Z Rechtsmed (1989) 102:107–115

Zeitschrift für
Rechtsmedizin

Fatal dextropropoxyphene poisonings in Jutland (Denmark)

E. Kaa[1] and J. B. Dalgaard[2]

[1] Institute of Forensic Medicine, Department of Forensic Chemistry, University of Aarhus, Skovagervej 2, DK-8240 Risskov, Denmark
[2] Institute of Forensic Medicine, University of Aarhus, Finsensgade 15, DK-8000 Aarhus C, Denmark

Summary. For many years dextropropoxyphene (dxp) has been the medicament most frequently occurring in drug poisoning cases examined at the Institute of Forensic Medicine, University of Aarhus.
This study includes 85 cases of acute fatal poisoning examined in the period 1985–1987 in which dxp alone (40 cases) or in combination with alcohol (29 cases) and/or other drugs (16 cases) contributed significantly to death. Two-thirds of the deceased were men and one-third women. The average age was 37 years for both sexes. More than half of the deceased were drug and/or alcohol misusers. Eighteen were drug addicts. Half of the deaths resulted from accidents, while 40% were suicides. Accidental deaths prevailed among younger men. In a majority of the cases the drug had been taken orally. In these cases the median total blood concentration of dxp and the metabolite nordextropropoxyphene (ndxp) was 17 mg/kg in the suicide cases and 7.1 mg/kg in the accident cases. The corresponding figures for dxp without metabolite were 9.4 mg/kg and 2.2 mg/kg, respectively. The median value of the quotient dxp/ndxp was 1.9 in the suicide cases and 0.5 in the accident cases. The quotient, together with the concentrations of the drug, may therefore indicate the manner of death in many cases.

Key words: Dextropropoxyphene, deaths – Poisoning, dextropropoxyphene

Zusammenfassung. Für viele Jahre war Dextropropoxyphen (dxp) im Institut für Rechtsmedizin der Stadt Aarhus das am häufigsten vorkommende Arzneimittel bei Arzneistoffintoxikationen. In der vorliegenden Studie werden 85 tödliche Intoxikationen der Jahre 1985–1987 ausgewertet, in denen dxp allein (40 Fälle) oder in Kombination mit Alkohol (29 Fälle) und/oder anderen Arzneistoffen ursächlich war. Zwei Drittel der Fälle betraf Männer, ein Drittel Frauen. Das Durchschnittsalter lag für beide Ge-

Offprint requests to: E. Kaa

schlechter bei 37 Jahren. Über die Hälfte betrieben Alkohol- und/oder Arzneimittelabusus. Achtzehnmal lag eine Abhängigkeit vor. Bei 40% handelte es sich um einen Suizid, bei 50% um eine akzidentelle Intoxikation, überwiegend bei jungen Menschen. Bei peroraler Einnahme lag der Medianwert der Blutkonzentration von dxp und nordxp (ndxp) bei 17 mg/kg (Suizid) oder 7,1 mg/kg bei akzidenteller Vergiftung. Entsprechend betrugen die Konzentrationen an dxp allein bei 9,4 bzw. 2,2 mg/kg und die Quotienten dxp/ndxp betrugen 1,9 bzw. 0,5. In Verbindung mit der Gesamtkonzentration kann der Quotient in vielen Fällen Aufschluß über die Art und Weise des Todes geben.

Schlüsselwörter: Dextropropoxyphen, Todesfälle – Vergiftungen, Dextropropoxyphen

Introduction

For many years dextropropoxyphene (dxp) has been a frequently used and misused drug in Denmark [1–8]. During the period from 1981 to 1985 its sale in daily doses of 0.2 g increased from 7.7 to 9.3 per 1000 inhabitants. The following years a decrease was observed, and in 1987 the corresponding figure was 6.2, according to the Danish drug statistics. Sales of the drug had a direct bearing upon the number of deaths it caused (Fig. 1).

The forensic institutes and The National Board of Health have warned about the danger of the drug on several occasions, but since 1982 dxp cases have been the most frequently encountered form of fatal drug intoxication at The Institute of Forensic Medicine, University of Aarhus [1–3].

