PHENYTOIN IN CHILDHOOD EPILEPSY

Report prepared for World Health Organization
October 2006

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

Phenytoin base (as EpanutinR) is available as 50mg chewable tablets and an oral suspension of strength 30mg/5ml, and 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 sodium valproate in the management of partial and tonic-clonic seizures in children.

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

Dr Tarun Dua, Management of Mental and Brain Disorders (MBD), Noncommunicable Diseases and Mental Health (NMH)
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

Phenytoin sodium.

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

Preparations
Phenytoin sodium (as EpanutinR) is available as 25mg, 50mg, 100mg capsules are already in the Model List. Phenytoin base (as EpanutinR) is available as 50mg chewable tablets and an oral suspension of strength 30mg/5ml, and are proposed for inclusion. Suspensions of other strengths are also available.

6. International availability - sources, if possible manufacturers

Pfizer Ltd (Walton Oaks, Dorking Rd, Walton-on-the-Hill, Surrey, KT20 7NS, UK**)** market Epanutin (phenytoin sodium) capsules (25mg, 50mg, 100mg, 300mg), Epanutin (phenytoin sodium) infatabs (50mg chewable tablet), Epanutin (phenytoin) suspension (30mg/5ml;500ml).

A non proprietary phenytoin sodium tablet 100mg is also available in the UK. Phenytoin injection (phenytoin sodium) 50mg/ml; 5ml ampoule is available as Epanutin from Pfizer (see above). A non-proprietary formulation is also available from Mayne Pharma PLC, Queensway, Royal Lemington Spa, Warwickshire, CV31 3RW, UK

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)

Background – Etiology, Incidence and Prevalence

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 and 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.

Licensed status (UK/USA)
In the UK and USA phenytoin is indicated for the control of tonic-clonic seizures (grand mal epilepsy), partial seizures (focal including temporal lobe) or a combination of these, and the prevention and treatment of seizures occurring during or following neurosurgery and/or severe head injury (8).

There is strong clinical recommendation in Europe that phenytoin should be considered as a second line agent for the management of focal seizures with/without secondary generalisation. Its use should be avoided in childhood absence epilepsy, juvenile absence epilepsy and juvenile myoclonic epilepsy, where it may worsen seizures (10,11). Intravenous phenytoin is also recommended for use in the management of established status epilepticus at a dose of 18mg/kg, in phenytoin naïve patients, administered over 20 minutes. The initial treatment of choice for status epilepticus is IV lorazepam. If IV access is unavailable diazepam rectal tubes or rectal paraldehyde should be considered first. If the patient has failed to respond to either of these measures and is in established status epilepticus, then IV phenytoin is considered appropriate. (10)

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

Dosage
Dosage of phenytoin should be individualised as there may be wide interpatient variability in phenytoin serum levels with equivalent dosage. The drug should be introduced in small dosages with gradual increments until control is achieved or until toxic effects appear. In some cases serum level determinations may be necessary for optimal dosage adjustments - the clinically effective level is usually 10-20mg/l (40-80 micromoles/l) although some cases of tonic-clonic seizures may be controlled with lower

serum levels of phenytoin. At recommended dosages a period of seven to ten days may be required to achieve steady state serum levels with phenytoin and changes in dosage should not be carried out at intervals shorter than seven to ten days. Maintenance of treatment should be the lowest dose consistent with control of seizures

In infants and children an initial oral dose of 1.5- 2.5 mg/kg/dose twice a day is recommended (12,13). This should be increased gradually to a maximum of 2.5-5mg/kg/dose twice daily (usual maximum is 7.5mg/kg/dose twice daily or 300mg daily) (500mg daily in adults). A recommended daily maintenance dosage is usually 4-8mg/kg. Exceptionally, a daily dose outside this range may be indicated. Dosage should normally be adjusted according to serum levels where assay facilities exist.

