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Case reports

Hemoperfusion in severe chlorprothixene overdose

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Abstract. Two to twelve hours after suicidal ingestion of an estimated dose of 10 g chlorprothixene, a 31-year-old female was admitted to the emergency ward of the clinic with cardiorespiratory arrest. After successful resuscitation, the further clinical course was complicated by persistent ventricular extrasystoles and ventricular fibrillation which necessitated repeated defibrillation. Since the patient did not respond satisfactorily to supportive treatment, a combined hemoperfusion/hemodialysis was performed. Under extracorporeal detoxication, elimination of chlorprothixene from plasma was accompanied by substantial improvement of the patient's clinical condition, although only about 1.6% of the estimated dose had been removed. This case seems to indicate that evaluation of the therapeutic efficacy of hemoperfusion should not be based exclusively on the relation of the amount of the eliminated drug to total absorbed dose.

Key words: Chlorprothixene-overdose – Hemoperfusion – Plasma concentrations

Chlorprothixene (CPT) is a thioxanthene derivative used clinically as a major tranquilizer and antipsychotic agent. Data on its pharmacology and toxicology are summarized in Table 1. CPT is metabolized primarily by the liver and is then excreted in the urine and feces. Metabolism occurs via N-demethylation, S- and N-oxidation [1, 5]. The main metabolites are desmethyl dilorprothixene chlorprothixene (DM-CPT) and chlorprothixene sulfoxide (CPT-SO).

The cardiovascular system, the CNS, and the liver are the primary target in CPT poisoning. The clinical picture of acute intoxication includes arrhythmias, tachycardia, cardiodepression, hypotension, seizures, respiratory arrest and reduced peristalsis of the gastrointestinal tract (anticholinergic effect) [1, 4]. Treatment of acute CPT poisoning includes primary detoxication (gastric lavage) and supportive measures, e.g. antiarrhythmic and anticonvulsive therapy. Physostigmine has been suggested for antagonizing the anticholinergic effect. However, administration of this drug carries the risk of increasing cardiodepression. If the patient does not respond to supportive treatment, extracorporeal detoxication has to be considered. From experience with similar drugs like phenothiazines and antidepressants it is known that hemodialysis has little effect because of the high level of protein binding which is >99% for chlorprothixene. The value of hemoperfusion seems to be questionable since the large volume of distribution indicates that only a small fraction of a CPT dose is present in the blood compartment [3].

Table 1. Pharmacological and toxicological data of chlorprothixene (CPT)

Oral dose	15 – 500 mg/die
Therapeutic serum concentration	0.04 – 0.3 µg/ml
Volume of distribution	11 – 23 l/kg
Elimination half-life	8 – 12 h after single dose of 30 mg CPT
Total clearance	0.97 – 1.48 l/min
Oral availability after liver first pass	23 – 64%
Plasma protein binding	>99%
Distribution between plasma and blood	0.81/1.0
Unchanged CPT in urine (rat)	5%
Elimination of CPT and its metabolites with the urine	5.9 – 29.0%
Elimination of CPT and its metabolites with the feces	0 – 41%
Toxicological data from autopsy cases	a) lethal dose: 2.5 – 5.0 g (adults) b) lethal blood concentration: 1 – 2 µg/ml

As there is no experience with extracorporeal detoxication, we present a case of severe CPT poisoning treated by combined hemoperfusion/hemodialysis (HP/HD).

Case report

Two to twelve hours after suicidal ingestion of an unknown amount of CPT, a 31-year-old female was found comatose near a lake. The patient had been under treatment for depression for several years.

On admission, the patient had a cardiorespiratory arrest, necessitating resuscitation. Physical findings included arrhythmia, respiratory insufficiency, hypotension (80/60 mmHg), anuria, grand-mal-like seizures and stage IV coma (Reed). Ventricular fibrillation repeatedly necessitated defibrillation. Admission laboratory tests revealed: leukocytosis 19000/µl; GOT 503 U/l, GPT 430 U/l, gamma-GT 16 U/l, AP 112 U/l, glucose 204 mg/100 ml, creatinine 2.9 mg/100 ml and uric acid 14.9 mg/100 ml. The EKG findings included atrial fibrillation, ventricular extrasystoles in salvos and QT prolongation (0.48 sec, mean frequency 85/min).

The patient was intubated and ventilated with 40% oxygen. For primary detoxication, gastric lavage with 10 l (0.9%) NaCl was performed. For interruption of the enterohepatic circulation of CPT, activated charcoal and sodium sulfate were given. Electrolytes and acid-base balance were restored by intravenous therapy. Additionally, the patient received an external pacemaker.

Considering the critical clinical condition and the failure to respond satisfactorily to supportive therapy, a combined HP/HD was performed for 4 h starting 2 h after admission (blood flow 160 ml/min, dialysate flow 600 ml/min). For HP, a cartridge with activated charcoal (Extracorporeal Inc.) and for HD, a PPD 1.3 (Cobe Inc.) were used.

