Alan M. Langford,[1] *Ph.D. and Derrick J. Pounder,*[1] *M.B.*

Possible Markers for Postmortem Drug Redistribution

REFERENCE: Langford AM, Pounder DJ. Possible markers for postmortem drug redistribution J Forensic Sci 1997;42(1):88–92.

ABSTRACT: The possibility that postmortem biochemical changes in blood might parallel drug redistribution and thus serve as markers was explored in a detailed case study. Eighteen blood and 14 tissue and fluid samples were taken at autopsy 16 h after the death of a 34-year-old female from amitriptyline overdose. Ranges of drug concentrations in blood were amitriptyline 1.8 to 20.2 μg/mL, nortriptyline 0.6 to 7.3 μg/mL, levels were lowest in femoral vein and highest in pulmonary vein blood. Corresponding levels of 17 amino acids showed markedly different patterns of site-to-site variability. There was a strong positive correlation between individual amino acid and drug concentrations in pulmonary blood samples (n = 5), particularly for glycine, leucine, methionine, serine, and valine. In blood samples from the great veins and right heart (n = 10), the correlation was less strong (r = 0.6 to 0.7). Methionine showed a strong positive correlation in pulmonary samples (r = 0.93), and negative correlation in great veing samples (r = −0.68). Lactic acid showed a strong negative correlation in pulmonary samples (r = −0.93) but a positive correlation in great vein samples (r = 0.71). Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, γ-glutamyl transferase, glucose, and bilirubin had a weak positive correlation with drug levels in great vein samples but not pulmonary samples. The results suggest that hepatic enzymes are relatively poor markers for postmortem hepatic drug shifts but that amino acids, particularly methionine, may be useful markers for pulmonary drug shifts.

KEYWORDS: forensic science, forensic toxicology, postmortem redistribution, amitriptyline, nortriptyline, biochemistry, glucose, liver enzymes, amino acids

The interpretation of drug levels in postmortem blood is complicated by the phenomenon of postmortem drug redistribution (12). In an individual fatality, the presence of site-to-site differences in blood drug levels is a good indicator that redistribution has occurred overall. Clearly, it would be helpful if there was a marker which indicated whether or not redistribution had affected the drug level in an individual blood sample. Through a detailed study of a case fatality, we explored the possibility that postmortem biochemical changes in blood might parallel drug redistribution and thus serve as markers.

Methods

Specimens for analysis were obtained from a case of fatal amitriptyline overdose. The deceased, a 34-year-old-depressed female alcoholic, was observed by her cohabitee, lying apparently asleep from 5 p.m. until about 7:30 p.m., when she then appeared blue in the face and pulseless. Resuscitation was attempted and this included two intra cardiac injections by ambulance personnel. She was pronounced dead at 8:30 p.m. at the scene. It appeared that she had taken 60 by 50 mg tablets of amitriptyline.

The body was refrigerated between 12:30 a.m. and 9 a.m. at which time a left femoral vein blood sample was obtained after exposing and cross clamping the vessel. All further samples were taken at autopsy commencing at 12:30 p.m. and finishing at 3 p.m. The body was opened and a pericardial fluid sample was taken; this appeared lightly sanguinous. The great vessels were cross clamped prior to obtaining samples from each at the heart. Multiple sequentially numbered 20-mL samples were obtained from the inferior vena cava and the superior vena cava. The aorta, pulmonary artery, left pulmonary vein, and right pulmonary vein were then sampled. Further samples were taken from the inferior vena cava at its lowest extremity, and from both the right and left external iliac veins. Blood samples were divided, such that a sufficient volume was available for toxicological analysis (approximately 5 mL, stored at 4°C) and the remainder spun down (3000 rpm for 5 min). The serum obtained was stored at −20°C prior to analysis.

Vitreous humour, bile, ascitic fluid (lightly sanguinous) from the right paracolic gutter, and urine were sampled. Approximately 50-g tissue samples were taken from the upper lobe apex and postero-basal segment of the left lung, from the posterior edge of the left liver lobe, and from deep within the substance of the right lobe. Samples of approximately 50 g of muscle were obtained from the right side of the diaphragm, the right gastrocnemius, and muscle from the left and right rectus abdominis was pooled. The gastric contents were collected in their entirety as were the combined contents of the duodenum and proximal jejunem. Both contained changed blood but no evident tablet debris.

