

Toxicology Experience Report

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Hexapropymate Self-Poisoning Causes Severe and Long-Lasting Clinical Symptoms

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Summary

Cases of hexapropymate poisoning requiring intensive care in an urban region of Sweden (420,000 inhabitants) were collected over 2.5 years (1985 to 1987). Only patients with serum hexapropymate concentrations above 5.5 mg/L (30 µmol/L) and with a negative history for intake of tricyclic antidepressants, phenothiazines, barbiturates, antihistaminic drugs and opiates were included. Clinical data about 8 intoxication events in 6 patients were evaluated retrospectively. Initial symptoms included coma, hypotension, hypothermia, and hypoventilation. Maximum coma depth (Glasgow coma score) was 3 to 5 in 5 out of 8 events. On 7 occasions assisted ventilation was required (for 12 hours or more in 5 events). There was no relationship between serum concentrations of hexapropymate and severity of clinical symptoms. All patients survived. Detailed analysis of the drug elimination in one patient showed a terminal elimination half-life of 21 hours, which is longer than previously reported (5 hours). The indications for use of this hypnotic drug may vary between doctors since an 8-fold variation was seen in drug prescription between Swedish counties in 1987. Poisoning with hexapropymate is a serious condition which may require symptomatic treatment in the intensive care unit. The clinical picture is similar to that seen in patients with barbiturate intoxication. There is no role for active forced elimination of the drug. It is questionable whether the clinical value of the drug is outweighed by its toxicity.

Hexapropymate is a carbamate hypnotic substance (fig. 1) with properties similar to those of the barbiturates, which are considered to be obsolete in the treatment of insomnia in some countries. A few brief clinical reports of intoxications with symptoms such as coma and hypotension have been published (Hassoun et al. 1978; Noirfalise 1971; Robbins & Brown 1978). In contrast to this,

12 fatal cases of poisoning with hexapropymate were seen in a Swedish study in which autopsy cases were analysed over a 3-year period (Bonnicksen & Holmgren 1974). Data on the pharmacokinetics of hexapropymate in intoxicated patients have not been reported in the literature.

We have experienced a cluster of severe cases of hexapropymate poisoning in a region of Stock-

holm, Sweden, with 420,000 inhabitants. The clinical course was studied and the elimination of hexapropymate was monitored in 2 of the patients.

Patients and Methods

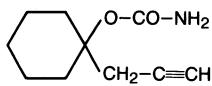
Patients

Verified cases of hexapropymate poisoning were identified retrospectively in the toxicological laboratory for the period January 1985 to May 1987 (8 patients, intoxicated on 12 occasions). In addition, during June 1987, 2 patients were studied with repeated serum samples for up to 3 days after admission to the hospital. Our toxicological service covers a catchment area with 420,000 inhabitants in Stockholm. The region has 2 intensive care units where severely intoxicated patients are treated (South and Nacka Hospital).

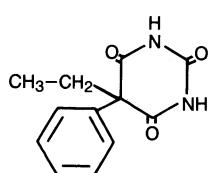
Clinical data about depth and duration of coma, body temperature, arterial blood pressure, duration of ventilatory support as well as social conditions and drug history were recorded from the medical records. Routine laboratory parameters were also screened.

The final patient material contains only cases of hexapropymate poisoning which met the following criteria:

1. No clinical or laboratory history of simultaneous intake of tricyclic antidepressants, opiates, amphetamine, phenothiazines, barbiturates or antihistaminic drugs.
2. Serum hexapropymate concentration above 5.5 mg/L (30 μ mol/L).
3. Ethanol concentration less than 1.4 g/L (30 μ mol/L).



Hexapropymate



Phenobarbitone

Fig. 1. The chemical structures of hexapropymate and phenobarbitone.

