

propoxyphene on 25 and 26 January. He felt generally unwell and developed abdominal pain on 26 January similar to that he had suffered after taking Distalgesic. The associated biochemical changes are shown in the table. Neither his temperature nor his eosinophil count rose. Subsequent exposure to paracetamol was uneventful. He has remained well since stopping Distalgesic.

### Case 2

On 1 January 1977 an obese 66-year-old woman was admitted for relief of severe low back pain, due to osteoporosis and vertebral collapse. During her admission she was given Distalgesic regularly. On 3 February she felt generally tired and her liver function was abnormal. There was no hepatic tenderness and the liver was not palpable.

She was receiving thyroxine and Navidrex K (cyclopentiazide 250 µg and potassium chloride 600 mg) regularly in addition to Distalgesic. On 9 February the Distalgesic was changed to dextropropoxyphene, which was itself stopped the next day. Her liver function values improved over the next five days. She was challenged with 130 mg dextropropoxyphene orally on 22 March and felt generally tired the next day. Her liver function became abnormal two days later (see table). On 26 March her temperature was 37.5 °C and she developed transient bilirubinuria, both of which settled rapidly. There was no eosinophilia.

*Liver function values in both patients related to dextropropoxyphene administration*

	Bilirubin (µmol/l)	Alkaline phosphatase (U/l)	Aspartate amino-transferase (U/l)	γ-Glutamyl-transpeptidase (U/l)
Normal	<23	20-90	<43	<54
Case 1				
21 Jan	10	66	22	
24 Jan	13	63	19	192†
25 Jan*	12	59	10	175†
26 Jan*	34	138	200	718
27 Jan	30	154	228	796
28 Jan	15	176	66	639
5 Mar	14	43	21	85
Case 2				
21 Mar	17	97	24	95†
22 Mar*	21	85	18	94†
23 Mar	18	86	22	95†
24 Mar	19	101	27	136
25 Mar	17	111	42	167
26 Mar	16	118	51	186
27 Mar	15	108	37	166
28 Mar	17	101	30	194

\* Dextropropoxyphene administered.

† γ-Glutamyltranspeptidase was raised, probably after exposure to Distalgesic in December in case 1 and in January in case 2.

### Comment

These cases seem to represent an uncommon hepatotoxic reaction to dextropropoxyphene, a constituent of Distalgesic. Because of the widespread use of Distalgesic mild reactions might be overlooked. The challenge dose of 130 mg dextropropoxyphene was the usual daily intake of the patients at the time of their past exposures and was similar to the doses associated with hepatotoxicity in the two previously reported cases.

The decrease in time between exposure to Distalgesic and abnormal liver function with repeated exposures and the relatively small dose of dextropropoxyphene required to reproduce the changes suggest a sensitivity reaction. The episodes of jaundice from 1971 to 1976 in case 1 may have been due to cross-sensitivity to codeine.

We should like to thank Dr R K Knight and Dr T Gibson for permission to report these two cases.

<sup>1</sup> Emmerson, J L, et al, *Toxicology and Applied Pharmacology*, 1971, **19**, 452.

<sup>2</sup> Klein, N C, and Magida, M C, *American Journal of Digestive Diseases*, 1971, **16**, 467.

<sup>3</sup> Daikos, G K, and Kosmidis, J C, *Journal of the American Medical Association*, 1975, **232**, 835.

(Accepted 15 June 1977)

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## Interstitial pulmonary fibrosis: a new side effect of practolol

Several adverse reactions attributed to long-term use of the beta-blocking agent practolol have been reported during the last three years. These include a lupus erythematosus-like syndrome,<sup>1</sup> a syndrome consisting of ocular damage, eczema, exfoliative dermatitis, lichen planus, and a psoriasis-like rash,<sup>2</sup> sclerosing peritonitis,<sup>3</sup> deafness,<sup>4</sup> nephrotic syndrome,<sup>5</sup> pleural effusion,<sup>6</sup> and joint effusion.<sup>7</sup> We describe here a patient who developed pulmonary fibrosis after exposure to practolol.

### Case report

A 43-year-old woman was admitted because of increasing dyspnoea. She had been well until three years earlier, when she had suffered cardiac palpitations and had been treated with practolol (150 mg) three times a day. One and a half years before admission to our hospital she developed signs of intestinal obstruction. A laparotomy was performed at which she was found to have a sclerosing peritonitis. The membranes surrounding the intestines were separated. Practolol medication was discontinued and she received prednisone 5 mg three times a day. Six months after discharge she developed a chronic cough for which doxycycline was prescribed. A chest radiograph showed a small right-sided pleural effusion. In view of previous prednisone treatment and a positive reaction to purified protein derivative of tuberculin, isoniazid treatment was started, though no tubercle bacilli were found in sputum or gastric washings. Shoulder pain, presumably due to diaphragmatic irritation, was treated with indomethacin. Furthermore, the patient claimed to have blurred vision for which no satisfactory explanation was found. As she became progressively dyspnoeic, she was admitted to our hospital for further evaluation.