In neonates the absorption of phenytoin following oral administration is unpredictable. Furthermore, the metabolism of phenytoin may be depressed. It is therefore especially important to monitor serum levels in the neonate, although alternative treatments may be more appropriate in this age group.

It is important to note that formulations of phenytoin may contain either the base or the salt form (phenytoin sodium). Although 100mg of phenytoin sodium is equivalent to 92mg of phenytoin on a molecular weight basis, these molecular equivalents are not necessarily biologically equivalent. Physicians should therefore exercise care in those situations where it is necessary to change the dosage form and serum level monitoring is advised.

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

Pharmacology

The mechanism by which phenytoin exerts its anticonvulsant action has not been fully elucidated however, possible contributory effects include:

1. Non-synaptic effects to reduce sodium conductance, enhance active sodium extrusion, block repetitive firing and reduce post-tetanic potentiation
2. Post-synaptic action to enhance gaba-mediated inhibition and reduce excitatory synaptic transmission
3. Pre-synaptic actions to reduce calcium entry and block release of neurotransmitter.

Efficacy

An extensive literature search has identified several systematic reviews (14,15,16) which suggest that phenytoin shows comparable efficacy to valproate, carbamazepine and phenobarbitone when used as monotherapy for partial onset and generalized onset tonic-clonic seizures. However when phenytoin was compared against phenobarbitone, phenobarbitone was more likely to be withdrawn, presumably due to adverse effects. A more recent systematic review comparing the newer anti-convulsant, oxcarbazepine with phenytoin in epilepsy(17) found that for patients with partial onset seizures, oxcarbazepine was significantly less likely to be withdrawn. However the data were insufficient to allow a comparison of efficacy of the two drugs in seizure control.

In 2001 The Cochrane Collaboration published a systematic review comparing phenytoin with valproate monotherapy for partial onset seizures and generalised onset tonic-clonic seizures (14). Randomised or quasi randomised controlled trials (double blind, single blind or unblended), which included a comparison of phenytoin monotherapy with

valproate monotherapy in children or adults were selected for inclusion in the review. The outcome measures considered were:

- Time to withdrawal of allocated treatment
- 12 month remission
- 6 month remission
- First seizure post-randomisation

Data from 669 subjects from five trials, (representing 60% of the participants recruited into the 11 trials that met the inclusion criteria) was included. The results were analysed and expressed as hazard ratios (HR) and 95% confidence intervals. (A hazard ratio greater than 1 suggests that an event is more likely on phenytoin.) The results suggest a clinical advantage for phenytoin for both remission outcomes, and a clinical advantage for valproate for the outcomes of time to withdrawal and time to first seizure, but do not suggest any overall statistically significant difference between the drugs for any of the outcomes. However the confidence intervals are too wide to confirm equivalence. The authors conclude that if future studies are to detect whether particular antiepileptic drugs are to be preferred for certain epilepsy syndromes they will need to be designed and powered accordingly.

Three of the studies included in the above review were exclusively conducted in children between 3 and 16years of age. Forsythe et al (18) assessed cognitive impairment in new cases of epilepsy randomly assigned to carbamazepine, phenytoin and sodium valproate. Thilothammal (19) undertook a comparison of phenobarbitone, phenytoin with sodium valproate in a randomized double blind study in children aged 4-12 years reporting on the proportion of participants with recurrence of seizures and the adverse effect profile. However neither study reported on the outcomes chosen for the above review. A long term, prospective randomized trial (20) compared the efficacy and tolerability of phenobarbitone, phenytoin, carbamazepine and sodium valproate in 167 children aged 3-16 years of age, with at least two previously untreated tonic-clonic or partial seizures. Details of this study are included in the submission on carbamazepine, but the results showed no significant differences in efficacy between phenobarbitone, phenytoin, carbamazepine and sodium valproate. However 9% of children on phenytoin discontinued treatment due to adverse effects/intolerance.