Analytical Methods

Tissue extracts (5.0 g) were homogenized with a blender (Ultra Turrax T25) for 1 min at 8500 rpm, and subsequently at speeds of 9500, 13,500, 20,500, and 24,000 rpm each for 1 min. The homogenate was made up to 20 mL distilled water, 4 mL of this homogenate was used for assay. The liquid samples were not diluted. All analyses were performed in duplicate to within 5% of the mean value. The assay used for determining drug concentrations follows the standard investigative procedure used and developed within the laboratory to determine drug concentration in various body fluids and times. Quantitation was performed using a 7 point calibration curve for each drug, with a correlation coefficient of r = 0.9995 for amitriptyline (n = 3), and r = 0.9999 for nortriptyline (n = 3).

For the analysis of amitriptyline and the metabolite, nortriptyline, 100 μL of internal standard solution (50 μg/mL doxepin)

[1]Doctor and professor, respectively, University of Dundee, Department of Forensic Medicine, the Royal Infirmary, Dundee, DD1 9ND, Scotland.

Received 23 Feb. 1996; and in revised form 21 May 1996; accepted 3 June 1996.

was added to the extraction sample and vortex mixed. A further 50 μL 10 M potassium hydroxide was added and the sample vortex mixed again. Two mL ethyl acetate was added, and the extraction sample rotated for 10 min. The organic layer was separated and evaporated to dryness. Following resuspension with 100 μL methanol, 20 μL was injected into the HPLC system. The HPLC conditions were as follows: Instrument, Gilson isocratic LC pump 307 with Gilson UV spectrophotometric detector 118 (wavelength 255 nm); column, Apex II ODS 5 μm, 150 × 4.6 mm with guard column 20 mm; mobile phase, 300 mL 10 mM disodium hydrogen phosphate, pH adjusted to 3 with phosphoric acid, 600 μL *n*-nonylamine, pH readjusted to 3 with phosphoric acid, 200 mL acetonitrile; flow rate 1.0 mL/min. Under these conditions, the retention times for doxepin (IS), nortriptyline and amitriptyline were 3.2, 4.2, and 4.8 min, respectively. The calibration range for amitriptyline was 1.25 μg/mL to 66 μg/mL and for nortriptyline 1.25 to 90 μg/mL.

For the analysis of amino acids, 10 μL of internal standard solution (2.5 μmol/mL nor leucine), was added to 10 μL of serum. The samples were then evaporated to dryness in a vacuum centrifuge (Hetovac). Following resuspension with 20 μL pyridine and 20 μL N-*tert* butyldimethylsilyl-N-methyltrifluoroacetamide (MTBSTFA), the samples were gently mixed and left for 10 min at room temperature, and then for a further 30 min at 70°C, 1.5 μL of this solution was injected into the gas chromatograph connected to a mass spectrometer (GC/MS) The GC/MS conditions were as follows: Instrument, Fisons GC 8000 series equipped with quadropole mass analyser MD 800; column, BPX5, 25 m by 0.22 mm ID with a 0.25 μm film thickness; temperature program, initial temperature, 80°C (1 min hold), ramped at 50°C/min to 200°C, then immediately ramped at 9°C/min to 300°C (2 min hold); injection port temp, 250°C; carrier gas, helium (linear velocity 37.1cm/sec); ionization energy, 70 eV; ion source temperature 200°C; transfer line temperature, 250°C. The amino acids were identified by a combination of retention time and their full mass spectra. Quantitation of sample and standard peaks was by selective ion monitoring (SIM) of the most intense ion of each amino acid. The peak area ratio was normalized to the internal standard and the sample amino acid concentration derived from the appropriate calibration curves.

Glucose analysis was performed using Glucostix® reagent strips (Bayer Diagnostics). Liver enzyme activities, bilirubin and albumin concentration were measured using an automated clinical diagnostic instrument (Axon; Bayer Technicon), with the appropriate commercially available assay kits (Bayer Technicon).

