SIDE EFFECTS OF DRUGS

Dextropropoxyphene and jaundice

Though dextropropoxyphene is a widely used analgesic, only two previous cases of jaundice attributable to its use have been described.^{1 2} We report three further cases in patients who had not had liver disease or exposure to hepatitis and who did not abuse alcohol.

Case 1

In November 1976 a 54-year-old woman was given Napsalgesic (dextropropoxyphene napsylate 50 mg and aspirin BP 500 mg) in a dose of four to eight tablets daily for backache. Within a week she developed rigors, progressively darkening urine, clay coloured stools, pruritus, and, finally, jaundice. She was afebrile and deeply icteric, and abdominal examination showed nothing abnormal. Her haemoglobin was 15 g/dl and white cell count $7.8 \times 10^9/l$ with 52% neutrophils, 34% lymphocytes, 5% monocytes, and 9% eosinophils. The results of liver function tests are shown in the table. Hepatitis B surface antigen and smooth muscle and antimitochondrial antibody tests gave negative results. A glucose tolerance test showed that she was mildly diabetic, and a hypotonic duodenogram was normal. At laparotomy no abnormality of the liver, pancreas, or biliary tree was found and operative cholangiography was normal. A wedge liver biopsy showed intrahepatic cholestasis, the portal triads containing an excess of plasma cells, lymphocytes, and eosinophils. The patient recovered uneventfully.

Case 2

A 32-year-old woman was prescribed Depronal SA (dextropropoxyphene hydrochloride 150 mg) in September 1974 for recurrent low backache. Shortly after starting treatment she developed epigastric discomfort, nausea, dark urine, and pale stools. Her backache disappeared and after stopping the Depronal SA she became asymptomatic within a week. She kept the remaining tablets, and when her backache recurred four months later she took further tablets and similar symptoms reappeared. An oral cholecystogram was normal and after stopping the Depronal SA she became well. One month later her backache recurred and was relieved by Depronal SA but the next day nausea, epigastric discomfort, and dark urine recurred and she became icteric. The liver function values are recorded in the table. Depronal SA was stopped and a week later she was asymptomatic. She has remained well and has not taken further dextropropoxyphene-containing compounds.

Results of liver function tests. Normal range is given in parentheses

Case No	Weeks after onset of jaundice	Bilirubin ($\mu\text{mol/l}$) (3-14)	Aspartate aminotransferase (U/l) (9-43)	Alkaline phosphatase (U/l) (20-85)
1	0	147	43	230
	2	68	35	178
	6	12	15	103
2	0	88	703	159
	2	11	39	119
	6	6	12	51
3	0	170	39	250
	2	147	38	238
	6	19	29	82

Conversion: SI to traditional units—Bilirubin: $1 \mu\text{mol/l} \approx 0.06 \text{ mg/100 ml}$.

Case 3

A 45-year-old woman was prescribed Distalgesic (dextropropoxyphene hydrochloride 32.5 mg and paracetamol 325 mg) in November 1975 after developing pain in the neck following yoga classes. Ten days later she developed pruritus, dark urine, pale stools, and subsequently jaundice. She was icteric but clinical examination showed no other abnormalities. The differential white cell count was normal, and the hepatitis B surface antigen and smooth muscle and antimitochondrial antibody tests gave negative results. Liver function values are shown in the table. A barium meal and follow-through examination and liver and spleen scan showed nothing abnormal. At laparotomy the gall bladder, pancreas, and an operative cholangiogram were all normal. A wedge liver biopsy confirmed intrahepatic cholestasis. The Distalgesic was stopped and she has remained well since.

Comment

Dextropropoxyphene is a widely prescribed analgesic similar in structure to methadone. In 1970 there were 2.5 million EC 10 pre-

scriptions for compounds containing dextropropoxyphene (Distalgesic, Napsalgesic, Doloxene, Doloxylal, and Depronal SA).³ There have been about 30 reports to the Committee on Safety of Medicines of hepatic disturbances in association with dextropropoxyphene, though a causal relation cannot be inferred from these reports (personal communication). Jaundice ascribed to dextropropoxyphene has been described only twice.^{1 2}

It seems reasonable to attribute the liver damage in our patients to dextropropoxyphene. In each case the illness began within 10 days of starting the drug in therapeutic doses, investigation revealed no alternative cause, drug withdrawal was followed by recovery, and in one patient inadvertent re-exposure to the drug reproduced the illness. Two patients had also taken drugs other than dextropropoxyphene (aspirin and paracetamol in case 1 and aspirin and parenteral cyanocobalamin in case 3). The amount of salicylate and paracetamol, however, was unlikely to have caused liver damage,^{4 5} and the third patient has continued to take cyanocobalamin without ill effect. Dextropropoxyphene-induced liver damage seems to be an idiosyncratic reaction in view of its rarity and the absence of hepatotoxicity in dextropropoxyphene addiction or acute intoxication.¹

We thank Professor R H Girdwood for permission to report on a patient under his care (case 3).

