to the effect is considerable. No side effect was seen during the epoxide therapy. Further studies on the effect of carbamazepine-10,11-epoxide administration in epilepsy are indicated.

Carbamazepine (CBZ) is one of the most important antiepileptic drugs and its clinical pharmacokinetics have been reviewed in the Journal (Bertilsson 1978). Since then the therapeutic indications for the drug have been broadened to include not only epilepsy and trigeminal neuralgia, but also bipolar depression (Post et al. 1984), excited psychosis (Klein et al. 1984), and alcohol withdrawal syndrome (Ritola & Malinen 1981). During the last few years considerably more knowledge has been gained about the metabolism of carbamazepine and the clinical pharmacokinetics of its active metabolite, carbamazepine-10,11-epoxide (CBZ-E). These recent studies (1978-1985) will be discussed in this updated review.

1. Analytical Methods

Simple but accurate immunotechniques (EMIT®, TDX®) have been developed for the routine monitoring of carbamazepine in plasma. These methods are specific for carbamazepine, judging from comparisons with methods based on gas chromatography and high performance liquid chromatography (HPLC) [Bertilsson & Rane 1980; Meijer et al. 1983]. As CBZ-E has much lower affinity than carbamazepine to the antibody used in EMIT, CBZ-E in plasma does not interfere in the determination of the parent drug (Monaco & Piredda 1980). The free plasma concentrations of carbamazepine measured by EMIT may, however, be overestimated by 35%, because of the higher concentrations of CBZ-E compared to carbamazepine in free than in the total plasma levels. Meijer et al. (1983) commented on the development of the many immunomethods: 'Future competition between immunotechniques will be less interesting with regard to analytical quality (which needs little improvement) or practicability than with respect to economy (cost of calibration, price of reagents).'

To determine CBZ-E in plasma, HPLC seems to be the method of choice. Since the first method was published (Eichelbaum & Bertilsson 1975), several modifications have been reported, e.g. MacKichan (1980) and Kumps (1984).

2. Pharmacokinetics of Carbamazepine in Adults

2.1 Absorption

After a single oral dose of carbamazepine as ‘Tegretol’, the absorption is slow with peak plasma concentrations occurring as late as 24 hours after drug intake (see Bertilsson 1978). In certain patients it seems important to reduce the fluctuations of the drug during the dosage interval (see section 4.3) and a slow absorption seems to be of advantage in such patients. Hooper et al. (1985) have shown that the ‘Tegretol’ tablet and syrup were equally bioavailable, but the absorption from the syrup was faster and gave higher maximum plasma concentrations of carbamazepine. Neuvonen (1985) compared three different brands of carbamazepine tablets registered in Finland (‘Tegretol’, Ciba-Geigy; ‘Neurotol’, Farmos; ‘Temporol’, Orion). Although they had an equal bioavailability, the ‘Neurotol’ tablet was absorbed faster and gave higher peak plasma concentrations than the two other preparations. ‘Neurotol’ also gave more pronounced side effects (dizziness, ataxia) than the other two brands of carbamazepine. Compared to ‘Tegretol’ and ‘Temporol’ the dissolution of the ‘Neurotol’ tablet in vitro was more rapid, probably because of the microcrystalline nature of this carbamazepine preparation (Neuvonen 1985).

The good absorption of the tablets with a slow