TABLE 1—*Concentration (μg/mL) of amitriptyline and nortriptyline in blood and fluid samples.*

Sample	Amitriptyline (μg/mL)	Nortriptyline (μg/mL)
Blood		
Femoral vein	1.8	0.6
Left and right iliac veins	2.6	1.1
Lower inferior vena cava 1	3.5	1.3
Lower inferior vena cava 2	2.7	1.3
Lower inferior vena cava 3	3.1	1.1
Inferior vena cava 1	2.4	1.0
Inferior vena cava 2	2.7	1.0
Inferior vena cava 3	3.0	1.2
Superior vena cava 1	2.8	1.2
Superior vena cava 2	3.0	1.1
Superior vena cava 3	3.8	1.0
Right heart	2.7	0.9
Pulmonary artery 1	3.4	1.4
Pulmonary artery 2	8.5	3.0
Pulmonary artery 3	15.2	5.7
Left pulmonary vein	18.8	7.3
Right pulmonary vein	20.2	7.0
Aorta	11.7	3.0
Vitreous	0.8	n.d
Pericardial fluid	2.1	0.4
Bile	42.1	4.9
Ascitic fluid	6.1	1.2
Urine	13.6	1.8

TABLE 2—*Concentration (μg/g) of amitriptyline and nortriptyline in tissue samples and in gastric contents.*

Sample	pH	Amitriptyline μg/g	Nortriptyline μg/g
Lung			
Left apex	6.41	140.1	44.6
Left postero-basal	6.31	130.1	43.5
Liver			
Left lobe	6.13	103.6	41.4
Right deep	6.13	115.1	37.4
Muscle			
diaphragm (right dome)	6.22	24.4	5.4
rectus abdominis (left and right)	6.32	9.8	7.6
gastrocnemius (right)	6.18	9.1	3.8
Stomach contents (64.7g)	5.15	214.3 (13.9mg)	2.5 (0.2mg)
Duodenal/jejunal contents (132.8g)	6.06	694.2 (92.2mg)	25.1 (3.3mg)

Results

The drug concentrations, together with tissue pH, are shown in Tables 1–2. Amitriptyline and nortriptyline levels were elevated in those blood vessels which are known to be influenced by postmortem diffusion. The drug concentration increased following sequential withdrawal of blood from pulmonary artery, inferior vend cava and superior vena cava, but not from the lower inferior vena cava. Lung and liver drug concentrations were greater than the fluid samples, and no within-organ variability was noted. The drug concentration in muscle was several fold higher than the peripheral blood sample, with diaphragm showing the greatest level of the three muscles investigated.

Tables 3 and 4 show correlations between blood drug concentration and serum biochemistry. Table 3 represents the correlation of all blood and serum samples. The five enzymes investigated were markedly elevated above normal clinical levels. They showed little correlation with drug concentration. Individual amino acid showed marked between site variability. Leucine, methionine, serine, and valine correlate best with drug concentration.

The pulmonary blood samples (artery, left and right vein) were grouped together and "liver associated" blood samples (IVC, SVC, lower IVC, and right heart) were also grouped to evaluate the correlation of serum biochemistry with drug concentration in each group. The results shown in Table 4 indicate a strong correlation between individual amino acid concentration and drug concentration in the pulmonary vessels. Glycine, leucine, methionine, serine, and valine correlate best. No strong correlation was found for the enzymes, with the exception of creatine kinase, which gave a strong negative correlation ($r = -0.93$). Lactic acid also gave a strong negative correlation in the pulmonary vessels ($r = -0.93$).

