A Comparison of Once-Daily Tramadol with Normal Release Tramadol in the Treatment of Pain in Osteoarthritis

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ABSTRACT. ***Objective.*** To compare the efficacy and tolerability of once daily (OD) tramadol tablets with normal release tramadol capsules (50 mg) taken 3 or 4 times daily in a multicenter, double blind, double dummy parallel study.

Methods. Patients with moderate to severe pain due to osteoarthritis (OA) were recruited from general practice. Following a titration period of a week, patients were assessed over one month for the analgesic efficacy and tolerability of the test medications.

Results. Both treatments were shown to be effective. There was no difference between treatments and both produced good pain control as shown by clinically relevant decreases from baseline pain scores, low escape medication use, and sleep disturbance. The efficacy of the OD tramadol over the 24 h dosing interval was confirmed by the low sleep disturbance, absence of "end of dose" effects in morning pain scores, and low escape medication use. Of the 279 patients recruited, 140 withdrew, mostly because of adverse events. The adverse event profiles were typical of opioids and were similar for both treatments.

Conclusion. Tramadol OD was at least as effective and well tolerated as normal release tramadol in the management of OA pain. However, OD tramadol offers the advantage of a reduced dosing regimen, which is especially valuable in the elderly population. (J Rheumatol 2002;29:2196–9)

Key Indexing Terms:
TRAMADOL OSTEOARTHRITIS

Tramadol has been shown in several studies to be an effective analgesic for patients with osteoarthritis (OA)[1-4]. In this and other chronic pain states, regular administration of analgesics is important and modified release preparations of analgesics represent an important advantage. It is generally accepted that by reducing the frequency of dosing from 3 or 4 times daily to once or twice, the level of patient compliance can be expected to improve. This is especially true of elderly patients who are likely to be taking medication for several concurrent illnesses. Typically, patients with OA fall into this category.

This study compares the efficacy and tolerability of a new once daily (OD) preparation of tramadol with Zydol® (normal release tramadol) administered 3 or 4 times daily for OA pain.

MATERIALS AND METHODS

Patients. Adult patients with radiographic evidence of OA of the spine, hip, and/or knee were recruited from general practice. Patients either were taking no analgesics or had poor pain control (with moderate to severe pain) despite taking medication. Excluded from the study were patients with any chronic painful condition (other than OA) that was likely to warrant the persistent use of escape analgesics, and those who were due to have hip/knee replacement surgery during the study. Patients who had taken monoamine oxidase inhibitors within the previous 2 weeks or long acting nonsteroidal antiinflammatory drugs (NSAID) within the last week, and those with a known sensitivity to paracetamol or opioids were also excluded. Patients with any medical condition or who were taking concomitant medication and were at risk from the additional effects of an opioid were also excluded, as were those who were pregnant, lactating, or inadequately protected against conception.

All patients gave written informed consent to participate and the study was approved by all the clinical investigators' local research ethics committees.

Study design. This was a multicenter study with a double blind, double dummy, parallel design. On entry, patients were sequentially assigned treatment according to a randomization schedule. Treatment allocation was in the ratio of 2:1, OD tramadol to normal release tramadol, so that more data could be generated for the OD tramadol. This uneven randomization resulted in only a slight reduction in the statistical power of the study. For each patient, a sealed code break was retained by the relevant investigator. Except for patients with serious adverse events, the treatment allocation codes were broken only after the study had been completed and the data analyzed.

On the first day of the study, patients used only paracetamol to control their pain. Their baseline pain scores were recorded using a 100 mm visual analog scale (VAS), where 0 mm = no pain and 100 mm = the most severe pain imaginable. Patients then entered a 7 to 10 day double blind titration period at the lowest of 4 dose levels of their study medication (Table 1). They adjusted their dose on a daily basis up to the next dose level until they required no more than 2 doses of escape medication per day. Additionally, all patients took placebo for the alternative treatment (double dummy technique).

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Table 1. Dose levels of study medication. Doses were taken at the following times: OD: on waking; TDS: on waking, at lunchtime, and at bedtime; QDS: on waking, at lunchtime, late afternoon, and at bedtime.

