SALES AND % DISTRIBUTION OF BENZODIAZEPINES REPORTED IN SUDDEN DEATHS

Drug	Sales (%)	As part of medication		As sole drug	
		Deaths	Suicides	Deaths	Suicides
Triazolam	29	10 (95)*	11 (47)	15 (31)	18 (14)
Temazepam	24	31 (294)	35 (146)	25 (50)	22 (17)
Midazolam	5	8 (77)	8 (31)	9 (8)	6 (5)
Oxazepam	20	39† (370)	30† (122)	43† (87)	47† (37)
Lorazepam	12	6 (60)	7 (29)	2 (5)	1 (1)
Alprazolam	10	6 (61)	9 (37)	6 (13)	6 (5)

*As % (column totals to 100%) and, in parentheses, numbers of cases.
†$p < 0.001$.

if triazolam is associated with paradoxical behaviour and other similar disturbances, this is not reflected in violent, sudden, or otherwise unexpected deaths. On the contrary, such deaths seem to be more associated with the "safer" benzodiazepines, oxazepam, temazepam, and midazolam.

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Spontaneous reporting of adverse reactions to psychiatric drugs

SIR,—The UK drug regulatory authorities (Medicines Control Agency and Committee on the Safety of Medicines [CSM]) rarely submit to public scrutiny, but on March 19 they will be represented at the official inquiry into Ashworth Hospital. Many of the questions they will face concern a patient who died in 1988 while taking pimozide 40 mg per day for 3 weeks plus trifluoperazine 15 mg daily; expert evidence to the inquiry has suggested pimozide toxicity as the likely cause of death.

The dosage of pimozide given to this patient was well below the maximum (60 mg) given in the 1988 data-sheet but twice as high as the maximum recommended in the USA, where pimozide was indicated only for Tourette syndrome. Pimozide was not recommended in the USA for schizophrenia because of the high risk of potentially fatal cardiovascular complications.[1] Since 1984, the US authorities have advised of the need for baseline and periodic electrocardiography, especially after dosage adjustment. Similar precautions, and reduction of the maximum dose to 20 mg daily were adopted by the CSM in August, 1990—only after it had received yellow-card reports of arrhythmias and 13 sudden deaths associated with pimozide.[2]

This is one of many cases in which UK drug regulators seem to have failed to act, long after risks were known, waiting instead until confronted with clear evidence of harm.[3] This policy reflects over-reliance on spontaneous adverse drug reaction (ADR) reporting, via the yellow-card system. Since its introduction in 1964, the yellow-card scheme has been successful in flagging some drug problems, but it has failed to gain acceptance by prescribers[4] and the CSM itself estimates that it receives reports of no more than one serious ADR in every 10.[5] The few dozen yellow-cards received by the CSM on some ADRs (eg, tardive dyskinesias,[6] and benzodiazepine dependence[3]) suggest that reporting levels of 1 per 1000 might sometimes be closer to the mark.

In other ways, psychiatric drug prescribing all but defeats the yellow-card system. One is polypharmacy: if patients are treated simultaneously with several neuroleptic drugs how can the yellow-card scheme resolve which was (were) responsible? Another difficulty is the prescribing of neuroleptic drugs at dosages far above the recommended maxima: we fear that these are the cases least likely to be reported if ADRs develop. We are also concerned about the apparently disproportionately high rate of drug injury among black patients. If this is so, yellow cards would mask it because they do not ask prescribers to record ethnic background. We have approached the Commission for Racial Equality about this.

The Ashworth Hospital inquiry will, we hope, at least touch on these issues, but only a full public inquiry into drug injury can resolve them.

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Hyperpyrexia and rhabdomyolysis after MDMA ("ecstasy") abuse

SIR,—Professor Schifano (Nov 23, p 1335) reports chronic atypical psychosis in a young man after 3,4 methylenedioxymethamphetamine (MDMA), "ecstasy", abuse. We agree that it is a far from harmless recreational drug, and have lately treated three patients in whom severe complications developed after taking MDMA.

