

SODIUM VALPROATE IN CHILDHOOD EPILEPSY

Report prepared for the World Health Organisation
November 2006

1. Summary statement of the proposal for inclusion, change or deletion

Sodium valproate sugar free liquid and oral syrup 200mg in 5ml; sodium valproate 100mg crushable tablets; are proposed for addition to the Model List of Essential Medicines, for use in the management of epilepsy in children. It is at least as effective as carbamazepine, phenobarbitone and phenytoin in the management of partial and tonic-clonic seizures in children.

2. Name of the focal point in WHO submitting or supporting the application

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Dr Martin Weber, Country Implementation Support (CIS), Family and Community Health (FCH).

3. Name of the organization(s) consulted and/or supporting the application

None.

4. International Nonproprietary Name (INN, generic name) of the medicine

Sodium valproate.

5. Formulation proposed for inclusion; including adult and paediatric (if appropriate)

As the brand Epilim^R, there is a sugar free liquid and oral syrup both containing sodium valproate 200mg in 5ml. It is also available as sodium valproate 100mg crushable tablets, 200mg and 500mg enteric coated tablets and 200mg, 300mg and 500mg modified release tablets. There are also a number of these preparations available as generic formulations both of sodium valproate and valproic acid. It is suggested that valproic acid has a 1:1 relationship with products containing sodium valproate but care is needed in making changes.

6. International availability - sources, if possible manufacturers

Sodium valproate is available in UK formulations either as sodium valproate or as valproic acid⁽⁹⁾. It is also available in many other countries.

7. Whether listing is requested as an individual medicine or as an example of a therapeutic group

As an individual medicine.

8. Information supporting the public health relevance (epidemiological information on disease burden, assessment of current use, target population)

Epilepsy is the most common serious neurological disorder and is one of the world's most prevalent noncommunicable diseases.

Due to differences in inclusion criteria, classification, diagnosis and case ascertainment methods, incidence and prevalence rates have varied considerably in different studies. If febrile seizures, neonatal seizures, single seizures or seizures in acute illnesses are included, the figures may be elevated several fold.

Data from the WHO⁽¹⁾ indicate there are over 50 million sufferers of epilepsy in the world today of whom 85% live in developing countries. Globally, there are an estimated 2.4 million new cases each year and at least 50% of these cases begin in childhood or adolescence.

Incidence is defined as the frequency of new cases of a disease in a defined population during a specified period of time (e.g. a calendar year). When epilepsy is defined as recurrent, unprovoked seizures, the average annual incidence in developed countries is quoted between 40-70 per 100,000 of the general population^(2,3,4,5,6).

In developing countries, this figure is much higher at around 100-190 per 100,000 of the general population per year^(4,5,6,7). The main reason for the higher incidence of epilepsy in developing countries is the higher risk of experiencing a condition which can lead to permanent brain damage e.g. parasitic infection such as neurocysticercosis and malaria; meningitis; pre and perinatal complications and malnutrition.

The incidence of recurrent seizures is highest in the first year of life and declines thereafter throughout childhood and adolescence⁽⁴⁾. Incidence decreases from ~ 150 per 100,000 in the first year of life to ~ 60 per 100,000 at ages 5-9 years and 45-50 per 100,000 in older children⁽²⁷⁾. Most studies that provide incidence rates separately for boys and girls find slightly higher total rates for boys⁽⁴⁾. This difference in sex-specific rates varies by age however as it is suggested that before 5 years, incidence rates are ~ 30-60% higher in girls than boys while rates tend to be 10-20% higher in boys through later childhood and adolescence⁽⁴⁾. Sex differences may reflect differences in predominant seizure types at different ages, differences in exposures to risk factors because of social differences in the rearing of male and female children, changes in susceptibility to seizures in boys and girls with age or variations in diagnosis by sex.

Prevalence is a measure of the number of new and existing cases (both new and old) of epilepsy in a defined population at either a specific point in time (point prevalence) or over a defined interval of time such as a year (period prevalence).

Again, like incidence rates, prevalence rates quoted can be influenced depending on whether persons with single seizures, febrile seizures, acute symptomatic seizures or only recurrent unprovoked seizures are counted as cases.

