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Tramadol (Ultram®) Concentrations in Death Investigation and Impaired Driving Cases and Their Significance*

ABSTRACT: We reviewed a series of 66 deaths in Washington State between 1995–2000 in which tramadol (Ultram® and Ultracet®, Ortho-McNeil) was detected in the decedent's blood, in order to assess the role tramadol was determined to have played. Additionally, we reviewed a series of 83 impaired driving cases in which tramadol was detected in order to establish a non-lethal blood tramadol concentration reference range. In both populations, tramadol was consistently found together with other analgesic, muscle relaxant, and CNS depressant drugs. Death was rarely attributable to tramadol alone. However, tramadol may be a significant contributor to lethal intoxication when taken in excess with other drugs, via the potential interaction with serotonergic antidepressant medications, as well as the potential for increased CNS depression. Although the incidence of tramadol detection has increased consistently over the last eight years, there is no evidence of a corresponding increase in the number of cases in which death was attributed solely to tramadol. Blood drug concentrations in many deaths exceeded the therapeutic serum range of 0.28–0.61 mg/L (1); however, the concentrations overlapped almost completely with the range identified in living subjects arrested for impaired driving. These findings suggest caution in the interpretation of blood tramadol concentrations outside of the recognized therapeutic range. It also suggests that the drug, even when used in moderate excess, is not a principle cause of death in suicidal or accidental deaths.

KEYWORDS: forensic science, postmortem toxicology, tramadol, drug interaction, death, impaired driving

Tramadol (Ultram® and Ultracet®, Ortho-McNeil) is a centrally acting synthetic opioid-receptor agonist that gains an additional effect by inhibiting the re-uptake of serotonin and norepinephrine. Clinically, it is used to treat moderate to severe pain and has been used in the United States since 1995. It is the most widely sold opioid analgesic in the world and is registered and marketed in more than 100 countries (2). The drug may be administered orally, rectally, or parenterally (intravenous, intramuscular and subcutaneous); however, in the United States it is only available orally. The advantages of tramadol are that it is thought to have a lower abuse potential (3) and there is a reduced risk of respiratory depression when compared with other opiates (4). Side effects include dizziness, nausea, vomiting, headache, sweating, drowsiness, and seizures (4–6). Analgesia in humans begins approximately one hour after oral administration and reaches a peak around two hours (1).

We last reported on the incidence of tramadol and its significance in death investigations in 1997 (7). We concluded that tramadol is frequently taken in combination with other drugs, primarily other opiates and/or antidepressants, and identified potential drug interactions to which tramadol might be susceptible. In that study, we concluded that tramadol alone is not responsible for a large percentage of deaths. That report, however, was based on a limited number of cases (12 deaths and 4 impaired driving cases), and considered the cause and manner of death, but did not include a review of the autopsy report.

In this report, we have reviewed data from a total of 66 death investigation cases between 1995 to 2000 in which tramadol was detected in the blood of the decedent. The objective of this review was to consider the cause and manner of the death, the significance of blood concentrations of tramadol present, and the patterns of drugs frequently present with tramadol with respect to their potential for drug-drug interactions.

Methods—Analytical Toxicology

Blood samples submitted to the Washington State Toxicology Laboratory between 1995 and 2000 for analysis in death investigation and suspected drug impaired driving cases in the state of Washington were subjected to testing for alcohol and drugs including tramadol, using methods outlined below. When present, drugs (including tramadol) were quantified, and in half of the cases, its metabolites O-desmethyl and N-desmethyl tramadol were also quantitated.

For alcohol analysis, specimens (0.2 mL) were mixed with internal standard (2 mL of 0.15 mL n-propanol/1 L deionized water/10 g sodium chloride solution), and injected on a headspace GC with flame ionization detection (GCFID). The limit of detection for ethanol is 0.005 g/100 mL.

Samples were screened for drugs of abuse and several prescription drug classes, excluding tramadol, using an Enzyme Multiplied Immunoassay Technique (EMIT) assay. Blood specimens (1 mL)

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underwent protein precipitation with methanol (1 mL) and acetonitrile (5 mL) while vortex mixing. The samples were centrifuged and the supernatant was evaporated to 50 μL, then reconstituted to 350 μL with methanol/EMIT buffer (1:1). The EMIT procedure screens for cocaine metabolites (cutoff limit 0.15 mg/L), opiates (0.3 mg/L), amphetamines (0.5 mg/L), carboxy tetrahydrocannabinols (0.02 mg/L), methadone (0.3 mg/L), phencyclidine (0.025 mg/L), propoxyphene (0.3 mg/L), barbiturates (0.2 mg/L), benzodiazepines (0.2 mg/L) and tricyclic antidepressants (0.3 mg/L).

