Int J Leg Med (1992) 104:347–353

International Journal of
Legal Medicine

Postmortem toxico-kinetics of co-proxamol

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Received June 12, 1991 / Received in revised form October 25, 1991

Summary. Postmortem drug redistribution in suicidal poisonings by co-proxamol (dextropropoxyphene and paracetamol) has been studied. Analytical data for 8 tissue samples, including muscle and fat, up to 8 blood samples, and gastric and small bowel contents were obtained in 4 cases. Blood samples were taken from multiple sites at the start of autopsy and after 24 or 48 h. Concentrations of both drugs were site dependent with the lowest concentrations in peripheral blood. Paracetamol concentrations varied two to threefold and propoxyphene concentrations varied seven to tenfold. Pulmonary artery concentrations of paracetamol did not change significantly with time; propoxyphene concentrations typically increased twofold over 24 h and threefold over 48 h. Propoxyphene concentrations in the inferior vena cava increased unpredictably but occasionally significantly (up to sevenfold). For both drugs the most dramatic elevations of blood concentrations were seen in the aorta; in one case paracetamol rose to 1.9 g/l, 8 times the peripheral blood concentration and 4 times the liver level (454 mg/kg); propoxyphene rose to 191.5 mg/l, 55 times the peripheral blood concentration. This appears to reflect postmortem diffusion of unabsorbed drug from the gastric lumen. It is likely that markedly higher concentrations in the putrefactive fluid from the left pleural cavity as compared with the right also reflect diffusion from the stomach.

Key words: Paracetamol – Dextropropoxyphene – Postmortem – Toxicology – Suicide

Zusammenfassung. Die postmortale Wirkstoffumverteilung bei suizidalen Vergiftungen mit Coproxamol (Dextropropoxyphen und Paracetamol) wurde untersucht. Die analytischen Daten von 8 Gewebsproben, incl. Muskeln und Fettgewebe, von bis zu 8 Blutproben und des Magen- und Dünndarminhalts lagen in 4 Fällen vor. Die Blutproben wurden von verschiedenen Orten zu Beginn der Obduktion entnommen und nach 24 oder nach 48 Stunden. Die Konzentrationen beider Wirkstoffe waren abhängig vom Entnahmeort, wobei sich die niedrigsten Konzentrationen im peripheren Blut fanden. Die Paracetamolkonzentrationen variierten um den Faktor 2–3 und die Propoxyphenkonzentrationen um das Sieben- bis Zehnfache. Die Paracetamolkonzentrationen im Pulmonalarterienblut veränderten sich nicht signifikant über der Zeit; die Propoxyphenkonzentrationen verdoppelten sich typischerweise innerhalb von 24 Stunden und verdreifachten sich über 48 Stunden. Die Propoxyphenkonzentrationen in der Vena cava inferior zeigten unregelmäßige Anstiege, jedoch z.T. signifikante (bis zu siebenfach). Für beide Substanzen waren die stärksten Zunahmen der Blutkonzentrationen in der Aorta zu beobachten; in einem Fall stieg das Paracetamol auf 1,9 g/l an, somit um ein Achtfaches der peripheren Blutkonzentration und ein Vierfaches der Leberkonzentration (454 mg/kg); das Propoxyphen stieg auf 191,5 mg/l, somit auf ein 55faches der Konzentration im peripheren Blut. Die Ursache scheint eine postmortale Diffusion der noch nicht resorbierten Wirkstoffe aus dem Mageninhalt zu sein. Es ist wahrscheinlich, daß deutlich höhere Konzentrationen in der Fäulnisflüssigkeit der linken Pleurahöhle im Vergleich zur rechten ebenfalls aufgrund eines Diffusionsprozesses aus dem Magen zu erklären sind.

