Depression induced by etretinate

Drs C A HENDERSON and A S HIGHET (York District Hospital, York YO3 7HE) write: We report three cases of depression associated with etretinate treatment.

In 1984 a 49 year old, 90 kg man with plaque psoriasis started taking etretinate 100 mg/day. Despite a reduction in dose the drug had to be discontinued owing to peeling skin, thinning hair, and depression. These effects resolved a few weeks later. In 1986 etretinate was restarted. Depression recurred, although it was minimal at doses below 50 mg/day.

A 60 year old, 70 kg housewife with plaque psoriasis started taking etretinate 75 mg/day. After six weeks she became "extremely depressed." Etretinate was discontinued and her mood returned to normal in a few weeks.

In 1985 a 38 year old, 100 kg man started taking etretinate 100 mg/day for plaque psoriasis. This was discontinued because of mucocutaneous side effects. In retrospect he admitted to mild depression. Etretinate 50 mg daily was restarted in 1986. This was followed by deep depression, which took two months to resolve after discontinuation of etretinate.

All three patients were otherwise well and had no history of depression. No concurrent drugs were taken except ibuprofen 1.2 g/day by the second patient. All three patients admitted to an alcohol intake of 14 to 32 pints of beer weekly. Depression has been reported with isotretinoin¹ and etretinate.² The manufacturers know of one further case implicating etretinate. The alcohol intake of the patients may be relevant as hepatic steatosis is associated with higher concentrations of etretinate in liver biopsy samples,³ and this may have affected the drug's subsequent metabolism.

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Hypertensive crisis and broad complex bradycardia after a single dose of monoamine oxidase inhibitor

Drs JULIAN GUNN, MARY M HAMILTON, and ROGER M BOYLE (York District Hospital, York YO3 7HE) write: Monoamine oxidase inhibitors are well known to interact with foods containing tyramine or drugs containing sympathomimetic agents to produce a hypertensive crisis. We describe a patient who took a single dose of tranylcypromine while avoiding all such substances yet developed a hypertensive crisis with a broad complex bradycardia.

A 49 year old woman with a long history of manic depression and intractable insomnia was admitted to psychiatric hospital for further treatment. She was taking lithium carbonate 750 mg, disulfiram 200 mg, and triazolam 10 mg. She had been a heavy drinker but had abstained for four years. She described occasional brief palpitations and reported an episode of syncope one month

earlier, when a low blood pressure had been recorded. She was otherwise well and there was no other relevant history.

She took a single tablet of tranylcypromine (10 mg) under supervision. Within an hour she developed a severe headache; her diastolic blood pressure was 120 mm Hg and the pulse regular at 40 beats/min. On her transfer to a medical ward an electrocardiogram showed a broad complex bradycardia compatible with a junctional rhythm with retrograde P waves. Serum potassium concentration was 3.9 mmol/l and lithium 0.53 mmol/l. By the next morning she felt well. The pulse was 72 beats/min in sinus rhythm, blood pressure was 95/50 mm Hg, and the electrocardiogram had returned to normal. She had no further problems of this kind.

The simplest explanation for these events is a hypertensive crisis leading to a reflex bradycardia. Yet this patient took no more than a single therapeutic dose of monoamine oxidase inhibitor and was not exposed to tyramine. Either there was an idiosyncratic reaction to the tranylcypromine or the combination of this with disulfiram, lithium, or triazolam was responsible. Tranylcypromine is the most hazardous of the monoamine oxidase inhibitors because of its stimulant action. These drugs lower resting blood pressure significantly, reduce heart rate modestly, but have not been shown to have any consistent effect on cardiac conduction or rhythm.¹ A few cases of "spontaneous" hypertension have been reported after their administration, but none followed a single tablet.^{2,4} A possible explanation in the case of tranylcypromine is an "autointeraction" between tranylcypromine and the amphetamine to which it is partly metabolised.¹ We could find no report of interaction between the drugs our patient was taking, though one experiment in rats linked massive doses of disulfiram and monoamine oxidase inhibitors with tremor, convulsion, and death.⁵ We conclude that this was probably an idiosyncratic effect and suggest that patients should be closely monitored after the first dose of a monoamine oxidase inhibitor.

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Thrombocytopenia and angiotensin converting enzyme inhibitors

Dr J F ACKROYD (Allergy Clinic, St Mary's Hospital, London W2 1NY) writes: Dr B Grosbois and colleagues described two sisters who developed severe acute thrombocytopenic purpura when treated with angiotensin converting enzyme inhibitors, one with enalapril and the other with captopril.¹ HLA typing showed that both sisters had the haplotype B8 DR3, and the authors suggested that both sisters had a genetic predisposition to develop thrombocytopenia in response to angiotensin converting enzyme inhibitors. The evidence that both sisters had developed thrombocytopenic purpura in response to angiotensin converting enzyme inhibitors is, however, not convincing. One sister (case 1) was also being treated with quinidine when she developed thrombocytopenia. When both drugs were stopped she rapidly recovered. Quinidine is one of the commonest causes of drug induced thrombocytopenic purpura. Aster quoted over 100 case reports in which evidence for a quinidine

dependent antiplatelet antibody had been shown.² Two cases of isolated thrombocytopenic purpura attributed to captopril have been reported,^{3,4} but enalapril does not appear to have been reported to cause isolated thrombocytopenia.

Dr Grosbois and colleagues considered that enalapril had caused thrombocytopenia in case 1 on the basis of a system of analysis in which points are allocated to details of the patient's symptoms and the clinical course.⁵ This system allocates a high score when the period of treatment before thrombocytopenia developed is less than 16 days. Since this period was 10 days for enalapril and two years for quinidine these workers may have been led to favour enalapril as the cause of the thrombocytopenia in case 1. Thrombocytopenic purpura may, however, occur even after a drug has been taken for years.⁶ In one reported case thrombocytopenic purpura, which was almost certainly due to quinidine, developed after 16 years of intermittent treatment.⁷ In another it developed after three years of intermittent treatment with quinidine. In this case a quinidine dependent platelet agglutinin was shown in the patient's plasma and accidental readministration of the drug caused recurrence of thrombocytopenia and purpura, thus confirming the diagnosis.⁸ Dr Grosbois and colleagues do not appear to have attempted to show drug dependent antibodies in either of the two sisters.

Apart from rechallenge, the only other way of identifying a causative drug with certainty is by showing a drug dependent antiplatelet antibody in the patient's serum. Although such antibodies cannot be shown in every case, drug specific antiplatelet antibodies have been shown in many cases of thrombocytopenic purpura, including many due to quinidine, using simple techniques.⁹ It would be worth while attempting to establish which drug caused thrombocytopenia in case 1 with these techniques or with more recently developed and sensitive but more complex techniques.¹⁰ Preferably, serum taken when the patient was thrombocytopenic should be used, but a fresh sample of blood may be used because, although some drug dependent antiplatelet antibodies are evanescent, many can be detected in the patient's serum even years after the thrombocytopenia developed.⁹

Only if it can be shown that the thrombocytopenia which the first sister developed was due to enalapril and not quinidine will it be possible to judge the importance of the authors' suggestion that the sisters had a genetically determined predisposition to develop thrombocytopenic purpura in response to two drugs which, although similar in pharmacological action, differ significantly in chemical structure.

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