

## **Metabolic Characteristics of Oxcarbazepine (®Trileptal) and Their Beneficial Implications for Enzyme Induction and Drug Interactions**

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### **Summary**

Hepatic oxygenases of the cytochrome P-450 family play a major role in the clearance of various anti-epileptic drugs. These enzymes are susceptible both to induction and to inhibition. Phenytoin, carbamazepine (CBZ), primidone, and phenobarbitone, for instance, are potent enzyme inducers. Other drugs, such as chloramphenicol, propoxyphene, verapamil, and viloxazine, inhibit cytochrome P-450. Pharmacokinetic behaviour is thus often altered, especially in combined medication, so that the dosage has to be re-adjusted if an optimum therapeutic outcome is to be ensured.

Oxcarbazepine (OXC) is a keto analogue of CBZ. In the human liver the keto group is readily reduced, and the resulting monohydroxy metabolite is cleared by glucuronidation. The two enzymes mediating these reactions, i.e. aldo-keto reductase and UDP-glucuronyltransferase, do not depend on cytochrome P-450. The monohydroxy metabolite is the major active substance in plasma. Its elimination is not enhanced by OXC. Moreover, OXC seems to have little effect on cytochrome P-450. Aldo-keto reductases and glucuronyltransferases are in general less sensitive to induction and inhibition than are P-450 dependent enzymes. On the whole, OXC possesses very little potential for metabolic drug interactions, and thus differs favourably from other anti-epileptic drugs.

### **Introduction**

Many patients suffering from epilepsy need combined medication, and a large proportion of the established anti-epileptic drugs (AEDs) which they use either induce the drug-metabolizing enzymes in the liver or are susceptible to inhibition of these enzymes. Interactions between drugs leading to pharmacokinetic alterations are therefore fairly frequent in epileptic patients. Moreover, the therapeutic plasma concentration range of most AEDs is narrow, so pharmacokinetic changes often result in a loss of therapeutic efficacy or in the appearance of unwanted side-effects, unless the dose is adapted (Levy *et al.*, 1989).

Ideally, an AED should be fully insensitive and inert regarding both

induction and inhibition of drug-metabolizing enzymes. Oxcarbazepine is a new drug which differs fundamentally from the established AEDs in its mechanisms of metabolic clearance (Editorial, 1989; Faigle and Menge, 1990). In the present paper these differences are discussed, with their implications for the therapeutic use of oxcarbazepine.

### Drug Interactions of Established AEDs

Most of the established first-line AEDs are potent inducers of membrane-bound enzymes in the endoplasmic reticulum of the hepatocyte (Levy *et al.*, 1989; Baciewicz, 1986; Breckenridge, 1987). Foremost among these substances are phenytoin, carbamazepine, primidone, and phenobarbitone; these AEDs represent different chemical classes – namely, hydantoin, dibenzazepines, and barbiturates. Nevertheless, they have one feature in common: they are predominantly cleared by oxidative metabolic reactions involving aromatic or aliphatic C-atoms in their molecules (Levy *et al.*, 1989) (Fig. 1).

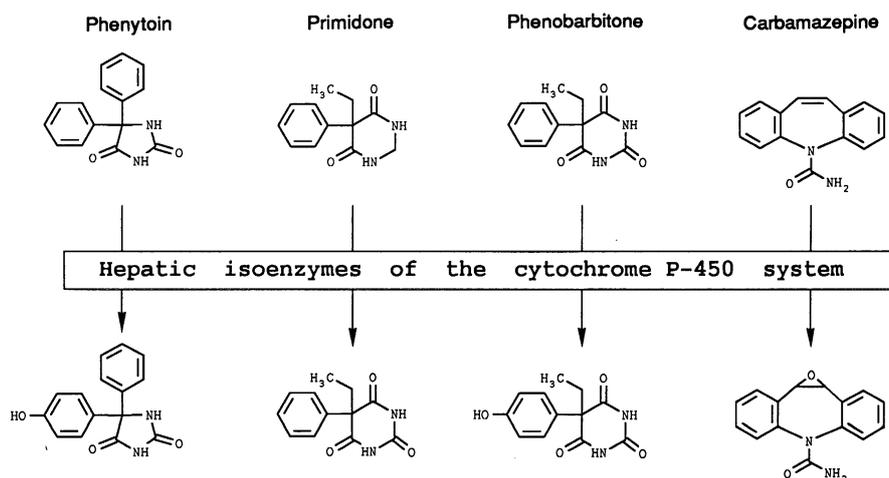


FIG. 1. Major metabolic pathways of enzyme-inducing AEDs in man.

