

Carbamazepine

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Introduction

Carbamazepine was first marketed for the treatment of trigeminal neuralgia in 1962 and is now recognised as a first line treatment for this condition. The anticonvulsant properties of the drug were soon recognised. The success of carbamazepine therapy to suppress seizures induced by both electricity and chemicals in rodents led to carbamazepine being used in the treatment of epilepsy. This has been a licensed indication in the UK since 1965.

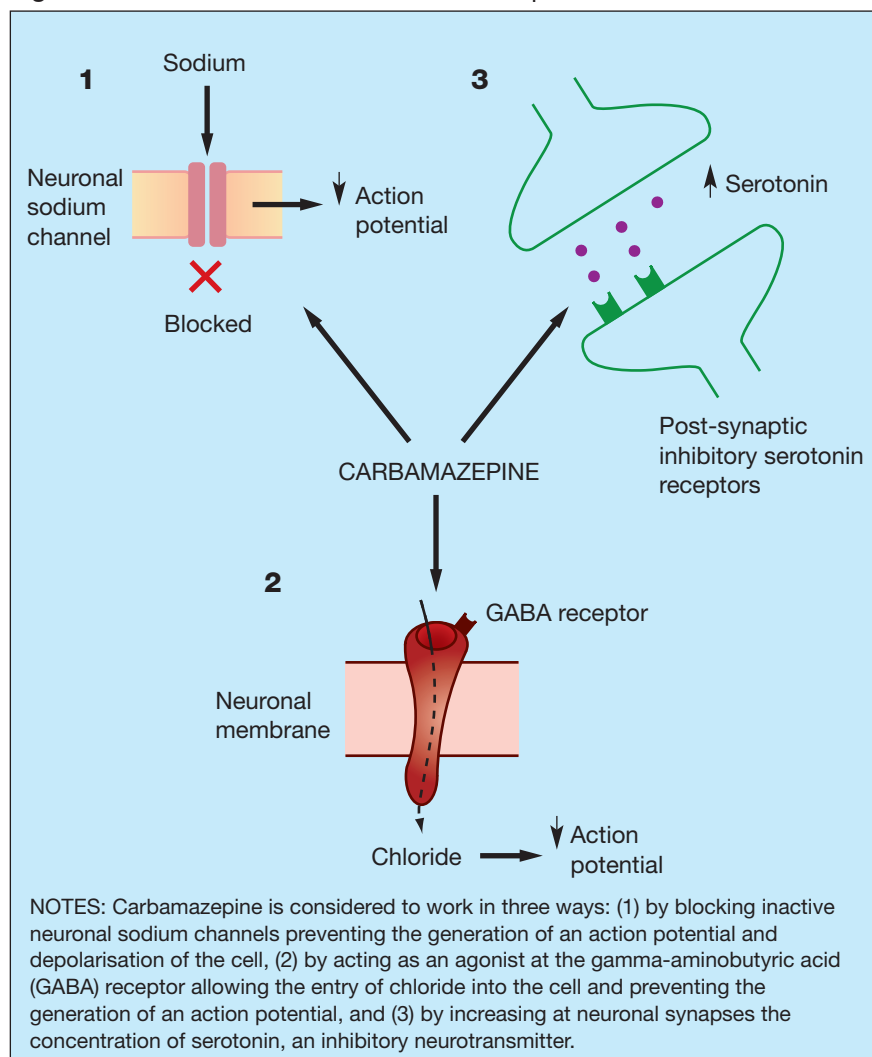
Carbamazepine is occasionally used in the prophylactic treatment of bipolar disorder under specialist supervision in patients who have been unresponsive to a combination of other prophylactic medications.

The place of carbamazepine in the management of diabetic painful peripheral neuropathy is the subject of this review.

Pharmacology

Carbamazepine is an iminostilbene (chemical name 5*H*-dibenz[*b,f*]azepine-5-carboxamide). Three mechanisms of action (Figure 1) are described. Each can be related to the clinical effects of carbamazepine in various conditions. The principal mechanism of action is the use-dependant blockade of inactivated neuronal sodium channels, preventing them from opening. This stops the neuronal sodium current from gaining sufficient amplitude to depolarise the nerve and inhibits the repetitive neuronal firing that occurs during a seizure. Excessive pain impulses from damaged sensory nerves may also be reduced through this mechanism. Neuronal transmission at normal frequencies is relatively unaffected by the drug because a smaller proportion of sodium channels are in an inactivated state. Carbamazepine is a

Figure 1. Mechanisms of action of carbamazepine



gamma-aminobutyric acid (GABA) agonist. The drug stimulates activation of the GABA receptor producing a sedative effect. It may also cause other outcomes such as anxiolytic and muscle relaxant effects. It is thought that this mechanism of action is useful in the treatment of bipolar disorder.

Carbamazepine increases extracellular levels of serotonin which is an inhibitory neurotransmitter. This

discovery may have fuelled interest in the drug as a possible therapy for neuropathic pain.