Treatment Protocol

Patients with known or suspected hexapropymate poisoning are assessed in the emergency department. Comatose patients, or those with any signs of cardiopulmonary disturbances, are admitted to the intensive care unit where they are monitored continuously for blood pressure, ECG, depth and frequency of breathing, arterial blood gas determinations, and an intravenous line is established. Endotracheal intubation and assisted ventilation are commenced if pCO₂ exceeds 6.5 kPa (50 mm Hg) or pO₂ is less than 7 kPa (55 mm Hg). Sodium bicarbonate is administered by rapid intravenous injection in case of metabolic acidosis (base excess less than 8 mnol/L). If circulatory shock occurs (systolic blood pressure \leq 80 mm Hg), isotonic sodium chloride is infused (500 ml over 10 to 20 minutes), and dobutamine added if blood pressure remains low. If within 6 hours of ingestion, in all patients gastric lavage with tap water is followed by oral administration of 50 g of activated charcoal. Serum concentrations of salicylate, paracetamol (acetaminophen), methanol, ethanol, acetone and isopropanol are determined in a routine toxicological screen. Other substances are determined only if there is clinical evidence of ingestion.

Analytical Methods

A gas chromatographic method developed for the detection of intoxications was used for determination of serum concentrations of hexapropymate. 1 ml of serum [either sample or serum containing hexapropymate 0, 10 or 20 mg/L (0, 50 or 100 μ mol/L)] was extracted in 0.5 ml chloroform with 20 mg/L methylnaphthalene as internal standard. The organic phase was collected and 2 μ l of this solution were injected on a packed capillary 3% OV-17 column (Supelco Inc, Bellafonte, PA, USA) with an oven temperature of 175° C. Injection and detection temperatures were kept at 250° C. The limit of detection of this method is 2.7 mg/L (15 μ mol/L) with a coefficient of variation of 5% and 2% at concentrations of 2.9 mg/L (16 μ mol/L).

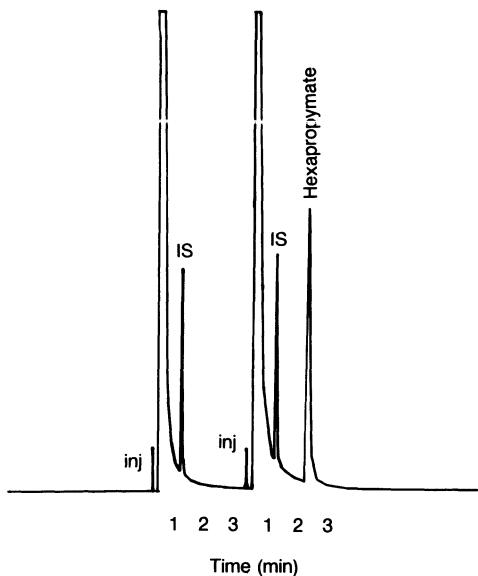


Fig. 2. Chromatogram of hexapropymate using gas chromatography with capillary column (3% OV-17). IS = internal standard (methylnaphthaline).

and 14.5 mg/L (80 $\mu\text{mol}/\text{L}$), respectively. A typical chromatogram is shown in figure 2. Alternatively a capillary CP-SIL 5 CB column (Chrompack Int, Middelburg, The Netherlands) at an oven temperature of 175° C may be used.

Samples were analysed as single determinations within 24 hours after collection. In 2 patients (nos 2 and 4) repeated samples were obtained and these were assayed in duplicate on a later occasion. The terminal half-life in serum was calculated in patient 2 by linear regression of the log concentration *vs* time curve.

In most patients serum was analysed for benzodiazepines (diazepam, desmethyldiazepam, nitrazepam, oxazepam or flunitrazepam). The serum concentrations of benzodiazepines were analysed by modified gas chromatographic methods (de Silva et al. 1976; Vessman et al. 1977; Weinfeld et al. 1977). Diazepam, desmethyldiazepam and flunitrazepam were determined after extraction with a limit of detection of 0.06, 0.06 and 0.01 mg/L (0.2, 0.2 and 30 $\mu\text{mol}/\text{L}$), respectively. Oxazepam and

nitrazepam were assayed after derivatisation. Limits of detection were 0.06 mg/L (0.2 $\mu\text{mol}/\text{L}$) for both compounds.

