Z Rechtsmed 84, 161–166 (1980)

Zeitschrift für
Rechtsmedizin

Fatal Case of Propoxyphene Overdose

Morphological and Toxicological Findings

Sylvester Ogbuihi, Gerhard Bohn, and Walburga Audick

Institut für Rechtsmedizin der Westfälischen Wilhelms-Universität, Von-Esmarch-Str. 86, D-4400 Münster, Federal Republic of Germany

Summary. The pathomorphological and toxicological findings of a case of fatal overdose of propoxyphene are reported. The chemico-toxicological findings revealed the presence of only one active substance that has been administered (in an amount of not less than 1.5 g dextropropoxyphene) in form of an analgesic tablet preparation (marketed under the trade name Dolo-Neurotrat), in which it represents the main active constituent.

The most striking histological findings are the changes in the myocardium which are consistent with cardiotoxicity. It is suggested that an estimation of shock duration by means of pathomorphological findings in combination with toxicological and other data be utilised for survival time determination.

Key words: Propoxyphene, suicide – Poisoning, propoxyphene

Zusammenfassung. Es wird über die pathomorphologischen und toxikologischen Befunde bei einer tödlichen Propoxyphenvergiftung berichtet. Nach den chemisch-toxikologischen Befunden lag die alleinige Einnahme dieses Wirkstoffes vor. Diese war mittels des Analgeticums Dolo-Neurotrat in einer Mindestmenge von 1,5 g Dextropropoxyphen HCl erfolgt.

Die auffälligsten histologischen Veränderungen fanden sich am Myocard. Die Befunde sind mit Cardiotoxicität vereinbar. Für die Überlebenszeit- bzw. Todeszeitschätzung wäre es zweckmäßig, auch die Schockdauer aus den histologischen Befunden zu schätzen und mitzubewerten.

Schlüsselwörter: Propoxyphen, Suizid – Vergiftung, Propoxyphen

The analgesic propoxyphene ((d)-1-Benzyl-3-dimethylamino-2-methyl-1-phenyl-propylpropionat) is available in the Federal Republic of Germany (FRG) under various trade names either as pure substance or in combination with vitamins and

Offprint requests to: Dr. Sylvester Ogbuihi (address see above)

0044-3433/80/0084/0161/$ 1.20

antiphlogistics, for example Develin, Erantin, and Dolo-Neurotrat. They contain propoxyphene in amounts varying from 75 to 150 mg.

Several cases of fatal, suicidal, or accidental overdosage have been reported. However, in most of the cases propoxyphene has been detected along with alcohol and other drugs, especially paracetamol (Cravey et al. 1974; Caplan 1977; Finkle et al. 1976; McBay 1976; Robinson et al. 1977; Miller 1977; Simonson 1977).

The toxicological data were obtained from autopsy specimens. Because of polyintoxication or at least the simultaneous presence of other drugs at toxicology, morphological findings have been rather vague and inconclusive.

In the FRG, reports of cases of propoxyphene intoxication including toxicological and pathomorphological data have been rare. At an average of about 80 toxicological investigations of autopsy material per year in our institute, we could report a first incidence.

In the following case only propoxyphene and its metabolite (norpropoxyphene) were found on toxicological analysis of autopsy specimens. There was no evidence of other drugs or alcohol. In other words, this case of fatal monointoxication would be referable to propoxyphene.

Case History

A 21-year-old unmarried female in the 4th to 5th month of her first pregnancy was found dead in her home around 8 p.m. On the morning of the day of death she was reported to have been quite normal, having prepared breakfast as usual for the man she lived with before he left for work. She was 162 cm tall and slim.

Autopsy Findings

At autopsy no fresh or old external injuries were found. The vaginal mucosa was slightly livid, but the cervix showed no erosion or other traumatic lesions. The cervical canal and the amniotic sac presented no pathological changes. The foetus was 20 cm long, weighed 270 g, and showed no abnormalities. The position, size, and structure of the placenta were normal and the umbilical cord had a central insertion. In the stomach there was a moderate amount of slimmy material mixed with yellowish chalky gritty masses suggestive of dissolved tablets. Similar masses were found in the upper segments of the jejunum.

The major gross pathological features of the internal organs were acute congestion and oedema. The brain weighed 1350 g, the right and left lungs 900 g and 750 g, respectively, the liver 1750 g, and the spleen 220 g. Both cardiac ventricles were dilated. The heart weighed 300 g.

Histological evaluation of tissue specimens from internal organs (brain, heart, lungs, liver, spleen, kidneys, suprarenal gland) confirmed acute congestion and edema. These changes were particularly pronounced in the lungs and in the liver.

In addition, the lungs showed scattered areas of collapse with edema fluid in the alveolae. The pulmonary blood vessels and the septal capillaries were

distended and engorged in all areas. In the liver there was a pronounced cloudy swelling of the hepatocytes, especially in the centrilobular areas with occasional cytolytic necrosis.