A second systematic review undertaken by the Cochrane collaboration (15) compared carbamazepine and phenytoin when used as monotherapy in people with partial onset seizures or generalized onset tonic-clonic seizures with or without other generalized seizure types. Randomised or quasi-randomised parallel group monotherapy trials (double-blind, single-blind or unblinded) were included in the review. The outcome measures considered were:

- Time to withdrawal of the allocated treatment (primary outcome – reflecting tolerability and efficacy)
- Time to achieve 12 months remission (seizure free period)
- Time to achieve 6 months remission
- Time to first seizure post-randomisation

Data from 551 participants from three trials (61% of individuals from all identified eligible trials) was available. No clear advantage for either drug was identified for any of the

defined outcome measures. Two of the studies included in the review were exclusively conducted in children (18,20); details of both studies have been described above.

A further Cochrane Collaboration systematic review of phenobarbitone versus phenytoin monotherapy for partial onset seizures and generalized onset tonic-clonic seizures was undertaken in 2003(16). Randomised or quasi-randomised monotherapy studies comparing phenobarbitone and phenytoin (double, single or unblended) were included in the review. The following outcome measures were assessed:

- Time on allocated treatment
- Time to achieve 12 month seizure free period
- Time to first seizure post-randomisation

Data on 65% of the subjects from four of ten eligible studies was available. Withdrawal information was available for 499 individuals in three trials supplying individual patient data (IPD). Phenobarbitone was significantly more likely to be withdrawn than phenytoin with an estimated hazard ratio of 1.62 (CI 1.22-2.14). The fact that a clear advantage for phenytoin was not seen for the seizure outcomes reported would imply that treatment was withdrawn primarily because of adverse effects. It is interesting to note that the two trials with the higher withdrawal rates for phenobarbitone compared to phenytoin were undertaken in the UK and were unblended, whereas the trial with the lower withdrawal rate for phenobarbitone was double blinded and undertaken in the USA. This suggests that clinicians are biased to expect adverse effects from phenobarbitone and might be more likely to withdraw patients from this drug in an unblinded trial.

Time to 12 month remission data was available for 555 individuals. The hazard ratio favoured phenytoin, but without demonstrating statistical significance. Data for Time to first seizure were available for 592 individuals; the hazard ratio favoured phenobarbitone, but without statistical significance. The authors concluded that the results of this review do not provide evidence on which a choice can be made between phenytoin and phenobarbitone with respect to seizure control. Phenytoin is significantly less likely to be withdrawn however, presumably based on adverse effects, making it the preferred choice of the two drugs compared in this review.

Newer anti-epileptic drugs are now available in Europe and the USA. A Cochrane systematic review in 2006 compared oxcarbazepine (similar chemical properties to its parent compound carbamazepine) and phenytoin when used as monotherapy in patients with epilepsy (17). Randomised controlled trials (double-blind, single blind or unblended) comparing oxcarbazepine or phenytoin as monotherapy were included in the review. The following outcome measures were assessed:

- Time on allocated treatment
- Time to achieve 6,12 and 24 month seizure free period
- Time to first seizure post-randomisation
- Quality of life measures if available.

A total of two trials (recruiting 480 patients) were identified as eligible for inclusion in the review. One trial recruited children and adolescents only (21). The overall pooled hazard ratio suggest a clinical advantage of oxcarbazepine over phenytoin when assessing time to withdrawal of allocated treatment. Results stratified for epilepsy type indicated a clinically important advantage for oxcarbazepine in partial onset seizures. No clear

clinical advantage of either drug was identified for the time to achieve 6 month remission, Time to achieve 12 month remission outcomes or time to first seizure post-randomisation; there were insufficient data to calculate Time to achieve 24 month remission. The authors conclude that oxcarbazepine should be considered as first line treatment for partial seizures in preference to phenytoin, however more evidence is needed regarding the comparative effects of oxcarbazepine and carbamazepine, which is recommended for partial seizures in current UK guidelines.

