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Acute buflomedil intoxication: a life-threatening condition

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Abstract. A 15-year-old girl was admitted to ICU in a comatose state. She presented with mydriasis, areflexia, hypoxemia and seizures. She was immediately intubated and connected to a ventilator. The seizures were reversed with intravenous diazepam. CT scan was negative. EEG showed a diffuse fast activity and theta waves with spikes in the anterior and temporal regions, bilaterally. The gastric lavage was suggestive of drug ingestion. The patient completely recovered after 6 h of mechanical ventilation and supportive management. Mydriasis was still present after the resolution of neurological symptoms. The girl told us she had ingested 10 tablets (3 g–55 mg/kg) of Loftyl (buflomedil) for suicidal intention. The buflomedil concentrations at 2–3 h from ingestion were 24.8 mg/l in the blood, 324.4 mg/l in the urine and 6.9 mg/l in the gastric content. The p-desmethyl metabolite was also identified in the urine. Buflomedil is a rheological agent largely used as a vasodilator in some European countries. Some recent reports have emphasized the risk of acute intoxication with this drug. Relatively low doses (50–60 mg/kg) have been associated with an important neurological toxicity and a high mortality. We suggest that the clinical picture we observed might be related to a neuroleptic-type action of buflomedil. We bring to attention the risk of a large, uncontrolled diffusion of a drug capable to cause serious consequences at relatively low doses.

Key words: Buflomedil – Acute intoxication – Partial anticholinergic syndrome – Neuroleptic action – Mydriasis

The frequency of intoxication by ingestion of buflomedil is quite low. However, some recent reports have emphasized the risk of the assumption of high doses of this drug [1–3].

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Buflomedil is a vasodilating agent with complex rheological effects. It seems to improve nutritional blood flow in ischaemic tissues of patients with peripheral or cerebral vascular disease by a combination of effects: inhibition of α-adrenoreceptors, inhibition of platelet aggregation, improved erythrocyte deformability, non-specific and weak calcium antagonistic effects and oxygen sparing activity [4]. It is readily absorbed by the gastrointestinal tract attaining mean maximal concentration between 1.5 and 4 h after oral administration. The bioavailability is high (50–80% of an oral dose), as well as the distribution volume (1.32±0.26 l/kg at the steady state). At therapeutic plasma concentrations in humans, buflomedil is 60–80% bound to plasma proteins. It is extensively metabolized by the liver and almost 90% of a single oral dose is excreted via the urine in 4 days, approximately 20% as unchanged buflomedil. The elimination half-life is 2–3 h [5]. The usual dosage is 450–600 mg daily.

The adverse effects most frequently reported during treatment include flushing, headache, vertigo, gastrointestinal discomfort and dizziness. Many authors reported extrapyramidal disturbances during long-term treatment with high doses of buflomedil [6]. A myoclonic encephalopathy was described as well [7]. Overdosage in humans produces coma, convulsions and respiratory depression [8, 9]. However, its relationship with neuroleptics had never been stressed previously, even if its chemical structure might show it clearly.

Case report

A 15-year-old female was found by parents at home in a comatose, unresponsive state. At admission to the Emergency Room the clinical and laboratory findings revealed: coma with no response to painful stimuli, fixed and dilated pupils, seizures, tachycardia, hypoxia (PaO_2 45 mmHg), respiratory and metabolic acidosis (pH 7.15). Arterial pressure was 120/70 mmHg. Objectively, cyanosis and bronchial crackles were present, thus the patient was immediately intubated and connected to a ventilator on IPPV with FiO_2 0.5 (Servo-C Siemens). The seizures were reversed with intravenous diazepam (10+10 mg i.v.). The parents were asked about the possibility of a drug intoxication

which was absolutely denied. The patient was not epileptic. No signs of cerebral lesion were shown at CT scanning. Serial EEG showed a diffuse fast activity and theta waves with spike activity in the anterior and temporal regions, bilaterally. A gastric lavage with activated charcoal was performed that was suggestive of drug ingestion. Because of signs of a partial anticholinergic syndrome were evident, a tricyclic antidepressant intoxication was suspected and a physostigmine test performed (1 mg i.v.), without any clinically significant improvement.

The patient spontaneously recovered after 6 h of mechanical ventilation and supportive management. Pupils remained fixed and dilated for the following 3 h. She told us she had taken, for suicidal intention, 10 tablets of LOFTYL 300 mg, corresponding to 3 g i.e. about 55 mg/kg of buflomedil.

Blood, urine, gastric lavage and residual of tablets were available for toxicological analysis. Qualitative and quantitative analyses were carried out by gas chromatography/mass spectrometry at the Forensic Toxicology Laboratory of University of Padua. The buflomedil concentrations at 2–3 h from ingestion were 24.8 mg/l in the blood, 324.4 mg/l in the urine and 6.9 mg/l in the gastric content. At 24 h later the concentration of the drug was negligible in the blood, in the urine it was 160.5 mg/l and the p-desmethyl metabolite was also identified.

Discussion

Between 1976 and 1981, 26 cases of acute poisoning due to buflomedil overdosage were referred to the Paris Poison Control Center. Few further cases of acute buflomedil overdosage have been reported to date [1–3, 8–11]. The most frequent clinical features are summarized in Table 1. Athanaselis [10] reported that a 19-year-old girl, developed epileptic convulsions, pulmonary edema and ventricular fibrillation after swallowing of 3 g of buflomedil. She died 2.5 h after the drug ingestion and toxicological analysis showed a plasma buflomedil concentration of 63.4 mg/l. In comparison with our findings, this value was higher, but the buflomedil urine concentration was lower (108 mg/l versus 324 mg/l), although the amount of drug ingested was the same in the 2 cases (3 g – 55 mg/kg), and the samples were made during a comparable phase of drug disposition (2–3 h from ingestion). Athanaselis' data might suggest a condition of early shock occurred in his patient, with a global perfusion deficit and, thus, a decrease in the drug clearance.

