Unexceptional Seizure Potential of Tramadol or Its Enantiomers or Metabolites in Mice

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ABSTRACT

Tramadol is one of the most widely used centrally acting analgesics worldwide. Of its multimodal analgesic mechanism (opioid plus nonopioid), the adverse effects profile of tramadol, similar to its analgesic profile, can be atypical compared with a single-mechanism opioid analgesics. The comparison is often favorable (e.g., less respiratory depression or abuse), but it is sometimes cited as unfavorable in regard to seizure potential. As part of a broader study of this analgesic, we compared seizure induction in mice produced by administration of tramadol, the enantiomers and metabolites [M1 (O-desmethyl tramadol), M2 (N-desmethyl tramadol), M3 (N,N-didesmethyl tramadol), M4 (O,N,N-tridesmethyl tramadol), and M5 (O,N-didesmethyl tramadol)] of tramadol, and opioid and nonopioid reference compounds. We found that tramadol, its enantiomers, and M1 to M5 metabolites were of intermediate potency in this endpoint (on either a milligram per kilogram or millimole per kilogram basis). The SD_{50} (estimated dose required to induce seizures in 50% of test group) of tramadol to antinociceptive ED_{50} ratio was almost identical to that of codeine. The enantiomers of tramadol were about equipotent to tramadol on this endpoint. The M1 to M5 metabolites (and M1 enantiomers) of tramadol were less potent than tramadol. The relative potency of tramadol to opioids was not altered by quinidine (an inhibitor of CYP4502D6), noxious stimulus (48°C hot-plate), multiple dosing, or in reserpinized mice. Tramadol seizures were increased by naloxone, principally at high tramadol doses and due to an effect on the (−)-enantiomer that overcame the opposite effect on the (+)-enantiomer. No synergistic effect on seizure induction was observed between concomitant tramadol and codeine or morphine.

Tramadol is a centrally acting analgesic that is widely used throughout the world (in more than 100 countries). Tramadol produces its multimodal antinociceptive and analgesic effects via two mechanisms (Raffa and Friderichs, 1996): one is opioid, and the other is nonopioid (Hennies et al., 1988; Friderichs et al., 1991, 1992; Raffa et al., 1992, 1993, 1995; Dayer et al., 1997; Ide et al., 2006). The opioid component involves weak affinity (approximately 1 μM) of the parent drug and approximately 300-fold greater affinity of the M1 metabolite of tramadol (Wu et al., 2002) for μ-opioid receptors (Hennies et al., 1988; Raffa et al., 1992; Lai et al., 1996; Gillen et al., 2000). The nonopioid component is related to inhibition of neuronal 5-hydroxytryptamine (5-HT; serotonin) and norepinephrine reuptake (Friderichs et al., 1991; Codd et al., 1995). The opioid component, predominant in the (−)-enantiomer, and the nonopioid component, predominant in the (−)-enantiomer (Friderichs et al., 1992; Raffa et al., 1992; Codd et al., 1995), combine in a complementary and sometimes synergistic manner to produce antinociception, but in an additive or subadditive manner in several side-effect measures (Raffa et al., 1993). The total contribution from all components is consistent with, and forms the basis for understanding of, the clinical profile of tramadol, including minimal respiratory depression (compensatory opposite effects of the enantiomers) and lower abuse (Adams et al., 2006). However, a question of whether tramadol induces seizures to a greater extent than that do other centrally acting (opioid) analgesics seems to have arisen from early reports (Kahn et al., 1997) and persists despite evidence to the contrary (Jick et al., 1998; Gasse et al., 2000; Marquardt et al., 2005).

