ARTICLE

Safe use of sodium valproate

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SUMMARY

Valproate is an anticonvulsant drug which is approved for use in epilepsy and bipolar disorder. It has also been used for neuropathic pain and migraine prophylaxis.

Gastrointestinal adverse effects are common, particularly at the start of therapy. Important adverse effects include pancreatitis, hepatitis, weight gain and sedation. There is an increased risk of fetal abnormalities if valproate is taken in pregnancy.

Measuring concentrations of serum valproate is often unnecessary. They do not correlate closely with its therapeutic effects.

If withdrawal of valproate is required, this should be done slowly if possible. Rapid cessation may provoke seizures in patients with epilepsy.

Introduction

Sodium valproate (valproate) was first marketed as an anticonvulsant almost 50 years ago in France. Its indications have expanded and it is now the most prescribed antiepileptic drug worldwide.[1] However, it has many potential adverse effects.

Pharmacology

Valproate is available in tablet (immediate-release or enteric coated), syrup and intravenous formulations. There is no single mechanism of action that can explain valproate's broad effects on neuronal tissue. Its pharmacological effects include:

- increased gamma-aminobutyric acid transmission
- reduced release of excitatory amino acids
- blockade of voltage-gated sodium channels
- modulation of dopaminergic and serotonergic transmission.[2]

When fasting, oral valproate is rapidly absorbed and reaches peak plasma concentrations within four hours (immediate-release formulation) to seven hours (enteric coated formulation). It is highly plasma protein bound and has a half-life of 8–20 hours in most patients, but this may occasionally be much longer, for example in renal impairment or overdose.[3] The relationship between dose, plasma concentration and therapeutic effect is not well understood.

Valproate is almost completely metabolised in the liver, mainly by glucuronidation. It then undergoes further metabolism with oxidation, which is complex and involves several cytochrome P450 enzyme systems. It has multiple metabolites which may contribute to both its efficacy and toxicity. There are many potential drug interactions.

Indications

Although there is clinical experience with valproate in epilepsy, some of its other accepted indications, such as migraine prophylaxis, have not been approved by the Therapeutic Goods Administration.

Epilepsy

Valproate is a broad spectrum antiepileptic drug and is used to treat either generalised or focal seizures. It is recommended in Australian[4] and international[5-7] clinical practice guidelines. There is evidence that it is more effective than lamotrigine or topiramate in treating:

- idiopathic generalised epilepsy syndromes
- seizures that are difficult to classify.[8]

Some authors have expressed concern that there remains a dearth of well-designed, properly conducted, randomised controlled trials for adults with generalised seizures/epilepsy syndromes and for children in general.[5]

Bipolar disorder

Valproate was first used for the maintenance treatment of bipolar disorder in Europe in 1966. Over the past two decades there has been a dramatic rise in its use for this condition.[9] However, the authors of a recent Cochrane review said that, in view of the lack of clear findings in their review and the limited available evidence, conclusions regarding the efficacy and acceptability of valproate compared to placebo or lithium cannot be made with any degree of confidence.[10] Longer-term and larger sample size randomised controlled trials are required to better assess the clinical utility of valproate in the maintenance therapy of bipolar disorder.[10]

Neuropathic pain

Although the guidelines of the UK National Institute for Health and Care Excellence[11] do not recommend valproate for neuropathic pain, an American Academy of Neurology practice parameter[12] suggests that it should be considered for the treatment of painful diabetic neuropathy. A Cochrane review concluded that, in view of the limited available evidence, valproate use should be reserved for cases of neuropathic pain where other proven treatment options have failed, are not available, or are not tolerated.[1]

Migraine

Preventative therapy for migraine is often undertaken if patients have more than one attack per month. First-line drugs for migraine prophylaxis include amitriptyline, propranolol and pizotifen. A systematic review found that valproate is also effective in reducing migraine frequency and is reasonably well tolerated.[3]

Adverse reactions

Common adverse effects of valproate include nausea, upper abdominal cramps, abnormal liver function, weight gain and diarrhoea. Neurological adverse effects such as tremor, fatigue, sedation, confusion and dizziness are often observed. Other potential adverse effects include alopecia, reduced bone density, thrombocytopenia, anaemia, leucopenia and hyperammonaemia.

There are several cutaneous adverse effects of valproate. They include pruritus, urticaria, erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome, and drug reaction with eosinophilia and systemic symptoms (DRESS).

Cases of polycystic ovarian syndrome and male infertility have also been reported.

There is a risk of hepatic dysfunction (>1%) and pancreatitis (<0.1%). Both adverse effects can be fatal. If liver failure occurs, it is usually in the first six months, but pancreatitis can occur after years of use. Although liver function tests may alter during treatment they are not reliable in predicting which patients will develop liver failure.

A pooled analysis of 199 clinical trials of 11 antiepileptic drugs (including valproate) by the US Food and Drug Administration (FDA) found that patients who were randomised to receive an antiepileptic drug had almost twice the risk of suicidal behaviour or ideation (0.43%) compared to patients randomised to receive placebo (0.24%).[13] This suggests that there would be one additional case of suicidal thinking or behaviour for every 530 patients treated with any antiepileptic drug.[13]

Contraindications and precautions

Valproate should be avoided in patients with liver disease or a family history of liver disease. Although uncommon, patients with a urea cycle disorder or porphyria should also avoid valproate. Renal failure can impair protein binding and lead to the accumulation of metabolites, so a lower dose may be required in patients with impaired renal function.

Routine laboratory studies should be performed before commencing therapy, but regular monitoring is not required for most patients.[6] The onset of lethargy, vomiting or ataxia is an indication to measure serum ammonia to exclude hyperammonaemic encephalopathy. Spontaneous bruising or bleeding may occur and necessitates clinical review and investigation. Such patients may have developed thrombocytopenia or altered platelet function.