Drug Utilisation Data

Data on deliveries of hexapropymate, barbiturates and benzodiazepines to pharmacies and hospitals in Sweden were collected from the National Corporation of Swedish Pharmacies for the period 1978 to 1987. For 1987, data on deliveries to each county were available. Drug delivery data were expressed as defined daily doses (DDD) per 1000 inhabitants per day. 1 DDD is equivalent to the mean daily dose which is recommended to be prescribed in the main indication of the drug (Bergman et al. 1975).

Data expressed as DDD/1000 inhabitants/day give an approximation of the exposure of the population to a specific drug.

Results

During the 2.5-year period, 6 patients with verified hexapropymate poisoning fulfilling our criteria were found. They were treated on 8 occasions in the 2 intensive care units in the region. Clinical data of the patients are presented in table I. This group of patients was homogeneous: age was about 40 and all of them had a long history of mixed abuse of alcohol, benzodiazepines, and of intravenous use of opiates and/or amphetamine.

On 7 occasions, the patients had to be treated with assisted ventilation. In one extreme case it had to continue for 4 days (table I, patient 1, first occasion). There was no apparent relationship between serum hexapropymate concentration and depth or duration of coma (cf. table I). The first 5 occasions listed in table I were seriously intoxicated as judged by low scores on the Glasgow coma scale (3 to 5), the duration of coma (96 to 18 hours), the duration of assisted ventilation (84 to 12 hours), hypothermia (29.8 to 35.2°C) and arterial hypotension. Coma was considered ended when scores reached 12. There was no sign of metabolic acidosis in any of the patients despite the marked drug

Table I. Clinical data from 6 patients with hexapropymate poisoning (8 occasions)^a

Patient no; intoxication event	Age/ sex	Maximum serum conc. [mg/L (μ mol/L)]	Maximum coma depth ^b	Coma duration (hours)	Ventilatory assistance (hours)	Maximum arterial pCO ₂ [kPa]	Lowest body temperature (°C)	Lowest arterial blood pressure (mm Hg)
1; 1st	42 F	15.4 (85)	3	96	84	7.10	30.3	100/55
2	40 M	32.6 (180)	3	37	18	7.6	34.7	75/50
3; 1st	37 M	72.5 (400)	3	24	17			75/-
1; 2nd	42 F	15.9 (88) ^c	5	20	12		29.8	70/-
3; 2nd	37 M	54.4 (300)	5	20	12	7.22	35.2	
4	41 F	16.3 (90)	7	18	3	5.62	37.7	110/80
5	43 M	7.6 (42) ^d	6	3	1	5.60	36.2	115/80
6	25 M	20.0 (110)	8	Somnolent	0	5.90	36.3	120/85

a The patients are listed according to the duration of coma.

b Glasgow coma scale.

c This patient had also signs of benzodiazepine intoxication. Maximum levels of flunitrazepam and diazepam were 94 μ g/L (300 nmol/L) and 1.4 mg/L (5 μ mol/L), respectively.

d Ethanol concentration of 1.3 g/L (28 mmol/L).

effect on respiration and arterial blood pressure. No cardiac arrhythmias or epileptic seizures were detected. Routine laboratory tests were within normal limits. All patients survived without any sequelae.

Case Reports

A man aged 40 years was admitted to the intensive care unit because of a heavy overdose of hexapropymate, probably 50 tablets of 0.4g, taken at intervals over 36 hours (patient no. 2, table I). On admission, he was deeply unconscious, did not react to painful stimuli and his breathing was irregular. No antidotes were given. Blood pressure was 75/50 mm Hg. Arterial blood gas analysis was: pH = 7.3, pCO₂ = 7.6 kPa, pO₂ = 7.4 kPa and base excess = 0.8 mmol/L. He was treated with gastric lavage after orotracheal intubation, followed by ventilator treatment for 18 hours. Chest x-ray and ECG were normal. Body temperature was 34.7°C on admission and was normalised within 10 hours. The arterial blood pressure was quickly normalised after intravenous infusion of glucose solution with electrolytes. He was unconscious for 37 hours, and survived without complications. Initial serum concentration of hexapropymate was 33

mg/L (180 μ mol/L). The estimated terminal half-life was 21 hours (fig. 3, r = -0.993).

