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Lethal Orphenadrine Intoxication: Report of a Case

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Summary. A case of lethal orphenadrine intoxication is reported. Included are the anatomical and toxicological findings. Most conspicuous histologically was the centrilobular necrosis of the liver.

Key words: Orphenadrine, lethal intoxication. – Liver necrosis, orphenadrine intoxication

Zusammenfassung. Ein Fall von Orphenadrin-Vergiftung wird beschrieben. Über anatomischen und toxikologischen Untersuchungsbefunde wird berichtet. Mikroskopisch fällt in erster Linie die Lebernekrose auf.

Schlüsselwörter: Orphenadrin, tödliche Vergiftung. – Lebernekrose, Orphenadrin-Intoxikation

Orphenadrine (2-dimethylaminoethyl-2-methyldiphenylmethyl ether hydrochloride) is usually employed at divided doses of 200-400 mg daily in the treatment of Parkinsonism. It has a weak parasympatholytic and antihistaminic action but has marked spasmolytic effects. It reduces muscular rigidity but tremors can become exaggerated as the spasticity is relieved [12].

The clinical course of acute intoxications by orphenadrine consist of a coma with or without hypoventilation, sometimes complicated by seizures, and shock, which does not respond to the usual methods of treatment. There are often disturbances of cardiac rhythm and conduction [15]. Death can supervene 3–5 hours after the ingestion of a lethal dose, which for adults is about 2–3 g [15], or 0.4–0.8 mg % ml in blood [17], the toxic dose being 0.2 mg % ml in blood [17]. Autopsy findings are generally non specific.

The present paper deals with a case of orphenadrine suicidal poisoning, which seems interesting not only for its rarity, but also for some clinical and histopathological features which can raise a note of alarm on the possible hepatotoxicity of this drug.

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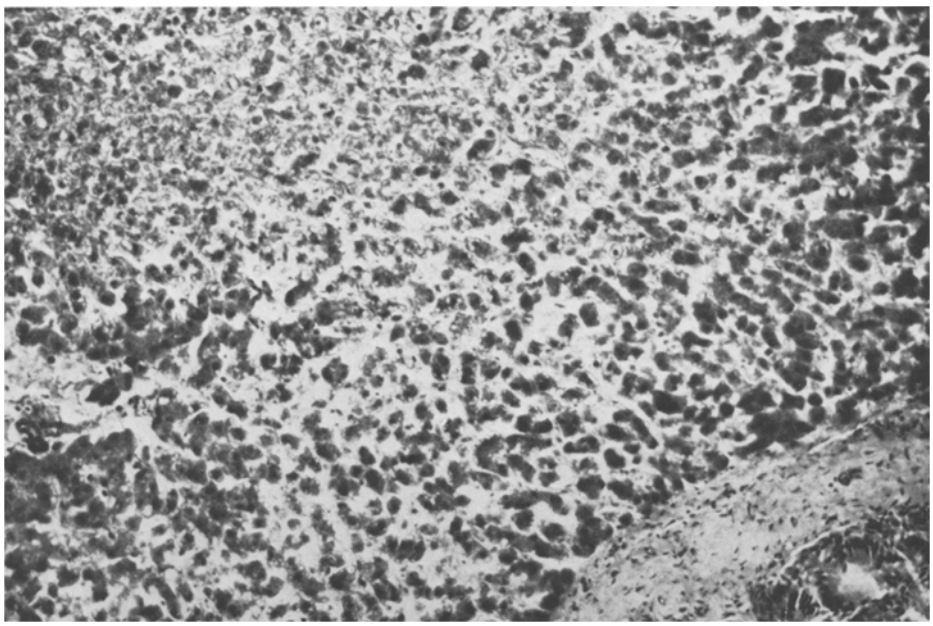

Fig. 1. Liver necrosis around the central vein (Hematoxylin and eosin, X 160).

Case History

C. I., 25-year-old woman, was in treatment with orphenadrine for parkinsonism. She took an unknown amount of Disipal® tablets. She was found unconscious at home. As soon as possible she was admitted to the Intensive Care Unit of this University Hospital, where she arrived without cardiac activity. No convulsions were reported by relatives.

Clinical Conditions at Admission. Coma (3rd grade), cyanosis, absence of cardiac activity, midriasis. After intensive therapy and treatment with physostigmine, the cardiac activity was reobtained, but the electrocardiogram showed a junctional rhythm of about 100/m, without identifiable atrial activity and with right bundle branch complete block. The electroencephalogram was persistently flat. The patient was maintained in life with mechanical ventilation for three days. The serum glutamic-oxalacetic transaminase level raised since the first day, and reached 1600 U. in the third day, as did the glutammic-piruvic transaminase level (1400 U. in the third day). The bilirubin level was normal. Prothombin time was 27" (control 11"5), prothrombin activity was 11 % of the normal activity, the fibrinogen level was reduced to 30 mg %. A transient hyperglycemia (224 mg %) was followed by hypoglycemia (34 mg %). There was hyperthermia (38°–40°C) together with blood leucocytosis (WBC 24.200, 90 % neutrophil granulocytes).

