Identification of Tramadol and its Metabolites in Blood from Drug-Related Deaths and Drug-Impaired Drivers

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Abstract

Tramadol is a centrally acting, binary analgesic that is neither an opiate-derived nor a nonsteroidal anti-inflammatory drug and that was approved for use in the United States in 1995. It is used to control moderate pain in chronic pain settings such as osteoarthritis and postoperative cases. Used in therapy as a racemic mixture, the (+)-enantiomer weakly binds to the μ-opioid receptor, and both enantiomers inhibit serotonin and norepinephrine reuptake. Tramadol's major active metabolite, *O*-desmethyltramadol (ODT), shows higher affinity for the μ-opioid receptor and has twice the analgesic potency of the parent drug. The synergism of these effects contributes to tramadol's analgesic properties with the (+)-enantiomer exhibiting 10-fold higher analgesic activity than the (–)-enantiomer. Although tramadol was initially thought to exhibit low abuse potential, Ortho-McNeil, the drug's manufacturer, recently reported a large number of adverse events attributed to tramadol including abuse by opioid-dependent patients, allergic reactions, and seizures. The high number of adverse reactions has prompted the company to update the prescribing information for the drug. An analytical method using gas chromatography–mass spectrometry (GC–MS) without derivatization for the determination of tramadol and its metabolites is reported. An *n*-butyl chloride extraction is followed by GC–MS analysis using a 5% phenylmethylsilicone column (30 m × 0.32-μm i.d.). Analysis of 12 blood samples from tramadol-related deaths and four nonfatal intoxications involving tramadol revealed concentrations ranging from 0.03 to 22.59 mg/L for tramadol, from 0.02 to 1.84 mg/L for ODT, and from 0.01 to 2.08 mg/L for *N*-desmethyltramadol. Three deaths were clearly attributable to acute morphine toxicity, one was a doxepin overdose, and six were multiple drug overdoses. The role of tramadol in each death is explored.

Introduction

Tramadol (Ultram®, Ortho-McNeil) is a centrally acting, binary analgesic that has been available for use in Europe for several years, although it was only approved for use in the United States in 1995. It is neither an opiate-derived nor a nonsteroidal anti-inflammatory drug (1). It undergoes *N*- and *O*-demethylation to *N*-desmethyltramadol (NDT) and *O*-desmethyltramadol (ODT) (Figure 1) and is a racemic drug believed to possess two modes of action. Both enantiomers inhibit the reuptake of serotonin and norepinephrine; the (+)-enantiomer is more effective at inhibiting the reuptake of serotonin, whereas the (–)-enantiomer more strongly inhibits norepinephrine reuptake (2). The synergism of these effects contributes to tramadol's analgesic properties; the (+)-enantiomer has been shown to exhibit 10-fold higher analgesic activity than the (–)-enantiomer.

Tramadol was originally introduced in Germany in the late 1970s by Grünenthal (Stolberg, Germany) as a weak opioid with an atypical clinical profile (3). The manufacturer claimed that the typical opioid side effects such as respiratory depression or effects on smooth muscles could be lessened or avoided altogether if doses providing analgesic efficacy similar to that of meperidine were used. Because of the (+)-enantiomer's relatively low affinity for the μ-opioid receptor, tramadol was also originally thought to have a low potential for abuse, tolerance, and dependence in treatment up to six months in length (4). In fact, despite increasing clinical use, tramadol did not become popular as a drug of abuse until the early 1990s, and a study published in 1993 found no significant abuse reported with tramadol (5). In studies of physical dependence-producing capacity, tramadol failed to suppress or precipitate withdrawal in morphine-dependent mice, rats, and rhesus monkeys (3,6–8). However, one study found that tramadol produced mild withdrawal signs when given to morphine-dependent, nonwithdrawn rhesus monkeys (8). Other work showed that tramadol produced a mild degree of physical dependence after repeated administration to rats, mice, and rhesus monkeys as demonstrated by the exhibition of withdrawal signs following opioid antagonist administration and abrupt drug termination (3,7–9). This may be because tramadol's active metabolite, ODT, has up to 200 times higher affinity for the μ-opioid receptor and twice the analgesic potency of the parent drug.