Schlüsselwörter: Paracetamol – Dextropropoxyphen – Postmortal – Toxikologie – Suizid

Introduction

The postmortem redistribution of drugs, along concentration gradients, from sites of high concentration in solid organs into the blood, can create major difficulties in the interpretation of postmortem blood drug levels [1]. An extensively documented case study highlighted the utility of studying poisonings by compound drug preparations, thus allowing comparison of the behaviour of 2 drugs known to have been taken simultaneously [2]. Other authors have emphasised the need to study the evolution of drug redistribution over time, both in case material [3] and experimental models [4]. We present detailed case data on postmortem drug redistribution in suicidal poisonings by coproxamol, a compound prepa-

ration of dextropropoxyphene and paracetamol. Extensive tissue and sequential blood sampling was undertaken to show the evolution of the changes during the early postmortem period.

Materials and methods

Suspected cases of drug overdose by co-proxamol were identified prior to autopsy. The protocol allowed for the sampling of numerous body tissues and fluids as well as the taking of multiple blood samples [2]. After opening the chest and abdomen the major vessels were clamped or ligated prior to blood sampling by needle puncture. Following the initial sampling the body was draped with a single cotton sheet and left undisturbed at ambient room temperature on the autopsy table for 24 or 48 h, after which time further blood samples were obtained and the dissection was completed.

Analytical methods. All samples were stored at −20°C until analysis. Liquid samples were diluted with water if necessary. Tissue samples were homogenised with a Waring Commercial blender and a weighed sample was homogenised again with an appropriate volume of water and then used for analysis.

Dextropropoxyphene was quantitated on a Perkin-Elmer 8500 GC equipped with nitrogen/phosphorus detector (NPD). To 1 ml liquid sample or 1 ml tissue homogenate were added 100 µl internal standard solution (125 µg/ml dothiepin), 2 ml 0.5 *M* sodium hydroxide, and 5 ml heptane : isoamyl alcohol (98.5 : 1.5). The samples were rotated for 15 min on a rotator (Spiramix 10, Denley, UK). The organic layer was separated and another 5 ml of heptane : isoamyl alcohol (98.5 : 1.5) were added and rotated similarly. The combined organic layer was back-extracted with 2 ml 0.1 *N* H_2SO_4, and the acid layer was then basified with 1 ml 1.0 *M* carbonate/bicarbonate buffer (pH 9.0) and extracted with 1 ml toluene : isoamyl alcohol (85 : 15) by rotating for 15 min. The organic layer was concentrated to about 50 µl in a vial, and 1 µl was analyzed by GC/NPD using a 15 m DB1 capillary column 0.25 mm i.d., film thickness 0.25 µm (J&W Scientific, UK). The oven program was 130°C (initial temperature) for 2 min, rate 25°C/min to 300°C. An injection temperature of 220°C was used to minimise thermal decomposition of propoxyphene on injection. Under these conditions the retention times of propoxyphene and dothiepin were 4.60 min and 5.30 min respectively. A calibration curve was obtained using spiked, out-dated transfusion blood standards in the range 0.25–10 µg/ml. The calibration was prepared for each analysis. The correlation coefficient between dextropropoxyphene concentration and dextropropoxyphene/dothiepin peak area ratio in every analysis exceeded 0.99.

Paracetamol was quantitated on a Phillips Pye Unicam PU 4500 gas chromatogram equipped with a flame ionization detector. To 1.0 ml liquid samples or 1.0 ml of tissue homogenate were added 1.0 ml internal standard (100 µg/ml 2-acetoamidophenol), 1 ml 0.03 *M* phosphate buffer (pH 7.4) and 5 ml ethyl acetate. The samples were mixed by rotation for 15 min on a rotator, and the organic layer was evaporated to dryness. As the fat samples had substantial amounts of oily residue after evaporation, the residue was resuspended in diethyl ether and paracetamol was back-extracted with water prior to the final extraction with 5 ml ethyl acetate. Paracetamol was derivatized with 25 µl of *N*-0-bis(trimethylsilyl)trifluoracetate with 1% trimethylchlorosilane (Pierce, USA) for 5 min at 60°C and analyzed by GC using a 2.0 m 3% SE-30 column 4.0 mm i.d. The oven temperature was 180°C (initial) for 2 min, rate 18°C/min up to 220°C with 5 min hold. Under these conditions the retention times of paracetamol and the internal standard were 1.04 min and 1.42 min respectively. Linear calibrations for fat samples and for all the other samples were obtained using spiked, out-dated transfusion blood standards in the ranges of 5 to 100 µg/ml prepared for each analysis. The correlation coefficient values between paracetamol concentration and paracetamol/internal standard peak area ratio in every analysis exceeded the value of 0.99. All analyses were performed in duplicate. All duplicate results were within 10% or the assay was repeated. The coefficient of variation for the assays was typically less than 10%.

