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Dextropropoxyphene-related deaths – a problem that persists?

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Summary. A total of 48 cases of dextropropoxyphene-related deaths that occurred over a 6-year period (1987–1992) in the Lothian and Borders region of Scotland were reviewed. No significant gender difference was found but a significantly greater proportion of the deaths occurred in the urban areas ($P < 0.05$). Suicide accounted for 81.3% of cases while the other deaths were caused accidentally and involved drug addicts, alcoholics and those who had taken their dextropropoxyphene-containing prescriptions following consumption of alcohol. Overall concomitant alcohol abuse was identified in 41.7% of all the victims. Compound analgesic preparations containing dextropropoxyphene are still widely prescribed and the persistence of deaths from its overdose may suggest the need for stricter prescription control and for educational programmes for users.

Key words: Dextropropoxyphene – Fatal overdose – Control – Suicide

Zusammenfassung: Insgesamt 48 Todesfälle im Zusammenhang mit Dextropropoxypen, welche sich über einen 6-Jahres-Zeitraum (1987–1992) in der Lothian- und Borders-Region von Schottland ereigneten, wurden untersucht. Es wurde kein signifikanter Geschlechtsunterschied gefunden, aber ein signifikant höherer Anteil der Todesfälle ereignete sich in den städtischen Regionen ($P < 0.05$). Suizid findet sich in allen 81,3% der Fälle, während die anderen Todesfälle akzidentiell waren. Diese involvierten ebenfalls Drogenabhängige, Alkoholiker sowie Personen, die ihre Dextropropoxyphen-Verschreibung nach Alkoholkonsum eingenommen hatten. Insgesamt wurde ein begleitender Alkoholmißbrauch in 41,7% aller Opfer festgestellt. Schmerzmittel-Präparate, welche Dextropropoxyphen enthalten, werden noch in großem Umfang verschrieben und die Fortdauer von Todesfällen aufgrund einer Überdosierung mag die Notwendigkeit für eine strengere Verschreibungskontrolle nahelegen und für Aufklärungsprogramme für Benutzer.

Schlüsselwörter: Dextropropoxyphen – tödliche Überdosis – Kontrolle – Suizid

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Introduction

Dextropropoxyphene (DXP), a centrally acting mild narcotic analgesic, structurally related to methadone, was introduced in the mid 1960's. It produces an agonist effect at the mu receptors in the brain (USPDI 1993). Following oral administration it is readily absorbed through the gastro-intestinal tract and a peak plasma concentration is reached in 1–2 hours (Jaffe & Martin 1985). A low incidence of side-effects and a lack of euphoria make it a commonly prescribed analgesic.

High concentrations are achieved quickly in the liver, brain, lungs and kidneys; the drug undergoes a process of N-demethylation in the liver to yield norpropoxyphene which has a half-life of 23 hours. Less than 10% of the drug is excreted within the first 6 hours while its metabolites appear over the next 6–48 hours (Clarke & Berle 1971; USPDI 1993).

That DXP has some addictive properties is no longer in doubt (Clarke & Berle 1971; Segest et al. 1993) but probably more worrying is that only a marginal difference exists between a therapeutic and a toxic dose (Dukes et al. 1992a; Segest et al. 1993). Though clinical recovery has followed ingestion of between 960 mg and 3.2 g of DXP, the minimum lethal dose in an adult is around 500 mg (Clarke & Berle 1971; Dreisbach 1983). Toxicity is greatly enhanced, even at low doses, by a concurrent consumption of alcohol and/or benzodiazepines (Young & Lawson 1980; Swensen 1988; Schumacher & Dowd 1991; Dukes et al. 1992b). Propoxyphene poisoning is often associated with instantaneous or suddenly developing grave respiratory and cardiac insufficiency even if the patient is awake at the time.

Reports on fatal DXP poisoning have emanated from North America (Finkle 1984), Denmark (Segest et al. 1993; Theilade 1989), Northern Ireland (Carson & Carson 1977) and England (Crowe 1989). Some of these deaths are accidental but a greater proportion were suicidal. A recent review of fatal substance overdose in the Lothian and Borders region of Scotland (LBRS) showed that DXP preparations are the most common (38.2%) narcotic analgesic overdosed and deaths from it have increased during the last few years, particularly among males (Obafunwa & Busuttil 1993). The present study is intended to provide

Table 1. Dextropropoxyphene fatal overdoses – distribution of deaths in the LBRS (1987–1992)

Year	No. of cases		Domicile		Manner of death			Known alcoholic	Remunerated employment	
	M	F	Urban	Rural	Suicide	Accident	Unascertained		Yes	No
1987	1	1	2	–	2	–	–	1	1	1
1988	3	4	7	–	7	–	–	1	2	5
1989	7	3	7	3	7	2	1	3	1	9
1990	6	3	9	–	6	2	1	3	1	8
1991	4	5	7	2	8	1	–	8	3	6
1992	9	2	6	5	9	2	–	4	7	4
Total	30	18	38	10	39	7	2	20	15	33

further insight into the problems of DXP-related fatalities as they apply to the LBRS in particular and to suggest preventive strategies. In the United Kingdom, the DXP-containing compound analgesics commonly prescribed are Co-proxamol and Distalgesic. These preparations contain 32.5 mg of DXP and 325 mg of N-acetyl-p-aminophenol (acetaminophen; paracetamol). Deaths from overdose could either result from DXP toxicity in which case death occurs within hours, or from acetaminophen-induced hepatotoxicity where death is delayed by 3–4 days.