The usual prevalence figure quoted is ~ 5-10 cases per 1000 of the general population^(3,4,5,6,7) (excluding febrile convulsions, single seizures and inactive cases). In children, estimates are of the order of 4-5 per 1000 children^(2,4).

Prevalence rates increase with age ranging from ~ 2-3 per 1000 in children up to 7 years of age to 4-6 per 1000 at 11-15 years of age. Rates tend to be slightly higher in boys than in girls⁽⁴⁾.

Some studies report the prevalence of epilepsy in developing countries to be higher than that in developed countries with quoted prevalence figures of 10-15 per 1000 of the general population^(4,5,6). However, Scott RA et al⁽⁷⁾ suggests that prevalence rates for active epilepsy are similar in both developing and industrialised countries. As the incidence of epilepsy is much higher in the former, it is suggested that a significant proportion of the affected population in developing countries may be dying from the seizure disorder or its underlying cause.

Geographic variation has been hard to assess because of a lack of standard techniques but a consistent finding is that prevalence rates are higher in rural than in urban areas⁽³⁾.

In developed countries, the prevalence of epilepsy is usually found to be slightly higher in the lower socio-economic groups⁽³⁾.

Since the aetiology of epilepsy is frequently multifactorial, the exact attribution of cause in the general population is often impossible. It has traditionally been said that 60-70% of all epilepsies have no clear cause and these are best referred to as cryptogenic epilepsies.

The annual incidence of epilepsy is relatively small and few studies have reported incidence cases by the type of seizure of epilepsy syndrome⁽⁴⁾. It has been suggested that 1/5th of recently diagnosed children and nearly ¾ of prevalent cases are reported to have experienced more than one type of seizure. These children are most often classified according to the predominant seizure type.

Generalised seizures are common in field studies, especially in developing countries, often because partial seizures are missed. In developed countries, over half the incidence cases are partial seizures. Partial and generalised seizures vary with age. Generalised seizures have the highest incidence in the first year of life. With the exception of absence seizures, for which incidence rates peak in 5-10 year olds, the incidence of generalised seizures in childhood declines after the first year of life. Incidence rates for partial seizures increase slightly during early childhood and remain relatively constant thereafter throughout childhood and adolescence. Among partial seizures, complex partial seizures are generally the most common^(4,6).

Given the correct treatment, epilepsy responds to treatment in up to 70% of patients. However, whilst 80% of the potential market for antiepileptic drugs is in the developing world, it is suggested that around ¾ of these people with epilepsy may not receive any or receive incorrect treatment. This is thought to be related to inadequacies in health care resources and delivery and also to the social stigma attached to the condition^(1,5,7).

Ideally, the choice of antiepileptic drug for each patient should be based on seizure type and/or the syndrome as well as the individual patient's needs.

In developing countries however, both the choice and the supply of drugs are limited. An analysis of the market suggests that while the use of older and cheaper drugs such as phenobarbitone has declined in developed, industrialised regions, the market share in developing countries is higher and increasing more quickly than that of the newer antiepileptic drugs. Alternative anti-epileptic drugs in developing countries are in very short supply and in such systems, the normal determinants for drug treatment

are the drugs cost and availability and not necessarily efficacy and lack of adverse effects.

Phenobarbitone is the WHO's first line anti-epileptic drug in developing countries where it is the most commonly prescribed anti-epileptic drug. Indeed, in their review Scott RA et al⁽⁷⁾ include a number of studies claiming phenobarbitone to be both effective and tolerated in patients with epilepsy treated in developing countries. However, whilst it is cheaper than other agents used frequently in developed countries (e.g. phenytoin, sodium valproate and carbamazepine), questions have been raised about its suitability with respect to its efficacy and profile of adverse effects. Certainly, in Europe and the USA, phenobarbitone is no longer considered a first line drug due to concerns over its efficacy and short and long-term tolerability.

Despite a lack of hard evidence from individual randomised controlled trials, there is a strong recommendation in Europe and the USA that sodium valproate should be considered as a first line treatment in generalised, partial and other epilepsies.

