CASE REPORT

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Death of Two Subjects due to Imipramine and Desipramine Metabolite Accumulation During Chronic Therapy: A Review of the Literature and Possible Mechanisms*

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ABSTRACT: In two unrelated cases, a 7-year-old boy and a 21-year-old woman died suddenly while receiving chronic imipramine therapy. In the boy, concentrations of imipramine were: Left femoral blood 0.5 mg/L, right femoral blood 1.2 mg/L, aorta blood 1.0 mg/L, liver 68 mg/Kg, and for the active metabolite, desipramine, left femoral blood 6.7 mg/L, right femoral blood 9.9 mg/L, aorta blood 8.7 mg/L, liver 400 mg/Kg. In the woman, the imipramine concentrations were: Femoral blood 0.6 mg/L, liver 37 mg/Kg, and of the active metabolite, desipramine, femoral blood 3.74 mg/L, liver 261 mg/Kg. In both cases, the scene investigation strongly indicated that neither individual had ingested an acute overdose. The very high ratios of desmethyl metabolite to parent drug are consistent with this observation. Impaired metabolism due to a genetically determined "slow metabolizer" phenotype of cytochrome CYP2D6, and/or concurrent therapy with phenothiazines, is suggested as a possible mechanism for the apparent fatal accumulation of these tricyclic antidepressants.

KEYWORDS: forensic science, forensic toxicology, imipramine, desipramine, thioridazine, chlorpromazine, phenothiazine, neuroleptic, metabolism, slow metabolizer, fast metabolizer, cytochrome P450, CYP2D6, accumulation, phenotype, polymorphism, isozyme, postmortem, redistribution

Tricyclic antidepressants (TCAs) are widely prescribed to adults for the treatment of depression and to children for depression, night enuresis, and attention deficit disorder (1–5). Sudden death attributable to suicidal overdosage with tricyclic antidepressants, alone or in combination with alcohol or other drugs, is not uncommon. Although a therapeutic range for TCAs is not clearly defined, serum or plasma tricyclic antidepressant concentrations are occasionally monitored to help assess compliance, and as an aid to determining whether patients may be receiving inadequate doses or too high a dose. Even in the living, there is tremendous interpatient variability in the blood or serum concentrations resulting from equivalent doses (5–7). The interpretation of TCA concentrations in postmortem blood is further complicated by postmortem redistribution and by the marked variation in drug concentration which can occur in blood collected from different body sites (8–11). This can result in increases in postmortem blood TCA concentrations to roughly 2–8 times the perimortem levels. Interpretation of postmortem TCA concentrations is therefore difficult, particularly if only blood is available for analysis.

We present two cases in which the blood and liver TCA concentrations are well above those expected following therapeutic doses, even allowing for the considerable degree of postmortem redistribution which can occur, but in which the circumstances of death are not consistent with acute or deliberate overdosage. These observations are supported by the high ratios of desmethyl metabolite to parent drug in blood and liver samples. A discussion of possible mechanisms is also presented.

Case Reports

Case #1

A seven-year-old boy collapsed about five min after he ran the several blocks from his school to his home. He was attended by paramedics within a few minutes and taken to the emergency room in cardiac arrest. Resuscitation was attempted but he did not revive.

The boy was a first grader who had been in the custody of the state children's services division for four years and had been living with the current foster family for about 10 months. He had severe behavioral problems which made his care difficult. The diagnosis of these problems was: An adjustment disorder with mixed disturbance of emotions and conduct, developmental articulation disorder, and severe stress. Imipramine medication of 25 mg/day was started about seven months prior to death to treat hyperactivity and insomnia. The daily dosage was raised to 50 mg after a week. At 3.5 months prior to death, the dosage was increased to 125

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mg/day and raised to 150 mg/day a week later. At two months prior to death, 50 mg/day of thioridazine was added and 19 days prior to death, the dosage was increased to 75 mg/day. The imipramine dosage continued at 150–175 mg/day until death.

