

## CARBAMAZEPINE IS AN OUTDATED DRUG THAT SHOULD NEVER BE USED FIRST LINE (YES)

Carbamazepine was synthesised by Schindler at Geigy in 1953, when the company was investigating tricyclic analogues of the recently introduced chlorpormazine. It was first licensed for the treatment of epilepsy in 1965. Carbamazepine is no more effective for focal and generalised tonic-clonic seizures than any of its appropriate competitors. Common side effects include dizziness, fatigue, diplopia, nausea, vomiting, drowsiness and ataxia. It produces dose-dependent hyponatraemia, which can be a particular problem for the elderly and patients taking diuretics and other drugs known to reduce serum Na<sup>+</sup>. Life threatening idiosyncratic adverse reactions, such as aplastic anaemia, hepatotoxicity and Stevens-Johnson syndrome can be an unusual complication of its introduction. Serious drug rashes are substantially more common in Asian patients possessing the HLA-B\*1502 and in Europeans possessing the HLA-A\* 3101 alleles. Carbamazepine is also a dose dependent teratogen.

The main reason, however, that carbamazepine is now an outmoded drug for first line use is the increasing appreciation of the adverse effects of its enzyme inducing properties on exogenous and, particularly, endogenous substrates. It has the property of increasing the synthesis of a wide range of oxidative and conjugating metabolic enzymes in the liver and throughout the body. Most therapeutic drugs are substrates for these pathways, resulting in a reduction in their elimination half-life and bioavailability by around 50-66%. This substantially reduces their efficacy unless the dose is appropriately increased, which can have major cost implications. Potential problems include unwanted pregnancy in patients taking oral contraceptives, increased cancer mortality, progressive AIDs, transplant rejection, uncontrolled hypertension, breakthrough pain etc. Doses of many other AEDs that are metabolised in the liver also need to be increased when combining them with carbamazepine. Withdrawal of carbamazepine, in addition, can more than double the circulating levels of all of these medicines leading to unexpected toxicity if their doses are not appropriately reduced. This too can be a problematic process.

More recently there has been increasing awareness of the effects of longterm enzyme induction with carbamazepine on vitamin D resulting in reduced bone density with subsequent osteoporosis and an increased propensity for fractures. The drug can also produce sexual dysfunction in both men and women by inducing the breakdown of a range of sex hormones. Lastly, and arguably most worrying, treatment with carbamazepine increases cholesterol levels leading to higher risks of myocardial infarction and stroke.

Enzyme induction with carbamazepine continues as long as the patient takes the drug. No one can predict what health problems lie in wait down life's journey. Managing concomitant treatment in enzyme-induced patients can be difficult and withdrawing the drug can have disastrous consequences, since many doctors across a range of clinical disciplines will be unaware of its pitfalls. In conclusion, enzyme induction with carbamazepine can subtly and unpredictably complicate the lives of people with epilepsy. I would not take the drug myself nor would I prescribe it for a member of my family and so why would I offer carbamazepine to my epilepsy patients when a number of other equally effective, safer and user-friendly alternatives are available?