Clearance of any of the aforementioned AEDs is primarily controlled by the rate of metabolic oxidation which is in turn regulated by the activity of the catalyzing enzyme. The enzymes or isoenzymes mediating oxidation belong to the cytochrome P-450 family, which is membrane bound and is located in the endoplasmic reticulum of hepatocytes or other cells. Upon separation into subcellular fractions, P-450 is found in the microsomes (Kappas and Alvares, 1975; Gonzalez, 1990).

Microsomal drug-metabolizing enzymes, including in particular the isoforms of P-450, are sensitive to inducing agents. Indeed, when phenytoin, carbamazepine, primidone, or phenobarbitone are administered repeatedly in therapeutic doses to a non-induced patient, the activity of an isoenzyme may increase several times over (Levy *et al.*, 1989; Perucca *et al.*, 1984). In

monotherapy, an enzyme-inducing drug will enhance its own elimination (auto-induction). In combined medication, other drugs may be affected (hetero-induction and hetero-inducibility). If two or more inducers are given concomitantly, their effects may be additive. After a few weeks of constant medication, the extent of induction will not change any further. When a dosage regimen is modified, however, it will again take some time before the enzyme activities have levelled up or down.

Carbamazepine provides a good example of the kind of pharmacokinetic changes which can occur as a result of enzyme induction (Eichelbaum *et al.*, 1985; Faigle and Feldmann, 1982). In non-induced subjects the mean elimination half-life of carbamazepine is about 35 h. In patients receiving monotherapy with carbamazepine, the half-life is reduced by auto-induction to about 15 h once steady-state has been achieved. Combined anti-epileptic medication may even result in a carbamazepine half-life of less than 10 h. In an extreme case of enzyme induction, therefore, clearance of carbamazepine is increased about fourfold, assuming that the drug's distribution volume remains unchanged.

Numerous drugs of different chemical classes are known to inhibit drug-metabolizing enzymes in the liver. In most cases it is a competitive process in that the inhibitor displaces the second drug reversibly from the binding sites of an isoenzyme (Levy *et al.*, 1989; Murray, 1987). Thus, a competitive inhibitor does not alter the amount of the enzyme, but reduces its activity for a certain metabolic reaction. Inducing agents, on the other hand, increase the amount of enzyme by stimulating its biosynthesis (Okey, 1990).

This mechanistic difference implies that the pharmacokinetic consequences of enzyme inhibition appear immediately, while those of induction need time to build up. Because cytochrome P-450 is particularly susceptible to inhibition, clearance of established AEDs may be critically impaired once an inhibitor is added to an existing anti-epileptic regimen. Clearance of phenytoin, for instance, is hampered by drugs such as chloramphenicol, phenobarbitone, and sultiame. Drugs impairing the elimination of carbamazepine include propoxyphene, verapamil, viloxazine, and others (Levy *et al.*, 1989; Baziewicz, 1986).

The clinical consequences of induction and inhibition of hepatic cytochrome P-450 are manifold. Induction results in a fall of the plasma concentration which may affect the inducing AED, or a second drug, or both. The therapeutic effect is then diminished or even lost. Enzyme inhibition by a second drug raises the plasma concentration of an AED and may hence precipitate unwanted side-effects. In either case the dose has to be carefully adjusted again. Not all the established AEDs are equally difficult in this respect. The individual properties will be discussed later on, together with those of oxcarbazepine.

### Metabolic Characteristics of Oxcarbazepine

Oxcarbazepine, 10,11-dihydro-10-oxo-5H-dibenz[b,f]-azepine-5-carboxamide, is chemically related to carbamazepine. Both drugs belong to the same series of tricyclic compounds, but only oxcarbazepine possesses a keto group

in the central ring of its molecule. In humans, oxcarbazepine undergoes enzymatic reduction at its keto group, yielding a monohydroxy derivative (MHD) as an active metabolite (Anonymous, 1986; Faigle and Menge, 1990). The pharmacological profile of MHD in animal models closely resembles that of oxcarbazepine and carbamazepine (Baltzer and Schmutz, 1978).

Oxcarbazepine is very efficiently reduced in the human liver, so that the parent drug reaches only negligible concentrations in the peripheral blood. MHD is actually the main active substance, as it predominates in blood after both single and multiple administration of oxcarbazepine (Faigle and Menge, 1990). The metabolite MHD is then inactivated by conjugation with glucuronic acid. This sequence of reactions is illustrated in Fig. 2. Other metabolic reactions also occur, but they are only of minor importance for the disposition of oxcarbazepine and MHD (Schütz *et al.*, 1986). Direct renal excretion of these two active substances is likewise of little consequence.

