monocytes 2%). Direct aspiration of the shunt reservoir yielded clear cerebrospinal fluid, which on examination showed white cell count $0{\cdot}01 \times 10^9$/l, protein 0·35 g/l, and glucose 3·8 mmol/l (68 mg/100 ml). The cerebrospinal fluid showed Gram-negative pleomorphic bacilli. Multiple blood cultures were obtained, and he was started on gentamicin and cloxacillin. Four days after admission the infected shunt was removed; a striking clinical improvement followed. Cultures of cerebrospinal fluid, blood, and shunt all yielded a growth of *Br abortus* biotype 2. Serological tests for brucellosis were set up immediately after the cerebrospinal fluid and blood culture results became available. The titre in the saline agglutination test was 1/80, antihuman globulin test 1/1280, and complement fixation test 1/64. Blood samples were obtained from members of his family for serological investigation for brucellosis. The table summarises the results.

By the age of 7 he was asymptomatic and without hepatosplenomegaly. His hydrocephalus had been arrested, and the shunt had not had to be replaced.

Results of bacteriological and serological tests carried out on patient's family

Family member	Blood culture	Saline agglutination test	Antihuman globulin test	Complement fixation test
Father	No growth	1/160	1/320	—
Mother	No growth	1/20	1/80	—
Sibling 1	No growth	1/20		—
Sibling 2	No growth	1/80		—
Sibling 3	No growth	1/20		—

Comment

Ventriculoatrial shunt colonisation has been described as "early" when the symptoms appear two or three months after operation and "late" when the patient remains symptom free for several months or even years after operation.[3] The early cases have been shown to originate at operation, when bacteria normally present on the skin become implanted at the site of the operation and subsequently colonise the shunt. Late colonisation has been attributed to ascending colonisation from the tip of the atrial catheter after transient bacteremia.[4] Both types of colonisation have recently been shown to have the same aetiology, however, the onset of bacterial colonisation of the shunt occurring at operation.[3 5]

Most cases of brucellosis in man result from direct contact with sick animals or ingestion of unpasteurised milk from infected animals. Our patient had animal contacts in an area where bovine brucellosis is a problem. He had also taken unpasteurised cows' milk on several occasions. The infecting organism appears to have entered the shunt and the cerebrospinal fluid from the blood stream after septicaemia caused by *Br abortus*.

Treatment in shunt colonisation consists of removing the shunt and replacing it when the cerebrospinal fluid is sterile. In brucellosis the treatment of choice is tetracycline. Our patient was initially given antibiotics directed against the organism (*Staph albus*) most commonly responsible for shunt colonisation, and the infected shunt was subsequently removed. By the time culture results had become available the cerebrospinal fluid and blood were sterile and he had shown a remarkable clinical recovery without having been treated specifically for brucellosis.

We thank Mr Barry O'Donnell for permission to report this case. We are greatly indebted to Dr L R Hill of the Central Public Health Laboratory, Colindale, and Dr D J H Payne of the Public Health Laboratory, Portsmouth, for identifying the strains.

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Ketotifen overdose: surveillance of the toxicity of a new drug

Self-poisoning is often with drugs that have been selected indiscriminately by the patient with no knowledge of their effects.[1] Hence doctors may be faced with overdoses of new and unfamiliar compounds for which there is little information on the likely symptoms or the most appropriate treatment. Such advice as can be offered is usually based on extrapolation from toxicity studies in animals and from clinical experience with other, similar drugs, but the value of such information is questionable.

A recent example of this was provided by the introduction of the antiasthmatic drug ketotifen (Zaditen, Sandoz Limited), a selective mast-cell stabiliser with many features of an antihistamine. Through the National Poisons Information Service effective surveillance of the acute toxicity of a new compound can be monitored from the first recorded cases. Within four months of ketotifen being marketed eight cases of overdose had been reported and a reasonable estimate could be made of the acute toxicity of the drug in man.