Results

Case 1 (318/90)

An 83-year-old white woman was found dead in bed 30 h after last having been seen alive. There was a letter indicating her intention to take her own life and a partially empty container of co-proxamol tablets nearby. The first set of blood samples was obtained 17 h after discovery of the body, a second set of blood samples was obtained 24 h later.

The body weighed 45 kg and measured 156 cm. There were no putrefactive changes. The stomach contained approximately 150 ml of light pink fluid and granular debris. There was no evidence of aspiration of gastric material.

Case 2 (417/90)

A 27-year-old white male was last seen alive at approximately 8 pm, after having consumed about 10 bottles of beer, and was found dead 41 h later. Empty sachets of co-proxamol tablets suggested that he had taken an overdose of a minimum of 40 and a maximum of 50 tablets. A postmortem examination was performed and the initial blood samples were obtained 23 h after discovery of the body, a second set of samples after a further 24 h.

The body weight was 73 kg and length 175 cm. There was early green putrefactive discolouration of both iliac fossae. The stomach contained approximately 100 ml brown fluid with no obvious tablet debris. There was no evidence of aspiration of gastric contents. Ethanol concentrations in the blood, urine and vitreous humour were 174 mg/dl, 246 mg/dl and 227 mg/dl respectively.

Case 3 (37/91)

A 34-year-old white female was found dead 46 h after she was last seen alive. Autopsy was performed 43 h after discovery of the body.

The body weight was 39 kg and the body length 152 cm. Drying of the fingers of both hands was prominent but there were no putrefactive changes. The stomach showed a mild haemorrhagic gastritis and contained some tan-coloured fluid with granular debris. There was no evidence of aspiration of gastric material. Ethanol concentrations in the blood, vitreous humour and urine were 329 mg/dl, 377 mg/dl and 385 mg/dl respectively.

Case 4 (24/91)

A 50-year-old white male was found dead in bed with a suicide note and alcoholic beverage at the bedside. Empty blister packs of co-proxamol suggested he had taken an overdose of up to 60 tablets. The body was dis-

Table 1. Drug concentrations (mg/l) in blood samples from different sites taken at the commencement of the autopsy ($t = 0$)

Site	Paracetamol				Propoxyphene			
	1	2	3	4	1	2	3	4
Peripheral	361	244	249	277	3.1	1.4	3.5	4.0
IVC-ir	464	242	548	338	4.6	2.0	17.9	5.5
IVC-sr	498	329	687	360	4.0	6.7	32.3	5.9
SVC	468	247	386	–	12.8	5.8	14.1	–
PA	427	261	619	–	10.8	6.9	19.9	–
PV	484	332	530	–	22.2	14.4	27.7	–
Left heart				307				3.5
Right heart				361				5.0
Aorta	439	321	1142	–	4.1	8.8	48.0	–
Portal vein	802	337	–	–	35.0	20.7	–	–

IVC-ir = inferior vena cava, infra-renal; IVC-sr = inferior vena cava, supra-renal; SVC = superior vena cava; PA = pulmonary artery; PV = pulmonary vein

Table 2. Paracetamol concentrations (mg/kg) in solid organs and total drug in bowel contents (mg)

