in psychopathology, which worsened after a three-day washout period and became similar to that seen before metoclopramide treatment.

The patient was then treated with the classical neuroleptic haloperidol. At a dose of 45 mg/day the same extrapyramidal syndrome re-emerged and was completely responsive to trihexyphenidyl 2 mg by mouth three times daily. After haloperidol dosage was increased to 100 mg/day the tremor emerged in a milder form. Psychopathology at this dosage was partially improved, but some disorganisation of thought, delusions, and hallucinations persisted. His state at this time (10th day of haloperidol treatment) was comparable to that noted after metoclopramide 1 g/day.

Comment

The syndrome that this patient developed on sodium valproate was clinically indistinguishable from one shown by the same patient after treatment with the classical neuroleptic agent haloperidol and the dopamine antagonist metoclopramide, though it differed in its clinical response to antimuscarinic agents. These agents failed to affect the syndrome when it occurred after sodium valproate, although they effectively suppressed the identical extrapyramidal signs when they occurred after haloperidol and metoclopramide.

The precise mechanisms underlying this differential responsiveness are not clear. Our observations may, however, be consistent with a report by Gerlach, who noted a clinical exacerbation of extrapyramidal symptoms after treatment with baclofen.[3]

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Metrizamide in venography

Despite the introduction of non-invasive techniques for investigating venous diseases of the legs, venography is still commonly used as it is diagnostically more accurate.[1] Serious complications of venography are rare but as many as 59% of patients experience pain.[2] Metrizamide is known to cause less pain than conventional contrast media when given as an intra-arterial injection.[3] We have compared metrizamide with a conventional ionic contrast medium for use in ascending venography of the legs in a prospective study.

Patients, methods, and results

A total of 100 patients with suspected and known venous disease of the legs were investigated by our standard method of ascending venography.[4] The patients had one leg examined using 50 ml of meglumine iothalamate (280 mg of iodine/ml, Conray 280) and the other using 50 ml of metrizamide with the same iodine content. The patients and one of the examining radiologists did not know which leg was injected with which medium. Patients were questioned immediately after the examination and sent a questionnaire one week later. The quality of the films obtained from each leg was compared by an independent radiologist.

Of the 200 legs examined, 88 were normal, 40 had incompetent perforating veins, 36 had post-thrombotic changes, and 36 had a recent thrombosis. The patients' responses are shown in the table: 74% answered the questionnaire. Immediately after the examination patients reported pain in 68% of the legs examined with meglumine iothalamate and in 15% examined with metrizamide. One week later patients reported pain in half of the legs examined with meglumine iothalamate and in 9·6% examined with metrizamide. The quality of the venographs was judged better on the metrizamide side in 45, better on the meglumine iothalamate side in 2, and the same in 35. Comparison was not possible in 18 because of considerably different pathology.

Comment

In most cases patients complained of more pain in the leg examined by venography using the conventional ionic medium than in that examined with metrizamide, both immediately after the examination and in the week after. The patients when receiving metrizamide experienced less generalised hot flushing, nausea, and vomiting; and there was less swelling of the foot or calf in the legs examined with metrizamide. The quality of the venographs was slightly better with metrizamide.

Patients are thus likely to experience much less discomfort if metrizamide rather than conventional ionic medium is used for ascending venography. But metrizamide costs about forty times as much as the conventional medium, and, as none of the patients examined using the conventional medium experienced intolerable discomfort, we do not recommend the routine use of metrizamide. But it might be used in some patients: those needing sequential venography; those with major veno-occlusive disease, in whom pain is often more severe; and those with a low pain threshold. We also hope that non-ionic contrast media may become more competitively priced.

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Immediate and delayed effects of venography of the legs using meglumine iothalamate or metrizamide

	Contrast media	No of legs examined	Pain in foot only	Pain in calf only	Pain in foot and calf	Generalised hot flushing	Nausea or vomiting or both	Swelling of foot	Swelling of calf
Immediate effects	Meglumine iothalamate	100	25	11	32	16	9		
	Metrizamide	100	9	2	4	7	3		
Delayed effects	Meglumine iothalamate	74	13	9	15			19	9
	Metrizamide	74	1	5	1			6	2

Humidifier fever in an operating theatre

Humidifier fever, an immunological reaction to the inhalation of allergens from a contaminated humidifier, presents as a transient, influenza-like illness usually occurring on the first day back to work after a break. It has been termed "Monday sickness."[1] Outbreaks have been described in industry, and we present a preliminary report on its occurrence in a hospital operating theatre.