Physical examination showed her to be in no acute distress. Her temperature was 37.4 °C and pulse rate 120/min. Both eyes showed signs of a keratitis superficialis with a decreased tear secretion (Schirmer test). Coarse moist ronchi were found over all lung fields along with signs of a right-sided pleural effusion. Further physical examination showed no disease and, although she produced purulent sputum, no bacteria were found. Laboratory data showed: erythrocyte sedimentation rate 20 mm in 1 h; white blood count  $7.1 \times 10^9/l$ ; liver chemistry, protein profile, and electrolyte, urea, creatinine, glucose,  $\alpha_1$ -antitrypsin,  $\alpha_2$ -macroglobulin, and complement concentrations were all normal. The IgA level was slightly raised (4.85 g/l). She was initially negative for antinuclear factor but later became slightly positive. The LE cell test gave a negative result, as did complement fixation tests for various viruses. Arterial  $Po_2$  was 8.98 kPa (67.4 mm Hg),  $Pco_2$  5.85 kPa (43.9 mm Hg), pH 7.44, and  $HCO_3$  29.1 mmol (mEq)/l.

A chest radiograph showed bilateral pleural effusions without signs of pulmonary fibrosis (fig 1). Bacteriological, cytopathological, and immuno-

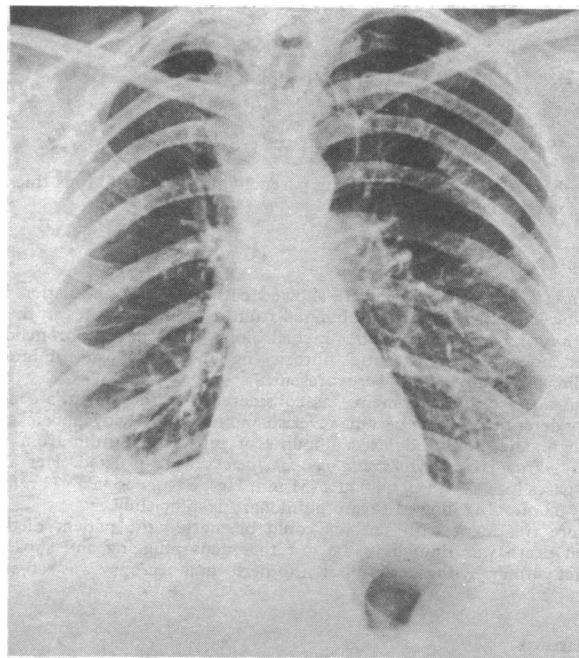


FIG 1: Chest radiograph taken one week after admission, showing bilateral pleural effusions.

pathological examination of a pleural tap specimen showed nothing abnormal. The pulmonary function test (fig 2) showed air trapping and a check-valve phenomenon. The total lung capacity was 6.65 l (normal 6.33 l) and residual volume 4.96 l (normal 2.09 l). The ventilatory capacity was 1.78 l (normal 4.24 l), forced expiratory volume in 1 s 0.32 l (normal 3.39 l), compliance 0.5 l/kPa (0.051 l/cm H<sub>2</sub>O) (predicted value 2.6 l/kPa (0.26 l/cm H<sub>2</sub>O)), and diffusion capacity 20 μmol/sec/kPa (6 ml/min/mm Hg) (16% of predicted value).

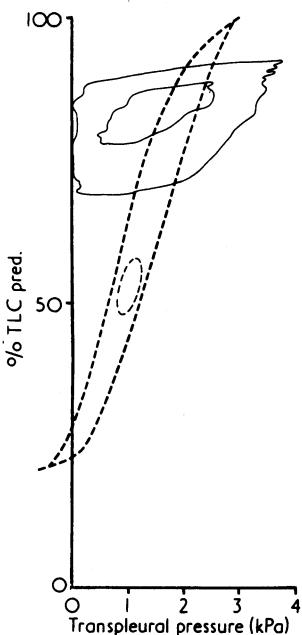


FIG 2—Pressure-volume curve (lung compliance) in patient (continuous line) compared with normal pressure-volume curve (interrupted line). Inner curves indicate tidal volume respiration; outer curves indicate maximal respiration.

able findings in a patient who had never had pulmonary complaints) and the other pulmonary function values suggested a bronchiolitis with interstitial fibrosis,<sup>8</sup> which was confirmed by a lung biopsy. Various agents cause this condition: viral infections, various inhaled gases, medication, collagen diseases, sarcoidosis, immunological reactions and physical influences. In the absence of other agents we postulate a direct relation between the pulmonary fibrosis and her long-term use of practolol, which had already caused sclerosing peritonitis, keratitis superficialis, and pleural effusions. The first symptoms of bronchiolitis with interstitial fibrosis became evident six months after practolol treatment was discontinued. A latent subclinical period is often seen in drug-induced interstitial pulmonary reactions<sup>9, 10</sup> as well as with the other adverse reactions attributed to practolol.<sup>10</sup> The precise mechanism remains unclear.

We thank Professor C A Wagenvoort for his evaluation of the biopsy specimens.

