ORIGINAL RESEARCH

Annals of Internal Medicine

Oral Prednisolone in the Treatment of Acute Gout

A Pragmatic, Multicenter, Double-Blind, Randomized Trial

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Background: Two recent double-blind, randomized, controlled trials (RCTs) showed that oral steroids and nonsteroidal anti-inflammatory drugs have similar analgesic effectiveness for management of gout, but the trials had small sample sizes and other methodological limitations.

Objective: To compare the effectiveness and safety of oral prednisolone versus oral indomethacin in patients presenting to emergency departments (EDs) with acute gout.

Design: Multicenter, double-blind, randomized equivalence trial. Patients were randomly assigned (1:1 ratio) to receive either indomethacin or prednisolone. (ISRCTN registry number: ISRCTN45724113)

Setting: Four EDs in Hong Kong.

Participants: 416 patients aged 18 years or older.

Measurements: Analgesic effectiveness was defined as changes in pain (at rest or with activity) greater than 13 mm on a 100-mm visual analogue scale. Outcomes were measured during the first 2 hours in the ED and from days 1 to 14.

Results: 376 patients completed the study. Equivalent and clinically significant within-group reductions in mean pain score were observed with indomethacin and prednisolone in the ED (approximately 10 mm [rest] and 20 mm [activity]) and from days 1 to 14 (approximately 25 mm [rest] and 45 mm [activity]). No major adverse events occurred during the study. During the ED phase, patients in the indomethacin group had more minor adverse events than those in the prednisolone group (19% vs. 6%; $P < 0.001$). During days 1 to 14, 37% of patients in each group had minor adverse events.

Limitation: Diagnosis of gout was usually based on clinical criteria rather than examination of joint fluid.

Conclusion: Oral prednisolone and indomethacin had similar analgesic effectiveness among patients with acute gout. Prednisolone is a safe, effective first-line option for treatment of acute gout.

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Gout, the most common type of inflammatory arthritis in men, is characterized by acute attacks of inflammation induced by monosodium urate (MSU) crystals (1–4). It affects approximately 1% to 2% of adults in the United Kingdom, mainland China, Polynesia, and Africa; 3% of those in Hong Kong; and more than 3% of those in the United States (2–5).

The evidence-based recommendations for the management of gout from the European League Against Rheumatism recommend nonsteroidal anti-inflammatory drugs (NSAIDs) and/or colchicine as first-line agents despite the recognized disadvantages associated with these drugs (6–13). These recommendations make little mention of the value of oral corticosteroids in the treatment of gout. The British Society for Rheumatology and British Health Professionals in Rheumatology recommend using steroids as treatment for acute gout, but only in patients who are unable to tolerate NSAIDs or who are refractory to colchicine (14).

The most recent American College of Rheumatology guideline on gout management recommends oral corticosteroids in addition to NSAIDs and colchicine as first-line options for treatment of acute gout, based on data from 2 small randomized, controlled trials (RCTs) (15–17). General clinical acceptance of oral corticosteroids as an initial treatment option may require more robust evidence (18). Thus, the aim of this large pragmatic trial was to investigate equivalence in pain reduction and differences in safety between corticosteroids and NSAIDs in the management of patients with gout.

See also:

Summary for Patients I-30

Web-Only
Supplement

METHODS

Design Overview

We obtained ethical approval from the local institutional Research Ethics Committees to conduct a multicenter, double-blind, double-dummy RCT to test for equivalence in analgesic effectiveness of oral indomethacin and prednisolone and for superiority in safety of corticosteroids for the treatment of acute gout. Informed written consent was obtained from all participants. From January 2010 to November 2012, all patients aged 18 years or older who presented to 4 emergency departments (EDs) between 9:00 a.m. and 4:00 p.m., Monday to Friday, with acute arthritis suggestive of gout were considered for the study. Patient follow-up was completed on 26 November 2012. The original protocol and a summary of changes to it are

presented in the Supplement (available at www.annals.org).

Setting and Participants

The study was conducted in the EDs of 4 acute hospitals (Prince of Wales Hospital, Queen Elizabeth Hospital, United Christian Hospital, and Pamela Youde Nethersole Eastern Hospital) out of 17 in Hong Kong. More than 2 million patients visit these 17 EDs each year, and one third of them are treated at the 4 hospitals involved in this study. The system of emergency medicine in Hong Kong is similar to that in the United States and the United Kingdom: EDs are open 24 hours a day, 7 days a week, and have 24-hour specialist coverage. The system of outpatient care by primary care physicians in Hong Kong is generally underdeveloped; thus, a high proportion of patients with gout visit EDs for care.

Patients were eligible for the study if they presented to the ED within 3 days of symptom onset, were considered to have gout by a specialist emergency physician, and fulfilled the following 2 criteria for the diagnosis of acute gout (1, 19, 20). First, patients had to have rapid onset of severe pain, swelling, tenderness, and erythema of an affected joint, which was maximal by 6 to 12 hours. Second, patients had to have at least 1 of the following clinical findings: 1) metatarsophalangeal (MTP) joint involvement (podagra) (category A), or 2) knee, ankle, wrist, or elbow joint involvement (category B) with gouty tophi (criterion B1), previous joint aspiration confirming a diagnosis of gout (criterion B2), hyperuricemia (criterion B3), or a clinical history of 1 or more clinical gouty arthritis attacks (criterion B4). If criteria B1 to B4 were not met, we sought to confirm the diagnosis by microscopic examination of aspirated fluid from the most affected joint for the presence of MSU crystals.

Patients were excluded if they had received corticosteroids or indomethacin within 24 hours before recruitment, had a history of bleeding disorders or anticoagulant use, were allergic to a study drug, had suspected septic arthritis or another joint disease (such as rheumatoid arthritis), or had no MSU crystals found after joint aspiration. Other exclusion criteria included unstable cardiac conditions (angina pectoris, acute myocardial infarction, or heart failure), significant comorbidities that could interfere with assessment (dementia, confusion, or active gastrointestinal symptoms), a serum creatinine level greater than 200 μmol/L (>2.26 mg/dL), or an estimated glomerular filtration rate less than 30 mL/min/1.73 m^2.