9. Treatment details (dosage regimen, duration; reference to existing WHO and other clinical guidelines; need for special diagnostic or treatment facilities and skills)

For oral administration an initial dose for infants and children from 1 month to 12 years of age is 5-7.5mg/kg/dose given twice daily. This can be gradually increased, as necessary, to a usual maintenance dose of 12.5-15mg/kg/dose twice daily. Clinical chemistry and haematological parameters should be measured if the dose exceeds 20mg/kg/dose twice daily⁽⁹⁾.

In those aged 12-18 years, an initial oral dose of 300mg/dose twice daily is suggested increasing in steps of 200mg daily at 3 day intervals to a usual maintenance dose of 0.5-1g/dose twice daily. The maximum recommended dose is 1.25g/dose twice daily⁽⁹⁾.

Plasma valproate concentrations are not a useful index of efficacy therefore routine monitoring is unhelpful.

10. Summary of comparative effectiveness in a variety of clinical settings

The most likely mode of action is the potentiation of the inhibitory action of gamma amino-butyric acid through an action on the further synthesis or further metabolism of GABA⁽⁸⁾.

There is a paucity of studies on the comparative efficacy of anti-epileptic drugs in specific epilepsy syndromes. In newly diagnosed epilepsies, across age groups and all seizure types, several randomised controlled trials of carbamazepine, sodium valproate, clobazam, phenytoin and phenobarbitone show they are effective but fail to identify significant differences in efficacy between these medications. The potential adverse effects of anti-epileptic drugs should be a major determinant of the choice of drug in the individual child.

In 1996, de Silva M et al⁽¹⁰⁾ reported on a randomised comparative trial in children. In this long-term, prospective trial, the efficacy and tolerability of phenobarbitone, phenytoin, carbamazepine and sodium valproate were compared in 167 children aged 3-16 years with at least 2 previously untreated tonic-clonic or partial seizures.

Children under the age of 3 years and those with myoclonic, absence, tonic or drop attacks were excluded.

Patients were randomly assigned to one of the four anti-epileptic drugs (identity of treatment was not masked) and were started on a small dose calculated on body weight with dosage increments as required and tolerated until seizures ceased or until the blood concentration was in the top half of the recommended optimum range. Seizure type and frequency were recorded. If seizures continued, monotherapy was deemed to have failed and either another drug was chosen by the physician or a second drug, usually carbamazepine was added.

Efficacy was assessed by time to first seizure after the start of treatment and time to achieving 1 year remission.

Results showed no significant differences in efficacy between phenobarbitone, phenytoin, carbamazepine and sodium valproate.

The outcome with each of the drugs was good with 12-25% (overall 20%) of children remaining seizure free at 3 years follow-up and 60-80% (overall 73%) achieving a 1 year remission by 3 years of follow-up. Comparison of the 4 drugs included an adjustment for seizure type and analysis showed no significant influence of the two different seizure categories on the comparative efficacy.

However, randomisation to phenobarbitone was discontinued early in the study period due to unacceptable side-effects. Six of the first 10 children allocated phenobarbitone had adverse effects (behavioural or cognitive) that necessitated withdrawal of the drug. Because of this unacceptably high rate of adverse effects, no further children were assigned phenobarbitone.

Carbamazepine and sodium valproate were the best tolerated with only 4% of children discontinuing treatment compared with 9% of children on phenytoin.

Thilothammanl N et al⁽¹¹⁾, 1996, conducted a randomised double-blind clinical trial in India of 151 children (aged 4-12 years) with generalized tonic-clonic seizures.

Patients received phenobarbitone, phenytoin or sodium valproate and at the end of 2 years, 127 children remained in the study. Each child was given one active drug and 2 placebo tablets. The main outcome measures were recurrence of seizures and side effects. The proportion of children with recurrence did not differ among the 3 groups. More than one side effect was observed in 16 (32%) children on phenobarbitone, 20 (40%) of children on phenytoin and 9 (19%) of children on sodium valproate – this difference was statistically significant.