	Case 1	Case 2	Case 3	Case 4
Left lung	399	260	306	357
Right lung	408	228	306	314
Heart	341	189	262	395
Liver	582	296	454	482
Kidney	491	262	761	768
Brainstem	205	65	102	143
Muscle	375	146	103	423
Fat	–	56	110	76
Stomach	2147	759	1100	1165
Duodenum	115	85	155	108
Small bowel 1	94	78	–	–
Small bowel 2	30	16	–	–
Small bowel 3	14	63	–	–
Total bowel	2400	1000	1255	1273

Table 3. Propoxyphene concentrations (mg/kg) in solid organs and total drug in bowel contents (mg)

	Case 1	Case 2	Case 3	Case 4
Left lung	46.8	59.4	125.0	7.9
Right lung	72.6	62.6	126.3	7.6
Heart	66.0	30.9	46.4	15.3
Liver	387.2	220.6	391.8	106.5
Kidney	50.4	28.4	66.6	13.9
Brainstem	41.3	14.8	38.4	25.6
Muscle	8.5	5.0	3.3	4.5
Fat	35.0	17.6	24.2	7.9
Stomach	125	89	151	53
Duodenum	21	14	28	6
Small bowel 1	32	12	–	–
Small bowel 2	5	5	–	–
Small bowel 3	0	15	–	–
Total bowel	183	135	179	59

covered 46 h after he had last been seen alive. An autopsy was performed 38 h after discovery of the body.

The body weight was 82 kg and body length 184 cm. There were early putrefactive changes with prominent venous marbling over the shoulders and green discolouration of the right lower quadrant of the abdominal wall. The stomach contained a small amount of reddish-brown fluid and granular debris. There was no evidence of aspiration of gastric material. Ethanol concentrations in the blood and urine were 36 mg/dl and 65 mg/dl respectively.

Analytical results

The drug concentrations in blood samples from different sites taken at the commencement of the autopsy are set out in Table 1. The drug concentrations of both paracetamol and propoxyphene were site dependent with the lowest concentrations of both drugs in peripheral blood. The peripheral blood samples were obtained from the left subclavian vein in case 1 and the left femoral vein in cases 2, 3 and 4. A left femoral artery sample taken in case 1 showed markedly lower drug concentrations than those found in the subclavian vein (paracetamol 287 mg/l and propoxyphene 0.34 mg/l). Site dependent concentration differences for propoxyphene were more marked and the overall pattern was more variable. Concentrations of both propoxyphene and paracetamol in solid organs showed broadly similar patterns in all 4 cases (Tables 2 and 3).

The relative changes in drug concentrations in the superior vena cava, the supra-renal part of the inferior vena cava, the pulmonary artery and the aorta are illustrated in Figs. 1 and 2. The drug concentrations are expressed as a percentage of the concentration of that drug in the initial peripheral blood sample; the absolute drug concentrations are included in Tables 4, 5 and 6. Changes in drug concentrations in the pulmonary artery (PA) between the 2 sampling times for cases 1, 2 and 3, together with corresponding drug concentrations in the

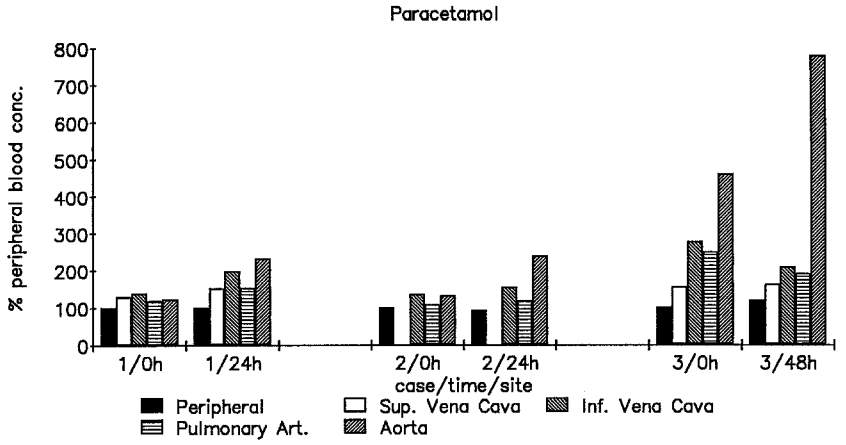

Fig. 1. Paracetamol concentrations in blood samples from 5 sites takes at the start of autopsy and 24 or 48 h later in 3 cases. Drug concentrations are expressed as a percentage of the drug concentration in peripheral blood at the start of autopsy