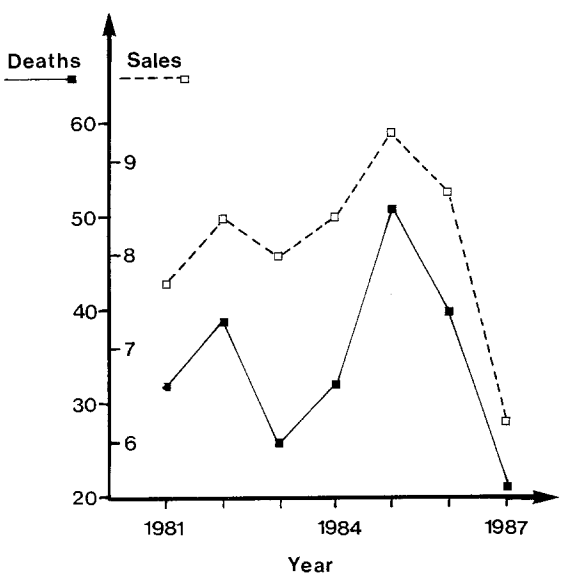

Fig. 1. Sales of dxp (daily doses of 0.2 g/1000 inhabitants) according to the Danish drug statistics (○----○) and deaths due to dxp as percentage of all drug fatalities examined at the Institute of Forensic Medicine, University of Aarhus (●——●)

In Denmark dxp is distributed either in the form of 100 mg/capsule of napsylate (Doloxene) or, more often, in the chloride form (Dextropropoxifen (65 mg/tablet), Abalgin (65 mg/capsule), Abalgin Retard (150 mg/capsule). Sixty-five milligrams of the chloride form contains the same amount of dxp as 100 mg of napsylate. Abalgin Retard is a slow release product which makes it especially dangerous for misusers. In Denmark combinations of dxp with other drugs are not registered.

Materials and methods

The material includes 85 fatal cases in which dxp alone or in combination with alcohol and/or other drugs was the cause of death or contributed significantly to the death. The cases were submitted to medicolegal autopsy at the Institute of Forensic Medicine, University of Aarhus, during the period 1985–1987. The institute performs approximately 550 medicolegal autopsies per year and covers a population of approximately 2 millions living on the peninsula of Jutland.

In all cases a police report was available including specific information on the death, such as findings of medicine and statements by family, friends and, in many cases, also the deceased's physician.

Cases in which the immediate cause of death was aspiration, hypothermia, or bronchopneumonia, but the underlying cause was considered to be intoxication, are included.

In all but three cases where the deceased had been receiving hospital treatment for several days prior to death, a quantitative determination of dextropropoxyphene (dxp) and the metabolite nordextropropoxyphene (ndxp) in the blood was performed using a combination of gas chromatography with nitrogen phosphorous detection (GC/NPD) and high performance thin-layer chromatography (HPTLC). In the very few cases with an extremely high concentration of dxp the GC-result was verified by UV-spectrophotometry. The calculations were made in proportion to blood references analyzed as the unknown samples.

The forensic chemical analysis also included a semi-quantitative screening of liver tissue, stomach contents or both, using gas chromatography, thin-layer chromatography and UV-spectrophotometry.

Results

In all cases a complete medicolegal autopsy, including microscopy, was performed. The most common findings were dark livid stains and organs, pulmonary edema and, in some cases, tablets visible in the stomach contents. As capsules containing the granula of Abalgin Retard are dark red, an immediate suspicion of dxp poisoning arose in particular when the typical "poppy seed"-like grains were observed in the red colored stomach and/or intestinal contents. In injection cases typical tablet granulomar could usually be seen on microscopic examination of the lungs.

Table 1 shows the 85 deaths according to cause of death and sex of the deceased. Two-thirds ($n = 55$) were men and one-third ($n = 30$) women. Deaths caused solely by dxp dominated the female material, while deaths caused by a combination of dxp and alcohol and/or other drugs were more frequently found amongst men.