Randomization and Interventions

Patients were randomly assigned in a 1:1 ratio to receive either indomethacin or prednisolone for 5 days. Initially, computer-generated randomization was performed with block sizes of 10 and was stratified by study center and category A (MTP joint involvement) or B (other joint involvement) gout. However, soon after study recruitment began, it became clear that stratification by gout type was not feasible; thus, we abandoned it and retained stratification by study center.

EDITORS' NOTES

Context

Two recent randomized, controlled trials (RCTs) showed that oral corticosteroids produced analgesic effects similar to those of nonsteroidal anti-inflammatory drugs in the management of acute gout, but these trials had methodological limitations.

Contribution

In this large, pragmatic, multicenter RCT of patients presenting with acute gout symptoms to emergency departments in Hong Kong, oral prednisolone therapy and indomethacin resulted in similar clinically significant reductions in pain. No major adverse events were reported.

Caution

The study's recruitment strategy may have missed approximately 50% of potentially eligible patients.

Implication

Oral prednisolone should be considered as a first-line treatment option for acute gout.

Our pharmacy staff prepared concealed double-dummy medication using numbered sealed envelopes and packages, with random numbers generated from a random-number table. Ten random numbers were selected for each block (5 for the prednisolone intervention and 5 for the indomethacin intervention). The randomization code was to be broken only if a physician or nurse caring for the patient (outside the study) was concerned about possible serious adverse events.

In the indomethacin group, patients initially received 50 mg (two 25-mg tablets) of oral indomethacin 3 times a day and 6 tablets of oral placebo prednisolone once a day for 2 days, followed by 25 mg of indomethacin 3 times a day and 6 tablets of placebo prednisolone once a day for 3 days. In the prednisolone group, patients initially received 30 mg (three 10-mg tablets) of oral prednisolone once a day and 2 tablets of placebo indomethacin 3 times a day for 2 days, followed by 30 mg (three 10-mg tablets) of prednisolone once a day and 1 tablet of placebo indomethacin 3 times a day for 3 days. Patients took the first dose in the presence of one of the investigators. All patients were prescribed oral paracetamol (1 g) to be taken every 6 hours as needed.

Outcomes and Follow-up

Appendix Table 1 (available at www.annals.org) provides a list of the study outcomes. We report the following outcomes: joint pain at rest and with activity (primary outcome); adverse events (secondary outcome); tenderness, redness, and swelling of the affected joint; time to resolution of symptoms; use of paracetamol; length of ED stay; patient satisfaction; adherence to study medication; visits to a general practi-

tioner or ED for further assessment and treatment; functional activity; score on the 36-Item Short Form Health Survey; demographic characteristics; and medical history (previous arthritis, kidney disease, or cardiovascular morbidity). Pain was assessed using a visual analogue scale (VAS) (0 mm [complete absence of pain] to 100 mm [the most severe pain the patient had ever experienced]) (21). Joint redness and tenderness were assessed using 3- and 5-point Likert scales, respectively.

Adverse events (each requiring a yes or no answer) were prespecified as dizziness, sleepiness, nausea, vomiting, abdominal pain, indigestion, rash, dry mouth, and any other symptom the patient reported. Major (or serious) adverse events were those that required hospitalization; all others were considered minor. Short periods of observation in an emergency medicine ward because of a possible adverse event were considered minor. We rated the type of adverse event but not the causality or duration.

Adherence was assessed in 2 ways: by checking the completeness of data in diaries and by counting unused drugs on day 5. Adherence was defined as 100% of the prescribed medications being taken on a given day; thus, if the patient reported taking less than 100%, they were categorized as being nonadherent. Patient satisfaction with analgesia and ED services was assessed on days 5 and 14 using a scale of 0 (complete dissatisfaction) to 100 (complete satisfaction).

Study outcomes were assessed in the ED by a research investigator at baseline and 30, 60, 90, and 120 minutes after the patient took the first tablets. The investigator showed patients how to assess pain with movement in a standardized way by gently moving the patient's joint through a range of motion until he or she told the investigator to stop. Patients were then asked to report their pain level using the VAS and were requested to do so during follow-up after discharge from the ED.

Patients were asked to self-rate their joints for swelling and pain and to record data in a trial diary once a day for 14 days after their visit to the ED. The trial diary included a detailed, preset checklist of all questions or questionnaires related to the study outcomes. Although the timing was left to the patients' discretion, they were instructed to score their pain level at the same time each day.

Patients were interviewed and examined by a research nurse on day 5, at which time the nurse reviewed the patients' diaries for recorded data. Each patient was contacted by telephone on day 14 for collection of data from days 6 to 14.

Statistical Analysis

The primary outcome was analgesic effectiveness, assessed as pain in the worst affected joint, which was measured using the VAS at rest and with activity. The other outcome for which we performed a sample size calculation was the presence or absence of adverse events.