Dose Level	OD Tramadol	Normal Release Tramadol
1	1 × 150 mg OD	1 × 50 mg TDS
2	1 × 200 mg OD	1 × 50 mg QDS
3	1 × 300 mg OD	2 × 50 mg TDS
4	1 × 400 mg OD	2 × 50 mg QDS
Escape medication	2 × paracetamol tablets (500 mg) to a maximum of 8 tablets in 24 h	

At the end of the titration period, patients entered a 4 week assessment period at their optimal dose level of treatment (at which their pain was controlled with acceptable or no adverse events, and the minimum amount of escape medication was required). The dose levels were adjusted if necessary to maintain optimal pain control at a scheduled visit after 2 weeks of the assessment period.

During the assessment period, escape medication was allowed to a daily maximum of 4 doses of paracetamol (Table 1), and not more frequently than every 4 h. The use of any NSAID, analgesic, or analgesic-containing drug other than the specified escape and study medication was not allowed during the study.

The primary measure of efficacy was the VAS pain score recorded daily by patients before the morning dose and at bedtime. Efficacy was also assessed by the use of escape medication and frequency of sleep disturbance due to pain. All patients with data for at least 21 days of the assessment period and compliant with the protocol were included in the efficacy analysis. Volunteered adverse events were recorded for all patients and graded for severity by the investigator at each scheduled visit. At the end of the study, patients and investigators made a global assessment of the pain relief on a 5 point categorical scale (poor, fair, good, very good, or excellent).

Statistical analysis. It was estimated that with 150 patients completing the study, there would be 90% power at the 5% significance level to detect a treatment difference of 10 mm in the mean VAS pain scores. A clinically relevant difference was considered to be 20 mm[4].

A direct comparison of the measures of efficacy, rather than a comparison of the changes from baseline, was used to evaluate the treatments. This was because it was considered inappropriate to assume a static baseline, as chronic pain is often variable and episodic. As the number of observations for pain scores were unbalanced between treatments, adjusted means were used to obtain a correct measure of the difference, using the baseline pain score as covariate in the analysis from which these estimates were obtained.

The VAS pain scores (morning and evening) were analyzed by ANOVA using the baseline values as covariates. The use of escape medication and the proportion of nights that patients woke with pain were analyzed using the Cochran-Mantel-Haenszel rank sum test. The number of times that patients woke with pain on their last night of the assessment period was also recorded.

The Mantel-Haenszel chi-square test was used to analyze the final doses of study medication, and the patients' and investigators' global assessment of the treatments. The incidence of adverse events was analyzed using Fisher's exact test.

Statistical comparisons by chi-square tests were drawn between the 2 treatment groups, with respect to sex, duration and site of disease, and proportion of patients that withdrew. A t-test was used to compare the mean age of the patients in the 2 treatment groups.

RESULTS

Of 279 patients recruited, 188 were allocated treatment with OD tramadol and 91 with normal release tramadol.

The disease sites in over half the patients were the knees and the spine, and most of the patients reported disease duration of more than 5 years. Patients in the 2 treatment groups were balanced at baseline with respect to age (mean 62.5 and 62.6 yrs), sex (54 and 63% female), disease duration, and disease site.

No statistically significant differences were seen between treatments in respect to the final doses taken by patients either at the end of titration or assessment.

Withdrawals. There was no statistically significant difference between treatments with respect to the proportion of patients that withdrew from the study (OD tramadol, 49%; normal release tramadol, 52%) or the reasons for withdrawal (Figure 1). Over half the withdrawals occurred during the titration period and the incidence declined with time. Most of the withdrawals (about 80%) were due at least to adverse events and the overall withdrawal profile was similar for both treatment groups (Table 2).