The foster mother had been dispensing the medication to the child; all tablets were accounted for at the time of death. There was no evidence that the boy had taken an overdose.

The autopsy findings were unremarkable. No anatomic cause of death was found. The boy's weight was estimated to be 26 kg at autopsy; his height was not recorded but was noted to have been 121 cm about six months prior to death. The death was eventually determined to be due to imipramine/desipramine toxicity.

Case #2

A 21-year-old woman with a history of manic depressive illness collapsed on the kitchen floor of her parent's home, in the middle of the night. She had gone to bed 6 h prior to her collapse, complaining of feeling unwell; she awoke 2 h later complaining of nausea, vomiting, plus stomach, and chest pains. Four hours later, she was heard to call out and was found in bed, semi conscious, cold, clammy, with irregular breathing, and with a great deal of saliva around her mouth. She was taken downstairs to be driven to hospital when she collapsed. Paramedics attended at the house, but she died on the way to hospital.

Her prior medical history and her actions and demeanor the evening before her death gave no indication of suicidal intent. Her medications were seized and found to be accounted for. Specifically, neither imipramine nor chlorpromazine tablets were missing. At the time of her death, this lady was prescribed 900 mg chlorpromazine daily in divided doses, 125 mg imipramine daily at night and 10 mg amphetamine in the morning. Her father stated that just before she retired to bed on the night of her death, she took 300 mg chlorpromazine and 125 mg imipramine (6 h before her final collapse). She had apparently been treated with carbachol for urinary retention by a urologist some weeks prior to her death, and was also taking a saliva stimulating medication or sialogogue (anetholtrithione, 25 mg per day).

At autopsy, she weighed 56 kg and measured 174 cm in length. The autopsy findings were unremarkable. No anatomic cause of death was found. The cause of death was eventually determined as toxicity due to imipramine and desipramine.

Analytical Methods

These cases were investigated in different laboratories therefore, the methods used in each laboratory are described.

Case #1

Mepivacaine internal standard was added to 5 mL of sample (blood or liver homogenate) and 100 μL of concentrated ammonium hydroxide. The sample was extracted with 15 mL of 1-chlorobutane for 20 min. Thirteen mL of the 1-chlorobutane layer were transferred to a separate tube and mixed with 4 mL of HCl (0.2 M), and extracted for 20 min. To 3 mL of the aqueous fraction was added 0.5 mL of concentrated ammonium hydroxide and 100 μL of chloroform. After vortexing and centrifuging, a portion of the chloroform fraction was analyzed by gas chromatography. A 12 m HP Ultra 2 column was used; oven program: 150°C for 0.5 min, 10°C/min up to 200°C, 5°C/min to 240°C, 20°C/min to 280°C, and a hold at 280°C for 1 min. Standards were prepared by adding imipramine and desipramine into outdated blood bank blood. The identity of imipramine and desipramine in the case blood was confirmed by analyzing a portion of the final chloroform fraction by GCMS and comparing the mass spectrum of each peak to reference spectra.

Case #2

Blood or other sample (2 mL), to which 2 μg each of methadone and maprotiline were added as internal standards, was made alkaline with 2 mL pH 12 borate buffer (saturated sodium tetra borate solution adjusted to pH 12 with sodium hydroxide pellets) and extracted with 8 mL 1-chlorobutane for 10 min. After centrifugation, the organic layer was transferred to a second tube and back-extracted with 3 mL sulfuric acid (0.1 M). The upper organic layer was aspirated to waste and the acid layer mixed with 0.5 mL sodium hydroxide (2 M). The basic solution was extracted with 3 mL 1-chlorobutane for 10 min, centrifuged, the organic layer was removed and concentrated to 100 μL. The organic extract was analyzed by gas chromatography using a NP detector. A 10 m by 0.32 mm Rtx-5 column was used for the separations; oven program: 160°C for 0.5 min, 20°C/min up to 280°C, and a hold at 280°C for 3 min. Standards were prepared by adding imipramine and desipramine into outdated blood bank blood. Drug identities in the case blood were confirmed by GCMS analysis and comparison to reference spectra.

