150 mg daily was started. The dose was increased to 200 mg daily in September 1977. At this time her other drugs were propranolol, guanethidine, and bendrofluazide. In February 1977 she developed pains in the anterior abdomen and thorax. Over the next nine months the pain spread to her wrists, elbows, shoulders, and right knee. She suffered from malaise and lost 6.4 kg. On admission to hospital in November 1978 her abdominal muscles were tender and she had conjunctivitis of the right eye. Two days after admission while still taking hydralazine, she developed diplopia and an inferior oblique muscle palsy and ptosis on the right side were observed. Results of investigations included erythrocyte sedimentation rate 92 mm in 1 hour, haemoglobin 10.3 g/dl; white cell count $2.4 \times 10^9/l$, normal differential count; normal appearances of bone marrow aspirate; no proteinuria; normal serum urea, creatinine, and immunoglobulin concentrations. Antinuclear antibody titre was 1/640 (IgG, homogeneous) and DNA binding was 12% (normal range 0-30%). The result of the latex fixation test was negative. A complement screen was normal. C1q binding material was found in fluid aspirated from the right knee. It was found in serum on only one out of five occasions.

Hydralazine was stopped and prazosin substituted. The diplopia resolved within three days. The joint and muscle pains improved slowly but continuously, the patient being almost symptom free four months later. Her weight returned to normal over a similar period. The leucopenia recovered over two to three weeks (figure). Three months after stopping the drug the antinuclear antibody titre was 1/160 and the ESR was 46 mm in 1 hour.

Response of total white cell count (●) and neutrophil count (○) to withdrawal of hydralazine. Hatching represents treatment with hydralazine 100 mg twice daily.

Metabolic studies—The patient was found to be a rapid acetylator on two occasions using sulphadimidine. A major product of acetylation of hydralazine is 3-hydroxymethyl triazolophthalazine. Both this and hydralazine were measured by gas chromatography⁴ in 0-24 h urine collections. The ratio of 3-hydroxymethyl triazolophthalazine to hydralazine is 1.1-2.5 for slow acetylators taking 200 mg hydralazine daily and 9.6-24.5 for rapid acetylators.⁵ For this patient the ratio was 3.8. Other urinary metabolites were measured and the amounts were characteristic of the slow acetylator phenotype. Details of these results and procedures will be published elsewhere.

Comment

Although this patient is a rapid acetylator of sulphadimidine her urinary metabolites when taking hydralazine were more characteristic of a slow acetylator. The metabolism of hydralazine is complex and, unlike that of sulphadimidine, includes several routes other than acetylation. One of these alternative pathways may be concerned in the development of toxicity. The activity of this pathway would probably be independent of acetylation, but slow acetylation would permit more of the drug to pass down the toxic pathway. If the toxic pathway were highly active, however, less drug would be available for acetylation and the lupus syndrome would develop despite the patient's constitution as a rapid acetylator.

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Department of Clinical Pharmacology, Royal Postgraduate Medical School, London W12 0HS

S J HARLAND, MB, MRCP, research fellow (present address: Institute of Cancer Research, Sutton, Surrey)

V FACCHINI, PHD, senior research officer

J A TIMBRELL, PHD, lecturer

Disturbed behaviour induced by high-dose antipsychotic drugs

Recently there has been a tendency to increase the doses of depot antipsychotic drugs in attempts to achieve better control of the more severe illnesses; two depot preparations have been introduced in concentrated form to facilitate this. We report on three patients with resistant schizophrenia who showed apparently paradoxical responses to high doses of these drugs.

Case reports

Case 1—A 27-year-old married woman with an eight-year history of schizophrenia relapsed after being well for three years taking fluphenazine decanoate 75 mg intramuscularly weekly when the dose was reduced. Her illnesses had always been characterised by disturbed behaviour, prominent delusions, and hallucinations. On admission the patient was severely disturbed; some control was achieved with oral chlorpromazine but, as there remained a serious management problem, intramuscular flupenthixol decanoate was substituted. The dose was titrated against symptoms and after three months 600 mg intramuscularly weekly was found to be effective and the patient was discharged without symptoms. After 10 doses she began to be excitable, restless, and overtalkative. The flupenthixol decanoate was reduced to 400 mg weekly with subsequent improvement. The patient has now been on this regimen for 2½ years and remains well. Procyclidine 10 mg three times a day has been needed throughout.

Case 2—A 20-year-old man with a four-year history of schizophrenia, most of this time spent in hospital, showed exacerbated symptoms. He had been receiving intramuscular fluphenazine decanoate 75 mg intramuscularly monthly and, after relapse, this was increased to 75 mg every three weeks; after three doses, however, he became excitable, overtalkative, and aggressive. These symptoms improved when his medication was replaced temporarily by oral chlorpromazine. He required no anti-Parkinsonian medication.

Case 3—A 27-year-old man had been admitted many times with episodes of schizophrenia characterised by florid delusions. When last discharged his illness was controlled on intramuscular flupenthixol decanoate 80 mg weekly. The patient failed to take his medication and on readmission he was again very deluded. He did not settle with oral chlorpromazine and a regimen of progressively increasing depot flupenthixol was begun. After a few weeks the intramuscular dose had reached 200 mg weekly. Two days after this injection he exhibited violent behaviour and attempted to stab a nurse with a knife. He remained excitable and aggressive but slowly settled with oral haloperidol. He needed no anti-Parkinsonian medication.

Comment

In all three cases the apparent relapse occurring with high drug dose was atypical for the patient, being characterised by excitement, restlessness, and aggression. Another brief article reported similar relapses, related to high doses of pimozide.¹

All antipsychotic drugs block postsynaptic dopamine receptors centrally. In schizophrenia there is a postulated functional hyperactivity of brain dopaminergic systems, which is supported by the finding that indirectly acting dopamine agonists, such as methylphenidate and amphetamine, may precipitate disturbed behaviour in patients with schizophrenia.² An explanation for the paradoxical responses reported may be that antipsychotic drugs have agonist

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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University of Cambridge Clinical School, Addenbrooke's Hospital, Cambridge CB2 2QQ

THOMAS R E BARNES, MB, MRCPsych, Wellcome research fellow

Department of Psychiatry, Guy's Hospital Medical School, London SE1 9RT

PAUL K BRIDGES, MD, PHD, senior lecturer

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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University Department of Bacteriology and Immunology, Glasgow G11 6NT

PENELOPE J REDDING, MB, BS, registrar

PAUL W MCWALTER, FIMLS, MIBIOL, senior medical laboratory scientific officer

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