Patient 1—A 19-year-old man presented in an acute confusional state, having been found outside a nightclub banging his head against the pavement. His core temperature was 43·3°C, and he had dilated pupils, tachycardia of 160 beats per min, and muscular rigidity. A deep laceration was noted over the occiput, which was fractured. He became progressively comatose in the next 15 min and needed mechanical ventilation. Presumptive diagnosis of amphetamine poisoning was made, which was subsequently confirmed by blood and urine analyses showing traces of amphetamine and MDMA. Initial treatment included rapid cooling with iced water, gastric lavage, bladder irrigation, and rehydration with cooled isotonic saline. His temperature was reduced to 38°C within 1 h. He began to bleed from the mouth and via the nasogastric tube while in the emergency room. Disseminated intravascular coagulation (DIC) was diagnosed, with platelet count of 40×10^9/l, prothrombin time 32 s (control 15), and fibrin degradation products (FDP) 32–64 mg/l. 1 h after admission the urine became dark brown, suggestive of rhabdomyolysis. This was later confirmed by a positive test for urinary myoglobin and plasma creatine kinase (initially normal) of 44 500 U/l. Computed tomography showed multiple cerebral haemorrhages. He was given platelet and fresh frozen plasma transfusions, and forced diuresis with mannitol. His neurological condition deteriorated, resulting in death.

Patient 2—A 19-year-old man, who claimed not to have taken the drug before, was given MDMA at a nightclub by friends. He became acutely confused and collapsed. On arrival at the emergency department, he had a core temperature of 41°C, muscular rigidity, and supraventricular tachycardia of 180 beats per min. He was rapidly cooled with ice and transferred to intensive care for mechanical ventilation because of inadequate airway. DIC developed during the next few hours, with platelet count falling to 28×10^9/l, international normalised ratio (INR) rising to 2·78, and positive D-dimer test. He was given platelet and fresh frozen plasma transfusions. Rhabdomyolysis developed within 2 h of admission with peak plasma creatine kinase of 29 700 IU/l. This was treated aggressively with forced alkaline diuresis induced with mannitol

and bicarbonate, which limited renal damage, with the plasma creatinine peaking at 250 μmol/l. 36 h after admission compartment syndromes developed in both lower legs. Decompression fasciotomies were done, and a considerable amount of necrotic muscle was present that needed resection. He made a full neurological recovery, but because of muscle loss, his walking remained severely impaired.

Patient 3—A third 19-year-old man was admitted after collapse, again while at a nightclub with friends. By contrast with patients 1 and 2, he had taken MDMA before, and on the night of admission had taken three tablets. His clinical presentation with pyrexia of 40°C, muscular rigidity, and tachycardia was similar to the other two patients. He was rapidly cooled and treated with forced alkaline diuresis. His clinical course was less problematic, although rhabdomyolysis developed with creatine kinase changing from normal to 3940 IU/l, as well as mild coagulopathy (INR 1·63), which did not need specific treatment. He discharged himself 30 h after admission.

The acute medical problems of amphetamine abuse have been rarely reported in the UK. Toxicity can occur with small doses, especially in the occasional user. It may be important that all our patients were young men admitted from nightclubs, where prolonged vigorous dancing and alcohol in a hot environment may well have compounded the effects of MDMA by causing hyperpyrexia with subsequent rhabdomyolysis and DIC. Hyperpyrexia and rhabdomyolysis after amphetamine ingestion have been reported in the USA.[1,2] The syndrome resembles heatstroke, and it may well be the hyperpyrexic response to amphetamine that sets in train the sequence of events leading to rhabdomyolysis and DIC.

We believe that the most important step in the management of these patients is rapid cooling, since hyperpyrexia may well be the initiating factor for rhabdomyolysis and DIC. A forced diuresis with mannitol should be established to enhance myoglobin clearance and prevent acute renal failure.[3] Alkalinisation of the urine, which is usually recommended in rhabdomyolysis, will reduce renal clearance of amphetamine; conversely, acidification of the urine, which is suggested for the treatment of amphetamine poisoning, will enhance renal damage by myoglobin.

