

Comparison of Ketorolac-Chlorpromazine With Meperidine-Promethazine for Treatment of Exacerbations of Chronic Pain

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Background: The aim was to compare the efficacy and safety of a combination of intramuscular ketorolac and chlorpromazine for the treatment of acute exacerbations of chronic pain with the more commonly used regimen of intramuscular meperidine and promethazine.

Methods: Use-effective case series were drawn from a real-life, rural emergency department practice, in which 200 consecutive patients coming to a rural emergency department with acute exacerbations of chronic pain syndromes were assigned on an every-other basis in a single-blind fashion to one of the two treatment conditions. Patients were given intramuscular doses of either 60 mg of ketorolac plus 50 mg of chlorpromazine (75 mg of chlorpromazine for patients weighing more than 100 kg), or 50 mg of meperidine plus 25 mg of promethazine (50 mg of promethazine for patients weighing more than 75 kg); patients weighing more than 100 kg were given 1.5 doses. Patients older than 65 years or whose blood pressure at the time of injection was less than 110/70 mmHg were given half-doses. Patients could receive one additional half-dose injection if they had no results within 30 to 60 minutes after the first injection. Patients were assessed on self-report and on a verbal and visual analog scale of pain rating. Temperature, blood pressure, heart rate, and respirations were monitored every 15 minutes.

Results: Both regimens performed well, with more than 90 percent of patients reporting good or excellent improvement on acute exacerbations of chronic pain. Ketorolac-chlorpromazine offered significant advantages compared with meperidine-promethazine when patients rated their pain on a visual analog pain scale ($P < 0.05$) but not on a verbal scale. Adverse reactions were minimal and consisted of more respiratory tract depression with meperidine and more vertigo or dizziness with chlorpromazine. There was no difference in incidence of hypotension between the two groups.

Conclusions: The combination of ketorolac and chlorpromazine is a safe and efficacious alternative to meperidine plus promethazine for the treatment of exacerbations of chronic pain in the rural emergency department setting. (J Am Board Fam Pract 1999;12:188-94.)

Exacerbations of chronic pain conditions are frequently encountered in the emergency department, with low-back pain and abdominal pain among the most common complaints. Narcotic analgesics, such as meperidine, have been the mainstay of emergency department therapy for these exacerbations, but these therapies are associated with the potential for abuse and addiction. In

the emergency department setting, unlike in a small group practice, each physician who sees a patient is often unaware of previous visits for treatments and prescriptions, and patients can have repeated visits for narcotic injections and prescriptions. For some patients this behavior is sufficiently reinforced that they return frequently and become labeled as drug-seekers. Because they might have genuine pain, an alternative to narcotic pain relief is desirable.

Ketorolac has been compared with narcotics for postoperative pain relief. It was superior to diflunisal in reducing pain severity during the first 9 hours of treatment, but only equally effective in overall reduction in pain severity and pain relief at the end of days 1, 2 and 3. Patients taking ketoro-

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lac reported fewer adverse events.¹ Ketorolac had a significantly faster onset of analgesia than placebo, whereas morphine just failed to reach significance compared with placebo; and there was no difference between the time of analgesic onset for ketorolac and morphine.² Among children with postoperative pain, ketorolac provided analgesia comparable to that of meperidine and significantly reduced opioid requirements, but it was not associated with reduction in postoperative vomiting or length of stay.³

The utility of ketorolac in treating acute pain when rapid relief is necessary is thought to be limited because it has a prolonged onset of analgesic action (30 to 60 min), and a significant number of patients have exhibited little or no response, slightly more than 25 percent in most studies.⁴ Ketorolac with or without meperidine is significantly better than meperidine alone for pain relief and time elapsed before the need for supplemental meperidine.⁵ Onset of analgesia with intravenous ketorolac was significantly faster than that for intramuscular ketorolac or placebo.⁶ The analgesic response and tolerability of oral ketorolac tromethamine and intramuscular morphine sulfate were significantly superior to placebo but not significantly different from each other. Morphine showed a small advantage compared with ketorolac in peak analgesic effect, but the onset of pain relief was comparable, and the incidence of adverse events favored ketorolac.⁷

