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Postmortem Investigation of Lamotrigine Concentrations

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ABSTRACT: Lamotrigine is a relatively new anticonvulsant. Therapeutic plasma concentrations generally range from 1 to 4 mg/L, although several studies have shown that good control of epilepsy has been achieved with concentrations reaching 10 mg/L generally, with little toxicity. In overdose, however, the drug has been linked to ECG changes that may suggest a possible arrythmogenic effect and hence cardiac toxicity. Lamotrigine has also been shown to cause encephalopathy and thus neurotoxicity.

There is no information concerning postmortem lamotrigine concentrations and their interpretation. We describe lamotrigine concentrations in postmortem specimens including blood, liver, bile, vitreous humour, and urine from eight cases. A high performance liquid chromatography (HPLC) method is described with extraction procedures for the various tissues.

Two possible groups were identified. The first being the "broader therapeutic" group with blood concentrations ranging from 0.9 to 7.2 mg/L and corresponding liver concentrations ranging from 16 to 36 mg/kg. The second being a "supratherapeutic" group with blood concentrations ranging from 20 to 39 mg/L and corresponding liver concentrations ranging from 53 to 350 mg/kg. Although none of the eight cases described were attributed to overdose by lamotrigine alone, the cause of death for one of the three cases in the "supratherapeutic" group was given as mixed drug toxicity. Cause of death for the remaining two cases in this group was reported as epilepsy. However, both these cases showed elevated concentrations of lamotrigine and both were co-medicated with valproic acid. Such co-administration has been shown in the literature to lead to elevated lamotrigine concentrations and a reduction in lamotrigine dose has been recommended. With such data, we highlight the importance of monitoring lamotrigine concentrations in cases co-medicated, particularly with valproic acid.

KEYWORDS: forensic science, forensic toxicology, lamotrigine, epilepsy, postmortem concentrations, human toxicology

Lamotrigine (3,5-diamino-6-(2,3-dichlorophenyl)–1,2,4–triazine) is a relatively new anticonvulsant which inhibits voltage dependent sodium channels and inhibits the release of excitatory neurotransmitters (1).

Pharmacokinetic aspects of lamotrigine were reviewed in an article by Fitton and Goa (1). Lamotrigine is rapidly absorbed after oral administration with an absolute oral bioavailability of 98%, reaching peak plasma concentration at approximately 1 to 3 h. The mean elimination half-life ranges from 23 to 37 h after a single dose. The drug is generally introduced at a low dose and titrated up. Maintenance dosages range from 100 to 200 mg/day (single or divided dose) when lamotrigine is taken as monotherapy. Co-medication of lamotrigine with liver enzyme-inducing antiepileptic drugs produces a reduction in its half-life to 15 h and subsequently maintenance dosages will range from 300 to 500 mg/day (divided doses). Co-medication with valproic acid produces an increase in the half-life to 60 h and thus, the maintenance dosages should range from 100 to 200 mg/day (single or divided doses). Lamotrigine displays 1-compartment model of pharmacokinetics with linear kinetics at doses up to 450 mg. The main route of metabolism is N-glucuronidation. Therapeutic plasma concentrations generally range from 1 to 4 mg/L (2).

To date, there is no information available regarding postmortem lamotrigine levels. Unexplained deaths in the population used in the worldwide lamotrigine clinical trials could not be attributed to drug treatment (3). Betts and co-workers (4), reviewing the human safety of lamotrigine, described common adverse effects including rash, dizziness, diplopia, somnolence, headache, ataxia and asthenia.

The current manuscript details our experience relating to lamotrigine levels in eight coronial deaths. Concentrations of free lamotrigine in postmortem specimens including blood, serum, liver, bile, vitreous humour, urine and stomach content are described.

An effective high performance liquid chromatography (HPLC) method is also described with extraction procedures for the varying tissues.

Subjects and Methods

The cases described in this article were autopsied according to the protocol of the Victorian Institute of Forensic Medicine (VIFM). Investigation included full macroscopic and microscopic examination of all major organs by pathologists. All specimens were collected as per usual VIFM protocol. Blood was collected in tubes containing 1% sodium oxalate/potassium fluoride as preservative and anticoagulant. Blood was taken from the femoral region unless otherwise noted. Serum was obtained by centrifuging postmortem blood without preservative or anticoagulant. The supernatant was aliquoted and the cells discarded. Blood, serum, urine, bile, vitreous humour, and liver were frozen until use. Stomach contents were refrigerated until use. Circumstances surrounding the deaths were obtained from police reports.

