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Saving two lives with one dialysis treatment

Successful treatment of life threatening diphenhydramine intoxication by intermittent hemodialysis using a high cut-off membrane

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Key words
extended dialysis – hemoperfusion – intoxication

Abstract. Hemodialysis is the extracorporeal treatment of choice for various life-threatening intoxications, with the exception of highly protein-bound substances, which are preferably removed by charcoal hemoperfusion. This technique, however, is limited by its availability and its significant side effects. We present a potentially life-threatening diphenhydramine (DPH) overdose in a stuporous female patient in which high cut-off hemodialysis was used. Timely detoxification resulted in rapid gain of consciousness, allowing the patient to state the existence and location of another poison victim.

Background

According to a recent statement of the Substance Abuse and Mental Health Services Administration (USA), there has been a significant rise in drug-related suicide attempts in the past few years. Especially hospital emergency department visits involving drug-related suicide attempts in people ages 45 to 64 doubled between 2005 and 2011 – rising from 28,802 cases in 2005 to 58,775 in 2011 [1]. According to the 30th Annual Report of the American Association of Poison Control Centers' National Poison Data System, 31,805 cases of diphenhydramine (DPH) exposures (over-the-counter strength) had been documented [2]. In ~ 8% of the 2,576 reported fatalities due to intoxications in 2012, DPH could be identified as the single or contributing toxin. DPH is a first-generation H1-antihistamine of the ethanolamine type. It has anticholinergic, antitussive, antiemetic, and sedative properties [3]. While its strong hypnotic properties lead to its decreased use as an antiallergic agent, these very properties are responsible for its continuous popularity as a FDA-approved over-the-counter sleeping pill. Abuse and overdose with DPH is seen on a regular basis [4]. DPH (hydrochloride) has a molecular weight of 291 D and a 98% protein binding. After oral administration, 60% of the drug is absorbed. Peak plasma levels, after a therapeutic dose of 50 mg, occur after 2.3 hours. DPH undergoes an extensive first pass effect. Its volume of distribution is 4.5 L/kg, and the elimination half-life is 8.4 hours [5]. DPH is metabolized by demethylation to nordiphenhydramine, dinordiphenhydramine, and diphenylmethoxyacetic acid. Only 1.9% of DPH is excreted unchanged in the urine. It is mainly metabolized in the liver, and the degradation products are almost completely excreted within 24 hours. Death cases have been described after doses of 500 – 2,800 mg per os. In a series of 55 deaths related to DPH, the plasma concentrations ranged from 0.3 to 119 µg/mL [6]. Overdose can result in ataxia, fever, and coma. In a retrospective review of the California Poison Control System, DPH was the second leading cause of drug induced seizures [7]. Further, rhabdomyolysis had been described. The anticholinergic effects are readily detectable by symptoms like dry mouth, tachycardia, and dilated pupils. Extracorporeal treatment by charcoal perfusion has been considered to be the treatment of choice in case of overdose. We herein report the first patient in whom intermittent hemodialysis with a high cut-off membrane resulted in rapid gain of consciousness helping to identify and locate a second poison victim. The patient consented to the publication of the anonymized report, which is in line with the policy of our ethics committee.

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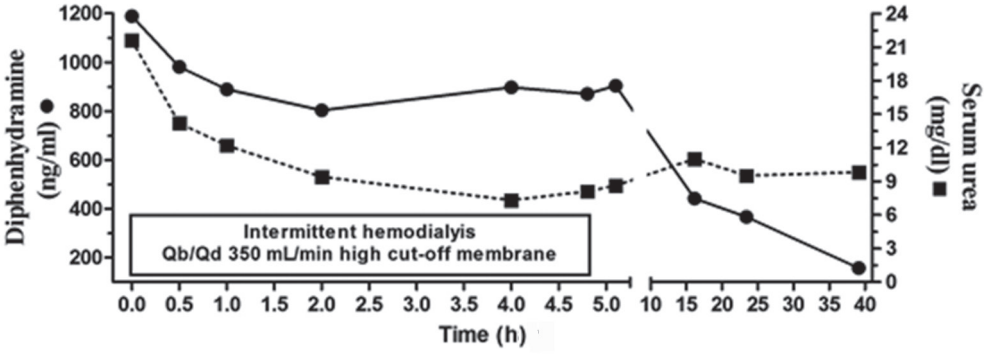

Figure 1. Diphenhydramine concentrations in a patient with diphenhydramine intoxication undergoing intermittent hemodialysis (IHD) using a high cut-off membrane. Treatment time of dialysis is indicated by the width of the box.

