Z. Rechtsmedizin 71, 148—152 (1972)

Dextropropoxyphene Concentrations in Blood in Cases of Fatal Poisoning

Alf Lund and Gunnar D. Nielsen

University Institute of Forensic Medicine,
Department of Forensic Chemistry, Copenhagen (Denmark)

Received May 5, 1972

Summary. Quantitative determinations of dextropropoxyphene (Doloxene®) in the blood from 20 cases of fatal poisoning with the drug has shown that the minimal fatal concentration of dextropropoxyphene in humans is 2—3 μg/ml of blood. An additive effect of the toxicities of dextropropoxyphene and alcohol and of barbiturates is demonstrated. Dextropropoxyphene is shown to be accumulated to a certain extent in the liver, but the liver concentrations vary widely and do not allow an estimate of a corresponding concentration of dextropropoxyphene in the blood.

Zusammenfassung. Bei 20 tödlichen Vergiftungen mit Dextropropoxyphen (Doloxan®) wurde eine quantitative Bestimmung der Droge im Organmaterial durchgeführt. Beim Menschen wurde die geringste tödliche Konzentration von Dextropropoxyphen mit 2—3 μg/ml Blut bestimmt. Es liegen Hinweise für eine additive Wirkung von Alkohol und Barbituraten bei der Dextropropoxyphen-Vergiftung vor. Bis zu einem bestimmten Umfang akkumuliert Dextropropoxyphen in der Leber, doch lassen die hierin bestimmten stark variierenden Konzentrationen keinen Rückschluß auf eine entsprechende Konzentration der Droge im Blut zu.

Key words: Additive effect, dextropropoxyphene and alcohol — Dextropropoxyphene, fatal poisonings — Toxicology, Dextropropoxyphene in blood.

During the last decennium dextropropoxiphene has gained widespread use as an analgesic, notably against rheumatic pains, where aspirin for many years has been the drug of choice. The analgesic effect of dextropropoxiphene is comparable to that of salicylic acid preparations or of aspirin (Miller *et al.*, 1970), whereas the toxicity of the drug seems to be substantially greater than that of aspirin. It is not surprising, therefore, that fatal cases of dextropropoxiphene poisoning have appeared with growing frequency during the last few years. In fact, dextropropoxiphene was surpassed only by barbiturates and carbon monoxide as the cause of death in the last year's material of cases of fatal poisoning at our institute.

In spite of the growing choice of dextropropoxiphene as an agent for suicide, only few data are available concerning the presence of the drug in blood and tissues from cases of poisoning, presumably owing to the analytical difficulties encountered in the quantitative determination of dextropropoxiphene in authopsy

material. Thompson *et al.* (1970) found dextropropoxiphene in liver tissue in concentrations varying from 31 to 126 μg/g in 17 cases of fatal poisoning, whereas blood concentrations were not determined. In 8 cases where dextropropoxiphene intake were considered to contribute essentially to the occurence of death, Worm (1971) found dextropropoxiphene concentrations in the blood from 0.4 to 23 μg/ml and in liver tissue 0.2—22 μg/g, the liver/blood ratio varying from 0.5 to 10. Therapeutic doses of dextropropoxiphene (65—130 mg orally) were shown by Wolen and Gruber (1968) to give peak concentrations of 0.1—0.3 μg/ml of blood. The scarce information on the blood concentrations of the drug in fatal poisonings does not allow an estimate of the average fatal concentrations of dextropropoxiphene in blood. The average fatal dose of the drug taken orally seems to be around 20 mg/kg body weight (for references, see Jensen and Sigurd, 1971).

The present material consists of 20 cases of fatal poisoning, mainly suicides, in which dextropropoxiphene is considered to be the sole cause of death or to have played a major role as a toxic agent. All cases occurred in 1 year (Febr. 1971 to March 1972), within the working field of the institute, representing a population of 2.4 millions. In each case dextropropoxiphene and alcohol were determined quantitatively in the blood, which was also screened for the hypnotics and sedatives commonly used, e.g. barbiturates, meprobamate and benzodiazepines.