Carbamazepine is slowly absorbed from the gastrointestinal tract over four to 12 hours. It is a powerful inducer of cytochrome P-450 (CYP450) that both controls the drug's own metabolism and leads to many of the principal clinically relevant interactions. Carbamazepine is metabolised in the liver by an

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Carbamazepine

isoform of CYP450 (isoform 3A4) producing the active metabolite carbamazepine epoxide. The active metabolite is almost entirely excreted in urine after degradation by further oxidative processes, conjugation or hydroxylation.

Carbamazepine is rapidly distributed throughout all tissues with 75–90% being bound to plasma proteins. After a single dose, the half-life of the drug is approximately 1.5 days. The auto-induction effect of the drug on its own hepatic metabolism reduces the half-life by two-thirds within the first two to three weeks of treatment, resulting in the need for dose increments in the early stage of therapy.

Carbamazepine, as a CYP450 enzyme inducer, increases the metabolism of other drugs, resulting in important metabolic drug–drug interactions (warfarin, theophylline, phenytoin, valproate and oral contraceptives).

Serious adverse effects fall into three major categories. Haematopoietic effects include marrow suppression, commonly neutropenia and thrombocytopenia. Dermatological effects include rash, and serious complications such as toxic epidermal necrolysis and Stevens-Johnson syndrome. Cardiovascular side effects can include fluid retention, worsening heart failure and oedema thought to be due to the effect of carbamazepine on inappropriate anti-diuretic hormone secretion and hyponatraemia. Minor adverse events include headaches, dizziness, blurred vision, nausea and vomiting.

Trials of safety and efficacy

Carbamazepine used in comparative trials of anticonvulsants has been titrated to a daily dosage of between 600mg and 1200mg in adults. This is significantly higher than that used in the studies of neuropathic pain where typical doses have ranged from 200mg to 600mg daily.¹

Specific evidence for use in diabetes

There is no high quality research describing the use of carbamazepine in the treatment of painful diabetic

Key points

- Carbamazepine is an effective first line treatment for trigeminal neuralgia and has an important place in the management of epilepsy and bipolar disorder
- There is no high quality evidence to support the use of carbamazepine in the management of symptomatic diabetic neuropathy
- Carbamazepine is a powerful CYP450 inducer leading to auto-induction of its own metabolism and clinically important drug interactions. Serious side effects can occur

neuropathy.¹ The Mexican paper from Rull *et al.* is the work most widely quoted in support of the efficacy of carbamazepine for diabetic peripheral neuropathy.² This trial would not fulfil today's modern standards of critical appraisal such as those used by the Scottish Intercollegiate Guidelines Network (SIGN) and the National Institute for Health and Clinical Excellence (NICE). Thirty subjects were recruited without standardisation for confounding characteristics, gender, type or duration of diabetes, and, perhaps most importantly, with no primary classification or verification of the existence of neuropathy as a cause for their symptoms. The method used to quantify symptoms is not described. The efficacy of carbamazepine in relieving patient reported 'symptoms' (ranging from 'pain' to 'numbness', 'cramp' and 'tingling') was reported as an 'algebraic sum of changes graded 0–5 ... by one of the authors who had not followed the patients clinically'.³ No description of this process is given. The incidence of side effects was high. The study drug was provided by the manufacturer and the trade name of the preparation was included in the title of the article.

In a further much referenced study from the same Mexican group, Gomez-Perez *et al.* compared the use of a combination tablet of nortriptyline-fluphenazine with carbamazepine in the treatment of painful diabetic neuropathy.³ The study again falls short of modern standards in terms of sample size (16), adequacy of blinding and validation of symptom scores. Both treatments were deemed to improve symptoms of pain and paraesthesia,

but there appears to have been an assumption that both drugs are beneficial prior to the study start.

Discussion

The evidence-based, step-wise approach to the pharmacological management of painful diabetic neuropathy includes first line agents such as tricyclic antidepressants nortriptyline or desipramine, and selective serotonin and norepinephrine reuptake inhibitors duloxetine or venlafaxine; second line agents are calcium channel $\alpha_2\text{-}\delta$ ligands pregabalin and gabapentin; and third line agents are the opioids. Topical lidocaine patches have a place where symptoms are localised.⁴ Carbamazepine does not have an evidence-based place in this algorithm.

Conflict of interest statement

There are no conflicts of interest.

References

1. Wiffen PJ, McQuay HJ, Moore RA. Carbamazepine for acute and chronic pain in adults. *Cochrane Database Syst Rev* 2005; Issue 3. Art. No.: CD005451. DOI: 10.1002/14651858.CD005451.
2. Rull JA, Quibera R, Gonzalez H, *et al.* Symptomatic treatment of peripheral diabetic neuropathy with carbamazepine (Tegretol): double-blind crossover trial. *Diabetologia* 1969; **5**(4): 215–218.
3. Gomez-Perez FJ, Choza R, Rios JM, *et al.* Nortriptyline-fluphenazine *vs.* carbamazepine in the symptomatic treatment of diabetic neuropathy. *Arch Med Res* 1996; **27**(4): 525–529.
4. Dworkin RH, O'Connor AB, Backonja M, *et al.* Pharmacologic management of neuropathic pain: Evidence-based recommendations. *Pain* 2007; **132**: 237–251.