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Accidental Lethal Pipazethate Poisoning in a Child

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Summary. A fatal case of accidental pipazethate poisoning in a child is reported. Clinical, pathologic, histological, and toxicologic findings are described.

Key words: Pipazethate, lethal intoxication – Poisoning, pipazethate

Zusammenfassung. Ein Fall von Pipazetat-Vergiftung wird beschrieben. Die klinischen, anatomischen und toxikologischen Untersuchungsbefunde werden angegeben.

Schlüsselwörter: Pipazetat, tödliche Vergiftung – Intoxikation, Pipazetat

Introduction

It is the second time that we have been concerned with a case of lethal pipazethate poisoning. Unlike our previous case [1], we have been able to carry out a more complete study on the clinical, pathologic, and toxicologic aspects. Moreover, we think the case is noteworthy because we have been unable to find a similar case in the literature we consulted.

Pipazethate, 2-(2-piperidinoethoxy)ethyl, 10-thia-1,9-diazanthracene-9-carboxylate, is an antitussive agent usually administered as a daily divided dose of 120 mg for adults, 30–40 mg for children, and 15–20 mg for babies.

Pipazethate is structurally correlated to the phenothiazines [2]. The antitussive effect is due to the action on the cough centers and, as a spasmolitic and local anesthetic, on the upper respiratory tract.

The drug, given in therapeutic doses, cannot be considered altogether void of toxic effects. So much so that it is currently suggested [2, 3] that different, more extensively tried antitussive drugs should be chosen, especially when they are to be prescribed to pregnant women or babies. As far as the latter are concerned it is not at all advisable to prescribe such a product.

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Table 1

Sample	Pipazethate mg% g
Blood	2.72
Liver	8.21
Kidney	5.85
Brain	5.57
Heart	3.58
Muscle	2.80
Urine	1.88
Gastric contents	320 mg in toto

Case Report

A 32-month-old female baby ingested approximately 22 ml of a 25-ml container of Selvijgon (pipazethate, 40 mg/ml). According to information available, she suddenly fell ill, and as she became progressively worse, she was carried to hospital about 25 min after ingestion. Upon arrival she showed tonic-clonic seizures, deep coma, respiratory deficiency. The baby died about 1 h after admission owing to respiratory insufficiency.

Results

Autopsy and Histological Findings

A postmortem examination was performed 26 h after death. The body weighed 12.1 kg. Macroscopic findings included extensive hypostasis, severe visceral congestion, remarkable cerebral and pulmonary edemas, few subpleuric pethechial hemorrhages, and, in the stomach, a few milliliters of mucous liquid.

The histological examination confirmed the main macroscopic findings and showed diffuse cytoplasmic degranulation and occasional disappearance of the nuclei in the neurons of gray matter. In the endocrine system we observed degranulation of the basophilic cells of the hypophysis (PAS-orange) and wide areas of rarefaction of the birefringent inclusions in the adrenal glands (Sudan III).

Toxicological Findings

Qualitative Analysis. A sample of the gastric contents was used for screening purposes in search of pipazethate. The specimen was made alkaline with concentrated ammonia and extracted directly with diethylether. The organic phase was evaporated and the residue, dissolved in 50 µl ethanol, was spotted onto a precoated thin-layer chromatographic plate of silice gel 60 F-254 and developed in the solvent system methanol-conc. ammonia (100:1.5). After inspection under 254 nm light and spraying it with acidified iodoplatinate reagent, a spot was visualized at Rf: 0.42, the same Rf as that of pipazethate in the standard solution.

Quantitative Analysis. The pipazethate and an internal standard were quantitated by gaschromatography.

Materials and Methods

Twenty grams of sample (blood, urine, gastric contents, liver, kidney, brain, heart, skeletal muscle) and 1 ml of imipramine internal standard solution (2 mg/ml) were, after preliminary hydrochloric acid digestion, extracted with diethylether at pH 11, using a solvent-to-a sample ratio of at least 4:1. The separated solvent was purified by re-extraction into 0.1 *N* hydrochloric acid, which was then made alkaline (pH 11) and extracted with diethylether. This extract was evaporated to dryness, and the residue was dissolved in 200 µl ethanol for gaschromatographic quantification.

The reference solution (20 ml aqueous pipazethate at several concentrations) used for quantitating the samples was prepared in the same manner.

Operating Conditions

Carlo Erba Fractovap model GI gaschromatograph equipped with a flame ionization detector; 2 m glass column of 3 mm ID, packed with 3% OV-17 on silanized 100–120 mesh Gas Chrom P; column temperature 265°C, injection port 320°C; nitrogen flow 60 ml/min.

Under the gaschromatographic conditions given above, the retention time of pipazethate was 6.2 min and that of imipramine was 8.3 min.

Extracts from the liver and kidney showed two small peaks, the retention times of which were shorter than those of pipazethate. Although their identity was not established, they could be referred to as pipazethate metabolites. Results are reported in Table 1.

Discussion

The case reported shows that in acute pipazethate poisoning, autopsy and histological findings are generic and do not enable one to ascertain the cause of death.

In our case, autopsy and histological data (visceral congestion, cerebral and pulmonary edemas, subpleural hemorrhages, degranulation and nuclear pyknosis in nerve cells, acute stimulation of hypophysis and suprarenal glands) are the results common to many anoxic syndromes [4], among which we think the toxic one caused by pipazethate can be included. As already stated [1] we think the drug to be active also in areas near the coughing center (respiration, vasomotor, vomiting centers). The negative effects of the drug are sometimes noted when other antitussive products with a central action are used [5].

Therefore, we think that after acute poisoning by pipazethate death takes place owing to a depressive effect on the breathing center and for the consequent serious hypoxy. Yet, we cannot exclude the possibility that the quinidine-like powerful effect produced by the drug [6] also caused depression of the heart excitability, contraction and conductibility. Hence, the toxic effects might be related to both the neurotropic and the cardiotropic actions.

In the case we studied no damage was found in other organs. This was probably due to the rapid progress of the toxic syndrome which made it impossible for the pathologic changes to take place, contrary to what happens in cases surviving longer.

The fact that death was caused by ingestion of about 800 mg (66.1 mg/kg) of pipazethate does not exclude the possibility that even smaller doses may cause death.

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