For the male material a distinct maximum was seen in the 30–39-year age group, while in women age distribution was fairly equal in the interval between

Table 1. Cause of death in 85 fatal intoxication cases

Sex	Cause of death			
	Group 1	Group 2	Group 3	Total
Men	23	20	12	55
Women	17	9	4	30
Total	40	29	16	85

Group 1: Death solely due to dxp
Group 2: Death due to a combination of dxp and alcohol
Group 3: Death due to a combination of dxp and other drugs and possibly alcohol

20 and 50 years (Fig. 2). The average age was 37 years for both men and women.

Twenty-two of the deceased were unemployed at the time of death and 25 received disability or old age pension. Fourteen were unskilled, 15 skilled workers, and two were self-employed. No information as to the occupation of the remaining victims was available.

Sixty-two of the deceased died in their own homes, six in the homes of friends or relatives, eight died in hospitals, three while being held in custody, two in shelters, three were found outdoors and one in a car.

Forty-nine of the deceased were drug or alcohol misusers, and of these, 18 were drug addicts (persons taking hard drugs either constantly or periodically).

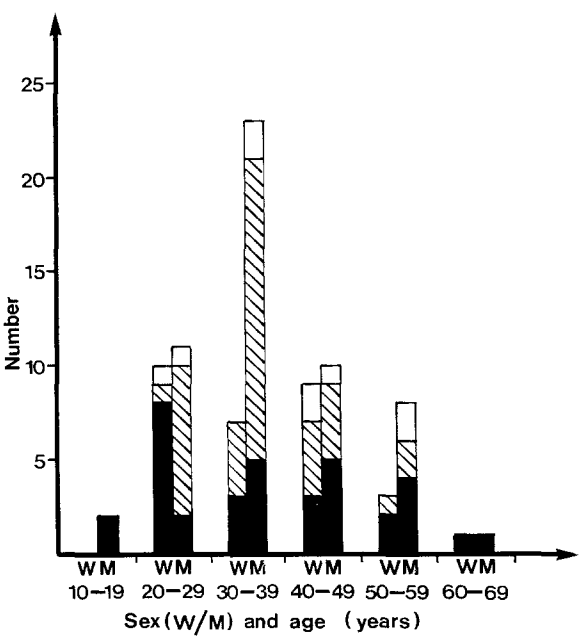

Fig. 2. Manner of death according to age of both sexes. ■ = suicides, ▨ = accidents, □ = not ascertained. W = women, M = men

In a large number of addict cases needle marks were found on the body at the autopsy. Nine of the persons had earlier attempted suicide.

In 66 of the 85 deaths information was available concerning which dxp-containing product had been used. In 19 cases, Abalgin Retard, in 20 cases Abalgin and in eight cases Abalgin without further specification was found. Dextropropoxifen was registered in 16 cases and Doloxene in seven cases. In four deaths more than one dxp-containing product was found.

In 42 cases the deceased had received the drug legally on prescription from his own physician. In nine cases the drug was prescribed to a relative. Only in three cases did positive information indicate that the drug had been bought on the black market. In the rest of the cases no information was available as to the source of the drug.

In 73 of the cases the drug had been taken orally, in eight cases injected and in four cases the administration form could not be ascertained from the information available and the results obtained.

Manner of Death

Whenever possible The Institute of Forensic Medicine classifies all examined cases according to the manner of death. This is done on the basis of information obtained from the police and medical investigations, together with the results from the autopsy and toxicologic analysis.

Approximately half of the deaths (42 cases) resulted from accidents, while 34 were suicide cases. In nine of the cases the manner of death could not be ascertained. Thirty-two of the 55 male cases were accidents and 17 suicides, while only ten of the 30 female cases were accidents and 17 suicides. This means that accidents dominated among men, while suicides dominated among women.

When comparing the manner of death to the age groups of both sexes, it was found that accidental deaths especially dominated among younger men, while suicide was the most common manner of death among women 20–29 years of age (Fig. 2). For both sexes suicides dominated in the age groups above 50 years.

