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CASE REPORT

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Skin absorption of Dexamphetamine base – a case report

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Introduction

Dexamphetamine, the biologically active dextrorotary enantiomer of amphetamine, is a non-catecholamine analogue of the biogenic amine methylphenethylamine, which in humans causes marked central nervous system arousal in addition to increased peripheral sympathomimetic activity (Dollery et al. 1991). Because of its potential for abuse and the risk of drug induced psychosis, its therapeutic use is limited. Dexamphetamine has also been used as a pharmacological tool in experimental psychiatric research and is also used as starting material in organic chemical synthesis.

I here report an accident where Dexamphetamine base was inadvertently poured on to my clothes in connection with a biochemical experiment. The solution was absorbed through the skin and pronounced symptoms of systemic poisoning appeared early and persisted for 30–50 h. A plasma concentration of Dexamphetamine of 0.52 $\mu g \cdot mL^{-1}$ was determined 150 min after the accident and were followed during the 1st day. The amount absorbed was estimated to be 200–400 mg, corresponding to 10 to 20% of exposed Dexamphetamine base.

Case history

I am a healthy 52-year-old pharmacist working part time in a nuclear medicine department and also taking part in research. I use no medicines. I was weighing Dexamphetamine base (>95% pure from Apoteksbolaget, Stockholm, Sweden) which was to be used in an animal experiment when I accidentally pushed the bottle so that the solution poured on to my shirt and trousers and penetrated to the abdomen and thigh. About 8 ml out of 15–20 ml was left in the bottle and at least 2 ml and 2–3 ml of the solution was poured on to my shirt and trousers, respectively. In a few minutes I took off my trousers and washed them with water and 70% ethanol in order to dissolve the Dexamphetamine base. The incident was reported to a fellow chemist, the table and floor were washed and the work finished. Some 15–20 min after the accident, I also realized that Dexamphetamine base had penetrated the shirt as I became aware of a sensation of heat affecting the skin, and then immediately poured several litres of water over the shirt and skin. At this moment, about 30 min after the accident I realized that there was a risk of skin absorption, but nevertheless chose to sit down and work at the computer. Some dizziness and increasing difficulty in managing easy computational tasks revealed that absorption of Dexamphetamine base had indeed occurred. A sensation of heat was felt on the stomach and also on the thigh. I was visited by a physician, who about 2 h after the accident referred me to the emergency department of the hospital. My blood pressure was 230/115 mmHg. An electrocardiogram (ECG) revealed no abnormalities and the pulse rate was 88 beats / min^{-1}. A grade 1 and 2 burn wound which was 10 cm in diameter was found on examination of the abdomen. Further symptoms, all confirmed by medical professionals throughout the study, were dry mouth, diaphoresis, headache, slight nausea and the fact that I was very talkative. I was referred to the department of medicine for further supervision. Oral metoprolol 100 mg was given but resulted in orthostatic symptoms and therefore felodipine 10 mg was given instead and this was better tolerated. I also noticed marked decreased appetite, reduced sensitivity with almost no pain from the wound, unawareness of a slight fever, ''rapid'' brain activity and that I was very talkative. A slight mydriasis was also observed.

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The pulse rate was constantly around 100 beats/min^{-1}, but the blood pressure gradually decreased to 180/100 mmHg 12 h after the accident. After about 16 h a sharp heating sensation from the wound occurred simultaneously with an increase in blood pressure to 195/105 mmHg. A slightly increased body temperature of 37.6 °C was also measured. Peripheral symptoms, such as inability to empty the bladder, low intestinal mobility and diaphoresis remained for at least 30 to 40 h. I also had an episode of tachycardia together with abdominal cramps, which occurred after about 36 h. The ability to sleep was regained 48 h after the accident. My appetite was still poor. The blood pressure had returned to 160/90 mmHg at this time point. I was discharged from hospital on the 2nd day after the accident. A pronounced feeling of a "jet lag" was recognized. The wound healed 10 days after the accident without complications. Sleep was irregular and an episode of anxiety was noted on the morning of the 5th day after the accident; otherwise no other symptoms were noted.