Case presentation

A 19-year-old Caucasian woman (weight: 54 kg, height: 160 cm) with a history of bipolar disorder and a previous suicide attempt, was admitted to our emergency department 7 hours after ingesting 500 mg of DPH in a suicide attempt. She was found by chance lying on a meadow. Upon arrival of the paramedics, she was unconscious and hypothermic. Next to her an empty tablet blister of Vivinox® (Diphenhydraminehydrochloride, 50 mg/tablet, Dr. Gerhard Mann Chem.-Pharm. Fabrik GmbH, Berlin, Germany) was found. Upon admission to the emergency service, the patient was somnolent and neither able to communicate nor to cooperate. Physical examination revealed a Glasgow Coma Scale of 8, dilated and fixed pupils. She had superficial scars on her thighs and arms from previous cuttings. Her heart rate was 180 beats per minute, blood pressure was 123/102 mmHg, and her body temperature was less than 27 °C. The initial respiratory rate of 15/minute and an oxygen saturation of 95% decreased to 10/minute with a drop in oxygen saturation to 80% requiring oxygen administration. Besides a respiratory acidosis (pH 7.16; p_{CO2} 67 mmHg, HCO^{3-}: 23 mmol/L) and a creatine kinase activity of 435 U/L, subsequently increasing up to 1,461 U/L, laboratory tests including liver function tests, revealed no other pathological findings. Chest radiography showed no abnormalities. Tests for blood alcohol and toxicology screening for tetrahydrocannabinol, opioids, cocaine, amphetamine, and benzodiazepines were negative. After transfer to the medical intensive care unit, the patient received 2 mg physostigmine to antagonize the anticholinergic effects of DPH.

DPH concentrations were quantified in serum, urine, and dialysate specimens by gas-chromatographic separation after fluid/fluid extraction, followed by nitrogen-selective flame ionization detection (A7890, Agilent Technologies, Waldbronn, Germany). The detection limit was 50 ng/mL. Metabolites were not determined. Urea was quantified photometrically using an enzymatic UV test.

Due to the initial DPH level of 1,189 ng/mL (therapeutic range 30 – 300 ng/mL) and in an attempt to increase body temperature, an intermittent hemodialysis using the GENIUS® dialysis system was initiated (Fresenius Medical Care, Bad Homburg, Germany). A 1.8 m^2 high cut-off polysulfone filter of 1.8 m^2 ($EMiC_2$ Fresenius Medical Care) was used. Vascular access was obtained by a double lumen catheter in the right femoral vein.

Serum DPH levels were monitored on a regular basis, including measurement of pre- and postfilter concentration to calculate extracorporeal clearances (Cl) using the following formula: (Cl = blood flow × (1-hct) × extraction rate). The initial whole blood dialyzer clearance of DPH at the start of a 4.8 hour treatment (blood and dialysate flow of 350 mL/min) was 91 mL/min. The dialyzer clearance decreased to 31 mL/min after 4 hours of dialysis. Body temperature increased from 28.4 °C at the start of dialysis to 34.5 °C at the end of the treatment. After 3 hours of hemodialysis, the patient quickly recovered clinically. After gaining consciousness, she reported the existence of another

poison victim. Due to the marked clinical improvement, extracorporeal therapy was not further continued. As the patient was not suicidal anymore, she was discharged from the hospital 2 days after admission. Further outpatient psychotherapy was refused. The other victim was found unconscious at home and was brought to a different hospital where she eventually recovered without dialysis. As we were unable to obtain consent of this patient, a more detailed description cannot be provided.

Discussion

The science of blood purification in toxicology has remained rather stagnant for a long period of time [8] and is still based on case reports and small case series. Over the last decade, several of those reports have shown that high-flux hemodialysis represents an excellent treatment method even for compounds that are predominantly protein-bound [9, 10]. Despite the frequency of DPH intoxication, extracorporeal treatments are rarely performed, as many of these intoxications are not life threatening. Moreover, the high protein binding of the drug is seen as contraindication for this treatment. Therefore, hemoperfusion had been reported to be of benefit [11]. A decade ago, Viertel et al. [12] showed that a 3-hour treatment with charcoal hemoperfusion (blood flow 150 mL/min) reduced initial DPH levels by 29%, resulting in marked clinical improvement. Using a 4.8-hour intermittent hemodialysis (blood and dialysate flow 350 mL/min) with a high cut-off dialysis membrane, we saw a dialyzer whole blood clearance of 91 mL/min, resulting in a reduction of the initial DPH levels by 27%. While the concentration decreased by ~ 17% from the baseline concentration within the first 60 minutes of dialysis treatment, it only decreased by another 10% from baseline until the end of the dialysis treatment. In parallel, the whole blood/plasma dialyzer clearance decreased from 91/55 mL/min at the start of dialysis to 31/19 mL/min, respectively, after 4 hours of dialysis. One explanation for this finding is that the toxicokinetics of a drug are different from its pharmacokinetics. A usually highly protein-bound drug like DPH can be removed by dialysis if the blood levels are in the toxic or supratherapeutic range. In this situation, there is a higher percentage of the drug not bound to proteins and therefore available for removal by dialysis. If the concentration of the drug approaches therapeutic levels, a higher percentage is protein-bound and, therefore, dialysis cannot remove as much of the drug as in severe overdose. The employed dialyzer had previously been shown to exhibit a high clearance of middle molecules like cystatin C or β2-microglobulin [13], so removal of DPH is not entirely surprising.

We conclude that hemodialysis with a high cut-off membrane appears to be a safe and efficient method of detoxification after DPH intoxication. As this type of dialysis is widely available, which at least in our case saved the lives of two patients.

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Conflict of interest

JTK received an unrestricted grant from Fresenius Medical Care for a clinical study not related to this report.

None of the other authors reports a conflict of interest.

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