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Lethal Nitrazepam Intoxications

Report of Two Cases

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Tödliche Nitrazepam-Vergiftung

Zwei Fallbeschreibungen

Summary. This report presents two cases of lethal nitrazepam intoxication with due regard to the anatomical and toxicological findings.

Key words: Nitrazepam, lethal intoxication – Poisoning, nitrazepam

Zusammenfassung. Dieser Bericht behandelt zwei Fälle von Nitrazepam-Vergiftung unter Berücksichtigung der anatomischen und toxikologischen Untersuchungsbefunde.

Schlüsselwörter: Nitrazepam, tödliche Vergiftung – Vergiftung, Nitrazepam

Nitrazepam is very seldom responsible for acute fatal poisoning. Nonetheless, it is frequently used as hypnotic throughout the world. For example, of a very large series of cases ($n = 4998$) of acute poisoning admitted to St. Camillo de' Lellis Hospital in Rome between 1970 and 1976, six cases of benzodiazepine-related death were registered, only one being due to nitrazepam [4]. A few cases of such death have been described by various authors [8, 9, 12]. Other rare cases can be found in statistical studies [6].

As this casuistry is so rare, it seemed advisable to report two cases of fatal poisoning by this drug.

Case Histories

No. 1. A 75-year-old man was found at home in a condition of deep coma. By the body, an empty container of dragées of Mogadon (nitrazepam 5 mg) was found. The drug was prescribed for insomnia.

Clinical Conditions at Admission: Deep coma, pin-point miosis, bilateral clonical jerks. Death came after 1 day for respiratory insufficiency and pulmonary edema.

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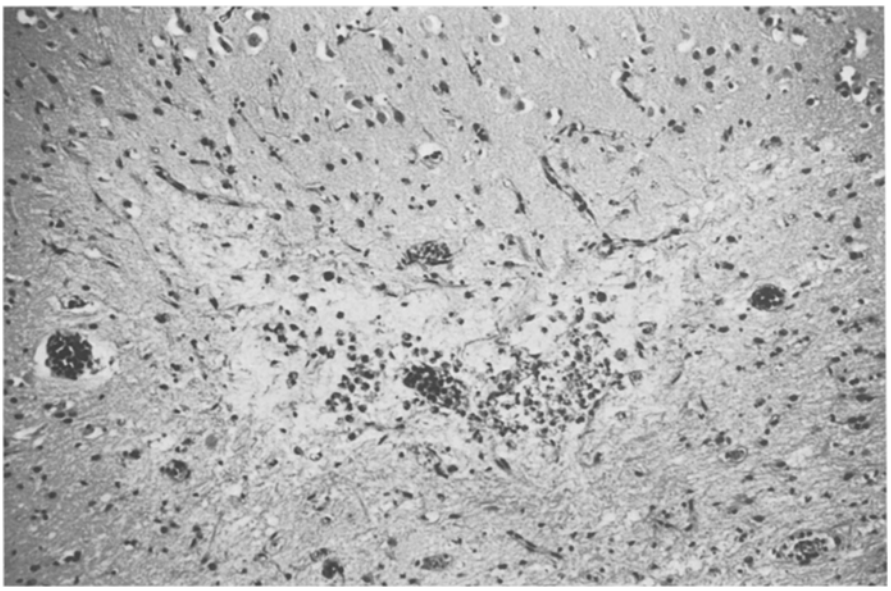

Fig. 1. Case no. 1. Mesencephalon. Note infiltrated thrombi surrounded by a severely edematous area. Hematoxylin and eosin (H & E)

Autopsy (48 h After Death): Visceral congestion and cerebral and pulmonary edema; senile myocardosis, moderate pulmonary emphysema, liver steatosis, chronic pyelonephritis.

Histology: The main gross findings were confirmed. Lungs showed a pseudohemorrhagic congestion. In the mesencephalon, capillary thromboses with granulocytic infiltration of the thrombus, surrounded by high degree edema and degenerated neuronal cells were observed (Fig. 1).

Toxicologic Analysis: Nitrazepam was extracted from organs and biological fluids according to Clifford and Francklin Smith [3], purified by thin-layer chromatography [7], and determined by gas-liquid chromatography [2]. Quantitative results were as follows: liver 0.07 mg% g, kidney 0.07 mg% g, brain 0.04 mg% g, blood 0.12 mg% ml. By TLC two metabolites were identified, 7-amino-1,3-dihydro-5-phenyl-1,4-benzodiazepin-2-one and the 7-acetamino derivative of the former; the 2-amino-5-nitro-benzofenone was not identified.

No. 2. A 40-year-old woman was found dead at home, 48–60 h after death. By the body some empty containers of Mogadon were found.

Autopsy: Visceral congestion, cerebral and pulmonary edema.

Histology: The main gross findings were confirmed. In the mesencephalon capillary thromboses surrounded by severe edema were noted. Some proteinaceous material was observed in the Bowman's capsule of the kidneys.

Toxicologic Analysis: Nitrazepam was determined as in case no. 1. Quantitative results: liver 0.15 mg% g, urine 1 mg% ml; traces in brain, blood, stomach content. Blood ethanol (head space GLG): 0.18 g‰.

Discussion

The two cases that we report can be compared with cases previously described with some difficulties, as the description is not always complete in every respect. Whatsoever, it should be noted, from the clinical point of view, that our first case was characterized by a condition of irreversible coma, while in the second case no data were available, as the woman was found dead.

Autopsy findings were very generic and did not allow to suspect the cause of the death. Constant findings were represented by cerebral and pulmonary edema and visceral congestion on gross observation, while microscopically capillary thromboses and small perivascular hemorrhages, surrounded by severe edema and degenerative changes of the neuronal cells, were noted in the mesencephalon.

The quantitative data of the toxicological analysis are comparable with those of the literature.

	Blood	Urine	Liver
Torry (1976)		0.1 mg% ml	
Loveland (1974)	0.9 mg% ml		0.4 mg% g
Oliver and Smith (1974)			
1st case		0.58 mg% ml	
2nd case		0.60 mg% ml	
Our 1st case	0.12 mg% ml		0.07 mg% g
Our 2nd case	Traces	1 mg% ml	0.15 mg% g

The diagnosis can be difficult as it is based on the results of the toxicological analysis, which is not fully satisfactory, mainly because of difficulties in the extraction procedures and in the detection of the drug. For these reasons, new analytical methods for benzodiazepine derivatives have been recently proposed [5, 10, 11].

Of course, the clinical symptoms represent a very useful diagnostic aid, but in medicolegal cases they are not always available. The histologic picture of the mesencephalon, for which we cannot advance any pathogenetic hypothesis, could also be an aid for a correct medicolegal diagnosis.

There is no doubt that the small number of fatal cases that we could find in the medical literature confirms the low toxicity of nitrazepam [6]. This drug, however, is potentially lethal, especially when administered to patients in bad general condition or in patients with respiratory failure [1], of taken in association with ethanol or other drugs which potentiate its action.

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