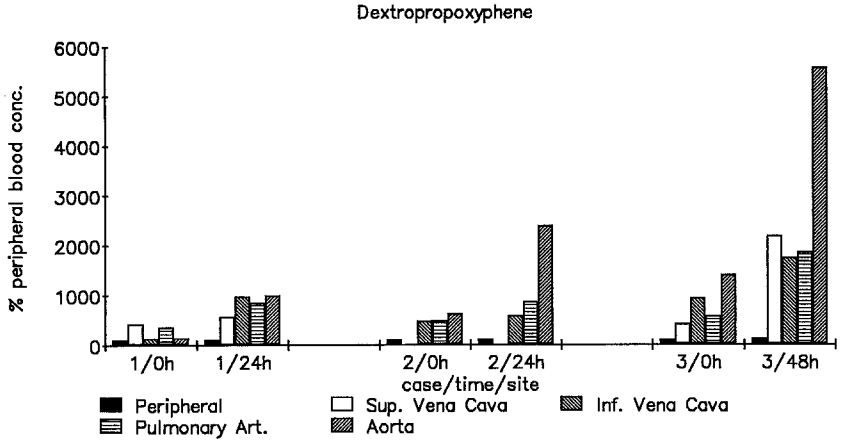

Fig. 2. Dextropropoxyphene concentrations in blood samples from 5 sites taken at the start of autopsy and 24 or 48 h later in 3 cases. Drug concentrations are expressed as a percentage of the drug concentration in peripheral blood at the start of autopsy

Table 4. Drug concentrations in lung (mg/kg) and blood (mg/l) at the time of commencing autopsy ($t = 0$) and after 24 or 48 h

	Lung	Pulmonary artery			Peripheral blood $t = 0$
		$t = 0$	$t = 24$ h	$t = 48$ h	
Case 1					
Paracetamol	404	427	552		361
Propoxyphene	59.7	10.8	26.0		3.1
Case 2					
Paracetamol	244	261	287		244
Propoxyphene	61.0	6.9	12.3		1.4
Case 3					
Paracetamol	306	619		474	249
Propoxyphene	126.3	19.9		64.0	3.5
Case 4[a]					
Paracetamol	336	361		381	277
Propoxyphene	7.8	5.0		5.2	4.0

[a] $t = 0$ is right heart and $t = 48$ h is mixed pulmonary artery/vein

lungs (mean of right and left lung samples) and the initial peripheral blood samples, are set out in Table 4.

The pattern of drug concentrations and the changes with time in the supra-renal part of the inferior vena cava (IVC-sr) were broadly similar to the PA (Table 5). Table 6 sets out the changes in drug concentrations in the aorta when contrasted with peripheral blood and the residual unabsorbed drug in the stomach.

In 2 instances (cases 2 and 4) it proved possible to obtain two urine samples at time intervals of 24 or 48 h. No significant changes in drug concentrations were observed (Table 7). In 2 instances (cases 3 and 4) putrefactive

Table 5. Drug concentrations in liver (mg/kg) and blood (mg/l) at the time of commencing autopsy ($t = 0$) and after 24 or 48 h

	Liver	Inferior vena cava (supra-renal)			Peripheral blood $t = 0$
		$t = 0$	$t = 24$ h	$t = 48$ h	
Case 1					
Paracetamol	582	498	714		361
Propoxyphene	387	4.0	29.9		3.1
Case 2					
Paracetamol	296	329	376		244
Propoxyphene	221	6.7	8.3		1.4
Case 3					
Paracetamol	454	687		518	249
Propoxyphene	392	32.3		60.0	3.5
Case 4					
Paracetamol	482	360		372	277
Propoxyphene	107	5.9		5.6	4.0