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<sup>3</sup> Brown, P, et al, *Lancet*, 1974, **2**, 1477.

<sup>4</sup> Gelder, L van, *Nederlandsch Tijdschrift voor Geneeskunde*, 1975, **33**, 1285.

<sup>5</sup> Farr, M J, Wingate, J P, and Shaw, J N, *British Medical Journal*, 1975, **2**, 68.

<sup>6</sup> Mackay, A D, and Axford, A T, *Lancet*, 1976, **1**, 89.

<sup>7</sup> Fraser, D M, and Irvine, N A, *Lancet*, 1976, **1**, 89.

<sup>8</sup> Liebow, A A, *Progress in Respiratory Research*, 1974, **8**, 1.

<sup>9</sup> Baum, G L (editor), *Textbook of Pulmonary Diseases*, 2nd edn. Boston, Little, Brown and Co, 1974.

<sup>10</sup> Kristensen, K, Kristensen, J S, and Thorborg, J V, *Lancet*, 1975, **1**, 741.

(Accepted 3 May 1977)

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## Hazards of intra-arterial diazepam

Diazepam is the drug of choice for status epilepticus.<sup>1</sup> Intravenous injection is needed for immediate effect, and in widespread use this has proved generally safe. Diazepam is also occasionally used to abolish seizures induced by spinal cord arteriography, and for this a local intra-arterial bolus of the drug before injection of the contrast material has been advised.<sup>2</sup> Despite evidence of the drug's safety when used intra-arterially in animals,<sup>3</sup> there have so far been two reported cases of accidental intra-arterial injection in children leading to extensive tissue necrosis and above-elbow amputation.<sup>4, 5</sup> The two cases described below illustrate further these dangers.

### Case 1

An 11-month-old boy was admitted in clonic status epilepticus. He was cyanosed and had a short respiratory arrest which responded to intermittent positive pressure ventilation (IPPV). He was obese and had poor peripheral vascular flow, and during an attempt to inject diazepam (Valium) into an antecubital vein 0.6 ml (3 mg) of diazepam was accidentally injected into the brachial artery. As the radial pulse remained palpable and there was no initial blanching of the arm distal to the injection, the needle was removed without any specific measures being taken.

Within half an hour, blotchy areas of pallor developed on the skin of the forearm, wrist, and palm of the hand and above the antecubital fossa. These areas of skin quickly became discoloured, and oedema of the forearm and palm of the hand developed. The fingers remained unaffected. Over the next 48 hours the swelling became tense (see figure), but fortunately the areas of localised skin damage did not progress to complete necrosis and sloughing, and the radial pulse always remained easily palpable with evidence of good distal blood flow to the fingers. Complete healing occurred within 14 days, and apart from limb elevation no specific measures such as anti-coagulant or steroid treatment were used.

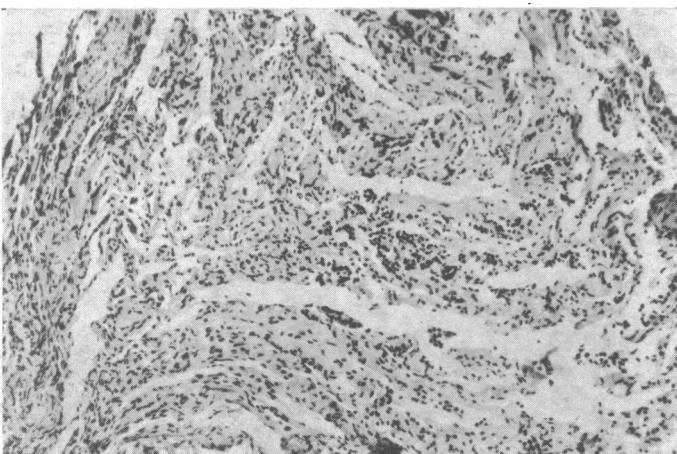


FIG 3—Representative areas of lung parenchyma showing fibrous thickening of alveolar walls. (H and E 98).

A lung scan with <sup>67</sup>Ga-citrate showed pathological accumulation in the right lower field. Lung tissue obtained from five different sites in the right lower lung by peripheral transbronchial biopsy via a flexible bronchoscope showed non-specific interstitial fibrosis (fig 3). No deposits of immunoglobulins or complement were present.

High-dose steroid treatment was considered, but the patient's condition rapidly deteriorated. She became feverish and increasingly dyspnoeic, started to cough, and produced large amounts of purulent sputum from which *Proteus mirabilis* and *Moraxella nonliquefaciens* were isolated. Her arterial blood gases (pH 7.34, Po<sub>2</sub> 6.80 kPa (51 mm Hg), Pco<sub>2</sub> 9.46 kPa (71 mm Hg), HCO<sub>3</sub> 38 mmol/l) showed severe pulmonary insufficiency.

Before treatment with steroids could be started the patient died. Her sudden death was thought to be due to mucus plugging and subsequent hypoxia with arrhythmia. Permission to perform a necropsy was refused.

### Comment

This 43-year-old woman died of rapidly progressive pulmonary insufficiency. The check-valve and air-trapping phenomena (remark-