A Comparative Review of the Adverse Effects of Anticonvulsants in Children with Epilepsy

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Summary

Phenobarbital (phenobarbitone) and phenytoin are the most useful anticonvulsants in neonates because adverse effects are most readily reversed when these drugs are used.

Most anticonvulsants are very rarely associated with haematological adverse effects. Platelet function is particularly vulnerable to valproic acid (sodium valproate) therapy.

Barbiturates and phenytoin can precipitate metabolic bone disease. Although very infrequent, lymphadenopathy is most common with phenytoin, and lupus-like illnesses with ethosuximide. Valproic acid may precipitate underlying metabolic disorders. Nephrolithiasis can occur with topiramate.

Liver disease is most likely with felbamate or valproic acid, but can occur with other anticonvulsants. Valproic acid and ethosuximide are the main precipitants of gastrointestinal symptomatology; while valproic acid and vigabatrin are frequently associated with excessive bodyweight gain.

Rash is most likely to occur with barbiturates, but there is a high risk of this adverse effect if large doses of lamotrigine are given with valproic acid. Adverse
cosmetic effects are most likely with phenytoin, but valproic acid may cause alopecia.

All anticonvulsants may cause unwanted neurological effects: when they occur, diplopia is usually precipitated by carbamazepine; tremor by valproic acid; and other motor disturbances are probably most common with phenytoin. Most anticonvulsants can cause drowsiness. Phenobarbital leads anticonvulsants as a cause of behavioural difficulties. Effects of anticonvulsants on cognitive function are difficult to assess, but subtle changes have been reported for all anticonvulsants in use up to the 1980s. Compared with other anticonvulsant drugs, phenytoin and felbamate are more often discontinued as a result of unwanted effects.

A comparative study of the adverse effects of anticonvulsants, used in childhood epilepsies, poses some difficulties. In well conducted, closely-monitored trials, all adverse events outside totally normal health are recorded, so that common childhood symptomatologies tend to be noted as adverse events. In the absence of a placebo group – regrettably, the usual state of affairs when a trial of a new anticonvulsant is being conducted in children – the background incidence of such adverse events is not identified, and their significance in relation to the anticonvulsant is difficult to assess.

Many children who are exposed to anticonvulsants are too young or developmentally delayed to make specific complaints in respect of effects that they find uncomfortable or irritating. Some parameters of health, such as liver function tests (especially alkaline phosphatase), may be less stable in childhood than in adults, leading to difficulties in interpretation of the significance of any change in liver function values.

Behavioural difficulties seen in children treated with anticonvulsants can be either be primary, or secondary to feelings of dizziness, headache, or general debility etc, or abdominal discomfort, which cannot be clearly defined. In children, and particularly in infants, the brain is a rapidly developing organ. Tests of cognitive ability, which may be appropriate at an early age, are unlikely to be suitable for older children, so it is often not possible to extrapolate from one series of assessments to another.

When serious adverse events occur, it is usual for these to appear as single or multiple case reports, and the actual incidence of such episodes is difficult to estimate. Nevertheless, it can be inferred that, if such serious events present in association with a much used anticonvulsant, and are considered worthy of publication, they must be very rare.

In an attempt to draw some conclusions about the relative risks of the various anticonvulsants in common use, and those that have been recently introduced, adverse effects are discussed according to the organ system involved. A statement about the relative risks of abnormalities in the organ system under review is given at the end of each section.

For the purposes of this review, only those adverse effects that occur at conventional (rather than toxic) dosages will be considered – i.e. those events that occur during ‘optimal’ management.

1. Basic Mechanisms of Action of Anticonvulsants

The 3 main possible mechanisms of action of anticonvulsants that have been identified are:

- an increase in \( \gamma \)-aminobutyric acid (GABA)-ergic inhibition at the GABAA receptor complex;
- blockade of sodium channels in their inactivated form leading to ‘use-dependent’ suppression of receptive discharges;
- inhibition of calcium T channels.

Phenobarbital (phenobarbitone), benzodiazepines, vigabatrin and tiagabine work primarily through GABA-related mechanisms. Primidone, by virtue of its breakdown to phenobarbital (as well as phenylethylmalondiamide) must also work via GABA inhibition. There is some evidence that bromides and topiramate also have GABA-related