The myocardium had a slight to moderate loosening of the interstitial connective tissue. Within several muscle fibres there were focal losses of striation. In others there were multivacuolated and granular areas within the sarcoplasm whereas other muscle fibers had undergone various degrees of sarcolysis. These changes were almost constantly remote from the nuclei, some of which show early karyorrhectic changes. Several glossy striations were dehiscent.

Analytical Method

Specimens taken at autopsy were homogenised in several portions (5 g portions of gastric content, 20 g portions each of liver, kidney, and blood) processed using the modified Stas-Otto Method (Clarke 1971).

The obtained aqueous solutions as well as 10 ml of urine were acidified, extracted with ether, and then further extracted with dichlormethane in basic and neutral media. The residues of the extracts obtained therefrom were analysed with a gas chromatograph Varian 2700 and a mass spectograph Varian MAT CH 7 (2 m glass column, 2 mm ID, 1% OV 17 on Chromosorb G, AW-DMCS, 80—100 mesh, temperature programme: oven 100—200° C and 150—280° C, 8° C min^{-1}, injector port 250° C, ion source temperature 200° C at 70 eV; carrier gas Helium 20 ml/min).

Peaks for propoxyphene and norpropoxyphene amid were found. At pH 11 norpropoxyphene is present as norpropoxyphene amid (Wolen et al. 1975; Robinson et al. 1977).

The mass spectrum of the peaks corresponded with those of the pure substances as well as available published data (Bonnichsen et al. 1973; Wolen et al. 1975; Due et al. 1976; Norheim 1976). No other organic compounds or metabolites were identified. Using Head-Space-Method (Machata 1967) no ethanol or other volatile substances were found in blood or urine.

Quantitative Determination

The quantitative determination of propoxyphene and norpropoxyphene in the amid form was done with gas chromatograph using the method described by Robinson et al. (1977).

The gas chromatograph was a Hewlett-Packard 5835 fitted with a flame ionisation detector. The 2 m glass column of 2 mm ID, was packed with 1% OV17 AW-DMCS 80—100 mesh chromosorb. The oven temperature was maintained at 200° C. The temperature of the injector port and the detector was 250° C. The carrier gas was nitrogen 2 ml/min. The retention time under these conditions were for propoxyphene 5.7 min (RI 2470) and for norpropoxypheneamid 16.5 min (RI 3020).

Result

Sample	Propoxyphene µg/g	Norpropoxyphene amid µg/g
Stomach content (total 65 g)	759 mg	traces
Urine	6.3	38.4
Blood	7.8	9.4
Kidney	15.0	16.3
Liver	74.2	44.9
Bile	42.6	106.1

Discussion

The toxicological analysis of the recovered autopsy material revealed propoxyphene intoxication. On the strength of this finding intensified police investigations brought a package of Dolo-Neurotrat R dragees to light. The package which originally contained 50 dragees now contained only 9. It was not possible at first sight to determine whether all of the missing 41 dragees were ingested immediately prior to death.

A Dolo-Neurotrat dragee contains 75 mg of Dextropropoxyphene-HCl, 100 mg of Aneurin-HCl, 100 mg of Pyridoxin-HCl, and 0.25 mg of Cyanocobalamin.

The quantity of propoxyphene (759 mg) in the 65 g stomach content corresponds to about 11 dragees of Dolo-Neurotrat. At a liver tissue concentration of 74.2 µg/g propoxyphene and 44.9 µg/g of norpropoxyphene, the 1750 g liver contained about 210 mg of propoxyphene corresponding to about three dragees.

Considering the determined concentrations of propoxyphene and norpropoxyphene in bile, kidney, urine, and especially blood, further six dragees could be estimated. The minimum number of ingested dragees would therefore be about 20, which makes an accidental overdosage very improbable.

The ingestion of 20 dragees of Dolo-Neurotrat corresponds to a dextropropoxyphene dosage of 27 mg/kg body weight. Fatal cases with comparable doses have been reported (Baselt et al. 1975; Lund et al. 1972; McBay 1976; Finkle et al. 1976; Christensen 1977). The autopsy blood concentration of 7.8 µg/g, which is a result of the rapid tissue uptake of propoxyphene, the comparatively higher liver tissue concentration of 74.2 µg/g, lies within the range in published fatal cases (Cravey et al. 1974; Christensen 1977a, b; Regent et al. 1977; Robinson et al. 1977; Sturner et al. 1973; Young et al. 1972).

The minimum autopsy blood concentrations consistent with fatal intoxication are stated to range between 1.0 and 1.2 µg/g (Angelo et al. 1977; Caplan 1977; Christensen 1977a, b; McBay 1976; Sturner et al. 1973).

However, values ranging from 2.0 to 3.0 µg/g have been mentioned (Miller 1977). Seven to eight-fold concentrations as in this case would possibly indicate a swift fatality. The victim was last seen alive 12 h before she was found dead. The

doctor called to the scene estimated the time of death to be about 10 a.m., i.e., about 2.5 h after she was last seen alive.

