SIDE EFFECTS OF DRUGS

Hyperpigmentation associated with oxprenolol administration

Skin sensitivity reactions to beta-adrenergic receptor blocking drugs, usually psoriasis-like eruptions, have been widely reported.¹⁻³ We report here a patient who developed generalised hyperpigmentation of the skin during treatment with oxprenolol (Trasicor).

Case report

A 62-year-old housewife presented with a three-month history of increasing generalised skin pigmentation, which was particularly marked round the mouth, both sides of the neck, and the back of the hands. She had been found to be hypertensive five months earlier and was treated with oxprenolol 240 mg/day in addition to the digoxin and quinine sulphate which she had been taking for five years.

Physical examination confirmed the striking brown pigmentation, which was also present over the exposed areas of both legs as well as on the corset and brassière pressure areas. There was no buccal or notable periareolar pigmentation. Examination was otherwise satisfactory, her blood pressure being 180/90 mm Hg. Haematological values, blood urea and electrolytes, protein-bound iodine concentration, skull and chest radiographs, and electrocardiogram were all normal. Diurnal variation of plasma corticosteroids and urinary 17-hydroxycorticosteroid (17-OHCS) and 17-oxosteroid (17-OS) excretion were also normal. All drugs, including oxprenolol, were withdrawn and the pigmentation rapidly diminished, the blood pressure remaining normal. To determine whether the pigmentation was related to the oxprenolol treatment, and after full discussion with the patient, the drug was reintroduced in a dose of 160 mg daily in divided doses, and the patient was reviewed carefully each week. Details of plasma and urinary corticosteroids, plasma melanocyte-stimulating hormone (MSH), and plasma ACTH levels over this period are shown in the table. The pigmentation gradually reappeared (see figure), and the oxprenolol was withdrawn after four weeks' treatment.

Hormone and steroid assays before and during treatment with oxprenolol 40 mg four times a day

	Before treatment	On treatment			
		Week 1	Week 2	Week 3	Week 4
Pigmentation		—	+	+	+
Plasma corticosteroids (μmol/l)					
Morning	0.62		0.47	0.28	0.58
Evening	0.25				0.35
Urinary 17-OHCS and 17-OS (μmol/24 h)	40.3, 32.3				63.3, 51.8
Plasma MSH (ng/l)	16.3, 13.9		32	35	23.8, 20.7
Plasma ACTH (ng/l)	13		<34	<36	60
	24	18			45

Conversion: SI to traditional units—Plasma corticosteroids: 1 μmol/l ≈ 0.036 mg/100 ml. Urinary 17-OHCS and OS: 1 μmol/24 h ≈ 0.29 mg/24 h.

Pigmentation during treatment with oxprenolol (left) which disappeared when treatment was withdrawn (right).

Comment

This patient developed pigmentation of her skin resembling that of Addison's disease during treatment with oxprenolol. The pigmentation regressed when the drug was withdrawn and recurred with further administration. Serum levels of MSH were not significantly raised during treatment when the pigmentation recurred. Plasma ACTH levels remained normal throughout the study. Plasma and urinary steroid levels remained unchanged.

The effect of oxprenolol in this patient may have been due to a local action of the drug on the skin, and it is most unlikely that MSH was implicated in the process. Photosensitisation is unlikely because of the generalised distribution of the pigment. The hyperpigmentation in this patient was therefore probably idiosyncratic in origin.

Beta-receptor blocking drugs, including oxprenolol, have been widely used for several years and it seems unlikely in the absence of other reports of hyperpigmentation with oxprenolol treatment that this effect is common. But in view of the delay that has sometimes occurred in recognising and reporting important side effects of drugs in widespread use, we have drawn attention to this association.

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Hepatotoxicity of dextropropoxyphene

Distalgesic is a commonly used analgesic, each tablet of which contains 32.5 mg dextropropoxyphene and 325 mg paracetamol. Emmerson *et al* showed that daily doses of dextropropoxyphene 40 to 110 times the maximum clinical dose produced hepatic enlargement and fatty changes in the livers of rats.¹ So far only two cases of jaundice have been associated with the normal clinical use of dextropropoxyphene,^{2,3} though paracetamol causes liver damage with jaundice in large doses but not in therapeutic doses. We report here two cases of hepatotoxicity induced by the dextropropoxyphene in Distalgesic.

Case 1

On 13 January 1977 a 56-year-old man was admitted for investigation of recurrent jaundice. He had first developed jaundice in 1944 and infective hepatitis was diagnosed. From 1971 to 1976 he had jaundice about twice a year. These episodes lasted two or three days, during which he passed dark urine. His usual analgesic at this time was codeine, but no convincing temporal relation could be established between the drug and the jaundice.

In July 1976 he was given Distalgesic to control low back pain. Ten days later he felt unwell and for a week noticed that his urine was dark, his motions pale, and his sclerae yellow. In October 1976 he again took Distalgesic and became jaundiced four days later. In December 1976 a third exposure to Distalgesic was followed by upper abdominal pain with jaundice beginning 24 hours later. He was not taking any other medication.

An intravenous cholangiogram was normal. A liver biopsy showed a minor degree of increase in fibrous tissue in the portal area with no liver cell necrosis and no bile stasis. After this biopsy he was given 130 mg dextro-

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 (cyclopenthyazide 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
<i>Case 1</i>				
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
<i>Case 2</i>				
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.

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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,¹ a syndrome consisting of ocular damage, eczema, exfoliative dermatitis, lichen planus, and a psoriasis-like rash,² sclerosing peritonitis,³ deafness,⁴ nephrotic syndrome,⁵ pleural effusion,⁶ and joint effusion.⁷ 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 rhonchi 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, α_1 -antitrypsin, α_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 P_{O_2} was 8.98 kPa (67.4 mm Hg), P_{CO_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.