TABLE 3—*Correlation of postmortem serum biochemistry with amitriptyline and nortriptyline concentration from different anatomical sites.*

Amino Acid	Serum Sample with Minimum Concentration	Serum Sample with Maximum Concentration	Range Between Individual Serum Samples nmol/mL	Amitriptyline vs Biochemical Markers r = *	Nortriptyline vs Biochemical Markers r = *
Alanine	Right heart	Lower inferior vena cava 1	609–26618	−0.1	−0.7
Asparagine	Pulmonary artery 1	Right heart	0.08–2268	−0.16	−0.16
Aspartate	Iliac	Right heart	13–1204	−0.12	−0.13
Gaba	Aorta	Right heart	0.5–2362	−0.17	−0.17
Glutamate	Superior vena cava 1	Lower inferior vena cava 1	377–4198	−0.11	−0.1
Glutamine	Superior vena cava 1	Right heart	108–4586	−0.18	−0.19
Glycine	Right heart	Lower inferior vena cava 1	44–4987	0.34	0.36
Histidine	Iliac/superior vena cava 1	Lower inferior vena cava 1	0–604	0.14	0.16
Isoluecine	Right heart	Lower inferior vena cava 1	39–1117	0.33	0.35
Leucine	Right heart	Lower inferior vena cava 1	52–2095	0.63	0.63
Malate	Right heart	Lower inferior vena cava 1	1–5	0.21	0.23
Methonine	Lower inferior vena cava 1	Right pulmonary vein	4–93	0.9	0.9
Proline	Iliac	Lower inferior vena cava 1	6–62	0.42	0.39
Serine	Inferior vena cava 1	Right pulmonary vein	100–570	0.63	0.65
Thereonine	Inferior vena cava 1	Right heart	1208–15334	−0.02	−0.02
Tyrosine	Inferior vena cava 1	Lower inferior vena cava 1	52–237	0.26	0.26
Valine	Right heart	Lower inferior vena cava 1	15–1186	0.65	0.66
Lactic acid	Right heart	Lower inferior vena cava 1	69–4361	−0.26	−0.22
Cytosolic enzymes					
Alanine aminotransferase	Superior vena cava 1	Lower inferior vena cava 1	381–1065	−0.23	−0.19
Alkaline phosphatase	Aorta	Iliac	159–348	−0.52	−0.46
Creatine kinase	Aorta	Right heart	622–25426	−0.31	−0.31
Aspartate aminotransferase	Superior vena cava 1	Right heart	618–1716	−0.26	−0.24
γ-Glutamyl transferase	Superior vena cava 1	Lower inferior vena cava 1	49–95	−0.06	−0.01
Glucose	Left & right pulmonary vein	Lower inferior vena cava 1	1–7	−0.61	−0.58
Bilirubin	Aorta/superior vena cava 1	Lower inferior vena cava 1	5–6	0.06	0.09
Albumin	Left pulmonary vein	Right heart	51–61	−0.38	−0.36

*This correlation was also performed without the aorta, the drug concentration of which is known to be influenced by postmortem diffusion from the gastric residue. No changes in the correlation were found.

Reference clinical ranges for laboratory: Alanine aminotransferase up to 35 u/L, alkaline phosphatase 25–85 u/L, creatine kinase up to 150 u/L, aspartate aminotransferase up to 45 u/L, γ-glutamyl transferase 5–42 u/L, glucose 3.3–5.8 mmol/L, bilirubin up to 17 μmol/L, albumin 36–50 g/L.

Individual amino acids were found to correlate with drug concentration in the vessels associated with the liver, but to a lesser extent (r = 0.6–0.7) than that found for the pulmonary vessels. Methionine gave a negative correlation in these vessels (r = −0.68). In contrast to the pulmonary vessels, lactic acid gave a positive correlation (r = 0.71). The enzymes did not show a strong correlation with drug concentration in these vessels.

Discussion

Postmortem, drug diffusion occurs from reservoirs of high concentration in solid organs into the blood, so-called "postmortem drug redistribution" (1,2), as well as from gastric residue into nearby organs and vessels (3,4). Based upon current knowledge, we interpret the blood and tissue drug concentrations in this case as follows: The lowest drug concentration is seen in the peripheral vessel (femoral vein) and is most representative of the drug concentration at the time of death, although it may reflect a slight artefactual elevation. The vitreous drug level provides some corroboration of the femoral vein level. Higher drug concentrations in torso vessels reflect postmortem diffusion artefact. The high concentrations seen in pulmonary vessels are the result of diffusion from the lung where the drug is concentrated at levels about 100 fold those in the blood Increasing drug concentrations in sequential pulmonary artery samples reflects a siphon effect due to the drawing of blood from vessels deeper within the lung parenchyma, which have been affected more by diffusion artefact. Pulmonary vein levels are higher than pulmonary artery levels reflecting the ease of diffusion into the thin walled vein when contrasted with the artery (5). There was no anatomical evidence of aspiration of gastric contents and therefore no suspicion of drug diffusion from gastric contamination of the airways (6). Less markedly elevated drug levels in the inferior vena cava reflect primarily diffusion from the liver (7). This is less pronounced than in the pulmonary vessels because diffusion from the lungs occurs earlier and more rapidly than from the liver (8).