In preclinical evaluation, tramadol displayed both pro- and anticonvulsant properties (Raffa and Friderichs, 1996). For example, it significantly reduced tonus, but not clonus, induced by pentetrazole or picrotoxin, but not by bicuculline, and it inhibited electrically induced seizures (maximal electroshock). High-dose tramadol induced seizures, its most

ABBREVIATIONS: tramadol, (1RS,2RS)-2-[[dimethylamino)(methyl)-1-(3-methoxyphenyl)-cyclohexanol HCl; M1, O-desmethyl tramadol; 5-HT, 5-hydroxytryptamine; M2, N-desmethyl tramadol; M3, N,N-didesmethyl tramadol; M4, O,N,N-tridesmethyl tramadol; M5, O,N-didesmethyl tramadol; SD_{50}, estimated dose required to induce seizures in 50% of test group; 95% FL, 95% fiducial limits.
prominent toxicity (not respiratory depression), in all of the species tested, including mouse, rat, rabbit, dog, and monkey (Raffa and Friderichs, 1996). Such a combination of mixed pro- and anticonvulsant effects has been described for other opioids (Corrada and Longo, 1961; Adler et al., 1976; Cowan et al., 1979; Foote and Gale, 1983; Lee et al., 1984; Tortella et al., 1984). To assess whether tramadol was unusual in this regard, we tested tramadol, the (+)- and (–)-enantiomers of tramadol, and the M1 to M5 metabolites of tramadol compared with opioid and other reference drugs. We expanded the investigation to examine the influence of naloxone, inhibition of CYP2D6, reserpine, i.p. and i.v. routes of administration (first-pass effect and not, respectively), noxious stimulus (48°C hot-plate), multiple dosing, and drug interaction with morphine or codeine.

Materials and Methods

Compounds. Tramadol HCl (molecular mass = 263.4 kDa) (Grüenthal, GmbH, Aachen, Germany), (+)-tramadol HCl (263.4) (Grüenthal, GmbH), (–)-tramadol HCl (263.4) (Grüenthal, GmbH), M1 HCl (249.4) (Grüenthal, GmbH), (+)-M1 HCl (249.4) (Grüenthal, GmbH), (–)-M1 HCl (249.4) (Grüenthal, GmbH), M2 fumarate (249.4) (Grüenthal, GmbH), M3 HCl (235.3) (Grüenthal, GmbH), M4 HCl (221.3) (Grüenthal, GmbH), M5 HCl (235.3) (Grüenthal, GmbH), amitriptyline HCl (277.4), buprenorphine HCl (503.2) (Sigma/RBI, Natick, MA), codeine phosphate (299.4), dextromethorphan hydrobromide (271.4) (Sigma/RBI), dextromethorphan tartrate (257.4) (Hoffman-La Roche, Nutley, NJ), fluoxetine HCl (295.3); and hydrocodone bitartrate (299.4) (U.S. Pharmacopeial Convention, Inc., Rockville, MD), dextrophan tartrate (257.4) (Hoffman-La Roche), hydroxymorphone HCl (285.4) (Malinkrodt, Hazelwood, MO and Sigma-Aldrich, St. Louis, MO), levallorphan tartrate (283.4) (Hoffman-La Roche), levomethorphan hydrobromide (271.4) (Hoffman-La Roche), levorphanol tartrate (257.4) (Sigma-Aldrich), meperidine HCl (247.3) (Winthrop Laboratories, New York, NY), methadone HCl (309.5) (Sigma-Aldrich), (–)-methadone HCl (309.5) (Sigma/RBI), (–)-methadone HCl (309.5) (Sigma/RBI), (–)-morphine sulfate (285.4) (Sigma-Aldrich), (–)-naloxone HCl (327.4) (Endo Laboratories, Chadds Ford, PA), norfluoxetine HCl (295.3), d-propoxyphene HCl (339.5) (Sigma-Aldrich), oxycodone HCl (315.4) (Malinkrodt), quinidine sulfate, and reserpine were dissolved in vehicle (sterile water), and all of the doses were calculated and are reported as the amount of base. The tramadol metabolites are designated as M1 to M5 (Fig. 1).

Animals. Male virus-free Swiss-derived albino Crl:CD-1(ICR)BR mice, 18 to 24 g at the time of testing, were purchased from Charles River Laboratories (Kingston, NY and Portage, ME) and group-housed five to 10 per plastic box under controlled temperature and humidity conditions and 12-h light/dark cycle (lights on at 6:00 AM) for at least 5 days before testing. Food and water were available ad libitum up to the time of testing. Each mouse (n = 3–30 mice per group) was used only once and was housed and treated in accordance with the recommendations and policies of the Institute of Laboratory Animal Resources (1996). The experiments adhered to the guidelines of the Committee for Research and Ethical Issues of the International Association for the Study of Pain and was reviewed by an Animal Resources (1996). The experiments adhered to the guidelines for the use of animals in research and were reviewed by an institutional animal care and use committee.