Full toxicological examinations were undertaken for all cases. These involved the use of enzyme multiplied immunoassay tech-

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nique (EMIT) for the analysis of drugs of abuse including opiates, amphetamines, cannabinoids, cocaine metabolite, benzodiaze-pines, and barbiturates. Blood extracts were analyzed for common drugs and poisons using gas chromatography (GC) (5) with confirmation by mass spectrometry (MS). Further testing of blood was conducted by gradient elution HPLC with confirmation by photodiode array detection (DAD) (6). All cases were tested for the presence of ethanol using packed column GC with flame ionization detection.

Other tests included the screening and quantification for carboxyhaemoglobin in blood using an IL682 Co-Oximeter (Instrumentation Laboratory: Coulter, Australia), and valproate using EMIT (Valproic acid kit 6G009: Dade Behring, Australia). Other anticonvulsants including lamotrigine were quantified by HPLC with UV detection.

Materials

Methanol and acetonitrile (ACN) were of HPLC grade (Mallinckrodt, Australia). Diethyl ether was of analytical reagent grade (Mallinckrodt, Australia). Sodium chloride and potassium dihydrogen orthophosphate were of analytical reagent grade (Ajax, Australia).

Lamotrigine was obtained from Wellcome via the Division of Analytical Laboratories (NSW, Australia) and the internal standard 5′-(4-methylphenyl)-5-phenylhydantoin (MPPH) was obtained from Sigma (Australia).

Reagents and Standards

Drug stock solutions (1 mg/mL) were prepared in methanol and dilutions in distilled water. Working standards were prepared in the same matrix as the sample of interest except for vitreous humour. Blood and serum standards were prepared using drug free whole blood and serum supplied by the Red Cross Blood Bank (Southbank, Australia). Urine standards were prepared using blank urine supplied from staff of the VIFM. Standards from bile and liver homogenates were spiked in drug-free matrix from other coronial cases. Standards for vitreous humour were prepared in PBS (0.9% sodium chloride/25 mM potassium dihydrogen orthophosphate, pH = 7.4).

Standard curves were prepared at appropriate concentrations with cases being diluted if necessary.

Lamotrigine Extraction Procedure

The following procedure was used for blood, serum, urine, and vitreous humour. Two hundred and fifty μL of sample were added to 2 mL Sarstedt tubes (Sarstedt, Australia). Two hundred and fifty μL of extraction solvent (acetonitrile-containing MPPH at 20 μg/mL) were added to samples and vortexed. Samples were allowed to stand for 10 min. Samples were then centrifuged at 10 000 rpm for 10 min. The supernatant was transferred to auto-injector vials and 20 μL aliquots were injected into the HPLC.

Liver homogenates were prepared by finely dicing 10 g of liver and then homogenizing in 10 mL of distilled water. The pH was adjusted to 10 using 10 M NaOH, then 10 mg of subtilisin (Sigma) was added. Liver homogenates were placed in a water bath at 55°C for 60 min. The pH was then adjusted to 7 using orthophosphoric acid. The extraction involved adding 1 mL of extraction solvent (acetonitrile containing MPPH at 20 μg/mL) to 500 μL of homogenate in 10 mL polypropylene tubes. Samples were vortexed and were allowed to stand for 5 min. The supernatant was transferred to 2 mL Sarstedt tubes (Sarstedt, Australia) and centrifuged at 10 000 rpm for 15 min. The supernatant was transferred to auto-injector vials and 20 μL aliquots were injected into the HPLC.

Five hundred μL of bile were added to 10 mL glass silanized tubes. Ten μL of MPPH stock and 500 μL of 10 mM KH_2PO_4 (pH = 7.4) were added and samples vortexed. Eight mL of diethyl ether were added, tubes stoppered and rotated for 30 min. Extracts were centrifuged for 5 min at 3500 rpm. The supernatant was transferred to clean extraction tubes and the solvent was evaporated to dryness in a savant concentrator (SpeedVac Concentrator). Samples were reconstituted in 250 μL of mobile phase (A) (see chromatographic conditions). Tubes were further centrifuged and the supernatant was transferred to auto-injector vials. Twenty μL aliquots were injected into the HPLC.