Results and Discussion

The analytical results are summarized in Tables 1 and 2. Clinically, optimal imipramine plus desipramine plasma concentrations for the treatment of major depressive disorders are usually in the range 0.125 to 0.25 mg/L. As the total tricyclic antidepressant (TCA) plasma levels increase above this range, and particularly above 0.45 mg/L, there is an increased risk of side effects. Plasma concentrations of about 1 mg/L or higher are predictive of potentially serious CNS and cardiac toxicity (6). However, it is also now well established that blood (and serum or plasma) concentrations of TCAs typically increase 2–8 fold after death. Concentrations tend to increase with increasing postmortem interval. The magnitude of increase, compared with the perimortem levels, tends to be

TABLE 1—*Summary of toxicology results from Case #1 (seven-year-old boy).*

Sample	Imipramine	Desipramine
R. femoral blood	1.2 mg/L	9.9 mg/L
L. femoral blood	0.5 mg/L	6.7 mg/L
Aorta blood	1.0 mg/L	8.7 mg/L
Liver	68 mg/Kg	400 mg/Kg
Gastric	0.3 mg,total	2.8 mg,total

TABLE 2—*Summary of toxicology results from Case #2 (twenty-one-year-old female).**

Sample	Imipramine	Desipramine	Chlorpromazine
Femoral blood	0.6 mg/L	3.74 mg/L	0.92 mg/L
Liver	37 mg/Kg	261 mg/Kg	111 mg/Kg
Gastric	0.07 mg, total	–	0.11 mg, total

*Small amounts of diphenhydramine and lidocaine were also detected, but were not quantitated.

greater in central blood (e.g., pulmonary, cardiac, hepatic) than in peripheral blood (e.g., femoral) (10,11). For most of the TCAs, postmortem blood concentrations greater than 1.5–2.0 mg/L are suggestive of potentially toxic levels at the time of death. However, because of differences in the site of collection, the postmortem interval, dosage, and individual tolerance, there is a great deal of overlap between the so-called therapeutic and toxic ranges. The determination of liver TCA concentrations can greatly assist interpretation in the vast majority of cases (8–11).

In both our cases, the medical examiners determined the cause of death to be imipramine/desipramine toxicity on the basis of the high tricyclic antidepressant concentrations found in both the blood and liver, the absence of significant anatomical findings and the circumstances surrounding the deaths. Certainly, the sum of the blood imipramine and desipramine concentrations in these cases is similar to that found in other deaths attributed to tricyclic antidepressants, as are the liver total tricyclic concentrations (8–13).

The manner of death in both instances was ruled as accidental. There was no evidence of acute overdosage or chronic abuse. The authors recognize that suicidal intent is sometimes very difficult to rule out absolutely. However, there was no evidence to suggest suicide in either of the two cases. The very low ratios of parent drug to desmethyl metabolite strongly indicated the chronic accumulation of both imipramine and desipramine, but particularly the latter. The relatively small amounts of imipramine recovered from the gastric contents in both cases is consistent with this conclusion. In blood from Case #1, the ratio of imipramine to desipramine ranged from 0.09 to 0.12; the ratio for Case #2 was 0.16. Similar ratios were observed for the livers (0.17 and 0.14, respectively). Bailey et al. (14) found an average imipramine to desipramine ratio of 12.9 in blood from 11 patients that survived acute overdoses of imipramine. Baselt and Cravey summarized the results of four cases of death from acute overdose of imipramine, which had an average blood imipramine to desipramine ratio of 2.6 (13). Jones and Pounder found the imipramine to desipramine ratios greater than 1.0 in blood drawn from ten different sites in a single case involving imipramine overdosage (11). In neither of our cases was desipramine itself ever prescribed to the individuals, nor to the best of our knowledge, anyone else in the respective households. In Case #2, retrospective review suggests there was clinical evidence of probable TCA toxicity, manifested as anticholinergic effects, prior to death. Dry salivary glands was a sufficiently serious problem for prescribing a sialogogue, a saliva stimulator. This young woman had also been seen by a urologist in the weeks prior to her death for the treatment of urinary retention.