There was no difference in pain behavior scores or recovery times among children receiving either ketorolac or morphine and metoclopramide postoperatively. The incidence of nausea and vomiting during the first 24 hours was less in the ketorolac group.⁸ After abdominal hysterectomy or cholecystectomy, patients receiving ketorolac had lower nursing use scores and higher levels of functioning than patients receiving meperidine during the first 3 postoperative days. Times to first bowel movement, walking without assistance, and first oral fluids were significantly shorter with ketorolac than with meperidine. Most adverse events reported by the patients were mild to moderate.⁹

In a pilot trial the use of ketorolac alone was not satisfactory for management of acute migraine pain because full efficacy for pain occurred in only 37 percent of patients (remarkably similar to a 29 percent response rate for narcotics). Patients did not feel satisfied with their pain relief or ready to

leave the emergency department. The addition of chlorpromazine seemed to be very effective, however. Because chlorpromazine alone had been used successfully to treat migraine,¹⁰⁻¹³ I designed a project to compare the combination of ketorolac and chlorpromazine with a more common narcotic combination, meperidine-promethazine, for exacerbation of chronic pain in a rural practice.

The mechanism for the effect of chlorpromazine on pain is incompletely understood but is thought to result from the ability of chlorpromazine to alter the perception of pain.¹⁴ The effect might also result from the potent antiserotonergic activity of chlorpromazine or its ability to induce an α -receptor blockade.¹⁵ Potential adverse effects include postural hypotension, seizures, and dystonic reactions.

Although randomized trials exist separately comparing ketorolac and chlorpromazine with narcotics for pain relief, no study has yet combined the two drugs. This study does so in a real-life practice, which is arguably different and more complex than the usual randomized, controlled trial environment. The objective was to determine whether a ketorolac-chlorpromazine combination could compare favorably with more common narcotic regimens in a rural emergency department setting.

Methods

A use-effectiveness case series was developed in which patients were alternately treated with one of the two treatment combinations.

Study Group

Two hundred patients were recruited from consecutive patients seen by the author. Patients were eligible for inclusion if they had a documented history of seeking treatment for the same pain at the emergency department at least twice in each of the preceding 2 years (minimum of 4 visits within 2 years for the same pain). On each of these visits they had received narcotics. They had no allergies to any of the four medications that would be given. Headache patients were not considered in this study but were part of another project. Patients were excluded if they had any evidence of malignancy; signs of nerve root compression, osteoporosis, and compression fractures; an imminently life-threatening illness; or if they were pregnant.

This subset of pain patients is burdensome for

primary care and emergency physicians. Patients whose pain is well controlled with standard, non-narcotic medications do not frequent the emergency department. The selection criteria were aimed at the subset of patients recurrently using the emergency department and narcotics for acute exacerbations of chronic pain.

Patients were told that two equally accepted methods of treating pain were being compared, either one of which the physician thought would be effective for their pain. They were told that they would receive one of the two treatments, and if it did not work, they would receive the other treatment. Patients who agreed to participate were assigned on an alternating basis to one of the two treatment conditions. Alternate assignment was most practical for the busy emergency department setting. Informed consent was requested, and patients signed a written consent-for-treatment form.

Patients with abdominal pain had been previously evaluated extensively for acute conditions potentially responsive to surgery with negative results. Patients with back pain all reported acute exacerbations of chronic conditions. Patients were not accepted into the study if their back pain was sufficiently mild to allow them to continue working uninterrupted. All patients with back pain who were included in the study suffered work loss.

A method of administration was needed that would be effective but minimize nursing time. The intravenous route has been studied best, but it is time-intensive for nursing staff; therefore, an intramuscular route of administration was chosen.

Outcome Measurement

The verbal and visual pain analog scales^{12,16} were already used routinely in the emergency department to rate pain and pain relief before and after the administration of pain medication. These pain-rating scales were administered on admission, 30 minutes after treatment, and at discharge by nurses who were not aware that a study was being conducted. The patient rates pain using five separate verbal categories (Table 2), each of which is associated with a face at five equally spaced intervals ranging from frowning with tears to happy and smiling. This scale was to aid non-English-speaking patients. The visual pain analog scale is measured in centimeters with 0 cm being no pain and 100 cm being unbearable pain. Side effects

and relief of nausea were routinely recorded in the nursing notes.

