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A randomised controlled study on the use of anti-inflammatory drugs in patients with cancer pain on morphine therapy: effects on dose-escalation and a pharmacoeconomic analysis

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Abstract

The role of non-steroidal anti-inflammatory drugs (NSAIDs) in cancer pain has been well established in the treatment of mild pain and in association with opioids in the treatment of moderate to severe pain. The aim of this study was to verify the effects of NSAIDs on morphine escalation in advanced cancer patients with pain followed-up at home and to assess the pharmacoeconomic implications. A prospective randomised controlled study was carried out in 156 consecutive advanced cancer patients with pain followed-up at home in the period December 1999–December 2000. In this group of patients, 47 were selected with pain progression after 1 week of opioid stabilisation. Patients were randomly assigned to one of two groups: group 'O' patients were treated with continuing opioid escalation according to their clinical needs; group 'OK' received ketorolac 60 mg/daily orally (p.o.) in three doses and then continued opioid escalation according to their clinical situation. Performance status, doses of morphine before and after starting treatment, mean weekly pain intensity (assessed by means of a numerical scale from 0 to 10), mean weekly symptoms intensity, adverse effects and pain mechanisms were recorded. Moreover, drug costs per day in both groups were calculated. Patients who received ketorolac in addition to morphine showed a better analgesia after a week in comparison to the group treated with morphine only ($P = 0.005$). Thereafter, morphine escalation was slower and the maximum morphine dose was lower in the group treated with ketorolac. The incidence and the severity of gastric discomfort was more evident in patients treated with ketorolac, while constipation was significantly increased in patients who received morphine only. Drug costs per day were similar in both groups; statistical differences were observed in patients who started on lower morphine doses (<100 mg/daily) in the two groups (€4.3 in the ketorolac–morphine group versus €3.4 in the morphine group; $P = 0.012$). The use of NSAIDs reduces the need for an opioid dose escalation or allows the use of lower doses. Their use is associated with a more intense gastric discomfort, but results in less opioid-related constipation. The eventual additive cost for NSAIDs therapy is negligible, especially in patients taking high doses of morphine. © 2002 Published by Elsevier Science Ltd.

Keywords: NSAIDs; Cancer pain; Morphine; Dose-escalation; Advanced cancer patients; Randomised controlled study; Pharmacoeconomic analysis; Palliative care; Home care

1. Introduction

The role of non-steriodal anti-inflammatory drugs (NSAIDs) in cancer pain has been well established in the treatment of mild pain and in association with opioids in the treatment of moderate to severe pain [1]. A good analgesic response after a course of NSAIDs has been shown to have a positive predictive value and a better prognosis in cancer patients experiencing pain, regardless of the pain mechanism [2]. NSAIDs can have additional uses than just as mild analgesics given over a short period of time, although the majority of patients with moderate to severe cancer pain may be expected to require a shift to opioids to achieve satisfactory control of their pain, owing to their well known ceiling effect. NSAIDs may still provide additive analgesia when

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combined with opioids, even for prolonged periods of time [3–5]. These observations are consistent with the results of several studies of patients with cancer pain. In cancer patients, the use of NSAIDs may delay the development of tolerance and allow the use of a lower dose of opioids, thereby reducing central nervous system (CNS) side-effects. NSAIDs have been shown to have a relevant opioid-sparing effect and their continued use in combination with opioids may explain the relatively low doses of opioids reported [6]. Among NSAIDs, ketorolac has been reported to have potent analgesic effects in advanced cancer populations presenting different pain syndromes that are unresponsive to opioids [7–14]. However, the simple finding of a narcotic-sparing effect may be questioned in cancer pain treatment and should not merely be an indication to add NSAIDs to an opioid regimen, as the same level of analgesia can be achieved by increasing opioid dose. Moreover, the addition of NSAIDs to a therapeutic regimen could introduce further adverse effects [15]. The benefits of the combination of NSAID and opioid over opioid monotherapy should be either better analgesia or reduced opioid doses and, as a consequence, a reduction in the risk of opioid-related side-effects.

