from that among normal controls and patients with osteoarthritis. Immobility per se does not seem to be a primary factor as the patients with osteoarthritis did not show an increased prevalence compared with the control group.

Certain medical conditions, including pure iron deficiency, uraemia, pregnancy, gastrectomy, and carcinoma, are associated with the syndrome, providing potential clues about its mechanism.³ Interestingly, these conditions lead to either pure iron deficiency or anaemia of chronic disease, and anaemic patients experience more severe symptoms.⁴ As patients with rheumatoid arthritis characteristically develop the anaemia of chronic disease the increased prevalence of the syndrome observed in the group with rheumatoid arthritis may relate to this secondary complication.⁵

The combination of the restless leg syndrome and rheumatoid arthritis contributes considerably to discomfort and anxiety, and in our experience few doctors are aware of this condition.

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Torsade de pointes after astemizole overdose

Astemizole is a comparatively new long acting antihistamine (H_1) preparation. Histamine receptors are present in the heart, though their function is not clear.¹ No case of self poisoning with astemizole has been recorded. I report a case of acute ventricular arrhythmia that occurred after astemizole overdose.

Case report

A 16 year old girl presented to the accident and emergency department five hours after swallowing 20 tablets of astemizole (total dose 200 mg), which had been prescribed for allergic rhinitis (10 mg daily). She had vomited several times and claimed not to have taken any other medication or substance. Examination showed nothing abnormal. As she was still vomiting gastric lavage was not performed and she was admitted to the ward for overnight observation.

Seven hours after the overdose she suddenly became unconscious and was found to have no palpable cardiac output. A sharp blow to the sternum restored output and the electrocardiogram monitor confirmed sinus rhythm. She regained consciousness and was transferred to the intensive therapy unit. Pulse was 80/min

TOP: Standard lead II of a 12 lead electrocardiogram recorded on admission to intensive therapy unit showing Q-T_c interval 0.65 s (paper speed 25 mm/s).
BOTTOM: Strip of ventricular tachycardia characteristic of torsade de pointes (paper speed 25 mm/s).

and regular and blood pressure 100/60 mm Hg supine. There were no signs of cardiac failure or decompensation. One hour later she developed a spontaneous ventricular tachyarrhythmia requiring DC cardioversion with 150 J. Bolus intravenous lignocaine (100 mg) was given and an intravenous infusion of lignocaine begun at 4 mg/min for 20 minutes, reduced in steps of 1 mg/min every 40 minutes.

Investigation showed a haemoglobin concentration of 134 g/l and a normal white cell count. Serum biochemical values were normal, in particular potassium 4.0 mmol(mEq)/l, corrected calcium concentration 2.7 mmol/l (10.8 mg/100 ml), and albumin 43 g/l. Blood and urine sent for analysis to both the poisons unit at New Cross Hospital, London, and the pharmaceutical company marketing astemizole showed results consistent with astemizole overdose. Despite the lignocaine infusion further episodes of ventricular tachyarrhythmia occurred. An amiodarone infusion was therefore substituted with a loading dose of 300 mg followed by an infusion rate of 300 mg over one hour. This also failed to prevent episodes of ventricular tachyarrhythmia.

A 12 lead electrocardiogram recorded on admission to the intensive therapy unit and before the administration of antiarrhythmic agents showed a prolonged Q-T interval (figure). Q-T interval corrected for heart rate (Q-T_c) was 0.65 s (normal 0.36-0.42 s). Recorded strips of ventricular tachyarrhythmia showed the changing morphology of ventricular complex characteristic of torsade de pointes (figure). An isoprenaline infusion was begun at an initial dose of 1 µg/min, which shortened the Q-T_c interval to 0.58 s. Seventeen episodes of ventricular tachycardia occurred before the use of isoprenaline, 11 of which did not revert spontaneously or respond to a blow over the sternum and thus required DC cardioversion. One further episode occurred during the isoprenaline infusion. This was controlled by increasing the infusion rate.

Over the next five days the isoprenaline infusion was gradually reduced, the dose being governed by the Q-T_c interval. There were no further episodes of torsade de pointes. Serial electrocardiograms showed the Q-T_c interval to have reduced to 0.41 s before the patient left hospital. She was discharged home with advice not to take astemizole in the future. Follow up in the outpatient department confirmed that she was well with a normal Q-T_c interval.