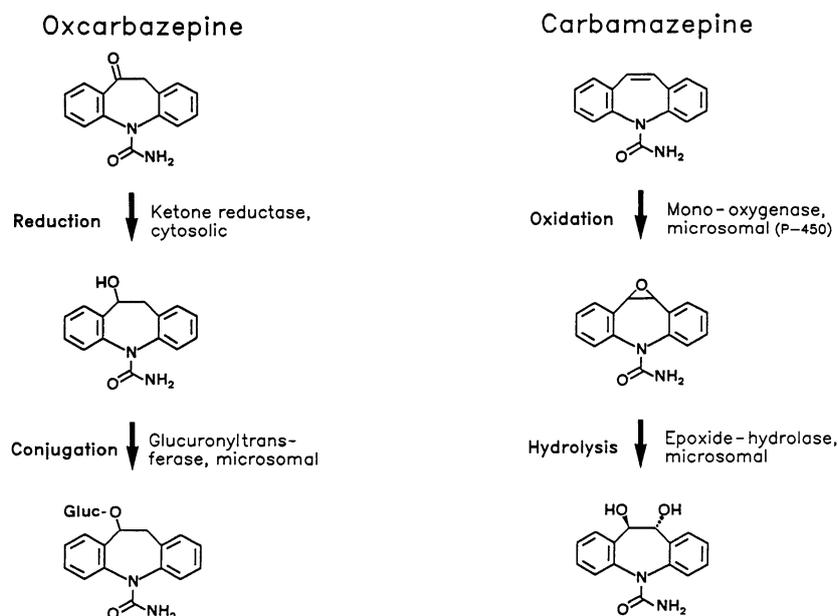


FIG. 2. Major metabolic pathways of oxcarbazepine and carbamazepine in man.

The pharmacokinetics of oxcarbazepine and MHD are thus largely controlled by two non-oxidative enzymatic processes. The rates of these processes depend in turn on the activities of the enzymes involved (Fig. 2). Reduction of aromatic ketones, such as oxcarbazepine, is catalyzed by an aldo-keto reductase, a cytosolic enzyme widely distributed in the human body, especially in the liver, where its activity is particularly high. Unlike microsomal drug metabolizing enzymes, this cytosolic reductase is not inducible (Nakayama *et al.*, 1985; Bachur, 1976).

Glucuronidation of xenobiotics is mediated by uridine diphosphoglucuronyltransferases, a family of membrane-bound microsomal isoenzymes which do not depend on cytochrome P-450. Some of the isoforms are inducible, but the extent of induction is generally lower than that of P-450 dependent oxygenases (Bock, 1988; Siest *et al.*, 1989). Other isoforms of the glucuronyltransferase family are not inducible. Although the isoenzyme catalyzing the glucuronidation of MHD in man remains to be identified, we know that it is not induced by oxcarbazepine treatment (Faigle and Menge, 1990).

Carbamazepine, as already mentioned, is eliminated mainly by oxidative metabolism, the predominant process being epoxidation of the 10,11-double bond in the central ring (Fig. 2) (Faigle and Feldmann, 1982). The pertinent enzyme is a microsomal mono-oxygenase dependent on cytochrome P-450. The epoxide metabolite, which contributes in part to the therapeutic effects of the drug, is inactivated by enzymatic hydrolysis, yielding a dihydroxy derivative. Both enzymes involved in this pathway are inducible. Additional pathways do exist, but their contribution is limited, especially in patients with induced liver enzymes.

Thus, oxcarbazepine and carbamazepine are disposed from the human body by essentially different mechanisms, in spite of the chemical similarity of the two compounds. The resulting pharmacokinetic patterns also differ from each other, as exemplified by the plasma concentrations of these drugs and their primary metabolites in healthy subjects after single-dose administration (Fig. 3). Oxcarbazepine produces low concentrations of the parent substance and high concentrations of MHD. Following carbamazepine, however, the parent drug predominates over the epoxide metabolite.

It is assumed that the keto group in the oxcarbazepine molecule serves as a "metabolic handle", which gives rise to simple non-oxidative biotransformation in humans. In this respect, oxcarbazepine stands out not only against carbamazepine, but also against other major AEDs (cf. Figs 1 and 2).

