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Prospective randomized, double-blind, placebo-controlled study of pre- and postoperative administration of a COX-2-specific inhibitor as opioid-sparing analgesia in major colorectal surgery

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Abstract

Purpose To demonstrate the opioid-sparing effect and reduction in postoperative ileus obtained with valdecoxib 40 mg administered pre- and postoperatively in patients undergoing colorectal resection.

Methods Patients for elective colorectal resection from December 2002 to June 2004 were randomized to receive either valdecoxib or placebo with standard patient-controlled analgesia (PCA) morphine. In the study arm, the first dose of valdecoxib 40 mg was administered orally as close as possible to 1 h prior to the start of surgery. Each subsequent dose was administered at 24-h intervals up to 120 h. Patients in the control arm were served placebos at the same time-points.

Results Forty patients were enrolled in the study arm and 39 (excluding one protocol violation) in the control arm. The groups were comparable in age, sex, American Society of Anesthesiology status, body mass index, incision length, and duration and types of operations. Mean PCA doses at 12 and 24 h were 18.6 and 28.3 mg in the study arm *vs* 26.2 and 41.2 mg in controls, representing a one-third opioid reduction. Bowel sound and movement first appeared at medians of 12 and 72 h in the study arm *vs* 24 and 84 h, respectively, in controls ($P < 0.05$). Tolerance of solid diet was at a median of 60 h and discharge at a median of 4 days in the study arm *vs* 72 h and 6 days in controls ($P < 0.05$ and $P < 0.01$, respectively). Seven (18%) morbidities occurred in the control *vs* six (15%) in the study arm.

Conclusions Patients treated with a cyclo-oxygenase 2-specific inhibitor have a shorter recovery time when compared with patients on a standard postoperative PCA morphine-only regimen after colorectal resection.

Keywords Colorectal surgery, preemptive analgesia, perioperative treatment, postoperative ileus

Introduction

Postoperative ileus is a period of gastrointestinal dysfunction that follows almost every intraabdominal operation and leads to patient discomfort, increases postoperative morbidity, and is the single most important factor in prolonging hospitalization after intraabdominal operations [1]. A recent study showed that in open as well as in laparoscopic colon resections, with an expedited postoperative care programme including perioperative epidural analgesia and postoperative intramuscular ketorolac, there was a significant reduction in the number of days to flatus and bowel movements as well as in the length of postoperative hospitalization [2]. As narcotics diminish bowel activity, avoidance of their use may reduce postoperative ileus, hasten the return of normal bowel function after surgery and ultimately aid in the recovery of patients [3,4].

Recent studies show that prolonged postoperative ileus is caused by an enteric molecular inflammatory response and the subsequent recruitment of leucocytes into the muscularis of the intestinal segments manipulated during surgery. This inflammation impairs local neuromuscular function and activates neurogenic inhibitory pathways, inhibiting motility of the entire

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gastrointestinal tract [5]. It has also been shown that cyclo-oxygenase 2 (COX-2) and prostaglandins participate in the pathogenesis of inflammatory postoperative ileus via primary afferent activation that may subsequently initiate inhibitory motor reflexes to the gut, contributing to postoperative ileus [6].

We therefore hypothesized that patients treated with valdecoxib, a COX-2-specific inhibitor, will have reduced postoperative ileus and a shorter recovery time when compared with patients on a standard postoperative patient-controlled analgesia (PCA) morphine-only regimen after colorectal resections. The aim of this study was to demonstrate a reduction in postoperative ileus and an opioid-sparing effect with the use of a COX-2-specific inhibitor administered pre- and postoperatively in patients undergoing major colorectal surgery.

Patients and methods

The study was performed at one institution from December 2002 to June 2004 by a single colorectal surgical team using similar surgical techniques, in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. The protocol received Institutional Review Board approval prior to patient accrual.

Using a randomized, prospective study design, patients presenting to the Colorectal Unit for elective colorectal resections were randomized by drawing sealed envelopes at the time of the preoperative visit to receive either valdecoxib (study arm) or standard PCA morphine (control arm) after informed consent had been obtained. The identity of the treatment arm to which a patient was assigned was concealed in a tear-off part of the label in a sealed pouch. The code was to be broken if an emergency situation arose that, in the investigator's opinion, required knowledge of the code.

