Sodium valproate

Introduction
Sodium valproate is an anticonvulsant that was discovered by French researchers in 1963. It first came to market in the UK in 1972. It is known to be effective across a broad spectrum of epilepsies, and sodium valproate remains a cornerstone of epilepsy management despite the discovery of many newer agents. Peripheral neuropathy is present in up to one-third of people with diabetes mellitus, and symptoms commonly persist despite conventional treatments. Although not currently licensed for this indication, sodium valproate has been shown in a number of small scale trials to be of benefit in painful peripheral neuropathy.

Pharmacology
The broad anticonvulsant activity of sodium valproate results from its effects on a number of neuronal pathways. It has close molecular structure to the inhibitory neurotransmitter γ-aminobutyric acid (GABA), and thus has strong GABA-ergic effects. It is thought to potentiate GABA activity by inhibiting enzymes that catabolise GABA or by blocking GABA reuptake to glia and nerve endings (Figure 1). Valproate also reduces repetitive neuronal firing by blocking voltage gated Na⁺ channels. Sodium channels exist in the resting, open or inactivated state, and continually cycle through these states in turn. This drug slows the recycling process by binding to the channel protein in the inactivated step (Figure 1). Anticonvulsant medications more traditionally used in painful neuropathy (e.g. gabapentin and carbamazepine) exert their influence through similar mechanisms.

Sodium valproate is also thought to blockade low voltage t-type calcium channels. These channels open in response to low levels of depolarisation and are potentially implicated in absence seizures.

The usual maintenance dose of valproate is 1–2g per day. Patients should be started at 600mg per day and up-titrated in 150–300mg increments every three days. At therapeutic levels valproate is highly protein bound (90%) and the half-life is 9–16 hours. It is available as tablet (immediate release or enteric coated), syrup and intravenous preparations. Switching between preparations may have effects on

![Figure 1. Primary mechanisms of action of sodium valproate in peripheral neuropathy](image-url)
the drug concentration; however, usually valproate can be switched on a 1:1 ratio between oral and intravenous administration.

Valproate is readily absorbed in the gastrointestinal tract and reaches peak plasma concentrations within 4 hours for immediate release preparations. It is metabolised by the liver via three main mechanisms. Around 50% undergoes glucuronidation and is excreted in urine as valproate glucuronide. Mitochondrial beta-oxidation accounts for 40%, and the metabolites from this mechanism are responsible for the hepatotoxic effects of this drug. Finally, around 10% is oxidised by cytochrome P450 enzymes. This is an important source of medication interactions, most frequently encountered when co-prescribing with an enzyme inducing anti-epileptic medication (e.g. carbamazepine, and phenytoin).

Important side effects of valproate include hepatotoxicity, pancreatitis and teratogenicity. Valproate should be avoided in patients with a personal or family history of liver disease. Significant hepatotoxicity (<1%) usually occurs within the first six months of therapy and liver function tests should be monitored during this period. Elevations in transaminases are usually transient, but the drug should be stopped if elevation is maintained or pro-thrombin time becomes impaired. Acute pancreatitis is a rare side effect (0.1%) but can occur at any time. The mechanism of this side effect is unclear, therefore other agents may be better first-line choices if there is a significant pancreatic history. Recent guidance from the Medicines and Healthcare products Regulatory Agency has suggested that due to teratogenicity valproate should be avoided in women of child-bearing age unless a pregnancy prevention programme is in place.

Other common side effects include drowsiness, tremor, hair loss, nausea and abdominal cramping. Weight gain is frequently reported when commencing valproate, a particular consideration if a patient with diabetes is overweight or obese. This has been specifically investigated in one double-blind, prospective controlled study, Patients were treated with valproate (n=68) or lamotrigine (n=65) and after 32 weeks there was a trend towards increased weight gain in the valproate group 5.8kg (+4.2kg) versus 0.5kg (+5.4kg).\(^1\)

**Specific evidence for use in diabetes**

Valproate in the treatment of peripheral neuropathy was the subject of a Cochrane review in 2011.\(^2\) Only three studies were found to be of adequate quality and two of these specifically focused on diabetic peripheral neuropathy. Agrawal\(^3\) and Kochar\(^4\) both completed prospective, single-centre, randomised, double-blind, placebo-controlled trials of three months in duration. Both studies used a combination of McGill’s pain questionnaire (SF-MPQ), visual analogue scale (VAS) and present pain index (PPI) to assess pain and reported mean changes as their primary outcome. Both studies are prone to overestimation of the association and the influence of random chance due to their small sample size, and this may account for their lack of consistency.

Agrawal\(^3\) included 20 participants, with both type 1 and type 2 diabetes, taking 20mg/kg/day of valproate and 20 control participants taking placebo. There was a significant reduction in SF-MPQ, VAS and PPI between 0 and 3 months in the treatment group; however, when compared with the placebo group there was no significant change.

Kochar\(^4\) had 21 participants with type 2 diabetes taking 500mg per day of valproate versus 18 taking placebo. In this trial, there was a significant reduction in SF-MPQ, VAS and PPI over the three months and when compared with the placebo group.

On the basis of the above studies the Cochrane review concluded that there is limited evidence for valproate in neuropathy and it should not be considered a first-line agent for this indication. The American Association of Neurology conducted a similar review,\(^5\) also published in 2011, which does recommend the use of valproate in peripheral neuropathy. Included in this review were studies of shorter duration and the literature search pre-dated the most recent paper\(^3\) which showed no difference between valproate and placebo.

**Discussion**

Sodium valproate may have benefit for patients with diabetic peripheral neuropathy; however, there is a lack of high-quality data to support this and the completed studies reveal inconsistent results. Current guidelines support the use of other anti-epileptics as first-line and second-line medications, so the use of sodium valproate in peripheral neuropathy should be only considered in treatment resistant cases.

Recently, valproate has also been found to promote histone acetylation through inhibition of HDAC enzymes. Histone acetylation has been linked to the pathogenesis of type 2 diabetes and diabetes-related complications, and it is also implicated in anti-tumour mechanisms. This may give rise to further indications for valproate in the future.

**Declaration of interests**

There are no conflicts of interest declared.

**References**

1. Rakitin A. Does valproic acid have potential in the treatment of diabetes mellitus? Front Endocrinol (Lausanne) 2017;8:147.