Basic Procedure. The mice were individually weighed and allowed to acclimate to laboratory conditions before testing. Compound or vehicle was administered by the route indicated (10 ml/kg for i.p. or s.c.). For i.v. injections, the mice were positioned in a plastic restrainer and the compounds were infused into a lateral caudal tail vein using a 27-gauge hypodermic needle or butterfly attached to a 1-cc disposable syringe. Successful venous puncture was confirmed by observing reflux of a small amount of blood into the transparent hub of the needle. The dose volume (usually 0.18–0.24 ml) was infused over 3 to 5 s. The mice were then placed into glass jars (approximately 14-cm diameter with cardboard on the bottom), containing two mice per each jar. The mice were observed for the first occurrence of a seizure or for a maximum of 15 min. At the first response, the animals were immediately removed from the observation chamber and euthanized by CO2. In the absence of a response, the animals were euthanized at the end of the 15-min observation period. The results were calculated for each dose as the percentage of responders in the group (number of responders/number of animals in group).

The SD50 value (estimated dose required to induce seizures in 50% of test group) and 95% fiducial limits (95% FL) were calculated using computer-assisted linear regression analysis, and the comparison of SD50 values was made using a computer-assisted relative-potency probit analysis (Tallarida and Murray, 1987). Treatments are significantly different (p < 0.05 criterion) if the fiducial limits do not include 1.0.

Quinidine Pretreatment. Selection of the dose of quinidine was based on its ability to inhibit codeine-induced anticonvulsion (i.e., inhibition of metabolic conversion to morphine). The tail immersion procedure (described in Raffa et al., 1992), with modifications, was used. The distal half of the tail was immersed in water maintained at 55°C, and the latency to remove (flick) the tail was recorded as the control latency. Mice that did not flick their tails within 5 s were not used. The procedure was repeated after administration of codeine (100 mg/kg s.c.) and recorded as the test latency. Mice that did not flick their tails within 15 s were removed from the nociceptive stimulus to avoid tissue damage and were assigned the maximal antinoceptive score of 100%. The mice were euthanized by CO2 immediately after exposure to the nociceptive stimulus. Anticonvulsion was calculated for each animal as the percentage of the maximal possible
effect (%MPE) according to the following: %MPE = 100 × [(test latency − control latency)/(15 − control latency)] and is reported as the mean for the group. Quinidine was administered as a pretreatment at 10, 30, or 100 mg/kg s.c. 60 min before codeine, and antinociception was assessed as described above.

**Reserpine Pretreatment.** To investigate the possible contribution of vesicular store of catecholamines, mice were pretreated with reserpine (10 μmol/kg) 24 h before testing for seizure induction (procedure is the same as described above).

**SD<sub>50</sub>, ED<sub>50</sub>.** Four reference drugs, amitriptyline, codeine, (−)-methadone, and morphine, were selected to span antinociceptive and seizure potencies and to include at least two of the mechanisms of antinociceptive action of tramadol—opioid and inhibition of neuronal monoamine reuptake. The tests were conducted such that antinociception and seizures were assessed in matched groups of mice at the same time after administration of drug. For the antinociception test (described in Raffa et al., 1992), test drugs or vehicle were administered i.v., and 5 min later the mice received an i.p. injection of 5.5 mg/kg acetylcholine bromide. The mice were then placed into large glass jars and observed for the occurrence of a single response defined as a wave of constriction and elongation passing caudally along the abdominal wall, accompanied by a twisting of the trunk and followed by extension of the hindlimbs. The animals were rated as protected if a response was not displayed during the 10-min observation period.