All 3 drugs were equally effective in controlling seizures; side-effects were minimal with sodium valproate followed by phenobarbitone. Though side effects were more frequent with phenytoin, most of them disappeared on adjusting drug dosage. Least expensive phenobarbitone may be preferred as the first drug of choice but only for pre-school children; sodium valproate is suggested for school children.

A prospective study between carbamazepine, phenytoin and sodium valproate as monotherapy in previously untreated and recently diagnosed patients with epilepsy was reported by Callaghan N et al⁽¹²⁾ in 1985. 181 patients were randomised to sodium valproate, phenytoin or carbamazepine as monotherapy and followed for 14 to 24 months. All 3 drugs were highly effective in the control of generalised seizures but were less effective for partial seizures. No significant difference between the overall incidence of side effects between the 3 drugs.

In 2001, the Cochrane Collaboration published a systematic review comparing sodium valproate with phenytoin as monotherapy⁽¹³⁾.

The reviewers include background information suggesting that, although there is no evidence from randomised controlled trials, it is generally believed that valproate monotherapy is more effective than phenytoin monotherapy in generalised onset

seizures (generalised tonic-clonic seizures, absence and myoclonus) while phenytoin is more effective than valproate monotherapy in partial onset seizures (simple partial, complex partial and secondary generalised tonic-clonic seizures).

The object of this review was to assess the best evidence comparing phenytoin and valproate when used as monotherapy in people with partial onset seizures or generalised onset tonic-clonic seizures with or without other generalised seizure types. The review includes randomised controlled trials in children or adults treated with phenytoin or valproate as monotherapy.

Data were available for 669 individuals from 5 trials, representing 60% of the participants recruited into the 11 trials that met the inclusion criteria. One important limitation is that in 4 of the 5 trials, for people classified as having generalised onset seizures, tonic-clonic seizures were the only seizure types recorded at follow-up and hence results apply only to generalised tonic-clonic seizures.

The outcome measures included were

- time to withdrawal of allocated treatment (primary outcome) – if treatment was withdrawn for poor seizure control, adverse effects, non-compliance or if additional add-on treatment was initiated
- time to achieve 12 month remission (seizure free period)
- time to achieve 6 month remission
- time to first seizure post randomisation
- quality of life measures if available

The following results were:

(a) time to withdrawal of allocated treatment

For people with generalised seizures, there was no clear advantage for either drug. For people with partial onset seizures, there was a potentially important advantage for valproate. Overall, there is a suggested potential overall advantage for valproate.

(b) time to achieve 12 month remission

For people with generalised (tonic-clonic) or partial onset seizures, there was no clear advantage for either drug.

(c) time to achieve 6 month remission

the most compatible analysis including only generalised tonic-clonic seizures suggested a potentially important advantage for valproate. For people with partial onset seizures, there was no clear advantage for either drug. Overall, a potential overall advantage for valproate is suggested.

(d) time to first seizure post randomisation

the most compatible analysis including only generalised tonic-clonic seizures indicated no clear advantage for either drug. For those with partial onset seizures, there was a potentially important advantage for phenytoin. Overall, results suggest a potential overall advantage for phenytoin

(e) quality of life

This was not recorded in any trial

As such, the review failed to demonstrate a statistically significant effect in favour of either valproate or phenytoin for the primary global outcome 'time to withdrawal of treatment'. This outcome is influenced by the relative efficacy of the 2 drugs as well as differences in tolerability and safety. There was also a failure to demonstrate any statistically significant differences between phenytoin and

valproate for analysis of 'time to 12 month remission' and 'time to 6 month remission'.

The results of this systematic review therefore do not provide hard evidence to overthrow or support the current practice of using valproate for people with generalised onset tonic-clonic seizures and phenytoin for people with partial onset seizures.

If future studies are to detect whether particular anti-epileptic drugs are to be preferred for certain epilepsy syndromes, they will need to be designed and powered accordingly.