Chromatographic Conditions

HPLC system consisted of two LC-6AD flow pumps (set for gradient), a SIL-6B autoinjector and SPD-6AV UV-VIS spectrometric detector linked to a system controller (Shimadzu Oceania, Australia). Data were collected via multi-functional data processor with built-in thermal plotter and floppy disk drive storage facility (C-R4A Chromatopac, Shimadzu, Oceania, Australia).

Detection was at 214 nm. Chromatographic separation was achieved on a Waters, Nova Pak C_{18} column (3.9 mm ID × 150 mm, 4 μm particle size) coupled to a Waters, Nova-Pak C_{18} precolumn.

The gradient system consisted of mobile phase (A) (5% ACN and 95% 10 mM KH_2PO_4, final pH = 3.2) and mobile phase (B) (60% ACN and 40% KH_2PO_4, final pH = 3.2). The gradient program was set at 100% A for 2.5 min and then linear gradient to 50% B over 6.5 min, isocratic at 50% for 17 min, then linear gradient to 100% B over 10 min, isocratic at 100% B for 10 min with a return to 100% A over 1 min.

Elution of lamotrigine and MPPH occurred at 12 min and 17 min, respectively.

Case Summaries and Findings

Case 1

A 29-year-old, 107 kg male was found dead in bed at a special accommodation unit. He had been diagnosed with autism, had a history of epilepsy, and was intellectually disabled. Findings at autopsy included slight cardiomegaly, pulmonary oedema, gingival hyperplasia, lymphocytic thyroiditis and scattered neurons in cerebral white matter (of uncertain significance). Toxicological findings included phenytoin at approximately 10 mg/L and lamotrigine at 0.9 mg/L in blood (Table 1). The deceased had been on lamotrigine for 14 months and was taking 300 mg/day at time of death. The cause of death was epilepsy.

Case 2

A 2-year-old male with a history of cerebral palsy, intellectual disability, epilepsy, and asthma was admitted to hospital suffering from asthma. He developed pneumonia and status epilepticus. He died approximately 12 days after admission. Histology showed changes of acute asthma, bronchopneumonia, and evidence of old meningitis/ventriculitis. Toxicology results in neck blood included phenytoin at approximately 0.8 mg/L, diazepam at trace levels (<0.05 mg/L) and its metabolite nordiazepam at 0.1 mg/L,

TABLE 1—*Lamotrigine concentrations.*

Case #	Tissue						
	Blood (mg/L)	Serum (mg/L)	Liver (mg/kg)	Bile (mg/L)	Vitreous Humour (mg/L)	Urine (mg/L)	Stomach Contents (mg)
1	0.9	0.6	16	12	0.3	3.3	n/a
2	2.2†	n/a	n/a	n/a	n/a	n/a	n/a
3	2.4	1.9	36	59	0.3	not detected	not detected
4	3.3	3.1	30	detected	1.8	7.8	0.5
5	7.2*	n/a	35	11	n/a	9.4	34
6	20	15	53	110	6.7	26	92
7	38	35	120	250	14	59	10
8	39*	62*	350	420	n/a	n/a	290

n/a= not available.
* Blood obtained from chest.
† Blood obtained from neck.

clobazam was not detected but its metabolite norclobazam was present at 0.2 mg/L. Trimethoprim and sulphamethoxazole were also detected. The lamotrigine blood concentration was 2.2 mg/L (Table 1). The deceased had been on lamotrigine for 15 months and was taking 100 mg/day, which had been established for 12 months at the time of death. The cause of death was bronchopneumonia, asthma, and status epilepticus.

Case 3

A 41-year-old, 74 kg male was found dead in bed. It was considered the deceased had died approximately two days before being discovered. The deceased had suffered a motor bike accident two years prior and developed epilepsy following this, however, neuropathological examination failed to reveal any evidence of old traumatic injury. Significant findings at autopsy included severe coronary artery atherosclerosis, and cardiomegaly with left ventricular hypertrophy. Toxicological results in blood included phenytoin at 6.0 mg/L, carbamazepine at 3.0 mg/L and lamotrigine at 2.4 mg/L (Table 1). The deceased had been on lamotrigine for 11 months and was taking 200 mg/day, established for 6 months at the time of death. The cause of death was coronary artery atherosclerosis and cardiomegaly in a man with epilepsy.

Case 4

A 35-year-old, 79 kg male, with intellectual disability and epilepsy drowned while swimming. Significant findings at autopsy included pulmonary oedema and bilateral hippocampal sclerosis. Toxicological results included carbamazepine at 11 mg/L in blood and 25 mg/kg in liver and lamotrigine in blood at a concentration of 3.3 mg/L (Table 1). The cause of death was drowning in a man with a history of epilepsy.