I organized blood sampling with 3- to 4-h intervals during the 1st day. Plasma was separated and stored at −18 °C until analysis. Plasma Dexamphetamine concentrations were determined by mass spectrometry (MS) following chromatographic separation at the National Board of Forensic Medicine, Department of Forensic Chemistry, Linköping, Sweden. The lower limit of determination of the method was 0.03 $\mu g \cdot mL^{-1}$.

Results

Absorption of Dexamphetamine base through the skin was rapid and the highest plasma concentration was seen in the first sample, taken about 2.5 h after the accident. Plasma concentrations of Dexamphetamine declined with an initial rapid phase and thereafter an elimination half-life of 10 h was determined. The absorbed amount was estimated to be 200–400 mg of Dexamphetamine base on the basis pharmacokinetic information of a volume of distribution of $L \cdot kg^{-1}$ 5 $L \cdot kg^{-1}$ (Dollery et al. 1991). Due to uncertainties about the actual volume of distribution, the volume of Dexamphetamine on the clothes and time of exposure, the absorbed fraction can only be estimated to be 10 to 20% of the exposed amount of Dexamphetamine. Typical symptoms of Dexamphetamine overdose were noticed; the peripheral symptoms vanished after 30–36 h, whereas others such as loss of appetite and insomnia were still obvious on the morning of the third day and then disappeared slowly.

Discussion

The first lesson to be learnt is that even the most experienced person in chemistry does not act rationally when at risk. I have for many years taught precautions against chemical hazards to students in the university. However, when exposed, I did not follow these simple guidelines and instead was more anxious to clean up and have the Dexamphetamine loss reported than to attend to the Dexamphetamine base which had poured on to my body.

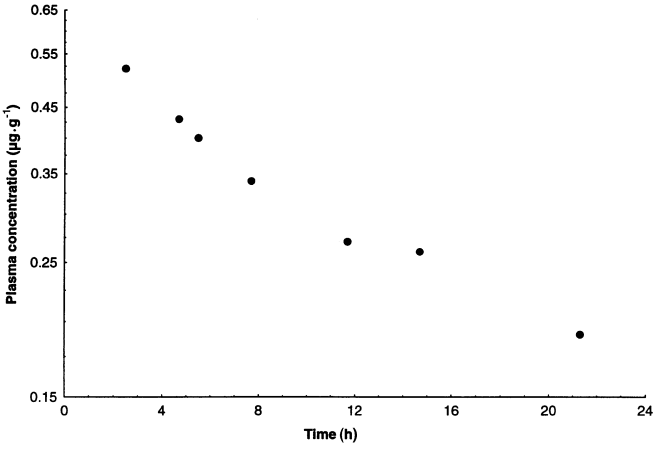

Fig. 1 Plasma concentrations of dexamphetamine following accidental skin absorption

The second lesson to be learnt is that Dexamphetamine as a base was readily absorbed by the skin. Symptoms appeared rapidly and the highest plasma concentration was already seen in the first blood sample taken about 2.5 h after the accident. The amount of Dexamphetamine that came into contact with the skin cannot be judged exactly. An absorbed amount of 300–400 mg would seem plausible from pharmacokinetic information on Dexamphetamine volume of distribution and plasma concentrations in recent reports (Angrist et al. 1987; Brown et al. 1979; Shappell et al. 1996), corresponding to an absorption of 10–20% of the Dexamphetamine through the clothes. Percutaneous absorption of amphetamines has been studied recently by application of the pure base on to cleaned skin (Vree 1973). The absorbed fraction judged from the urinary excretion was low, $< 1\%$. However, excretion of amphetamine occurs also via sweat glands resulting in an underestimation of the absorbed dose (Vree et al. 1972). Good percutaneous absorption of organic bases such as ephedrine (Beckett et al. 1972) has been shown, and transdermal preparation of the analogue bases e.g. phenylpropanolamine (Devan et al. 1991) and selegyline (Barrett et al. 1997) showed similar plasma concentrations as after the same oral dose. Thus, estimations of absorbed amounts from plasma concentrations of Dexamphetamine comply with a high and rapid skin absorption of organic bases.