¹ Klein, N C, and Magida, M G, *American Journal of Digestive Diseases*, 1971, **16**, 467.

² Daikos, G K, and Kosmidis, J C, *Journal of the American Medical Association*, 1975, **232**, 835.

³ *British Medical Journal*, 1977, **1**, 668.

⁴ Zimmerman, H J, *Annals of Internal Medicine*, 1974, **80**, 103.

⁵ Prescott, L F, et al, *Lancet*, 1976, **2**, 109.

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Eastern General Hospital, Edinburgh

M J FORD, MRCP, medical registrar

R J KELLETT, MRCP, consultant physician and senior lecturer

Western General Hospital, Edinburgh

A BUSUTTIL, MRCPATH, consultant pathologist

Department of Therapeutics, Royal Infirmary, Edinburgh

N D C FINLAYSON, PHD, MRCP, consultant physician and senior lecturer

Chloroquine toxicity due to long-term Elestol for osteoarthritis

Chloroquine is of proved value in rheumatoid arthritis¹ but there is little evidence to support its use in other articular disorders. Long-term use in rheumatoid arthritis is limited by its ocular toxicity, and most authorities recommend regular examination to exclude retinal damage.² Similarly, systemic steroids have a place in the treatment of the inflammatory arthritides but not in degenerative disease. Unfortunately some drug combinations contain toxic agents and may be prescribed for prolonged periods without the unwary realising the risks being run. One such agent is Elestol (Bayer), which contains chloroquine phosphate 40 mg, prednisone 750 μg , and aspirin 200 mg per tablet. We report a case in which this agent was used for at least 15 years without ophthalmic checks.

Case history

An 82-year-old man presented in July 1976 with two small basal-cell carcinomas on his face. Extensive blue-grey pigmentation was noted on the dorsum of the hands, the forearms, and the right shin. (His left leg had been amputated above the knee after an accident in 1936.) Examination of the joints showed large Heberden's nodes with some fixed flexion deformity of

the fingers, painful limitation of the hips, and bony swelling of the right knee. Radiographs of the joints showed widespread degenerative changes with no evidence of erosions. His latex test result was negative. Close questioning disclosed that he had been taking two Elestol tablets three times a day for at least 15 years for his hands. It also transpired that in 1972 he underwent an open prostatectomy without steroid cover. Ophthalmological examination was performed by Mr B Cobb and showed no retinopathy or loss of central visual acuity.

Comment

This man was ingesting 240 mg of chloroquine phosphate, 4.5 mg of prednisone, and 1.2 g of aspirin daily. He presented with chloroquine pigmentation of the skin, a well-known complication.³ He was most fortunate not to have suffered ocular damage and not to have had adrenal suppression problems at the time of his operation. Neither his general practitioner nor the surgeon seemed to be aware of the problems with this preparation.

Until recently Elestol was listed in the *Monthly Index of Medical Specialities (MIMS)* under the heading "Anti-inflammatory agents." Since the regrouping of headings in *MIMS* Elestol has been listed under "Corticosteroids and related drugs," and now the note "Ophthalmological examination necessary during prolonged admin" has been added. Nevertheless, the indications for the drug remain "rheumatoid arthritis, osteoarthritis, muscular rheumatism." There is also a note under the entry advising referral to the notes at the beginning of the section, and included in this note, underlined, is the advice to refer to individual product literature. There is, however, no entry for Elestol in the *Data Sheet Compendium*,⁴ the reason given being that the drug is not being "actively marketed."⁵

We feel that this agent is a particularly dangerous combination and that there is a strong case for its discontinuance.

¹ Popert, A J, *Rheumatology and Rehabilitation*, 1976, **15**, 235.

² Arden, G B, and Kolb, H, *British Medical Journal*, 1966, **1**, 270.

³ Rook, A, Wilkinson, D S, and Ebling, F J G, *Textbook of Dermatology*, 2nd edn. Oxford, Blackwell Scientific, 1972.

⁴ Association of British Pharmaceutical Industries, *Data Sheet Compendium*. London, 1976.

⁵ Allen, H B, personal communication.