Studies that suggest tramadol may have abuse potential

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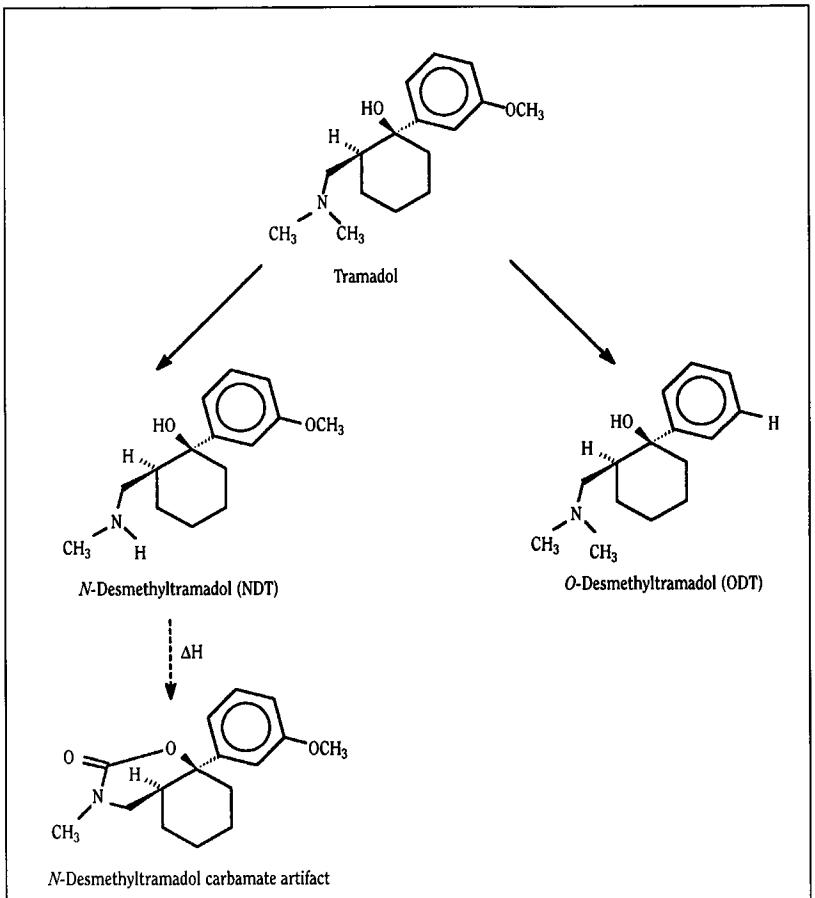

Figure 1. Structures of tramadol, NDT, and ODT.

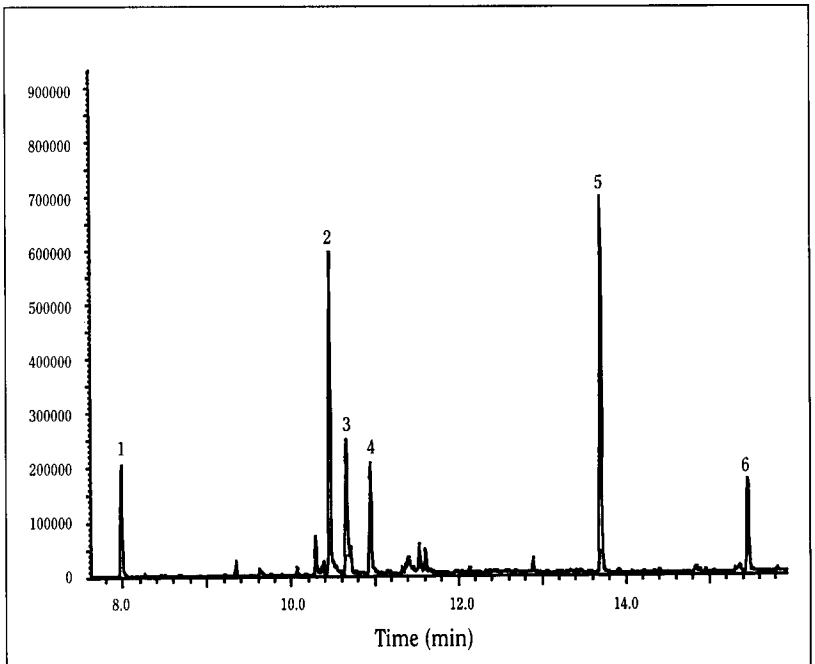

Figure 2. Gas chromatographic separation of tramadol, NDT, and ODT from the internal standards, papaverine and diphenylamine. Peak identification: 1, diphenylamine; 2, tramadol; 3, *N*-desmethyltramadol; 4, *O*-desmethyltramadol; 5, diisooctylphthalate; and 6, papaverine.

have been performed. In three self-administration studies in lefetamine-trained and drug-naive rhesus monkeys, tramadol maintained drug taking (8). Preston et al. (10) concluded that although the drug does appear to have some potential for abuse, a much larger dose of tramadol than morphine is required to produce subjective effects in patients in a study of the effects of tramadol in postaddicts to assist in its abuse potential assessment.