Table 6. Total residual drug (mg) and drug concentrations (mg/kg) in the stomach and drug concentrations in blood (mg/l) at the time of commencing autopsy ($t = 0$) and after 24 or 48 h

	Stomach		Aorta			Peripheral blood $t = 0$
	Total	Conc.	$t = 0$	$t = 24$ h	$t = 48$ h	
Case 1						
Paracetamol	2147	17893	439	835		361
Propoxyphene	124.6	1038	4.1	30.2		3.1
Case 2						
Paracetamol	759	8622	321	581		244
Propoxyphene	88.8	1009	8.8	34.0		1.4
Case 3						
Paracetamol	1100	12222	1142		1931	249
Propoxyphene	150.7	1675	48.0		191.5	3.5

Table 7. Drug concentrations in urine (mg/l) at the time of commencement of autopsy and after 24 or 48 h

	Paracetamol			Propoxyphene		
	$t = 0$	$t = 24$ h	$t = 48$ h	$t = 0$	$t = 24$ h	$t = 48$ h
Case 2	82	75		1.0	1.8	
Case 4	1138		1172	51.3		43.6

Table 8. Putrefactive fluid accumulation (ml) in the left (L) and right (R) pleural cavities and drug concentration (mg/l)

	Volume[a]		Paracetamol		Propoxyphene	
	Left	Right	Left	Right	Left	Right
Case 4						
$t = 0$	225	135	1045	297	5.7	2.2
$t = 24$ h	180	135	813	305	6.9	2.9
$t = 48$ h	190	150	1036	321	8.7	2.7
Case 3						
$t = 48$ h	15	7	1669	334	30.3	20.5

[a] Not sequentially corrected for volume of analytical samples taken, (20 ml, except for 55 ml from left chest at $t = 0$)

fluid accumulated in the pleural cavities during the experiment and in case 4 had been present at the time of the initial examination. The drug concentrations in the putrefactive fluid are set out in Table 8.

Discussion

In the four cases described the circumstances of death and toxicological findings established the cause of death as co-proxamol poisoning and the manner of death as suicide. Co-proxamol (British Approved Name) is a compound preparation of dextropropoxyphene hydrochloride and paracetamol in the mass proportions 1 part : 10 parts (32.5 mg : 325 mg).

Dextropropoxyphene (BAN) or propoxyphene (USAN) is a mildly effective narcotic analgesic with an estimated minimum lethal dose of 500–800 mg [5] or 15–20 tablets of co-proxamol [6]. Reports emphasise the rapidity with which death ensues so that in many cases death occurs within one hour of ingestion [7]. Since death typically occurs very soon after ingestion of co-proxamol it is to be expected that the body burden of both dextropropoxyphene and paracetamol will be rising

at the time of death and that autopsy will usually show considerable unabsorbed drug residues in the stomach and proximal small bowel. This is borne out by the analyses of bowel contents in these 4 cases (Tables 2 and 3).

Dextropropoxyphene and paracetamol have significantly different clinical pharmacokinetic characteristics. Dextropropoxyphene has a large volume of distribution (10–18 l/kg), a high degree of protein binding, and a high organ concentration [8]. By contrast paracetamol has a volume of distribution of approximately 0.75–1 l/kg, is up to 50% plasma protein bound at toxic concentrations, and shows little organ concentration. The contrasting behaviour of these two drugs with regard to concentration in solid organs is well illustrated by the data in Tables 2 and 3.