The high drug concentration in the aorta likely reflects diffusion from drug residue in the stomach, with or without associated reflux into the oesophagus (9) rather than diffusion from solid organs. However, postmortem diffusion of drug from the gastric residue has not been pronounced as evidenced by the absence of an elevated drug concentration in the left postero-basal lung when contrasted to the apex and the left liver lobe when contrasted to the right. The pericardial fluid drug level is not much elevated when contrasted with the femoral vein and vitreous indicating that there has been minimal drug diffusion from the gastric residue, corroborating the observations on the lung and liver, and supporting the interpretation that elevated pulmonary blood vessel drug levels are the result of diffusion from the lung per se (3). The drug level in the bile reflects the concentrating effect during life and is not likely to have been artefactually elevated by postmortem diffusion from gastric or duodenal drug residue, given the lung, pericardial fluid, and liver observations.

TABLE 4—*Correlation of drug concentration with serum amino acids and enzymes in pulmonary blood vessels and great veins.*

Amino Acid	Pulmonary Vessels*		Great Veins†	
	Amitriptyline vs Biochemical Marker	Nortriptyline vs Biochemical Marker	Amitriptyline vs Biochemical Marker	Nortriptyline vs Biochemical Markers
Alanine	−0.63	−0.64	0.66	0.73
Asparagine	0.95	0.94	−0.16	−0.49
Aspartate	0.95	0.95	−0.09	−0.44
Gaba	−0.76	−0.77	−0.16	−0.49
Glutamate	0.95	0.97	0.57	0.23
Glutamine	−0.35	−0.36	−0.02	−0.39
Glycine	0.84	0.86	0.77	0.7
Histidine	0.77	0.72	0.38	0.44
Isoleucine	0.86	0.86	0.76	0.88
Leucine	0.94	0.94	0.76	0.82
Malate	0.97	0.96	0.4	0.3
Methionine	0.93	0.92	−0.68	−0.35
Proline	0.98	0.97	0.37	0.1
Serine	0.94	0.94	0.78	0.72
Threonine	0.87	0.86	0.1	−0.26
Tyrosine	0.83	0.81	0.65	0.47
Valine	0.93	0.92	0.71	0.84
Lactic Acid	−0.93	−0.93	0.71	0.77
Cytosolic Enzymes				
Alanine Aminotransferase	0.03	0.04	0.72	0.68
Alkaline Phosphatase	−0.63	−0.63	0.41	0.5
Creatine Kinase	−0.93	−0.94	−0.16	−0.5
Aspartate Aminotransferase	−0.17	−0.18	0.32	0.04
γ-Glutamyl Transferase	0.34	0.35	0.71	0.73
Glucose	−0.95	−0.95	0.51	0.27
Bilirubin	0.24	0.26	0.71	0.59
Albumin	−0.29	−0.3	0.04	−0.12

*The same correlations were performed without the peripheral blood sample. No changes in correlation were noted.

†The same correlations were performed without the right heart. The correlation with amino acids and the enzymes was generally increased.

Pulmonary vessels = pulmonary artery 1–3 & left and right pulmonary vein. Great veins (liver diffusion associated) = inferior and superior vena cava 1–3, right heart and lower inferior vena cava 1–3.