However, both opioids and NSAIDs may require additional adjuvant medications, such as laxatives and antiemetics to prevent opioid-adverse reactions, and drugs to prevent the gastropathy associated with NSAID. The cost-effectiveness of monotherapy with opioids compared with combinations of NSAIDs and opioids has not to our knowledge been previously reported.

The aim of this study was to evaluate the benefits of combining NSAIDs with opioids in advanced cancer patients who have had pain controlled by monotherapy with opioids. A second purpose was to compare the pharmacoeconomics of combined therapy with opioids and NSAIDs with opioid monotherapy.

2. Patients and methods

A prospective randomised study was carried out in a sample of 156 consecutive advanced cancer patients with pain followed-up at home from December 1999 to December 2000 (Fig. 1). Patients with co-existing liver or renal disease, history of gastritis or gastroduodenal ulcers, or cognitive impairment, were excluded. 47 patients requiring strong opioids for their pain (moderate to severe pain no longer responsive to opioids for moderate pain), were selected. For all the patients on the study an informed consent was obtained. Morphine was the opioid chosen for this study. All patients had their morphine dose optimised at home for 1 week prior to entering the study (pain intensity less than 4 on a numerical scale 0–10). The dose achieved was considered

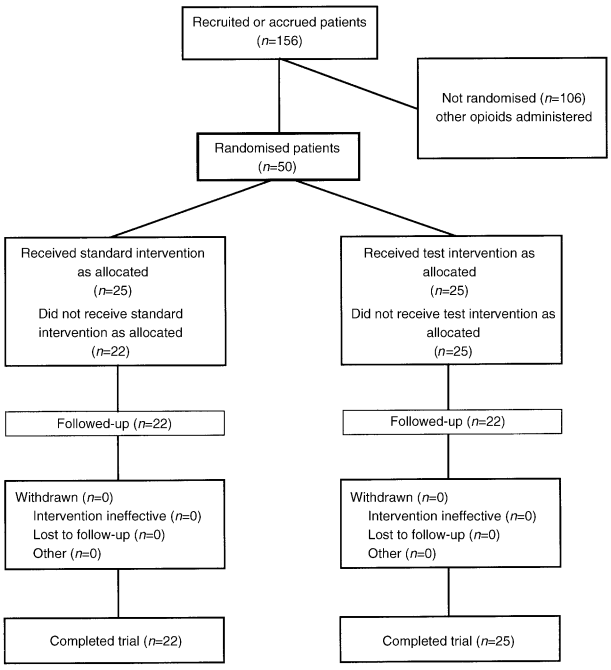

Fig. 1. Flow chart of the progress of patients through the trial (adapted from Ref. [31]).

the opioid starting dose (OSD). If patients developed progressive disease thereafter they were randomised into two groups. Randomisation was done using blocks of patients' surnames. Group 'O' continued on morphine monotherapy with dose escalation to adequately control the pain, group 'OK' received ketorolac 60 mg per day in three divided doses in addition to morphine dose escalation to adequately obtain analgesia. The last group of patients received misoprostol 200 micrograms twice a day, as this was the common practice of the team, to prevent gastric lesions from NSAIDs.

Patients were divided into two groups, according to the OSD, $<$ or $\geqslant$100 mg of oral morphine daily. In the 'OK' group, there were 16 patients on 100 mg or more of morphine as the OSD, and 9 patients on less than 100 mg of morphine as the OSD. In the 'O' group, there were 11 patients on 100 mg or more of morphine as the OSD, and 11 patients on less than 100 mg of morphine as the OSD.