Blood Concentrations in Fatal Dxp Intoxications

As the metabolite itself is poisonous, it is relevant to use the sum of both dxp and ndxp when evaluating the significance of the concentrations for death. Moreover, the quotient dxp/ndxp (= K) may be used to differentiate between an acute and a chronic poisoning. This is possible because the half life of the metabolite is much greater than the half life of dxp, which means that in most cases the metabolite will be present in a concentration higher than the concentration of dxp [8]. An exception to this is found in acute poisonings or chronic/intermittent poisonings in combination with an acute poisoning.

In suicide cases death is expected to occur before all of the drug has been metabolized. The quotient K may therefore be rather high in these cases. In 26 of the 33 suicide cases with the drug taken orally, $K \geq 1$ was found, whereas only nine of the 29 accident cases had a $K \geq 1$. The highest K-values were found

Table 2. The median blood concentrations according to manner and cause of death in 62 fatal poisonings following oral administration of the drug. Concentrations in mg/kg

Manner of death		Cause of death					
		Group 1 ($n = 26$)		Group 2 ($n = 24$)		Group 3 ($n = 12$)	
		Median	(Range)	Median	(Range)	Median	(Range)
Accidents ($n = 29$)	dxp + ndxp	10	(1.9–17)	7.9	(3.8–21)	2.6	(2.2–9.0)
	dxp	3.0	(1.1–9.4)	4.1	(1.5–14)	0	(0 –0.8)
	dxp/ndxp	0.6		0.8		0	
Suicides ($n = 33$)	dxp + ndxp	17	(6.8–3800)	21	(0.4–51)	17	(2.6–24)
	dxp	9.0	(0.8–3800)	19	(0.4–47)	8.3	(1.5–18)
	dxp/ndxp	1.9		7.5		1.3	

Group 1: Death solely due to dxp
Group 2: Death due to a combination of dxp and alcohol
Group 3: Death due to a combination of dxp and other drugs and possibly alcohol

when alcohol was involved (Table 2). This indication of more sudden deaths emphasizes the danger of the combination of dxp with alcohol. The median value of K was 1.9 in the suicide cases and 0.5 in the accident cases. $K \geq 1.0$ may therefore indicate suicide, while $K < 1.0$ may indicate an accidental death (Fig. 3).

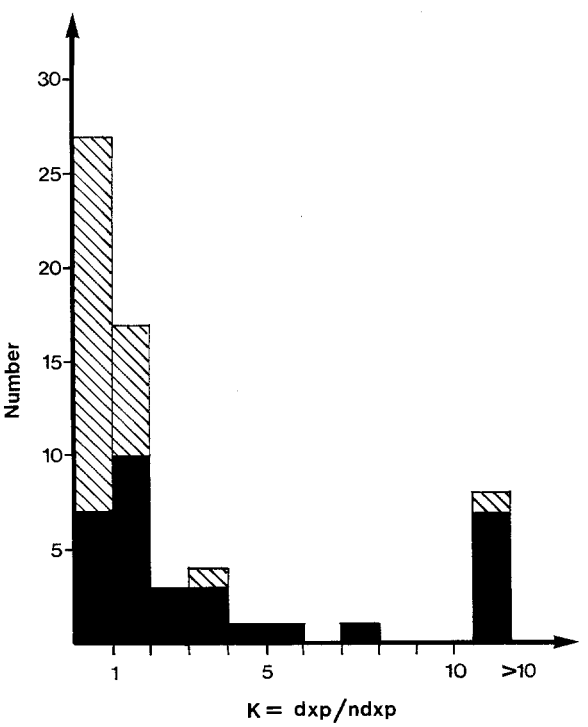

Fig. 3. The quotient K (dxp/ndxp) in 62 cases of fatal poisoning following oral administration. ■ = suicides ($n = 33$), ▨ = accidents ($n = 29$)

