properties at high blood concentrations. MacLeod and Lamberts³ have shown the dopamine agonist effects of high concentrations of haloperidol and pimozide on prolactin release. Seeman⁴ has shown that very high concentrations of some antipsychotic drugs may enhance presynaptic release of neurotransmitters, including dopamine.

Alternatively, at high concentrations of antipsychotic drugs maximal dopaminergic blockade may occur. Additional dosage increments would not produce further dopamine blockade, but other pharmacological effects, such as anticholinergic activity, might continue to increase and might be responsible for the presentations described. Toxic psychoses have been associated with high doses of anticholinergic drugs,⁵ usually combined with moderate doses of antipsychotic drugs. The episodes reported in these studies also appear to have been characterised by excitement and aggression, as in our cases.

Requests for reprints to Dr Bridges.

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Pseudomonas fluorescens cross-infection due to contaminated humidifier water

Ventilated patients in intensive therapy units are particularly susceptible to respiratory infections by Gram-negative organisms. In the case of *Pseudomonas aeruginosa* this susceptibility has been associated with the administration of broad-spectrum antibiotics, pre-existing immunosuppression, and corticosteroids.¹

Cross-infection has often been by way of contaminated ventilator equipment. This may be due to inadequate disinfection of the apparatus after use.² Dilution of topical anaesthetics with deionised tap water has produced an outbreak of *Ps cepacia* respiratory tract infection.³ *Pseudomonas* species are of a low order of pathogenicity and are rarely implicated as a cause of clinical infection. Nevertheless, they have been known to cause a granulomatous pneumonitis under certain circumstances.⁴

Patients and methods

During routine twice-weekly bacteriological monitoring of an intensive therapy unit *Ps fluorescens* was consistently isolated from the tracheal aspirates of those patients who had been ventilated for four days or more. Twenty-nine consecutive admissions for mechanical ventilation were finally analysed. Only seven of these patients were ventilated for four days or more, and from all these *Ps fluorescens* was isolated. *Ps fluorescens* was identified by means of both the analytical profile index (API Products Ltd) and fluorescein-pyocyanin production. All isolates had the same analytical profile index number, produced fluorescein only on King's medium, and had the same antibiogram.

On more detailed bacteriological examination of the intensive therapy units, *Ps fluorescens* was isolated from the humidifier water of all the ventilators in use, from the inspiratory tubing, and from the pre-filter expiratory tubing. At this time it was also noted that the temperature of the humidifiers, which are connected between the ventilator and the patient, was between 38°C and 41°C. Bacteriological examination was then performed on the humidifiers, humidifier water, and ventilator tubing before use. Only the

distilled water, used to fill the humidifiers, yielded *Ps fluorescens* (20 organisms/l).

The distilled water was delivered from the pharmacy in 8-litre plastic containers; one container was used for all the patients. The organism was isolated from the empty containers but not from freshly prepared distilled water collected into sterile specimen bottles directly from the distillation unit in the pharmacy. *Ps fluorescens* was not isolated on environmental screening of the unit. Suspicion was then directed to the 8-litre plastic containers. These were not sterilised or dried out before refilling and were therefore presumed to be acting as a reservoir for the *Ps fluorescens*.

In the light of these findings commercially prepared bottles of sterile water are now used. Each patient is strictly allocated his own bottle of sterile water for "topping up" the humidifier. Furthermore, the humidifiers are now operated at the manufacturer's recommended temperature of 50°C to maintain the inspired gases at the patient end at 37°C (Cape Engineering Limited, personal communication). The humidifiers and tubing are also renewed daily. After instituting this practice only two unrelated isolates of *Ps fluorescens* were found among the next 104 patients admitted to the unit.

Comment

Ps fluorescens causes clinical infection infrequently, but when this occurs treatment with appropriate antibiotics may be ineffective. Of the seven patients who had been ventilated for four days or more only one, a chronic bronchitic, developed a clinical infection which required treatment with gentamicin. The other six patients had supportive treatment with active and frequent physiotherapy and were gradually weaned from their ventilators. This cautionary tale shows how a change in clinical practice may lead to a potentially dangerous contamination of ventilators. It illustrates too the advantages of continuous bacteriological monitoring and of a close link between clinician and bacteriologist, both in prevention and eradication of cross-infection.

We thank the staff of the intensive therapy unit for their help and co-operation.

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Low bioavailability as a cause of apparent failure of dihydroergotamine in orthostatic hypotension

Dihydroergotamine (DHE) has been used to improve postural hypotension in patients with autonomic insufficiency. It constricts capacitance vessels and so lessens venous pooling on standing.¹ Comparative pharmacokinetic investigations with tritium-labelled dihydroergotamine after oral and intravenous administration to man suggest that on average about 30% of an oral dose is absorbed.² We describe two patients whose postural hypotension was greatly improved with intravenous DHE but whose apparent failure to respond to DHE by mouth was due to low bioavailability.

