

# PAIN MANAGEMENT IN DENTAL PRACTICE: TRAMADOL VS. CODEINE COMBINATIONS

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## ABSTRACT

**Background.** Tramadol hydrochloride is a novel, centrally acting analgesic with two complementary mechanisms of action: opioid and aminergic. First marketed in 1994, tramadol is frequently prescribed by physicians for the management of moderate-to-moderately severe chronic pain. The author evaluates its unique analgesic pharmacology and limited clinical utility for managing acute pain in dentistry.

**Types of Studies Reviewed.** Clinical drug trials in medicine and dentistry were reviewed to assess analgesic efficacy. Postmarketing surveillance studies and reports of adverse drug events were evaluated to determine short- and long-term safety.

**Results.** Tramadol's maximum analgesic efficacy for relieving acute pain after oral surgery

appears to be similar to that of 60 milligrams of codeine alone but less than that of a full therapeutic dose of a nonsteroidal anti-inflammatory drug or a codeine combination, such as aspirin/codeine or acetaminophen/codeine. Adverse events reported by patients receiving tramadol therapy since it was approved by the Food and Drug Administration suggest a risk of seizures, drug abuse and anaphylactoid reactions.

**Clinical Implications.** Tramadol has limited indication for management of acute pain in dentistry, possibly as an alternative analgesic when gastrointestinal side effects contraindicate the use of nonsteroidal anti-inflammatory drugs and when codeine/acetaminophen combination analgesics are not well-tolerated or are contraindicated.

**M**anagement of acute orofacial pain in dentistry has traditionally relied on peripherally acting analgesics (that is, acetaminophen, ibuprofen, naproxen) and centrally acting analgesics (that is, codeine, hydrocodone, oxycodone). When managing moderately severe or severe postoperative dental pain, clinicians frequently prescribe peripheral and opioid analgesic combinations. A recent survey of community pharmacies revealed that three opioid/acetaminophen combinations were among the 50 most prescribed drugs in the United States in 1998: hydrocodone/acetaminophen, codeine/acetaminophen and propoxyphene/acetaminophen.<sup>1</sup>

## TRAMADOL HYDROCHLORIDE

Although available in Germany since 1977, tramadol hydrochloride (Ultram, McNeil Pharmaceuticals) was only recently approved for use in the United States as an orally administered analgesic. Tramadol is unique in that part of its centrally acting pain relief is mediated through non-opioid mechanisms.<sup>2</sup> Since its introduction to the U.S. market in 1994, surveys of community pharmacies have reported a dramatic increase in the number of prescriptions for tramadol. In 1995, tramadol was ranked as the 113th most frequently prescribed drug<sup>3</sup>; in 1998, tramadol's

ranking had jumped to 37th.<sup>1</sup>

This article summarizes tramadol's unique analgesic pharmacology, compares its efficacy with that of commonly prescribed analgesic formulations containing combinations of codeine and peripherally acting analgesics, and concludes with recommendations for its possible use in dental practice.

#### ANALGESIC PROPERTIES

Tramadol hydrochloride is a novel, centrally acting analgesic with two complementary mechanisms of action: opioid and aminergic. Part of its analgesia is thought to be due to inhibition of norepinephrine and serotonin reuptake within pain pathways of the central nervous system.<sup>2,4</sup> Additional analgesia is derived from tramadol's relatively weak affinity for the opioid receptor. The opioid receptor-mediated analgesia seen with tramadol partially depends on its demethylated metabolite. Subjects who extensively metabolize tramadol and have higher plasma levels of this metabolite report better pain relief after receiving oral tramadol therapy.<sup>5,6</sup>

Codeine's analgesia primarily is mediated through a  $\mu$ -receptor opioid mechanism. The majority of codeine's analgesia is not due to its direct action, but is derived from its demethylated metabolite morphine.<sup>7</sup> Because tramadol's analgesia is partially due to nonopioid mechanisms, respiratory depression and drug dependence—side effects that are associated with codeine and other opioids—occur less frequently with tramadol.<sup>8</sup>

Although administered both orally and parenterally in Europe, tramadol is available

only in an oral formulation in the United States. In patients with moderate-to-severe postoperative pain, tramadol (100 milligrams) administered intravenously or intramuscularly is approximately equal in potency to meperidine (100 mg), morphine (10 mg) and fentanyl (0.10 mg).<sup>9</sup> When administered orally, tramadol has been shown to be an effective analgesic for the treatment of moderately severe chronic pain due

***Because tramadol's analgesia is partially due to nonopioid mechanisms, respiratory depression and drug dependence occur less frequently with tramadol than with codeine and other opioids.***

to cancer.<sup>10</sup> However, when this pain becomes severe, morphine appears to provide superior pain relief.<sup>11</sup>