A woman aged 41 with a history of alcohol abuse took about 40g hexapropymate in a suicide attempt (patient no. 4; table I and fig. 3). On admission she was unconscious and reacted only to severe pain stimuli. Gastric lavage failed because of technical problems. She was still somnolent with no signs of ventilatory depression 24 hours later. Her maximum hexapropymate concentrations of 16.5 mg/L (90 μ mol/L) occurred at 28 and 46 hours (fig. 3). Two days after hospitalisation, her condition worsened, and she developed tachycardia, tachypnoea and cyanosis, probably due to a minor aspiration during the night. She was intubated and required artificial ventilation for 3 hours. Otherwise the clinical course was uneventful.

Drug Utilisation Data

Hexapropymate has a very small share of the total use of hypnotic and sedative drugs in Sweden, 0.4 out of 66.2 DDD/1000 inhabitants/day in 1987 (table II). During the last 10 years, the use of hexapropymate has diminished continuously (table II). The usage of hexapropymate varies, however, 8-fold (0.1 to 0.8 DDD/1000 inhabitants/day) be-

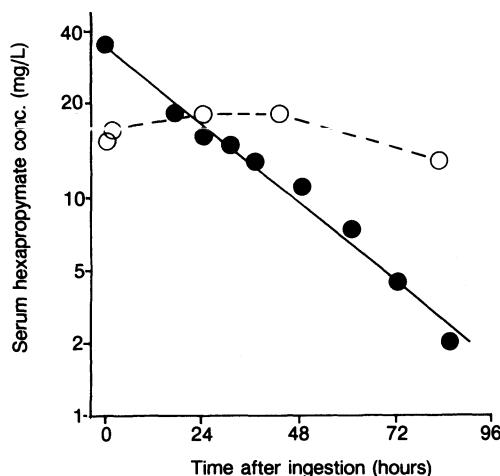


Fig. 3. Serum disposition curves of hexapropymate after intake of 20g (patient no. 2; ●) and 40g of the drug (patient no. 4; ○). Patient no. 2 ingested hexapropymate over a period of 36 hours.

tween the counties (fig. 4). The corresponding figures for the benzodiazepines ranged from 29 to 63 DDD/1000 inhabitants/day between the counties.

Discussion

This material shows that hexapropymate may cause intoxication with severe symptoms such as coma, hypothermia, hypotension and ventilatory depression. The clinical picture is similar to severe barbiturate poisoning (Gary & Tresnewsky 1983). Most remarkable is the extended ventilatory

depression that required assisted ventilation for up to a day or more in some cases (cf. patient nos 1, 2 and 3, table I). Our patient material includes clear cases of hexapropymate poisoning. Only patient no. 1 (second occasion) had a high concentration of a benzodiazepine (flunitrazepam) which may have affected the duration of the coma. The clinical picture should be predominantly influenced by hexapropymate because the decreased body temperature and blood pressure is uncommon in cases of intoxication with benzodiazepines only (Höjer & Baehrendtz 1988).

A detailed pharmacokinetic analysis of hexapropymate disposition in patient no. 2 gave an estimated terminal half-life of 21 hours. This is much longer than the terminal half-life of 2.7 to 8.1 hours found in 6 healthy subjects given a single oral dose of 400mg hexapropymate (Plym Forshell 1988). The sampling period was 24 hours. This difference may be explained by slower elimination of the drug during intoxication because of concentration-dependent kinetics. Such a phenomenon occurs for salicylate and several tricyclic antidepressant drugs in intoxicated patients (Furst et al. 1979; Levy & Tsuchiya 1972; Pedersen et al. 1982). The alternative explanation is that with a longer sampling period (in our case 80 hours), it is possible to detect a slower elimination phase. This phenomenon has been seen in studies with methaqualone (Alván 1974; Alván et al. 1973). The flat concentration-time curve in patient no. 4 (fig. 3) can either be caused by delayed absorption secondary to the