Pregnancy and lactation

Maternal exposure to valproate was first linked to an increased risk of congenital spina bifida in the 1980s. Valproate has an increased risk of major congenital malformations and poor cognitive outcomes compared to other antiepileptic drugs.[14]

In the Australian categorisation system valproate is in pregnancy category D, so women of childbearing age should use effective contraception (e.g. oral contraceptive, intrauterine device, subdermal etonogestrel). The safe use of valproate in women of childbearing age is fraught with challenges.[15] Ideally, the indications for using valproate should be reviewed and its risks discussed before pregnancy occurs.

A recent systematic review[16] of the teratogenicity of antiepileptic drugs advised clinicians to:

- avoid valproate if equally effective antiepileptic drugs are available
- aim for monotherapy
- prescribe the lowest effective dose whenever possible, avoid valproate doses of 700 mg daily or above (if possible)
- avoid withdrawal or changes of antiepileptic drugs after conception has occurred.

The FDA has announced that valproate is contraindicated for the prevention of migraine during pregnancy. It should only be used during pregnancy by women with epilepsy or bipolar disorder if other drugs are ineffective or unacceptable.

Folic acid supplementation (at least 0.4 mg daily), one month pre-conception and during the first trimester, is recommended for all women to reduce the risk of fetal neural tube defects. Women taking antiepileptic drugs, particularly valproate, are at greater risk of having a child with neural tube defects and other

malformations which may be related to altered folate metabolism. Consequently, they require a higher dose of folic acid supplementation (5 mg daily).[17] An American Academy of Neurology systematic review of the available literature concluded that, although the data are insufficient to show that folic acid supplementation is effective in women with epilepsy, there is no evidence of harm and no reason to suspect that it would not be effective in this group.[14]

Although valproate probably does not enter breast milk in clinically important amounts,[14,18] the drug's manufacturers advise against breastfeeding.

Women with epilepsy who are currently pregnant or who have given birth recently are encouraged to contact the Australian Pregnancy Register at www.neuroscience.org.au/apr or 1800 069 722.

Drug interactions

For a variety of pharmacokinetic and pharmacodynamic reasons, valproate use has the potential to interact with a large number of drugs (see Box). The consequences of such interactions range from mild to life-threatening. Of particular clinical relevance is valproate's effect on other antiepileptic drugs (for example carbamazepine, lamotrigine, phenobarbitone, phenytoin, topiramate).

Box Potential drug interactions with valproate

aspirin

large doses increase valproate concentration

carbamazepine

reduces valproate concentration

valproate increases the concentration of the active metabolite of carbamazepine

carbapenems

reduce valproate concentration

lamotrigine

valproate increases lamotrigine concentration (risk of Stevens-Johnson syndrome)

olanzapine

valproate decreases olanzapine concentration

phenobarbitone

reduces valproate concentration

valproate increases phenobarbitone concentration

phenytoin

reduces valproate concentration

valproate increases phenytoin concentration (initially free, later total)

topiramate

increases the risk of valproate-associated adverse effects (e.g. hyperammonaemia)

zidovudine

valproate increases zidovudine concentration

Drug monitoring

With the exception of phenytoin (and possibly lamotrigine), antiepileptic drugs do not require routine therapeutic drug monitoring assays.[6,19] Although measuring serum valproate concentrations may be useful in screening patients for toxicity[20] or poor compliance, there is little evidence linking concentration to clinical efficacy.[19,21] A retrospective study within a major Australian teaching hospital found that most requests were ordered inappropriately and many tests were not taken at the correct time (at least eight hours after the last dose).[21]

Signs and management of toxicity

The majority of patients with acute valproate intoxication experience mild to moderate lethargy and recover uneventfully. Central nervous system dysfunction is the most common manifestation of toxicity and this can range in severity from mild drowsiness to coma or fatal cerebral oedema. Hypernatraemia, metabolic acidosis, hyperammonaemia and liver failure may develop in some patients.

Toxicity can occur within the therapeutic range and includes hyperammonaemic encephalopathy. This can present with confusion, increased seizures and focal neurological signs.

Supportive care is the principal treatment for valproate intoxication and results in good outcomes in the vast majority of cases. Activated charcoal may be considered for alert patients who have taken a severe overdose.[22]

Withdrawal

Some doctors favour a gradual withdrawal of antiepileptic drugs (for example over a six-month period) to lessen the risk of seizure recurrence.[23] However, a Cochrane review has highlighted the lack of evidence to guide clinicians on the optimal rate of withdrawal in patients whose seizures are well controlled.[24] There is little evidence to guide antiepileptic drug withdrawal tapering periods in non-epileptic patients.

The Austroads Assessing Fitness to Drive guide recommends that private licence holders do not drive while withdrawing antiepileptic drugs and for three months afterwards.[25] Commercial licence holders with epilepsy will not be eligible to drive if their antiepileptic drug is ceased. The Austroads guidelines do not specifically address antiepileptic drug withdrawal by patients without epilepsy.[25]

Conclusion

Valproate has been prescribed widely for decades. Given that new indications continue to emerge, it is increasingly important for clinicians to remain cognisant of the drug's adverse effects. A key component of safe valproate use involves the provision of tailored counselling and education to each patient before starting therapy. ◁

Conflict of interest: none declared

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Q:

SELF-TEST QUESTIONS

True or false?

3. Patients with epilepsy should have their serum valproate concentration measured at least once a year

4. Liver function tests can be used to predict patients at risk of hepatic failure during treatment with valproate

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