Another fatal case was described in 1988 by Danel [11]. A 16-year-old girl ingested 6.75 g of buflomedil (plasma concentration 43 mg/l) and suffered post-anoxic coma that led her to death. The Lyon Poison Control Centre (unpublished data) reported, between 1978 and 1985, 18 cases of acute buflomedil overdosage: 4 presented the same symptomatology of convulsions, coma, respiratory and cardiac arrest, and death. The minimum oral dose able to cause such symptomatology was 40–50 mg/kg (Table 1). These data are in agreement with some experimental studies performed on animals: doses of 60–70 mg/kg caused seizures and death in dogs (data of Lafon Laboratory).

These features have been related to the vasodilating effect of buflomedil, that might produce hypotension and a condition of hypovolemic shock. However, we did not notice any hypotension during the acute phase of buflomedil intoxication, in agreement with other authors [1, 3, 8, 9], whereas neurologic distress was prevalent. Some other authors further emphasized that the most serious circulatory effects always followed neurologic distress [2, 11]. We conclude that the main clinical manifestations of buflomedil poisoning may be related to a direct neurotoxic effect of the drug.

Moreover, a partial anticholinergic syndrome has not been previously described.

Buflomedil chemical structure is neuroleptic-type. In fact, it is 2′,4′,6′-trimethoxy-4-(1-pyrrolidynil) butyrophenone (Fig. 1).

Neuroleptics have very complex effects on cerebral neurotransmitters [12]. Their clinical antipsychotic action

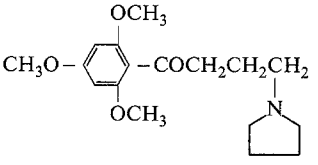

Fig. 1. Chemical structure of buflomedil

Table 1. Buflomedil acute intoxication: available data

Sex	Age	Dose	Clinical features	Plasma level	Outcome	References
F	16	6.75 g	Coma, respiratory depression, mydriasis, cardiac arrest	43 mg/l	Dead	[11]
M		7.5 g	Coma, convulsions, mydriasis, cardiac arrest		Dead	[3]
F	15	3.9 g	Coma, convulsions, mydriasis, cardiac arrest, respiratory depression		Dead	[2]
F	22	3.05 g	Coma, respiratory depression, convulsions, pyramidal syndrome		Recovered	[1]
F	21	3.75 g	Coma, respiratory depression, convulsions	63.4 mg/l	Dead	[9]
F	19	3 g	Coma, pulmonary edema, convulsions, ventricular fibrillation		Dead	[10]
4 patients		150 – 190 mg/kg	Coma, convulsions, respiratory depression		Dead	Centre Antipoison Lyon 1978 – 1985 (CA)
4 patients		35 – 250 mg/kg	Convulsions, vomiting		Recovered	CA Lyon 1978 – 1985
2 children		45 – 75 mg/kg	Convulsions		Recovered	CA Paris 1976 – 1981
9 patients		>3 g	Coma (2), stupor (3), vomiting (1), agitation (2), tachycardia (2), convulsions (3)		8 Recovered 1 Dead	CA Paris 1976 – 1981

is linked to a block of DA-2 post-synaptic receptors of dopaminergic neurons. At the same time they also block other receptors: α1-adrenergic, cholinergic, muscarinic, H1 and H2 histaminergic, serotoninergic. These actions, at the usual dose, are clinically negligible. However, they may become important at high doses of the drug. Neuroleptic overdosage can cause, at CNS level, both excitatory and depressing effects, leading to "mixed syndromes" which are difficult to interpret. The symptomatology we describe may appropriately be related to a neuroleptic overdosage. On the other hand, a tricyclic antidepressant intoxication could be suspected as well considering the presence of mydriasis, tachycardia and seizures. Indeed, the physostigmine test was negative.

Blery et al. did not find mydriasis in a patient intoxicated with 7.5 g of buflomedil and concluded that buflomedil does not cause mydriasis and other anticholinergic effects [3]. On the other hand, other authors reported paralytic mydriasis in intoxicated patients, but ascribed it to severe anoxia causing cerebral death [2, 11].

However, our patient exhibited fixed and dilated pupils that persisted also after the complete resolution of neurological symptomatology. We think that mydriasis might have been caused by an anticholinergic action of buflomedil. It is commonly accepted that the eye may be one of the targets of neuroleptic toxicity, but the effect on the pupil is variously described by most references in literature: miosis is frequently reported after acute poisoning with phenothiazines [13], but mydriasis is described as well, referring to their anticholinergic action [14]. The degree of the existing sympathetic tone seems to be important in the determination of pupil reactivity to high doses of neuroleptics [15].

Seizures were presumably caused by a direct neurotoxic action of buflomedil although other authors ascribed them to a condition of low-perfusion and cerebral ischemia due to a deep vasoparalysis [2]. Neuroleptics can, however, lower the convulsive threshold. The convulsive doses of buflomedil reported in the literature are quite low: 45–75 mg/kg in pediatrics, 3–4.5 g in adults (600 mg tablets are available!).

At present, the treatment of buflomedil acute intoxication remains only supportive. An early gastric lavage is useful. Seizures can be adequately reversed by anticonvulsants like diazepam, and mechanical ventilation is helpful to optimize oxygenation and pulmonary gas exchange.

In conclusion, buflomedil intoxication can be a life-threatening condition that must be readily and aggressively treated. We suggest that the clinical picture might be related to a neuroleptic-type action of high doses of buflomedil. We also bring to attention the risk of a large, uncontrolled diffusion of a drug capable of causing serious consequences at relatively low doses.

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