The primary end-point for calculating sample size was days to first bowel movement. A sample size of 40 patients per group is sufficient to detect a difference of 1 day (25%, assuming average 4 days to first bowel movement) with at least 80% power and type I error of 0.025 (for a two-sided test adjusted for two treatment comparisons).

Inclusion criteria

The patient is a male or female of more than 18 years of age and:

1 requires elective colorectal resection for reasons including cancers;
2 is in satisfactory health as determined by the investigator on the basis of medical history and physical examination;
3 conforms to American Society of Anesthesiology class I–III;
4 is able to use PCA;
5 has provided written informed consent prior to admission to this study.

Exclusion criteria

The patient:

1 has sulphonamide allergy;
2 requires emergency surgery/laparoscopic-assisted surgery;
3 has inflammatory bowel disease;
4 needs epidural or other regional analgesia;
5 has known opioid intolerance or inability to use PCA;
6 has known acetylsalicylic acid or nonsteroidal antiinflammatory drug (NSAID) hypersensitivity;
7 has active peptic ulcer disease, asthma, coagulopathy or renal failure;
8 is pregnant or lactating;
9 uses conventional NSAIDs, COX-2 inhibitors or tramadol during the 6 h preceding surgery, during surgery or subsequent to the end of surgery;
10 received oxaprozin or piroxicam within 1 week prior to randomization;
11 is required to take muscle relaxants, tricyclic antidepressants, tranquilizers, sedatives, hypnotics or neuroleptics in the postoperative period;
12 has any cognitive impairment that would, in the investigator's opinion, preclude study participation or compliance with protocol-mandated procedures;
13 has a history of uncontrolled chronic disease, which, in the opinion of the investigator, would contraindicate study participation or confound interpretation of results;
14 has dysphagia, has difficulty swallowing capsules or tablets, or is unable to tolerate oral medication;
15 has lactose intolerance, which requires significant dietary modification or treatment with enzyme supplementation.

Only patients who satisfied all inclusion and exclusion criteria were included in the study.

In the study arm, the first dose of study medication, valdecoxib 40 mg, was administered orally as close as possible to 1 h and <3 h prior to the start of surgery, defined as incision. Each subsequent dose was administered at 24-h intervals after the first dose (0 h): 24, 48, 72, 96 and 120 h, up to a maximum of 120 h. Patients in the control arm were served placebos at the same time-points. It was expected that a patient would have the first flatus within 5 days, and that after 5 days there would be minimal pain and therefore valdecoxib and/or PCA would no longer be necessary.

Both groups received the same general anaesthetic agents in the operating theatre which included air/oxygen, isoflurane, succinylcholine, rocuronium, morphine and fentanyl. The dosage of each medication was altered at the discretion of the anaesthesiologist.

All patients received a PCA pump infusing intravenous morphine. The patient could commence administration of morphine using the PCA pump after 30 min following the end of surgery. The demand dose was 1–2 mg with a lockout of 5 min and maximum 10 mg/h. Whether patients should or should not receive a basal rate of 1 mg/h was left to the discretion of the pain management service. For breakthrough pain, use of intravenous fentanyl 25 μg boluses was left to the discretion of the pain management service. Any further interventions for pain relief such as regional nerve blocks mandated withdrawal from the study. The PCA pump was used for analgesia uniformly and stopped by the pain management service when there was adequate analgesia with paracetamol 1 g per oral every 6 h as required.

Patients completed categorical pain intensity assessments related to their operative site postoperatively every 1–2 h while on PCA and thereafter 12-hourly until early termination or end of study. If the patients were asleep at night during the scheduled time for their pain assessments, they were not awakened but the actual time the patient was assessed was noted in a diary. All pain assessments were completed after patients had been in a resting supine position for at least 15 min.

All patients (both regimens) were offered a clear liquid diet on the first postoperative day. Once the oral intake exceeded 30 ml/kg of body weight without nausea or vomiting, the diet was advanced to a low-fat, gastrointestinal diet.

The patients were evaluated every 12 h, once in the morning and again in the evening for the end-points of bowel sound, flatus and bowel movement.