The LBRS is located in Southeast Scotland; it covers an area of 8,100 km^2 and has a population of about 853,200 representing 16.7% of the population of Scotland. Males and females in the age group 15–74 years comprise a population of 316,988 and 329,403 respectively, of which 382,058 and 266,333 live in the urban and rural areas respectively.

Materials and methods

The 48 cases of fatal DXP-related deaths that occurred in the LBRS during the period January 1987 to December 1992 (inclusive) were reviewed. Included in this study were only the cases in which the time interval between the ingestion of the compound analgesic preparations and death was limited to a few hours. Over this period, acetaminophen, unless taken in very large doses, would not *per se* have been fatal. Cases of delayed death in which toxicological studies and histological examination showed that death had resulted from acetaminophen-induced hepatotoxicity were excluded. Also excluded from this survey were cases where toxicological assays revealed fatal levels of other drugs which had been consumed together for the purpose of suicide. Only if "therapeutic" levels of such drugs were found or if alcohol had been present at non-fatal levels, were such cases included. Available in each case were a detailed medical history (obtained from family practitioners and hospital doctors) a social history (obtained by police officers from next of kin and cohabitees), information on the circumstances of death (including where necessary a visit to the scene of death), complete autopsy report including histology and toxicological studies on blood taken from the iliac or femoral vessels and/or on liver parenchyma.

The Forensic Medicine Unit, University of Edinburgh, on behalf of the Procurators Fiscal (only legal officials responsible for sudden death investigations in Common Law) in the LBRS, investigates all the deaths resulting from substance overdose, and indeed, all suspicious deaths. The present study is therefore a complete overall record of all DXP-related deaths during the period under investigation. Statistical tests were carried out where possible using the Chi Square test.

Table 2. Dextropropoxyphene fatal overdoses – age-group distribution in the LBRS (1987–1992)

Age groups (years)	No. of cases		Manner of death		
	M	F	Suicide	Accident	Unascertained
15–24	5	–	4	1	–
25–34	9	3	9	3	–
35–44	6	4	9	–	1
45–54	3	4	7	–	–
55–64	4	6	9	1	1
65–74	3	1	2	2	–
Total	30	18	39	8	2

Results

The results are as shown in Tables 1, 2 and 3. Males and females account for 62.5% and 37.5% of deaths respectively. Considering the population at risk alone (the 15–74 year age range) and excluding the figures for 1987 (due to small sample size), the incidence for males and females are 1.83 and 1.03 per 100,000 respectively with a M:F ratio of 1.8:1 ($P < 0.05$; $\chi^2 = 5.20$; $df = 1$). The urban and rural areas account for 79.2% and 20.8% of cases respectively; based on the population at risk (and ignoring the figures for 1987), the incidence for urban and rural areas are 1.88 and 0.75 per 100,000 respectively ($P < 0.05$; $\chi^2 = 5.20$; $df = 1$).

The mode of death attributed to each death was as ascribed by pathologists on the basis of the information available in the case: no legislative method such as a Coroner's Inquest for determining mode of death is available in Scotland.

Suicide accounted for 81.3% (39) of all deaths (M = 76.7% [23]; F = 88.8% [16]); 14.6% (7) were accidental deaths (M = 6; F = 1). Of the accidental deaths among males, two (aged 18 and 27 years) were known to be DXP addicts, one (aged 26 years) was a heroin addict, another

Table 3. Socio-medical factors associated with DXP-related suicidal deaths

Associated socio-medical factors	No. of cases ($n = 39$)
"Depression"	8
Chronic alcoholism	7
Personality disorders	6
Deteriorating/poor health	5
Problems in relationship or marriage	5
Problems with the law	2
Financial difficulties	1
Recent loss of spouse	1
Combination of chronic alcoholism with one of the above	4

Table 4. Dextropropoxyphene fatal overdoses – blood alcohol levels in association with non-lethal levels of dextropropoxyphene

Blood level of dextropropoxyphene (μg/g)	Blood alcohol level (mg/dl)
0.2	242
0.2	246
0.3	330
0.3	227
0.3	189
0.7	174
0.7	168
0.8	130

(aged 30 years) was a chronic alcoholic. In 2 deaths (aged 66 and 68 years) alcohol had been consumed together with the DXP-containing prescriptions. The only female accidental death was a chronic alcoholic. Chronic abuse of alcohol was known in 41.7% of all the victims.