A further lesson is that Dexamphetamine is a strong base (pKa 9.9) and may cause severe wounds to the skin, which in this case required medical supervision and treatment. Interestingly, a second plasma concentration peak was traced at the time when blood pressure, pulse and body temperature increased slightly about 16 h after the accident. This phenomenon was probably due to a vasodilatation in the wound area occurring late after the

accident with some further uptake of Dexamphetamine base. The measured elimination half-life of Dexamphetamine of 10 h is similar to that reported in adults after administration of low doses of amphetamines (Beckett and Rowland 1965; Cook et al. 1993; Dollery et al. 1991). Acidification of urine may increase elimination of unchanged amphetamines and an elimination half-life of 7 h has been reported for Dexamphetamine with a urinary pH = 5 (Beckett and Rowland 1965, Vree 1973). Overdose of amphetamine may therefore require treatment with ammonium hydrochloride to enhance elimination rate (Rowland and Beckett 1966). High plasma concentrations still remained at discharge from the hospital when symptoms had mainly vanished. A shorter duration effect of Dexamphetamine in relation to the slow plasma elimination has been reported previously (Angrist et al. 1987; Brauer et al. 1996). Dexamphetamine-induced effects declined after 2-h following a low dose oral dose of 0.25 $mg \cdot kg^{-1}$, and following a higher dose of 0.5 $mg \cdot kg^{-1}$ after about 4 h (Angrist et al. 1987).

The primary effect of Dexamphetamine was a rapid increase in both systolic and diastolic blood pressure due to vasoconstriction caused by stimulating action on peripheral α- and β-adrenoreceptors. Accidental death due to amphetamine overdose is rare. However, risks of intracranial haemorrhage have been clearly associated with abuse of amphetamine and oral doses as low as 20 mg have been claimed to be responsible for intracerebral haemorrhage (Dollery et al. 1991). The pathogenesis is not established but the hypertensive effect of acute Dexamphetamine administration was explained as the precipitating event, although in some cases associated with a pre-existing vascular malformation (Goodman and Becker 1970). A case of aorta dissection has recently been reported (Dihmis et al. 1997). Dexamphetamine use has also been associated with a hypermetabolic state and in some cases with death due also to a cardiovascular collapse (Dollery et al. 1991). Plasma concentrations less than 0.5 $\mu g \cdot L^{-1}$ are not usually associated with serious toxicity (Dihmis et al. 1997).

Dexamphetamine releases a newly synthesized pool of dopamine and other monoamine transmitters in the brain (Butcher et al. 1988). This transmitter release causes the alerting as well as anorectic and locomotor stimulating effects. The releasing effect is thus limited to a fraction of dopamine (Hartvig et al. 1997) and hence higher Dexamphetamine doses might not further aggravate symptoms. Dexamphetamine has dual effects on synaptic dopamine concentrations since it also inhibits the re-uptake of dopamine from the synaptic cleft (McMillen 1983). The re-uptake dopamine transporter thus balances synaptic neurotransmitter content (Leshner 1996). These effects, with the exception of the high dose and drug-induced alteration of receptor sensitivity (Brown et al. 1979) may explain the long duration of CNS effects experienced. Although, an uneventful clinical outcome and recovery was experienced, Dexamphetamine base should be regarded as a potential hazard when handled. Furthermore, organic amines are strong bases, which may cause severe burn wounds and may readily penetrate the skin in uncharged form.

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