**Multiple Dosing.** Each mouse received four daily s.c. injections (each administered at approximately 11:00–11:30 AM) of vehicle or codeine, morphine, or tramadol followed by an i.p. test agent (codeine, morphine, or tramadol) on day 5 approximately 24 h after the last s.c. injection. The doses were based on estimated antinociceptive ED<sub>50</sub> values that were previously determined (0.2, 0.3, and 0.1 mmol/kg for tramadol, codeine, and morphine, respectively) (Raffa and Friderichs, 1996).

**Test for Drug Interaction.** Tramadol was tested pairwise in combination with codeine and morphine, and morphine was tested pairwise with two reference opioids (codeine and oxycodone). The combinations consisted of the drugs in constituent amounts having the same proportion as their individual SD<sub>50</sub> values. For example, tramadol/codeine was tested in a combination in which 0.325 of the total was tramadol and 0.675 was codeine. Dilutions of each combination, retaining the fixed proportions, were tested and yielded regressions of probit against the logarithm of the total dose in the mixture (milligram per kilogram) from which SD<sub>50</sub> and log(SD<sub>50</sub>) values were obtained for each mixture. The data were sent to Dr. Ronald J. Tallarida (Department of Pharmacology, Temple University School of Medicine, Philadelphia, PA) for statistical evaluation. The test for interaction (Tallarida, 2000) involves the experimental determination of the total dose that yields a 50% response (Z<sub>add</sub>), and the corresponding quantity (Z<sub>sub</sub>) was calculated from the assumption of additivity. Additivity is indicated when Z<sub>add</sub> = Z<sub>com</sub>. Deviation from additivity suggests supra-additivity (synergy) if Z<sub>add</sub> < Z<sub>com</sub> or subadditivity (antagonism) if Z<sub>add</sub> > Z<sub>com</sub>.

**Results**

**Seizure Induction.** At sufficiently high doses, seizures were induced by i.p. administration of codeine, dextromethorphan, hydrocodone, hydromorphone, meperidine, methadone [also by (+) and (−)-methadone], (−)-morphine, (−)-naloxone, oxycodone, d-propoxyphene, and tramadol [also by (+)-tramadol and (−)-tramadol], M1 [also by (+)-M1 and (−)-M1], M2, M3, M4, and M5. Seizures were not induced up to lethality (due to apparent respiratory depression) by dextromethorphan, levallorphan, levomethorphan, or levorphanol (1.17, 1.06, 1.11, and 0.39 mmol/kg, respectively). Buprenorphine did not cause seizures or lethality up to the highest dose tested (300 mg/kg; 0.6 mmol/kg). For the other drugs, the SD<sub>50</sub> (95% FL) ranged from 0.08 (0.07–0.09) mmol/kg for (−)-methadone to 2.19 (1.50–3.20) mmol/kg for hydromorphone. The SD<sub>50</sub> of tramadol was 0.33 mmol/kg (85.6 mg/kg), essentially the same on a molar basis as that of codeine (0.32 mmol/kg; 126.9 mg/kg), dextromethorphan (0.30 mmol/kg; 82.5 mg/kg), and meperidine (0.30 mmol/kg; 73.7 mg/kg), and significantly larger than that of (−)methadone (0.08 mmol/kg; 24.8 mg/kg). The SD<sub>50</sub> value of tramadol did not differ significantly from that of its (+)– or (−)-enantiomer [0.38 (0.30–0.46) and 0.29 (0.25–0.35) mmol/kg, respectively] (p > 0.05, relative potency analysis). The SD<sub>50</sub> of M1, (+)-M1, and (−)-M1 was 0.62 (0.35–0.89), 1.20 (0.94–1.71), and 2.06 (1.51–2.71) mmol/kg, respectively. The SD<sub>50</sub> for tramadol metabolites M2 to M5 was 0.88 (0.77–1.03), 0.85 (0.69–1.01), 1.62 (1.41–2.10), and 0.93 (0.78–1.10) mmol/kg, respectively, each of which was significantly larger than the SD<sub>50</sub> of tramadol (p < 0.05). Graphical presentation of the rank order of the SD<sub>50</sub> values is shown in Fig. 2A.