Samples testing positive for drugs on the EMIT were then confirmed by additional testing. Ethyl acetate and n-butylchloride extracts of specimens underwent separate screens for weak acid, neutral, and basic compounds using GC-MS.

To test and confirm basic compounds, sample (1 mL), internal standard (metycaine, 50 μL of a 10 mg/L solution in ethyl acetate), and pH 9 saturated potassium borate buffer (1 mL) were mixed, and then extracted with n-butyl chloride (3 mL). The organic layer was back extracted into 3 M hydrochloric acid (200 μL), which was then made alkaline with concentrated ammonium hydroxide and ammonium carbonate (100 μL of each) and re-extracted into chloroform (150 μL). A 2-μL aliquot of the chloroform fraction was then analyzed by gas chromatography with nitrogen/phosphorus detection (GCNPD) and gas chromatography/mass spectrometry (GCMS) (Hewlett Packard/Agilent). Basic drugs including tramadol, N-desmethyl tramadol, and O-desmethyl tramadol were identified by GCMS, and quantitated by GCNPD, using a multipoint calibration curve ($R^2 = 0.999$). The method has a limit of quantitation for tramadol of 0.01 mg/L.

Weakly acidic and neutral drugs were quantitated using gas chromatography with flame ionization detection (GCFID) and confirmed using GCMS. Sample (1 mL), XAD-2 resin (Supelco) (1 g), distilled water (5 mL) and internal standard (50 μL cyclopentobarbital) were mixed and the blood and water mixture was removed (8). Ethyl acetate (6 mL) was then added, mixed, and transferred to a fresh tube. The ethyl acetate was evaporated and reconstituted with acetonitrile (75 μL) and heptane (500 μL), mixed, and the heptane was discarded and the acetonitrile layer injected into the GCFID/GCMS for analysis (9). The limits of quantitation are as follows: ibuprofen (25 mg/L), acetaminophen (10 mg/L), butalbital (1 mg/L), meprobamate (2 mg/L), carisoprodol (1 mg/L), phenobarbital (1 mg/L), carbamazepine (1 mg/L), and phenytoin (2 mg/L).

Methods—Data Collection

Data from all death investigation cases that had tested positive for tramadol between 1995 and 2000, and impaired driving cases testing positive were tabulated. Fields examined included name, date of receipt, county, age, gender, and drug and alcohol test results. In total, tramadol was detected in 75 death investigation cases. From 1995–2002, tramadol was detected in 83 drivers. A copy of the Vital Registration System-annual statistical data from the Washington State Department of Health (DOH) was obtained for the death investigation cases. These records contained details surrounding individual deaths, including the underlying and contributory causes of death. The DOH data were merged with the quantitative toxicology data from the laboratory records based on subject name, county of death and date of death.

Cause of death data was translated from the International Classification of Diseases codes, ninth and tenth revisions (ICD-9 and -10), (National Center for Health Statistics, Centers for Disease Control, US Department of Health and Social Services) provided by DOH. Additionally, death certificates and autopsy findings from medical examiners and coroners were matched with the cases and reviewed to determine the contribution of tramadol and other drugs to the individual's death. The cases were reviewed and where appropriate, reclassified by us based on the available investigative, autopsy, and toxicological data. Cases were excluded because of the absence of the death certificate ($n = 3$), autopsy information ($n = 1$), or in which no autopsy was conducted ($n = 5$), leaving 66 cases. Our classification system was as follows: Deaths were assigned as non-drug caused, including natural deaths and deaths due to unnatural causes other than drugs, such as trauma, falls, or gunshots ($n = 20$), or they were assigned as drug caused deaths ($n = 46$). The latter category was subdivided as cases in which the tramadol was an incidental finding in a drug caused death ($n = 15$), a contributory cause of death ($n = 27$), or the primary cause of death ($n = 4$).

Results

We observed an increase in the incidence of tramadol detection in both death investigation and impaired driving cases between 1995 and 2002. In 1995, there were five death investigation cases sent to the laboratory that tested positive for tramadol, and in 2002, there were 24 cases testing positive—a five-fold increase. With respect to driving cases, in 1995, one case tested positive for tramadol, while in 2002, 30 cases did.

