Things We Do for No Reason:™ Prescribing Tramadol for Inpatients in Pain

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Inspired by the ABIM Foundation's Choosing Wisely® campaign, the "Things We Do for No Reason™" (TWDFNR) series reviews practices that have become common parts of hospital care but may provide little value to our patients. Practices reviewed in the TWDFNR series do not represent clear-cut conclusions or clinical practice standards but are meant as a starting place for research and active discussions among hospitalists and patients. We invite you to be part of that discussion.

CLINICAL SCENARIO

The hospitalist admits an 80-year-old man for a chronic obstructive pulmonary disease exacerbation. The patient's history is significant for chronic right knee pain. While hospitalized, the patient reports worsening of his knee pain. Radiographs of the right knee show severe osteoarthritic changes. Since acetaminophen does not relieve the patient's pain, the hospitalist orders tramadol as needed.

BACKGROUND

Hospitalists, who commonly evaluate and treat acute and chronic pain in the inpatient setting, have a wide selection of interventions from which to choose, including tramadol. Tramadol hydrochloride is a synthetic, central-acting analgesic with multiple mechanisms of action. It is a serotonin-norepinephrine reuptake inhibitor (SNRI) with a structure similar to venlafaxine and produces antineuropathic analgesic effects.[1] Tramadol and its primary active metabolite O-desmethyltramadol (also known as the M1 metabolite) mediate its effects by binding at the mu-opioid receptor.[2] Phase I metabolism in the liver by cytochrome P450 isoenzyme 2D6 (CYP2D6) facilitates conversion of tramadol to M1 (Figure). Importantly, genetic polymorphisms in CYP2D6 result in individual variations in gene expression, which impacts the metabolism of tramadol.[2]

Although tramadol is available over the counter in some countries, in the United States it is a Schedule IV controlled substance. Tramadol consistently ranks among the top 50 prescribed medications in the United States.[3]

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WHY YOU MIGHT THINK PRESCRIBING TRAMADOL FOR PAIN MAY BE HELPFUL

Given the growing concerns regarding the use of opioids, the pharmaceutical industry has marketed tramadol as a safer opioid option for pain management. Tramadol binds at the mu-opioid receptor with an affinity that is less than 4000-fold that of morphine; the binding potency of M1, the metabolite of tramadol, is less than 5-fold that of morphine.[4] Due to its lower binding affinity at the mu-opioid receptor, tramadol is considered a weak opioid, one believed to have minimal withdrawal symptoms and a lower potential for overdose or misuse compared to other opioids.[1,5] Based on this characterization, many clinicians prescribe tramadol for elderly patients or patients otherwise at risk for medication misuse or adverse effects of opioids.[6] In addition, hospitalized patients often have contraindications to nonopioid medications (eg, acetaminophen, nonsteroidal anti-inflammatory drugs [NSAIDs]), limiting their options for pain management.

WHY PRESCRIBING TRAMADOL FOR PAIN SHOULD BE AVOIDED

Despite being marketed as an effective and safe medication, tramadol has an unpredictable metabolism, complex pharmacology, and drug-drug interactions that can cause significant adverse effects. Similar to other opioids, tramadol is associated with a risk of misuse, physiologic dependency, and overdose. In addition, tramadol has a black box warning for addiction, misuse, respiratory depression, ultra-rapid metabolism, neonatal opioid withdrawal syndrome, CYP450 drug interactions, and interactions with other central nervous system depressants.

While tramadol has multiple mechanisms of action, the literature lacks high-quality evidence (eg, large randomized controlled trials) supporting its use, especially in hospitalized medical patients. A recent retrospective study of tramadol looked at the diagnoses of 250 hospitalized patients who received tramadol for pain management. While this study did not examine efficacy, it found mild-to-moderate acute noncancer pain to be the primary reason for prescribing tramadol.[7] This study also showed the risk of severe drug-drug interactions increased the longer patients were on tramadol.[7]

As a result of the limited evidence in hospitalized patients, hospitalists must rely on outpatient studies.[8-10] The size and quality of these studies, especially given the magnitude of tramadol prescribing in the United States, make them less useful. A series of Cochrane reviews examining the beneficial effects of tramadol for neuropathic pain, osteoarthritis, and cancer pain show insufficient evidence for tramadol when compared