The fatal blood level for DXP in the present series ranged from 1.1–5.6 μg/g; the therapeutic range is taken to be 0.1–0.4 μg/g while levels of 0.5 μg/g and above are toxic/fatal (Tietz & Logan 1987). In this series 8 of the victims had levels lower than 1.1 μg/g (as low as 0.2 μg/g) but they had associated blood alcohol levels ranging from 130–330 mg/dl (Table 4). Eight others had consumed DXP preparations in addition to alcohol and/or other drugs such as temazepam, diazepam, aspirin, dihydrocodeine, chlordiazepoxide, amitriptyline and dothiepin. These other drugs were present only at therapeutic levels but could to some extent have acted synergistically and augmented the effect of DXP. The concentration of DXP found in the liver in this series ranged from 14.6–65 μg/g.

The acetaminophen levels in all the 48 cases were less than the accepted toxic level of > 200 μg/g (Tietz & Logan 1987); the observed blood levels range from 95–165 μg/g.

Two-thirds of the victims were not in active remunerated employment; these include the retired and housewives. Among the suicides, psychiatric illness (comprising "depression", personality disorders and chronic alcoholism) were known in about 50% of cases. The mean age was 43.3 for males and 48.0 years for females ($P < 0.05$; $\chi^2 = 0.14$; $df = 1$).

The method of acquisition of DXP preparations is shown in Table 5. It is to be noted that in 37 cases (77%) DXP preparations had been legitimately prescribed either to the deceased or to a person close to the deceased and in 30 of these patients death was suicidal.

Discussion

The number of DXP-related deaths in the LBRS appears to have stabilised following the 1989 peak (Table 1). No statistically significant gender difference was observed ($P < 0.05$) but more of the DXP-caused fatalities continued to occur in the urban areas ($P < 0.05$). About four-fifths of the deaths were suicidal, a pattern shared by both sexes (Table 1); suicide also predominated in all age groups (Table 2). These observations contrast with the findings of Kaa and Gregersen (1992) in Denmark where accidental deaths due to DXP predominated in males, and suicides in females. The observations in the LBRS do not necessarily translate to a greater use of DXP preparations for purposes of self-destruction but are probably a reflection of a much wider problem of drug-related suicide in this regions. Suicide victims will tend to make use of what happens to be readily to hand.

Table 5. Fatal dextropropoxyphene overdoses – source of drug and manner of death

Source	No. of cases	Manner of death		
		Suicide	Accident	Unascertained
Personal prescriptions for muscular pains, recent injuries, etc.	28	22	4	2
Drug prescribed to others close to the deceased (eg spouse, friend, parent, etc.)	8	8	–	–
Illicit "street" acquisition	3	1	2	–
Prescription to known DXP abuser	1	–	1	–
Information on source not available	8	8	–	–
Total	48	39	7	2

The circumstances of the accidental deaths due to DXP in this series further highlight the risk of this drug and the potentiating effect of alcohol and other central nervous system (CNS) depressants consumed together with it (Young & Lawson 1980; Swensen 1988; Schumacher & Dowd 1991).

Moderately toxic doses of DXP cause CNS and respiratory depression with larger doses resulting in delusions, hallucinations, confusion, cardiotoxicity, pulmonary oedema, convulsions and death. It remains unclear whether the cardiotoxic and CNS-excitatory effects are due to norpropoxyphene (Jaffe & Martin 1985). The respiratory-depressant effect is greatly potentiated by concurrent use of alcohol or other sedative and/or hypnotic agents. It is against this background that the use of DXP preparations are contra-indicated in chronic alcoholism, in patients being prescribed psychotropic drugs, muscle relaxants and indeed, in anyone with a known history of emotional disturbance or suicidal ideation.

Two-thirds of the victims in this present series were unemployed and this perhaps only reflects the general and national incidence of unemployment. The observation that about half of the suicides from the ingestion of DXP preparations had suffered from psychiatric illness, demands that stricter prescription policies be adopted by physicians.

The tightening of dispensing regulations by the Danish National Board of Health in 1988 regarding the prescription of DXP (Kaa & Gregersen 1992; Segest et al. 1993) has resulted in a decline in DXP deaths. A similar measure may be probably overdue in the United Kingdom.

Such preventative strategy would involve the following measures:

a) Increasing the public's awareness of the dangers associated with the use of compound analgesics containing DXP either alone or in combination with other CNS-acting agents.
b) Educating physicians not to prescribe DXP preparations to known alcoholics and drug abusers, to those with emotional disturbance, to 'at risk suicides' and to all those on psychotropic drugs: there is no substantial scientific evidence that it has advantages over many other analgesics.

   The prescribing situation can be monitored with ease from central pharmacy returns. Recurrent prescribers of DXP preparations may have to be counselled on their use of this drug as an analgesic.
c) Including DXP preparations under statutory control, i.e. the Misuse of Drugs Act (1971). DXP is already a controlled substance in the United States of America and Canada (USPDI 1993).
d) Continuous clinical auditing and monitoring of the trends in DXP-related deaths (Soumerai et al. 1987).

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