Verity CM et al⁽¹⁴⁾, on behalf of the Paediatric EPITEG Collaborative Group, reported on a multicentre comparative trial of sodium valproate and carbamazepine in paediatric epilepsy. In this, 260 children with primary generalised epilepsy or with partial epilepsy (with or without secondary generalisation) at 63 outpatient clinics in the UK and Ireland participated in a 3-year study. Children aged 5-16 years were included and randomised to receive either sodium valproate or carbamazepine. For both drugs, treatment was initiated at a fairly low dose and increased as necessary until seizures were controlled or until toxic symptoms appeared. Maximum daily dose for sodium valproate was 30mg/kg/DAY and for carbamazepine 20mg/kg/DAY. No other antiepileptic medication was allowed – the necessity for additional anticonvulsant medication during the treatment period was classed as treatment failure.

The analysis of treatment failures (i.e. drug withdrawal following unacceptable adverse events, inadequate seizure control or both), showed that there was little difference in failure rates between the drugs. Remission analysis showed that there was no difference in the overall efficacy between sodium valproate and carbamazepine in controlling either generalised or partial seizures. Both drugs achieved a high degree of seizure control with 75% of patients having at least 12 months and 45-55% at least 2 years, of freedom from seizures.

Treatment was withdrawn because of adverse effects in 12% patients on carbamazepine and 15% patients on sodium valproate. Only 5 (3%) children on carbamazepine were withdrawn because of rashes in the first few months of treatment which is far lower than that reported in the EPITEG Study in adults when 9% of patients on carbamazepine had severe rashes.

The above study by Verity et al was included in a Cochrane Review published in 2000⁽²¹⁾ which compared carbamazepine with sodium valproate monotherapy in the treatment of adults and children with epilepsy.

The studies included in the review were randomised controlled monotherapy studies comparing carbamazepine and sodium valproate and included children or adults with partial onset seizures (simple partial, complex partial or secondarily generalising tonic-clonic seizures) or generalised onset tonic-clonic seizures.

1256 participants from 5 trials (representing 85% of the participants recruited into the 8 trials available) met the inclusion criteria. The intervention was carbamazepine or sodium valproate monotherapy. The primary outcome measure was time to withdrawal of allocated treatment (i.e. treatment was withdrawn for poor seizure control or adverse effects or both, or additional add-on treatment was initiated). Secondary outcomes were time to 12-month remission from seizures and time to first seizure post-randomisation.

Results from this review did not find an overall difference between carbamazepine and sodium valproate for the primary global outcome time to treatment withdrawal. For efficacy outcomes, the analysis for time to first seizure found a significant interaction between treatment and epilepsy type, where patients with a partial

epilepsy do better on carbamazepine. For time to 12 month remission, results for the subgroup of people with a partial epilepsy indicate a significant advantage for carbamazepine, although the test for an interaction between treatment and epilepsy type was not significant.

Sodium valproate has also been compared with some of the newer antiepileptic drugs, notably lamotrigine and topiramate.

Steinhoff BJ et al⁽¹⁵⁾ conducted an open label 24 week monotherapy trial in 239 newly diagnosed epilepsy patients of 12 years and over. Patients with focal epilepsy were treated with lamotrigine or carbamazepine and those with generalized epilepsy received lamotrigine or sodium valproate. The primary efficiency variable was the number of seizure-free patients during study weeks 17 and 24. There were 63 patients in the generalised epilepsy group of whom 30 received valproate. During study weeks 17 and 24, 61% of the lamotrigine patients and 84% of the valproate patients became seizure free. The drop out rate due to lack of efficacy or adverse effects was 12% with lamotrigine and 3% with valproate.

Coppola G et al⁽¹⁶⁾ also conducted a study comparing lamotrigine with valproic acid. This was a randomised, open-label parallel group design study of 38 children (3-13 years) with newly diagnosed childhood or juvenile typical absence seizures. Patients received either lamotrigine (dose gradually increased until seizures controlled or maximum dose 12mg/kg/DAY) or valproic acid (dose gradually increased until seizures controlled or maximum dose 30mg/kg/DAY). After 1 month of treatment, 10/19 children taking valproic acid and 1/19 taking lamotrigine were seizure free; by 3 month follow-up 12/19 taking valproic acid and 7/19 taking lamotrigine were seizure free; at 12 months 13/19 taking valproic acid and 10/19 taking lamotrigine were seizure free. Side effects were mostly mild and transient and were recorded in 2 children treated with valproic acid and in 6 treated with lamotrigine.