Before beginning the study, the full-time emergency department nurses were compared in their use of pain-rating scales; the results of more than 1 nurse assessing the same patient reached complete agreement 87 percent of the time. This outcome was expected, because the scale depends primarily on the patients, who must rate their pain from 0 to 10 or choose a point on a visual scale that corresponds to their pain. The rating at time of discharge was used for assessing medication effectiveness. Patients who left before 1 hour were reassessed at the time of discharge. The author's prestudy bias was that the patients treated with meperidine-promethazine would have better pain relief.

Treatment Conditions

Patients were given intramuscular doses of either (1) 60 mg of ketorolac combined with 50 mg of chlorpromazine, or (2) 50 mg of meperidine combined with 25 mg of promethazine if less than 75 kg or 50 mg of promethazine of more than 75 kg. Patients older than 65 years were given one-half dosages of all drugs. Patients whose blood pressure at the time of injection was less than 110/70 mmHg were also given half-doses. Patients weighing more than 100 kg were given a 1.5 dose. Patients could receive one extra injection of 0.5 mg/kg (0.25 mg/kg if older than 65 years) if they had no results within 30 to 60 minutes after the first injection. Blood pressures were monitored automatically every 15 minutes for up to 1 hour after injections. Patients with marked hypotension were given a fluid bolus of normal saline solution. If patients were pain-free or sufficiently pain-free to request discharge and had shown no hypotensive tendencies, they could be discharged after 1 half hour of observation (two postinjection blood pressure recordings). Additional medication was not given if any hypotension was observed. Dosages chosen were standard for the respective medications.

Nurses knew which medications they were giving and were asked to use only generic names with patients. The nurses were asked to communicate enthusiasm about whatever medications they used for pain relief, though a bias appeared to exist in favor of meperidine-promethazine being more effective than ketorolac-chlorpromazine.

Table 1. Demographic Characteristics of Pain Patients.

Characteristics	Ket-CPZ	Mep-PMZ	Chi-Square
Male, %	40	39	0.0209
Female, %	60	61	0.0209
Age, years (range)	33.17 (18 - 91)	41.91 (21 - 81)	1.0601 (<i>t</i> -test)
Duration of acute pain, hours (range)	21.5 (2 - 431)	19.8 (7 - 350)	0.3587 (<i>t</i> -test)
Type of pain, %*			
Back	45	34	2.5316
Abdominal	36	41	0.5279
all other	19	25	1.0490
Race, %			
Hispanic	35	44	1.6947
White	38	37	0.0213
African American	20	15	0.8658
Native American	7	3	1.6842
Asian	0	1	1.0050

Ket-CPZ - ketorolac-chlorpromazine, Mep-PMZ - meperidine-promethazine.

*The same patient could have more than one type of pain.

Statistical Analysis

Log-likelihood estimates were used with the chi-square method for calculating levels of statistical significance for comparisons between groups, except that the Student's *t* test procedure was used for comparing values that were means.

Results

There were no statistically significant demographic differences between the two groups of patients being treated with ketorolac-chlorpromazine and with meperidine-promethazine (Table 1). Female patients were more common in both groups. Patients were generally in their fourth decade of life. Duration of acute pain was almost 24 hours from exacerbation to arrival at the emergency department. The two most common types of chronic pain were back pain and abdominal pain.

Ketorolac-chlorpromazine and meperidine-promethazine provided similar levels of pain relief as rated by the verbal analog scale (Table 2). Ketorolac-chlorpromazine was better for the relief of nausea. On the visual analog scale, ketorolac-chlorpromazine performed better for mean pain rating on discharge and maximum pain rating on discharge (Table 3).

Respiratory tract depression, dry mouth, and vomiting were more common with meperidine-promethazine (Table 4). There were no differences

Table 2. Patients' Pain Assessment Using a Verbal Analog Scale.