All patients were followed-up at home by a team consisting of doctors and nurses experienced in palliative care with three visits a week until their death. The use of other drugs was allowed including ones generally administered in palliative care to control symptoms due to illness or opioid treatment. Specifically, the use of laxatives or antiemetic drugs (at different dosages) for opioids, as well as prostaglandins (200 mcg twice a day) for ketorolac. These drugs are routinely used to treat the side-effects associated with analgesics according to palliative care guidelines. Parenteral administration (subcutaneous) was used when the oral administration of

medications was no longer possible due to an inability to swallow, or neurological impairment. No other adjuvant-analgesic drugs were allowed.

The following data were recorded: (1) Performance status at admission and demographic data (gender, age, primary tumour); (2) dose of morphine at randomisation (OSD), mean weekly dose as determined by morphine consumption measured three days a week, and maximum opioid dose per day (OMD); (3) mean weekly pain intensity assessed by means of a numerical scale from 0 to 10; pain was evaluated by the patient's self-report three times a week; (4) mean weekly symptom (or adverse effects) intensity, analgesic-related or not, assessed by means of a scale ranging from 0 to 3 (not at all, slight, a lot, awful) measured three times a week as part of the regular monitoring of 10 symptoms performed at home, at the same intervals; symptoms were assessed by patients when possible; (5) pain mechanisms, on the basis of clinical history, the anatomical site of the primary tumour and distant metastases, clinical examination, radiographical investigations, and so on, when available.

Opioid escalation index per cent (OEI%) was calculated as the mean increase of opioid dosage per cent from OSD using the following formula: [(OMD−OSD)/OSD]/days×100. Reductions of opioid dosage are unlikely to occur in advanced cancer patients who are not undergoing antitumour therapy. The calculated OSD–OMD was determined at the maximum dose of morphine taken per day at any time during the course of the patient's cancer after entering trial.

Opioid escalation index in mg (OEI mg) was calculated as the mean increase of opioid dosage in mg using the following formula: (OMD−OSD)/days. These indexes have already been usefully validated to monitor the opioid requirement when other interventions are given [16,17].

Finally, a pharmacoeconomic analysis was performed comparing both groups including adjuvant medications.

2.1. Statistical analysis

Frequency analysis for gender, primary diagnosis and pain mechanisms was performed by Chi-square test to evaluate differences between the two treatment groups. One-way analysis of variance (ANOVA) and Mann–Whitney U statistic test were used for parametric and non-parametric analysis, respectively, to evaluate differences between the two treatment groups (intergroup analysis). The paired Wilcoxon signed rank test was used to compare pain and symptom intensity scores, and paired samples Student's *t*-test was used to compare the morphine mean dose, between different weekly periods in every single group (intragroup analysis). All *P* values were two-sided and *P* values less than 0.05 were considered statistically significant.

Table 1
Epidemiological data of patients in the two groups[a]

	Group 'OK'	Group 'O'
Age (years)	62.6 (56–68)	64.6 (58–71)
Gender (M/F)	13/12	12/10
Karnofsky	34 (31–36)	35 (32–39)
Survival (days)	24 (21–27)	32 (24–39)
Primary cancer		
Gastrointestinal	5	4
Genitourinary	10	8
Liver-pancreas	4	2
Lung	3	4
Breast	1	2
Others	2	2

95% CI, 95% confidence interval; M/F, male/female. Group 'OK', patients treated with ketorolac and opioid (morphine); Group 'O', patients treated with opioid only (morphine).

[a] Age, survival days and Karnofsky status are expressed as a mean (95% C.I.).

Table 2
Opioid starting dose (OSD), opioid maximum dose (OMD), opioid escalation index in mg (OEImg) and in percentage (OEI%), and *P* value in the two groups[a]

	Group 'OK'	Group 'O'	*P* value
OSD	138 (107–168)	119 (85–152)	0.263
OMD	173 (141–206)	246 (210–282)	0.003*
OEImg	1.49 (0.85–2.12)	4.93 (3.38–6.4)	<0.0005*
OEI%	1.46 (0.78–2.15)	5.44 (3.09–7.80)	<0.0005*

95% CI, 95% confidence interval. Group 'OK', patients treated with ketorolac and opioid (morphine); Group 'O', patients treated with opioid only (morphine); *statistically significant.

