30 minutes atrial fibrillation recurred, and ouabain 0.5 mg intravenously failed to reduce the rate. Amiodarone (300 mg intravenously over 10 minutes) reduced the apex rate to 90/min, after which an intravenous infusion was established (600 mg per 24 hours for 48 hours); over the same period he was given digitalis. The next day he reverted to sinus rhythm and remained well.

Comment

Amiodarone is a benzofuran derivative with a class III action, prolonging the duration of the action potential in conducting fibres and increasing their refractory period.¹ It has a broad range of action, having a similar effect on atrial, nodal, and ventricular tissues. Coronary blood flow is increased and there is no negative inotropic effect—both valuable assets in treating arrhythmias with an ischaemic aetiology.

Cardioversion and cardiac glycosides should be regarded as first-line treatment in the control of fast atrial fibrillation occurring after myocardial infarction. In resistant cases, however, and especially when prompt control of the arrhythmia is mandatory to maintain a cardiac output, we suggest that intravenous amiodarone has a valuable place in the management.

We thank Dr A C Burden and Dr J E F Pohl for permission to report these cases.

¹ Singh BN, Williams EMV. The effect of amiodarone, a new antianginal drug, on cardiac muscle. *Br J Pharmacol* 1970;**39**:657-67.

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Thrombocytopenia and haemolytic anaemia due to feprazone

Feprazone is a non-steroidal anti-inflammatory agent. Rashes and dyspepsia are common adverse effects.¹ Serious blood dyscrasias are a well-recognised side effect of the structurally related drug phenylbutazone. This relation has prompted warnings about similar effects with feprazone,² but no cases seem to have been reported. We report a case of haemolytic anaemia and severe thrombocytopenia due to feprazone.

Case report

A 21-year-old student went to his general practitioner complaining of cramps in his legs while playing football. He was given feprazone 400 mg daily. Five days later he had the first of several episodes of epistaxis. Six days after the onset of epistaxis he developed a rash and was admitted to hospital. There was no past or family history of bleeding problems. He had been treated with phenobarbitone over several years for epilepsy but had stopped this two years previously without recurrence of fits. Six years previously he had developed a rash while taking ampicillin. He was not receiving any other current drug treatment.

On examination he had a widespread erythematous rash with purpura. There was moderate cervical and axillary lymphadenopathy but no enlargement of the liver or spleen. Initial investigations showed haemoglobin concentration 11.8 g/dl, white cell count $5.5 \times 10^9/l$, and platelets $11 \times 10^9/l$. The following day investigations showed haemoglobin concentration 9.3 g/dl with 3.5% reticulocytes, white cell count $4.8 \times 10^9/l$ with normal differential count, and platelets $11 \times 10^9/l$. Haptoglobin concentration was less than 0.12 g/dl (normal 0.30-5.0 g/dl). A direct Coombs test was positive, showing only C3d specificity. An autoagglutinin was present in the serum. Bone-marrow examination showed erythroid and megakaryocytic hyperplasia.

These findings were thought to be related to feprazone and the drug was stopped. Lymphadenopathy, however, is not typical of drug-induced haemolysis or thrombocytopenia, and a lymph-node biopsy was performed. This showed reactive hyperplasia. Paul-Bunnell, antinuclear factor, and toxoplasma dye tests were negative.

Five days after admission the platelet count was still below $10 \times 10^9/l$ and there was recurrent epistaxis. Prednisone 60 mg daily was started and within three days the haemoglobin concentration had risen to 11.7 g/dl and platelet count to $197 \times 10^9/l$. He was discharged and the prednisone stopped within six weeks. The haemoglobin concentration and platelet count subsequently remained normal.

Comment

The haematological findings indicate immune platelet destruction and red-cell haemolysis. The close temporal relation with the use of feprazone in an otherwise fit individual suggests a causal relation. A rapid rise in the platelet count after the drug was stopped might have been expected, but with little rise after five days we decided that steroids could not be withheld because of the continuing bleeding problems encountered.

The positive result of the direct Coombs test with anti-C3d specificity is in keeping with a drug-induced immune-complex-mediated haemolysis, and a similar mechanism is often present in drug-induced thrombocytopenia.³ An immune mechanism has been described in thrombocytopenia due to phenylbutazone.⁴ A similar mechanism may be implicated in this case.