A meta analysis of controlled trials assessing "Antiepileptogenesis and seizure prevention trials with antiepileptic drugs" included 47 studies with a total of 8,218 patients (22). Phenytoin produced a significant decrease in seizures postcraniotomy when compared with carbamazepine, and in post-traumatic brain injury seizures compared to phenobarbitone.

Therapeutic Drug Monitoring

Phenytoin is highly protein bound and extensively metabolised by the liver. Reduced dosage to prevent accumulation and toxicity may therefore be required in patients with impaired liver function. Where protein binding is reduced, as in uraemia, total serum phenytoin levels will be reduced accordingly. However, the pharmacologically active free drug concentration is unlikely to be altered and total phenytoin levels in plasma can be misleading indicators of clinical efficacy. The clinically effective total phenytoin serum level is usually 10-20mg/l (40-80 micromoles/l) (8)

Tandon et al (23) have proposed an approach for correcting phenytoin levels based on total phenyotin levels and serum albumin. They assessed their method in 50 patients in India and found that the corrected phenytoin levels were better indicators of clinical outcome than the total levels. They concluded that in patients with serum albumin levels in the hyper- and hypo-albuminaemic ranges, corrected phenytoin levels were better indicators of clinical outcome. In developing countries where estimation of free drug levels is expensive and suitable equipment is not available in most centres, serum albumin adjusted levels can be used to predict response and assist in clinical decision making.

11. Summary of comparative evidence on safety

Adverse effects

Adverse effects can be one reason for discontinuing treatment or transferring to alternative anti-epileptic drug therapy. Some adverse effects are dose-related and may be managed by careful dose titration in response to tolerance and symptom control. Detailed information regarding the adverse effects of phenytoin can be obtained from the manufacturers Summary of Product Characteristics (8).

The following adverse reactions have been commonly reported:

CNS: Nystagmus, ataxia, slurred speech, decreased co-ordination, mental confusion, paraesthesia, drowsiness and vertigo.

Gastrointestinal disturbances: Nausea, vomiting and constipation.

Dermatological: Dermatological manifestations sometimes accompanied by fever have included scarlatiniform or morbilliform rashes. A morbilliform rash is the most common; dermatitis is seen more rarely. Other more serious and rare forms have included bullous, exfoliative or purpuric dermatitis, lupus erythematosus, Stevens-Johnson syndrome and toxic epidermal necrolysis

Phenytoin should be discontinued if a skin rash appears. If the rash is exfoliative, purpuric, or bullous or if lupus erythematosus or Stevens-Johnson syndrome or toxic epidermal necrolysis is suspected, use of the drug should not be resumed. If the rash is of a milder type (measles-like or scarlatiniform), therapy may be resumed after the rash has completely disappeared. If the rash recurs upon reinstitution of therapy, further phenytoin medication is contra-indicated.

Connective Tissue: Coarsening of the facial features, enlargement of the lips, gingival hyperplasia, hirsutism, hypertrichosis.

Blood dyscrasias: Haemopoietic complications, some fatal, have occasionally been reported in association with administration of phenytoin. These have included thrombocytopenia, leucopenia, granulocytopenia, agranulocytosis, pancytopenia with or without bone marrow suppression, and aplastic anaemia. While macrocytosis and megaloblastic anaemia have occurred, these conditions usually respond to folic acid therapy.
Frequent blood counts should be carried out during treatment with phenytoin.

Hypersensitivity reactions: Hypersensitivity syndrome has been reported and may in rare cases be fatal (the syndrome may include, but is not limited to, symptoms such as arthralgias, eosinophilia, fever, liver dysfunction, lymphadenopathy or rash), Several individual case reports have suggested that there may be an increased, although still rare, incidence of hypersensitivity reactions, including skin rash and hepatotoxicity, in black patients.