Pain Assessment	Ket-CPZ	Mep-PMZ	Chi-Square
Description of Pain	(n = 100)	(n = 100)	
Worse	4	3	0.1480
No better	10	10	0.0000
Minimal improvement*	4	15	7.0369
Good improvement	60	52	3.0202
Excellent improvement	22	20	0.5436
Total number improved	86	87	0.2861
Effects of nausea	(n = 49)	(n = 50)	
Worse	8	7	0.1042
No better	2	2	0.0000
Minimal improvement†	1	21	25.2666
Good improvement	8	10	0.2245
Excellent improvement†	30	10	21.1564
Total number improved	39	41	0.2026

Ket-CPZ - ketorolac-chlorpromazine, Mep-PMZ - meperidine-promethazine.

**P* < 0.05.

†*P* < 0.01.

otherwise in the incidence of drowsiness, hypotension, nausea, burning at the injection site, or nasal congestion. All patients with marked hypotension responded to a fluid bolus of normal saline.

Discussion

While not a strict, randomized, clinical trial, this case series shows that the ketorolac-chlorpromazine combination can be successfully used in a rural practice setting and is as effective as narcotics in treating pain. Ketorolac-chlorpromazine had slightly significantly better results on the visual analog scale. This difference between the verbal and visual analog scale might have resulted from the use of faces, but probably has no clinical importance. Ketorolac-chlorpromazine worked better for nausea, presumably because meperidine is known to cause nausea in some patients and because chlorpromazine is a more potent antiemetic than promethazine.

Intravenous chlorpromazine for pain relief of migraine headache has been shown to be superior to intravenous dihydroergotamine or intravenous lidocaine.¹⁰ More patients experienced persistent headache relief and complete relief. Success rates in the complete relief of pain and nausea have been reported as high as 96 percent in uncontrolled trials.¹¹ Placebo-controlled trials have shown significant efficacy of chlorpromazine compared with

Table 3. Patients' Pain Assessment Using a Visual Analog Scale.

Pain Rating	Ket-CPZ	Mep-PMZ	Chi-Square
Initial			
Minimum	4.87	4.71	0.5025
Maximum	10.00	10.00	0.0000
Mean	6.45	6.12	0.4050
Final			
Minimum	0.00	0.00	0.0000
Maximum*	5.54	8.31	2.5511
Mean*	0.61	2.18	2.6056

Ket-CPZ - ketorolac-chlorpromazine, Mep-PMZ - meperidine-promethazine.

*Statistically significant difference at $P < 0.05$.

placebo for the side effects of drowsiness and asymptomatic drop in blood pressure (10 mmHg systolic).¹² Intravenous chlorpromazine has been compared favorably with intravenous meperidine,¹⁴ as has intramuscular chlorpromazine.¹⁷ Others have also reported efficacy of intravenous chlorpromazine.^{18,19} For acute, nonmigrainous headache pain, ketorolac, meperidine, and placebo did not differ in degree of pain relief.²⁰

Ketorolac has also been studied elsewhere as an agent for acute pain relief. Among children ketorolac provided a degree of postoperative analgesia comparable with that of meperidine.²¹ In one study ketorolac had a significantly faster onset of analgesia when compared with placebo and no difference in onset of analgesia when compared with morphine,²² whereas in another study meperidine had a more rapid onset of action than ketorolac during the first 2 postoperative hours; thereafter, meperidine and ketorolac were equally effective.²³

Among postoperative adults being medicated for postoperative pain, intramuscular ketorolac and intramuscular morphine had comparable times of analgesic onset and similar analgesic effects.^{24,25} The exception to these findings was a study showing that morphine was more efficacious for the treatment of postoperative pain following tubal ligation.²¹ Similarly, neither intravenous ketorolac nor intravenous morphine adequately controlled moderate to severe postoperative pain among women undergoing major abdominal gynecologic surgery.²⁶ Pelvic pain might be different from that of other surgeries. Ketorolac and the combination of ketorolac with morphine performed better than meperidine alone for

Table 4. Number of Adverse Effects Reported by Patients Taking Ketorolac-Chlorpromazine and Meperidine-Promethazine.