At sufficiently high doses, seizures were induced by i.v. administration of all drugs [buprenorphine did not cause seizures or lethality up to the highest dose tested (0.1 mmol/kg)]. The SD<sub>50</sub> (95% FL) ranged from 0.01 (0.01–0.02) mmol/kg for (−)-methadone to 0.51 (0.29–0.91) mmol/kg for codeine and morphine. The SD<sub>50</sub> of tramadol was 0.08 (0.06–0.09) mmol/kg.
kg, essentially the same as its (+)- or (−)-enantiomer [0.09 (0.06–0.11) and 0.08 (0.05–0.13) mmol/kg, respectively]. The SD\textsubscript{50} of M1, (+)-M1, and (−)-M1 was 0.08, 0.20, and 0.15 mmol/kg, respectively. The SD\textsubscript{50} for tramadol metabolites M2, M3, and M5 was 0.09, 0.25, and 0.30 mmol/kg, respectively. Graphical presentation of the rank order of the SD\textsubscript{50} values of these and reference drugs is shown in Fig. 2B.

**Therapeutic Index.** As a measure of antinociception/seizure therapeutic index, the ratio of i.v. SD\textsubscript{50} to i.v. ED\textsubscript{50} (the estimated dose required to produce antinociception in 50% of mice tested) was determined. The antinociceptive and seizure dose-response curves for tramadol were not parallel (p < 0.05), whereas those for the reference compounds, with the exception of (−)-methadone, were parallel (data not shown). The SD\textsubscript{50} values ranged from a low of 12.8 μmol/kg for the (−)-enantiomer of methadone to a high of 461 μmol/kg for morphine. The SD\textsubscript{50} value for tramadol was 90.2 μmol/kg. The i.v. SD\textsubscript{50}/ED\textsubscript{50} ratio for tramadol (110) was essentially the same as that for codeine (111), greater than that for (−)-methadone (86), and much less than that for morphine (1246) (see Table 1 for details).

**Naloxone: Test for an Effect of Opioid Receptor Antagonism.** Naloxone itself induced seizures by either i.p. or s.c. route of administration. A dose at least 500-fold less than the lowest seizure-inducing dose was chosen for the antagonist study (0.3 mg/kg administered s.c. 20 min before the test agent). Naloxone significantly decreased (p < 0.05) the seizure potency of (−)-morphine and (−)-methadone to 2.75 and 0.20 mmol/kg (786.0 mg/kg and 75.1 mg/kg, respectively). Naloxone also significantly decreased (p < 0.05) the potency of tramadol by 1.4-fold to 0.19 mmol/kg (50.2 mg/kg) and 0.98 mmol/kg (258.4 mg/kg), respectively. Naloxone had no effect on the potency of the other compounds tested. The results are shown graphically in Fig. 3.

**Quinidine: Test for Effect of Inhibition of CYPD6.** Quinidine (100 mg/kg s.c.) administered 60 min prior produced a significant (p < 0.05) antagonism of codeine-induced antinociception (interference with its metabolism to morphine), demonstrating effective inhibition of CYP2D6. Therefore, 100 mg/kg s.c. quinidine was selected for the seizure studies. Quinidine alone did not produce seizures at this dose or at 3-fold this dose (300 mg/kg s.c.). Quinidine (60 min before the test agent) produced a leftward, parallel shift of the dose-response curve of codeine, naloxone, the M2 metabolite of tramadol, and the (−)-enantiomer of the M1 metabolite of tramadol, but it had no significant effect on the dose-response curves of the other drugs. The SD\textsubscript{50} value of each of the compounds with and without quinidine pretreatment is given in Table 2 and displayed in Fig. 4.

