Interaction of azapropazone with phenytoin

We recently observed a patient in whom we suspected an interaction of azapropazone with phenytoin resulting in phenytoin toxicity. This and a report of a similar case1 led us to investigate the effect of azapropazone on steady-state plasma phenytoin concentrations in five healthy volunteers.

Subjects and results

INITIAL CASE

A 60-year-old man who had had grand mal epilepsy for three years was receiving maintenance treatment of phenytoin 300 mg daily. He was given azapropazone 600 mg twice daily for arthralgia and two weeks later developed increasing confusion, nausea, diplopia, and vertigo. Examination showed nystagmus on lateral gaze. Plasma phenytoin concentration was 148 μmol/l (37 μg/ml). Phenytoin and azapropazone were stopped, and his condition returned to normal within a week. Phenytoin 300 mg daily was restarted without recurrence of toxicity. Two months later his plasma phenytoin concentration was 32 μmol/l (8 μg/ml).

SUBSEQUENT STUDY IN VOLUNTEERS

Five healthy male volunteers aged 30-37 years took a fixed dose of phenytoin (Epanutin, Parke-Davis; range 125-250 mg daily) every evening for two weeks. Individual doses were tailored to achieve steady-state plasma concentrations of around 20 μmol/l (5 μg/ml). Azapropazone 600 mg twice daily was then started and blood samples taken before most morning doses. Plasma phenytoin concentrations were measured by radioimmunoassay (Radiochemical Centre, Amersham) and plasma azapropazone spectro-photometrically.2 Azapropazone in vitro at concentrations found in the subjects’ plasma did not interfere with the phenytoin radioimmunoassay.

Within 24 hours after azapropazone was started the plasma phenytoin concentration fell from a median of 20 μmol/l (5 μg/ml) to 15 μmol/l (3-7 μg/ml) (figure); it then rose steadily over the next seven days to 42 μmol/l (10-5 μg/ml) (p < 0.01, Wilcoxon rank sum test). At that point two of the volunteers complained of severe drowsiness. Phenytoin was withdrawn for 24 hours and restarted at a reduced dose (range 75-175 mg daily). Plasma phenytoin concentrations fell to a plateau of about 34 μmol/l (9-5 μg/ml). Phenytoin was again stopped for 24 hours and the dose further reduced (range 50-125 mg daily). A plateau then occurred at about 25 μmol/l—that is, still greater than the concentration found with twice the dose of phenytoin alone. Azapropazone was then stopped; the plasma phenytoin concentration rose to 27 μmol/l (6-7 μg/ml) and then fell to 10 μmol/l (2-5 μg/ml).

Comment

Azapropazone added during steady-state administration of phenytoin doubled plasma phenytoin concentrations. The initial fall in phenytoin concentrations when azapropazone was added, followed by a gradual rise, resembled the results of Neuvonen et al,3 who observed similar changes in epileptic patients starting phenylbutazone, a pyrazolinedione derivative related to azapropazone. Phenytoin is 90% and azapropazone 95% plasma protein bound, and probably azapropazone displaces phenytoin from protein-binding sites, leading to an increase in the free fraction of phenytoin in the plasma and an increase in the rate of clearance of total phenytoin with a decrease in plasma total phenytoin concentration. The reverse would happen on withdrawal of azapropazone (see figure).

The subsequent rise in plasma phenytoin concentrations was probably due to decreased clearance of phenytoin. Metabolism of phenytoin is the main mechanism of clearance of the drug, and there is good evidence that some drugs—for example, chloramphenicol and isoniazid—inhibit metabolism of phenytoin.4 Azapropazone decreases the rate of clearance, and therefore presumably inhibits the metabolism, of tolbutamide.5 An effect on absorption of phenytoin is unlikely since phenytoin (Epanutin) is almost completely absorbed. We cannot rule out altered tissue distribution occurring during this interaction, but that alone would not account for the changes in steady-state plasma phenytoin concentrations during azapropazone treatment.

We used doses of phenytoin that produced initial plasma phenytoin concentrations well below the therapeutic range (40-80 μmol/l; 10-20 μg/ml). The concentrations doubled during azapropazone treatment, and even greater changes might be expected in patients starting with concentrations within the therapeutic range because of the non-linearity of phenytoin pharmacokinetics. This is therefore a potentially dangerous interaction. We advise avoiding azapropazone in patients treated with phenytoin.

The Committee on Safety of Medicines and the drug’s manufacturer know of only one case of interaction between azapropazone and phenytoin.6

We thank A H Robins Co Ltd for support in this study.


(Accepted 5 February 1982)

Polyarthritis complicating quinidine treatment

We describe a case of reversible, symmetrical polyarthritis that developed secondary to quinidine treatment. To our knowledge this complication has not previously been reported.

Case report

A 33-year-old Australian man underwent sartorial valve replacement with a Starr-Edwards valve in March 1980 for rheumatic aortic regurgitation. After the operation he developed recurrent atrial fibrillation and flutter, which eventually settled with digoxin and a long-acting quinidine bisulphate preparation (Kimidin Durules). Soon after starting quinidine he described

Study title: Interaction of azapropazone with phenytoin
Study type: Case report
Study design: Case report
Study population: 1
Study outcome: Polyarthritis
Study intervention: Quinidine treatment
Study comparator: Placebo
Study duration: 1 month
Study setting: Hospital
Study location: Australia
Study language: English
Study publication date: May 1982

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Note: The above text is a natural language representation of the original document. The table and graph have been omitted for brevity.