DRUG POINTS

Stillbirth due to intravenous amphetamine

Drs J C DEARLOVE and T J BETTERIDGE (Yeovil District Hospital, Somerset BA21 4AT) and Dr J A HENRY (Guy's Hospital, London SE1 9RT) write: Misuse of amphetamines by pregnant women has been well described.[1] We report an intrauterine death that seemed to be causally related to an intravenous injection of amphetamine.

A 29 year old amphetamine addict was pregnant for the third time. Although she lived with her 6 year old son, her eldest daughter had been adopted. She requested a termination when she was nine weeks pregnant but made no further contact with her general practitioner. When she was 34 weeks pregnant she was brought to the accident and emergency department by a friend. She admitted having taken 500 mg of amphetamine intravenously two hours previously.

She was lean, agitated, flushed, and restless. Her pulse rate was 110/min. The fetal heart rate was 90-100/min and increased when she lay on her left side. She complained of abdominal pain. Over the next 20 minutes the fetal bradycardia worsened, and about 50 minutes later the fetal heart was inaudible.

Twenty four hours after admission she gave birth to a stillborn female infant weighing 3000 g. Postmortem examination showed no congenital abnormalities. A virological screen and chromosome analysis also gave normal results. The baby's cord amphetamine concentration was 0·11 mg/l and the plasma concentration 0·09 mg/l. The mother developed acute tubular necrosis but recovered without haemodialysis. She declined hospital follow up.

This is the first report suggesting amphetamine as a direct cause of fetal death, although deaths have been associated with chronic amphetamine misuse. Interestingly, Eriksson *et al* found that babies whose mothers misused amphetamine during pregnancy had a higher perinatal mortality, were more often born prematurely, and had a higher incidence of drowsiness neonatally (necessitating tube feeding) than those born to mothers with a history of amphetamine misuse who had stopped taking amphetamine during pregnancy.[2] Follow up of these children showed an increase in aggression and hyperactivity, suggesting that these were specific effects of chronic exposure to amphetamine in utero.[3] This prospective study was, however, hampered by not having a control group.

Although in our case there was a clear temporal association between acute maternal toxicity and sudden fetal death at 34 weeks, the evidence favouring a causal relation between the two is based on the mother's symptoms and signs of toxicity accompanied by an initial fetal bradycardia[1] and then death associated with a high cord amphetamine concentration.[4,5] In addition, other common drug metabolites were not detected in the maternal urine or the baby's cord blood.

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Overdose of yohimbine

Dr S VARKEY (Rotherham District General Hospital, Rotherham S60 2UD) writes: A 38 year old man with insulin dependent diabetes was admitted two hours after taking 350 mg of yohimbine. The drug had been prescribed by a consultant psychiatrist for erectile impotence complicated by depression.

On admission to hospital he was alert and oriented. His blood pressure was 130/80 mm Hg and his pulse regular at 88 beats/min. Six hours after admission he discharged himself. He was readmitted 17 hours later in a drowsy and confused state. He was having rigors and complained of retrosternal pain. As far as could be ascertained he had not taken any other drug. His rectal temperature was 35·5°C and his blood pressure 135/85 mm Hg. His hands and feet were warm and well perfused. Blood urea concentration was 12·8 mmol/l, serum creatinine 175 μmol/l, and blood glucose 16·7 mmol/l. An electrocardiogram showed atrial fibrillation with a ventricular rate of 150 beats/min. The day after admission an electrocardiogram showed sinus rhythm, and retrograde amnesia for the preceding 24 hours persisted for four days.

As far as we are aware, atrial fibrillation and loss of memory after an overdose of yohimbine have not been reported before. Only one case of yohimbine overdose has been reported in English journals.[1]

Yohimbine is an indole alkaloid derived from the yohimbine tree (*Pausinystalia yohimbe*), which grows in west Africa and the Congo. This drug has predominantly α_2 antagonistic actions. Recent trials showing yohimbine to be useful in men with vascular, diabetic, and psychogenic impotence[2,3] have caused a surge in prescriptions for the drug. The number of suicide attempts in which yohimbine is taken is therefore likely to increase.

I cannot explain the 17 hour delay between this patient taking the drug and developing atrial fibrillation, drowsiness, and confusion and suffering a drop in body temperature. Studies of the pharmacokinetics of yohimbine have shown its plasma half life to be roughly 35 minutes,[4] but a latency of response of two to three weeks after the start of treatment was noted in men with psychogenic and organic impotence.[3] The atrial fibrillation is probably due to noradrenergic blockade by yohimbine on α_2 receptors in the central nervous system. At high doses yohimbine no longer acts preferentially on α_2 receptors and instead causes peripheral α_1 blockade.[5] This would explain the peripheral vasodilatation and drop in body temperature. It is not clear whether the amnesia is a specific effect of yohimbine or a non-specific psychogenic response to stress.

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Fatal toxic epidermal necrolysis associated with etretinate

Dr ANDREW MCIVOR (Wellesley Hospital, Toronto M5R 1A8, Canada) writes: Dermatological side effects of etretinate are well recognised. The most prominent is peeling of the skin on the palms and soles. Patients complain of dryness of the lips and mucous membranes, which may result in epistaxis and conjunctivitis. About a tenth of patients describe a subjective change in their oral mucosa.[1] Recently, however, a patient developed fatal toxic epidermal necrolysis 16 days after starting etretinate.

A 65 year old east African man with a 16 year history of psoriasis started taking etretinate 25 mg twice a day (0·75 mg/kg/day). He had no history of erythroderma or pustule formation. His main complaint was of psoriatic arthropathy, but he had had psoriatic skin lesions for the past eight years. His treatment included ultraviolet B light and coal tar preparations for the psoriasis and indomethacin 25 mg three times a day for the arthritis. He suffered from non-insulin dependent diabetes mellitus, for which he took chlorpropamide 100 mg daily, and chronic renal failure (serum creatinine concentration 360 μmol/l).

He responded well initially, but 16 days after starting etretinate he complained of a sore mouth and eyes and dysphagia. Ulcers developed on his mucous membranes and erythematous blisters on his skin. The blisters progressed rapidly with loss of epidermis over 40% of his total body surface area. A skin biopsy confirmed the diagnosis of toxic epidermal necrolysis. Despite prompt treatment with broad spectrum antibiotics and transfer to the intensive care unit he developed pseudomonas septicaemia with pancytopenia. His condition deteriorated, and he died 72 hours later.

Etretinate has been associated with photosensitivity and erythroderma.[2,3] Fragility of the skin was reported in one patient, who had alcoholic cirrhosis and toxic blood concentrations of etretinate.[4] The toxic effects of retinoids on the skin may be explained by the cytopathic effect of lysosomal enzymes. These are released when lysosomes are destabilised by vitamin A and its derivatives and cause separation and degeneration of keratinocytes.[5]

No other cases of toxic epidermal necrolysis associated with etretinate have been reported to the manufacturer. Owing to the other adverse effects associated with the drug the manufacturer states that it should be prescribed only by doctors who are experienced in using systemic retinoids and only to patients who are unresponsive to, or intolerant of, standard treatment. Etretinate is contraindicated in patients with glomerular filtration rates less than 50 ml/min. Caution is also advised in diabetes mellitus. Use of the full dose in our patient may have contributed to the development of toxic epidermal necrolysis. Extra vigilance and perhaps a smaller starting dose should be considered in all patients with even mild renal impairment. Mucous membranes should be inspected and the possibility of toxic epidermal necrolysis considered during etretinate treatment.

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