When the volume of distribution of a drug exceeds 3 l/kg tissue depots sequester the high drug concentrations [9]. It is these tissue depots of drug which provide a reservoir for drug diffusion into the blood postmortem with consequent elevation of blood drug levels. The low volume of distribution of paracetamol is reflected in minimal drug concentration in the solid organs, the lack of a reservoir of drug for postmortem diffusion into the blood and consequently relatively stable postmortem blood drug levels. By contrast dextropropoxyphene with its high Vd shows intense drug concentration in solid organs which in turn provides a large reservoir for postmortem drug movement into the blood by diffusion and readily explains the rising postmortem blood drug levels. The site dependence of blood drug levels for dextropropoxyphene is a reflection of the distance of the sampling site from a solid organ reservoir of the drugs. Thus knowledge of the Vd of a drug should allow a prediction of its liability to postmortem redistribution, and an awareness of the solid organs which particularly sequester it should allow prediction of the blood sampling sites likely to be most seriously effected.

Since deaths from co-proxamol poisoning occur rapidly when the ingested drug is still being absorbed, distribution of the drug to the tissues will be strongly influenced by blood flow. For adipose tissue, blood flow is low (about 3 ml/100 g per min) so that distribution into body fat will occur slowly [10]. This may be one explanation for the high variability and occasionally low paracetamol and dextropropoxyphene levels in fat in this study. It may also explain the somewhat similar pattern seen in skeletal muscle (Tables 2 and 3). This suggests that skeletal muscle may not be as useful a sample for postmortem toxicological studies as has been proposed recently [11].

In the forensic literature, attention on the solid organs responsible for postmortem drug redistribution has tended to focus on the liver at the expense of the lungs. However diffusion of drugs from depots in the lungs into the pulmonary circulation appears to occur more rapidly and to a greater extent than from the liver into the inferior vena cava. Both the initial blood levels for dextropropoxyphene in these 4 cases (Table 1) and the temporal changes in the pulmonary artery (Table 4) suggest that this phenomenon begins soon after death and continues unabated throughout the early postmortem period.

The observation of very high drug levels in the thoracic aorta (Table 6) was unexpected in the light of previous studies which used a similar protocol [1, 2]. One possibly important difference in the protocol used was that, in the present cases, the aorta was not cross-clamped at the approximate level of the dome of the diaphragm. Consequently the aortic blood samples in these 4 cases reflect drug diffusion into the contiguous abdominal aorta and lower thoracic aorta. The dramatic postmortem rise in drug concentrations seen in one case (case 3 in Table 6) appears to reflect postmortem diffusion of unabsorbed drug from the gastric lumen. If this explanation is correct then this previously undescribed phenomenon of postmortem drug absorption adds a new and worrisome twist to the problem of interpreting drug levels in postmortem blood.

In 2 instances there was an opportunity to study drug levels in putrefactive fluid accumulating in the pleural cavities (Table 8). Others [12] have suggested that putrefactive pleural cavity fluid might prove useful for toxicological studies when blood is unavailable. The most striking feature in both cases is the high concentration of drugs in the left chest when contrasted with the right. In case 3 this may be, in theory, the result of blood leakage from a needle puncture sampling site in the thoracic aorta but this is not a possible explanation in case 4 where aortic blood was not sampled until the end of the experimental period. It is clear that putrefactive pleural fluid is subject to the same artefact of postmortem diffusion of drugs as is the blood. It also seems that, like aortic blood, it is subject to postmortem diffusion of unabsorbed drug from the gastric lumen.

In summary, the detailed case data presented here, as well as that presented by other workers, demonstrates that the postmortem redistribution of drugs, from sites of antemortem sequestration in solid organs into the blood, follows patterns which are generally predictable but apparently idiosyncratic in individual cases. It appears also that there may be "postmortem absorption" of drug from the stomach and/or small bowel. A further influencing factor, eliminated by the experimental method in the present study, is the significant postmortem movements of blood, the so-called "postmortem circulation" [13], which facilitates drug diffusion. Other influencing factors must include body position and the highly variable changes of autolysis and putrefaction. In our view the dynamic nature, extreme complexity, and interpretive significance of these phenomena, taken together, justify designating this area of study as "postmortem toxicokinetics", a phrase we have chosen to use in the title of this paper.

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