Treatment of Mild to Moderate Pain of Acute Soft Tissue Injury: Diflunisal vs Acetaminophen With Codeine

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Acute soft tissue injuries create pain and limitation of function. Treatment requires analgesia and time for full recovery. Acetaminophen with codeine (650 mg plus 60 mg, respectively, every 4 to 6 hours) is used frequently as the analgesic of choice. Diflunisal (1,000 mg initially then 500 mg twice a day) vs acetaminophen with codeine was prospectively studied in the treatment of acute mild to moderate pain from soft tissue injuries. Thirty-five patients with acute strains, sprains, or low back pain were randomized to treatment (17 acetaminophen with codeine vs 18 diflunisal). Both groups were similar in the amount of pain and type of injury at initiation of therapy. Patient pain rating went from 3.3 ± 0.6 to 1.6 ± 1.5 for acetaminophen with codeine and from 3.3 ± 0.6 to 1.3 ± 1.1 for diflunisal. However, 65 percent of acetaminophen with codeine patients experienced side effects, with 35 percent of these patients stopping the medication because of intolerable side effects. In the diflunisal group, 28 percent of the patients experienced side effects and 5 percent had to stop the medication early. Diflunisal was found to be an effective analgesic in mild to moderate pain of acute soft tissue injuries, and caused fewer and more tolerable side effects than did acetaminophen with codeine.

Minor injuries of the soft and musculoskeletal tissues commonly occur during normal activity at work, in the home, and during recreation. These injuries, while not of a serious nature, are unpleasant and can cause considerable discomfort and alteration in lifestyle for days or even weeks. Treatment of these injuries usually involves the use of analgesics and adjunctive therapy, consisting of rest and the use of ice or elevation.[1]

An appropriate analgesic would be generally efficacious, have a minimum of side effects, and low addiction potential. Diflunisal, a nonsteroidal anti-inflammatory drug with a duration of action of 10 to 12 hours,[2] has been shown to be an effective analgesic in oral surgery,[2,3] postoperative pain,[4] and the pain associated with osteoarthritis[5] or rheumatoid arthritis.[6] Diflunisal was shown to be associated with less gastrointestinal occult blood loss[7] and less interference with platelet function[8] than aspirin. Habituation, tolerance, or addiction have not been reported. Acetaminophen combined with codeine has frequently been used in the treatment of minor soft tissue injuries, but may be habit forming.[9] The dosage schedule for diflunisal is every 8 to 12 hours, whereas acetaminophen with codeine is taken every 4 to 6 hours. To compare efficacy and tolerability, a prospective randomized study of diflunisal and acetaminophen with codeine in the management of mild to moderate pain associated with acute soft tissue injuries was undertaken.

METHODS

Patients who presented at a primary care setting for the treatment of mild to moderate acute pain from a sprain or strain or with mild to moderate low back pain were eligible for participation. Patients were excluded if they had severe pain as judged by the physician, a fracture, laceration requiring sutures, hematoma greater than 3 cm, were pregnant or breast feeding, were taking other nonsteroidal anti-inflammatory medications, or had a history of peptic ulcer disease, bleeding disorder, or sensitivity to analgesics. After obtaining informed consent, patients were randomly

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TABLE 1. EFFICACY OF DIFLUNISAL VS ACETAMINOPHEN WITH CODEINE IN ACUTE SOFT TISSUE INJURIES

	Pain Relief		Limitation of Function	
	Initial Rating	Final Rating	Initial Rating	Final Rating
Diflunisal (mean ± standard deviation)	3.3 ± 0.6	1.3 ± 1.1	3.1 ± 0.8	1.5 ± 1.3
Acetaminophen with codeine (mean ± standard deviation)	3.3 ± 0.6	1.6 ± 1.5	2.9 ± 0.9	1.9 ± 1.8

Pain: 1 = minimal, 2 = mild, 3 = moderate, 4 = severe
Limitation: 1 = minimal, 2 = mild, 3 = moderate, 4 = severe

assigned to receive either diflunisal (Dolobid MSD) 1,000 mg initially, followed by 500 mg every 12 hours as needed, or acetaminophen (650 mg) with codeine (60 mg), one or two tablets initially, and then one or two every four to six hours as needed for the treatment of mild to moderate pain. Concomitant therapy with the use of ice, elevation, or rest was allowed, but no other drugs for pain or sedation were utilized.

Patients completed an initial assessment of their perception of the degree of pain and the degree of limitation of motion and then completed a daily report card indicating the amount of pain and limitation and the amount of medication taken. Pain was assessed as none(0), minimal(1), mild(2), moderate(3), or severe(4). Limitation of motion was assessed as none(0), minimal(1), mild(2), moderate(3), or severe(4). Patients were followed for a maximum of seven days or until they discontinued medication because of either no further pain or disability, or the development of side effects that were not tolerable. Statistical analysis was done using the *Statistical Package for Social Studies* program for personal computers,[10] comparing patients on entry and at the discontinuation of the medication, and comparing incidence of side effects.

RESULTS

Forty-two patients entered into the study. Seven patients (four in the group taking acetaminophen with codeine and three in the group taking diflunisal) failed to return for follow-up evaluation. Analysis of the results is based on the 35 patients who were available for final follow-up. Eighteen patients received diflunisal and 17 patients received acetaminophen with codeine.

The mean age was 30.1 ± 11.1 years for acetaminophen with codeine and 36.7 ± 13.0 years for diflunisal (nonsignificant). Sixty percent of both groups were male. The number of days the injury occurred before initiation of therapy was similar, 2.1 ± 2.5 acetaminophen with codeine vs 3.1 ± 3.1 diflunisal (nonsignificant).