Autopsy (48 hrs After Death): Main findings were represented by visceral congestion and severe cerebral and pulmonary edema; the liver showed a firm yellowish brown parenchima dotted with small dark red areas of necrosis.
Histology: The main gross findings were confirmed; the hepatic cells at the periphery of the central vein showed a true disintegration or rarely a condition of atrophy (see Figure 1).

Toxicologic Analysis: Blood (60 ml) and gastric content (60 ml) were alcalinized with n NaOH and extracted directly with chloroform. One hundred gram of liver were homogenized, proteins were precipitated with ammonium sulfate, and the supernatant after alcalinization was extracted with

Table 1

Case n°	1	2	3	4	5	6-10	11-20	21	22	23
Reference n°	7	8	9	11	3	1	13	4	10	This case
Gastric content (mg)	950	715	600	163	4.5	163-1100	0-1860		715	40
Blood mg/100 ml	0.04	0.375	4-8	0.5		0.8-7.6	0.55-3.7	0.5	0.4	2.1
Brain mg/100 g					1.0	17-41		1-2		
Liver mg/100 g	5	4	5-8	2.5	14,5		2.3-11 (2 cases)	0.7	4	0.8
Blood liver mg100 ml							0.05-8.2			
Bile mg/100 ml							8.5-23.4 (5 cases)			
Urine mg/100 ml			2-5			0.85-9.1	0.3-12.2	10 (in vivo) 3.1 (post mortem)		
Kidney mg/100 g							0.98-10.5 (2 cases)	3.1		
Lung mg/100 g					6.3		1.95-4.5 (2 cases)			
Muscle mg/100 g					2.0					
Spleen mg/100 g							2.65-11 (2 cases)			

chloroform. Thin layer chromatography was performed on silica gel G plates, and the solvent system methanol/conc. ammonia 100/1,5 was used. After spraying with acidified iodoplatinate reagent, a spot was visualized at Rf=0.5, the same Rf of orphenadrine. GLC was carried out according to Clarke [6] (SE 303 % columns, T 225/275°C, nitrogen 1.10^5 Pa od. 1.10^5 N/cm^2). By comparison with standard solutions of orphenadrine, the following results were obtained: gastric content (total) 40 mg, blood 2.1 mg % ml, liver 0.8 mg % g (see Table 1).

Discussion

The present case showed some peculiarities in the clinical course, which was however very similar to cases described in the pertinent literature. Spasticity or seizures were not observed or reported: these conditions are frequent in orphenadrine poisoning cases [3, 14, 16]. The occourrence of such conditions cannot however be excluded, as the woman was found unconscious at home, where she lived alone. It should be noted also that the course was apparently prolonged, but the very early absence of EEG activity confirms that the death after the administration of large amounts of orphenadrine supervenes in few hours. Unequivocal signs of hepatic injury were demonstrated by the rapid and impressive elevation of serum transaminases and by the lowering of prothrombin time and of fibrinogen.

On gross observation, centrilobular necrosis of the liver was suspected, and confirmed on microscopic observation. The extension of such lesion should be considered responsible of the severe alterations of liver function parameters, and possibly of hyperthermia and blood granulocytosis.

The hypothesis explicitly advanced by Bozza-Marrubini et al. [4], that orphenadrine can exert a toxic effect on the liver, receives support from our data and from results reported by other Authors. A centrilobular fatty degeneration of the liver has been noted by Bösche and Mallach [3], and a centrilobular necrosis by Bruno Monti et al. [5] and high transaminase levels by Boidi et al. [2].

The analytical data of our case are compared in the Table with all the data that we could collect in the literature on this topic. Our results are sufficient to justify the diagnosis of orphenadrine poisoning, although they are much lower compared with other ones, but the patient was intensively treated for three days before death. Particularly, the level of orphenadrine in the liver was low, but neverthless comparable with the data reported by Bozza-Marrubini et al. [4]. It seems more than a mere coincidence that in both cases the liver was severely damaged.

In conclusion, the clinical course of the case and the morphologic and analytic data confirm the features of the intoxication by orphenadrine, and moreover offer support to the thesis that orphenadrine can exert a severe toxic action on hepatic cells.

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