Table 3. Eight cases of fatal poisoning following injection of dxp

Case no.	Blood conc. (mg/kg)		Alcohol (g/kg)		Manner of death
	dxp	ndxp	Blood	Urine	
1	2.6	2.2	0	0	Accident
2	3.4	11.6	0	0	Accident
3	3.8	0	1.06	2.02	Accident
4	6.4	0	0.49	1.11	Accident
5	14	0	0.46	0.52	Accident
6	15	22	0	0	Accident
7	15	4.9	0	0	Accident
8	79	4.4	1.10	1.14	Suicide

Following oral administration of the drug the median blood concentration of dxp and ndxp was 17 mg/kg in the 33 suicide cases and 7.1 mg/kg in the 29 accident cases. The corresponding figures for dxp without the metabolite were 9.4 mg/kg and 2.2 mg/kg, respectively. As expected, the lowest concentrations were found in the accident cases when other drugs were involved (Table 2). The concentrations in the suicide cases were significantly higher for all groups. At total concentrations above 21 mg/kg all cases were suicides.

In 55 of the 62 cases described in Table 2 a total concentration of dxp and ndxp of less than 30 mg/kg was found. In five suicide cases the sum was in the range of 30–75 mg/kg but in two cases a value of more than 75 mg/kg was found. In one of these cases approximately 6 g dxp had been taken, and concentrations of 190 mg/kg of dxp and 65 mg/kg of ndxp were measured. In the other case no information was available as to the amount ingested, but the extremely high value of 3.8 g/kg of dxp and 65 mg/kg of ndxp were found. The liver values were 190 mg/kg and 90 mg/kg for dxp and ndxp, respectively. The blood concentrations were checked by analyzing another blood sample taken from another part of the body at the autopsy.

The time of possible survival, i.e., the time between the death being discovered and the deceased being last seen varied from 0 min to 5 days. In nine of the cases the time of possible survival was less than 1 h, in 44 between 1 and 12 h, and in ten between 13 and 24 h. In 19 of the cases the possible survival time was more than 24 h, and in three of the cases information was not available. The possible survival time does not reflect the real time the deceased had been alive before death occurred. Some may have been dead for some time before their body was discovered. In addition, the deceased may have been unconscious for some time before death and thus metabolized some of the drug. This may explain some of the low concentrations found and to a certain degree the proportion of dxp to ndxp. When evaluating a case, the possible survival time in proportion to the concentrations found must always be considered.

Seven accident cases and one suicide case following injection of the drug are shown in Table 3. All the victims were drug addicts and at least five died while

they injected the drug. Three were not found until later, and nobody witnessed their death. These victims may well have died immediately. A syringe containing dxp found near the body was analyzed in six of the cases. Fresh needlemarks were revealed at the autopsy in all cases. In three of the eight injection cases Abalgin Retard had been used, in one case Abalgin and in three cases Abalgin without specification of strength. In one case there was no information as to which dxp-containing product had been used, but the insoluble napsylate salt is obviously not used for injection purposes.

Discussion

The 85 deaths due to dxp described in this study do not reflect the total number of deaths caused by the drug, as not all poisonings in Denmark are submitted to a medicolegal autopsy and/or forensic chemical analysis. Particularly in cases of obvious suicides only a medicolegal inspection of the body is often performed. Moreover, the misuse of dxp in the eastern part of Denmark is greater than in Jutland [6, 7].

According to a special regulation, all deaths in Denmark related to misuse of euphoriants are subjected to medicolegal autopsy and toxicological analysis. The study is therefore supposed to include all drug addicts who had died of dxp during the 3-year period.

Eighteen deaths among drug addicts due to dxp corresponds to approximately 30% of all drug fatalities among addicts during the survey period. Compared to all drug poisonings examined at the Institute during the period, the dxp fatalities corresponded to approximately 40%. Therefore, even though dxp is also a drug of abuse among drug addicts, deaths caused by the drug did not occur particularly frequently among addicts. Yet, persons dying of dxp are most often drug and/or alcohol misusers. This corresponds with the results of other studies [9, 10].