TABLE 2

<table>
<thead>
<tr>
<th>Compound</th>
<th>SD\textsubscript{50} (95% FL)</th>
<th>ED\textsubscript{50} (95% FL)</th>
<th>SD\textsubscript{50}/ED\textsubscript{50}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>138.6 (0.35)</td>
<td>79.3 (0.20)</td>
<td>1.74</td>
</tr>
<tr>
<td>Dextromethorphan</td>
<td>76.2 (0.28)</td>
<td>56.5 (0.21)</td>
<td>1.35</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>70.1 (0.23)</td>
<td>55.4 (0.19)</td>
<td>1.27</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>418.7 (1.47)</td>
<td>354.9 (1.24)</td>
<td>1.20</td>
</tr>
<tr>
<td>Methadone</td>
<td>74.7 (0.30)</td>
<td>72.7 (0.29)</td>
<td>1.03</td>
</tr>
<tr>
<td>Methadone</td>
<td>60.4 (0.13)</td>
<td>52.8 (0.08)</td>
<td>1.17</td>
</tr>
<tr>
<td>Morphiine</td>
<td>335.3 (1.88)</td>
<td>211.8 (1.83)</td>
<td>1.57</td>
</tr>
<tr>
<td>Naloxone</td>
<td>167.6 (0.51)</td>
<td>122.9 (0.38)</td>
<td>1.36</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>171.6 (0.56)</td>
<td>124.5 (0.39)</td>
<td>1.40</td>
</tr>
<tr>
<td>Tramadol</td>
<td>235.0 (0.69)</td>
<td>222.8 (0.66)</td>
<td>1.07</td>
</tr>
<tr>
<td>Tramadol</td>
<td>98.1 (0.37)</td>
<td>73.2 (0.28)</td>
<td>1.35</td>
</tr>
<tr>
<td>(+)-Tramadol</td>
<td>167.3 (0.43)</td>
<td>73.5 (0.28)</td>
<td>1.43</td>
</tr>
<tr>
<td>(−)-Tramadol</td>
<td>70.5 (0.27)</td>
<td>58.2 (0.22)</td>
<td>1.22</td>
</tr>
<tr>
<td>M1</td>
<td>145.5 (0.58)</td>
<td>136.2 (0.55)</td>
<td>1.00</td>
</tr>
<tr>
<td>(+)-M1</td>
<td>273.1 (1.10)</td>
<td>211.4 (0.85)</td>
<td>1.30</td>
</tr>
<tr>
<td>(−)-M1</td>
<td>529.2 (2.12)</td>
<td>281.1 (1.13)</td>
<td>1.88</td>
</tr>
<tr>
<td>M2</td>
<td>214.5 (0.86)</td>
<td>190.5 (0.52)</td>
<td>1.13</td>
</tr>
<tr>
<td>M3</td>
<td>378.0 (1.71)</td>
<td>306.3 (1.38)</td>
<td>1.25</td>
</tr>
<tr>
<td>M5</td>
<td>214.5 (0.91)</td>
<td>213.1 (0.91)</td>
<td>1.00</td>
</tr>
</tbody>
</table>
for tramadol, the (−)-enantiomer of tramadol, amitriptyline, codeine, d-propoxyphene, fluoxetine, and norfluoxetine.

**Multiple Dosing.** The SD50 values (95% FL) are summarized in Table 5. There was no significant difference (p > 0.05) between any SD50 values of the tramadol-test groups, with the exception of a marginal difference for the 4-day pretreatment with morphine. Likewise, there was no significant difference (p > 0.05) between the codeine SD50 values of vehicle-pretreated mice and codeine-pretreated (1 or 4 days) mice.

**Drug Interaction Tests.** The SD50 values (and 95% FL) for oxycodone, tramadol, codeine, and morphine were 0.08 (0.06–0.10), 0.09 (0.08–0.10), 0.16 (0.10–0.24), and 0.46 (0.26–0.74) mmol/kg i.v., respectively, equivalent to 24.4 (18.1–32.9), 23.8 (20.0–27.0), 49.4 (31.5–71.7), and 131.7 (73.9–210.1) mg/kg, respectively, when each was administered individually. The SD50 value (and S.E.M.) for the concurrent i.v. administration of tramadol with codeine was 36.6 (3.6) mg/kg; for tramadol with morphine it was 77.7 (10.3) mg/kg; for morphine with codeine it was 90.5 (10.9) mg/kg; and for morphine with oxycodone it was 78.0 (10.4) mg/kg. Each combination yielded an SD50 (Zmix) less than the calculated additive SD50 (Zadd) (Table 6), but the variances of each median and the closeness of the values themselves precluded a demonstration of statistical difference (p > 0.05).