In order to propose an explanation for the accumulation of imipramine and desipramine in these patients, it is necessary to understand the metabolism and clearance of the drugs. Imipramine is primarily metabolized by oxidative demethylation to desipramine and by hydroxylation at the 2-position, and to a lesser extent at the 10-position. These processes occur predominantly in the liver. The majority of oxidative metabolic process are mediated by cytochrome P450, now known to be a complex mixture of several isozymes. Cytochrome P450 2D6 (CYP2D6; previously called P450IID6, P450IID1, or P450db1) is the isozyme primarily responsible for the 2-hydroxylation of imipramine and desipramine (15–18). There is evidence that CYP2D6 is capable of some N-demethylation activity also, however, a major portion of the N-demethylation of imipramine to desipramine is mediated through other isozymes which have been identified as CYP2C8, CYP1A2, CYP3A4, and $CYP2C_{MP}$ (17–21).

There is a genetic diversity for most isozymes, but particularly for CYP2D6. Those people who are deficient in, or who have substantially reduced amounts of CYP2D6, are termed poor metabolizers (PM) and those with normal or above average amounts of the isozyme are termed extensive metabolizers (EM). The PM polymorphism is found in 5–10% of Caucasians, with different proportions in other racial groups (22). Individuals who are PMs will tend to have higher than average levels of imipramine and much higher concentrations of desipramine (23). In the PM the hydroxylation of both imipramine and desipramine will be impaired, but N-demethylation of both imipramine and desipramine will still occur because it is predominantly mediated by different isozymes. This will lead to a high ratio of metabolite to parent drug. One study of imipramine pharmacokinetics (24) found that two PM individuals had, on average, slightly higher blood imipramine concentrations and much higher desipramine concentrations than EM individuals when all were treated with 100 mg of imipramine/day. The concentration of imipramine plus desipramine was 0.43 and 0.54 mg/L for the two PMs and averaged 0.103 mg/L (range 0.023–0.392) in the 28 EMs. The imipramine to desipramine ratios in the two PMs were 0.17 and 0.40 whereas the mean and range for the 28 EMs was 0.58 (0.14–2.0).

However, it is also known that some drugs, including many phenothiazines and some other neuroleptics, can reversibly convert an EM to a PM. Lennard (25) summarized several studies showing that phenothiazines are potent inhibitors of debrisoquine or sparteine oxidation by CYP2D6. Spina (26) reported that four of eight healthy subjects with EM phenotype for CYP2D6 were transformed to apparent PM phenotype by treatment with 50 mg/day of thioridazine. Although this has mainly been demonstrated for other TCAs, it is almost certain to occur with imipramine, because CYP2D6 is a major pathway for the metabolism of both imipramine and desipramine, and the phenothiazines are known to inhibit that pathway. For example, thioridazine is known to inhibit the 2-hydroxylation of desipramine (27). Although not a tricyclic antidepressant or phenothiazine, fluoxetine is a very potent inhibitor of CYP2D6, as are the other selective serotonin reuptake inhibitors (SSRIs), and can markedly affect the metabolism of TCAs (28,29).

It is known that in Case #1, thioridazine was prescribed at a dosage of 75 mg/day. The drug was not detected by the organic base extraction method which has a limit of detection of approximately 1.2 mg/L. Most patients on chronic therapy would be expected to have plasma thioridazine concentrations below this level (30,31). Thioridazine is known to be a potent inhibitor of CYP2D6 at a dosage of 50 mg/day in adults (26,27,32). Chlorpromazine is a weaker inhibitor of CYP2D6 than is thioridazine (33), and has been shown to impair the metabolism of nortriptyline (34). In Case #2, the relatively high dose prescribed (900 mg/day) and the high concentrations attained would have compensated for the less potent inhibitory effect. It is also known that some TCAs can themselves competitively inhibit CYP2D6, which will in turn inhibit the metabolism of some of the phenothiazines. Concentrations of phenothiazine neuroleptics are notoriously difficult to interpret, not so much because of possible postmortem changes, but because of the enormous range of dosages prescribed, their complex, extensive and variable metabolism, the varied response of different patients, and severity of the psychosis being treated (35). However, in Case #2, both the blood and liver concentrations are very high, even considering a dose of 900 mg/day. Inhibition of chlorpromazine metabolism by the high imipramine and desipramine levels and/or due to a genetic PM polymorphism are possible explanations for the accumulation of the chlorpromazine.