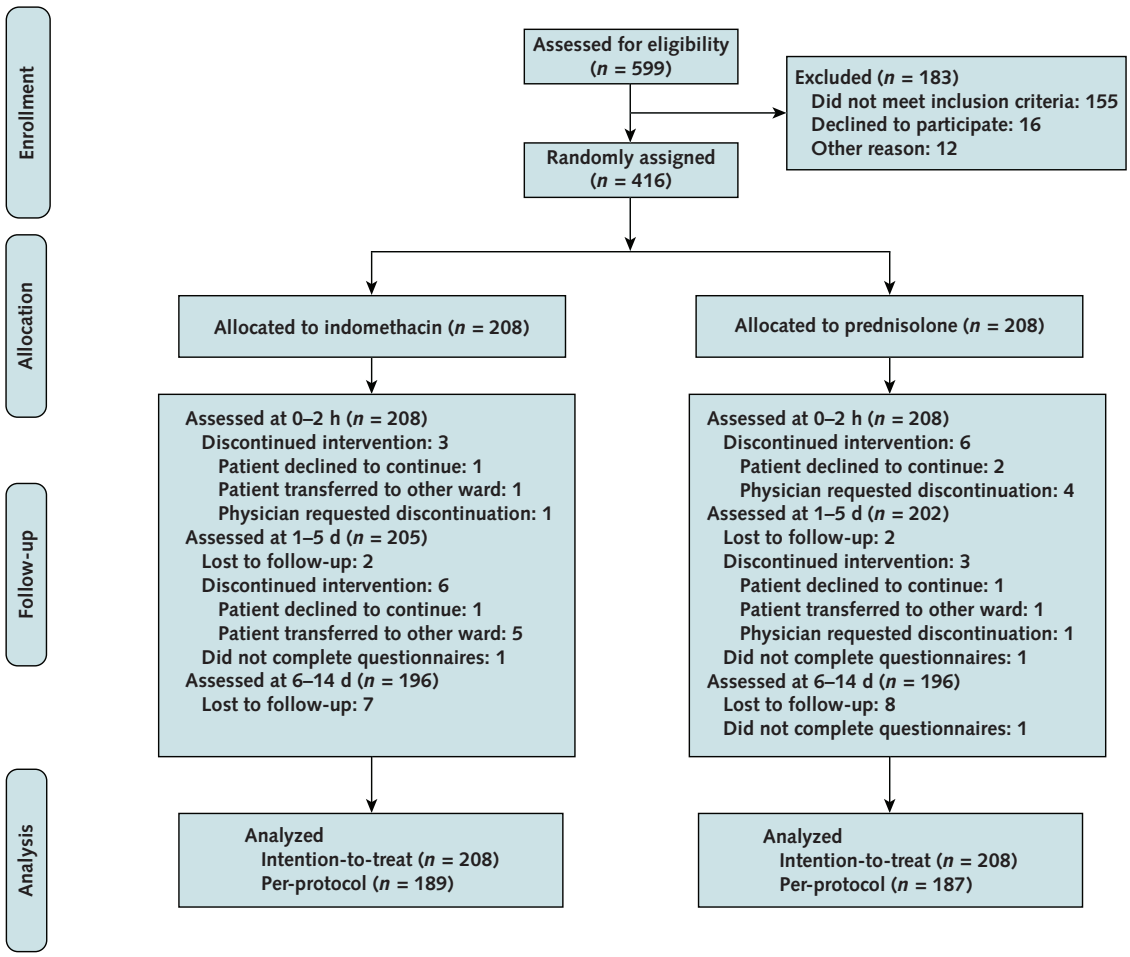
We determined that equivalence of the 2 treatments would be established if the 95% CI for the difference in analgesic effect (that is, changes in pain) was within a predefined clinically relevant range, defined for this study as ±13 mm on a 100-mm VAS. This equivalence limit was chosen because previous studies suggested that a clinically relevant difference in pain score on a 100-mm VAS is greater than 13 mm (22). Our sample size of 318 patients (159 per group) was based on a binary equivalence margin with a 2-sided significance level of 2.5%, a power of 80%, a success rate of 85%, and an equivalence limit of greater than 13 mm (yes) versus 13 mm or lower (no) (23). We aimed to enroll an extra 32 patients in each group (191 total per group) to account for a potential dropout of 20%. If we assumed a continuous margin of 13 mm and an SD of 20 mm, 100 patients (50 per group) would provide at least 80% power to detect a significant difference. In terms of adverse events, we assumed that prednisolone would be superior to indomethacin. A previous study (15) showed that the adverse event rate was 11% in the NSAID group and 2% in the steroid group. Assuming a similar difference in our study, we required a sample size of 138 patients per group (assuming a type I error rate of 2.5% and a power of 80%).

Data were analyzed using IBM SPSS Statistics software for Windows, version 20.0 (SPSS). Data are presented as means and SDs (analyzed with the *t* test) or counts and percentages (analyzed with the chi-square test unless the number of expected events in a single cell was <5, in which case the Fisher exact test was used), as appropriate. We analyzed data using both the per-protocol (PP) approach (including only patients who completed 2 weeks of follow-up) and the intention-to-treat (ITT) approach (including all randomly assigned patients) because some analysts may consider the former more appropriate for equivalence studies.

The change in pain score per hour over the 2 hours in the ED phase and the change per day in the post-ED phase (days 1 to 14) were analyzed separately. When we plotted the pain score data, we observed that the slopes decreased between days 1 and 5 but were essentially flat from days 6 to 14. Therefore, in addition to analyzing the post-ED data as a single phase, we also analyzed the data in 2 phases (days 1 to 5 and days 6 to 14). To produce summary measures of the serial readings (21) for each patient and each time frame, a multivariate linear regression curve was fit to obtain the slope (coefficient) for the change in pain score over the time frame for that patient. The means of the slopes for the patients in each treatment group were compared using the *t* test.

Categorical outcomes, such as the incidence of adverse events, joint redness and tenderness, use of paracetamol, and reattendance rate, were analyzed using the chi-square test or the Fisher exact test. Continuous outcomes, such as the number of paracetamol tablets and patient satisfaction, were analyzed using the 2-sample *t* test. A *P* value less than 0.05 was re-

Figure 1. Study flow diagram.



garded as statistically significant, and all analyses were 2-sided.

Role of the Funding Source

The Health and Health Services Research Grant Committee of the Government of the Hong Kong Special Administrative Region funded the study but had no role in the analysis, conclusions, or preparation of the manuscript for submission for publication.

RESULTS

Of 599 patients considered to have gout by the specialist emergency physician in charge, 416 fulfilled the criteria for inclusion in the study and were included in the ITT analysis. Of these, 40 did not complete follow-up (median follow-up, 2 days [25th, 75th percentiles: 0.08, 6.75 days]), leaving 376 patients for the PP analysis (Figure 1).

In both the ITT and the PP analyses, we found no important differences between treatment groups at baseline (Table 1). Most patients were male, and the mean age was 65 years. Hypertension was the most frequent comorbidity (50%), and a history of hyperuricemia or renal insufficiency was reported by 35% and 13% of patients, respectively. Most patients (74%) had a history of recurrent gout, 83% had monoarthritis, and 9% reported use of allopurinol.

The average duration of symptoms before study enrollment was 2.74 days among patients in the indomethacin group and 2.91 days among those in the prednisolone group. Forty-one percent of patients in the indomethacin group and 45% of those in the prednisolone group had MTP joint involvement (category A gout), and 65% and 60% had other joint involvement (category B gout), with tophi (criterion B1) seen in 13% to 16% of patients. At baseline, the mean pain scores for patients in the indomethacin and prednisolone groups were 36.8 mm (SD, 31.1) and 27.6 mm (SD, 28.8), respectively, at rest and 81.6 mm (SD, 21.5) and 81.4 mm (SD, 20.6), respectively, with activity.