### Drug Interactions and Oxcarbazepine

The potential of one drug to interact with another depends mainly on two separate features – namely the intrinsic potency of the active substance to induce or inhibit drug metabolizing enzymes and the sensitivity of these enzymes to inducing and inhibiting agents. In this respect, some interesting evidence has been obtained suggesting that oxcarbazepine behaves rather differently from other AEDs.

Experimental findings in a rat model suggest that MHD induces the hepatic enzymes only slightly, if at all (Wagner and Schmid, 1987). In the same model, the influence of oxcarbazepine contrasts quite starkly with that of MHD: if oxcarbazepine persists in the form of unchanged substance in the body (as it does in the rat) it increases the activities of hepatic enzymes rather markedly, in a pattern comparable to that of carbamazepine; in humans, however, oxcarbazepine does not persist as unchanged substance, owing to its rapid metabolic reduction (cf. Fig. 3). One might therefore expect that administration of oxcarbazepine in man does not lead to significant enzyme induction.

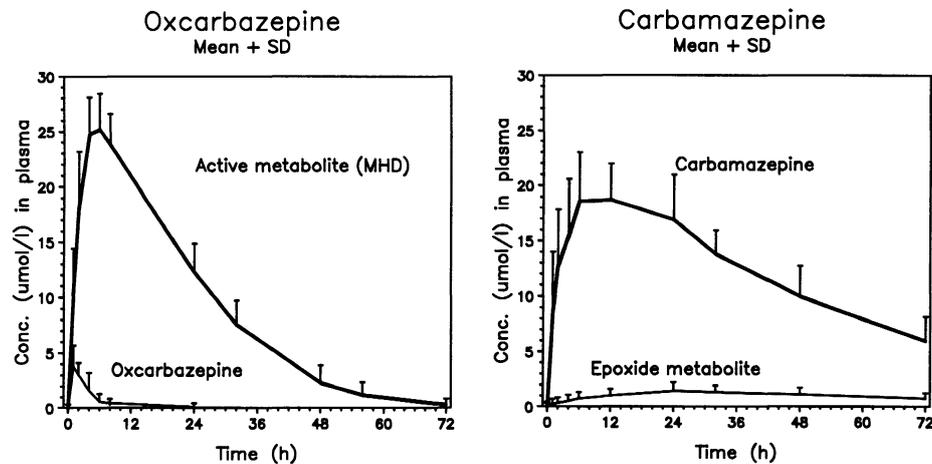


FIG. 3. Single-dose plasma concentrations in healthy subjects. ( $n=6$ ; 600 mg oxcarbazepine; 400 mg carbamazepine; p.o.)

As discussed above, it is unlikely that oxcarbazepine causes auto-induction by stimulating the two major enzymes involved in its own disposition in man (cf. Fig. 2). Cytosolic aldo-keto reductases are reported to be non-inducible, and glucuronyltransferases do not appear to be very responsive to induction in general. The latter enzyme system is particularly important for oxcarbazepine, because it controls the elimination of the active metabolite MHD.

Indeed, from two separate studies in healthy subjects it is known that repeated administration of oxcarbazepine does not alter the elimination half-life of MHD (Larkin *et al.*, 1990; Krämer *et al.*, 1985). The mean values are invariably between 11 and 14 h (Table 1). The highest daily dose given to the subjects was 1200 mg, which lies well within the dose range recommended for the therapeutic use of oxcarbazepine. When tested under similar conditions, carbamazepine showed a distinct reduction of its half-life (Table 1) (Krämer *et al.*, 1985; Pitlick, 1975).

Antipyrine is a marker substance which allows the activities of oxidizing enzymes belonging to the cytochrome P-450 family to be determined (Poulsen and Loft, 1988). The available data on the elimination half-lives of antipyrine in humans during repeated administration of oxcarbazepine are summarized in Table 2. In healthy subjects the half-life of antipyrine remained unaltered in the oxcarbazepine group, while it was markedly reduced in the carbamazepine group (Larkin *et al.*, 1990; Shaw *et al.*, 1985). In epileptic patients receiving monotherapy with carbamazepine first, antipyrine half-life was shortened. It approached normal values, however, when the patients were switched to monotherapy with oxcarbazepine (Hulsman *et al.*, 1987). Although another clinical study revealed no such increase when carbamazepine was replaced by oxcarbazepine (van Emde Boas *et al.*, 1989), the findings here were undoubtedly confounded by the fact that most of the patients were receiving combined medication which included inducing AEDs such as phenytoin, phenobarbitone, and clobazam.

