Community Clinics in Clinical Pharmacology

Epilepsy

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Problem

A boy, aged 17, began to have major epileptic seizures when he was 7 and has taken phenytoin ever since. He has never been completely free from seizures for more than a few months at a time, and during the past two months has been having at least one attack every week. As adding primidone produced only temporary improvement it was stopped. Increasing the dose of phenytoin to 400 mg a day and adding clonazepam have also produced no benefit. Would any other drugs be worth trying?

Advice

I saw the boy earlier this week and can add nothing relevant to Dr Smith's history. The patient seems to be under no particular psychological stress, and there are no other obvious factors that could possibly have led to a recent increase in seizure incidence. Examination showed minimal hypertrophy of the gums but no abnormal neurological signs—in particular, he had neither nystagmus nor ataxia.

Phenytoin is now generally regarded as the anticonvulsant of first choice in treating tonic-clonic epilepsy. Patients may fail to respond, however, for one of two reasons—either because they have an inadequate concentration of drug in their plasma (and thus their brain), or because they have a form of epilepsy that is only partly controllable by phenytoin—even when the plasma concentration is in the "therapeutic range."

We measured his phenytoin concentration in a blood sample I took when I saw him, and the result was 28 $\mu\text{mol/l}$ (7 mg/l). Although for some epileptics this would prevent seizures, the best therapeutic results are obtained at concentrations in the range 40–80 $\mu\text{mol/l}$ (10–20 mg/l). There are two possible reasons

why his plasma phenytoin concentrations are low in relation to the dose he is taking: he may not be taking the prescribed dose (and poor compliance is very common among epileptics); alternatively, he may be metabolising the drug very rapidly in his liver. In fact his mother told me that she personally supervises all his treatment and so I think that poor compliance is unlikely. I think therefore that, as a first step, you should increase his phenytoin dose so as to achieve a "therapeutic" concentration in his plasma.

Choosing the right dose of phenytoin is not easy because the liver's capacity to metabolise the drug is limited: as larger doses are given saturation point is reached, and very small additional increments in dosage will then lead to disproportionate increases in plasma concentration. Severe toxicity may easily result from injudicious increases in phenytoin dosage. Nevertheless, by making certain assumptions, it is possible, using a formula (or nomogram) to estimate to the nearest 50 mg the dose required, to bring the plasma concentration into the "therapeutic range." Then, having changed the dose and achieved a new steady state (which will take seven to ten days), you can remeasure the plasma concentration and make finer adjustments—if necessary using 25 mg capsules (which are now commercially available). I have estimated that for this patient a dose of 500 mg a day should raise his plasma concentration to about 60 $\mu\text{mol/l}$ (15 mg/l), and this could be taken either in two divided doses or as a single daily dose.

Although most epileptic patients become free of fits at "therapeutic" plasma concentrations, some do not. Such patients will need additional anticonvulsant treatment—phenobarbitone, carbamazepine, clonazepam, or sodium valproate—but which of these is best is uncertain. If this boy falls into this category I would suggest gradually increasing his dose of clonazepam up to 12 mg a day. Phenobarbitone, of course, has already been tried—it is the major active metabolite of primidone.

Postscript

Taking phenytoin, 500 mg daily, the boy's plasma concentration rose to 68 $\mu\text{mol/l}$ (17 mg/l) but, despite this, his seizures continued. Tragically, before treatment could be changed again he was found one morning dead in his bed. Necropsy showed signs of suffocation, and it was presumed that he had had a further major seizure and been smothered by his pillow.

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