Summary of cases

The table gives brief details of the eight cases. Gastric lavage was used in six patients, one (case 5) was given syrup of ipecacuanha, and in case 6 no attempt was made to empty the stomach. All eight patients received supportive treatment only and made a full recovery within 12 hours of admission. Toxicological screens were performed at the poisons unit and plasma ketotifen concentrations measured by Sandoz, Basle Limited, using mass spectrometry after gas chromatographic separation.[2]

Details of eight cases of overdose with ketotifen

Case No	Age (years)	Sex	Stated ingested dose (mg)	Symptoms	Comments
1	27	F	20	Confused, bradycardia	
2	21	F	120	Mild abdominal pain, headache	Plasma concentration of ketotifen-base 122 mg/l 20 hours after ingestion. Negative drug screen
3	34	M	40	Drowsy, bradycardia, confused	Plasma concentration of ketotifen—5 mg/l two hours after ingestion. Negative drug screen
4	23	F	60	Drowsy, nystagmus, tachypnoea	
5	6	F	10	Drowsy, disorientated, nystagmus, tachypnoea, tachycardia	Negative drug screen. Plasma concentration of ketotifen 16 mg/l five hours after ingestion
6	18	F	25	Drowsy, grand-mal convulsions, depressed respiratory rate, tachycardia	
7	21	M	50	Unconscious on admission; recovered consciousness in two hours	Negative drug screen. Plasma concentration of ketotifen 54 mg/l three hours after ingestion
8	20	F	60	Drowsy, confused, bradycardia	

Comment

Studies of the toxicity of ketotifen in animals suggested that likely symptoms of overdosage in man would include drowsiness, confusion, dyspnoea, cyanosis, tachycardia, hyperexcitability and convulsions. The predicted symptoms were quite accurate, although their severity appeared to be less than that initially expected. The experimental studies also suggested that induced diuresis could be of value. So far, however, such treatment has not been needed.

Monitoring the clinical presentation and outcome in alleged drug overdosage can provide useful information,[3] but before the toxicity of a compound can be assessed with any certainty it is important to prove that the drug concerned was present in toxic amounts. Therapeutic plasma concentrations of ketotifen range from 1 to 4 mg/l. Thus case 3 is typical of many patients who patently did not take the dose of the drug which was claimed, while in case 2 the patient had definitely

taken a massive overdose compatible with the stated amount. Assessing drug toxicity in overdosage is also complicated by the frequent occurrence of multiple drug overdoses. Thus negative results from a comprehensive toxicological screen,[4] as in cases 2, 3, 5, and 7, are important to establish that the symptoms observed are due to the alleged overdose.

Illingworth and Prescott[5] recently reviewed the information on drug overdosage in manufacturers' data sheets and concluded that the information provided was often inadequate and sometimes inaccurate. We believe that our report shows that co-operation between the National Poisons Information Service and manufacturers can be an important factor in correcting these shortcomings.

We thank the many doctors who helped to collect these data and Sandoz Limited, UK and Basle, for their co-operation.

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Persistent involuntary movements after treatment with flupenthixol

Flupenthixol decanoate, a thioxanthene derivative chemically similar to the phenothiazines, is a depot neuroleptic used in the treatment of psychosis. We describe a patient who developed intractable, involuntary movements after treatment with this drug.

Case report

A 17-year-old boy developed a paranoid psychosis with auditory hallucinations and was admitted to psychiatric care in May 1979. He had been a full-term, low-cavity forceps delivery and had had normal milestones and average scholastic ability. A febrile convulsion at age 3 had been followed by several major fits during the next year. From then until this admission he had been treated with phenytoin and had no further seizures. There was no family history of neurological disease, and physical examination was normal. Treatment was started with chlorpromazine 300 mg daily and electric convulsion therapy. He made a good recovery and was discharged, but was re-admitted in August 1979 with a relapse. Treatment was started with depot flupenthixol alone 40 mg monthly.