Figure 2 shows the changes in pain score for the ED and follow-up phases in the PP analyses. Throughout all phases, there was little difference in mean pain score between groups. The 95% CI for the difference in

Table 1. Baseline Patient Characteristics, by Intention-to-Treat and Per-Protocol Analyses*

Characteristic	Intention-to-Treat Analysis (n = 416)		Per-Protocol Analysis (n = 376)	
	Indomethacin (n = 208)	Prednisolone (n = 208)	Indomethacin (n = 189)	Prednisolone (n = 187)
Hospital				
Prince of Wales Hospital	131 (63.0)	131 (63.0)	122 (64.6)	119 (63.6)
Pamela Youde Nethersole Eastern Hospital	22 (10.6)	21 (10.1)	20 (10.6)	19 (10.2)
Queen Elizabeth Hospital	31 (14.9)	29 (13.9)	26 (13.8)	28 (15.0)
United Christian Hospital	24 (11.5)	27 (13.0)	21 (11.1)	21 (11.2)
Mean age (SD), *y*	64.37 (16.01)	65.91 (14.95)	64.64 (15.59)	65.22 (15.14)
Male	164 (78.8)	145 (69.7)	153 (81.0)	134 (71.7)
Symptoms				
Mean duration (SD), *d*	2.74 (3.87)	2.91 (4.60)	2.64 (3.50)	2.79 (4.37)
Mean pretreatment pain score (SD), *mm*				
At rest	36.79 (31.13)	27.62 (28.75)	37.15 (30.71)	28.66 (29.21)
With activity	81.56 (21.53)	81.44 (20.61)	81.87 (20.49)	81.18 (20.75)
Method of arrival at ED				
Walking	38 (18.3)	34 (16.3)	34 (18.0)	30 (16.1)
Wheelchair	132 (63.4)	152 (73.1)	123 (65.1)	139 (74.3)
Stretcher	38 (18.3)	22 (10.6)	32 (16.9)	18 (9.6)
Gout-related characteristics				
Recurrent gout	148 (71.2)	158 (76.0)	134 (70.9)	142 (75.9)
High-purine diet	75 (36.1)	78 (37.5)	68 (36.0)	72 (38.5)
Family history of gout	26 (12.5)	28 (13.5)	22 (11.6)	24 (12.8)
Allopurinol use	18 (8.7)	18 (8.7)	17 (9.0)	16 (8.6)
Monoarthritis	172 (82.7)	172 (82.7)	157 (83.1)	159 (85.0)
Medical history				
Hyperuricemia	65 (31.2)	76 (36.5)	56 (29.6)	69 (36.9)
Hypertension	102 (49.0)	108 (51.9)	95 (50.3)	95 (50.8)
Hypercholesterolemia	39 (18.7)	36 (17.3)	30 (15.9)	30 (16.0)
Renal insufficiency	28 (13.5)	28 (13.5)	23 (12.2)	25 (13.4)
Joint injury	6 (2.9)	6 (2.9)	4 (2.1)	5 (2.7)
Menopause†	40/44 (90.9)	54/63 (85.7)	33/36 (91.7)	44/53 (83.0)
Myocardial infarction	13 (6.2)	5 (2.4)	10 (5.3)	5 (2.7)
Ischemic heart disease	22 (10.6)	19 (9.1)	18 (9.5)	18 (9.6)
Heart failure	17 (8.2)	11 (5.3)	14 (7.4)	11 (5.9)
Stroke	11 (5.3)	9 (4.3)	10 (5.3)	8 (4.3)
Transient ischemic attack	2 (1.0)	2 (1.0)	2 (1.1)	2 (1.1)
Peripheral vascular disease	3 (1.4)	1 (0.5)	3 (1.6)	1 (0.5)
Recent medication use				
Antihypertensive	106 (51.0)	104 (50.0)	98 (51.9)	92 (49.2)
Antidiabetic	44 (21.2)	29 (13.9)	39 (20.6)	25 (13.4)
Antihypercholesterolemic	40 (19.2)	33 (15.9)	32 (16.9)	28 (15.0)
Diagnostic inclusion criteria‡				
A	86 (41.3)	94 (45.2)	77 (40.7)	86 (46.0)
B	135 (64.9)	124 (59.6)	123 (65.1)	107 (57.2)
B1	27 (13.0)	34 (16.3)	23 (12.2)	33 (17.6)
B2	1 (0.5)	0 (0)	1 (0.5)	0 (0)
B3	70 (33.7)	74 (35.6)	61 (32.3)	63 (33.7)
B4	148 (71.2)	158 (76.0)	134 (70.9)	142 (75.9)
Joint aspiration	0 (0)	3 (1.4)	0 (0)	3 (1.6)
ED				
Admission	28 (13.5)	26 (12.5)	24 (12.7)	18 (9.6)
Mean length of stay (SD), *d*	0.21 (0.79)	0.21 (0.77)	0.16 (0.59)	0.19 (0.78)

A = metatarsophalangeal joint involvement (podagra); B = knee, ankle, wrist, or elbow joint involvement with B1, B2, B3, or B4; B1 = gouty tophi; B2 = previous joint aspiration confirming a diagnosis of gout; B3 = hyperuricemia; B4 = clinical history of ≥1 clinical gouty arthritis attack; ED = emergency department.

* Values are numbers (percentages) unless otherwise indicated. Percentages may not sum to 100 due to rounding.

† Based on the number of women in each group.

‡ Also included rapid onset of severe pain, swelling, tenderness, and erythema of an affected joint, which was maximal by 6 to 12 h. Some patients satisfied the criteria for categories A and B.

