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 case[1] led us to investigate the effect of azapropazone on steady-state plasma phenytoin concentrations in five healthy volunteers.

Subjects and results

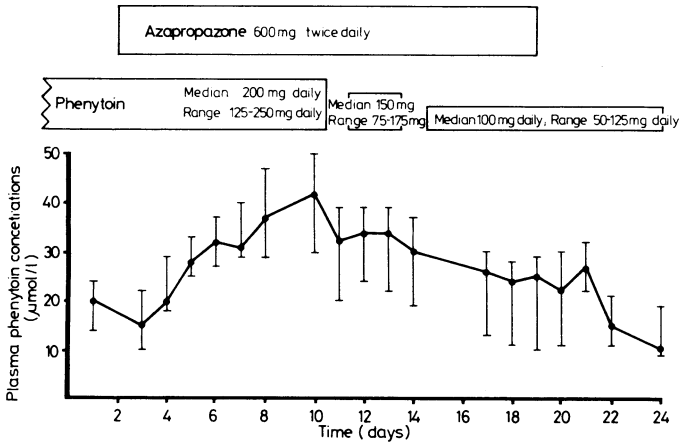
INITIAL CASE

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 spectrophotometrically.[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 Phenytoin was withdrawn for 24 hours and restarted at a reduced dose (range 75-175 mg daily).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 (8·5 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).



Median and range of plasma phenytoin concentrations in five volunteers before, during, and after azapropazone.

Conversion: SI to traditional units—Phenytoin: 1 μmol/l ≈ 0·25 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 pyrazolidine 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.[1]

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

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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 aortic valve replacement with a St Jude medical 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 (Kinidin Durules). Soon after starting quinidine he described

unusual numbness and weakness in his fingers in the absence of objective clinical signs. This resolved on withdrawal of the drug. Atrial flutter recurred in December 1980, in association with a respiratory tract infection; at this time he was taking only warfarin and digoxin. Reversion to sinus rhythm was achieved with the addition of quinidine, and once again he noticed pain and weakness in his fingers and wrists occurring within four days of starting the drug and resolving within a week of its withdrawal.

With his informed consent he was formally rechallenged with quinidine to assess the response. He was given Kinidin Durules, two tablets twice a day, and his dose of digoxin was reduced from 0·25 mg to 0·125 mg daily. Within 24 hours he noticed a gradual onset of arthralgia in both hands, peaking five days after the start of quinidine. Quinidine was stopped two days later, and the symptoms settled over 48 hours. Symptoms consisted of mild pain but appreciable stiffness and weakness with slight swelling affecting in a symmetrical fashion the metacarpophalangeal joints, carpal, and wrist joints. He experienced difficulty in writing and with fine motor function of the hands. He also had mild aches and pains in both ankle and knee joints without limitation of movement. On examination at the peak of symptoms there was evidence of mild inflammation mainly affecting the metacarpophalangeal joints of both hands and also the proximal interphalangeal joints, with slight swelling over the dorsum of the hands. Moderate tenderness was noted over these joints, but there was no reddening and passive movements were limited only slightly. There was no associated rash and no other systemic disturbance. Grip strengths in both hands were measured using a dynamometer and showed an average 33% reduction in power after challenge with the drug.

The following variables were assessed before quinidine was given: full blood examination, platelet count, rheumatoid factor, complement concentrations, erythrocyte sedimentation rate, antinuclear factor, microurine examination, serum electrolyte concentrations and renal function, and immune complexes. All these variables were assessed again on the last day of rechallenge with quinidine, and there was no appreciable alteration in any of the values. Serum quinidine concentration was measured at the peak of symptoms and was in the lower bracket of the therapeutic range.

Comment

The temporal relation of the polyarthritis to administration of quinidine was documented on three separate occasions, and there seems little doubt that a cause and effect relation existed. We were, however, unable to document any possible mechanism for the arthritis; in particular there were no abnormalities in immunological variables.

The Australian Drug Evaluation Committee and the manufacturers of the drug have not received any previous reports of this reaction to quinidine.

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Severe deafness in systemic lupus erythematosus: its immediate relief by plasma exchange

Plasma exchange was introduced for systemic lupus erythematosus in 1974[1] and, in some cases, has had a dramatic effect in relieving symptoms. It has not yet, however, established a place in the routine management of the disease. We report here a case in which its effect was more dramatic than most.