Ortho-McNeil's recent letter (11) to health care professionals across the U.S. provided new information regarding the potential for abuse, seizures, and anaphylactoid reactions associated with the use of tramadol. The large number of adverse events attributed to tramadol has prompted the company to update the prescribing information for Ultram. Specifically, the new product insert specifies that Ultram is contraindicated in patients with past or present histories of addiction to or dependence on opioids, those with allergies to Ultram or other opioids, and those taking concomitant medications that may reduce the seizure threshold, such as tricyclic antidepressants, other tricyclic compounds, and selective serotonin reuptake inhibitors (SSRIs).

It is important to consider tramadol's ability to inhibit serotonin reuptake when prescribing the drug for patients already taking drugs with serotonergic activity. It is possible that subjects stabilized on SSRIs or other antidepressants could be susceptible to developing serotonin toxicity upon starting tramadol therapy. In addition, it is highly probable that ODT, tramadol's active metabolite, plays a role in toxicity in which high concentrations of the metabolite are present because of either serotonin syndrome or tramadol toxicity. ODT has a higher affinity for the μ-opioid receptor and has twice the analgesic potency of tramadol.

Isoenzyme metabolism is also important to consider in tramadol-related fatalities. CYP2D6, the Cytochrome P-450 isoform for which many SSRIs and tricyclic antidepressants are substrates (12–14), has been shown to be responsible for the metabolism of tramadol to ODT. Consequently, competitive inhibition of 2D6 resulting in enzyme saturation and subsequent lengthened half-life and an increase in peak plasma concentration may occur in cases in which one or more substrates for this isoenzyme are present with tramadol. Such interactions can lead to toxic side effects that may play an important role in tramadol-related fatalities. There are no known inducers of 2D6.

Isolation methods for tramadol and its metabolites from blood and urine using gas

chromatography–mass spectrometry (GC–MS), GC with nitrogen-selective detection, and high-performance liquid chromatography (HPLC) were previously reported (15–19). However, all of the GC methods involved derivatization of all three compounds before analysis. We report analytical methods using GC–MS without derivatization for the determination of tramadol and its metabolites. This method was applied to cases of suspected drug-related deaths and drug-impaired driving.

Materials and Methods

Tramadol, NDT, and ODT were gifts from R.W. Johnston (Raritan, NJ). One of the internal standards, papaverine hydrochloride in GC-grade methanol, was obtained from Sigma (St. Louis, MO). All other reagents were analytical grade or better and were obtained from Fisher (Santa Clara, CA).

GC–MS was performed on a 5890/5970 GC–MS from Hewlett Packard (Palo Alto, CA) that was operated in full-scan mode. Chromatographic separation was achieved using a 5% phenylmethylsilicone column (30 m × 0.32-µm i.d., Econocap, Alltech, Deerfield, IL). Analyses were performed with the temperature programmed from 80 to 295°C at 15°C/min and held at the final temperature for 8 min.

Blood samples collected at autopsy during the investigation of 12 unrelated fatalities were each placed in separate 10-mL vials containing sodium fluoride and potassium oxalate (Vacutainer, Becton Dickinson, Franklin Lakes, NJ). The samples were refrigerated until analysis was performed. Most samples were peripheral blood, some were central blood, and some were not labeled as to collection site.

Liquid–liquid extractions were performed using a procedure based on that described by Foerster and co-workers (20,21) that was modified for general use in our laboratory for screening basic drugs. Blood (1 mL), internal standards (diphenylamine and papaverine, 100 µL of 1- and 0.5-mg/L solutions, respectively), and pH 9 saturated potassium borate buffer (1 mL) were mixed and extracted with *n*-butyl chloride (3 mL) after centrifuging at 2000 rpm for 5 min. The organic fraction was back extracted into 3M hydrochloric acid (200 µL), which was then basified with concentrated ammonium hydroxide and re-extracted into chloroform (100 µL). The chloroform fraction was then analyzed by GC–MS.