Case 5

A 39-year-old, 54 kg male died as a result of a fire in a special accommodation unit. The deceased had a history of intellectual disability due to unknown prenatal influence. Findings at autopsy included dilation of the lateral and third ventricles with presence of glial nodules in the ependymal region suggesting old ventriculitis. Toxicology results included carboxyhaemoglobin saturation of 95% in heart blood, hydrogen cyanide at 3.0 mg/L in chest blood, valproate at 110 mg/L in chest serum, and the anti-parkinsonian drug benztropine at approximately 0.2 mg/L. Thioridazine was present at a concentration of 0.3 mg/L in chest blood with the metabolites mesoridazine present at 0.4 mg/L and sulforidazine not detected. Lamotrigine was present at 7.2 mg/L in chest blood (Table 1). The cause of death was carbon monoxide poisoning due to fire.

Case 6

A 33-year-old, 41 kg male with a history of epilepsy was a resident of a special accommodation unit. He suffered an epileptic seizure but despite treatment continued to suffer seizures until his death some hours later. Findings at autopsy included early bronchopneumonia with foreign material in giant cells present in the airways. Fitting may cause aspiration and produce bronchopneumonia. The tongue showed recent bruising. The brain was small and showed a number of anomalies including gyral abnormalities and the presence of heterotopias. The changes were consistent with developmental anomaly occurring in early intrauterine life. Toxicology results included serum valproate at 65 mg/L, diazepam at approximately 0.1 mg/L in blood, and lamotrigine in blood at 20 mg/L (Table 1). The deceased had been on lamotrigine for two months and was taking 300 mg/day since commencement until time of death. The cause of death was epilepsy.

Case 7

A 20-year-old, 34 kg male with cerebral palsy and epilepsy was found dead in bed at a community residential unit. A significant finding at autopsy was florid prostatitis. Toxicological results included serum valproate of 100 mg/L and blood lamotrigine concentration of 38 mg/L (Table 1). The deceased had been on lamotrigine for almost three years and was taking 475 mg/day at time of death as well as sodium valproate prescribed at 1000 mg/day, established for 11 months. The cause of death was epilepsy in a young man with cerebral palsy and acute prostatitis.

Case 8

A 21-year-old, 63 kg female with temporal lobe epilepsy and depression was found lying face down at a waste disposal area with a number of prescription drugs in her handbag. She had written a letter stating her intentions to commit suicide. Significant findings at autopsy were old craniotomy in the temporal region and marked

decompositional change in the head and neck. Toxicology results included blood alcohol at 0.05 g/dL; chest blood carbamazepine at 18 mg/L, 28 mg/kg in liver, and 610 mg in the stomach; chest blood paroxetine at 2.7 mg/L and 26 mg/kg in liver; chest blood thioridazine at 3.7 mg/L, and 12 mg/kg in liver with the metabolites mesoridazine not detected in blood or liver, and sulforidazine not detected in liver but detected in chest blood at 0.1 mg/L. Lamotrigine chest blood concentration was 39 mg/L (Table 1). The deceased had been on lamotrigine for over three years and was taking a dosage of 600 mg/day at time of death. The cause of death was mixed drug toxicity (carbamazepine, lamotrigine, paroxetine and thioridazine).

Discussion

No information is available in the literature describing postmortem tissue concentrations of lamotrigine. None of the causes of death in the eight cases described herein were attributable to toxicity by lamotrigine, however, case 8 was attributed to mixed drug toxicity.

Blood concentrations for Cases 1, 2, 3, 4, and 5 ranged from 0.9 to 7.2 mg/L (mean = 3.2 mg/L). Generally concentrations of drugs present in Cases 1 to 4 were in the therapeutic range or at the lower therapeutic end. Four of the eight cases presented showed higher concentrations than the generally accepted therapeutic range of 1 to 4 mg/L (2). However, several studies have shown that good control of epilepsy has been achieved with concentrations outside this therapeutic range. These patients, with some concentrations reaching above 10 mg/L showed clinical benefit without toxicity (7,8). Thus, Case 5, a fire related death with a blood concentration of 7.2 mg/L has been included in the group of cases which fall within a so-called "broader therapeutic range." Three cases (6, 7, and 8) with blood concentrations considerably higher than 10 mg/L may be considered as "supratherapeutic" concentrations.