The patients were discharged when they were (i) tolerating a solid diet, (ii) passing flatus, (iii) without fever or other medical problems requiring hospitalization.

Early termination was defined as occurring when:

1 the patient withdrew consent and discontinued participation in the study;
2 the patient had breakthrough pain and needed nerve blocks;
3 an adverse event necessitated the withdrawal of the patient from the study;
4 the randomization code of the patient was broken.

End of study was defined as the day on which the patient was fit for discharge from the hospital and therefore excluded extension of hospital stay for social reasons.

Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 11.0 (SPSS Inc., Chicago, Illinois, USA). Intergroup comparisons were made using Student's *t*-test for continuous variables and the two-tailed chi-square test for discrete variables. The amount of morphine administered and time-specific pain intensity (categorical) were analysed using analysis of variance with treatment as factor. The times to first flatus, bowel sound and movement, tolerance of liquid and solid diet and last dose of morphine were analysed using the methods of survival analysis. Statistical significance was set at $P < 0.05$.

Results

From December 2002 to June 2004, 295 patients met the inclusion criteria, of whom 98 were eligible after exclusion criteria were applied. Eighty patients (82%) agreed to enrol. Forty patients were included in the study arm and 39 (excluding one protocol violation as a result of invalid consent) in the control arm. The groups were comparable in age, sex, American Society of Anesthesiology status, body mass index, incision length, and duration and types of operations (Table 1).

Table 2 summarizes the main end-points. Mean PCA doses at 12 and 24 h were 18.6 mg [standard deviation (SD) 13.8 mg] and 28.3 mg (SD 18.0 mg) in the study arm *vs* 26.2 mg (SD 18.8 mg) and 41.2 mg (SD 23.6 mg) in controls, representing a one-third opioid reduction. Mean PCA doses at 48 h were 35.0 mg (SD 38.1 mg) in the study arm *vs* 65.3 mg (SD 40.8 mg) in controls, representing a 46% opioid reduction (Fig. 1). The total PCA dose per 12-h period was significantly higher in the placebo group for every period up to 120 h postoperatively and also showed a much wider range in distribution (Fig. 2). PCA was stopped at a median of 60 h *vs* 72 h in the study and control arms, respectively ($P < 0.001$). At 12 and 24 h, 18 and 23 study patients *vs* 14 and 19 control patients, respectively, had pain score 0 ($P < 0.05$) (Fig. 3a). Bowel sound and movement first appeared at median 12 and 72 h in the study arm *vs* 24 and 84 h, respectively, in controls ($P < 0.05$) (Figs 4 and 5). Passage of flatus occurred earlier in the study group at 36 h *vs* 48 in the placebo group ($P < 0.01$) (Fig. 6). There was no difference in the time to tolerance of liquids (Fig. 7). Tolerance of solid diet was at a median of 60 h (Fig. 8) and discharge at a median of 4 days in the study arm *vs* 72 h and 6 days in controls ($P < 0.05$ and $P < 0.01$, respectively).

Sedation and nausea were similar in the two groups (Figs 3b,c). However, global evaluation at 24 h by

Table 1 Patient characteristics and operative details.

Patient characteristics	Study ($n = 40$)	Placebo ($n = 39$)	*P*-value
Age (years)			
Mean (SD)	61.0 (11.4)	63.1 (10.4)	0.585
Range	24–77	39–78	
Sex (%)			
Male	20 (50.0)	18 (46.0)	0.654
Female	20 (50.0)	21 (54.0)	
Medical problems (COAD, DM, IHD, hypt.) (%)			
Yes	26 (65.0)	24 (62.0)	0.777
No	14 (35.0)	15 (38.0)	
BMI (kg/m^2)			
Mean (SD)	23.0 (3.7)	23.0 (3.7)	0.511
Range	17.8–33.2	16.0–33.0	
Diagnosis (%)			
Colorectal cancer	36 (90.0)	39 (100.0)	0.136
Benign (sigmoid diverticulitis, sigmoid volvulus)	4 (10.0)	0	
Type of operation (%)			
AR	15 (37.5)	16 (41.0)	0.158
AR (with extended resection)	6 (15.0)	2 (5.1)	
Low AR	4 (10.0)	4 (10.2)	
Low AR with stoma	3 (7.5)	1 (2.6)	
Hartmann's procedure	3 (7.5)	0	
Abdomino-perineal resection	1 (2.5)	4 (10.0)	
Hemicolectomy/segmental colectomy	5 (12.5)	11 (28.2)	
Others (small bowel resection, panprotocolectomy, Hartmann's reversal)	3 (7.5)	1 (2.6)	
Stoma (%)			
Yes	8 (20.0)	5 (12.8)	0.405
No	32 (80.0)	34 (87.2)	
Incision length (cm)			
Mean (SD)	17.8 (11.1)	17.0 (4.2)	0.436
Range	10–25	7–28	
Duration of operation (min)			
Mean (SD)	158.0 (61.1)	152.0 (55.3)	0.733
Range	65–320	75–300	