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Endotoxin antibody for sepsis in infants

SIR,—Dr Syed and colleagues' description (Feb 22, p 496) of an infant with meningococcal sepsis treated with monoclonal antibody to endotoxin (HA-1A) raises important issues.

A European multicentre, randomised, placebo-controlled trial of HA-1A in children with fulminant meningococcal septicaemia is in progress. Those taking part feel that the empirical use of HA-1A in such children is not justified on the basis of clinical trials of monoclonal antibodies against endotoxin in adults with gram-negative sepsis.[1,2] Although both those studies reported reduced case-fatality rates in the treated groups, they gave discrepant results for the subgroups in which most benefit was found. The trial of E5[1] revealed most benefit in patients not in shock at entry, with a comparable reduction in mortality in bacteraemic and non-bacteraemic patients. In the trial of HA-1A[2] there was significant reduction in mortality in patients with gram-negative bacteraemia, the difference being most striking in those who were in shock at trial entry. Furthermore, data on epitope specificity and mode of action of these antibodies are not available.

Levels of circulating endotoxin are much higher in meningococcal sepsis[3] than in other gram-negative sepsis, and affect the release of the inflammatory mediators responsible for many of the clinical changes seen in the sepsis syndrome.[4,5] The use of E5 or HA-1A in meningococcal sepsis might therefore seem rational. However, there are theoretical reasons why their use might exacerbate the clinical status. If monoclonal antibodies were to increase the uptake of circulating endotoxin into neutrophils and macrophages this might cause increased release of inflammatory mediators. In mice, HA-1A did not suppress endotoxin-induced release of tumour necrosis factor and interleukin-6.[6]

The patient reported by Syed and colleagues improved, but around the same time inotropic support and fluid resuscitation were provided and metabolic acidosis was corrected, manoeuvres that could have led to a clinical response that might not have been instantaneous. Indeed a rapid response to HA-1A seems unlikely since the circulating endotoxin would have already precipitated the cascade of events known to cause the sepsis syndrome.

The risk of death from meningococcal septicaemia has not altered much in the past 30 years[7] and an adjuvant therapy is required. However, there is only anecdotal experience with HA-1A in children with meningococcal sepsis, and this antibody is only an investigational agent in these children. We understand the desperation clinicians feel when faced with a child with meningococcal septicaemia who is clearly getting worse but paediatricians should be encouraged to use conventional therapy and, if possible, participate in the trial.

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Single-blind Mazzotti test for onchocerciasis

SIR,—In the diagnosis of onchocerciasis, the Mazzotti test has a useful role in patients with mild infections whose skin snips are negative for microfilaria. By the traditional Mazzotti test, one observes the clinical reaction to a 50 mg test dose of diethylcarbamazine (DEC) in patients who are suspected of being infected with *Onchocerca volvulus*.[1] A positive response is characterised by an exacerbation or new onset of pruritis or rash within 24 hours of DEC administration. This response is the result of drug-induced microfilaria death in the skin of infected individuals.

One of the drawbacks of the Mazzotti test is that many indigenous persons and long-stay travellers living in endemic areas are very knowledgeable about the effects of DEC on those with onchocerciasis. Hence, one is faced with the dilemma of distinguishing the DEC-induced pruritic reaction from the placebo effect of the drug.

To overcome patient expectation bias we have devised a single-blind Mazzotti test. A 50 mg tablet of DEC is crushed, inserted into a capsule, and placed in a numbered envelope by our pharmacy. Two identical placebo capsules are similarly prepared. Patients are told what symptoms to expect with DEC administration, but are not told which envelope contains the active drug. They are instructed to take one capsule every second day; the capsule containing DEC is always given as the third dose. The rationale for this order is to avoid overlapping drug effect due to delayed onset of symptoms.

Our single-blind Mazzotti test was done on eight consecutive