A possible explanation for high concentrations found in this study is postmortem redistribution. This phenomenon is one where drugs diffuse from sites of high concentration such as solid tissue into blood. Drugs such as the tricyclic antidepressants including amitriptyline and doxepin, and the narcotic analgesic propoxyphene show higher concentrations if blood sampling occurs from central cavity sites compared to peripheral sites such as the femoral region (9). Three of the cases presented have blood results from non-femoral regions. Blood from Case 2 was obtained from the neck and blood from Cases 5 and 8 from the chest. Lamotrigine, however, is chemically unrelated to any drug in use and no study has detailed if this drug is subject to postmortem redistribution. From Table 1, it can be seen that liver concentrations are higher than blood, and the phenomenon of postmortem redistribution is possible. This is an area that requires further investigation.

Serum concentrations for Cases 1, 3, and 4 (Case 2 and 5 were unavailable) ranged from 0.6 to 3.1 mg/L (mean = 1.9 mg/L). The "supratherapeutic" cases (6, 7, and 8) showed higher serum concentrations ranging from 15 to 62 mg/L (mean = 37 mg/L). No information could be found in the literature relating to blood/serum ratios. Blood and serum levels compared favorably except in Case 8 where serum results were higher. However, this case showed significant signs of decomposition, which may have affected the results. The mean blood/serum ratio with standard deviation (excluding Case 8) was 1.25 ± 0.18 ($n = 5$).

Liver concentrations for Cases 1, 3, 4, and 5 (Case 2 unavailable) ranged from 16 to 36 mg/kg (mean = 29 mg/kg). The "supratherapeutic" cases (6, 7, and 8,) showed higher liver concentrations ranging from 53 to 350 mg/kg (mean = 174 mg/kg).

Bile concentrations for Cases 1, 3, and 5 (Case 2 unavailable) ranged from 11 to 59 mg/L (mean = 27 mg/L). The bile lamotrigine level was detected in Case 4, but a concentration was not obtained due to an interfering peak. The "supratherapeutic" cases (6, 7, and 8,) showed higher bile concentrations ranging from 110 to 420 mg/L (mean = 260 mg/L).

Vitreous humour concentrations for Cases 1, 3, and 4 (Case 2 and 5 were unavailable) ranged from 0.3 to 1.8 mg/L (mean = 0.8 mg/L). The "supratherapeutic" Cases 6 and 7 (Case 8 unavailable) showed higher vitreous humour concentrations of 6.7 and 14 mg/L, respectively. Urine concentrations for Cases 1, 4, and 5 ranged from 3.3 to 9.4 mg/L (mean = 6.8 mg/L) with lamotrigine not detected in Case 3 and urine unavailable in Case 2. The "supratherapeutic" Cases 6 and 7 (Case 8 unavailable) again showed higher urine concentrations of 26 and 59 mg/L, respectively.

Although the data provided are difficult to interpret due to the small population size and the varying factors in each case, we are able to suggest some tissue concentration ranges which may represent "therapeutic" levels (Cases 1, 2, 3, 4, and 5) and "supratherapeutic" levels (Cases 6, 7, and 8).

Cases 1 and 2 were co-medicated with phenytoin, Case 4 with carbamazepine and Case 3 with both phenytoin and carbamazepine. Such co-medication with drugs that induce liver enzymes produces an increase in metabolism with a reduction in the half-life of lamotrigine to approximately 15 h (10). Blood concentrations of Cases 1 to 4 ranged from 0.9 to 3.3 mg/L. The level in Case 1 at 0.9 mg/L is at the low end of the generally accepted therapeutic range of 1 to 4 mg/L (2) and the cause of death for this case was given as epilepsy. This may highlight the importance of clinical monitoring of lamotrigine in cases co-medicated with drugs inducing liver enzymes, to ensure adequate concentrations of lamotrigine are being achieved.

Case 5 included in the so-called "broader therapeutic group" is one of the more difficult cases to interpret. The cause of death in this case was fire related. The blood lamotrigine concentration in this case was 7.2 mg/L. There are two possibilities, which may have acted in conjunction to produce such an elevated level. One is the phenomenon of postmortem redistribution as this sample was obtained from the chest and the other is the co-medication with valproic acid. If postmortem redistribution did not play a role, then this may be an individual who could tolerate higher concentrations as mentioned in previous reports (7,8). Three of the cases (6, 7, and 8) showed considerably elevated levels ranging from 20 to 39 mg/L (mean = 32 mg/L). Cases 5, 6, and 7 were positive for valproate. No information is available concerning lamotrigine dosage of Case 5. Case 6 was on an established dose of 300 mg/day for approximately two months, and Case 7 was on an established dose of 475 mg/day for approximately 10 months, as well as sodium valproate at 1000 mg daily. Although these doses had been established for some time, lamotrigine concentrations were considerably elevated in these two cases. As a note of interest, as mentioned earlier, co-medication with valproic acid leads to recommended doses of lamotrigine from 100 to 200 mg/day (1).