SD, standard deviation; COAD, chronic obstructive airway disease; DM, diabetes mellitus; IHD, ischaemic heart disease; hypt., hypertension; BMI, body mass index; AR, anterior resection.

patients was significantly better for the study group than the placebo group (Table 2).

Early termination occurred in four patients from each group. In the placebo group, three had breakthrough pain that required intercostal nerve blocks and one patient had an acute myocardial infarct on postoperative day 4. In the study group, three patients had breakthrough pain separately requiring intercostal nerve block, intramuscular pethidine and oral tramadol; one patient had an anastomotic dehiscence. End-points were analysed where available on an intention-to-treat basis.

Seven (18%) morbidities occurred in the control *vs* six (15%) in the study arm (Table 3). There was no mortality in either group. Readmission rate within 30 days of surgery was similar for the two groups (Table 3).

Hospitalization cost was not significantly different between the two groups. The patient who had an anastomotic leak requiring reoperation skewed the cost for the study group.

Discussion

Whether preemptive analgesic interventions are more effective than conventional regimens in managing acute postoperative pain remains a matter of debate. Although many clinical studies have been carried out in the past

Table 2 Postoperative outcome, length of stay and cost of hospitalization.

Patient characteristic	Study ($n = 40$)	Placebo ($n = 39$)	*P*-value
PCA total dose per 12-h period (mg morphine)			
Median	635	1303	0.001
Range	168–1480	135–2612	
PCA stopped (hours postop)			
Median	60	72	0.001
Range	24–120	24 – >120	
First bowel sound (hours postop)			
Median	12	24	0.046
Range	12–60	12–72	
First flatus (hours postop)			
Median	36	48	0.003
Range	12–84	24–108	
First bowel movement (hours postop)			
Median	72	84	0.041
Range	36–120	24 – >120	
Liquid tolerated (hours postop)			
Median	24	24	0.579
Range	12–120	12–84	
Solid tolerated (hours postop)			
Median	60	72	0.029
Range	36 – >120	36 – >120	
Global evaluation at 24 h (patient)			
Excellent	1	0	0.001
Good	28	19	
Fair	11	20	
Global evaluation at 24 h (surgeon)			
Excellent	1	0	0.317
Good	26	24	
Fair	13	15	
Length of stay (days)			
Mean (SD)	4.9 (2.7)	6.3 (2.3)	0.009
Median	4.0	6.0	
Range	2–19	4–14	
Hospitalization cost ($)			
Mean(SD)	11 210 (14 510)	8767 (2188)	0.447
Median	8652.35	8673.65	
Range	6115–98 524	6324–15 025	

PCA, patient-controlled analgesia; SD, standard deviation.

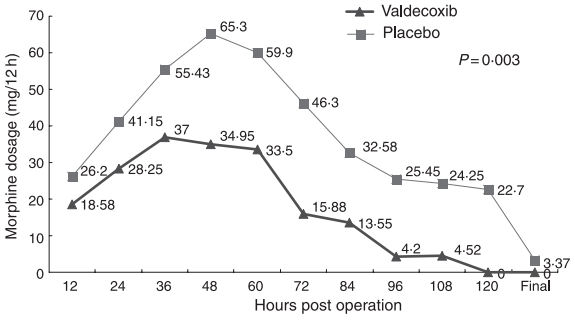

Figure 1 PCA dose: mean.

