

Erythromelalgia due to calcium antagonists may be more frequent than reported. It is probably often reported as flushing or paraesthesia of the hands and feet. Doctors prescribing these drugs should be aware of this inverse Raynaud's phenomenon and withdraw the drug(s) before sending their patients for extensive investigations.

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### Tamoxifen-warfarin interaction: the Aberdeen hospitals drug file

Drs LEWIS D RITCHIE AND SANDRA M T GRANT (Medicines Evaluation and Monitoring Group, Aberdeen Royal Infirmary, Aberdeen AB9 2ZB) write: In Aberdeen for the past 17 years a computerised file of the drug history of each patient during hospital admission has been maintained.<sup>1</sup> The drug information is linked to personal and morbidity data, routinely collected for the Scottish Morbidity Return (SMR1). At the end of 1988 the file contained 932 000 admissions with over 2.5 million drug prescriptions.

Following the report by Dr P Tenni and others on life threatening interactions between tamoxifen and warfarin,<sup>2</sup> we examined all admissions to the Aberdeen general hospitals from 1980 to 1988 in which the two drugs had been prescribed together. Twenty nine such patients were identified and their case notes scrutinised. Seven were excluded (initial treatment elsewhere, or the two drugs were not given concurrently). In the remaining 22 cases no problems had been noted in 17. In the five other cases two patients had grossly raised British comparative ratios on introduction of warfarin but no episode of bleeding; one had no noted problem with control but experienced a subconjunctival haemorrhage; one had difficulty with control and developed a haematoma of the thigh; and one, who was taking long term warfarin, had problems with intraocular haemorrhage and haemorrhagic rashes after tamoxifen was introduced. Our findings confirm those of Dr Tenni and colleagues and we echo their concerns about this life threatening interaction.

The Aberdeen hospitals drug file offers the opportunity for studying potential drug interactions. We would welcome further inquiries about specific uses for this facility.

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- 2 Tenni P, Lalich DL, Byrne MJ. Life threatening interaction between tamoxifen and warfarin. *Br Med J* 1989;298:93. (14 January.)

### Reversal of chloral hydrate overdose with flumazenil

Drs K L DONOVAN AND D J FISHER (Cardiff Royal Infirmary, Cardiff CF2 1SZ) write: Dr J G Whitwam says that flumazenil has been used in many conditions other than to reverse sedation

induced by benzodiazepines.<sup>1</sup> We observed an interesting interaction between flumazenil and chloral hydrate taken in overdose.

A young man with a history of drug overdose was brought to the casualty department unconscious with respiratory depression and hypotension. Both pupils were constricted and his breath smelt sweet. Intravenous naloxone (0.4 mg × 4 doses) produced no improvement, but flumazenil 200 µg, followed at one minute intervals by three further 100 µg doses, produced a dramatic response with increased level of consciousness, verbalisation, and pupillary dilatation; both respiratory rate and blood pressure returned to normal. The sludge obtained by gastric lavage was shown to be chloral hydrate and he later admitted to having taken a total of 10 g of the drug in isolation.

Although flumazenil is a specific competitive benzodiazepine receptor antagonist, it has been shown to have a dramatic but inconsistent effect in ethanol intoxication,<sup>2,4</sup> possibly by modifying the response of the γ aminobutyric acid-benzodiazepine ionophore receptor complex to the effects of ethanol.<sup>5</sup> The sedative mode of action of chloral hydrate, similar to that seen with benzodiazepines and ethanol, is poorly understood. The rapid reversal of recognised effects of chloral hydrate overdose seen in this case may therefore provide further information about the modes of action of both flumazenil and chloral hydrate. So far as we and the manufacturers are aware this has not been reported before, though attempted reversal of benzodiazepine-chloral hydrate induced sedation with flumazenil precipitated ventricular arrhythmias.<sup>6</sup> The mechanism is unclear, but it may be that while flumazenil antagonised the benzodiazepine element it failed to protect against chloral hydrate arrhythmogenesis, a well recognised side effect.

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### Cross sensitivity to antithyroid drugs

Drs A SMITH, R F GLEDHILL, and P JENKINS (East Surrey Hospital, Redhill, Surrey RH1 5RH) write: Medical practitioners have come to rely on the *British National Formulary* for sound prescribing advice. The section on antithyroid drugs states, "Propylthiouracil may be used in patients who suffer sensitivity reactions to carbimazole as sensitivity is rarely displayed to both drugs."<sup>1</sup> This statement runs counter to views expressed elsewhere,<sup>2,5</sup> a standpoint which we highlight through the following case report.

A 66 year old woman presented to the accident and emergency department in June 1988 with a 24 hour history of pain in the wrists, elbows, shoulders, and interscapular area. Four months earlier she had had a myocardial infarction complicated by cardiac arrest and consequent thoracic spinal cord infarction. A flaccid, hyporeflexic paraplegia with diminution of pain sensation distal to either ankle had remained. She had been readmitted three months later in left ventricular failure with atrial fibrillation. At that time the serum free thyroxine concentration was 37 pmol/l

(normal 10.4-24.2) and the thyroid stimulating hormone value 0.16 mU/l (0.44-3.16). Carbimazole 15 mg three times daily had been started on 23 May. This had been replaced on 13 June by propylthiouracil 100 mg three times daily after the appearance (one week earlier) of a pruritic macular eruption. Daily concurrent medication comprised nifedipine (60 mg), digoxin (250 µg), and amiloride hydrochloride 5 mg plus frusemide 40 mg (Frumil; 2 tablets).

On admission her temperature was 38.4°C and pulse 84 beats/min with a regular rhythm. The rash had disappeared. Both arms were held immobile and in a disordered posture, the slightest displacement evoking an anguished response. No joint swelling or erythema was evident. A full blood count and standard biochemical profile gave normal results. The erythrocyte sedimentation rate (Westergren) was 30 mm in the first hour. Tests for rheumatoid factor and antinuclear antibody gave negative results. The antibody titre to thyroglobulin was 1/1700 and to thyroid microsomes 1/110 000. Propylthiouracil was withdrawn on 17 June and dispersible aspirin 600 mg four times daily given. The temperature settled and less opioid analgesic was required for pain relief. Two days later the patient suffered a fatal cardiac arrest.

Arthralgia without joint inflammation was the second most common side effect in a recent survey of 500 patients with thyrotoxicosis given antithyroid drugs.<sup>6</sup> Of the five patients affected, four displayed sensitivity also to the alternative agent. Such events are not limited to rheumatic symptoms, cross sensitivity having been described in agranulocytosis,<sup>7,8</sup> marrow aplasia,<sup>9</sup> and hepatic injury.<sup>10</sup> The reaction to a second agent may also be more severe than that to the first.<sup>7,9</sup> Extensive immunological cross reactivity to all three antithyroid drugs was shown in patients who had developed agranulocytosis during treatment with either propylthiouracil or carbimazole.<sup>5</sup> The thioamide group, common to each compound, may either have been the antigen or have become antigenic by forming a complex with a neutrophil protein. Cross sensitivity might also arise on the basis of close chemical analogy.

Our patient's rheumatic symptoms developed 24 hours after both the introduction of propylthiouracil and the withdrawal of carbimazole. Although the carbimazole rash had already resolved, this drug, rather than propylthiouracil, might have been responsible. At all events, some authors, having regard to the potential for cross sensitivity, advocate using alternate treatments for patients who manifest an adverse reaction to one antithyroid drug and who need further treatment for hyperthyroidism.<sup>2,3</sup> The prudence of this policy merits an amendment to the *British National Formulary*.

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