**Tramadol vs. codeine combinations.** When evaluated for relief of pain after oral surgery, 50 mg and 100 mg of tramadol have been shown to provide maximum pain relief that is somewhat greater than that of codeine alone and somewhat less than that of aspirin with codeine or acetaminophen with codeine.<sup>12-15</sup> Using the established third-molar extraction model to evaluate oral analgesic drugs,<sup>16,17</sup> a recent study<sup>13</sup> evaluated 192 subjects for six hours after they received a single dose of 100 mg of tramadol, 50 mg of tramadol, 60 mg of codeine, 650 mg of aspirin

with 60 mg of codeine, or placebo. At the one-hour evaluation, the aspirin/codeine combination provided the maximum pain relief. Tramadol (100 mg and 50 mg) was more effective than 60 mg of codeine, particularly at the four-, five- and six-hour pain assessments.

In another study, Brown and colleagues<sup>12</sup> administered four doses of tramadol at six-hour intervals after dental surgery and found that 100 mg and 75 mg provided effective analgesia. When evaluated for pain relief in patients after orthopedic surgery, 100 mg of tramadol was reported to be less effective than 1,000 mg of acetaminophen in combination with 60 mg of codeine.<sup>18</sup> Unlike aspirin, acetaminophen and codeine, which have three- to four-hour analgesic durations, tramadol has an analgesic duration that appears to extend to the fifth and sixth hour after single-dose administration.<sup>12,13</sup>

Few studies in the oral surgery model have compared tramadol with a full therapeutic dose of acetaminophen or one of the nonsteroidal anti-inflammatory drugs, or NSAIDs, such as aspirin, ibuprofen, naproxen or diflunisal. In one study that evaluated pain relief in patients after undergoing gynecologic procedures, the authors found that the analgesic efficacy of tramadol was similar to that of a full therapeutic dose of naproxen.<sup>19</sup> Because a placebo was not included in the study design, the significance of this study's conclusion is limited.

**Tramadol vs. an NSAID.** In their study of patients who underwent hysterectomy, Ilias and Jansen<sup>20</sup> compared intravenous tramadol with two doses of intravenous lornoxicam, a

parenteral NSAID, and reported a patient preference for the higher dose of the NSAID. It is difficult to compare findings in hospitalized surgical patients with findings in patients undergoing third-molar extractions on an outpatient basis. Analgesic efficacy in these two settings may vary, particularly when opioids and opioid combinations are studied.<sup>21</sup>

Although the peak pain relief provided by oral tramadol, when administered alone, does not appear to be as great as that of aspirin/codeine or acetaminophen/codeine, there may be some therapeutic advantage to tramadol if it is used in combination with a peripherally acting NSAID analgesic. Clinical evaluations should be undertaken to determine if a combination of tramadol with a long-acting NSAID is an effective postoperative analgesic formulation. The findings of a preliminary report on the combined use of tramadol and diclofenac support the possibility of greater pain relief provided by this combination strategy than that provided by tramadol alone.<sup>22</sup>

#### SIDE EFFECTS

The most common side effects reported in patients receiving tramadol therapy are predominantly of mild intensity: dizziness, nausea and vomiting; headache; and somnolence.<sup>21</sup> The prescribing information for tramadol reports incidences of dizziness (26 percent of patients), nausea (24 percent), constipation (24 percent), headache (18 percent), somnolence (16 percent), sweating (6 percent) and dry mouth (5 percent) with short-term use (letter

to healthcare professionals, Ortho-McNeil Pharmaceuticals, March 20, 1996). According to the manufacturer, the rates of adverse events with tramadol are similar to those for acetaminophen with codeine (30 mg) and aspirin with codeine (30 mg). The incidence of gastrointestinal side effects in patients receiving tramadol therapy as well as codeine and codeine combination therapy

***There may be some therapeutic advantage to tramadol if it is used in combination with a peripherally acting nonsteroidal anti-inflammatory drug.***

may be increased by the ambulatory nature of outpatient dental treatment.<sup>23</sup>

Investigations of tramadol therapy in patients with pain due to cancer and in patients receiving methadone maintenance therapy found that the potential for drug abuse of tramadol is low.<sup>24,25</sup> Data from 13,802 patients evaluated during early postmarketing surveillance studies indicated that the opioid adverse events of respiratory depression, urinary retention and constipation are seldom reported with tramadol therapy.<sup>26</sup> A review of tramadol overdose reactions seen in emergency departments noted that neurological toxicities such as agitation and seizures were more apparent than respiratory depression.<sup>8</sup>

An unpublished 1996 review

of adverse events spontaneously reported by some of the approximately five million patients who have received tramadol therapy in the United States noted a possible risk of seizures, drug abuse and anaphylactoid reactions (letter to health care professionals, Ortho-McNeil Pharmaceuticals, March 20, 1996). Patients who have seizure disorders or are taking concomitant medications that increase the risk of seizures, such as tricyclic antidepressants, neuroleptics, monoamine oxidase inhibitors and selective serotonin reuptake inhibitors (for example, fluoxetine and sertraline), should not be given tramadol.<sup>27</sup> However, adhering to dosage guidelines appears to minimize many of these reactions.