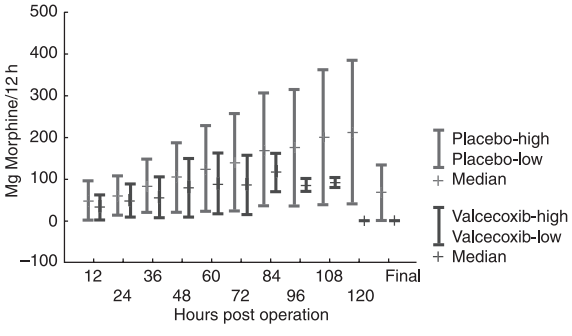

Figure 2 PCA dose: total.

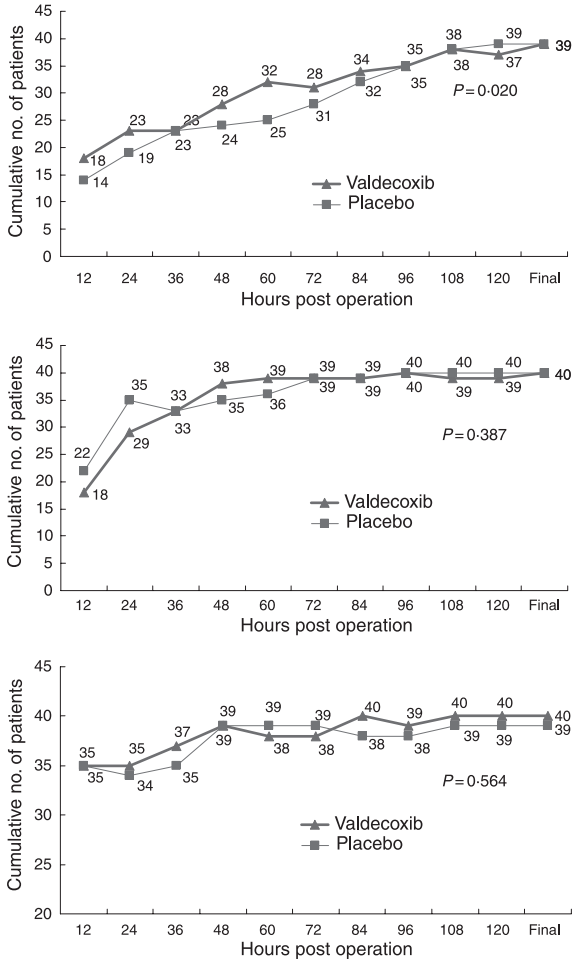

Figure 3 Study and placebo groups.

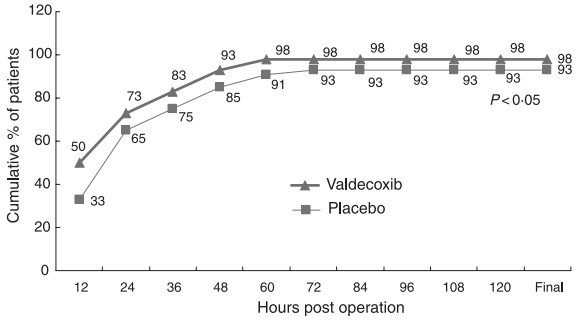

Figure 4 First bowel sound.

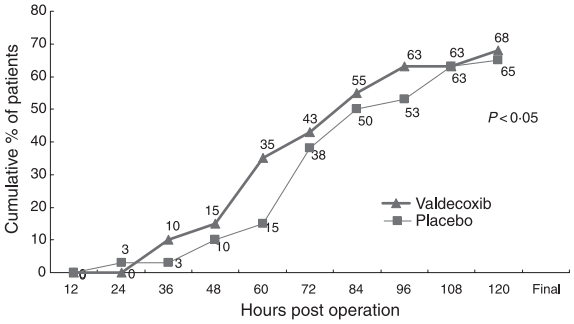

Figure 5 First bowel movement.

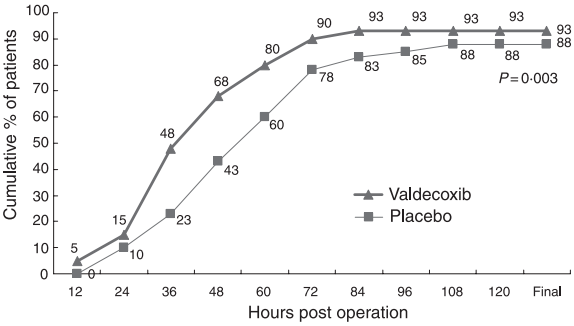

Figure 6 First flatus.