Postmortem redistribution must be considered in any case in which high TCA concentrations are found. It has been suggested that postmortem heart blood parent TCA concentrations greater than 1.0 mg/L (1000 ng/mL) are indicative of acute overdosage, and that the measurement of tissue drug concentrations are not required (12,36). However, the cases presented here suggest that this assumption is not warranted. Hanzlick's (12) cases were suicides and therefore acute overdose ingestions in which the parent drug was probably present at higher concentrations than the metabolite. In our two cases, the parent drug concentration in the blood is not particularly high but the metabolite is markedly higher, consistent with accumulation of the metabolite under chronic dosing conditions. Therefore, blood TCA concentrations should be interpreted with care. At the very least, a detailed case history should be examined before such determinations are made; the analysis of at least one tissue sample in addition to blood is also highly advisable. A discussion of this issue has recently been made by Popper and Elliott (37). It is worth emphasizing that in both our cases, peripheral blood which is less subject to postmortem redistribution was examined; the TCA (imipramine plus desipramine) blood concentrations were 7.2–11.1 mg/L and 4.34 mg/L, respectively. These concentrations are somewhat higher than would be expected in patients who had therapeutic concentrations of the drugs before death.

Because one of the subjects described in this paper is a child, it is appropriate to discuss recent reports of other desipramine related deaths in children. Popper and Zimnitzky (38) reported what they describe as the fifth case of sudden death putatively related to desipramine treatment in youth. However, in their case, the postmortem blood desipramine concentration was only 1.1 mg/L. Given that cardiac blood was sampled and that the postmortem interval was 38 h, the concentration could be regarded as well within the range expected from the reported therapeutic dosage of 300 mg per day. Although a cardiac abnormality was identified at autopsy and suspected as a possible underlying cause of death, no clear anatomic cause of death was determined. In the three other cases referred to (39,40), the desipramine serum or blood concentrations were either clearly therapeutic or were not determined. Therefore, the high blood desipramine concentrations in our pediatric case set it apart from these other cases.

Conclusions

Tricyclic antidepressants concentrations in postmortem blood must be interpreted cautiously, especially in the absence of an explicit suicide note. It is highly recommended that at least one tissue sample is analyzed in addition to blood, whether or not the blood is obtained from a peripheral site. Where a large (e.g., 20–60 mL) volume of blood is skillfully drawn from a femoral vein, it is likely that at least some of the blood will be drawn down from the iliac vein and inferior vena cava, increasing the likelihood of contribution from postmortem redistribution from the major organs. Where feasible, the major desalkyl metabolite of the tricyclic antidepressant should always be measured and the parent to metabolite ratio noted. Although this can be performed in the absence of liver or other tissue, the level of confidence is increased if tissue values are available, particularly if the postmortem blood concentrations lie in the grey zone between those which are clearly therapeutic and those which are clearly consistent with an overdose. Although the parent to desalkyl metabolite ratio will vary considerably from case to case (and even somewhat from site to site in the same body), very low parent to metabolite ratios invariably do not support a conclusion of acute overdosage. Although the coprescription of tricyclic antidepressants and phenothiazines is not necessarily contraindicated, some neuroleptics and other drugs are known to inhibit CYP2D6, may cause elevation of the parent drug(s) and metabolite; this effect is likely to be exaggerated if the person genetically has a PM phenotype. Finally, evaluation of the toxicology findings should not be made without as detailed a medical and circumstantial history as practical.

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