Comment

Torsade de pointes is a recognised complication of treatment with antiarrhythmic agents, whose mode of action includes prolongation of the Q-T interval. Such drugs include membrane stabilisers (for example, lignocaine, flecainide); sotalol,² a β blocker with additional group III antiarrhythmic properties; and amiodarone. There are no reports, however, of torsade de pointes occurring after the use of either anti-H₁ or anti-H₂ antihistamines.

Astemizole is currently used in doses of up to 100 mg/day for mastocytosis. The events after the overdose in this patient (with 200 mg) question the safety of treatment with high dose astemizole.

I thank Dr P L Golding for permission to report this case.

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Exposure to quinalbarbitone sodium in pharmaceutical workers

Few studies have been reported of exposure to and absorption of drugs among operatives in the pharmaceutical industry. All too often the measures taken to prevent contamination of the product are believed to protect the worker also. In workers manufacturing oral contraceptive pills, however, gynaecomastia and menstrual disorders due to the absorption of ethinyl-oestradiol have been recorded,¹ as has adrenocortical suppression in workers making synthetic glucocorticosteroids.² We report finding a group of workers manufacturing quinalbarbitone sodium who were exposed to the drug and had absorbed measurable amounts, a hazard that would have been overlooked in the absence of biological testing.

Methods and results

A small pharmaceutical company manufactured quinalbarbitone sodium capsules using semiautomatic encapsulating machines. Filling the machine hoppers with quinalbarbitone sodium powder and inserting empty capsules into moulds were performed by hand. A female process worker developed a rash on

the hands, which was diagnosed by an employment medical adviser as endogenous eczema exacerbated by contact with quinalbarbitone sodium powder. The operatives routinely wore protective overalls and caps but no gloves or masks. To check whether possible systemic absorption of quinalbarbitone sodium by inhalation or skin contact was occurring blood samples were obtained from the six workers towards the end of the shift and analysed by specific ion mass spectrometry at the Health and Safety Executive Occupational Medicine and Hygiene Laboratories.

Blood quinalbarbitone sodium concentrations (table) approached those to be expected after an adult therapeutic dose, the highest being 3.9 µmol/l (93 µg/100 ml). For comparison single oral doses of 231 mg/70 kg body weight result, on average, in maximal blood concentrations of 8.4 µmol/l (200 µg/100 ml) after three hours.³ An adult oral dose of 100 mg quinalbarbitone sodium is sufficient to produce a hypnotic effect⁴ and, assuming a linear kinetic model, would produce a blood concentration of 4.2 µmol/l (100 µg/100 ml). Personal air samples from the breathing zones of six workers were analysed by high performance liquid chromatography; the mean concentration of quinalbarbitone sodium in the dust was 0.46 mg/m³ (range 0.08–1.49 mg/m³). Dust extraction was subsequently improved so that the highest concentration in the air samples fell to 0.36 mg/m³; operatives were also instructed to wear airline masks and surgical gloves. Despite these improvements we still detected quinalbarbitone sodium in blood samples taken towards the end of the shifts on two subsequent occasions (second and third surveys; table). Further discussions then disclosed that quinalbarbitone sodium powder regularly contaminated the home clothing worn beneath the protective overalls and that the wearing of gloves, but not airline masks, was being neglected. Skin contact with quinalbarbitone sodium powder had therefore continued to occur but further efforts to reduce exposure could not be made because the company had closed down.

Blood concentrations of quinalbarbitone in workers manufacturing capsules before and after measures to reduce exposure from inhalation of powder

	Before measures (first survey)	After measures	
		Second survey	Third survey
Blood concentration (µmol/l):			
Mean	1.7	1.0	0.6
Range	0.4–3.9	0.6–1.3	0.2–1.1
No of workers	6	4	6

Therapeutic blood concentration 4.2–8.4 µmol/l (100–200 µg/100 ml) (see text).
Conversion: SI to traditional units—Quinalbarbitone: 1 µmol/l=24 µg/100 ml.