Patients, methods, and results

Index case. Four to six weeks after starting work in the recovery room of an operating theatre a nursing sister noticed feverish episodes (38°C) with shivering, myalgia, a tight chest, and headache. They occurred in the evening of the first day back at work each week and would subside by the next day except for the expectoration of white phlegm for 24 hours. When first seen she was recovering from acute bronchitis (*Haemophilus parainfluenzae*) and taking a course of ampicillin. Physical examination and chest *x*-ray picture were normal, white cell count (WBC) $8{\cdot}4 \times 10^9$/l (8400/mm^3) with 70% neutrophils and no eosinophils. Erythrocyte sedimentation

rate (Westergren) was 9 mm in first hour. Serological tests showed strongly positive precipitins to "humidifier fever" antigens (baffle plate material, humidifier water, and the amoeba *Naegleria gruberi*). Pulmonary function tests showed peak expiratory flow rate (PEFR) 470 l/min; forced expiratory volume in one second (FEV_1) 3·00 l; forced vital capacity (FVC) 3·30 l; total lung capacity (TLC) 5·39 l; vital capacity (VC) 3·41 l; residual volume (RV) 1·98 l; functional residual capacity (FRC) 3·41 l; and carbon monoxide transfer factor (T_{LCO}) 6·4 mmol/min/kPa (19·1 ml/min/torr). All these were within her predicted normal range. On the evening of her first day back at work she experienced symptoms as described above. Her WBC rose to $17·1 \times 10^9$/l (17 100/mm^3) with 94% neutrophils and no eosinophils, and the ESR was 39 mm in 1st h. PEFR fell to 335 l/min, with an FEV_1 of 2·75 l, FVC 3·35 l, TLC 4·54 l, VC 3·14 l, RV 1·40 l, FRC 2·83 l, and T_{LCO} 5·8 mmol/min/kPa (17·4 ml/min/torr). After the next weekend off duty tests before work showed PEFR 480 l/min, FEV_1 3·25 l, FVC 3·70 l, TLC 5·12 l, VC 3·52 l, RV 1·60 l, FRC 3·36 l, and T_{LCO} 6·9 mmol/min/kPa (20·7 ml/min/torr).

The humidifier was of the static spray type where mains water was chilled and recycled under pressure through sprays that humidified filtered external air. Baffle plates eliminated large droplets, and the outgoing air was warmed to the appropriate temperature by steam coils. Gel diffusion testing of samples of the water concentrated $\times 1000$ by air dialysis revealed antigens associated with humidifier fever using sera from previous outbreaks of the disease. There was a high degree of cross-reactivity between the sera and antigens from three outbreaks, suggesting a common source of allergenic material.

Sixty other theatre staff were interviewed, examined, and their sera tested by double gel diffusion against material derived from the humidifier water. The physician sought symptoms of humidifier fever, particularly in relation to the first working day, without knowing the results of serological tests. Chest radiographs were taken and pulmonary function tested, but not on any particular working day. Symptoms compatible with humidifier fever were reported in 10 cases. There was a highly significant relationship ($P < 0·001$ by χ^2) between symptoms and results of serological tests (table). Chest radiographs and pulmonary function were normal in all those with suggestive symptoms or serological findings, or both. Six of the remaining subjects had abnormalities related to pre-existing chest diseases.

Humidifier fever: symptoms in relation to results of serological tests

Symptoms	Serological tests		
	Negative/weakly positive	Positive	Strongly positive
Negative	34	12	4
Positive	1		9

Comment

Humidifier fever has been described in offices and factories.[2–5] We report the first recorded instance of humidifier fever associated with an operating-theatre humidifier. As in previous outbreaks,[1] the humidifier had a recirculating water system that allowed the build-up of allergenic material. Fungi, bacteria, and amoebae were isolated from the humidifier, and their characterisation is in progress. Since the humidifier is of a common design and used in other operating theatres the problems we have described could well be present in other hospitals and be contributing to morbidity among theatre staff. We recommend that such humidifiers be inspected and tested for the presence of humidifier-fever antigens. We have found it difficult to keep our humidifier free of antigens and a different type may have to be installed.