**Discussion**

It has long been known that the usual high-dose toxicity of tramadol in animals and in humans results in seizures rather than respiratory depression (e.g., Spiller et al., 1997; Tobias, 1997; Matthiesen et al., 1998; Marquardt et al., 2005). The small number of seizures, and the exceedingly small number with tramadol alone, makes it difficult to define susceptible individuals. There might be a susceptible
subset (also true for other opioids?) for reasons yet unknown (Gardner et al., 2000). However, a letter-to-editor (Kahn et al., 1997) suggested that tramadol may cause seizures at recommended dosages, particularly when administered together with antidepressant medications, which themselves lower seizure threshold (Skowron and Stimmel, 1992). Subsequent studies suggested a relatively low risk (Jick et al., 1998; Gasse et al., 2000; Marquardt et al., 2005). Yet, periodically, a letter-to-editor implies a greater risk (e.g., Labate et al., 2005).

The preclinical studies in animal models (summarized in Raffa and Friderichs, 1996) showed that tramadol had mixed actions, proconvulsant in some tests and anticonvulsant in others. Thus, the profile of tramadol is not unusual in that analgesic doses of opioids display some anticonvulsant activity, but high-doses produce seizures that are not fully naloxone-reversible, and opioids probably produce seizures in epilepsy-prone, kindled, or seizure-experienced animals (Corrada and Longo, 1961; Frenk, 1983; Mansour and Valenstein, 1984; Tortella et al., 1984; Czuczwar and Frey, 1986; Reigel et al., 1988; Potschka et al., 2000; Manocha et al., 2005). The mechanistic explanation for these effects is not clear. The mechanism of tramadol’s dual pro- and anticonvulsant properties has been examined. In one study, tramadol and its enantiomers were anticonvulsant within the tramadol analgesic range in a kindling model in rats of temporal lobe epilepsy, but seizures were induced at only slightly higher doses (Potschka et al., 2000). In other studies, tramadol displayed an anticonvulsant effect in the maximal electroshock test in mice by a mechanism that seems to involve multiple neurotransmitter systems (Manocha et al., 1998, 2005).

In the present study, we endeavored to accomplish the following: 1) put into perspective the high-dose seizure activity of tramadol relative to other opioids (on both a milligram per kilogram and millimole per kilogram basis and also as the ratio to antinociceptive potency); 2) investigate each of the components of the pharmacology of tramadol, ie, parent drug, its enantiomers, the M1 metabolite and its enantiomers, and the M2 to M5 metabolites; 3) investigate the contribution of an opioid (naloxone-sensitive) component or a nonopioid (reserpine-sensitive) component; 4) test for possible influence of noxious stimulus; 5) determine the effect of multiple dosing; and 6) test for a possible interaction with other opioids.

In regard to inducing high-dose seizures, tramadol was not unusual. Some opioids caused lethality without seizures (dextromorphan, levallorphan, levomepromazine, and levophanol), but codeine, dextromethorphan, hydrocodone, hydromorphone, meperidine, (−)methadone, morphine, oxycodone, and d-propoxyphene induced dose-related seizures at sufficiently high doses. Of these, (−)methadone was the most potent and morphine was the least potent. Tramadol, its enantiomers, M1, its enantiomers, and M2 to M5 metabolites had intermediate potency (on either a milligram per kilogram or millimole per kilogram basis), similar to that of oxycodone, hydrocodone, codeine, and hydromorphone. The fact that one of the enantiomers of tramadol might be particularly potent was not found to be the case; the (+)- and (−)-enantiomers were about equipotent to (±)-tramadol. The fact that the M1 metabolite or its enantiomers might be particularly potent was also not found to be the case. M1 and its (+)- and (−)-enantiomers were less potent than tramadol. Likewise, the fact that one of tramadol’s other metabolites might be particularly potent was not found to be the case. The M2 to M5 metabolites were less potent than the parent drug. The question of metabolites was tested in a second way, using quinidine. Quinidine administered at a dose demonstrated to inhibit codeine-induced antinociception (i.e., prevent metabolism to morphine via CYP2D6) and enhance the seizure potency of codeine had no effect on tramadol, its enantiomers, M1 or its enantiomers, or the M2 to M5 metabolites of tramadol. Thus, it seems that the metabolites do not play a significant role in the seizure activity of the parent compound. To put seizure potency into clinical perspective, seizure potency was compared with antinociceptive potency (abdominal irritant test). (−)Methadone had the smallest such ratio; morphine had the largest ratio; the ratio of tramadol—slightly greater than two orders of magnitude—was essentially identical to that of codeine.