The concentrations of dxp and ndxp in this study are in accordance with other studies [4, 9–15]. Concentrations above 75 mg/kg have – although they are exceptions – also been described previously [11, 12]. The frequent occurrence of high concentrations in this study do not support the theory about an upper limit of dxp saturation in blood of approximately 10 mg/kg after oral administration [15].

Studies from other countries have shown a decreasing misuse of dxp [10, 16, 17]. The decrease may have different reasons. In Norway, the dispensing regulations were tightened, and probably as a consequence of this and a debate in the press, a decrease was observed [16, 17]. Owing to the marked increase in dxp deaths in Denmark in 1985, a more restricted dispensing form or, eventually, the complete removal of dxp from the list of registered drugs was proposed [2, 7].[1] Probably as a result of the warnings and the discussion in the press, a decrease in deaths together with a decrease in sales has already been observed. This trend will hopefully continue.

[1] A tightening of the dispensing regulation of dxp has been passed on in Denmark as from July 1988.

References

1. Kaa E, Dalgaard JB (1986) Deaths from poisoning in Jutland during the period 1981–1983. Ugeskr Laeger 148:344–348 (in Danish with English summary)
2. Kaa E, Dalgaard JB (1987) Deaths due to dextropropoxyphene in Jutland in 1985. Ugeskr Laeger 149:1629–1634 (in Danish with English summary)
3. Kaa E (1987) Deaths from poisoning in Jutland 1981–85. Arch Pharm Chem 15:50–64
4. Christensen H (1977) Dextropropoxyphene and norpropoxyphene in blood, muscle, liver, and urine in fatal poisonings. Acta Pharmacol Toxicol 40:298–309
5. Simonsen J (1977) Accidental fatal drug poisoning with particular reference to dextropropoxyphene. Forens Sci 10:127–132
6. Theilade P (1987) Deaths due to dextropropoxyphene in east Denmark. Ugeskr Laeger 149:2560–2564 (in Danish with English summary)
7. Segest E (1987) Poisoning with dextropropoxyphene in Denmark. Human Toxicol 6:203–207
8. Schou J, Angelo A, Dam W, Jensen K, Christensen JM (1978) Pharmacokinetics of dextropropoxyphene in acute poisoning. Arch Toxicol [Suppl] 1:343–346
9. Finkle BS, McCloskey KL, Kiplinger GF, Bennett IF (1976) A national assessment of propoxyphene in postmortem medicolegal investigation, 1972–1975. J Forens Sci 21:706–742
10. Finkle BS, Caplan YH, Garriott JC, Monforte JR, Shaw RF, Sansalla PK (1981) Propoxyphene in postmortem toxicology 1976–1978. J Forens Sci 26:739–757
11. Caplan YH, Thompsen BC, Fischer RS (1977) Propoxyphene fatalities: Blood and tissue concentrations of propoxyphene and norpropoxyphene and a study of 115 medical examiners cases. J Anal Toxicol 1:27–35
12. Eberhardt RD, Cash DK (1984) A high propoxyphene concentration. J Anal Toxicol 8: 246–247
13. Baselt RC, Wright JA, Turner JE, Cravey RH (1975) Propoxyphene and norpropoxyphene tissue concentrations in fatalities associated with propoxyphene hydrochloride and propoxyphene napsylate. Arch Toxicol 34:145–152
14. McBay AJ (1976) Propoxyphene and norpropoxyphene concentrations in blood and tissue in cases of fatal overdose. Clin Chem 22:1319–1321
15. Sturner WQ, Garriott JC (1973) Deaths involving propoxyphene. A study of 41 cases over a 2-year period. J Am Med Assoc 223:1125–1130
16. Teige B (1985) Drug and alcohol fatalities outside the hospital. Tidsskr Nor Laegeforen 27:1857–1859 (in Norwegian)
17. Teige B, Kaa E, Bugge A (in press) A comparison of drug-related deaths in Oslo, Norway and Aarhus, Denmark. J Forens Sci Soc

Received June 9, 1988