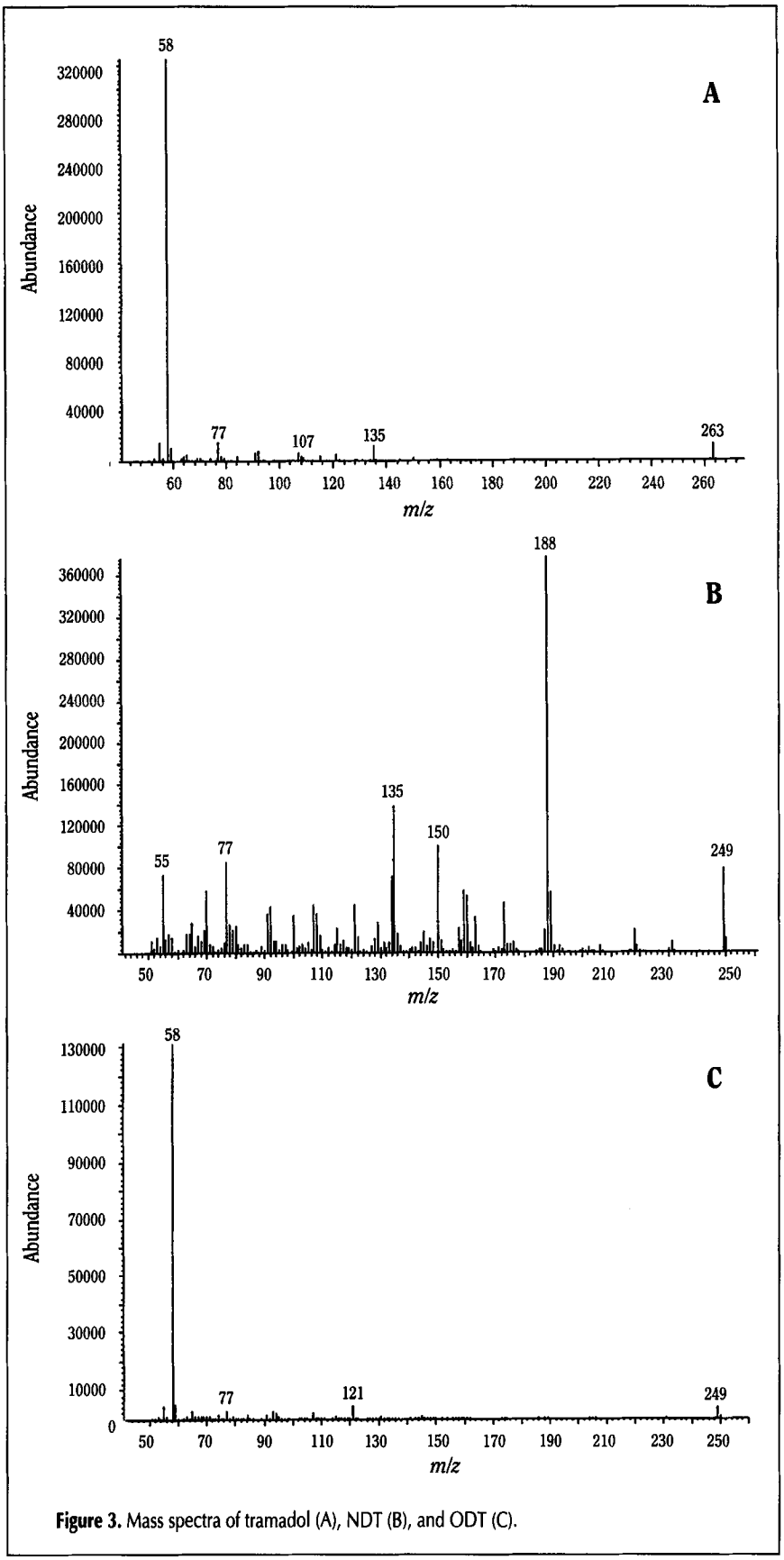

Figure 3. Mass spectra of tramadol (A), NDT (B), and ODT (C).

Results

As shown in Figure 2, tramadol, NDT, and ODT were resolved from both internal standards, papaverine and diphenylamine, in GC–MS analysis. The method was not susceptible to interference from other common therapeutic drugs. Mass spectra of the three analytes are shown in Figure 3. Periodically, variable amounts of an artifact of NDT appeared both in samples from patients and in quantitative standards with molecular ion *m/z* 261 (the molecular weight of NDT is 249). This was investigated by the drug's manufacturer (22), which conducted proton- and ^{13}C-nuclear magnetic resonance spectroscopy of the standard and concluded that the *m/z* 261 peak corresponds to a carbamate derivative of NDT, presumably formed in the injection port of the GC (Figure 4). The variable nature of this phenomenon might affect reliability of quantitative results from NDT. However, this should not affect interpretation because NDT is an inactive metabolite.