Naloxone produced a rightward, parallel shift of both the morphine and methadone seizure dose-response curves, significantly reducing their seizure potencies. Naloxone produced a leftward, nonparallel shift of the upper end of the tramadol dose-response curve, a significant parallel rightward shift of the (+)-enantiomer of tramadol, and a nonparallel leftward shift of the (−)-enantiomer of tramadol. The (+)-enantiomer of tramadol has a greater opioid component (affinity) than tramadol or its (−)-enantiomer (Raffa et al., 1993). Assuming that naloxone did not alter pharmacokinetic or metabolic parameters, an interpretation of these findings is that seizure induction in this model can be produced by both opioid and nonopioid mechanisms. However, seizure induction did not correlate with norepinephrine or 5-HT neuronal reuptake inhibition (Codd et al., 1995). Thus, the nonopioid contribution cannot be specified from the naloxone results. If inhibition of neuronal monoamine reuptake is a major mechanism of action, then seizure-induction potency should be less in mice pretreated with reserpine. Reserpine pretreatment increased (1.7-fold) the potency of tramadol, suggesting that inhibition of neuronal monoamine reuptake is not a major mechanism.

The possibility that tramadol, its enantiomers, or metabolites might be particularly prone to produce seizures under conditions of noxious stimulus was found not to be the case. The potency of all of the compounds tested (opioids and norepinephrine and 5-HT reuptake inhibitors) was slightly increased in mice tested on a 48°C hot-plate than off the hot-plate. The range of change was 1.1 (morphine and M2) to 3.0 (amitriptyline). The ratio for each tramadol enantiomer and M1 and M2 metabolites was 1.1 to 1.4. The increase in potency of tramadol was identical to that of codeine.

The possibility that multiple dosing might increase seizure induction was examined. The potency of i.p. tramadol was not significantly altered by single s.c. injection of tramadol, codeine, or morphine or by multiple (daily for 4 days) s.c. injections of tramadol or codeine. The i.p. potency of tramadol was slightly decreased by multiple s.c. injections (daily for 4 days) of morphine. This change was about the same as that of codeine after single or multiple injections of codeine.

The possibility of opioid drug interaction was also examined. Tramadol, morphine, codeine, or fixed-ratio combinations of tramadol plus morphine or tramadol plus codeine were tested. There were no interactions. We did not investigate interactions with monoamine oxidase inhibitors or with
selective serotonin reuptake inhibitors. There is only one known published report of a death caused by seizure activity in a patient taking tramadol in combination with other drugs that affect 5-HT (Ripple et al., 2000).

In summary, the present series of experiments examined the relative potency of high-dose tramadol-induced seizures compared with other opioids, the degree of contribution of the enantiomers and metabolites of tramadol, opioid or nonopioid components, the influence of noxious stimulus or multiple dosing, and drug interaction. We report the following: high doses of commonly used opioid analogues induced seizures in mice; the seizure-induction potency of tramadol was intermediate among opioids; tramadol’s seizure to anticonvulsant potency ratio was essentially identical to that of codeine; neither enantiomer of tramadol was more potent in this endpoint, nor were the metabolites of tramadol (M1, enantiomers of M1, or M2–M5 metabolites); naloxone increased tramadol seizures, principally at highest tramadol doses; no evidence directly implicated either an opioid mechanism or mechanism involving inhibition of monoamine reuptake; neither noxious stimulus nor multiple dosing affected tramadol seizures, principally at highest tramadol doses; no evidence directly implicated either an opioid mechanism or mechanism involving inhibition of monoamine reuptake; neither noxious stimulus nor multiple dosing affected tramadol in a manner different from codeine; and no interaction was observed between tramadol and codeine or morphine.

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