Table II. Deliveries of hypnotic and sedative drugs to hospitals and pharmacies in Sweden 1978 to 1987 (DDD/1000 inhabitants/day)

Drug	1978	1980	1982	1984	1986	1987
Hexapropymate	0.7	0.6	0.5	0.4	0.4	0.4
Benzodiazepines	46.3	46.3	48.1	51.9	54.4	53.2
Barbiturates ^a	5.9	4.8	3.6	2.2	1.0	0.9
Various (especially antihistamine, sedative drugs)	11.5	12.2	13.7	11.5	11.5	12.6
Total	64.4	63.9	65.9	65.9	67.4	67.1

a After 1984, only phenobarbitone has been on the market. It is registered as an antiepileptic drug.

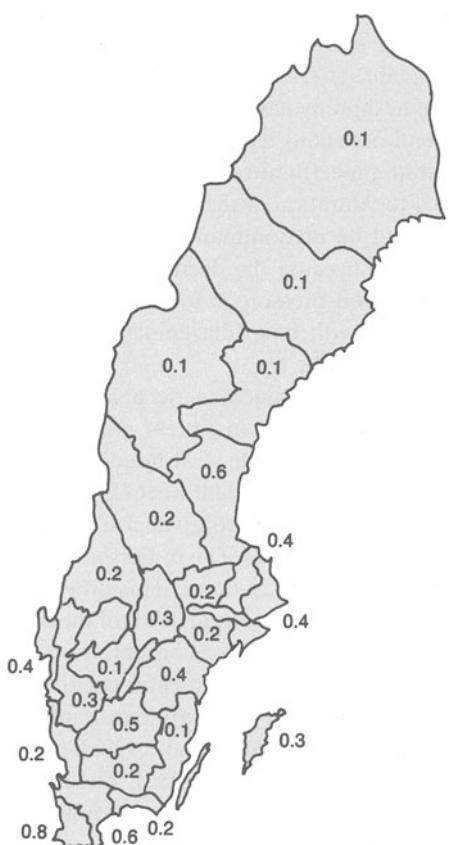


Fig. 4. Deliveries of hexapropymate to Swedish counties in 1987 (DDD/1000 inhabitants/day). The national figure was 0.4 DDD/1000 inhabitants/day.

coma or by concentration-dependent drug elimination (cf. Pedersen et al. 1982).

We have used a treatment schedule including symptomatic and prophylactic measures such as ventilatory and circulatory support. Haemodialysis or haemoperfusion has not been used because of the relatively large volume of the drug, which has been estimated as 1.5 to 3.5 L/kg from pharmacokinetic studies of different preparations (Plym Forsell, personal communication 1988). The efficiency of active elimination procedure is low, illustrated by the following theoretical calculation [haemoperfusion for 4 hours, flow rate of 200 ml/min, hexapropymate serum concentration 18 mg/L (100 µmol/L) and 100% extraction rate]. It is assumed that the drug concentration is constant over this period. A total of 874mg (4.8 µmol/L) hexapropymate will be extracted during 4 hours of haemodialysis. Consequently, under optimal conditions the equivalent of only 2 tablets would be extracted (each tablet contains 400mg of hexapropymate).

From drug utilisation data about hexapropymate (0.4 DDD/1000 inhabitants/day) it may be estimated that 160 persons out of 420,000 in the catchment area are continuously treated with hexapropymate. It is then assumed that each person is using 1 DDD per day. This gives a substantial risk of severe hexapropymate poisoning (5%) in our region during a 2.5-year period for persons treated with the drug (8 occasions of hexapropymate poisoning in 160 persons).

Therapeutic Implications

Hexapropymate poisoning is severe but there is no role for active forced elimination of the drug. Symptomatic treatment in the intensive care unit is needed. This potent drug poses a special risk when it is prescribed to our patients who represent a group with severe and long lasting alcohol and drug abuse. Fatal cases of poisoning with hexapropymate included patients who also had severe addiction problems (Bonnichsen & Holmgren 1974). It is questionable whether the risk of severe poisoning outweighs the clinical value of the drug; it was withdrawn from the market in Sweden on 1 April 1989.

Acknowledgements

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