Drug concentrations in muscle are several fold higher than those in femoral vein blood suggesting a survival time after drug ingestion sufficient to allow effective drug distribution, which is corroborated by the marked drug concentration in liver and lung (10). The elevated drug level in the diaphragm when contrasted to the other muscles is as expected (11), although the reason is not yet clarified. The overall pattern of drug levels in blood and tissue samples indicates a prolonged survival time following drug ingestion, with effective distribution of the drug to solid organs in accord with its high Vd, and subsequent postmortem redistribution into blood from solid organ reservoirs but little artefactual diffusion from gastro-intestinal drug residue.

Postmortem drug redistribution into blood is hypothesized to be primarily a consequence of loss of cell membrane integrity consequent on cellular death (7). It has long been recognized (12) that a wide variety of biochemical parameters in blood change postmortem as a result of a similar cell leakage process. We sought to demonstrate whether or not the two processes could be measurably linked. Several enzymes which are primarily intracellular show a prominent postmortem blood elevation and many have a hepatic origin (13). Similarly, postmortem hepatic glycogenolysis causes a rise in blood glucose in the right heart and related vessels (12). This released glucose may in turn be converted to lactate by anaerobic glycolysis. Serum amino acids are known to undergo significant postmortem changes also and the extent of change varies between amino acids (12). We were unable to locate recent literature on this subject but the older literature (14,15) suggests that the postmortem site-to-site changes in serum amino acid levels may be a useful measure of cell autolysis.

Recognizing that the two primary organs responsible for postmortem release of amitriptyline and nortriptyline are the liver and lungs (5), the blood samples were grouped into "lung diffusion associated" and "liver diffusion associated." The pulmonary artery and venous samples (n = 5) were used to assess diffusion from the lung. The great veins and the right heart (n = 10) were used to assess diffusion from the liver (Table 4). The correlation analysis for the pulmonary vessels was performed with and without the iliac blood sample but this made no appreciable difference to the result. Similarly, including or excluding the right heart sample had no significant effect on the analysis of the great veins.

There is a striking contrast between the correlation analyses for the pulmonary vessels and the great veins. The four hepatic enzymes, glucose, and lactic acid all show some correlation with the drug concentrations in the great veins but not in the pulmonary vessels. However, the correlation between hepatocyte markers and drug concentrations in the great veins is not sufficiently high to have an immediate practical application, although it merits further investigation. Bilirubin shows a similar contrast, suggesting that there has been some postmortem bilirubin rise as a result of hepatocyte leakage and that it is not entirely stable postmortem (12). Neither albumin, which is stable postmortem, nor creatine kinase, which is a useful myocyte marker but found in all cells, show a correlation with drug concentrations in either the pulmonary vessels or the great veins.

The 17 amino acids show a wide range of correlation, positive and negative, with drug concentrations in both pulmonary vessels and great veins. Some (asparagine, aspartate, malate, methionine, proline, and threonine) show a strong positive correlation in the pulmonary vessels but not in the great veins. Others show an opposite, but not as extreme, pattern of correlation. Of all the amino acids, methionine stands out as showing a dramatic reversal of correlation between the pulmonary vessels ($r = 0.93$) and the great veins ($r = -0.68$). Taking into account both the correlation analysis and the absolute concentrations and ranges of the serum amino acids, it would seem that serine, methionine, valine, and leucine may be potential markers for postmortem drug diffusion from the lung. Further interpretation of these amino acid levels is constrained by the lack of modern reference data on postmortem blood levels as well as temporal changes and site-to-site variations.

If the critical factor in the loss of drugs and biochemical markers from cells postmortem were loss of cell membrane integrity, then it would be expected that the rate of loss of any particular molecule would be broadly proportional to its molecular weight and the diffusion gradient. Amitriptyline and nortriptyline have molecular weights similar to many of the biochemical markers and very much less than the enzymes studied. Nevertheless, the rise in drug concentrations postmortem is often not as great as the rise in concentration of the biochemical markers (Table 1 for drugs and Table 3 for ranges of biochemical markers). It may be that drug loss from the lung and liver is influenced by the intracellular location of the drug and possibly intracellular drug-binding. Information on the subcellular localization and possible binding of drugs is limited. For example, metamphetamine accumulates in the smooth endoplasmic reticulum of hepatocytes and the alveolar and bronchiolar epithelia of the lung (16). The search for a suitable biochemical marker could be more focused if there was more knowledge of subcellular drug localization. It is also possible that the postmortem rise in drug concentrations in blood is, at least in part, a result of shedding of drug-rich endothelial cells. There is some indirect evidence to support this in that some drugs such as phenobarbitone are concentrated in endothelial cells (17), and endothelial cell loss is an early change following somatic death (18).