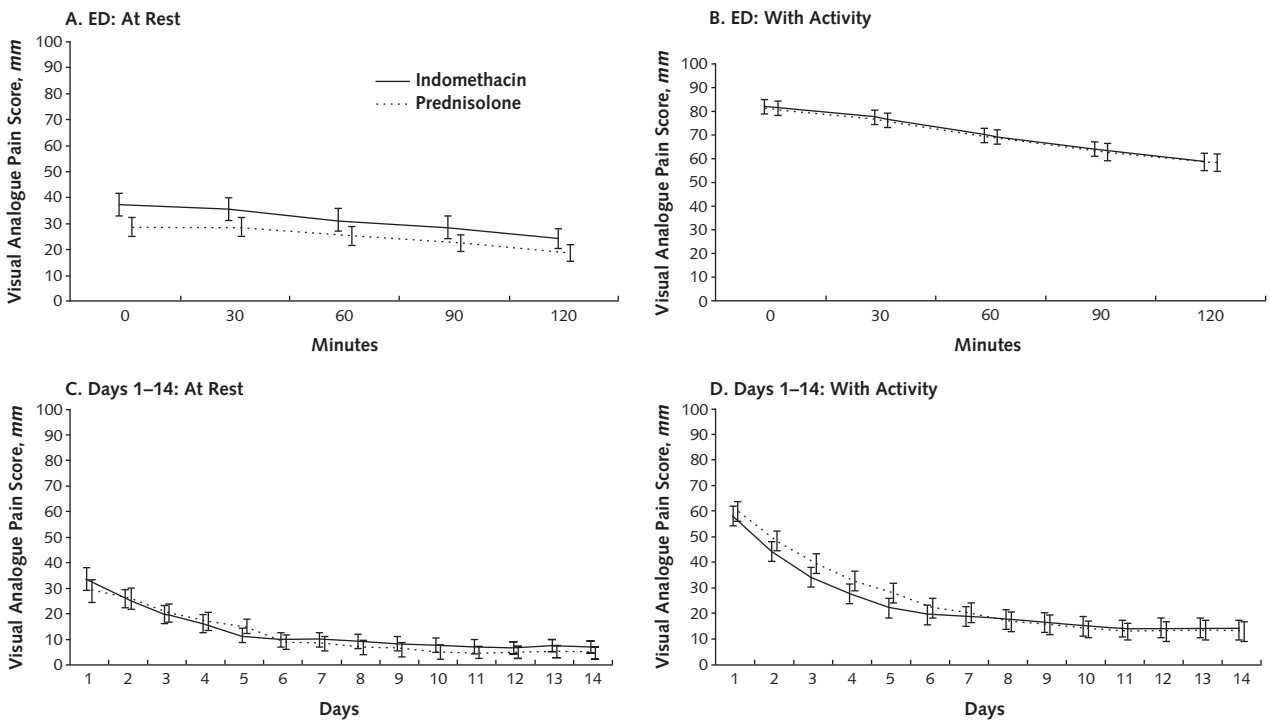
analgesic effect was within the predefined clinically relevant range of ± 13 mm in both the ED and follow-up phases and both at rest and with activity. Equivalent, clinically significant within-group reductions in mean pain score at rest and with activity were observed with indomethacin and prednisolone during the 2-week study (**Figure 2**). During the ED phase, the changes in mean pain score were approximately 10 mm at rest and 20 mm with activity, whereas during days 1 to 14, the changes were approximately 25 mm at rest and 45 mm with activity. **Appendix Table 2** (available at www.annals.org) shows the changes in pain score in the ITT (n = 416) and PP (n = 376) analyses. The number of patients with a clinically meaningful (>13 mm) decrease in pain score did not statistically differ between groups, except in patients at rest during days 1 to 5 (99 of 208 in the indomethacin group vs. 76 of 208 in the prednisolone group). Results were consistent for the PP and ITT analyses. In stratified analyses of pain at rest and with activity during the ED phase, findings were relatively consistent across the 4 hospitals (**Appendix Table 3**, available at www.annals.org).

Eight patients required discontinuation of treatment, as requested by the treating physician, because of suspected serious clinical signs or symptoms. Of these, 7 (3 with abdominal pain, 3 with dizziness, and 1 with lethargy) were from the indomethacin group. The patient from the prednisolone group had mild hyperkalemia (5.4 mmol/L; the normal range in Hong Kong is 3.5 to 5.1 mmol/L). After further observation, no patient was found to have had a serious adverse event.

A significantly greater proportion of patients in the indomethacin group had minor adverse events in the ED phase (including dizziness, sleepiness, and nausea) and the post-ED phase (including nausea and vomiting) (**Table 2**). No patients died, required hospitalization, became disabled, or were permanently harmed. A greater proportion of patients in the prednisolone group had rashes in the post-ED phase.

Changes in joint redness and tenderness, additional intake of paracetamol, and mean patient satisfaction with analgesia or ED services were similar between groups (**Appendix Table 4**, available at www.annals.org). Patients receiving indomethacin were more likely to seek further follow-up with a general practitioner or attend an outpatient clinic than those receiving prednisolone. The percentage of adherent patients (those who took 100% of the prescribed study drugs) de-

Figure 2. Mean pain scores and 95% CIs at each assessment (n = 376).



Data were analyzed per protocol. The means and 95% CIs of the coefficients (slopes) of change in pain over unit time for patients in each group were compared using the t test. ED = emergency department. **A.** Pain score at rest in the ED phase. We found no statistically or clinically significant differences between groups (P = 0.69). The mean decrease in pain score was 6.54 mm/h (95% CI, 5.02 to 8.06 mm/h) for indomethacin and 5.05 mm/h (CI, 3.56 to 6.55 mm/h) for prednisolone (mean difference, −1.49 mm/h [CI, 0.64 to −3.61 mm/h]). **B.** Pain score with activity in the ED phase. We found no statistically or clinically significant differences between groups (P = 0.56). The mean decrease in pain score was 11.69 mm/h (CI, 10.10 to 13.28 mm/h) for indomethacin and 11.38 mm/h (CI, 9.98 to 12.79 mm/h) for prednisolone (mean difference, −0.31 mm/h [CI, 1.80 to −2.42 mm/h]). **C.** Pain score at rest from days 1 to 14. We found no statistically or clinically significant differences between groups (P = 0.80). The mean decrease in pain score was 1.80 mm/d (CI, 1.46 to 2.13 mm/d) for indomethacin and 1.68 mm/d (CI, 1.39 to 1.97 mm/d) for prednisolone (mean difference, −0.12 mm/d [CI, 0.32 to −0.55 mm/d]). **D.** Pain score with activity from days 1 to 14. We found no statistically or clinically significant differences between groups (P = 0.20). The mean decrease in pain score was 2.96 mm/d (CI, 2.62 to 3.30 mm/d) for indomethacin and 3.19 mm/d (CI, 2.85 to 3.52 mm/d) for prednisolone (mean difference, 0.22 mm/d [CI, 0.70 to −0.25 mm/d]).

