SHORT REPORTS

Fatal cholestatic jaundice in elderly patients taking benoxaprofen

Benoxaprofen is a relatively new propionic acid derivative that is extensively prescribed for patients with arthritis. The most important adverse effect so far reported is a photosensitivity skin reaction. We report five cases of cholestatic jaundice with fatal outcome in elderly women taking this preparation.

Case reports

All patients were women over the age of 80 years and were treated with benoxaprofen 600 mg daily.

Case 1—An 86-year-old woman presented in January 1981 with a confusional state. She had a smooth firm liver palpable 6 cm below the costal margin, erythrocyte sedimentation rate of 75 mm in first hour, and a slightly raised alkaline phosphatase activity. She recovered spontaneously and was not seen until June 1981 when benoxaprofen was started for longstanding rheumatoid arthritis. Her final illness began in November 1981, when she developed progressive painless jaundice over two weeks. She deteriorated rapidly and died four days after admission to hospital with acute renal failure and rectal bleeding due to a coagulopathy (prothrombin time three times control value). Necropsy showed intrahepatic cholestatis and a mild inflammatory reaction in the portal triads. There was no evidence of extrahepatic bile duct obstruction or infective hepatitis. The kidneys showed tubular damage secondary to the hepatic dysfunction, with casts, blood, and bile thrombi.

Case 2—An 82-year-old woman had a two-year history of confusion and difficulty in walking. She had had several falls and benoxaprofen was started in June 1981 for back pain. In December 1981 she became anorectic and complained of vague abdominal pain. At the time of her admission to hospital in January 1982 she had jaundice and slight right hypochondrial tenderness. The jaundice deepened and she died of hepatorenal failure one week later. At necropsy the liver showed predominant centrilobular cholestasis with inspissated bile in the canaliculi. There was a mild chronic inflammatory infiltrate in the portal triads but no hepatitis. The kidneys were of normal size and showed acute tubular necrosis and the pancreas was acutely inflammed.

The presentation and course of the final illness were similar in cases 3, 4, and 5; the table gives clinical details. In case 3 necropsy showed intrahepatic cholestasis and acute tubular necrosis.

Comment

Although recently introduced, benoxaprofen is already the third most commonly prescribed non-steroidal anti-inflammatory drug in Northern Ireland and about 3000 patients are known to be taking the drug in a total population of 1·5 million (DHSS Northern Ireland Research and Intelligence: unpublished data on general practice prescribing collated by Department of Therapeutics and Pharmacology, Queen's University). The five patients described here and a sixth, who also died of renal failure but had no jaundice, represent all the patients treated in the past year with benoxaprofen by one of us (HMcAT). Benoxaprofen is said to have fewer gastrointestinal side effects than related drugs, possibly owing to its weak inhibition of prostaglandin synthetase activity.[1] A recent report, however, has suggested that these side effects may be more common in the elderly.[2] In a dose of 600 mg daily it has a much longer half life in very old patients (111 hours at mean age 82 years)[3] than in younger patients (29 hours at mean age 41 years).

The pathological findings in the three cases that came to necropsy were remarkably similar and came into the category of the canalicular cholestatic type of drug-induced jaundice,[4] in which there is no hepatocellular disease and little portal inflammation. A striking feature of all these cases was the rapidly fatal course after the onset of jaundice despite the immediate withdrawal of the drug. This was associated with acute renal failure in at least four of the patients. Benoxaprofen was the only drug common to all five cases and is the probable cause of the jaundice. Structurally related drugs have not been reported to cause cholestatic jaundice and we must await further evidence to establish whether the association is causal. Nevertheless, we suggest that caution should be exercised in the use of benoxaprofen in elderly patients.

The manufacturers of benoxaprofen (Dista Ltd) have been aware of problems with the drug in frail elderly patients but only one death from jaundice (in a younger man abusing several drugs) has been reported to them. The cases in this study have been reported to the Committee on the Safety of Medicines.

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[1] Yeung Laiwah AC, Hildich TE, Horton PW, Hunter JA. Anti-prostaglandin synthetase activity of non-steroidal anti-inflammatory drugs and gastrointestinal microbleeding: a comparison of Flurbiprofen with Benoxaprofen. *Ann Rheum Dis* 1981;**40**:455-61.

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[3] Hamdy RC, Murnane B, Perera N, Woodcock K, Koch IM. The pharmacokinetics of benoxaprofen in elderly subjects. *European Journal of Rheumatology and Inflammation* 1982;**5**:69-76.

[4] Zimmerman HJ. Drug hepatoxicity: spectrum of clinical lesions. In: Davis M, Tredger JM, Williams R. *Drug reactions and the liver*. London: Pitman Medical, 1981.

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Clinical details of patients with jaundice

Case No	Age	Diagnoses	Length of treatment (months)	Onset of jaundice to death (weeks)	Alkaline phosphatase U/l (normal range 60–170)		Gamma glutamyl transferase U/l (normal range 5–60)		Aspartate transaminase U/l (normal range 2–35)		Bilirubin μmol/l (normal range 2–20)		Urea mmol/l		Other drugs
					Before treatment	Highest before death	Before treatment	Highest before death	Before treatment	Highest before death	Before treatment	Highest before death	Before treatment	Highest before death	
1	86	Rheumatoid arthritis, glaucoma	6	3	224	229	44	392	21	314	5	51	11·2	82·5	Timolol eye-drops, frusemide, potassium chloride
2	82	Senile dementia, back pain	7	1		400		295		217		74		44·1	Naftidrofuryl oxalate, paracetamol
3	80	Bilateral strokes, osteoarthritis, epileptic fits, depression	4½	1	82	503		868	19	450	3	50	6·8	48·6	Phenytoin, primidone, dothiepin, triamterene, benzthiazide
4	81	Osteoarthritis, varicose leg ulcers	7	1	188	562	16	443	42	151	4	137	10·8		Folic acid, paracetamol, codeine
5	88	Osteoarthritis, osteoporosis	3	3	134	175	25	363	21	111	5	137	10·3	50·7	Paracetamol

Conversion: SI to traditional units—Bilirubin: 1 μmol/l ≈ 0·05 mg/100 ml. Urea: 1 mmol/l ≈ 6 mg/100 ml.

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