A. Introduction

The history of the development of carbamazepine was outlined in an earlier volume in this series (Schmutz 1985). By that time, the drug had already been in clinical use for two decades and was a well established antiepileptic agent, with certain other uses in human medicine. Its animal pharmacology and toxicology were reasonably adequately documented and some information on its human pharmacokinetics was available, though the drug’s essential mechanism of action at the molecular level was unclear. The latter has now been elucidated, and considerable additional information has become available concerning the disposition, interactions and toxicity of the drug, mainly in humans, whilst its range of therapeutic uses has expanded. The present chapter deals chiefly with this newer information.

B. Chemistry and Use

I. Chemistry

Carbamazepine (5H-dibenz[b,f]azepine-5-carboxamide) is a white neutral lipophilic material (MW 236.3) which is virtually insoluble in water, though more easily dissolved in certain organic solvents. For human use the drug is supplied either in tablet form (some preparations having modified release characteristics) or as a syrup. No parenteral preparation has been marketed, though one has been used in experimental studies (Lösch et al. 1995; Lösch and Hönack 1997), and the drug has been administered rectally in solution in certain pharmacokinetic investigations (Graves et al. 1985; Neuvonen and Tokola 1987; Arvidsson et al. 1995).

Carbamazepine is biotransformed to a biologically active metabolite, carbamazepine-10,11-epoxide, whose pharmacological properties have undergone some study in their own right (Kerr and Levy 1995). These properties will be mentioned in the following account, where appropriate. At concentrations likely to be encountered in human therapeutics, no other known metabolite of the drug appears to possess significant pharmacological activity.
II. Use

In clinical practice, carbamazepine is used mainly in the treatment of epilepsy. It is effective in preventing simple and complex partial seizures, and in preventing their generalization into secondarily generalized seizures. It is also effective in preventing the bilateral tonic, clonic and tonic-clonic seizures of generalized epilepsy, but is not useful in treating absence, atonic and myoclonic seizures or juvenile myoclonic epilepsy (JOHNSON et al. 1984). Recently it has been shown effective in managing neonatal seizures (SINGH et al. 1996). It is ineffective in the prophylaxis of simple febrile seizures in infancy (ANTONY and HAWKES 1983).

The first reported successful clinical use of carbamazepine was in preventing attacks of trigeminal neuralgia (BLOM 1962), and it remains the treatment of choice for this disorder (GREEN and SELMAN 1991; SIDEBOTTOM and MAXWELL 1995). The drug will also prevent attacks of glossopharyngeal neuralgia (KING 1987). It decreases the severity of symptoms in certain painful peripheral neuropathies, including those of diabetes (CALISSI and JABER 1995) and Fabry’s disease (FILLING et al. 1989) and it relieves the lightning pains of tabes (EKBOM 1972). The drug is of little value in postherpetic neuralgia (KILLIAN and FROMM 1968). It has been reported useful in managing various involuntary movement disorders, e.g. chorea (ROIG et al. 1988), paroxysmal choreoathetosis (JAN et al. 1995; WEIN et al. 1996), dystonia (FAHN 1987), restless legs (ZUCCHI et al. 1989; O’KEEFE 1996), diaphragmatic flutter (VANTRAPPEN et al. 1992), palatal myoclonus (LAPRESLE 1986), and myotonia (SECHI et al. 1983; TOPALOGLU et al. 1993; SQUIRES and PRANGLEY 1996) and neuromyotonia, both generalized (KUKOWSKI and FELDMANN 1992) and ocular (EZRA et al. 1996; YEE et al. 1996), as well as Isaac’s syndrome of continuous muscle fibre activity (THOMAS et al. 1994), myokymia (AUGER et al. 1984), and superior oblique myokymia (BRAZIS et al. 1994). However, in the latter disorder the response may be temporary (ROSENBERG and GLASER 1983). Cerebellar tremor (SECHI et al. 1989 a,b), familial rectal pain (SCHUBERET and CRACCO 1992) and cataplexy (VAUGHN and D’CRUZ 1996) have also been reported to benefit from use of the drug.

In psychiatry, carbamazepine has found a major use in the prophylaxis of bipolar affective disorder (manic-depressive psychosis) (DENICOFF et al. 1994; EMILIANI et al. 1996), where it is sometimes used in combination with lithium. In clinical trials it has proved useful in managing benzodiazepine (GALPERN et al. 1991; GARCIA-BORREGUERO et al. 1991) and alcohol withdrawal (BUTLER and MESSIHA 1986).

The drug is also used to manage milder degrees of neurogenic diabetes insipidus, though not more severe instances of the disorder (WALES 1975).

C. Pharmacodynamics

In the following account, particular attention has been paid to studies carried out at carbamazepine concentrations similar to those encountered in human therapeutics.