Table 2. Adverse Events in All Randomly Assigned Patients (n = 416)*

Variable	Intention-to-Treat Analysis		
	Indomethacin (n = 208)	Prednisolone (n = 208)	*P* Value
First 2 h in ED			
≥1 adverse event	39 (18.8)	13 (6.3)	<0.001
Dizziness	19 (9.1)	0 (0)	<0.001
Sleepiness	15 (7.2)	3 (1.4)	0.004
Nausea	7 (3.4)	0 (0)	0.015
Vomiting	2 (1.0)	1 (0.5)	1.00
Abdominal pain	4 (1.9)	0 (0)	0.123
Indigestion	1 (0.5)	0 (0)	1.00
Skin rash	0 (0)	2 (1.0)	0.24
Dry mouth	10 (4.8)	6 (2.9)	0.31
Other adverse event	4 (1.9)	3 (1.4)	1.00
Days 1–14			
≥1 adverse event	77 (37.0)	77 (37.0)	1.00
Missing	19 (9.1)	19 (9.1)	
Dizziness	31 (14.9)	24 (11.5)	0.30
Missing	23 (11.1)	22 (10.6)	
Sleepiness	27 (13.0)	26 (12.5)	0.85
Missing	24 (11.5)	22 (10.6)	
Nausea	15 (7.2)	4 (1.9)	0.009
Missing	24 (11.5)	23 (11.1)	
Vomiting	10 (4.8)	1 (0.5)	0.006
Missing	24 (11.5)	23 (11.1)	
Abdominal pain	23 (11.1)	12 (5.8)	0.051
Missing	23 (11.1)	23 (11.1)	
Indigestion	19 (9.1)	13 (6.3)	0.27
Missing	23 (11.1)	23 (11.1)	
Skin rash	2 (1.0)	11 (5.3)	0.011
Missing	24 (11.5)	23 (11.1)	
Dry mouth	22 (10.6)	35 (16.8)	0.064
Missing	24 (11.5)	23 (11.1)	
Other adverse event	18 (8.7)	22 (10.6)	0.52
Missing	24 (11.5)	23 (11.1)	
Randomization code broken	7 (3.4)	1 (0.5)	0.068

ED = emergency department.
* Values are numbers (percentages). The proportions of patients with adverse events were compared between groups by using the chi-square or Fisher exact test.

creased from 100% to 80.8% between days 1 and 5 (Appendix Table 5, available at www.annals.org).

DISCUSSION

Our findings show that oral prednisolone had analgesic effectiveness equivalent to that of an NSAID in treating pain at rest and with activity in patients with acute gout. Patients reported no serious adverse events.

Although our findings are generally similar to those of 2 recent RCTs (15, 16), we found a lower rate of major adverse events among patients treated with indomethacin (15). However, both of these trials had substantially smaller samples than our study and had methodological limitations. The first study did not present a PP analysis, which is recommended when studying equivalence (15). The second study followed patients for 90 hours and selected participants only after identification of MSU crystals, which does not reflect the real-life practice of diagnosing gout in most EDs or primary care (16). We addressed the limitations of these trials by studying a large, representative sample of patients who visited the ED for acute gout and following them for 14 days.

Gout usually affects middle-aged to elderly persons (24), who often have multiple medical problems (such as hypertension, cardiovascular disease, and renal insufficiency) (25–28). The mean age of patients in our study was 65 years, and persons in this age group have increased risk for NSAID-related gastrointestinal complications. Although the risk for severe gastrointestinal complications can be as high as 10% in patients with gout who are receiving indomethacin (15), none of these complications was seen in our study and no patient required hospitalization. One reason may be because patients with a history of upper gastrointestinal bleeding were excluded. With regard to adverse events, exclusion of these patients might have provided a slight advantage to the indomethacin group, which may have performed worse if such patients had been included, as occurred in a previous trial (15).

Our study has several potential limitations. First, the diagnosis of gout was based on clinical criteria rather than joint aspiration, and we cannot exclude the possibility that some of the enrolled patients did not have gout. Of note, however, the clinical criteria used in our study were derived from the European League Against Rheumatism guidelines and seem to be specific for gout in primary care and hospital populations in other studies (29, 30). Second, our recruiting strategy may have missed 50% of eligible patients, including those with more acute or severe symptoms who needed to visit a physician during the evening hours or weekends. Third, indomethacin was the comparator drug in our study. Although patients assigned to this drug did not have any serious adverse events, our findings may not be applicable to other NSAIDs in terms of adverse effects (2). Finally, we did not address cost-effectiveness. This may be important, especially in view of a recent Dutch meta-analysis that suggested that proton-pump inhibitors are not necessary in older patients who are treated with prednisolone as opposed to NSAIDs (31).

For many years, NSAIDs and colchicine have been used as first-line treatments for acute gout. However, their use is limited in elderly adults and in patients with comorbid conditions (such as renal insufficiency or gastrointestinal disease) because of their potential adverse effects and drug interactions. Our study provides robust evidence that oral corticosteroids are as effective at treating pain and as acceptable to patients as NSAIDs and that they should be considered as a first-line alternative to NSAIDs in the treatment of patients with acute gout.

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Appendix Table 1. Summary of the Study Measures and When and by Whom They Were Collected

Study Measure	ED	Days 1–5	Days 6–14
Pain at rest	RA	Patient	Patient
Pain with activity	RA	Patient	Patient
Adverse events	RA	Patient	Patient
Joint swelling	RA	Patient	Patient
Joint redness	RA	Patient	Patient
Joint tenderness	RA	Patient	Patient
Time to symptom resolution	RA	Patient	Patient
Use of paracetamol	RA	Patient	Patient
Length of ED stay	RA	NA	NA
Patient satisfaction	RA	Patient	Patient
Adherence to study medication	–	RA	Patient
Health care utilization for gout (visits to GP or ED)	–	Patient	Patient
Functional activity	RA	Patient	Patient
SF-36 score	RA	Patient	Patient
Demographic characteristics	RA	NA	NA
Medical history	RA	NA	NA

ED = emergency department; GP = general practitioner; NA = not applicable; RA = research assistant; SF-36 = 36-Item Short Form Health Survey.