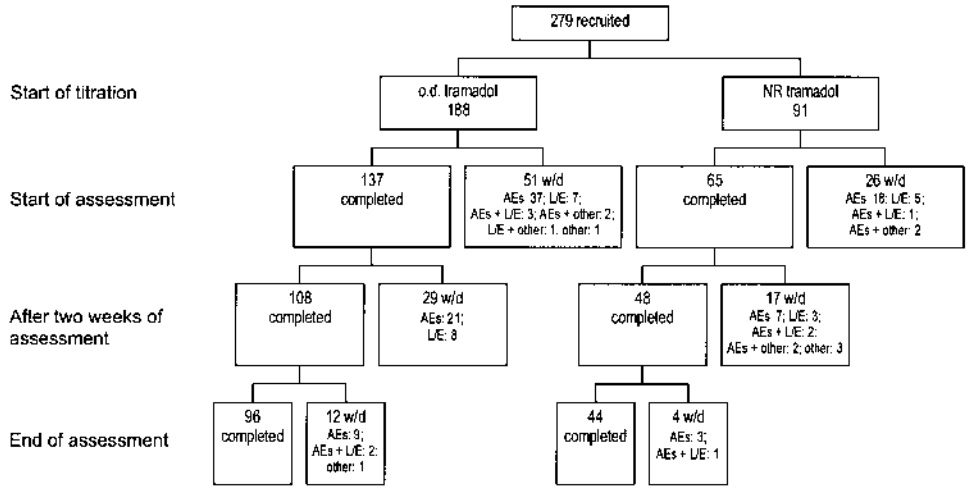

Figure 1. Disposition of patients. w/d: withdrawn; L/E: lack of efficacy; AE: adverse events; NR: normal release.

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Table 2. Reasons for withdrawals from the study.

Reason for Withdrawal	OD Tramadol, n = 92 (%)	Normal Release Tramadol, n = 47 (%)
Adverse event	69 (75)	32 (68)
Lack of efficacy	16 (17)	8 (17)
Adverse event and lack of efficacy	5 (5)	4 (9)
Other	2 (2)	3 (6)

Efficacy. Of the 146 patients eligible for inclusion in the efficacy analysis, 101 were in the OD tramadol group and 45 in the normal release tramadol group. Both treatments improved pain control. The morning or evening pain scores did not differ significantly between treatments, both at baseline (overall 47 and 51 mm, respectively) and after treatment (overall 21 and 22 mm, respectively) (Figure 2). The adjusted mean differences between treatments (normal release tramadol – OD tramadol) for the VAS pain scores in the morning were –7.2, 95% CI –14.5, 0.1 and in the evening, –0.3, 95% CI –7.8, 7.1.

Figure 3 shows the low use of escape medication by patients over their last 24 h of the study. No significant differences were seen either in the mean use of escape medication (overall 0.82 times/day) or in the proportion of nights that patients woke with pain. About 60% of the patients did not wake with pain at all on their last night of assessment, although a small proportion (< 10%) woke more than twice.

Tolerability. The 6 most commonly reported adverse events were nausea, constipation, vomiting, drowsiness, dizziness, and headache (Table 3). Overall, most of the adverse events were mild or moderate in intensity, and related to the gastrointestinal (63% of patients) or central nervous systems (49% of patients).

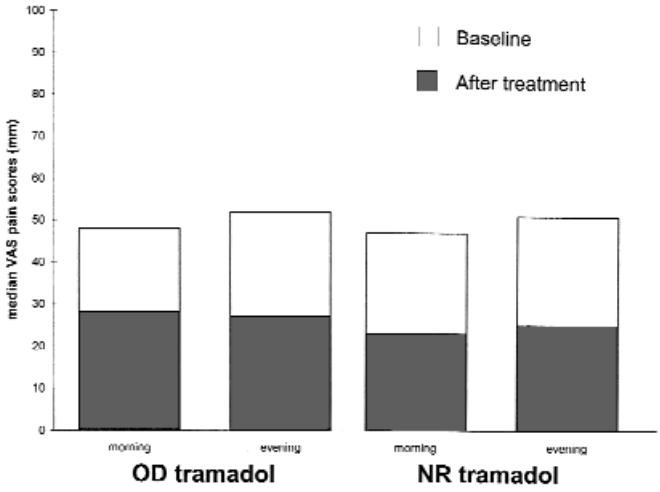

Figure 2. Median VAS pain scores for each treatment group. NR: normal release.

The treatment difference in the incidence of each adverse event was not statistically significant, with the exception of confusion and depression, which occurred more frequently among patients receiving normal release tramadol than those receiving OD tramadol (p = 0.04 and p = 0.039, respectively).