The GC–MS method was linear for tramadol and both metabolites over the range 0.01–10.00 mg/L with regression coefficients for tramadol, NDT, and ODT of 0.996, 0.993, and 0.990, respectively. For quantitation, *m/z* 58 was used for tramadol and ODT, and *m/z* 188 was used for NDT. The following qualifying ions were used for each compound: *m/z* 135 and 263 for tramadol, *m/z* 135 and 249 for NDT, and *m/z* 121 and 249 for ODT. Limits of detection (LOD) and quantitation (LOQ) were 0.01 and 0.02 mg/L, respectively, and were determined according to a method described by Jones and Schuberth (23). Replicate analyses of tramadol and metabolite standards at concentrations ranging from 0.01 to 10.00 mg/L were performed, and the average concentration and standard deviation determined from these results. Standard deviation was then plotted as a function of concentration, and the y-intercept was taken to be SD_0. To determine the LOD and LOQ for each compound, the equations $LOD = 3 \times SD_0$ and $LOQ = 8 \times SD_0$ were used. Tramadol and its metabolites are distinguished from all common basic therapeutic drugs, including antidepressants and analgesics, such as the tricyclics imipramine, desipramine, doxepin, nordoxepin, amitriptyline, and nortriptyline, and the SSRIs (24). Concentrations of tramadol, metabolites, and other drugs found in each case, as well as cause and manner of death, are shown in Table I.

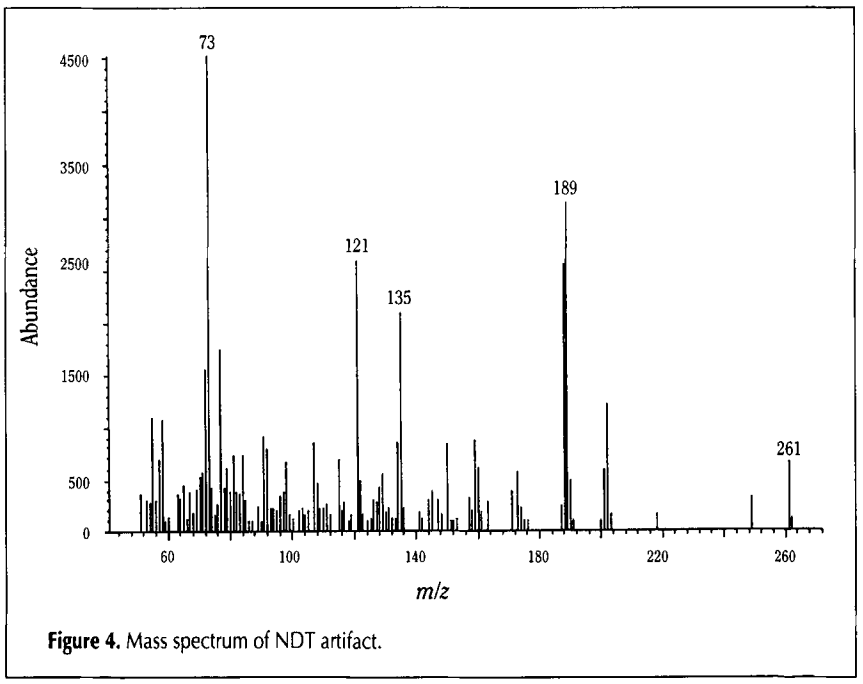

Figure 4. Mass spectrum of NDT artifact.

Discussion

In clinical trials, peak-plasma levels for tramadol and ODT, which were reached within 2 and 3 h of administration of a single 100-mg dose, were 0.306 + 0.078 and 0.055 + 0.020 µg/mL, respectively. Within 2 days of 100-mg Q.I.D. dosing, steady-state tramadol and ODT plasma levels (0.592 + 0.177 µg/mL) have been reported (1). Tramadol and ODT have half-lives of 6.3 and 7.4 h, respectively, and tramadol is 20% plasma bound. Sixty percent of the dose is excreted in urine as metabolites, and the rest is eliminated as unchanged drug. There has been only one tramadol-related fatality reported in the literature, although the extent to which tramadol contributed to the death is unclear as high concentrations of other drugs were present (25). In that case, the authors suspected the involvement of serotonin syndrome as a result of the moclobemide-clomipramine interaction as has been previously reported (26). The authors further suggested that tramadol could have had a synergistic effect on the serotonin syndrome because of its serotonin reuptake-inhibiting ability. Other fatalities involving tramadol have occurred (27), although the cases have not been published. The tramadol concentrations in these cases were 2.7 and 1.3 mg/L; however, metabolite concentrations were not measured, and it is unknown if other drugs were involved.

The presence of other drugs seems to be typical of cases involving tramadol. For example, three drug-impaired drivers, all of whom were found to have therapeutic levels of tramadol in their blood, and one who had elevated tramadol levels in her urine, also had other drugs present. Table II summarizes these cases.

As mentioned previously, tramadol is metabolized to ODT by CYP2D6, and, as such, its metabolism may be inhibited by the presence of other substrates, which may affect plasma levels of the parent drug. The presence of such drugs should therefore be taken into consideration in cases involving tramadol. The therapeutic effect of the drug might be increased or decreased by the presence of a 2D6 inhibitor, as both tramadol and ODT are pharmacologically active.