Determination of Dextropropoxyphene in Blood

Extraction

5 ml of blood (or liver homogenized with an equal volume of water) is added 3 ml of 1 M sodium carbonate and shaken twice with 50 and 30 ml of ether for 5 min. The combined ether extracts are shaken with 5 ml of 0.05 M sulfuric acid for 1 min. Traces of ether are removed from the acid phase by immersion in a 50°C water bath for 10 min. After the addition of 0,5 ml of 1 M sodium carbonate the aqueous phase is extracted by vigorous shaking with 1.2 ml of chloroform. After centrifugation 1.0 ml of the chloroform phase is transferred to a rotation evaporator and evaporated to dryness at room temperature.

Chromatography

The dry residue is transferred to a silica plate (20 × 20 cm, HF 254) to form 2 spots of equal size, one on each half of the plate. Spots of 10 μg of pure dextropropoxiphene (standard) and of 10 μg of caffeine (reference) are likewise applied on each half of the plate. Finally, the residue from a recovery experiment is transferred to the plate in the same manner as the residue from the actual determination. In our experience it is essential that each determination of dextropropoxiphene be accompanied by systematic recovery experiments. These were carried out by analyzing blood to which was added a known amount of dextropropoxiphene, usually 25 μg added either to 5 ml of normal blood or to another 5 ml of the blood sample in question. Before the chromatographic development of the plate with methanol (12 cm run) a purification development is carried out with chloroform and ether (85 + 15) which carries most of the blood impurities to the solvent front (14 cm). This is cut off after drying the plate and before the final development

Table 1. Concentrations of dextropropoxyphene, alcohol and possibly other drugs found in blood and liver in cases of fatal poisoning

Case No.	Sex	Age (years)	Estimated intake of D-prop.	Dextropropoxyphene in blood (μg/ml)	Dextropropoxyphene in liver (μg/gm)	Alcohol in blood (mg/ml)	Other drugs found in blood
M 1444/71	M	33	0.9 g	1.1	26	1.23	None
E 107/71	Fm	53		1.1	12	1.73	
E 94/71	M	43	[a]	1.6	8	0.88	
A 10018/71	M	44	1.3 g	2.3		0.23	
D 388/71	M	41	1.7 g	2.6	45	0	
D 96/72	Fm	46		2.6	19	0	
M 1094/71	Fm	50		3.4		0.55	
F 269/71	Fm	49	[a]	4.9	63	0	
D 256/71	M	38	[a]	6.7		0.34	
F 109/71	M	42		7.0		1.93	
D 62/71	Fm	25	[a]	15.6		0.71	
M 100/72	Fm	41		21.0		0	
D 157/71	M	47	[a]	24.8		3.04	
M 1540/71	Fm	39		0.4	38	0.71	phenemal 5 μg/ml
M 9/72	Fm	89		0.6	19	0	meprobamate 29 μg/ml
M 1976/71	M	50		0.7		0	allypropymal 6 μg/ml
D 296/71	Fm	63		1.0		0	barb. (?)
M 1169/71	Fm	54	[a]	1.3		0	barb. 19 μg/ml
F 24/72	Fm	48		5.0	14	0	hexemal 12 μg/ml
M 439/71	Fm	43	[a]	7.0		1.81	diazepam 0,6 μg/ml

[a] Near the body was found an empty bottle originally containing 25 capsules of a slow release preparation of dextropropoxyphene (Abalgin retard, 150 mg), the intake of the drug thus being maximally 3.75 g.

with methanol. The R_F values are 0.51 for dextropropoxiphene and 0.62 for caffeine. The latter substance has proved useful as a reference substance for dextropropoxiphene, since caffeine forms visible spots under the UV-lamp, which dextropropoxiphene does not, and in all respects behaves like dextropropoxiphene in the chromatographic procedure. After the chromatographic development spots of caffeine and possibly other visible spots are marked under the UV-lamp, and the left half of the plate is sprayed with Dragendorff reagent making dextropropoxiphene visible as orange-coloured spots.