[a] Data are expressed as means (95% CI).

3. Results

47 patients completed the study. Epidemiological data are presented in Table 1. The two groups were similar, as no differences in age, gender, survival days, performance status, primary cancer, pain mechanisms were found. Morphine escalation was slower, as demonstrated by the significantly lower OEI% and OEImg, and the reduced OMD reached in the patients of the 'OK' group when compared with the patients in the 'O' group. No significant difference between the two groups was found in the OSD (Table 2). Patients who received ketorolac in addition to morphine showed a better analgesia after a week in comparison to the group treated by morphine only (week 3, $P=0.005$) (Table 3).

With regard to the intragroup analysis (between the time intervals in each group), in both groups there was a worsening of some symptoms, such as nausea, vomiting, drowsiness, confusion, that was particularly evident in the morphine monotherapy arm of the trial.

In the intergroup analysis ('OK' versus 'O' group), significance was found for constipation only ($P=0.006$ at week 3, $P=0.018$ at week 4, $P=0.006$ at week 5) that

Table 3
Number of patients and mean weekly pain intensity (95% CI) in the two groups at weekly intervals

Week	*n*	Group 'OK'	*n*	Group 'O'	*P* value
1	25	2.45 (2.05–2.84)	22	2.12 (1.66–2.57)	0.247
2	25	5.31 (4.83–5.79)	22	5.36 (4.75–5.98)	0.932
3	23	3.34 (2.84–3.84)	20	4.83 (4.05–5.61)	0.005*
4	13	3.63 (2.93–4.34)	14	4.5 (3.68–5.31)	0.127
5	5	3 (1.47–4.52)	8	3.58 (2.73–4.44)	0.324
6	1	2.5	7	2.9 (2.31–3.48)	0.485
7			5	3.14 (1.06–5.21)	
8			4	3.07 (2.83–3.31)	
9			2	4.5	

95% CI, 95% confidence interval. Group 'OK', patients treated with ketorolac and opioid (morphine); Group 'O', patients treated with opioid only (morphine); *statistically significant.

Table 4
Differences (expressed as *P* values) between the two groups on different dosages of morphine (more or less 100 mg daily)

	OSD $\geqslant$ 100 *P* value	OSD $<$ 100 *P* value
Age	0.521	0.970
Gender	0.930	0.653
Karnofsky	0.721	0.594
OMD	0.031*	0.002*
OEImg	0.001*	0.025*
OEI%	0.001*	0.012*
Primary cancer	0.778	0.314
Pain mechanism	0.120	0.312

OSD, opioid starting dose; OMD, opioid maximum dose; OEImg, opioid escalation index in mg; OEI%, opioid escalation index in percentage; * statistically significant.

was more evident in the 'O' group. In contrast, the incidence and the severity of gastric discomfort was more evident in patients treated with ketorolac ($P < 0.0005$ at week 3, $P = 0.008$ at week 4, and $P = 0.004$ at week 5).

In patients with morphine starting doses below and greater than or equal to 100 mg per day were compared, the OEI and maximum opioid doses were significantly less in the 'OK' group when compared with the 'O' group (Table 4).

Drug costs per day were not significantly different overall. However, in the group with a starting OSD of less than 100 mg of morphine per day, the cost in the O group was significantly less than that of the OK group (€3.4 and 4.3, respectively, $P = 0.012$).