Consequently, it is important to consider ODT levels when interpreting tramadol levels. Comparing the levels of the parent drug and metabolite may provide information on whether the drug was chronically

Table I. Case Information on Subjects Testing Positive for Tramadol

Case	Age	Gender	T* (mg/L)	ODT (mg/L)	NDT (mg/L)	Alcohol (g/100mL)	Other drug use	Circumstances surrounding death	Cause of death	Manner of death
1	18	F	0.03	0.06	0.11	neg	carbon monoxide (< 5% sat) nicotine/cotinine	Subject was poorly nourished w/ below normal exercise, Hx of alcohol & drug abuse; became short of breath & collapsed after mild exertion, unable to be resuscitated	Sudden cardiac death from unknown etiology	Undetermined
2	41	M	0.08	0.07	0.03	0.02	morphine (0.18)	Hx of drug abuse, found dead by friend during camping trip; had ingested large quantities of alcohol, heroin, & pain medication	Acute intrvenous narcotism	Accidental
3	48	M	0.41	0.04	0.27	neg	morphine (0.14) propoxyphene (0.04) norpropoxyphene (0.23)	Hx of drug abuse, died suddenly & unexpectedly	Acute substance abuse	Undetermined
4	54	M	0.05	0.04	0.01	0.06	morphine (0.275) codeine (0.07) norpropoxyphene (<0.05) nordiazepam (0.16)	Hx of emphysema & drug abuse; found dead w/ drug paraphenalia at scene; autopsy findings include pulmonary edema, arteriosclerosis, & atherosclerosis	Acute morphine intoxication	Undetermined
5	28	F	0.05	0.46	0.73	neg	dextromethorphan (0.90) propoxyphene (0.40) norpropoxyphene (0.90) morphine (<0.025)	Hx of drug abuse; died suddenly & unexpectedly after ingesting morphine & various pain medications; drug paraphenalia found at scene; autopsy revealed pulmonary edema	Multiple drug abuse	Undetermined
6	57	F	0.48	0.02	0.32	neg	doxepin (10.00) desmethyldoxepin (1.4) nicotine/cotinine	Hx of depression, on medication for same, found deceased at home; empty pill bottles (doxepin, paxil, lodine) found in bedroom	Acute doxepin overdose	Undetermined
7	36	M	0.16	1.84	0.05	neg	alprazolam (0.11) propoxyphene (1.9) norpropoxyphene (3.0)	Hx of back pain, found dead in parked motor vehicle w/ upper torso slumped towards passenger seat; Ambien (zolpidem tartrate) found on right passenger seat	Acute combination drug intoxication	Probably accidental
8	58	F	0.12	0.28	0.60	0.10	amitriptyline (0.13) nortriptyline (<0.1)	Subject died at home after 2 days discharged from hospital, on Inapsine IV given by daughter, but investigators unable to find same; coroner delayed decision to do autopsy, and body not refrigerated so moderately decomposed	Coronary artery disease, although determination made before receiptof toxicology results	Undetermined
9	39	M	1.43	0.03	0.18	neg	amitriptyline (0.59) nortriptyline (0.68) diazepam (0.27) nordiazepam (0.19)	No known medical history, found dead, face down, at home; prescription drugs include: prednisonediazepam, tramadol, & methocarbonal	Positional asphyxia secondary to acute drug intoxication	Accidental
10	38	F	2.47	0.06	0.16	neg	amitriptyline (0.43) nortriptyline (0.71) hydrocodone (0.07)	Died suddenly & unexpectedly; Rx include: ultram, amitriptyline, deltazone, buspar	Acute tramadol intoxication	Undetermined
11	32	M	22.59	0.34	2.08	0.02	propranolol (3.90) desipramine (1.00) trazodone (3.70)	Admitted to ER because of "multiple drug overdose— tricyclic & beta-blocker", died shortly after admission; HIV+; Rx include propranolol, ultram, trazodone, klonopin, desipramine, hydroxyz, lithonate	Multiple drug overdose	Suicide
12	44	M	1.13	0.46	0.3	0.14	nordiazepam (0.20) carisoprodol (2.70) meprobamate (5.90)	Released from mental hospital in morning & walked to train tracks after leaving friend's house; placed head on tracks when he heard train coming; engineer was unable to stop in time	Decapitation	Suicide

* Abbreviations: T, tramadol; ODT, *O*-desmethyl tramadol; NDT, *N*-desmethyl tramadol; Hx, history.

or acutely ingested. In addition, ODT contributes to toxicity by way of its analgesic activity, which is twice that of the parent compound. Its higher μ-opioid receptor affinity also contributes to toxicity through depression of the central nervous system.