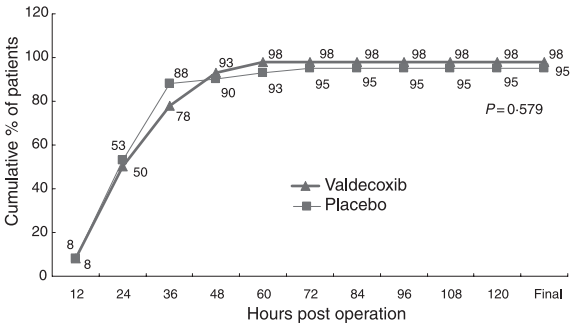

Figure 7 Tolerating liquid diet.

decade, the contribution of central sensitization to the overall postoperative pain state remains unclear. To what degree central facilitation amplifies pain after surgery is unknown in humans. Even with these shortcomings, a fair number of studies have documented modest benefit comparing patients' preincisional to postincisional interventions. Most of these studies were carried out in dental, gynaecological and orthopaedic patients [7]. Of those carried out in abdominal surgery patients, most involved either nonmajor or nonbowel-related surgery [8–10]. To our knowledge, there have been no previous studies that examined preemptive analgesia in major colorectal resections using an oral agent as postoperative ileus was deemed to preclude oral analgesics in the early postoperative period.

The present study shows that an orally administered COX-2-specific inhibitor, valdecoxib, given preoperatively,

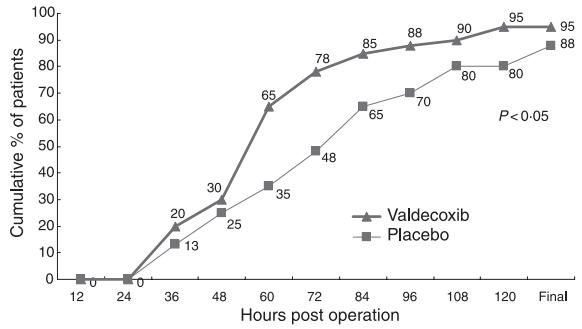

Figure 8 Tolerating solid diet.

Table 3 Postoperative morbidity and readmission within 30 days.

	Study ($n = 6$)	Placebo ($n = 7$)	*P*-value
Major morbidity (%)			
Acute myocardial infarct	0	1 (14.2)	0.317
Anastomotic dehiscence	1 (16.6)	0	
Pneumonia	1 (16.6)	2 (28.5)	
Minor morbidity (%)			
Urinary tract infection	0	1 (14.2)	0.317
Wound related	2 (33.3)	1 (14.2)	
Prolonged ileus	0	2 (28.5)	
Thrombophlebitis	1 (16.6)	0	
Postoperation confusion	1 (16.6)	0	
Readmission within 30 days (%)	($n = 5$)	($n = 3$)	
Adhesion colic	1 (20.0)	2 (66.6)	0.317
Bleeding per rectum/stoma	2 (40.0)	1 (33.3)	
Stoma related	1 (20.0)	0	
Wound related	1 (20.0)	0	

reduces the amount of morphine required to control pain in the first 24 h postoperatively in patients who have had major colorectal surgery. Postoperative ileus was also reduced, probably as result of (i) reduced opioid usage, (ii) early ambulation with better pain control and (iii) attenuated inflammatory response (as postoperative ileus is part of a local and probably systemic inflammatory response to surgical trauma [5,6] that can be inhibited with a COX-2-specific inhibitor). What the study did not address was the relative contribution of each factor towards the reduction in postoperative ileus, although it is evident that all these factors can be attributed to COX-2 inhibition. The study also could not demonstrate the degree to which the preoperative, preemptive administration of the COX-2 inhibitor contributed to the observed benefits of reduction in postoperative ileus and opioid usage, as the COX-2 inhibitor was also continued postoperatively. The early preemptive trials comparing preincisional *vs* postincisional treatment groups are now regarded by the authors to be too simplistic. Many of the postinjury interventions are adequate to reverse central sensitization. Furthermore, once adequate afferent blockade to the spinal cord is lost, postsurgical inflammatory injury may establish central facilitation. Thus, any preemptive treatment alone is unlikely to provide any benefits unless the initial postoperative period is also covered.