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Drug-induced haemolysis and fast haemoglobin A_1 in diabetes mellitus

Measurement of the fast components of haemoglobin A_1 (HbA_1) has created a new dimension in the assessment of blood glucose control in diabetic patients, because abnormally high values reflect either intermittent or more constant hyperglycaemia during the life of the red cell.[1 2] Although haemolytic anaemia is known to cause falsely low HbA_1 values as a result of increased red cell turnover,[3] it is perhaps not appreciated that even minor degrees of drug-induced haemolysis may have similar effects. We report the case of a chronically hyperglycaemic diabetic who had normal HbA_1 values associated with haemolysis induced by dapsone.

Case report

A 48-year-old diabetic man, whose disorder was well controlled by diet and glibenclamide 10 mg daily, attended the dermatology clinic in 1973 on account of dermatitis herpetiformis. Treatment with dapsone 100 mg three times a day was started. The haematological findings a month later and at subsequent visits are shown in the table. The patient returned to the diabetic clinic in 1978 because symptoms of uncontrolled diabetes had recurred while taking glibenclamide 10 mg daily and dapsone 100 mg twice daily. The blood glucose concentration two hours after breakfast was significantly raised at 21·8 mmol/l (392·4 mg/100 ml) yet a normal fast HbA_1 of 4·2% was recorded (upper limit of normal 8·5%; Isolab microcolumn method).

Haematological findings in diabetic with drug-induced haemolysis

Date	Drug treatment (mg/day)	Haemoglobin concentration (g/dl)	Reticulocyte count (%)	Heinz bodies	Plasma glucose concentration 2 h after breakfast (mmol/l)	Fast haemoglobin A_1 (%)
25 Sept 1973	Glibenclamide 10, dapsone 300	14·7	5	Absent	10·5	Not estimated
12 March 1974	Glibenclamide 10, dapsone 200	14·7	3	Absent	2·5	Not estimated
31 Aug 1978	Glibenclamide 10, dapsone 200	13·7	3	Absent	21·8	4·2
13 Dec 1978	Glibenclamide 20, dapsone 200	14·6	4	Present	23·8	3·7

Conversion: SI to traditional units—Glucose: 1 mmol/l ≈ 18 mg/100 ml.

Despite increasing the glibenclamide to 20 mg daily, one month later the postprandial blood glucose concentration remained raised at 23·8 mmol/l (428·4 mg/100 ml) and the fast HbA_1 was only 3·7%. Although the reticulocyte count was raised on each occasion Heinz bodies were found only once and the patient was never anaemic (table).

Comment

Although dermatitis herpetiformis is associated with thyroid disease, villous atrophy, and an increased prevalence of parietal cell antibodies haemolysis is not a feature.[4] In a series of 42 cases given oral glucose tolerance tests only one patient was diabetic. Dapsone, sulphasalazine, phenacetin, and many other drugs in high enough doses shorten red cell life by overwhelming the intracellular mechanism for maintaining haemoglobin in the reduced state with consequent methaemoglobin or Heinz body formation. Damaged cells will be preferentially removed from the circulation, particularly by the spleen. Older red cells have a lower enzyme content and are more susceptible to chemical damage. Increasing glycosylation of haemoglobin proceeds throughout red cell life,[3] thus premature destruction of older red cells removes an undue proportion of glycosylated haemoglobin (HbA_1) as well as inducing a compensating increase in the output of young cells with low HbA_1 content. Both these factors tend to produce false low HbA_1 measurements in diabetics treated with such a drug or in people with congenital haemolytic states such as congenital spherocytosis. On the other hand, in acquired haemolytic states such as autoimmunity red cells are randomly destroyed so that only the second factor operates and a lesser reduction in HbA_1 values is to be expected.

The findings in this patient, who was never anaemic, show that altered red cell turnover profoundly influences HbA_1 values. Recent doubts about the reliability of this test in assessing diabetic control[5] indicate that further methodological and clinical evaluation of its