4. Discussion

A useful adjuvant analgesic added to morphine monotherapy should either provide better analgesia than monotherapy or reduce the opioid-associated adverse effects without producing additional toxicity or economic burden. Most studies have demonstrated an increased analgesia when NSAIDs are added to morphine. The single-dose equivalence of a maximal NSAID dose has been reported to be approximately 5–10 mg of parenteral morphine [18,19]. However, the effects of NSAIDs when added to different doses of morphine has never been assessed. The benefit of combination therapy may be morphine dose-dependent and/or time-dependent under various states of opioid tolerance or be dependent upon individual characteristics or the type of pain. Moreover, in most studies, doses of opioids previously administered were rarely reported, as well as the methods used for symptom assessment; also, other trials were quite short, or comparison groups were lacking. It is unclear whether the morphine-sparing effect was sufficiently large to have clinical significance, or whether the trend to better pain relief could have been achieved through increasing the morphine dose, as similar results could have been achieved by increasing the opioid dose without adding a second agent. Because of the limitations of these previous studies, definitive conclusions cannot be drawn.

In our study, significant pain relief after a week of NSAID occurred at lower doses of morphine than would have occurred with the monotherapy. This effect was sustained throughout the time period of the study, as evidenced by the lower OEIs and the maximum morphine dose found in a similar group of patients who were followed-up at home. The study design facilitated the selection of patients with similar characteristics, i.e. the use of stable morphine doses for 1 week prior to study entry. Moreover, no other analgesics were allowed.

The opioid-sparing effect was achieved regardless of the morphine dose administered ($<$ or $\geqslant$100 mg a day). This has important clinical implications as lower morphine doses could reduce the occurrence of opioid adverse effects. The patients on monotherapy with morphine had a greater symptom intensity than patients in the combined therapy group, although significant results were attained only for constipation. A larger sample of patients might have provided more data in terms of the prevalence of opioid-adverse effects.

This observation confirms previous studies which have demonstrated excellent analgesia and reduced opioid-related bowel complications in advanced cancer patients when ketorolac was added to morphine [8]. However, a possible NSAID-induced renal damage could increase opioid toxicity due to a metabolite accumulation in the presence of renal dysfunction [20]. Although the trend in the intragroup analysis was more favourable in the 'OK' group, the data obtained in this selected group of patients cannot be extrapolated to general cancer populations who possibly present with renal dysfunction or severe states of dehydration.

Bleeding, gastric and renal damage are the most feared complications of NSAID treatment [19,21]. Such rare complications would require a larger study population, with an appropriate specific design to determine how serious a problem such complications would be.

Most advanced cancer patients followed-up at home are managed clinically and only occasionally have biochemistry screening. No effort was made to biochemically monitor renal function, although no overt renal failure was observed. However, urinary output normally diminishes shortly before death. Prostaglandins appear to prevent, to the same extent, both gastric and duodenal ulcerations in patients taking NSAIDs for at least 3 months [22]. Patients on NSAIDs had a greater prevalence of dyspepsia, despite receiving prostaglandins. The occurrence of gastrointestinal symptoms does not predict more important gastrointestinal events [19]. Thus, use of prostaglandins could be questioned. However, cancer patients should be considered at risk, at older ages, after receiving previous and concomitant therapies, and when experiencing sub-clinical dehydration states. In a quantitative estimation of rare adverse events, it has been calculated that 1 in 1200 patients taking NSAIDs for at least 2 months will die from gastrointestinal complications [23]. Cost-effectiveness studies reached different conclusions, depending on various assumptions about the clinical effect of misoprostol [24]. A recent study [25] has demonstrated that selective Cox 2 inhibitors may be less expensive than combinations of ketorolac and misoprostol with a lower nephrotoxicity. However, further data on analgesic efficacy on cancer pain are warranted to confirm these preliminary observations, reported in non-cancer patients, in the setting of palliative care.