Case reports

(1) A 56-year-old diabetic man had symptoms of severe postural hypotension (standing systolic blood pressure less than 70 mm Hg) despite good diabetic control, a high sodium diet, and fludrocortisone 0.9 mg/day. Thirty minutes after being given DHE 10 µg/kg intravenously his standing systolic blood pressure had risen by 109 mm to 169 mm Hg and the postural drop in pressure had lessened from 84 to 17 mm Hg. Postural symptoms were relieved for several hours. Single doses of up to 10 mg DHE by mouth failed to reproduce the results of intravenous treatment nor was

there symptomatic improvement when he sucked a 12.5 mg lozenge made from crushed 2.5 mg DHE tablets,³ although his standing systolic pressure rose slightly. His symptoms were relieved between two and six hours after a single 30-mg dose of DHE by mouth and his standing systolic pressure, which had been below 30 mm Hg before DHE on that day, was 110 mm Hg at three hours and above 100 mm Hg for five hours. Giving 5 ml of a 2.5 mg/ml DHE suspension failed to affect the standing systolic pressure. Plasma concentrations of DHE measured by radioimmunoassay⁴ after the various doses are shown in the figure.

Plasma concentration of dihydroergotamine at various times after administration of 0.5 mg intravenously, 30 mg orally, a 15-mg lozenge, and 15 mg in suspension in case 1 and after 0.86 mg intravenously, 1.0 mg intramuscularly, and 25 mg orally in case 2.

(2) A 69-year-old woman with symptoms of severe autonomic insufficiency of the central pattern⁵ had been treated with fludrocortisone 1.5 mg/day and DHE 25 mg/day by mouth without significant benefit. Thirty minutes after she was given DHE 10 µg/kg intravenously her standing systolic blood pressure rose from 90 to 130 mm Hg and her symptoms improved. Her standing pressure gradually returned to pretreatment levels over the next four hours. A single dose of DHE 25 mg by mouth failed to affect her standing pressure or symptoms, but a deep intramuscular injection of DHE 1 mg caused a small rise in standing pressure. DHE 15 mg twice daily by mouth supplemented with 1 mg intramuscularly completely relieved her

postural symptoms and her standing pressure rose to over 100 mm Hg. This improvement was still maintained after two months, with a nurse giving daily injections in the patient's home. Chronic intramuscular injection produced no obvious adverse effect. Plasma concentrations at various times after intravenous, intramuscular, and oral dosage are shown in the figure.

Comment

The standing systolic blood pressure rose and symptoms were relieved in both patients after intravenous DHE when the plasma concentration of DHE was above 2 ng/ml. The initial failure of both to respond to DHE by mouth over the first four hours appears to be due to the low plasma concentrations obtained with oral DHE in doses below 30 mg. The bioavailability of DHE taken by mouth, calculated from the area under the plasma concentration-time curve, comparing oral and intravenous doses, was 1% and 0.5% for patients 1 and 2 respectively. We do not know whether the difficulty in achieving satisfactory plasma concentrations of the drug in these patients was due to poor absorption or high hepatic clearance. Attempts to increase bioavailability by giving DHE in suspension were unsuccessful. The lack of measurable plasma concentrations over the first two hours with DHE lozenges suggested that their effect was not due to buccal absorption but to absorption further down the gastrointestinal tract, similar to oral administration.

The problem of failure to respond to oral DHE may be resolved in some patients by giving bigger doses to achieve adequate plasma concentrations or, alternatively, by supplementary injections. Pharmacokinetic and pharmacodynamic studies of this drug are needed in patients with autonomic insufficiency and in normal subjects in view of possible abnormalities in gastrointestinal function and blood flow distribution in patients.

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ONE HUNDRED YEARS AGO It is proposed to open a cottage hospital for women at Walham Green in the western district of the metropolis. The plan has already met with distinguished patronage, and preliminary steps have been taken. The sketch which accompanies the prospectus represents seventeen cottages and a chapel ranged round a garden; the whole occupying an area of three acres. The hospital will afford "complete isolation" to each patient, i.e., each woman will have a room to herself. There will be only four patients in each cottage, and the whole will be constructed in such a manner that any cottage may be closed without affecting the others. The special objects which the promoters have in view are as follows: 1. To furnish a school for training the highest class of nurses, whose services may be available in the middle and upper ranks of society, as well as for district and parochial purposes in town and country; 2. To afford clinical instruction in obstetrics to medical men; 3. The safe delivery in the hospital of women whose homes are unfit; 4. To facilitate the delivery of the deserving poor at their own homes, if fit; 5. The treatment of diseases peculiar to women.—It is hoped that the income derived from the nurses, the pupils, and the paying patients, will make the institution entirely self-supporting. The committee do not, therefore, ask for annual subscriptions, but they solicit donations to the amount of £20,000 to meet the initial expenses. As a

means of raising this large sum, debentures have been issued of £50 and £100 each, secured in the freehold, bearing interest at 3 per cent, and carrying with them the privileges of governors; so that the return which the debenture-holders may expect for their money is estimated as equivalent to 6 per cent. This scheme is ingeniously devised, and there are features about it which will probably recommend it to the public; yet we venture to think that the medical profession will look upon it with some misgiving. It is questionable whether there is any advantage in bringing together lying-in-women even in a cottage. As we lately showed, the risks of maternity hospitals are so numerous and so subtle that, unless there is the most watchful supervision and management, women had far better remain in their own homes. With regard to the paying patients, we should be glad to know what scale of charges is to be adopted and what class of patients are to be received. The Hospital for Women in Soho Square is by many considered to have done great injury to general practitioners. The opening of a somewhat similar hospital in Walham Green is probably regarded with anything but favour by the medical men of the neighbourhood. We should like to call the special attention of the committee to this point, in order that their arrangements may be so carefully guarded as to avoid all just cause of complaint. (*British Medical Journal*, 1880.)