Six reports documenting thrombocytopenia associated with the use of feprazone have been forwarded to the Committee on Safety of Medicines. As our findings do not seem to be an isolated occurrence, this report should serve to emphasise the potential hazards inherent in the use of "second-generation" anti-inflammatory drugs.

We acknowledge the help of the Committee on Safety of Medicines. We thank Dr J R Hayes and Dr J H Robertson for their help and advice, and Mrs L Thompson for typing the manuscript.

Requests for reprints should be addressed to Dr Caroline A Humphrey, The Laboratories, Belfast City Hospital, Belfast.

¹ Harris PG. A monitored-release study of methazone in general practice. *J Int Med Res* 1980;**8**:276-82.

² Committee on the Review of Medicines. Recommendations on phenylbutazone, oxyphenbutazone, feprazone, allopurinol, colchicine, probenecid, and sulphinpyrazone. *Br Med J* 1978;**i**:1466-7.

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⁴ Meiers G, Gehrman W, Gahlen SW. Antitroperbedingte thrombocytopenische Purpura nach Phenylbutazon. *Dtsch Med Wochenschr* 1963;**12**:580-4.

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Failure with the new triphasic oral contraceptive Logynon

A new type of oral contraceptive has been introduced recently. A case of probable drug failure, an uncommon occurrence with the combined oral contraceptive preparations, is reported here.

Case report

A 24-year-old nulliparous woman had been using oral contraceptives for six years without problems. Her prescription was changed from a monophasic preparation (Eugynon 30) to the new triphasic preparation Logynon by her general practitioner because of headaches. She started the first treatment cycle five days after finishing the monophasic preparation and, as recommended, used a contraceptive sheath for the first 14 days. She had a normal menstrual period at the end of the first treatment cycle and so started the second course, as prescribed. At the end of that cycle she did not have a menstrual period, and soon afterwards a pregnancy test gave a positive result.

The patient had no gastrointestinal disturbances during these months and did not take any antibiotics or other drugs. She was seen at the hospital antenatal clinic 19 weeks after her last menstrual period. Clinical examination and ultrasound scan confirmed the gestational age of the fetus. Antenatal progress was uneventful, and 10 days after term she went into labour spontaneously and delivered a normal 3800-g girl, who showed signs of postmaturity.

Comment

Logynon was introduced into Britain in May 1980 after initial pilot studies.^{1,2} The preparation contains three different combinations of ethinylestradiol and levonorgestrel: 30 and 50 µg respectively for six days; 40 and 75 µg for five days; and 30 and 125 µg for 10 days.

Lachnit-Fixon³ cited 8028 treatment cycles with no pregnancies

despite medication errors of one or several omissions of tablets, though treatment with a closely related triphasic contraceptive (SHB261AB) did result in one pregnancy owing to drug failure. In a report of 480 treatment cycles with no failures, Briggs and Briggs⁴ stated that suppression of midcycle gonadotrophins and oestradiol and late-cycle progesterone occurred from the first treatment cycle and that "an oral contraceptive formulation must approach 100% effectiveness when properly used."

Every contraceptive method has a failure rate, and that of the combined (monophasic) oral contraceptives is 0.1-0.4/100 woman-years. The present case was almost certainly one of drug failure, as the patient had been successfully using oral contraceptives for several years; furthermore, conception was confirmed as having occurred in the second treatment cycle with Logynon by midpregnancy clinical examination and ultrasound scan and subsequent obstetric history.

Failure with a new type of oral contraceptive so soon after it has become available is disturbing. Seven further confirmed cases of "unintended pregnancy" with triphasic oral contraceptives have been reported to the Committee on Safety of Medicines, five with Logynon and two with Trinordiol.

I thank Mr J Richardson for permission to report this case, and Dr D W Zutshi, of the Committee on Safety of Medicines secretariat, for making information from recent reports available.

¹ Schneider WHF, Lachnit-Fixon U, Schmid R, Spona J. Sur kontrazeptiven Wirksamkeit von Dreistufenpräparaten. *Med Klin* 1977;72:2081-5.

² Schneider WHF, Spona J, Schmid R, Lachnit-Fixon U. Efficacy of three-phase oral contraceptives. Amsterdam: Excerpta Medica, 1977:126-35. (*International Congress Series*, No 441.)

³ Lachnit-Fixon U. Clinical investigations with a new triphasic oral contraceptive. In: Greenblatt RB, ed. *Development of a new triphasic oral contraceptive. Proceedings of a special symposium held at the X world congress of fertility and sterility, Madrid, July 1980*. Lancaster: MTP Press, 1980:99-107.

