Piroxicam spares buprenorphine after total joint replacement

Controlled study of pain treatment in 81 patients

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In a blinded, placebo-controlled study, the nonsteroidal antiinflammatory drug piroxicam, in combination with the partial morphine agonist/antagonist buprenorphine, was compared with buprenorphine alone for analgesic effect and side-effects in a 10-day period following total replacement of the hip or knee. 117 patients entered and 81 completed the study. The patients receiving piroxicam consumed less buprenorphine. There were no differences concerning side-effects between the two treatment groups, apart from a tendency towards less nausea after the third postoperative day in the group receiving piroxicam.

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The traditional treatment of postoperative pain following total joint replacement is based on opioids in the early phase after operation, followed by mainly peripherally-acting drugs. We have evaluated the analgesic effect of a combination therapy, combining a central-acting drug and a non-steroid antiinflammatory drug (NSAID).

Patients and methods

The drugs chosen were the partial morphine agonist-antagonist buprenorphine and the NSAID piroxicam. The study was conducted as a double-blind, randomized, placebo-controlled investigation, respecting the rules of the Helsinki Declaration. Considered for randomization were all patients in whom total hip or knee replacement was to be performed. The following patients were not included: patients with active rheumatoid arthritis, NSAID intolerance, history of gastric ulcer, senility or other mental deficiency, and those who did not give informed consent.

The patients were randomized to two treatment groups, hips (n 56) and knees (n 61) separately. The piroxicam group received a 40 mg suppository of piroxicam immediately after the operation and 20 mg once daily on the following days. The control group received placebo instead of piroxicam. Both groups received buprenorphine immediately after the operation (0.3 mg i.m.) and on demand on the day of operation (day 1, 0.2–0.4 mg sublingually or i.m.). 10 sublingual tablets of buprenorphine 0.2 mg were given daily on the following days for self-administration. The trial was discontinued after the 10th postoperative day.

The daily consumption of buprenorphine was recorded and used as a measure of the analgesic effect of piroxicam. The overall analgesic effects of the treatments were evaluated once daily by a visual analogue score (VAS) for pain (Huskisson 1974). Day 1 was not included, since the patients were operated on at different times of the day and did not receive piroxicam until after the operation. All unpleasant or unexpected clinical manifestations were recorded as possible side-effects, without making any attempt to decide whether they were caused by the analgesic treatment or not. They were graded as: 1) disappeared without intervention, 2) tolerated by the patient, no need for intervention, 3) requiring symptomatic treatment, 4) necessitating exclusion from the study. Finally, the method of anesthesia (epidural/spinal/general) and the daily blood loss from the drain were recorded. A combination of heparin and dihydergotamine was used to prevent thrombosis. There was no difference in the total volume of blood loss in the drains between the two drug groups.

117 patients entered the study, which was completed by 36 hip patients and 45 knee patients.

Table 1. The total average buprenorphine consumption (number of 0.2 mg sublingual tablets) in the period days 2–10

Treatment groups	Hips n	Knees n	Buprenorphine consumption	*P*
Piroxicam	20	26	36	0.01
Placebo	16	19	47	
Hip patients	36	...	34	0.004
Knee patients	...	45	46	

Statistics

The buprenorphine consumption on days 2–10 and the VAS were subjected to an analysis of variance in repeated measures models. Three factors were included: type of operation (hip or knee), treatment (piroxicam or not), and type of anesthesia. Randomization was stopped according to the group-sequential method (Pocock 1982), requiring interim analyses for each 40 patients and a nominal level of significance of 0.0158. The total level of significance was 0.05 for the main effect variables and 0.01 for supplementary analyses.

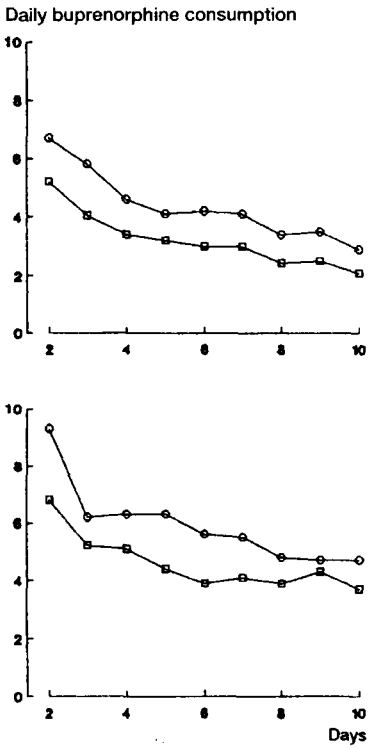

Figure 1. The average daily buprenorphine consumption (Temgesic, 0.2 mg sublingual tablets) on days 2 to 10 for hip patients (top), and knee patients (bottom) treated with piroxicam (□) and placebo (○).

