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Lethal Orphenadrine Intoxications

A Report of Five Cases

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Summary. Five cases of lethal orphenadrine intoxications are reported. The concentration of the drug in liver ranged from 17 to 41 mg per 100 g. The results are compared with findings in fatal intoxications with phenothiazines and other tricyclic amines.

Key-Words: Orphenadrine, lethal intoxication.

Zusammenfassung. Fünf Fälle von Orphenadrin-Vergiftungen werden beschrieben. Die Konzentration des Arzneimittels in der Leber schwankt zwischen 17–41 mg/100 g. Die Ergebnisse werden mit tödlichen Vergiftungen mit Phenothiazinderivaten und Ami- und Nortriptylin vergleichen.

Orphenadrine is used in the treatment of Parkinson's disease and as a muscle-relaxing drug often in combination with some analgetic compound. 100 to 200 mg a-day is a recommended dose. The acute oral LD_{50} in rats is about 400 mg/kg body weight. To our knowledge six cases of fatal orphenadrine intoxications are found in literature where the concentrations in the organs were determined [1–6]. The amount of orphenadrine in liver reported in five of the cases were much lower than our values, in fact so much lower that there can be some doubt about the role played by orphenadrine. In the case reported by Bösche and Mallach in 1969 [6] the concentration in the liver was of nearly the same order of magnitude as in our cases.

Methods

In routine search for sedatives and certain other drugs we employ the following analytical screening procedure (details will be published in a forthcoming paper): extraction of homogenized tissue with ethanol (70%)—evaporation of an aliquot (corresponding to 10 g of liver)—dissolution of the residue in dilute hydrochloric acid—removal of interfering lipids (Bonnichsen *et al.*, 1961 [7])—extraction with chloroform—extraction of a part ($^1/_5$–$^2/_5$) of the chloroform with ammonium hydroxide solution—evaporation of the extracted chloroform. The residue is dissolved in 1.0 ml of alkaline ethanol (0.025 N ammonia in 75% ethanol) and the absorption in ultra-violet is recorded.

Orphenadrine concentrations exceeding 5 mg per 100 g of liver is detected in this way. The reason for the rather low sensitivity is due to the low extinction coefficient of this drug. In comparison to the values found in our material (Table) a detection limit of 5 mg per 100 g of liver seems to be sufficient in fatal poisoning.

The detection limit can be lowered considerably by using thin-layer chromatography with silica gel as the absorbent and methanol-25% ammonia (100:1.5) as the solvent. 2–5 μg orphenadrine can be seen by spraying with Dragendorff's reagent. As an extract, corresponding to 2 g liver can be run without over-loading, the detection limit is 0.25 mg or less per 100 g of liver. Quantitative determinations are preferably carried out with gas chromatography. The acid extract is shaken with a small volume of ammonium hydroxide solution before beeing

chromatographed, in order to get the free base. In most cases we used a Varian aerograph 1200 (with f.i.d.) equipped with a column 1.8 m × 3 mm (I.D.) filled with 2% SE-30 on Gas Chrom Q (100–120 mesh) and operated at 180° C. The retention time for orphenadrine is about $2^1/_2$ min, when the carrier gas flow is 75 ml/min.

Case History

Case 1. 29 years old male. He had been treated many years for psychotic disorder, with schizophrenic reaction. Death occured a few hours after intake of the drug.

Case 2. 28 years old female. Several times hospitalized for mental disorder with schizophrenic reaction, narcotics and alcohol misuse. She was found dead in her bed.

Case 3. 24 years old female. She had several times been hospitalized for psychotic disorders and died on the way to hospital in convulsions.

Case 4. 42 years old female. She was at the hospital when she committed suicide and died within a few hours after the drug intake in convulsions.

Case 5. 29 years old male. Died over night in his apartment after a party with heavy alcohol consumtion. Earlier at hospital for psychotic disorders with schizophrenic reactions.

In none of the cases was any somatic cause found at the autopsy that could account for the death. In 4 of the cases the stomach contained a rather large amount of a porridge assembling mass probably the remainder of the tablets although only in one case it was stated that fragments of tablets were present in the stomach. In none of the cases was fatty infiltration of the liver observed macroscopically in spite of the history of alcohol misuse.

Results and Discussion

The analytical data are presented in the Table. It is not likely that other drugs significantly contributed to death, beside the fact that orphenadrine poisoning was clearly indicated in the police report, other sedative drugs should have been detected in the screening procedure employed. However, the presence of certain tranquillizers in "therapeutic" concentrations cannot be excluded.

Neither repeated extraction of the acid solution nor extraction at an alkaline pH as used for phenothiazine drugs by Bonnichsen *et al.* (1970) [8] significantly increased the yield, and it can be concluded that orphenadrine is extracted quantitatively in the routine procedure described above.

The concentrations of orphenadrine in the Table are of the same order of magnitude as those reported by Bonnichsen *et al.* (1970) [8] for phenothiazine derivatives and by Bonnichsen *et al.* for amitriptyline and nortriptyline in 1970 [9] in cases where the drugs probably were the only reason for death and where no somatic cause was observed by the autopsy. Fatal cases of dibenzepine poisonings exhibited a wider concentration range [10].

Fatal poisonings with all the above mentioned drugs are usually accompanied by convulsions in agreement with observations of patients hospitalized for suicide attempts with these drugs as reported by e. g. Heinonen *et al.* (1968) [11] and by Bösche *et al.* (1969) [6]. In our case number 4 the convulsions were treated with diazepam.

After the administration of the drug to rats, several metabolites were found by Hespe *et al.* (1965) [12]. Some of them were identified, indicating that N-demethylation and O-dealkylation were important metabolic pathways. The mono-N-demethylated product is active [14], whereas the dealkylated products are not—

Table. *Orphenadrine concentration (mg/100 g)*

Case no.	Liver acid extraction		Liver alkaline extraction		Urine alkaline extraction GLC	Blood alkaline extraction		Stomach acid extraction UV	Other substances	
	UV	GLC	UV	GLC		UV	GLC		alcohol %	drugs mg/100 g
1	(9)	—	17	17	—	—	—	—	0.08 in blood	fluphenazine in liver < 0.25
2	—	—	—	41	—	—	—	—	—	thioridazine in liver < 3
3	22	—	23	34	—	—	—	163	—	—
4	38	28	—	41	9.1[a]	—	0.8	—	0.07 in urine	diazepam in urine 1.2[c]
5	21	20	—	23	0.85[b]	7.5	7.6	1100	—	—

[a] After acid hydrolyzis only 0.017 mg/100 g was gained.
[b] All the drug present was extracted without acid hydrolyzis.
[c] The patient got an injection of diazepam to stop convulsions at the hospital.

the importance of other not yet identified metabolites is not known as mentioned by den Besten *et al.* (1970) [13].

Thin-layer chromatography of extracts from our cases reveal the presence of metabolites, (we used the same system (n-BuOH:25% ammonia, 98:2) and received spots with R_f-values very nearly the same as reported by Hespe *et al.*, 1965 [12]) but no extensive investigation is yet carried out on this subject. The poisonings in all the cases terminated fatally in only a few hours, and metabolites were probably not formed in sufficient amounts to have important effects.

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