Under HP/HD, the patient's clinical condition improved substantially: sinus rhythm was restored and the QT-time was in the normal range; the stage of coma was reduced to stage I (Reed). The neurologic status revealed no demonstrable abnormality. However, 2 h after HP/HD, the patient's consciousness was again impaired (coma stage I–II), probably due to a rebound phenomenon. The patient was completely awake and alert on the third day, when plasma CPT was beyond the limit of detection. Laboratory findings normalized, and the patient was transferred to a psychiatric clinic 8 days after admission.

Methods and results

For determination of CPT, DM-CPT and CPT-SO in serum and urine, gas chromatography/mass spectrometry (GC/MS) was used as after extraction of 1–2 ml of serum or urine at pH 11. Mass spectra were run on Finnigan GC/MS 4021. Quantitation was made by single ion monitoring of the most characteristic ions of CPT and its metabolites (m/z 44, 58, 332).

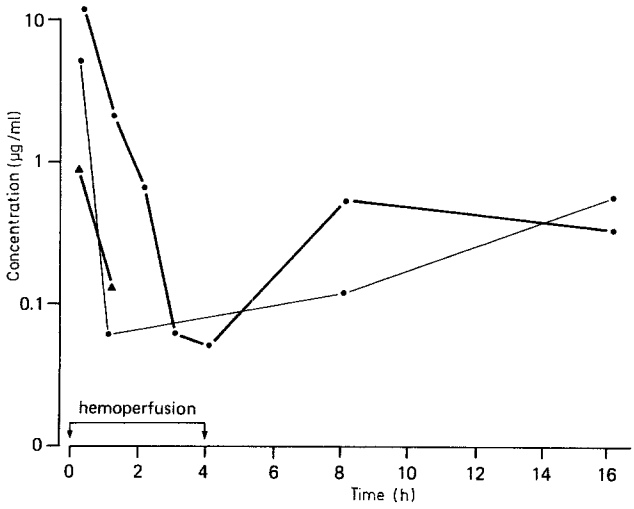

Fig. 1. Plasma concentration profile of chlorprothixene and its metabolites (time 0 = 4–12 h after ingestion; hemoperfusion 0–4 h)
●——● chlorprothixene; ●——● desmethyl chlorprothixene; ▲——▲ chlorprothixene sulfoxide

Serum concentrations were measured during HP/HD (0–4th h), and 4 and 8 h after HP/HD (Fig. 1). From the third day onward, plasma levels of CPT and its metabolites were beyond the limit of detection. A GC/MS screening of the first blood sample gave no indication that drugs or chemicals other than CPT had been ingested. In the gastric lavage fluid, 200 mg CPT were determined. From the initial chlorprothixene serum level and the volume of distribution an absorbed dose of 10 g was estimated.

For evaluation of the therapeutic value of HP, in vitro experiments were carried out using miniature HP cartridges. More than 95% of the drug and its metabolites were extracted from the blood by HP.

Discussion

In the case presented an estimated dose of about 10 g of CPT was absorbed. Only 2% of the dose was eliminated by gastric lavage, indicating almost complete absorption. The initial CPT plasma level which was substantially higher than intoxications reported in the literature exceeded the metabolite plasma level by a factor of ~10. This CPT/metabolite ratio points to an early stage of poisoning, since metabolites predominate in the later stage of intoxication [2].

Under HP/HD, the CPT plasma level on admission was reduced to ~1% of its initial value with a

half-life of 30 min. This value compares favorably with the spontaneous plasma half-life of 8–12 h [1]. However, only 1.6% (160 mg) of the estimated dose was eliminated by HP/HD from the plasma compartment. Since the plasma compartment initially contained ~60 mg CPT, an additional amount of approximately 100 mg (of a total of 160 mg) was removed from tissue stores by HP/HD. The in vitro HP experiments indicated that HP eliminates CPT, DM-CPT and CPT-SO almost completely from blood. The contribution of HD to removal of CPT was probably negligible because of the high level of protein binding.

Extracorporeal detoxication was accompanied by a substantial improvement in the patient's clinical condition, although the relation of the eliminated fraction to the total absorbed dose does not explain this effect. The assumption of a three-compartment-model might explain this discrepancy: CPT is distributed between the central blood compartment, a "shallow" and a "deep" compartment. The "shallow" compartment includes tissues with high perfusion and rapid exchange, heart, CNS, liver and kidney, whereas the "deep" compartment consists of tissues with low perfusion and slow exchange, fat, muscle, connective tissue, skin etc.. The latter compartment represents most (~85%) of the body mass. The clinical condition of a patient with CPT overdose is almost exclusively determined by the concentration of the drug in the "shallow" compartment. Hemoperfusion probably lowered selectively the CPT concentration in the "shallow" compartment, which led to an impressive stabilization of the cardiac function and to a considerable reduction in the level of coma. Redistribution of the drug from the "deep" compartment was obviously considerably slower than extracorporeal elimination. However, two hours after HP/HD, a moderate rebound phenomenon with raise in CPT plasma level was observed.

Although the hypothesis presented here requires further confirmation by evaluation of more cases of human CPT overdose, we conclude that judgement on the efficacy of HP should not be based on comparison of the eliminated fraction and the total absorbed dose. The details of distribution of a drug, the mechanism of toxicity, and the kinetics of redistribution have all to be considered.

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