Adverse Effects	Ket-CPZ	Mep-PMZ	Chi Square
Drowsiness	73	94	21.2303
Nausea	14	17	0.3436
Vomiting†	1	6	3.7010
Dizziness, vertigo	6	3	1.0471
Hypotension	14	10	0.7576
Burning at injection site	2	5	1.3323
Dry mouth†	1	6	3.7010
Nasal congestion	16	18	0.1417
Respiratory depression†	1	8	5.7010
Adverse effects other than sedation	16	12	0.6645
Patients receiving fluid bolus for hypotension	7	10	0.5786

Ket-CPZ - ketorolac-chlorpromazine, Mep-PMZ - meperidine-promethazine.

* $P < 0.01$.

† $P < 0.05$.

renal colic.²⁷ Ketorolac was less efficacious than meperidine as an adjunct for conscious sedation before upper gastrointestinal endoscopy.²⁸

In patients undergoing cholecystectomy, ketorolac was associated with lower per-case costs in inpatient care (length of stay), direct nursing labor, as-required procedures, and medications relating to emesis and to gastrointestinal distress. Higher per-case costs were recorded for the primary analgesic (study drug) and for supplemental pain medications. In contrast to the substantial difference in the acquisition cost of ketorolac compared with the cost of morphine sulfate or meperidine, the cholecystectomy group taking ketorolac was associated with lower overall resource costs per patient. In joint-replacement procedures, however, the ketorolac group was associated with higher overall resource costs per patient, attributable primarily to a slightly longer postoperative length of stay.²⁹

Side effects of chlorpromazine given in the above manner are usually acceptable. Mariani³⁰ called attention to 2 patients who received a total of 60 mg of intravenous chlorpromazine (more than is usually used in the above studies); 1 experienced restlessness and an inability to take deep breaths, and the second complained of a dry mouth, restlessness, and a vague dysesthetic feeling. The symptoms in the first patient resolved

with a 5-mg intravenous dose of diazepam, and the patient was discharged. Symptoms in the second patient spontaneously resolved within 1 hour. Lane and Ross¹⁴ reported 1 patient who, after chlorpromazine was given intravenously, complained of agitation and vertigo, which also spontaneously resolved.

These paradoxical reactions are known to occur with phenothiazines, including promethazine; they can range from sensorimotor restlessness and agitation to outright toxic psychosis and should be remembered when these medications are used.^{31,32} Considered by some to be part of the spectrum of akathisia, these symptoms can occur after a single parenteral dose.³³ Women appear to be about twice as likely as men to develop these symptoms.³⁴ Patients in renal failure are particularly at risk, perhaps as a result of decreased clearance of phenothiazine metabolites.³⁵ These reactions are usually short-lived except in patients in renal failure or who are already taking oral neuroleptics.³⁰ The anticholinergic effects of phenothiazines have been implicated as a potential mechanism.³¹

The side effects encountered in this study were relatively minimal. Drowsiness was most common, which was considered desirable, because patients would go home and sleep, and when they awoke, their pain would be considerably reduced from their chronic pain condition. Because most patients visit the emergency department in the evenings, drowsiness is compatible with the patients' desires as well.

The findings of this study are consistent with those described above. For chronic pain the number of patients experiencing good or excellent improvement was high for both therapies.

Chlorpromazine has also been shown to be effective for nonmigrainous headaches,³⁶ including subarachnoid hemorrhage and subdural hematoma. This finding and the effectiveness of chlorpromazine in chronic pain syndromes argue for a general effect on pain rather than a specific effect on migraines.

The medical literature on the use of chlorpromazine for acute exacerbations of chronic pain conditions is minimal. No studies could be found of chlorpromazine being combined with ketorolac. This study reports a case series of its use, finding the combination equal to the more standard meperidine-promethazine combination. The added benefits of the ketorolac-chlorpromazine

combination are its relative lack of potential for abuse or addiction. Physicians can administer this combination without fear of reinforcing emergency visits to obtain narcotics. The combination of ketorolac and chlorpromazine might be a treatment of choice for acute exacerbations of chronic pain in the emergency setting. A possible role for oral chlorpromazine-nonsteroidal anti-inflammatory drug combinations in the management of chronic pain awaits further study.

Questions unanswered by this report include the effect of the emergency department environment and the act of giving injections for pain, the difference in effectiveness between the same medications given orally and intramuscularly, actual return rates for patients treated each way, and the question of what is lost by giving a narcotic medication. These questions await further studies.

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