Appendix Table 2. Change in Pain Score in the Intention-to-Treat (n = 416) and Per-Protocol (n = 376) Analyses

Variable	Intention-to-Treat Analysis*				Per-Protocol Analysis*			
	Indomethacin (n = 208)	Prednisolone (n = 208)	Difference	*P* Value	Indomethacin (n = 189)	Prednisolone (n = 187)	Difference	*P* Value
First 2 h in ED								
At rest								
Mean decrease in pain score (95% CI), *mm/h*	6.09 (4.68 to 7.50)	4.94 (3.54 to 6.34)	−1.15 (0.83 to −3.14)	0.79	6.54 (5.02 to 8.06)	5.05 (3.56 to 6.55)	−1.49 (0.64 to −3.61)	0.69
Patients with clinically significant change in pain score†, *n (%)*	71 (34.1)	56 (26.9)	−15 (−7.2)		70 (37.0)	53 (28.3)	−17 (−8.7)	
With activity								
Mean decrease in pain score (95% CI), *mm/h*	11.35 (9.84 to 12.86)	11.45 (10.12 to 12.78)	0.10 (2.10 to −1.91)	0.52	11.69 (10.10 to 13.28)	11.38 (9.98 to 12.79)	−0.31 (1.80 to −2.42)	0.56
Patients with clinically significant change in pain score†, *n (%)*	123 (59.1)	133 (63.9)	10 (4.8)		116 (61.4)	120 (64.2)	4 (2.8)	
Days 1–14								
At rest								
Mean decrease in pain score (95% CI), *mm/d*	1.67 (1.36 to 1.98)	1.52 (1.25 to 1.79)	−0.15 (0.26 to −0.56)	0.92	1.80 (1.46 to 2.13)	1.68 (1.39 to 1.97)	−0.12 (0.32 to −0.55)	0.80
Patients with clinically significant change in pain score†, *n (%)*	111 (53.4)	101 (48.6)	−10 (−4.8)		108 (57.1)	100 (53.5)	−8 (−3.6)	
With activity								
Mean decrease in pain score (95% CI), *mm/d*	2.80 (2.47 to 3.13)	2.92 (2.59 to 3.24)	0.12 (0.58 to −0.35)	0.15	2.96 (2.62 to 3.30)	3.19 (2.85 to 3.52)	0.22 (0.70 to −0.25)	0.20
Patients with clinically significant change in pain score†, *n (%)*	151 (72.6)	160 (76.9)	9 (4.3)		147 (77.8)	158 (84.5)	11 (6.7)	
Days 1–5								
At rest								
Mean decrease in pain score (95% CI), *mm/d*	3.93 (3.23 to 4.63)	2.63 (2.03 to 3.24)	−1.30 (−0.38 to −2.22)		4.17 (3.42 to 4.92)	2.78 (2.13 to 3.43)	−1.39 (−0.40 to −2.38)	
Patients with clinically significant change in pain score†, *n (%)*	99 (47.6)	76 (36.5)	−23 (−11.1)		93 (49.2)	72 (38.5)	−21 (−10.7)	
With activity								
Mean decrease in pain score (95% CI), *mm/d*	6.42 (5.64 to 7.20)	5.78 (4.99 to 6.57)	−0.64 (0.47 to −1.74)		6.71 (5.89 to 7.52)	6.16 (5.35 to 6.98)	−0.54 (0.61 to −1.70)	
Patients with clinically significant change in pain score†, *n (%)*	144 (69.2)	138 (66.3)	−6 (−2.9)		136 (72.0)	134 (71.7)	−2 (−0.3)	
Days 6–14								
At rest								
Mean decrease in pain score (95% CI), *mm/d*	0.31 (0.08 to 0.54)	0.42 (0.18 to 0.66)	0.11 (0.44 to −0.21)		0.30 (0.06 to 0.55)	0.47 (0.20 to −0.73)	0.17 (0.52 to −0.19)	
Patients with clinically significant change in pain score†, *n (%)*	27 (13.0)	33 (15.9)	6 (2.9)		22 (11.6)	33 (17.6)	11 (6.0)	
With activity								
Mean decrease in pain score (95% CI), *mm/d*	0.64 (0.30 to 0.97)	0.87 (0.52 to 1.21)	0.23 (0.70 to −0.24)		0.59 (0.24 to 0.93)	0.96 (0.58 to 1.34)	0.38 (0.89 to −0.14)	
Patients with clinically significant change in pain score†, *n (%)*	51 (24.5)	62 (29.8)	11 (5.3)		42 (22.2)	58 (31.0)	16 (8.8)	

ED = emergency department.

* The change in pain score per hour over the 2 h in the ED phase and the change in pain score per day for the post-ED phase (days 1 to 14) were analyzed separately. When we initially plotted the data, we observed that the slopes decreased between days 1 and 5 but were essentially flat from days 6 to 14. Therefore, in addition to analyzing the post-ED data as a single phase, we also analyzed the data in 2 phases (days 1 to 5 and days 6 to 14). To produce summary measures of the serial readings (21) for each patient and each time frame, a multivariate linear regression curve was fit to obtain the slope (coefficient) for the change in pain score over the time frame for that patient. The means of the coefficients for the patients in the 2 treatment groups were compared using the t test.

† Defined as >13 mm on a 100-mm visual analogue pain scale.

Appendix Table 3. Change in Mean of Summary Pain Score Coefficient for Emergency Phase Data, by Hospital (Intention-to-Treat Analysis)

Hospital	Indomethacin		Prednisolone		Difference (95% CI), *mm/h*	*P* Value*
	Patients, *n*	Change in Mean of Summary Pain Score Coefficient (95% CI), *mm/h*	Patients, *n*	Change in Mean of Summary Pain Score Coefficient (95% CI), *mm/h*		
Pain at rest						
Prince of Wales Hospital	131	6.30 (4.42 to 8.19)	131	4.88 (3.18 to 6.57)	−1.43 (1.10 to −3.95)	0.27
Pamela Youde Nethersole Eastern Hospital	22	5.10 (−0.2 to 10.40)	20	1.75 (−0.43 to 3.93)	−3.35 (2.19 to −8.89)	0.23
Queen Elizabeth Hospital	31	6.00 (3.21 to 8.79)	29	7.55 (2.06 to 13.04)	1.55 (7.52 to −4.41)	0.60
United Christian Hospital	24	5.87 (2.03 to 9.71)	27	4.78 (1.01 to 8.54)	−1.09 (4.17 to −6.36)	0.68
Pain with activity						
Prince of Wales Hospital	131	11.52 (9.63 to 13.40)	131	11.84 (10.12 to 13.55)	0.32 (2.85 to −2.21)	0.80
Pamela Youde Nethersole Eastern Hospital	22	11.50 (4.71 to 18.30)	20	10.13 (5.23 to 15.02)	−1.38 (6.73 to −9.48)	0.73
Queen Elizabeth Hospital	31	9.92 (5.93 to 13.90)	29	10.78 (7.49 to 14.06)	0.86 (5.93 to −4.21)	0.74
United Christian Hospital	24	12.17 (8.74 to 15.61)	27	11.30 (7.47 to 15.12)	−0.88 (4.21 to −5.97)	0.73

* Analyzed with the *t* test.