Wheless JW et al⁽¹⁷⁾ reported on a double blind randomised study in which topiramate, carbamazepine and valproate monotherapy demonstrated similar times to study exit, times to first seizure and proportions of patients who were seizure-free during the first 6 months of follow-up. Of the total 613 patients (119 of whom were children or adolescents), 46% completed the study. Adverse effects accounted for 19% and 23% of discontinuations in the topiramate and traditional therapy arms respectively. Ineffective treatment accounted for 11% and 12% of discontinuations in the topiramate and traditional therapy arms. The time to exit and the time to first seizure did not differ. The proportion of patients who did not experience a seizure during the last 6 months of the study was 49% of the topiramate patients and 44% each of the carbamazepine and valproate patients.

Sodium valproate is also sometimes used in the treatment of absence seizures and the Cochrane Collaboration in 2005⁽¹⁸⁾, conducted a systematic review of the evidence for the effects of ethosuximide, valproate and lamotrigine as treatments for children and adolescents with absence seizures when compared with placebo or each other. Studies included were randomised parallel group monotherapy or add-on trials which included a comparison of any of the following in children or adolescents with absence seizures. Unfortunately however, of the 5 small trials found, 4 were of poor methodological quality and did not have a sufficient number of participants.

11. Summary of comparative evidence on safety

Adverse Effects

All anti-epileptic drugs have a relatively high incidence of adverse reactions and they are a major cause of discontinuing treatment. Monotherapy is recommended wherever possible – monotherapy is effective in controlling the majority of seizures and adverse effects and interactions are less likely than with the multi-drug regimens^(8,19,20).

All anti-epileptic drugs are associated with and often cause CNS adverse effects which include behavioural effects and cognitive dysfunction. This effect is more likely with polytherapy. Children may be more susceptible to these effects which can have consequences in terms of difficulty with behaviour, learning and development. Many adverse effects of anti-epileptic drugs are dose related and may occur at therapeutic doses. To minimise these, the drug should be introduced at a low dose and be slowly increased to the minimum dose that achieves seizure control.

The common adverse effects attributable to sodium valproate are

- Hepatobiliary disorders – increased liver enzymes are common, particularly in early treatment and may be transient (there are very cases of severe liver dysfunction – see below)
- GI disorders – nausea and diarrhoea occur frequently at the start of treatment but disappear after a few days without discontinuing treatment. Take with or after food. Very rare cases of pancreatitis have been reported
- Nervous system disorders – occasionally sedation is reported, usually when sodium valproate is used in combination with other anti-epileptic drugs. Hyperactivity and behavioural deterioration have also been reported. Tremor is reported at high doses.
- Metabolic disorders – cases of isolated and moderate hyperammonaemia without change in liver function tests may occur frequently, are usually transient and should not cause treatment discontinuation. However, they may present clinically as vomiting, ataxia and increasing clouding of consciousness. If these symptoms occur, treatment should be stopped.
- Weight gain – this is significant and being overweight at the start of treatment may be a significant predictor of further weight gain with sodium valproate
- Hair loss – usually transient and sometimes dose related. Regrowth normally begins within 6 months
- Blood dyscrasias – relatively frequent and usually return to normal when sodium valproate is discontinued
- Reproductive system and breast disorders – amenorrhoea and irregular periods have been reported

Severe liver damage has been very rarely reported with sodium valproate. Those most at risk, especially in cases of multiple anticonvulsant therapy, are infants and young children less than 3 years of age and those with severe seizure disorders, organic brain disease and/or congenital metabolic or degenerative disease associated with mental retardation. In most cases, reported liver damage occurred during the first 6 months of therapy with the period of maximum risk being 2-12 weeks. It is suggested that liver function be monitored before and then periodically during the first 6 months of therapy, especially in those at most risk and those with a prior history of liver disease.