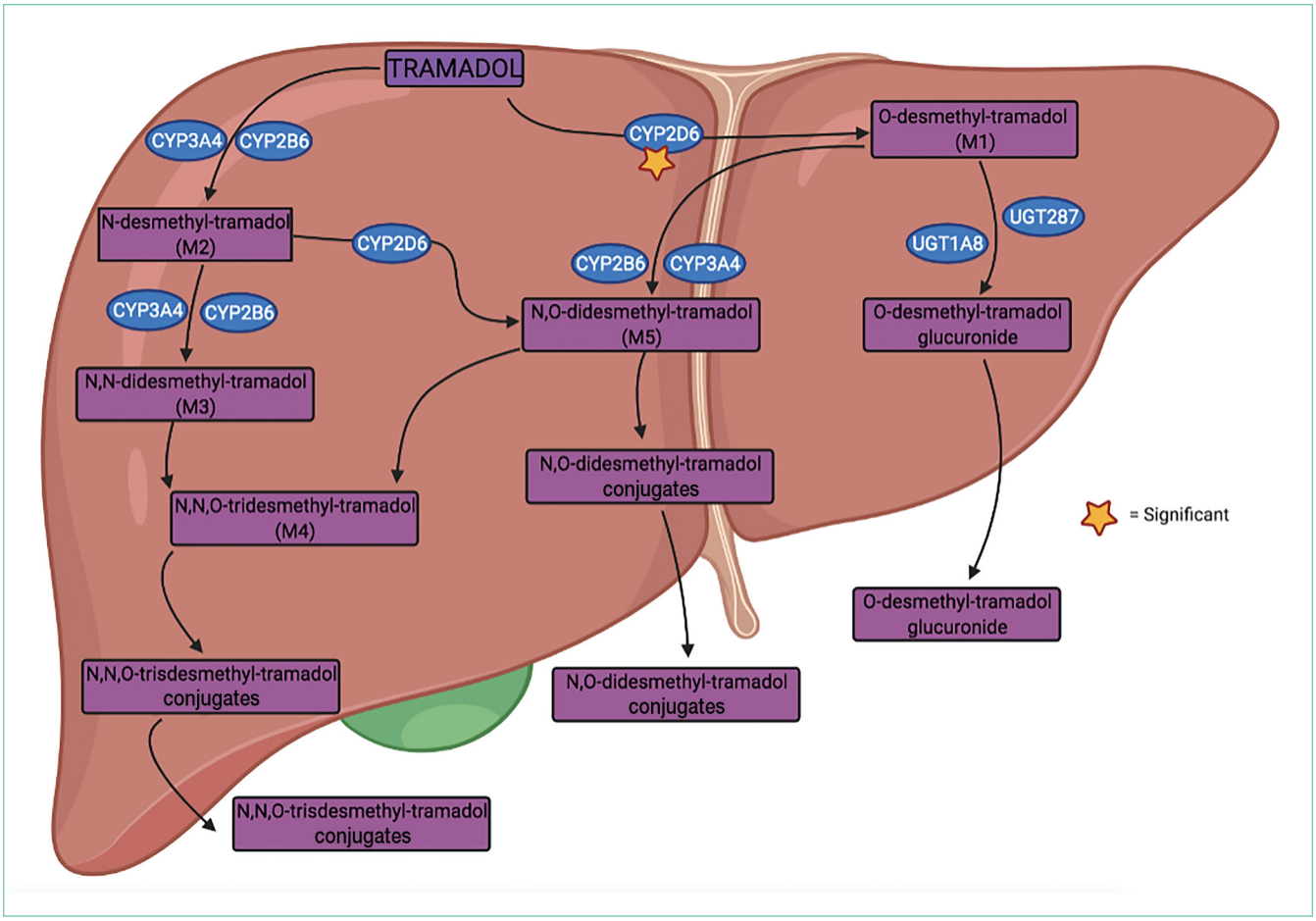

FIG. Tramadol Metabolism. Adapted from Gong et al.[2] Image is available under a Creative Commons BY-SA 4.0 license (www.pharmgkb.org/page/dataUsagePolicy).

to placebo or active controls such as acetaminophen, NSAIDs, or other opioids.[8-10]

The side-effect profile of tramadol outweighs its mild analgesic effects. The 2019 American Geriatric Society Beers criteria for potentially inappropriate medication use in older adults strongly recommends clinicians use caution when prescribing tramadol to older adult patients, as tramadol may worsen or cause hyponatremia.[11] In one large, population-based study, the use of tramadol doubled patients' risk of hospitalization for hyponatremia when compared to codeine, though the incidence remains rather low at 4.6 per 10,000 person-months.[12] Studies have also demonstrated an increased risk of hospitalization for hypoglycemia in nondiabetic patients receiving tramadol.[13] A large propensity-score matched cohort study of patients with osteoarthritis found tramadol to have an associated higher all-cause mortality compared to NSAIDs; however, these differences may be due to confounding variables.[1] In addition to hyponatremia and all-cause mortality, patients taking tramadol also have an associated increased risk of falls and hip fractures when compared to codeine or NSAIDs.[14]

The increased serotonergic activity associated with tramadol can lead to serotonin syndrome (serotonin toxicity), a rare but serious condition. Although serotonin syndrome can develop in patients taking tramadol as a monotherapy, the risk for this toxidrome increases when tramadol is taken in combination with other serotonergic agents or agents that inhibit metabolism of tramadol at CYP2D6.[5] Seizures may also occur with tramadol at therapeutic and supratherapeutic doses. Population-based studies estimate seizures occur in 0.15% to 0.86% of patients receiving tramadol, which is two to six times the risk of those not on tramadol.[5] Patients concurrently taking tramadol with a tricyclic antidepressant (TCA) or selective serotonin reuptake inhibitor (SSRI) are estimated to have seizures five to nine times more often than patients not taking a TCA or SSRI.[5] Risk factors for tramadol-induced seizure include tramadol misuse or overdose, tramadol doses >1000 mg daily (maximum recommended dose is 400 mg/day), chronic tramadol use, concurrent use of a serotonergic agent or medications that inhibit CYP2D6, and history of epilepsy, renal disease, stroke, or traumatic brain injury.[5]