The role of tramadol in fatalities is difficult to determine because no fatal overdoses in which tramadol alone was present have been reported. However, an investigation of the circumstances surrounding each case in this study provided investigators with baseline information regarding the blood levels associated with different types of fatalities. No antemortem medical evaluation was performed on any of the subjects described; therefore, consideration of the role of serotonin syndrome in these fatalities was based solely on the presence or lack of serotonergic activity of all drugs present. The therapeutic and toxic ranges for drugs present in the blood samples and their relative abilities to inhibit neurotransmitter reuptake and the CYP450 isozyme(s) (if known) for which they are substrates (12–14,28–31) are summarized in Table III.

The low levels of tramadol and metabolites in Case 1 make it unlikely that the drug played a role in this death. Similarily, the very low carbon monoxide levels rule out smoke inhalation as a cause of death. The true cause of the subject's sudden death remains undetermined.

Cases 2, 3, and 4 are clearly attributable to acute morphine intoxication (32). In each case, the morphine concentration is quite high, whereas the levels of other drugs present, including tramadol, are well within or below the therapeutic window. However, it is possible that tramadol may have contributed slightly to these deaths because of its μ-opioid receptor affinity. The occurrence of sudden death, as in Case 3, and the autopsy finding of pulmonary edema, as in Case 4, are both common in morphine overdoses (33). It is unclear how these subjects obtained tramadol, although the drug is not a scheduled narcotic. Tramadol's abuse potential was originally reported to be much lower than that of morphine (1). However, Ortho-McNeil's recent letter to health care professionals providing additional information on this subject reports 115 spontaneous domestic adverse events described as drug abuse, dependence, withdrawal, or intentional overdose, not including cases of accidental overdose. Patients with a past or present history of addiction or dependence on opioids account for a majority of these reports (11). The fact that 4 of the 12 cases involving tramadol reported here were also positive for morphine suggests that the manufacturer's concerns are well founded.

Morphine concentrations reported as less than 0.025 μg/mL, as in Case 5, mean that the sample tested positive, although the level is below the limit of quantitation of the analytical method. Blood morphine levels in morphine-caused deaths can be significantly lower when the survival period is longer than 3 h (33).

The tramadol level in Case 5 was low, but its effect, combined with that of ODT, may have contributed to the opioid effect of morphine. Further, the presence of dextromethorphan and propoxyphene, which are both CYP2D6 substrates, may have contributed to decreased clearance of tramadol because of competitive metabolic inhibition, thereby prolonging or enhancing tramadol's effects. In addition, it is conceivable that the serotonin reuptake-inhibiting ability of both dextromethorphan and propoxyphene, combined with that of tramadol played a role in this subject's death.

Case 6 is clearly attributable to doxepin overdose. However, interaction from tramadol could contribute to cause of death because of the moderate serotonergic effect of both drugs. The levels of tramadol and metabolites are within therapeutic ranges, but concomitant administration with very high levels of doxepin may have contributed to serotonergic crisis, which was due to the chronotropic and inotropic effects of serotonin, as well as the increased vasoconstriction produced by norepinephrine, angiotensin II, and histamine (34).

Case 7 is interesting in that, although the tramadol concentration is fairly low, the ODT concentration is extremely high, and propoxyphene and alprazolam, which are both CYP2D6 substrates, were also present in fairly high concen-

Table II. Tramadol Levels in Four Drug-Impaired Drivers

Case	Age	Gender	Sample tested	T* (mg/L)	ODT (mg/L)	NDT (mg/L)	Alcohol (g/100mL)	Other drug use	Case history
1	44	M	blood	0.07	0.05	0.09	neg	cocaine (<0.1) diazepam (<0.1) nordiazepam (<0.1) propoxyphene (<0.1) norpropoxyphene (0.31) benzoylecgonine (pos)	Hx of open heart surgery,marijuana use; admitted taking marijuana, darvocet, voltaren
2	39	F	blood	0.17	0.11	0.04	neg	morphine (<0.01)	Hx of heroin abuse; admitted taking heroin, diazepam, and dextromethorphan
3	39	F	blood	0.29	0.05	0.03	neg	methadone (0.09)	Stopped on return from methadone clinic; told police she had just been given methadone
4	40	F	urine	31.37	4.32	6.51	0.10	methamphetamine amphetamine	Stopped for erratic driving; prescription bottle of ultram found in subject's car

* Abbreviations: T, tramadol; ODT, *O*-desmethyltramadol; NDT, *N*-desmethyltramadol; Hx, history.

trations. Although it is possible that a metabolic interaction took place, the likely explanation is that the subject ingested a large but not fatal dose of tramadol at an earlier time. Acute, combined-drug intoxication seems reasonable as a cause of death.

Case 8 was certified as a natural death before toxicology testing was complete. In reviewing the toxicology results, however, it is possible that there was some serotonergic interaction between the drugs present that, together with the alcohol, may have been important.