Two serious adverse events were reported, although neither was considered by the investigator to be related to study medication. Both serious adverse events (incapacitating low back pain and urinary outflow obstruction) required hospitalization but were subsequently resolved.

Global assessment. There was no statistically significant difference between treatments in the global assessment of the study drugs by patients or investigators. Over 65% of the patients who completed the study obtained good to excellent pain relief with their study drug. This was consistent with the investigators' rating of the pain relief in these patients.

DISCUSSION

The reduction from baseline in the VAS pain scores, the primary measure of efficacy, showed clearly that both treatments were effective analgesics. Patients' and investigators' assessments of global pain relief confirmed the efficacy of both treatments. For both morning and evening pain scores, the width of the 95% CI of the adjusted mean difference was smaller than the predefined clinically relevant difference (20 mm). This supports a statement of equivalence between the 2 treatments.

The 24 h duration of action of the OD tramadol was confirmed by the low sleep disturbance, the absence of "end of dose" effects in the morning pain scores, and the low use of escape medication (with no clustering) throughout the dosing interval.

The relatively high withdrawal rate seen in this study was not unexpected. In a previous study, Dalgin reported a similar proportion of patients with chronic pain withdrew during the first week of tramadol treatment[5]. Further, patients with longstanding OA are often, and expect to be, switched to an alternative drug with the onset of intolerance or lack of efficacy. This has become common clinical practice on the basis that patients who do not tolerate or respond to one treatment often respond well to another.

The tolerability profiles of the 2 products in this study were similar and predictable. The reported adverse events corresponded to those known to occur with opioids and have no known harmful or progressive effects. NSAID produce gastrointestinal complications, but can also aggravate hypertension and precipitate congestive heart failure as a result of fluid retention[6]. The use of tramadol in chronic painful conditions affecting the elderly, such as OA, may result in fewer serious side effects than NSAID.

Although the efficacy and tolerability of the 2 products were comparable in this study, the reduced frequency of dosing of the OD tablet provides it with a significant

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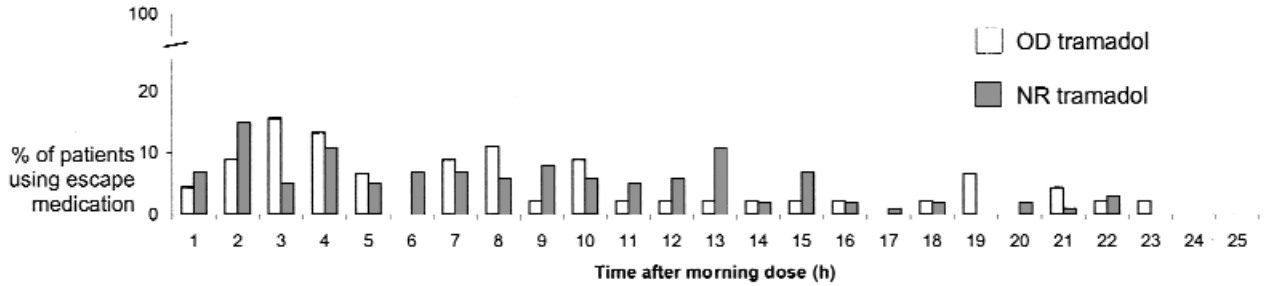

Figure 3. Time to use of escape medication after the morning dose. NR: normal release.

Table 3. Incidence of adverse events.

Adverse Event	OD Tramadol (%)	Normal Release Tramadol (%)
Six most commonly reported adverse events		
Nausea	36	36
Constipation	23	31
Drowsiness	15	24
Dizziness	20	17
Vomiting	19	18
Headache	18	15
No statistically significant treatment difference for these adverse events.		
GI related	62	65
CNS related	48	52

compliance advantage over the normal release capsule. Multiple dose regimens are undesirable in elderly patients, as they are usually taking several different drugs on a daily basis. In these situations, even when compliance is good, dosing at proper and regular intervals is rare.

In conclusion, OD tramadol tablets are at least as effective and well tolerated as a currently marketed short acting tramadol formulation in the management of OA pain, and in addition, they offer a reduced dosing regimen that is especially valuable in the elderly.

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