Differences in the genetic polymorphisms of CYP2D6 can produce a range of CYP2D6 activity from "poor metabolizers" (little-to-no analgesic effect) to "ultra-rapid metabolizers" (enhanced analgesia and increased risk of adverse effects), leading to unpredictable pharmacodynamic effects of tramadol.[2] In North Africa and the Arabian peninsula, more than 25% of the population rapidly metabolizes tramadol; these pharmacogenomic effects result in higher rates of tramadol addiction

and overdose in these regions.[5] An estimated 7% to 10% of Caucasians slowly metabolize tramadol, which may place them at risk of adverse effects from tramadol in addition to inadequate analgesia.[15] In contrast, Ethiopian populations have the highest rate of ultra-rapid tramadol metabolism at 29%.[15]

Drugs that induce CYP2D6 (eg, dexamethasone, rifampin) or inhibit CYP2D6 (eg, bupropion, fluoxetine) also impact tramadol efficacy, pharmacokinetics, and pharmacodynamics.[16,17] Patients taking strong CYP2D6 inhibitors require significantly higher doses of tramadol to achieve analgesic effects.[17] Tramadol undergoes extensive hepatic metabolism, producing several active metabolites, including M1 (Figure). Hepatic impairment increases the elimination half-life of tramadol and its metabolites.[18] The majority of tramadol and its metabolites are eliminated through the kidneys. Accumulation of tramadol and its metabolites may occur in patients with renal impairment, placing them at increased risk of adverse effects.[2]

Finally, although some clinicians assume that tramadol has lower rates of misuse, diversion, or overdose compared to other opioids, rates of nonprescription use have increased with its proliferation.[19,20] The US Substance Abuse and Mental Health Services Administration estimates that 1,287,000 persons misused tramadol in 2019.[21] Patients may exhibit symptoms of physiologic opioid dependence and withdrawal from chronic tramadol use.[2,22] In one study, patients prescribed tramadol monotherapy for acute pain from elective surgery had an increased risk for prolonged opioid use compared to patients prescribed other short-acting opioids.[22]

WHAT YOU SHOULD DO INSTEAD

Clinicians should determine the nature of the patient's pain by obtaining a complete medical history, performing a thorough physical examination, and ordering diagnostic tests and imaging studies, as necessary. After consulting with the patient's primary care physician, the clinician should employ a multimodal approach to pain that includes topical agents, psychotherapy, injections or interventions, and nonopioid medications. Patients with neuropathic pain may benefit from adjuvant analgesics such as gabapentinoids, TCAs, or SNRIs. In patients with evidence-based indications for opioid therapy (eg, pancreatitis, cancer pain, postsurgical pain), the hospitalist should assess the risk for opioid misuse and discuss risks and benefits with the patient before considering a time-limited trial of opioid therapy. If available and when indicated, clinicians should consult with specialists in pain management or palliative care. For cases wherein clinicians have already prescribed tramadol to the patient, they should discuss deprescribing strategies and alternative analgesic options with the patient and the patient's primary care physician. Finally, before initiating tramadol therapy for hospitalized patients with pain, hospitalists should consider the risks, benefits, and alternative approaches to prescribing tramadol.

RECOMMENDATIONS

- For hospitalized patients reporting pain, complete a pain assessment by history, physical exam, chart review, and diagnostic studies to examine the etiology of the pain.
- Utilize multiple modalities for pain control when possible, including acetaminophen, NSAIDs, topical agents, ice or heat, neuropathic pain medications, and interventions such as injections, psychotherapy, or radiation, if indicated.
- Avoid prescribing tramadol due to unpredictable pharmacodynamics, adverse effects, and lack of quality evidence for efficacy in hospitalized medical patients.

CONCLUSION

Tramadol is a commonly used opioid medication associated with adverse effects and unpredictable analgesia. Regarding this case scenario, the use of tramadol in this patient places him at risk for drug-drug interactions, hyponatremia, hypoglycemia, serotonin syndrome, seizures, and pronounced side effects of opioid medications. Moderate quality evidence in the outpatient setting suggests that tramadol is unlikely to provide significant analgesia for his osteoarthritic pain.[9] Instead of prescribing tramadol, the hospitalist should consider alternative treatments for this patient's pain, such as intraarticular glucocorticoids, a short course of oral NSAIDs (unless contraindicated), topical treatments (eg, menthol, capsaicin, NSAIDs), physical therapy, and close follow-up with an orthopedist after hospital discharge. Further randomized controlled studies of tramadol vs active controls are needed.

Do you think this is a low-value practice? Is this truly a "Thing We Do for No Reason™"? Share what you do in your practice and join in the conversation online by retweeting it on Twitter (#TWDFNR) and liking it on Facebook. We invite you to propose ideas for other "Things We Do for No Reason™" topics by emailing TWDFNR@hospitalmedicine.org.

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