In their randomised comparative monotherapy trial of phenobarbitone, phenytoin, carbamazepine and sodium valproate, de Silva et al⁽¹⁰⁾ found a frequency of unacceptable adverse effects of 4% for carbamazepine and sodium valproate

compared to 9% patients on phenytoin and 60% (6/10) patients given phenobarbitone. Of the two patients on sodium valproate in whom treatment was withdrawn, one was due to behavioural side-effects and the other due to tremor.

In his study comparing sodium valproate with carbamazepine, Verity et al⁽¹⁴⁾ showed a similar incidence of adverse effects and treatment withdrawal between the two drugs. Treatment was withdrawn because of adverse effects in 12% patients on carbamazepine and 15% patients on sodium valproate.

Callaghan N et al⁽¹²⁾, also reported no significant difference between the overall incidence of side effects between carbamazepine, phenytoin and sodium valproate.

Drug Interactions^(8, 20)

(a) Effect of sodium valproate on other drugs

Sodium valproate can affect the plasma concentration of other drugs either through displacement from plasma proteins (sodium valproate is 80-94% plasma protein bound) or inhibition of hepatic metabolism

- valproate may potentiate the effect of antipsychotics, MAO inhibitors, antidepressants and benzodiazepines
- valproate increases phenobarbitone concentrations due to inhibition of hepatic enzymes and sedation may occur, especially in children
- valproate may also inhibit the metabolism of primidone, carbamazepine and lamotrigine with potential for increased levels and toxicity of these anti-epileptic drugs
- valproate decreases phenytoin total plasma concentration; valproate displaces phenytoin from its plasma protein sites and reduces its hepatic metabolism
- valproate may increase zidovudine plasma concentration
- anticoagulant effect of warfarin and other coumarin anticoagulants may be increased following displacement from plasma protein binding sites by valproate

(b) Effect of other drugs on sodium valproate

- Anti-epileptic drugs with enzyme inducing effect (eg phenytoin, phenobarbitone, carbamazepine) decrease valproic acid concentrations
- Mefloquine and chloroquine increase valproate metabolism and may lower the seizure threshold
- Levels may be affected by other drugs including macrolide and carbapenem antibiotics

Plasma valproate concentrations are not a useful index of efficacy therefore routine monitoring is unhelpful

Use in Pregnancy⁽⁸⁾

In offspring born to mothers with epilepsy receiving any anti-epileptic drug the overall rate of malformations has been demonstrated to be 2-3x higher than the rate (~3%) reported in the general population. An increased number of children with malformations have been reported in cases of multiple drug therapy.

Developmental delay has been reported in children born to mothers with epilepsy; it is not possible to differentiate what may be due to genetic, social, environmental factors, maternal epilepsy or antiepileptic treatment.

Risk with valproate

- associated with neural tube defects such as myelomeningocele and spina bifida
- frequency of this effect is estimated to be 1-2%
- increased incidence of minor or major malformations (incl neural tube defects, craniofacial defects, limb malformations, CV malformations, hypospadias) has been reported in offspring born to mothers with epilepsy treated with valproate
- association between in-utero exposure to valproate and risk of developmental delay, particularly of verbal IQ

Folate supplementation prior to pregnancy has been shown to reduce the incidence of neural tube defects

Anticonvulsant monotherapy is preferred with lowest effective dose

Incidence of neural tube defect rises with increasing dosage, particularly above 1000mg daily

Use in Lactation⁽⁸⁾

Excretion of valproate in breast milk is low with a concentration between 1-10% of total maternal serum levels. Appears to be no contraindication to breastfeeding

13. Licensed Status

Sodium valproate has a product licence in Europe and the USA for the treatment of generalised, partial and other epilepsies in adults and children. There is no lower age limit specified for its use either as monotherapy or as adjunctive therapy. However, due to an increased risk of severe liver damage, it is not recommended as a first line therapy in infants less than two years of age and use of sodium valproate in this age group is generally reserved for more difficult cases.

14. Availability of pharmacopoeial standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia)

British Pharmacopoeia.

15. Proposed (new/adapted) text for the WHO Model Formulary

To be provided.

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