Endocrine system: Phenytoin therapy may interfere with Vitamin D metabolism. In the absence of an adequate dietary intake of Vitamin D or exposure to sunlight, osteomalacia, hypocalcaemia or rickets may develop. Phenytoin may cause a slight decrease in serum levels of total and free thyroxine, possibly as a result of enhanced peripheral metabolism. These changes do not lead to clinical hypothyroidism and do not affect the levels of circulating TSH. Phenytoin may cause raised serum levels of glucose, alkaline phosphatase, and gamma glutamyl transpeptidase and lowered serum levels of calcium and folic acid. It is recommended that serum folate concentrations be measured at least once every 6 months, and folic acid supplements given if necessary. Phenytoin may affect blood sugar metabolism tests.

Drug interactions [8]

1. Drugs which may increase phenytoin serum levels include:

Amiodarone, antifungal agents (such as, but not limited to, amphotericin B, fluconazole, ketoconazole, miconazole and itraconazole), chloramphenicol, chlordiazepoxide, diazepam, dicoumarol, diltiazem, disulfiram, fluoxetine, H2-antagonists, halothane, isoniazid, methylphenidate, nifedipine, omeprazole, oestrogens, phenothiazines,

phenylbutazone, salicylates, succinimides, sulphonamides, tolbutamide, trazodone and viloxazine.

2. Drugs which may decrease phenytoin serum levels include:

Folic acid, reserpine, rifampicin, sucralfate, theophylline and vigabatrin.
Serum levels of phenytoin can be reduced by concomitant use of the herbal preparations containing St John's wort (*Hypericum perforatum*).

3. Drugs which may either increase or decrease phenytoin serum levels include:

Carbamazepine, phenobarbital, valproic acid, sodium valproate, antineoplastic agents, certain antacids and ciprofloxacin. Similarly, the effect of phenytoin on carbamazepine, phenobarbital, valproic acid and sodium valproate serum levels is unpredictable.
Acute alcohol intake may increase phenytoin serum levels while chronic alcoholism may decrease serum levels.

4. Although not a true pharmacokinetic interaction, tricyclic antidepressants and phenothiazines may precipitate seizures in susceptible patients and phenytoin dosage may need to be adjusted.

5. Drugs whose effect is impaired by phenytoin include:

Antifungal agents, antineoplastic agents, calcium channel blockers, clozapine, corticosteroids, ciclosporin, dicoumarol, digitoxin, doxycycline, furosemide, lamotrigine, methadone, neuromuscular blockers, oestrogens, oral contraceptives, paroxetine, quinidine, rifampicin, theophylline and vitamin D.

6. Drugs whose effect is altered by phenytoin include:

Warfarin. The effect of phenytoin on warfarin is variable and prothrombin times should be determined when these agents are combined.
Serum level determinations are especially helpful when possible drug interactions are suspected.

13. Licensed Status

Oral phenytoin is licensed in the UK for control of tonic-clonic seizures (grand mal epilepsy), partial seizures (focal including temporal lobe) or a combination of these, and the prevention and treatment of seizures occurring during or following neurosurgery and/or severe head injury.

Parenteral phenytoin is indicated for the control of status epilepticus of the tonic-clonic (grand mal) type and prevention and treatment of seizures occurring during or following neurosurgery and/or severe head injury.

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

Monographs for phenytoin and phenytoin sodium are included in the European Pharmacopoeia 2004. Monographs for individual formulations (capsules, injection, oral suspension and tablets) are included in the British Pharmacopoeia 2007.

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

Use in Pregnancy

Anticonvulsants including phenytoin may produce congenital abnormalities in the offspring of a small number of epileptic patients. Phenytoin should only be used during pregnancy, especially early pregnancy, if in the judgement of the physician the potential benefits clearly outweigh the risk.

In addition to the reports of increased incidence of congenital malformations, such as cleft lip/palate and heart malformations in children of women receiving phenytoin and other antiepileptic drugs, there have more recently been reports of a foetal hydantoin syndrome. This consists of prenatal growth deficiency, micro-encephaly and mental deficiency in children born to mothers who have received phenytoin, barbiturates, alcohol, or trimethadione. However, these features are all interrelated and are frequently associated with intrauterine growth retardation from other causes (8).