⁴ Briggs M, Briggs M. A randomized study of metabolic effects of four oral contraceptive preparations containing levonorgestrel plus ethinyl-oestradiol in different regimens. In: Greenblatt RB, ed. *Development of a new triphasic oral contraceptive. Proceedings of a special symposium held at the X world congress of fertility and sterility, Madrid, July 1980*. Lancaster: MTP Press, 1980:79-98.

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Inaccuracy of London School of Hygiene sphygmomanometer

The London School of Hygiene (LSH) sphygmomanometer is a mercury in glass manometer incorporating special features to reduce observer bias and digit preference. Originally intended for use by epidemiologists, it has been used in therapeutic trials, to compare direct and indirect blood pressures,¹ and as a reference standard against which automatic devices are tested.² Though validated against the standard mercury sphygmomanometer,^{3,4} it gave lower recordings than the standard sphygmomanometer when both were compared with intra-arterial recordings.⁵ We carried out a study to assess the accuracy of the LSH sphygmomanometer.

Methods and results

Two LSH sphygmomanometers were compared statically with a standard mercury manometer throughout the pressure range 0-250 mm Hg by connecting both devices to a single cuff wrapped around a cylinder. The internal diameters of the reservoirs and glass tubes of the LSH sphygmomanometers were measured by a micrometer. The LSH sphygmomanometers underestimated pressure, the error increasing with pressure so that at 200 mm Hg they recorded 196 mm Hg. The error was consistent with failure to calibrate for the relative diameters of the reservoir (24 mm) and glass column (3.8 mm). The scale of a mercury manometer is calibrated to compensate for the fall of mercury in the reservoir when pressure is applied. The correction factor (h_1), added to the recorded rise of mercury in the glass tube, is calculated as $h_1 = h_2(d_2)^2/(d_1)^2$, where h_2 is the rise of mercury in the glass tube and d_1 and d_2 the diameters of the reservoir and glass tube respectively.

The LSH sphygmomanometer was compared with the Hawksley random-zero sphygmomanometer in 20 patients with a wide range of blood pressures. Two trained observers unaware of the possible error in the LSH sphygmomanometer recorded the pressures (diastolic phase V) at a deflation rate of 2 mm Hg per second. Both devices were connected to a single cuff through a Y connector. A two-channel stethoscope was used so that both observers auscultated the same sounds, and the observers were separated by a partition. Four paired recordings (LSH and Hawksley sphygmomanometers) were made in each patient. The LSH sphygmomanometer underestimated the Hawksley recordings (figure) by a mean of 7.1 mm Hg ($p < 0.001$) and 3.6 mm Hg ($p < 0.001$) for systolic and diastolic blood pressures respectively (Student's t test for paired data). There was a negative correlation between the diastolic, but not systolic, error and heart rate ($r = -0.27$, $p < 0.05$).

Comparison of mean recordings of blood pressure made in 20 patients with London School of Hygiene (LSH) and Hawksley random-zero sphygmomanometers.

Comment

The differences between the readings made with the LSH and Hawksley sphygmomanometers were greater than could be explained by the calibration error of the former alone. With a standard mercury manometer the observer watches a falling mercury column against a scale. If, as often happens, he is uncertain that he has heard the first sound he may delay a decision until he has confirmed the presence of sounds and then refer back to the point on the scale at which he thought sounds were first heard. Similarly, with the diastolic pressure the point of disappearance of sounds is referred to only after confirming that all the sounds have disappeared. In contrast, when the LSH sphygmomanometer is used the falling mercury column and pressure scale are not visible. Systolic pressure is indicated after the first sound when the observer is satisfied that sounds are being heard. Similarly, the diastolic pressure is indicated after the last sound, at the point where a sound is expected but fails to occur. There is therefore a tendency to underestimate blood pressure when using the LSH sphygmomanometer, and the error would be expected to increase at slower heart rates. This interpretation is supported by the finding of a negative correlation between the diastolic error and heart rate.

Our findings show that because of a calibration error and an interpretive tendency to underestimate systolic and diastolic pressures the LSH sphygmomanometer is not suitable for studies of blood pressure and should not be used as a reference standard.

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¹ Holland WW, Humerfelt S. Measurement of blood pressure. Comparison of intra-arterial and cuff values. *Br Med J* 1964;ii:1241-3.