The survival time of about 2.5 h seems to be in keeping with our histological findings. A much longer survival time of about 10 h would give evidence of shock-induced changes, especially in the kidneys.

Attempts to correlate survival time with autopsy blood concentrations and blood/liver ratio have been made (Finkle et al. 1976) in full knowledge of the fact that the results represent only a guideline.

The histological findings in the myocardium are suggestive of cardiotoxicity. A follow-up determination of myocardial tissue concentration might be very useful. If shock-induced changes were to be found in other organs, such as the lungs and kidneys, an estimation of shock duration by means of pathomorphological parameter (Remmele et al. 1973a, b; Sandritter 1973; Young et al. 1972) in combination with toxicological and investigative data would definitely enhance the precision of survival time estimation.

References

Angelo HR, Christensen IM (1977) Gas chromatographic method for the determination of dextropropoxyphene and norpropoxyphene in human plasma, serum and urine. J Chromatogr 140:280–283

Baselt RC, Wright IA, Turner IE, Cravey RH (1975) Propoxyphene and norpropoxyphene tissue concentrations in fatalities associated with propoxyphene hydrochlorid and propoxyphene napsylate. Arch Toxicol 34:145–152

Bonnichsen R, Fri C-G, Hgälm R, Petrovics I, Ryhage R (1973) Identification of a dextropropoxyphene metabolite by gas chromatography—mass spectrometry. Z Rechtsmed 71: 270–273

Caplan YH, Thompson BC, Fisher RS (1977) Propoxyphene fatalities: blood and tissue concentrations of propoxyphene and norpropoxyphene and a study of 115 medical examiner cases. J Anal Toxicol 1:27–35

Christensen H (1977a) Determination of dextropropoxyphene and norpropoxyphene in autopsy material. Acta Pharmakol Toxicol 40:289–297

Christensen H (1977b) Dextropropoxyphene and norpropoxyphene in blood muscle, liver and urine in fatal poisoning. Acta Pharmakol Toxicol 40:298–309

Clarke EGC (ed) (1971) Isolation and identification of drugs, The Pharmaceutical Press, London, p 22

Cravey RH, Shaw RF, Nakamura GR (1974) Incidence of propoxyphene poisoning: A report of fatal cases. J Forensic Sci 19:72–80

Due SL, Sullivan HR, McMachon RE (1976) Propoxyphene: Pathways of metabolism in man and laboratory animals. Biomed Mass Spectrometry 3:217–225

Finkle BS, McCloskey KL, Kiplinger GF, Bennet IF (1976) A national assessment of propoxyphene in post-mortem medicolegal investigation, 1972–1975, J Forensic Sci 21:706–742

Lee KP, Walker IE (1972) Plasma concentrations of propoxyphene in man. Int J Clin Pharmacol 5:371–380

Lund A, Nielsen GD (1972) Dextropropoxyphene concentrations in blood in cases of fatal poisoning. Z Rechtsmed 71:148–152

Machata G (1967) Über die Gaschromatographische Blutalkoholbestimmung. Blutalkohol 4: 252–260

McBay AI (1976) Propoxyphene and norpropoxyphene concentrations in blood and tissues in cases of fatal overdose. Clin Chem 22:1319–1321

Miller RR (1977) Propoxyphene: a review. Am J Hosp Pharmacol 34:413–423

Norheim G (1976) Determination of dextropropoxyphene and norpropoxyphene in autopsy material by gas chromatography. Arch Toxicol 36:89–95
Rejent TA (1977) Propoxyphene-associated deaths: methods post-mortem levels in blood and liver. Clin Toxicol 11:43–51
Remmele W, Loew D (1973) Pathophysiologie der Thrombozyten im Schock. Klin Wochenschr 50:3–9
Remmele W, Loeper H (1973) Zur pathologischen Anatomie des Kreislaufschocks beim Menschen. Klin Wochenschr 51:10–24
Robinson AE, Sattar H, McDowall RC, Holder AT, Powell R (1977) Forensic toxicology of some deaths associated with the combined use of propoxyphene and acetaminophene (paracetamol). J Forensic Sci 22:708–717
Sandritter W (1973) Zur pathologischen Anatomie des Schocks. Klin Wochenschr 51:1–2
Simonson I (1977) Accidental fatal drug poisoning with particular reference to dextropropoxyphene. Forensic Sci 10:127–132
Sturner WQ, Garriott IC (1973) Deaths involving propoxyphene. A study of 41 cases over two-year period. Jama 223:1125–1129
Wagner IG, Welling PG, Roth SB, Sakmar E, Lee KP, Walker IE (1972) Plasma concentrations of propoxyphene in man. Int J Clin pharmacol 5:371–380
Wolen RL, Ziege EA, Gruber CM jr (1975) Determination of propoxyphene and norpropoxyphene by chemical ionization mass fragmentography. Clin Pharmacol Ther 17:15–20
Young DJ (1972) Propoxyphene suicides. Report of nine cases. Arch Int Med 129:62–66

Received July 5, 1979