Appendix Table 4. Other Secondary Outcomes Analyzed in Intention-to-Treat (n = 416) and Per-Protocol (n = 376) Analyses

Secondary Outcome	Intention-to-Treat Analysis*			Per-Protocol Analysis*		
	Indomethacin (n = 208)	Prednisolone (n = 208)	*P* Value	Indomethacin (n = 189)	Prednisolone (n = 187)	*P* Value
Joint redness						
Mean change from day 0 to day 14 (SD), *mm*	1.15 (0.73)	1.10 (0.72)	0.57	1.15 (0.74)	1.09 (0.72)	0.50
Joint tenderness						
Mean change from day 0 to day 14 (SD), *mm*	2.37 (1.48)	2.32 (1.44)	0.76	2.36 (1.48)	2.31 (1.44)	0.73
Use of paracetamol						
Days 1 to 5, *n (%)*						
No	93 (44.7)	97 (46.6)	0.84	89 (47.1)	92 (49.2)	0.91
Yes	101 (48.6)	101 (48.6)		94 (49.7)	95 (50.8)	
Missing	14 (6.7)	10 (4.8)		6 (3.2)	0 (0)	
Mean tablets taken (SD), *n*	5.2 (8.5)	5.9 (9.6)	0.49	5.4 (8.7)	5.9 (9.6)	0.61
Days 6 to 14, *n (%)*						
No	127 (61.1)	131 (63.0)	0.71	120 (63.4)	127 (67.9)	0.63
Yes	61 (29.3)	58 (27.9)		61 (32.4)	58 (31.0)	
Missing	20 (9.6)	19 (9.1)		8 (4.2)	2 (1.1)	
Mean tablets taken (SD), *n*	4.9 (11.0)	5.7 (12.9)	0.51	5.1 (11.1)	5.8 (13.0)	0.56
Return visits to GP, OPD, or ED, *n (%)*						
Days 1 to 5						
Visited GP						
No	186 (89.4)	190 (91.3)	0.97	175 (92.6)	180 (96.3)	0.96
Yes	7 (3.4)	7 (3.4)		6 (3.2)	6 (3.2)	
Missing	15 (7.2)	11 (5.3)		8 (4.2)	1 (0.5)	
Visited OPD						
No	193 (92.8)	197 (94.7)	–	181 (95.8)	186 (99.5)	–
Missing	15 (7.2)	11 (5.3)		8 (4.2)	1 (0.5)	
Visited ED						
No	183 (88.0)	183 (88.0)	0.33	173 (91.6)	172 (92.0)	0.154
Yes	10 (4.8)	15 (7.2)		8 (4.2)	15 (8.0)	
Missing	15 (7.2)	10 (4.8)		8 (4.2)	0 (0)	
Days 6 to 14						
Visited GP						
No	175 (84.1)	179 (86.1)	0.045	169 (89.4)	176 (94.2)	0.065
Yes	12 (5.8)	4 (1.9)		11 (5.8)	4 (2.1)	
Missing	21 (10.1)	25 (12.0)		9 (4.8)	7 (3.7)	
Visited OPD						
No	183 (88.0)	184 (88.5)	0.12	176 (93.1)	181 (96.8)	0.061
Yes	4 (1.9)	0 (0.0)		4 (2.1)	0 (0)	
Missing	21 (10.1)	24 (11.5)		9 (4.8)	6 (3.2)	
Visited ED						
No	174 (83.7)	171 (82.2)	0.97	167 (88.3)	169 (90.4)	0.83
Yes	13 (6.3)	13 (6.3)		13 (6.9)	12 (6.4)	
Missing	21 (10.1)	24 (11.5)		9 (4.8)	6 (3.2)	
Mean patient satisfaction (SD)†						
Analgesia	70.92 (24.29)	71.86 (22.01)	0.69	71.24 (24.26)	71.46 (22.25)	0.93
ED services	73.56 (28.55)	74.40 (26.33)	0.76	76.88 (24.75)	79.01 (19.15)	0.35

ED = emergency department; GP = general practice; OPD = outpatient department.
* Categorical variables, such as joint redness and tenderness, use of paracetamol, and reattendance rate, were analyzed using the chi-square or Fisher exact test. Continuous variables, such as number of tablets of paracetamol and patient satisfaction, were analyzed with the *t* test.
† Assessed on a scale of 0 (complete dissatisfaction) to 100 (complete satisfaction).

Appendix Table 5. Adherence to Study Medication (n = 416)*

Variable	Overall (n = 416)	Indomethacin (n = 208)	Prednisolone (n = 208)
ED phase	416 (100)	208 (100)	208 (100)
Day 1†	389 (93.5)	192 (92.3)	197 (94.7)
Day 2†	376 (90.4)	185 (88.9)	191 (91.8)
Day 3†	358 (86.1)	174 (83.7)	184 (88.5)
Day 4†	351 (84.4)	171 (82.2)	180 (86.5)
Day 5†	345 (82.9)	168 (80.8)	177 (85.1)

ED = emergency department.
* Values are numbers (percentages) and are based on the proportion of prescribed tablets taken on a given day. Patients were classified as adherent if they took all (100%) of the prescribed study medication on a given day. Patients who did not take all of the medication were classified as being nonadherent. Reasons for nonadherence were not sought.
† Number of patients who were counted as being adherent (proportion of adherent patients compared with total number overall or in each treatment group).