Causes of death for both Cases 6 and 7 were reported as epilepsy, however, it is difficult to discount that lamotrigine played a role as both these cases were co-medicated with valproic acid and showed considerably elevated concentrations of lamotrigine. The concentration of valproate in Case 7 was also at the higher end of the therapeutic range at 100 mg/L. A study by Yuen et al. (11) involved volunteers being given lamotrigine as a single dose or co-medicated with valproic acid. The results showed a reduction in total

clearance of lamotrigine by approximately 21% as well as an increased elimination half-life. There was no effect on renal elimination of lamotrigine and the cause postulated by the investigators was hepatic competition for glucuronidation between valproic acid and lamotrigine.

Elevated lamotrigine concentrations have been linked with ECG changes and cardiac toxicity (12) as well as encephalopathy (13) due to neurotoxicity.

A report of a deliberate lamotrigine overdose described a man taking lamotrigine at 1350 mg who developed symptoms of vertical nystagmus and became hypertonic with brisk reflexes, though alert and oriented (12). An electrocardiogram (ECG) showed a QRS interval of 112 ms. The patient was given gastric lavage and activated charcoal. Lamotrigine concentrations were measured at 17.4 and 6.4 mg/L, 3 and 17 h after overdose, respectively. The following day, the patient displayed mild ataxia but was able to walk. He had natural reflexes and no nystagmus. The QRS interval reduced to 110 ms and two months later, returned to less than 100 ms. These ECG changes may suggest a possible arrhythmogenic effect in overdose, and hence, cardiac toxicity.

Another report by Hennessy and Wiles (13) described a woman co-medicated for some time with lamotrigine at 400 mg and phenytoin. For clinical reasons, phenytoin was then replaced by sodium valproate at a dose of 1400 mg without altering the lamotrigine dose. This drug regimen continued for months until the patient developed symptoms of agitation, ataxia, and incontinence. The valproic acid and lamotrigine concentrations were 73 mg/L and 19 mg/L, respectively. Doses of both valproic acid and lamotrigine were reduced, with further stepwise reductions in lamotrigine dose, each time corresponding to reductions in lamotrigine concentrations and further improvement in the patient's condition. The physicians concluded her condition was caused by high lamotrigine concentration leading to encephalopathy, perhaps precipitated by a urinary tract infection.

Blood concentrations for Cases 6, 7, and 8 were, in fact, greater than the two reported overdoses. In Case 6, a physician witnessed the epileptic seizures. However, it is still difficult to discount the contribution of the high lamotrigine concentration producing adverse physiological effects, which may have attributed to death. The cause of death for Case 7 (located dead in bed) was given as epilepsy and acute prostatitis. However, this case bears a striking resemblance to a previously reported case citing encephalopathy caused by high lamotrigine concentration precipitated by a urinary tract infection, a report which also involved co-medication with valproic acid.

The cause of death for Case 8 was given as mixed drug toxicity. The drugs detected were found in high concentrations consistent with toxicity. However, the specimens received showed significant signs of decomposition, which may have changed the concentrations and even prevented the detection of drugs and poisons. Decomposition may have contributed to the apparent discrepancy between blood and serum lamotrigine levels of 39 mg/L and 62 mg/L, respectively. This case was positive for carbamazepine, which as mentioned earlier leads to an induction of liver enzymes and increases lamotrigine elimination. However, this case was also positive for paroxetine, a drug with similar pharmacological effects to sertraline. Sertraline has been shown in the literature to increase lamotrigine concentration possibly by the inhibition of glucuronidation (14). There is no evidence in the literature thus far to confirm or disprove any drug interaction between lamotrigine and paroxetine. Some further investigation into this class of drugs would also be useful.

Larger scale studies of postmortem lamotrigine concentrations are clearly warranted and such data highlight the importance of monitoring lamotrigine concentrations in cases co-medicated, particularly with valproic acid.

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