The majority of death investigation cases were classified as a drug caused death (Table 1). Within this category, tramadol had a contributory role in more than half, meaning that in most drug overdose cases, death could not be attributed to a single drug; rather, it was the combination of multiple drugs that caused the death. With the exception of a single natural death, all cases tested positive for at least one other drug (excluding nicotine and caffeine) (Table 2).

Death Investigation

Non-Drug Caused—There were 20 death investigation cases where the individuals died from natural causes, accidents, or non-drug suicides (Table 3). In cases where death was not attributed to a drug overdose, cardiovascular disease was the most common cause

TABLE 1—*Concentrations of tramadol (mg/L) and number of other drugs detected.*

Cause of Death	*n*	Mean	StDev	Median	Range	Number of Other Drugs		
						Mean	Median	Range
Drug Caused								
Primary	4	6.90	5.33	6.06	1.6–13.9	3.75	3	1–8
Contributory	27	3.50	5.52	1.12	0.27–22.2	3.48	3	1–6
Incidental	15	0.20	0.19	0.11	<0.05–0.68	4.20	4	1–8
NonDrug Caused								
Drug Related	7	1.37	0.92	1.00	0.61–2.95	2.86	3	1–6
Natural	13	0.64	0.72	0.25	<0.05–2.47	2.31	2	0–6

TABLE 2—*Drugs most frequently found in combination with tramadol.*

Drug	# of Drivers	% of Drivers	# of Deaths	% of Deaths	Drug Caused		
					Incidental	Contributory	Primary
Morphine	1	1.72	18	27.69	7	8	0
Nortriptyline	3	5.17	16	24.62	2	10	1
Amitriptyline	3	5.17	15	23.08	2	9	1
Nordiazepam	11	18.97	12	18.46	3	4	1
Trazodone	4	6.90	10	15.38	1	2	2
Acetaminophen	10	17.24	9	13.85	0	3	0
Carisoprodol	12	20.69	8	12.31	4	1	1
Meprobamate	17	29.31	7	10.77	4	1	1
Propoxyphene	3	15.17	7	10.77	2	4	0
Alprazolam	6	10.34	7	10.77	2	5	0
Hydrocodone	11	18.97	5	7.69	0	2	0
Diazepam	9	15.52	6	9.23	1	3	0

TABLE 3—*Manner of death in cases with tramadol present but attributed to causes other than drug intoxication.*

Non-drug Caused Deaths ($n = 24$)			Tramadol Concentrations (mg/L)		
	# of cases	% of total	Mean	Median	Range
Accidental	5	25.0	1.24	0.76	0.61–2.95
Natural	15	65.0	0.64	0.25	<0.05–2.47
Suicide	2	10.0	1.70	1.70	1–2.40
Undetermined	0	0.0	0.00	0.00	0
Homicide	0	0.0	0.00	0.00	0

of death (nine cases), followed by motor vehicle accidents (four cases), and trauma (two cases). The concentrations of tramadol in this group ranged from <0.05 to 2.95 mg/L (mean 0.78, median 0.70). Although the concentration in half of the cases exceeded the recognized therapeutic range of 0.28–0.61 mg/L, there were clear causes of death in these cases not related to the subjects' drug ingestion. Additionally, as is discussed later, there were drivers who were able to survive at concentrations well in excess of the therapeutic range.

Drug Caused–Tramadol Incidental—There were 15 drug caused deaths in which the tramadol was determined to be an incidental finding. Tramadol concentrations ranged from <0.05–0.68 mg/L (mean = 0.20 mg/L median = 0.11 mg/L). In 12 cases, the tramadol concentrations were less than 0.28 mg/L, considered the lower end of the therapeutic range, and were considered to be non-contributory or incidental findings. In three additional cases, the tramadol concentrations were within or slightly above the therapeutic range of 0.28–0.61 mg/L, but there were abundant concentrations of other drugs that readily accounted for death.

Drug Caused–Tramadol Contributory—A second group of cases ($n = 27$) were those in which the tramadol concentration was within or above the therapeutic range but was determined to have contributed to the death because death could not be readily accounted for by the other drugs present alone, or by an anatomical cause. Likewise, the other drugs in these cases could not definitively have accounted for death without considering the tramadol. The tramadol concentration in this group ranged from 0.27–22.2 mg/L (mean 3.50 mg/L, median 1.12 mg/L). The other drugs frequently encountered in combination included amitriptyline and its metabolite nortriptyline, morphine, and alprazolam (Table 2). This group did contain some cases with very elevated tramadol concentrations and it is likely (based on the third group discussed below) that even without the other drugs present, the deaths would have occurred; however, a contributory role for the other agents could not be discounted due to their elevated concentrations.