TABLE 1. Half-lives of active substances in man following single and multiple doses of oxcarbazepine and carbamazepine

Oxcarbazepine Dose (mg/day)	Metabolite MHD $t_{1/2}$ (h)	Carbamazepine Dose (mg/day)	Carbamazepine $t_{1/2}$ (h)
300 (1×)	11.3	400 (1×)	33.9
(14×)	13.9	400 (22×)	19.8
(healthy, n = 8)		(healthy, n = 6)	
600 (1×)	12.0	400 (1×)	35.0
600-1200 (42×)	13.5	400-800 (42×)	15.3
(healthy, n = 7-10)		(healthy, n = 6-10)	

Data from: Larkin *et al.* (1990); Krämer *et al.* (1985); Pitlick (1975).

TABLE 2. Half-lives of antipyrine in man after exposure to oxcarbazepine and carbamazepine

Oxcarbazepine Dose (mg/day)	Antipyrine <sup>1</sup> $t_{1/2}$ (h)	Carbamazepine Dose (mg/day)	Antipyrine $t_{1/2}$ (h)
600 (14×)	10.4 ± 1.7	200-600 (20×)	8.3 ± 1.1
(healthy, n = 8)		(healthy, n = 6)	
500-1800	10.8 ± 5.1	500-1200	7.5 ± 2.0
(patients, n = 8)		(patients, n = 8)	
900-2400	6.4 ± 1.9	600-1500	6.2 ± 1.2
(patients, n = 8)		(patients, n = 8)	

<sup>1</sup>Half-lives in unexposed controls:  $t_{1/2}$  = 10-11 h.

Data from Larkin *et al.* (1990); Hulsinan *et al.* (1987); Shaw *et al.* (1985); van Emde Boas *et al.* (1989).

On the whole, the antipyrine data obtained so far indicate that oxcarbazepine has little or no potential for hetero-induction of human hepatic enzymes. This is supported by additional clinical evidence obtained in patients on combined anti-epileptic medication. When carbamazepine was substituted in these patients by oxcarbazepine, the steady-state plasma concentrations of phenytoin and valproic acid rose by 20-30% although their doses were kept constant (Houtkooper *et al.*, 1987). Thus, oxcarbazepine tends to normalize the activities of enzymes induced by carbamazepine. Similarly carbamazepine reduced the circulating levels of various endogenous steroids in healthy subjects, while oxcarbazepine did not (Larkin *et al.*, 1990).

Most of the known enzyme inhibitors act on cytochrome P-450. Even though such agents are unlikely to interfere with the relevant enzymes of oxcarbazepine disposition, clinical studies with inhibitors such as cimetidine, erythromycin, propoxyphene, verapamil, and viloxazine are ongoing. Indeed, preliminary results suggest that they do not affect the kinetics of oxcarbazepine or MHD. There are also no signs whatsoever to suggest a reverse effect – namely, enzyme inhibition by oxcarbazepine or MHD.

Table 3 summarizes the characteristics of enzyme induction and inhibition for oxcarbazepine and some other AEDs (Levy *et al.*, 1989). It is clear that

oxcarbazepine possesses a very favourable profile.

TABLE 3. *Enzyme induction and inhibition of commonly used AEDs*

	<i>Auto-induction</i>	<i>Hetero-induction</i>	<i>Hetero-inducibility</i>	<i>Inhibition by a 2nd drug</i>	<i>Inhibition of a 2nd drug</i>
Phenytoin	+	+	(+)	+	o
Primidone	+	+	+	+	(+)
Phenobarbitone	o	+	+	+	(+)
Carbamazepine	+	+	+	+	+
Valproic acid	o	o	+	o	+
Oxcarbazepine	o	(+)	o	o	o

+ common; (+) sporadic; o absent or insignificant

### Conclusions

Oxcarbamazepine differs from other AEDs by virtue of the way in which it is disposed from the human body. The new drug undergoes non-oxidative metabolism, while the major established AEDs are cleared by oxidative processes.

Major AEDs, such as phenytoin, carbamazepine, primidone, and phenobarbitone, induce the hepatic enzymes which catalyse metabolic oxidation, and accelerate their own elimination. As the same enzymes are also susceptible to inhibiting agents, pharmacokinetic interactions requiring dose adaptation are common.

Oxcarbazepine has little or no effect on oxidizing enzymes. Likewise, oxcarbazepine does not induce the specific enzymes governing either its own kinetic behaviour or that of its active metabolite. These enzymes are generally rather insensitive to induction and inhibition.

As a consequence of its favourable intrinsic properties and its particular pathway of biotransformation, oxcarbazepine has little if any potential for metabolic drug interactions.

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