It would be helpful in the interpretation of postmortem drug levels in blood if there were a marker which indicated whether or not postmortem drug redistribution had occurred in an individual sample Biochemical markers invite scrutiny for this purpose because many are known to undergo postmortem elevations similar to postmortem drug redistribution. This preliminary investigation using a detailed case study suggests that hepatic enzymes are relatively poor markers for hepatic drug shifts but that amino acids, particularly methionine, may be useful markers for pulmonary drug shifts. These suggestions will require validation in a large case series and animal model before any attempt is made to apply them in case work.

References

1. Prouty RW, Anderson WH. The forensic science implications of site and temporal influences on postmortem blood-drug concentrations. J Forensic Sci 1990;35(2):243–70.
2. Pounder DJ. The nightmare of postmortem drug changes. Legal Medicine 1993;163–91.
3. Pounder DJ, Fuke C, Cox D, Smith D, Kuroda N. Postmortem diffusion of drugs from gastric residue: An experimental study. Am J Forensic Med Pathol 1996: in press.
4. Pounder DJ, Adams E, Fuke C, Langford A. Site to site variability of postmortem drug concentrations in liver and lung. J Forensic Sci 1996, 41(6): in press.
5. Pounder DJ, Owen V, Quigley C. Postmortem changes in blood amitriptyline concentration. Am J Forensic Med Pathol 1994; 15(3):224–30.
6. Pounder DJ, Yonemitsu K. Postmortem absorption of drugs and ethanol from aspirated vomitus—an experimental model. Forensic Sci Int 1991;51:189–95.
7. Pounder DJ, Jones GR. Postmortem drug redistribution—a toxicological nightmare. Forensic Sci Int 1990;45:253–63.
8. Yonemitsu K, Pounder DJ. Postmortem toxico-kinetics of co-proxamol. Int J Legal Med 1992;104:347–53.
9. Pounder DJ, Smith DRW. Postmortem diffusion of alcohol from the stomach. Am J Forensic Med Pathol 1995;16:89–96.
10. Garriott JC. Skeletal muscle as an alternative specimen for alcohol and drug analysis. J Forensic Sci 1991;36(1):60–9.
11. Christensen H, Steentoft A, Worm K. Muscle as an autopsy material for evaluation of fatal cases of drug overdose. J Forensic Sci Society 1985;25:191–206.
12. Coe JL. Postmortem chemistry update: Emphasis on forensic application. Am J Forensic Med Pathol 1993;14:91–117.
13. Naumann HN. Postmortem liver function tests. Am J Clin Pathol 1956;26:495–505.
14. Schleyer F. Determinations of the time of death in the early postmortem interval in Methods of Forensic Science, Vol II, John Wiley and Sons Publishers, New York 1963;253–93.
15. Pucher G, Burd L. A preliminary study of the chemistry of postmortem blood and spinal fluid. Bull Buffalo Gen Hosp 1925;3:11–3.
16. Ishiyama I, Mukaida M, Yoshii T, Suyania H. Histochemical demonstration of metamphetamine by immunohistochemistry. J Forensic Sci 1987;32(3):658–72.
17. Ishiyama I, Mukaida M, Tanabe R, Ueyama M. Histochemical demonstration of phenobarbital by immunocytochemistry. J Forensic Sci 1987;32(5):1221–34.
18. Yu QC, Mergner WJ, Vigorito RD, Resau JH. Postmortem viability and early changes in organ culture of human and rabbit aortic endothelial cells. Pathobiology 1990;58:138–45.

Additional information and reprint requests:
Professor Derrick J. Pounder
University of Dundee
Department of Forensic Medicine
The Royal Infirmary, Dundee
DD1 9ND, Scotland