Neonatal coagulation defects have been reported within the first 24 hours in babies born to epileptic mothers receiving phenytoin. Vitamin K1 has been shown to prevent or correct this defect and may be given to the mother before delivery and to the neonate after birth (8).

Use in Lactation

Infant breast-feeding is not recommended for women taking phenytoin because phenytoin appears to be secreted in low concentrations in human milk(8).

References

(1) WHO – Epilepsy Facts

(2) Prodigy Guidance 2006

(3) www.e-epilepsy.org.uk. The incidence and prevalence of epilepsy. Institute of Neurology, UCH, London

(4) Cowan LD. The epidemiology of the epilepsies in children. Mental Retardation and Developmental Disabilities Res Reviews, 2002; 8: 171-181

(5) WHO Fact Sheet 165, February 2001. Epilepsy: aetiology, epidemiology and prognosis

(6) WHO-Epilepsy Atlas 2005

(7) Scott RA et al. The treatment of epilepsy in developing countries: where do we go from here? Bulletin of the WHO, 2001; 79(4): 344-351

(8) Epanutin: Summary of Product Characteristics. May 2005 Accessed 29/10/06 via the Electronic Medicines Compendium (www.medicines.org.uk).

(9) Drugdex (Micromedex)

(10) NICE Clinical Guideline 20: Epilepsy in Children and Adults. October 2004

(11) SIGN Guideline 81. Diagnosis and Management of epilepsies in children and young people. March 2005

(12) British National Formulary for Children (BNF-C) 51: September 2006
(13) Medicines for Children 2nd edition, 2003. Publisher Royal college of Paediatrics and Child Health, UK.
(14) Tudor-Smith C et al. Phenytoin versus valproate monotherapy for partial onset seizures and generalized onset tonic clonic seizures. Cochrane database of Systematic Reviews 2001. Issue 4 Art No CD001769 DOI:10.1002/14651858.CD002769
(15) Tudor-Smith C et al Carbamazepine versus phenytoin monotherapy for epilepsy. Cochrane database of Systematic Reviews 2002, Issue 2 Art No CD001911 DOI:10.1002/14657858.CD001911.
(16) Taylor S et al. Phenobarbitone versus phenytoin monotherapy for partial onset seizures and generalized onset tonic-clonic seziures. Cochrane Database of Systematic Reviews 2003. issue 2 Art No CD002217 DOI:10,1002/14651858. CD002217
(17) Muller M et al Oxcarbazepine versus phenytoin monotherapy for epilepsy. Cochrane Database of Systematic reviews 2006 Issue 2. Art No CD003615 DOI 10.1002/14651858. CD003615. pub2
(18) Forsythe I et al. Cognitive improvement in new cases of epilepsy randomly assigned to carbamazepine, phenytoin and sodium valproate. Developmental Medicine and Child Neurology 1991:33;524-34
(19) Thilothammel et al. Comparison of phenobarbitone, phenytoin with sodium valproate randomized double blind study. Indian Paediatrics 1996 33;549-55
(20) de Silva M et al. Randomised comparative monotherapy trial of phenobarbitone, phenytoin, carbamazepine or sodium valproate for newly diagnosed childhood epilepsy. The Lancet 1996; 347:709-13
(21) Guerreiro M et al. A double-blind controlled clinical trial of oxcarbazepine versus phenytoin in children and adolescents with epilepsy. Epilepsy Research 1997; 27(2):205-13
(22) Tenkin NR. Antiepileptogenesis and seizure prevention trials with antiepileptic drugs:meta-analysis of controlled trials. Epilepsia 2001;42(4):515-524
(23) Tandon M et al. serum albumin-adjusted phenytoin levels: an approach for predicting drug efficacy in patients with epilepsy, suitable for developing countries. International Journal of Clinical Pharmacology and Therapeutics. October