Three months later his mother noticed that he was walking on the outside of his feet. After discharge in January 1980 this became more pronounced and he developed in addition involuntary limb jerking and dystonic hyperextension of the neck and trunk. These involuntary movements started after each injection and lasted for about two weeks. A period of normal motor activity then followed until the next injection. This symptom-free period gradually shortened until the movements were continually present. A total of 360 mg flupenthixol was administered over a nine-month period. His condition did not improve on stopping treatment, despite anticholinergics being given, and he was transferred to the neurological unit in June 1980.

On examination he was found to have severe, continuous movements of neck, trunk, and limbs, with spasmodic myoclonic jerking of arms and legs. He was sweating profusely, feverish, unable to sit or stand unaided, and had to be fed. No other abnormality was evident. Serological and copper studies yielded negative results, and cerebrospinal fluid, a computed tomogram, and an electroencephalogram were normal. Limb myoclonus improved on administration of intravenous clonazepam, and oral treatment with 3 mg thrice daily was started. Neither this, nor the subsequent introduction of pimozide, had any effect on the dystonic movements. Over six months he improved sufficiently to walk unaided. Dystonic posturing of neck and trunk persisted, however, particularly on exercise.

Comment

Dystonia as a side effect of neuroleptic medication is most often seen in young people.[1] It usually occurs during the first week of treatment and responds to anticholinergics and withdrawal of the drug. Neurological sequelae to accidental tranquilliser overdosage in children are seen more often in those with an abnormal birth history or who had childhood convulsions.[2] Persistent dystonia after chlorpromazine has been described in a brain-damaged child.[3] Our patient had been a forceps delivery and had had several seizures as a child, but we have found no report of persistent dystonic side effects occurring in patients with minimal epilepsy. Protracted choreathetosis occurred in one patient after treatment with depot flupenthixol, but in this case only mild dystonia and no myoclonus was reported.[4] Flupenthixol has been suggested to be the depot preparation most likely to cause generalised chorea, but there is no evidence to suggest that it induces other extrapyramidal disorders more often than similar preparations.[5]

The development of involuntary movements in this case were clearly associated with the administration of depot flupenthixol. We believe that it is important to draw attention to this complication of treatment; as our case suggests, patients with a history of birth trauma or childhood convulsions may be particularly at risk.

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Dangers of amiodarone and anticoagulant treatment

An interaction between the antiarrhythmic drug amiodarone and the anticoagulant warfarin has not been reported previously. We describe a patient in whom the addition of amiodarone on two occasions led to dangerous increases in the anticoagulant effect of warfarin treatment. We confirmed the generality of the phenomenon in animal experiments.

Case report

A 57-year-old woman with rheumatoid arthritis who had had a cerebrovascular accident attributed to embolus associated with intermittent atrial fibrillation was treated with warfarin (3 mg daily). Rhythm monitoring showed episodes of supraventricular tachycardia, sinus bradycardia, and atrial fibrillation with fast ventricular response. Sinoatrial disorder was diagnosed and a permanent pacemaker inserted. After trials of other antiarrhythmic drugs, treatment was started with amiodarone 200 mg thrice daily, and on the same day the daily dose of warfarin was increased from 3 mg to 5 mg because the British corrected ratio of prothrombin times (BCR) was only 1·5 (figure). The BCR rose, and the patient developed gastrointestinal bleeding, requiring treatment with vitamin K.

One month later she was admitted to hospital elsewhere after another cerebrovascular accident, and treatment with warfarin was restarted. She had inadvertently stopped taking amiodarone three weeks before this admission. She was transferred back to our care and amiodarone was started again, but on this occasion warfarin was stopped on the same day because of the suspicion of possible interaction. The BCR, which had been steady at 2·5 for the preceding three days, rapidly rose to 4·5 after adding amiodarone (and stopping warfarin) and remained at this level until treated with vitamin K four days later (figure).