Results

The total buprenorphine consumption on days 2–10 showed differences between hip and knee patients and between the two drug groups (Table 1), while the type of anesthesia had no influence. The piroxicam patients consumed less buprenorphine on average on each of the days in the period of investigation of both hip and knee patients (Figure 1). The buprenorphine consumption was gradually reduced in both drug groups, but even in the piroxicam group the patients still consumed buprenorphine on day 10 (knee patients 0.74 mg, hip patients 0.42 mg on average). The type of analgesic treatment, operation or anesthesia had no significant influence on the VAS over days 2–10.

There were 36 withdrawals from the study, 12 at the patients' own request because of unpleasant manifestations (Table 2), 4 because of insufficient analgesia (2 in each group; 3 knees, 1 hip), 15 because the protocol was violated by mistake, and 5 because of miscellaneous reasons: 2 operations of excessive duration, one postoperative respiratory depression, before administration of the trial drugs, one acute pulmonary embolism, one having difficulties in using sublingual tablets.

58 patients experienced clinical manifestations that were recorded as possible side-effects of grades 2–4 (Table 2). There were no differences between treatment groups considering side-effects generally or, when considering the subgroups, action on the central nervous system or dyspepsia. Nausea was the main problem: 23/46 in the piroxicam group and 15/35 in the control group experienced nausea. In both groups, the nausea decreased markedly after day 3 and this decrease was significant in the piroxicam group (*P* 0.003) and in knee patients (*P* 0.001). After day 3, there was marginally more nausea in the control group (*P* 0.051).

Discussion

Several reports have demonstrated the opioid-saving effect of NSAIDs in treating pain following abdominal, dental and certain orthopedic operations (Torda 1983, Herrlinger and Kamp 1985, Lindgren and Djupsjö 1985, Hodsman et al. 1987, Serpell and Thompson

Table 2. Possible side-effects (number of patients) other than clinical manifestations that disappeared within one day without intervention

Treatment groups	n	CNS[a]	GI[b]	Miscellaneous	Total
Patients who completed the study					
Piroxicam	46	19	26	1	33
Placebo	35	11	20	4	25
Patients who dropped out					
Piroxicam	14	3	1	1	4
Placebo	22	4	3	1	8
All patients					
Piroxicam	60	22	27	2	37
Placebo	57	15	23	5	33

[a]Central nervous system manifestations; dizziness, confusion, fatigue
[b]Gastrointestinal manifestations; dyspepsia, nausea

1989, Taivainen et al. 1989, Yrjola et al. 1988). These studies dealt with the very first postoperative days and did not take pain during early mobilization into consideration. They did not include the probably most painful of orthopedic operations: total knee replacement. Our study confirmed this opioid-saving effect of piroxicam in hip surgery. The same effect was demonstrated also in knee replacement. The study did not reveal any reduction of the pain scores when using the combination therapy instead of buprenorphine alone. This may not be surprising, since the patients were allowed to take buprenorphine without restriction until maximal pain relief was obtained.

It is not possible to determine with certainty whether the recorded clinical events really were side-effects caused by the trial drugs. In connection with treatment of postoperative pain, there usually are three main problems: nausea, dyspepsia and respiratory depression or other action on the central nervous system. In addition to these, increased bleeding caused by NSAIDs has been suggested as a possible side-effect. Postoperative nausea is due to multifactorial causes. In an analysis based on the literature published after 1935 and including 23, 198 patients, it occurred in 34 percent of the cases (Gellet and Christiansen 1988). There seems to be an advantage in using the combination therapy to reduce this problem. Postoperative bleeding was not increased by piroxicam.

The self-administration of sublingual buprenorphine had evident advantages: the patient compliance is high, the dose can be titrated by each patient, and the costs in terms of the nursing staff are low. The method seems to be safe, since no cases of misuse occurred, and no patient withdrew from the study because of respiratory depression after administration of the trial drugs or other symptoms of serious overdosage.

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