There was no difference in the time to take liquids in the two groups as all patients were offered liquids on the first postoperative day and allowed to regulate their intake based on their own progress rather than on a fixed schedule. Subsequently, patients in the study group progressed more quickly to tolerate a solid diet some 12 h earlier than those in the placebo group. Patients in the study group were also discharged 48 h sooner. This together with the better global evaluation scores in the study group seemed to suggest that the benefits of improved functional restoration marked by a faster return to usual activity levels postoperatively may be an outcome of preemptive analgesia. The smaller range of distribution of opioid requirement for every 12-h period up to 120 h postoperatively in the COX-2 inhibitor group may also reflect more reliable and predictable pain control with preemptive analgesia.

The efficacy of valdecoxib was clearly shown in the present study in a randomized, double-blind, placebo-controlled setting. There was also no safety issue in this small study in which the only cardiac morbidity occurred in the placebo group. However, the cardiovascular safety issues with COX-2 inhibitors are now well known. In September 2004, Merck withdrew rofecoxib from the market because a trial of the drug, designed to test the hypothesis that COX-2 inhibitors could prevent recurrent colonic polyps, showed increased cardiovascular toxicity [11]. The National Cancer Institute stopped a similar trial of celecoxib when an independent panel of cardiovascular experts reviewed the data and also found a greater risk of cardiovascular events among patients treated with celecoxib [12]. Another trial, which examined pain relief in patients recovering from coronary artery bypass surgery, showed an increased incidence of cardiovascular end-points at 30 days among patients who had received a total of only 10 days of valdecoxib and its prodrug parecoxib [13]. Taken together, these three large, randomized, controlled trials designed to test the efficacy of different COX-2 inhibitors for a variety of indications confirmed their cardiovascular toxicity. As all three different COX-2 inhibitors were found to be associated with cardiovascular complications, it appears that this is a class effect. On 7 April

2005, the FDA issued a Public Health Advisory [14] which announced that the overall risk *vs* benefit profile of valdeocoxib is unfavourable and has requested Pfizer, Inc. to withdraw valdecoxib (Bextra) from the market.

In clinical trials, NSAIDs, aspirin and acetaminophen are just as effective in relieving pain as the COX-2 inhibitors [15], and hence it is reasonable to expect that the benefits of preemptive analgesia demonstrated in this study can be duplicated with other analgesics to some extent. This study has demonstrated in principle that recovery after major abdominal bowel surgery can be shortened by a potent anti-inflammatory analgesic administered orally pre- and postoperatively without the need for parenteral administration. With the withdrawal of rofecoxib and now valdecoxib, alternatives that are safer than COX-2 inhibitors and that extend indications are keenly awaited. Much attention has focused on nitric oxide-donating NSAIDs, also known as cyclo-oxygenase-inhibiting nitric oxide donors, and another class that acts as dual inhibitors of cyclo-oxygenase and 5-lipoxygenase [16]. Although alvimopan, a peripherally acting mu opioid antagonist, and perhaps tegaserod, a partial 5-hydroxytryptamine-4 receptor agonist, may also reduce postoperative ileus [17], an anti-inflammatory analgesic is still theoretically more attractive as it addresses the dual problems of postoperative ileus and pain control – both major determinants of postoperative recovery after abdominal surgery. Besides new drugs, attention should also focus on such simple interventions as gum chewing [18], abdominal massage [19] and exposure to sunlight [20], which have all been shown to have beneficial effects on postoperative recovery.

In conclusion, usage of valdecoxib will not be possible because of the potential cardiovascular toxicity which has resulted in the withdrawal of the drug from the market, but we have provided proof of principle that the addition of an oral COX-2-specific inhibitor pre- and postoperatively can reduce opioid use, postoperative ileus and length of stay when compared with a standard postoperative PCA morphine regimen after colorectal resection.

Disclaimer

None declared.

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