In cases where tramadol appears to be within the therapeutic range, or where other drug concentrations are elevated, it is important to look at potential drug interactions. One such interaction is through interaction with the neurotransmitter serotonin (5-hydroxytryptamine, 5-HT). Tramadol increases the level of synaptic serotonin by inhibiting its reuptake. If taken with other drugs that also increase serotonin levels, an individual would be at risk for developing Serotonin Syndrome (SS). The most current diagnostic criteria require three of the following symptoms: agitation, mental status changes (confusion, hypomania), myoclonus, shivering, tremor, hyperreflexia, ataxia, diarrhea or fever. If not properly diagnosed, it can lead to life-threatening complications or death (10). Drugs frequently associated with Serotonin Syndrome include tricyclic antidepressants (TCAs) such as amitriptyline, desipramine, and doxylamine, and drugs with serotonin reuptake blocking ability, such as mirtazepine, venlafaxine, and the selective serotonin reuptake inhibitors (SSRIs) fluoxetine, sertraline and paroxetine. Table 2 illustrates that tramadol is often found combined with drugs that increase serotonergic activity, primarily amitriptyline (nine cases) with its metabolite nortriptyline (ten cases), and trazadone (two cases). This interaction may contribute to the overall toxicity when multiple drugs with a common effect are present.

A second potential for interaction is through metabolic inhibition. Tramadol is primarily metabolized by the CYP2D6 isoenzyme to O-desmethyl tramadol and N-desmethyl tramadol. It was noted that tramadol is often found in combination with drugs that can inhibit the metabolic action of the 2D6 enzyme. Cocaine and methadone are strong inhibitors of 2D6 metabolism and propoxyphene, sertraline, and amitriptlyine are weak inhibitors. Table 2 shows propoxyphene and amitriptyline among those drugs frequently taken in combination with tramadol, which could contribute to elevated tramadol in some cases. There were two drug-caused deaths in which tramadol was a contributory cause of death and methadone was present. The concentrations of tramadol in these cases were 0.76 mg/L (O- and N-desmethyl tramadol not quantitated) and 0.51 mg/L (O-desmethyl tramadol 0.45 mg/L and N-desmethyl tramadol 1.96 mg/L). However, there were no cases reviewed in which a metabolic interaction had to be invoked to account for the toxicity.

The final mechanism for interaction is through concerted action with other drugs having CNS depressant properties. All of the drugs listed in Table 2, with the exception of acetaminophen, cause CNS depression. This is the most likely contributory interaction for tramadol in those cases characterized as drug caused.

Drug Caused–Tramadol Primary—The third group of drug-caused death cases comprised those in which tramadol was present in concentrations above the therapeutic range, and in which there was no other evident anatomic or toxicological cause of death. Other drugs present were at therapeutic or sub-therapeutic concentrations. There were four cases in which tramadol was determined to be the primary cause of death. The cases had tramadol concentrations of 1.6, 4.21, 7.9, and 13.9 mg/L. This group is the most significant in terms of assessing the toxicity or potential lethality of monointoxications involving tramadol and are discussed below:

Case 1

This 43-year-old male had a history of mental illness and was unemployed due to a back injury. He reportedly had complaints of back pain and was taking medications and drinking alcohol. An acquaintance reported locking medications in a car to prevent him from taking too much, but did not have control of the lorazepam prescription, which he was taking frequently during the day and "chasing" it with alcohol. The decedent was last seen alive early in the evening, when he said he was going to lie down for a while. He staggered into a bedroom and fell asleep. He was found unresponsive 2 h later, lying on a day bed. CPR was begun, but he was later pronounced dead at the scene. The decedent was reported to have previously told the acquaintance that he "would be better off if he just took an overdose of his medications and was dead." Autopsy found pulmonary edema, fatty liver, cardiomegaly, and mild atherosclerosis. In the absence of any obvious anatomical cause of death, the death was certified as a poisoning (tramadol 1.60 mg/L, O-desmethyl tramadol 0.44 mg/L, N-desmethyl tramadol 0.09 mg/L, lorazepam 0.04 mg/L, atropine). Here we see an elevated level of tramadol and a therapeutic level of lorazepam. We are unaware of any interactions between tramadol and lorazepam, other than lorazepam would contribute to the CNS depression this subject would have experienced from the tramadol. The staggering and drowsiness reported by the acquaintance are consistent with this. The witness had also reported that the decedent was consuming alcohol, yet none was detected in his blood. A possible explanation is that there was a significant time period between which the drugs and alcohol were consumed and when the death actually occurred.