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Lewisham Hospital, London SE13 6LH

A K CLARKE, MRCP, senior registrar in rheumatology and rehabilitation (present address: Royal National Hospital for Rheumatic Diseases, Upper Borough Walls, Bath)

R LL MEYRICK, FRCP, clinical assistant, skin unit

Severe cerebral confusion produced by prajmalium bitartrate

Patients usually tolerate prajmalium bitartrate (Neo-gilurhythm) well, and side effects, which include nausea, gastrointestinal disturbances, dizziness, bradycardia, and intraventricular disturbances, are not widespread. We describe here a patient who suffered cerebral confusion after taking prajmalium bitartrate. Such an effect has not been described before.

Case report

A 67-year-old White man had suffered from diabetes mellitus for 10 years, but he was well controlled on oral treatment. Eight years earlier he had suffered from a proved myocardial infarction. He had had no other illnesses and there was no personal or family history of drug allergy or cerebral disease. He was well until he was admitted to a different hospital with palpitations, and the electrocardiograph showed a supraventricular tachycardia at 150 beats/min.

He was given oral prajmalium bitartrate 100 mg daily in divided doses. Within 24 hours he developed signs of confusion, unrest, disorientation in time and place, and did not respond to simple commands or requests. The prajmalium bitartrate was discontinued and his arrhythmia controlled with quinidine sulphate. Within a few hours the signs of confusion disappeared completely and there was no residual neurological deficit.

He was readmitted four months later with a resistant ventricular tachycardia that responded only to direct-current electric shock, which was administered after intravenous lignocaine and procaineamide had failed to convert him. He subsequently responded well to ajmaline (Gilurhythm), given intravenously to control the residual ventricular ectopics, and was then given oral prajmalium bitartrate 100 mg in divided doses as maintenance treatment. Within 36 hours he again developed signs of confusion and disorientation in time and place. The drug was discontinued and ajmaline substituted intravenously. The confusion promptly disappeared but the ventricular arrhythmia recurred. Despite intensive treatment, during which the patient remained unconfused, the arrhythmia could not be suppressed, and he died some days later.

Comment

Confusional states have not been previously noted on oral prajmalium bitartrate treatment.¹ Our patient developed this condition on two separate occasions, during which time he received no other drug common to both periods or known to produce disorientation. Furthermore, his cerebral state improved immediately after discontinuing the drug, and it seems reasonable to accept that prajmalium bitartrate was the direct cause of the confusion. Routine blood tests including measurement of serum electrolytes, blood sugar, and blood gases were normal on both occasions. Despite the similarity in structure between prajmalium bitartrate and ajmaline, the latter did not produce cerebral changes when given intravenously, whereas prajmalium bitartrate was associated with these symptoms when given in an acceptable dose by mouth. This contrasts with the results of Weidner and Philipson,² who did not find any difference in the toxicity of the two drugs.

It would seem reasonable to consider alternative antiarrhythmic agents for use in patients who develop a confusional state when receiving prajmalium bitartrate.

¹ Weidner, A, personal communication.

² Weidner, A, and Philipson, G V, *Arzneimittel-Forschung*, 1971, **21**, 685.

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Municipal Government Medical Centre, Tel-Aviv, Israel

J B LESSING, MD, physician

I J COPPERMAN, MRCP, physician

Peripheral and autonomic neuropathy after treatment with perhexiline maleate

Perhexiline maleate is a useful drug in the prophylaxis of angina pectoris.¹ Nevertheless, its potential value may be limited by the occasional development of side effects, including peripheral neuropathy^{2 3} and myopathy.⁴ We describe the details of three patients who developed peripheral and autonomic neuropathy after treatment with this drug.

Case reports

Case 1—A 56-year-old man underwent aortocoronary saphenous vein graft to the right coronary artery in 1971 for relief of angina pectoris. Six months after operation his symptoms recurred due to occlusion of the graft. He gained no benefit from propranolol but his symptoms were partially relieved by perhexiline. In June 1976, having taken his drug for 10 months (200-400 mg/day), he presented with symptoms of numbness and pain in both legs, paraesthesiae in both hands, and postural dizziness. Examination confirmed sensory loss in "glove-and-stocking" distribution with weakness of all muscle groups in the legs. Systolic blood pressure was 100 mm Hg lying and 70 mm Hg erect. Motor nerve conduction velocity (MCV) was delayed in both arms and legs and the Valsalva ratio (VR)⁵ reduced (table). The drug was withdrawn and over the next two weeks his symptoms improved, with relief of pain and paraesthesiae and resolution of postural dizziness. There was associated improvement in postural hypotension and in MCV in the arms, but MCV in the legs and VR remained abnormal three weeks after stopping treatment. Withdrawal of perhexiline was associated with return of severe anginal symptoms at rest, again unrelieved by propranolol, so