Case report

A 47-year-old auxilliary nurse presented in June 1977 with a six-week history of a photosensitive rash on her face and upper chest. She also complained of malaise, sore throat, and joint and muscle pains, but the main cause of her distress was bilateral deafness, which had started abruptly that day. On examination she had facial erythema of a typical lupoid distribution. There was tenderness over the muscles of her upper arms and in the small joints of the hands. Her temperature was 37·5°C and her pulse 88/min; her blood pressure was 130/90 mm Hg. There was no hepatosplenomegaly. Aural examination showed unobstructed ear canals and healthy intact tympanic membranes. The deafness was bilateral, of equal severity, and entirely sensorineural. Although tests of loudness function could not be carried out, clinical features—such as a feeling of fullness in the ears and a distortion of loud sounds—suggested that the lesion was situated in the cochlea.

Investigations showed haemoglobin concentration 12·8 g/dl, white cell count $3{\cdot}4\times10^9$/l, neutrophils 64%, lymphocytes 26%, monocytes 8%, eosinophils 2%, and platelets 154×10^9/l. There was proteinurea with a 24-hour excretion of 0·3 g. Plasma urea was 7 mmol/l (42 mg/100 ml) (normal range 2·5-6·7) and electrolyte concentrations were normal. Lupus erythematosus cells were present. Creatinine clearance was 61 ml/min. Liver function tests were normal. Antinuclear antibody was present at a concentration of 200 IU/ml. DNA binding was 42% (normal range <10%), serum C3 0·25 g/l (normal range 0·8-1·5 g/l), and C4 0·06 g/l (normal range 0·25-0·45 g/l). Circulating immune complexes were detected by the C1q solid phase assay at 42·4 mg/l (normal range <10 mg/l). Skin biopsy from an unaffected area showed deposits of IgG and C3 at the dermolepidermal junction by direct immunofluorescence. Electroencephalography showed slow-wave disturbances over both hemispheres. Audiograms showed a 30-40 decibel sensorineural loss in both ears over a wide range of frequencies. Tympanograms and acoustic reflexes were normal.

In view of these findings a diagnosis of systemic lupus erythematosus was made and she was treated with prednisolone 40 mg daily. After two weeks there was some general improvement but her deafness remained. She was then treated by plasma exchange. Two litres of plasma were exchanged for 1·2 l plasma protein fraction and 1 l isotonic saline, using a Haemonetics Model 30 Celltrifuge. There was an immediate and complete restoration of her hearing. Her plasma was exchanged three more times in the next week and the dose of prednisolone was reduced to 5 mg daily. After this she was clinically well. Her DNA binding had fallen from 42% to 22% and her C1q binding from 42·4 mg/l to 24 mg/l.

Three months later her deafness returned. Her DNA binding at this time was 31% and her C1q binding 40·6 mg/l. She was again treated by plasma exchange, and this time an audiogram was performed immediately before and after the procedure. It showed complete restoration of her hearing. After three further plasma exchanges her DNA binding was 17% and her C1q binding 19·8 mg/l; she was very well. Over the past two years she has remained well for most of the time, but every three to six months her deafness returns. On each occasion it has been completely abolished by a single plasma exchange. She remains on prednisolone 5 mg daily.

Comment

Although neurological features occur in 60% of patients with systemic lupus erythematosus,[2] deafness is not an established characteristic of the disease. In our patient the deafness started abruptly even though she had had other features of the disease for several weeks. Audiological tests and clinical features suggested that the deafness was of the cochlea type. Plasma exchange is thought to work in systemic lupus erythematosus by clearing circulating immune complexes and thus removing blockade of the reticuloendothelial system.[3] The rapid and dramatic response to plasma exchange in our patient implies a vascular mechanism and suggests that circulating immune complexes cause sludging in the microcirculation of the stria vascularis in the scala media of the cochlea. The presence of immune complexes in the microcirculation may cause swelling of the endothelial cells and diminish the flow through the small vessels by reducing the size of the lumen. This leads to anoxia and a temporary change in the ionic composition of the endolymph. A cochlea-type deafness results which clears as the anoxia is reversed by the removal of the immune complexes. Vascular mechanisms causing anoxia in the stria vascularis but not involving immune complexes possibly account for the reversible deafness which is a feature of Menière's disease.

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