Comment

In this plant exposure to quinalbarbitone sodium occurred initially through the inhalation of airborne powder during machine operation and filling of the hoppers as well as through skin contact. Wearing airline masks should have greatly reduced exposure from inhalation, but we surmised that skin contact had continued as a result of the airborne dust penetrating the protective overalls and from the failure to wear gloves regularly; the latter interfered with the fine hand movements required to handle the capsules. Despite the small number of operators available for study we concluded that substantial absorption of quinalbarbitone sodium was most likely to be occurring through the skin, a finding to be expected given that quinalbarbitone sodium is very lipid soluble⁴ but which to our knowledge has not been described before. Exposure may also have occurred by accidental ingestion of powder from contaminated hands, intentional self medication, or inadequate respiratory protection, but we considered that these were all less likely than skin absorption, which would have been overlooked if exposure had been assessed using dust in air alone.

The intermediate acting barbiturates such as quinalbarbitone sodium are still used as hypnotics in severe intractable insomnia and as sedatives in anxiety states. Although the workers were not apparently affected by the drug, repeated occupational exposure to barbiturates may place the fit worker at risk from adverse effects without any therapeutic advantage. These effects include tolerance and dependence, additive or synergistic interaction with other drugs or alcohol, induction of liver enzymes, and possible tumour promotion,⁴ though to our knowledge none of these has been reported in barbiturate workers. Increased proneness to accidents at work or elsewhere—for example, when driving—is also possible, especially if the workers are unaware that absorption of drug is occurring. Unlike barbiturates, very sensitive methods for measuring absorption are not available for most drugs, but our study shows the potential value of such testing in the occupational setting. In the United Kingdom exposure limits to airborne dust, but not biological limit values, have been set for only three drugs (aspirin, warfarin, and glyceryl trinitrate).⁵ Exposure limits for other drugs which address the problems of skin absorption, where applicable, are clearly needed.

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Synergism of spironolactone and lithium in mania

Plasma aldosterone concentrations are raised in manic patients.¹ Antagonism between aldosterone and lithium has been suggested because of their opposing effects on adenylyl cyclase.¹ The disorder in manic depression has also been attributed to altered membrane functioning through the action of aldosterone.² Moreover, endogenous aldosterone is active in the hypothalamus and may be localised there, as may spironolactone.² When six manic depressive patients were taken off lithium because of side effects spironolactone was substituted and follow up at one year showed that five of these patients were still in remission.²

It has been suggested that when diuretics, particularly thiazides, are used in conjunction with lithium, lithium toxicity may develop through hyponatraemia and excessive retention of lithium.^{3,4} A group of manic patients refractory to lithium at therapeutic serum concentrations were shown to become responsive, however, when lithium was combined with thiazides or a low sodium diet.⁵ The improvement of lithium action was not considered to be due only to the very small increases in serum lithium concentrations as many patients improved despite not having higher concentrations or in some cases having lower ones. Moreover, even when the lithium concentrations were raised during treatment with these combinations, if subsequently the dosage of lithium was increased without added thiazide or a low sodium diet patients did not show an equivalent improvement.⁵

Case report

A married, 42 year old woman had had recurrent manic illnesses over the past 15 years; for the past four years she had been maintained in remission with lithium alone (serum lithium concentrations 0.5–0.7 mmol(mEq)/l). During the past year she had suffered two manic relapses for which she had been treated in hospital elsewhere. During her first admission she received lithium, carbamazepine, and a course of electroconvulsive treatment and remained well for the next three months taking lithium alone. She was discharged after her second relapse taking verapamil, clonidine, and lithium and when seen two days later was found to be suffering from lithium toxicity (serum concentration 2 mmol/l). After inpatient treatment at a renal unit she was discharged on no medication. At this point she was admitted to a local hospital, where lithium was cautiously administered to a concentration of 0.68 mmol/l. Concurrently she was given spironolactone 100 mg a day; serum potassium concentrations were checked daily to prevent hyperkalaemia. Thioridazine 100 mg and promethazine 100 mg at night were given as necessary. Within 24 hours of starting the spironolactone she became deeply sedated. Because of possible synergism between lithium and spironolactone the lithium was stopped, although at this stage the lithium concentration was only 0.68 mmol/l. Over the next few days she became more alert, and she was discharged a week later in remission taking spironolactone 50 mg daily, thioridazine 100 mg at night, and promethazine 100 mg at night. Over the next four months the sedation at night was stopped but she continued to take spironolactone 50 mg; she remained well.