Quantitative Determination

On the unsprayed half of the plate areas corresponding to the visible dextropropoxiphene spots on the sprayed half of the plate and situated just beneath the marked caffeine spots are scraped off and extracted with 4 ml of methanol. The extract is filtered and evaporated to dryness on the rotation evaporator. The

residue is dissolved in 50 µl of methanol, and 2 µl of the extract is injected into the gas chromatograph: Perkin-Elmer, model 881, QF-1 in 1.8 m glass column, inj. temp. 245° C, column 160° C, flame detector 205° C. 1 µg of dextropropoxiphene gives a peak (height 9 cm at attenuation 50) with the retention time 7 min.

Results and Discussion

Our results are listed in Table 1 in the order of rising concentrations of dextropropoxiphene in blood. There is apparently a synergistic (additive) effect of dextropropoxiphene and alcohol: Where death occured at low concentrations of dextropropoxiphene (1—2 µg/ml), the blood contained a considerable amount of alcohol (1—2 mg/ml). When alcohol and other toxic substances were absent, the minimal fatal concentration of dextropropoxiphene in the blood is seen to be 2—3 µg/ml. The dextropropoxiphene concentration in blood may reach very high values, in the present material 25 µg/ml, an illustration of the fact wellknown in toxicology, that the concentration of any poison may reach values greatly exceeding the minimal fatal concentration, before the person dies. The cases listed in the lower half of the table show that synergism also exists between dextropropoxiphene and barbiturates.

The concentrations of dextropropoxiphene in liver tissue vary widely. The liver/blood ratio ranged between values of from 3 to 95 and was not correlated to the concentration in blood. The liver concentration was invariably higher than the corresponding blood concentration, but it was not possible even roughly to estimate a blood concentration from a concentration of dextropropoxiphene found in the liver.

The few data available on the ingested amount of the drug suggest that the minimal fatal amount of dextropropoxiphene is 1.5 g. This corresponds to about 25 mg/kg body weight and is in close agreement with other estimates (Jensen and Sigurd, 1971). The toxicity of dextropropoxiphene is thus comparable to that of the barbiturates. It is rather surprising, therefore, that the fatal level of dextropropoxiphene in blood is about 10 times lower than that, for instance of pentymal (pentobarbitone), the therapeutic doses of the two drugs being nearly equal. At least two explanations for this are at hand. Dextropropoxiphene may be bound to or accumulated in certain structures as for instance the central nervous system, where it may exert its toxic action. It is quite evident from the police reports of the present cases that respiratory depression ("snoring respiration", "blue in the face") is a prominent feature in dextropropoxiphene poisoning.

Another explanation may be that dextropropoxiphene is metabolized to form a product, possibly a demethylation product, the toxicity of which might be equal to or even greater than that of the parent compound. We have made no attempts to determine the demethylation product or any other metabolites of dextropropoxiphene possibly present in the blood in cases of dextropropoxiphene poisoning. Studies are in progress to further elucidate this problem.

Our thanks are due to Mrs. Inga Dige for skilful technical assistance.

References

Jensen, G., Sigurd, B.: Propoksifenforgiftning. Ugeskr. Læg. **133**, 1070—1073 (1971).

Miller, R., Feingold, A., Paxinos, J.: Propoxyphene hydrochloride, a critical review. J. Amer. med. Ass. **213**, 996—1006 (1970).

Thompson, E., Villaudy, J., Plutchak, L., Gupta, R.: Spectrophotometric determination of d-propoxyphene (darvon) in liver tissue. J. forens. Sci. **15**, 605—609 (1970).

Wolen, R., Gruber, C.: Determination of propoxyphene in human plasma by gas chromatography. Analyt. Chem. **40**, 1243—1246 (1968).

Worm, K.: Determination of dextropropoxyphene in organs from fatal poisoning. Acta pharmacol. (Kbh.) **30**, 330—338 (1971).

Alf Lund
Gunnar Damgaard Nielsen
Retsmedicinsk Institut
Juliane Maries Vej 16
DK-2100 Copenhagen Ø