A systematic review by the Cochrane Group [26], regarding the prevention of chronic NSAID-induced upper gastrointesinal toxicity concluded that: (a) standard dose H2 receptor blockers were not effective; (b) double dose H2 receptors standard proton pump inhibitors are effective prophylaxis; (c) misoprostol is effective in NSAID prophylaxis, but it is associated with adverse effects; (d) in the pharmacoeconomic analysis, the highest cost of prophylaxis was with misoprostol. Unfortunately, at the onset of this study, these data were not yet available and, consequently, we used misoprostol for the prevention of gastric discomfort. Moreover, the only study performed on cancer patients has demonstrated the preventive effects of misoprostol at the doses used in this study on NSAID-induced gastrointestinal adverse effects [27]. Diarrhoea is of concern for patients receiving prostaglandins. However, it has not been reported in advanced cancer patients. The reduced diarrhoea with misoprostol may be due to the balancing constipating effects of morphine.

In the present study, the use ketorolac in doses of 60 mg a day produced a significant pain relief in patients receiving different doses of morphine, allowing for a reduced requirement of the opioid. The choice of ketorolac could be questioned in favour of other drugs that are potentially less toxic, such as ibuprofen [21]. However, this drug was chosen as it has been frequently reported in the setting of palliative care to be particularly effective for the treatment of different pain conditions [7–13]. In the European experience, and in the setting of palliative care, ketorolac is widely used with a good cost-benefit ratio, even if a careful patient selection is essential in minimising the adverse effects of this treatment [7–13,28,29].

Both analgesic regimens are effective regardless of the type of pain. Anecdotal reports suggest that NSAIDs are the most effective for somatic and visceral pain associated with an inflammation, i.e. pain arising from myofacial, joint, serous membrane, periosteal nociceptors. Pain intensity was reduced by the addition of NSAID to opioids, regardless of the nature of the nociceptive pain. However, the duration of the effect may be shorter with visceral pain [4]. In the present study, no differences in the intensity or response between visceral and somatic pain was found. Recent investigations suggest that NSAIDs may be effective in some forms of neuropathic pain. High doses of NSAIDs can produce stable analgesia in neuropathic pain syndromes, which are poorly responsive to opioids [3,12,27]. However, in a mechanistic approach study, no patient with deep somatic pain achieved satisfactory pain relief with NSAIDs. In the same way, in patients with neuropathic pain receiving amitriptyline first, all required opioids [30]. Therefore, both opioids and NSAIDs are effective in the management of cancer pain, regardless of the mechanism of pain involved.

Our cost analysis revealed interesting findings. Minimal differences in costs were found between the two groups. However, in patients starting with lower doses of morphine, the addition of ketorolac and misoprostol was more expensive than using morphine, and adjuvant medications, alone. However, these differences disappeared in patients on higher doses of morphine, rendering this approach particularly convenient. Furthermore, if prostaglandins use was stopped, this cost would be even less.

5. Conclusions

The use of NSAIDs reduces the need for an opioid dose escalation or allows the use of lower doses, resulting in less opioid-related adverse effects, such as constipation. It is associated with a more intense gastric discomfort. The advantage involves a minimal additive cost, that is just evident in patients on lower doses of opioids.

Different conclusions can be drawn from this study. For example, given the effects produced even in patients taking relatively high doses of morphine, one could

suggest to inverse the World Health Organization (WHO) analgesic ladder. In the analgesic ladder, NSAIDs are given in the first instance, and then are possibly continued in the subsequent steps in association with opioid drugs. It means that NSAIDs should be given for prolonged periods of time in patients with a certain life-expectancy. The possible advantages are restrained by the cost, as the same analgesia could be obtained using opioids, and the possible increased risk with a prolonged administration. Alternatively, opioids could be given first, alone, and then their analgesic effects could be reinforced in patients with difficult pain control, or who tend to develop adverse effects, in which further increases in doses are prevented by the occurrence of adverse effects. The use of NSAIDs in these circumstances could also be more convenient and shorter in time, so limiting the possible long-term adverse effects. Further studies should be performed to confirm these preliminary observations in a larger sample of patients with a longer expected survival.

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