The initial pain rating (1 minimal, 2 mild, 3 moderate, and 4 severe) was identical, 3.3 ± 0.6 acetaminophen with codeine vs 3.3 ± 0.6 diflunisal. Only patients whose pain was assessed as mild to moderate by the physician were included. Initial limitation of motion rating (1 minimal, 2 mild, 3 moderate, 4 severe) was not significantly different, 2.9 ± 0.9 acetaminophen with codeine vs 3.1 ± 0.8 diflunisal.

The predominent injury type in both treatment groups was a muscle strain (71 percent acetaminophen with codeine, 72 percent diflunisal). The most common location of the injury was the back (44 percent acetaminophen with codeine, 61 percent diflunisal).

Final pain rating was less in the diflunisal group, but not significantly different from the acetaminophen with codeine group, 1.6 ± 1.5 acetaminophen with codeine vs 1.3 ± 1.1 diflunisal. Final limitation rating was also less in the diflunisal group but again not significantly different, 1.9 ± 1.8 acetaminophen with codeine vs 1.5 ± 1.3 diflunisal (Table 1).

Pretreatment and post-treatment pain assessment showed that both groups did receive pain relief, 3.3 ± 0.6 to 1.6 ± 1.5 acetaminophen with codeine ($P < .05$) and 3.3 ± 0.6 to 1.3 ± 1.1 diflunisal ($P < .007$). However, for those patients who required a full seven days of treatment, the pain rating in the acetaminophen with codeine group went from 3.5 ± 0.5 to 2.3 ± 1.6, whereas the diflunisal group went from 3.0 ± 0.5 to 1.5 ± 1.0. Perception of limitation at the end of seven days of treatment went from 3.2 ± 1.2 to 3.0 ± 1.5 for the acetaminophen with codeine patients and from 3.2 ± 0.7 to 1.7 ± 1.0 for the diflunisal patients.

Although the diflunisal-treated group seemed similar in outcome to the acetaminophen with codeine group, a closer look revealed some important differences. More patients had to discontinue acetaminophen with codeine than diflunisal.

Discontinuation of the medication was primarily related to side effects. Eleven patients treated with acetaminophen with codeine experienced at least one side effect (65 percent) whereas only five patients treated with diflunisal experienced side effects (28 percent) ($\chi^2 = 3.43$, $P = .06$). Multiple side effects occurred in five patients treated with acetaminophen with codeine and in only one patient treated with diflunisal.

The acetaminophen with codeine group had 17 different side effects with the most frequent problems being nausea (5), drowsiness (3), dizziness (3), and constipation (2). Indigestion, abdominal cramps, headache, and chest tightness occurred only once.

The diflunisal group had seven different side effects with one patient experiencing nausea, indigestion, and diarrhea. The other side effects occurring in one patient each were nausea, drowsiness, sweating, and dysuria.

DISCUSSION

Injuries at home, at work, and during recreation are a significant cause of morbidity in today's society. The treatment of these injuries requires an appropriate analgesic with an acceptable efficacy and tolerability profile so that there will be a minimal amount of lost time from work, school, recreation, or other activities of daily living. Diflunisal has been shown to be an effective analgesic in a number of clinical settings and significantly better than placebo.[11]

Patients with acute soft tissue injuries were randomized to compare the analgesic efficacy and tolerability of diflunisal with acetaminophen with codeine. Patients were instructed to use the medication until (1)they had no further pain, (2)they experienced side effects that were not tolerable, or (3)they had completed seven days of therapy. Diflunisal provided equal relief of pain and showed a trend toward better tolerability compared with acetaminophen with codeine. This comparable analgesic efficacy of diflunisal has been demonstrated when compared with other commonly used oral analgesics.[12-14]

Pain is not the sole concern of patients with soft tissue injuries. The limitation of normal function due in part to the presence of pain may be more critical to the resumption of their daily activities. Again, in the present study diflunisal was as effective as acetaminophen with codeine and had a trend toward greater efficacy in reducing this limitation.

Additionally, patients who required seven days of therapy had different outcomes between the groups. These patients probably reflect a more severe injury, and since treatment with either medication may not alter the time required to achieve normal function, it is instructive to see where these patients were after seven days of analgesics. The acetaminophen with codeine patients' pain rating improved slightly (3.5 to 2.3) but not limitation of function (3.2 to 3.0). However, the diflunisal patients' pain rating (3.0 to 1.6) and limitation of function (3.2 to 1.7) improved significantly. While the treatment provided equivalent pain relief, the diflunisal group felt they had less restriction of daily functioning after seven days of therapy.

The side effects profile of these medications was quite different, however. Significantly more patients had at least one side effect with acetaminophen with codeine, and 35 percent of these patients had to discontinue the medication because of intolerable side effects. Most side effects encountered involved the gastrointestinal and central nervous systems and were similar to side effects reported in other studies.[11] Similarly low incidence of tolerable side effects with diflunisal have been reported in young adults[12,13] and in the elderly.[15]

In summary, acute soft tissue injuries in a primary care setting are usually self-limiting. Treatment goals are to reduce pain and disability with minimal side effects until sufficient healing time has elapsed. In this study, diflunisal was found to be an effective analgesic in the treatment of mild to moderate pain of acute soft tissue injuries. Diflunisal is particularly useful in this ambulatory setting by providing significant analgesic efficacy with a long duration of action. This longer duration of action permits the convenience of less frequent dosing with no reports of tolerance or habituation. Diflunisal has an excellent tolerability profile and is a suitable alternative to acetaminophen with codeine in the management of mild to moderate pain of acute soft tissue injuries.

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