Case 2

This case was reported as the death of a 37-year-old female who was found dead in bed. She had a history of ethanol and drug abuse and of depression. She was known to "take pills by the hand full". Autopsy found no anatomic cause of death, and the death was certified as a poisoning (tramadol 4.21 mg/L, O-desmethyl tramadol 0.56 mg/L, N-desmethyl tramadol 0.79 mg/L, oxycodone 0.2 mg/L trazodone 0.3 mg/L, mirtazepine <0.05 mg/L, meprobamate <2.5 mg/L, carisiprodol <2.5 mg/L, nordiazepam <0.05 mg/L, clonazepam <0.05 mg/L, hydroxyzine 0.33 mg/L, benzoylecgonine <0.05 mg/L). There are clearly many drugs present here, and they are all at or below therapeutic concentrations with the exception of tramadol, oxycodone, and hydroxyzine. However, there are no reports of death attributed to oxycodone or hydroxyzine with levels similar to what was found here. Therefore, we can conclude that this individual would have survived, had the tramadol not been present. All of the drugs present (with the exception of the inactive cocaine metabolite, benzoylecgonine) would have caused additional CNS depression. Hydroxyzine is the only drug capable of inhibiting the metabolism of tramadol; however, the inhibition is weak, and was not significant in this case because of the presence of the tramadol metabolites. The trazodone and mirtazepine could have caused serotonin like symptoms, contributing to her death.

Case 3

This death investigation case is that of a 28-year-old man found dead in bed. He was prescribed pain medications for back pain and anti-depressants because he was bi-polar. Autopsy failed to find a cause of death. After the toxicology report came back, his death was certified as a "prescription drug overdose from the ingestion of tramadol" (tramadol 7.9 mg/L, O-desmethyltramadol 3.1 mg/L, N-desmethyltramadol 1.3 mg/L, venlafaxine 0.23 mg/L, O-desmethyvenlafaxine 0.14 mg/L, trazodone 0.08 mg/L, mirtazepine <0.05 mg/L, ethanol 0.02 g/100 mL, caffeine). In this case, tramadol was significantly elevated above the recommended therapeutic dosage. While venlafaxine is present, and it is known to inhibit weakly the metabolism of tramadol, it is unlikely that it would account for such a high level, especially because the tramadol metabolites are present. Finally, this individual was also taking mirtazapine, which could potentially have contributed to elevated serotonin from the tramadol and venlafaxine. The mirtazapine also would have caused additional CNS depression.

Case 4

This 43-year-old male was found in his backyard, having appeared to collapse while working on his vehicle. He was dead on arrival at the hospital from what was thought to be a cardiac arrest. The autopsy revealed dilated cardiomyopathy; however, the death was certified as an accidental poisoning (tramadol 13.9 mg/L, O-desmethyl tramadol 0.50 mg/L, N-desmethyl tramadol 9.7 mg/L, amitriptyline 0.50 mg/L, nortriptyline 0.85 mg/L, caffeine). The tramadol concentration in this case is extremely high. Again, it is known that certain drugs, such as amitriptyline can inhibit tramadol metabolism. However, because the metabolites are present, it can be assumed that this individual was not having difficulty metabolizing the drug. It is more likely that he took a quantity that exceeded the recommended dosage. However, the amitriptyline would have caused an additional increase in the levels of synaptic serotonin and would have also caused additional CNS depression.

Impaired Drivers

Between 1995 and 2002, tramadol was detected in blood from impaired drivers in Washington State in 83 cases; however, it should be noted that drivers were preliminarily tested for alcohol and if the concentration exceeded 0.09 g/100 mL, no drug testing was performed. The number of cases annually testing positive for tramadol was typically between 5 and 12, although in 2002 there were 30 cases. We have been unable to find information on the extent of local changes in prescriptions of the drug to assess to what extent it follows this observed trend. The median concentration of tramadol in blood from these drivers was 0.16 mg/L (mean 0.39 mg/L), and concentrations ranged between 0.01 mg/L (LOD) and 5.36 mg/L. The difference between the mean and median reflects a tendency for the concentrations to be skewed towards the lower, therapeutic end. Fifty percent of the drivers were male and the average age was 41.2 years for both genders. The youngest driver was 25 and the oldest, 60. Limited information on the driving behaviors involved and concentrations of other drugs present were assessed in 57 of these cases.