The very high tramadol levels and low metabolite concentrations in Case 9 point to an acute tramadol ingestion in a combined-drug overdose. Again, the effect of elevated concentrations of several serotonergic drugs that are also 2D6 substrates may have contributed to the increased plasma concentrations that played a role in this fatality.

The presence of amitriptyline and hydrocodone, which are both substrates for CYP2D6, indicated a possible competitive inhibition of the isoenzyme. The high concentration of tramadol relative to ODT also supported this. It is also conceivable that the combined serotonergic activity of amitriptyline and tramadol was significant in this person's death.

In addition to significant concentrations of several substrates of 2D6 in Case 11, high levels of desipramine, an inhibitor of 2D6, were also present. As in Case 10, extremely high levels of tramadol relative to those of its metabolites supported the possibility of competitive inhibition. It is likely that the serotonergic activity of several drugs present in the subject's blood also played an important role.

The concentrations of tramadol and ODT in Case 12 are both well above the therapeutic range, and they, along with the high blood alcohol level, may have contributed to central nervous system depression. However, decapitation was clearly the cause of death in this case.

In summary, tramadol is usually present with antidepressants and/or other opiates, both of which can interact with tramadol and its active metabolite when the drug is present. ODT levels should be taken into consideration when interpreting tramadol concentrations, especially when morphine is also present. The appearance of the two drug interactions discussed, the competitive inhibition of CYP2D6 causing enzyme saturation and subsequent decreased clearance of tramadol

Table III. Properties of Drugs Found in Postmortem Blood*

Drug	Therapeutic concentration (mg/L)	Toxic concentration (mg/L)	Reuptake inhibition		
			NE†	DA	ST
Alprazolam (3A4, 2D6 minor)	0.02–0.04	>0.07	0	0	0
Amitriptyline (2D6,3A4 minor)	0.06–0.22	>1.0	±	0	++
Codeine (2D6 - to morphine)	0.03–0.34	1.00–8.80	0	0	0
Desipramine (3A4; inhibits 2D6)	0.01–0.28	1.20–15.00	+++	0	0
Dextromethorpan (2D6, 3A4 minor)	0.38	LOD = 0.5 g	0	0	+‡
Doxepin	0.03–0.15	>0.1	±	0	+
Diazepam (2C19)	0.1–2.5	>1.5	0	0	0
Hydrocodone (2D6)	0.002–0.024	0.13–7.00	0	0	0
Morphine	0.01–0.07	0.12–4.70	0	0	0
Propoxyphene (2D6)	0.05–0.75	1.0–2.0	+	0	+‡
Propranolol (2D6)	0.01–0.26	4.00–29.00	0	0	0
Tramadol (2D6)	0.23–0.77	LOD = 0.5 g	+	0	+
Trazodone	0.49–1.60	>15.00	0	0	+

* All levels come from Baselt and Cravey (32) except those for tramadol, which come from the revised product insert from Ortho-McNeil (29).
† Abbreviations and symbols: NE = norepinephrine; DA = dopamine; ST = serotonin; + to +++ = active to strongly active; ± = weakly active; 0 = lacking.
‡ Dextromethorphan's serotonin reuptake inhibiting ability is discussed in a paper by Skop et al. (30) and that of propoxyphene was reported by Codd et al. (31).

potentially leading to toxic side effects, and the combined serotonergic activity of two or more drugs should also be considered when interpreting tramadol levels. A third mechanism of toxicity in the subjects who had histories of heart disease may result from increased serotonin levels. Under normal vascular conditions, platelets release serotonin to promote vasodilation and platelet aggregation, which cause vascular holes and tears to seal without causing thrombus formation (35). However, in patients with vascular disease, vasoconstriction can occur when serotonin levels are increased (36). The combination of increased serum serotonin levels, which are due to the presence of serotonin reuptake inhibiting drugs, and the decreased ability of the endothelium to metabolize serotonin, which is due to ischemic damage, compounds the seemingly contradictory vasoconstriction seen with a damaged endothelium (29).

Conclusion

We have described several fatalities in which tramadol was found along with other drugs. It is imperative that clinicians maintain heightened awareness of the risks associated with tramadol use to help minimize the prescription of medication combinations that are likely to induce abnormally high serotonergic activity or contribute to metabolic interactions or other adverse reactions. Clinicians and physicians should also watch for evidence of tramadol abuse and should attempt to determine if patients are taking other agents with μ-opioid receptor affinity. It is hoped that these findings will provide guidance to toxicologists and pathologists in recognizing the possibility of drug interactions involving tramadol, as well as tramadol's contribution to heroin/morphine overdoses.

Acknowledgments

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