Clinicians should not prescribe tramadol for patients with a history of opioid drug dependence. They should adjust the tramadol dosage for patients who have limited renal and hepatic function, are older than 75 years of age or are concomitantly taking a drug that alters oxidative drug metabolism. Tramadol is contraindicated in patients with a history of allergy to tramadol, codeine or other opioids.

Unlike combinations of acetaminophen with codeine, hydrocodone or propoxyphene as well as aspirin/codeine formulations that are classified as Schedule III drugs, tramadol is not at this time considered a controlled substance and can be prescribed without a Drug Enforcement Administration license. Because of limited experience in the United States, tramadol is not currently recommended for children younger than 16 years of age. For a com-

TABLE

TRAMADOL VS. ACETAMINOPHEN WITH CODEINE.		
VARIABLE	TRAMADOL*	ACETAMINOPHEN WITH CODEINE†
Formulations	50-milligram tablets	Acetaminophen (325 mg)/codeine (30 mg) tablets; acetaminophen (325 mg)/codeine (60 mg) tablets; other formulations with varied acetaminophen dosages
Dosing Regimen	50 to 100 mg every four to six hours, not to exceed 400 mg per day	Acetaminophen (650 mg)/codeine (60 mg) every four to six hours, not to exceed 4,000 mg acetaminophen/360 mg codeine per day
Metabolic Half-life‡	Six to nine hours	One to four hours
Duration of Analgesia	Four to six hours	Four hours
Analgesic Efficacy After Oral Surgery	Fair to good	Good to excellent
Indications	Primarily chronic pain	Acute pain
Side Effects	Nausea, dizziness, somnolence, headache	Nausea, dizziness, somnolence, shortness of breath, headache
Primary Contraindications§	Hypersensitivity to tramadol or opioids, seizure disorders, psychotropic drugs, history of drug abuse, concomitantly administered central nervous system depressants, renal and hepatic disorders, elderly and debilitated patients	Hypersensitivity to acetaminophen or codeine, head injuries, renal and hepatic disorders, elderly and debilitated, concomitantly administered central nervous system depressants, metabisulfite sensitivity**
Cost Per tablet Two-day supply††	\$0.62 \$5.58	\$0.10 to \$0.12 \$2.40 to \$2.88

\* Tramadol (Ultram, McNeil Pharmaceuticals).  
 † Acetaminophen with codeine (Tylenol with codeine, McNeil Pharmaceuticals; Phenaphen with codeine, A.H. Robbins Co.).  
 ‡ Includes half-life of active metabolites.  
 § Complete manufacturer's product information should be consulted before prescribing any medication.  
 \*\*Codeine formulations contain sodium metabisulfite preservatives.  
 †† Wholesale prices are for nine tablets of tramadol (50 mg) and 24 tablets of generic acetaminophen (650 mg)/codeine (30 mg), as listed in the Drug Topics Red Book 1997.<sup>28</sup>

parison of tramadol vs. acetaminophen with codeine, refer to the table.<sup>28</sup>

**CONCLUSIONS**

Tramadol is the first drug in a new class of centrally acting analgesics that may be a useful alternative to the opioid analgesics currently available to treat patients with moderate chronic pain. Tramadol (100 mg) may have a therapeutic advantage over codeine (60 mg)

because it induces less respiratory depression while providing equivalent or enhanced analgesia. The limited potential for drug dependence is particularly important when recommending tramadol rather than a codeine combination for chronic pain management.<sup>29</sup>

The therapeutic advantage of tramadol in managing acute postoperative pain is limited. Tramadol's maximum analgesic efficacy for relieving acute pain

after oral surgery appears to be similar to that of codeine (60 mg) alone but less than that of a full therapeutic dose of an opioid combination such as aspirin/codeine or acetaminophen/codeine.<sup>13,15</sup> Tramadol may be an appropriate alternative analgesic for treating patients with acute pain when gastrointestinal side effects contraindicate the use of NSAIDs and when codeine/acetaminophen combination analgesics

In the late 1980s, Dr. Moore received a research award sponsored by McNeil Pharmaceuticals to study the analgesic efficacy of tramadol. He currently has no financial relationship with any pharmaceutical company.

### are not well-tolerated or are contraindicated. ■

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