The blood drug concentrations in this group provide a useful reference population for comparison with both normal therapeutic use, and with concentrations in fatalities. Other CNS acting drugs were present together with tramadol in all but 6 of the 57 cases. The drugs most frequently encountered were meprobamate, carisoprodol, hydrocodone, nordiazepam, acetaminophen, diazepam, venlafaxine, alprazolam, desmethylvenlafaxine, norpropoxyphene, and marijuana metabolite. With the exception of acetaminophen, and venlafaxine and its metabolite, all these compounds have known CNS impairing effects, which at sufficient doses would be expected to impair the faculties necessary for safe driving.

The fact that tramadol was present in combination with other drugs in almost all cases makes it difficult to assess the specific contribution of the tramadol to the evident impairment that led to these subjects being arrested. A review of the cases revealed that in instances in which tramadol was present at lower concentrations, there were typically other drugs present in sufficient quantities to account for the impairment. The case with the lowest concentration in which tramadol appeared to be the principle causative agent was an incident where a vehicle crossed the center line and impacted an oncoming vehicle. In that case, the tramadol concentration was 0.19 mg/L, below the normal therapeutic range, and the subject had a low but positive blood alcohol concentration (0.02 g/100 mL). Certainly, other factors not related to drug use could have contributed to that accident; however, no other drugs were present. The next case where tramadol apparently played a significant contributing role had a concentration of 0.22 mg/L, combined with a 0.03 g/100 mL alcohol. That subject was displaying marked weaving, and subsequently performed poorly on field sobriety tests.

The third case involved a subject with no other drug or alcohol present, but a blood tramadol concentration of 0.67 mg/L. This is considered to be approximately the upper end of the therapeutic range. That driver made a wide turn entering the lane of oncoming traffic, and also performed poorly on field sobriety tests.

Two cases with tramadol concentrations of 1.78, and 2.43 mg/L both had 0.05 mg/L of alprazolam present. This benzodiazepine is used for anxiety, and the concentrations are within the accepted therapeutic range; however, even these concentrations could have significant CNS depressant effects in naive users. The drivers in each case were involved in a rear end collision, and another unspecified collision, respectively. The remaining two cases had tramadol concentrations of 1.32, and 5.36 mg/L. Driving behaviors in these cases were a two car hit-and-run accident, and in the case with the highest concentration, the driver simply drove his vehicle off the road, striking a fixed object.

The concentrations in the four latter cases are informative since they are considerably in excess of the expected average therapeutic concentration of 0.70 mg/L normally achieved after ingestion of two 50 mg doses (1), or 400 mg/day divided dose reported by the manufacturer (Ortho-McNeil).

In chronic trials of tramadol (dose unspecified) there was a persistent increase in reported side effects with duration of use (11). Thirty-three percent of subjects reported dizziness or vertigo at 90 days use compared to 26% at 7 days, similarly somnolence in 25% of patients at 90 days compared with 16% at 7 days. Together with other effects such as nausea, vomiting, headache, and CNS stimulation with frequencies of between 7 and 40%, it is clear that this drug has a complex and significant side effect profile (11). Based on our results, it is not possible to relate a minimum concentration at which a subject will predictably be impaired; however, driving after excessive dosing, shortly after beginning a course of therapy with the drug, or when combining it with other CNS depressant medications clearly will all generate increased risks for driving impairment.

Conclusions

In nearly all of our cases, tramadol was present with at least one other drug. We had four cases where death was attributed exclusively to tramadol, but in all of these cases, tramadol was present with other drugs. With the exception of the 13.9 mg/L finding, our cases where death was attributed exclusively to tramadol were below the reported concentrations of 9.6 and 15.1 mg/L in fatalities where tramadol was the only drug detected (12,13). There were also other cases where tramadol was clearly the underlying cause of death but the other drugs present were contributory to death. We know that it is possible to survive at concentrations well in excess of the therapeutic levels, as we saw in the individuals who died of natural or nondrug-related deaths, and as we saw in our drivers. Finally, we do know that there is a potential for drug interaction on three different levels. There are drugs that increase in serotonergic activity, inhibition of the metabolism of tramadol, and there are drugs that would cause additional CNS depression. Therefore, when certifying deaths where tramadol is present, drug interactions should be carefully considered.

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