Influence of bolus size on efficacy of postoperative patient-controlled analgesia with piritramide

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We have examined the influence of bolus size on efficacy, opioid consumption, side effects and patient satisfaction during i.v. patient-controlled analgesia (PCA) in 60 patients (ASA I–II, aged 32–82 yr) after abdominal surgery. Patients were allocated randomly, in a double-blind manner, to receive PCA with a bolus dose of either piritramide 0.75 mg or 1.5 mg (lockout 5 min) for postoperative pain control. Mean 24 h piritramide consumption differed significantly between groups (11.4 (SD 5.8) mg *vs* 22.5 (18.3) mg; $P=0.001$). There were no significant differences in the number of applied bolus doses, pain scores, pain relief (VAS), sedation, nausea, pruritus and patient satisfaction. We conclude that a PCA regimen with a bolus dose of piritramide 0.75 mg and a lockout time of 5 min was effective in the treatment of postoperative pain, but did not reduce the occurrence of side effects.

I.v. patient-controlled analgesia (PCA) has become a well recognized and widely accepted technique for providing postoperative pain relief. Indeed, in numerous studies it was shown clearly that PCA allows optimum individual titration of analgesia and enhances patient satisfaction with postoperative pain management.[1] However, sedation and nausea are still the most frequent side effects during PCA with opioids. Theoretically, reducing the opioid dose could reduce side effects, but may also lead to insufficient pain relief. There is cumulating evidence that the efficacy of PCA is at least partly related to non-pharmacological and psychological factors such as coping, anxiety, emotional distress and self-control.[2 3]

We hypothesized that a PCA regimen with a small bolus dose and a short lockout time would enable the patient to titrate analgesic effect more effectively against side effects. Therefore, we have examined, in a prospective, randomized, double-blind study, the relative efficacy, patient satisfaction and side effects of i.v. PCA with a low (0.75 mg) bolus dose of piritramide compared with our routinely prescribed bolus dose (1.5 mg).

Patients and methods

After obtaining approval from the Medical Ethics Committee of the Ruhr-University of Bochum and written informed consent, we studied 60 patients, ASA I–II, aged 32–82 yr, undergoing elective lower abdominal surgery (mostly total abdominal hysterectomy and major inguinal hernia repair). We excluded patients undergoing regional and/or combined general anaesthesia and patients receiving opioids before operation.

All patients were instructed before operation on the use of the PCA pump and visual analogue scale (VAS). A preoperative questionnaire was completed in an interview conducted by one investigator with each patient. This investigator (A. W.) was not involved in patient treatment. The preoperative questionnaire included a verbal pain rating scale (VRS) and items on expected pain, anxiety and personal pain experience. A visual analogue scale (VAS; 0–100 mm) was used to measure pain intensity (at rest and during movement), pain relief and general wellbeing.

All patients were premedicated with clorazepate 15–20 mg orally on the evening before surgery and diazepam 10 mg orally, 1 h before surgery. Anaesthesia was induced with thiopental (thiopentone) 3–5 mg kg^{-1}. Tracheal intubation and positive pressure ventilation were facilitated by the use of atracurium 0.4 mg kg^{-1}. Anaesthesia was maintained with 0.8–1.2% enflurane and 70% nitrous oxide in oxygen, and fentanyl 3 μg kg^{-1}. Additional doses of atracurium and fentanyl were administered at the

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Table 1 Patient characteristics (mean (SD or range)). No significant differences

	Bolus 0.75 mg	Bolus 1.5 mg
Sex (M/F)	30 (6/24)	30 (6/24)
Age (yr)	56.8 (32–82)	53.0 (34–81)
Weight (kg)	74.1 (13.0)	73.1 (13.1)
Duration of anaesthesia (min)	134 (38.7)	143 (60.9)
Duration of surgery (min)	105 (38.5)	107 (50.6)
Intraoperative fentanyl (µg)	280 (90)	280 (80)

anaesthetist's discretion. Antagonism of neuromuscular block or residual fentanyl effects was not necessary.

After arrival in the recovery room, patients were allocated randomly (sealed envelopes) to receive piritramide (Dipidolor) by PCA (Cadd-PCA 5800 R, Sims-Deltec) with a bolus of either 1.5 mg or 0.75 mg (lockout 5 min). The bolus volume was the same in both groups by changing the concentration of piritramide in the reservoir. The anaesthetist and investigators were blinded to the contents of the PCA reservoir. During the immediate postoperative period, piritramide was administered i.v. in 3.75-mg increments until pain control was judged to be comfortable and satisfactory by the patient. PCA was then commenced.

After operation (24 h), sedation and ventilatory frequency were measured and VAS, VRS scores for pain, nausea and satisfaction were assessed. All interviews were undertaken by the same blinded observer (A. W.). Total PCA bolus doses given were recorded. Also, the frequency of unsatisfied demands was recorded and the ratio between the number of successfully delivered doses to the number of attempts calculated. The follow-up questionnaire included scores on pain at rest and during movement, pain relief, sedation, nausea, itching and satisfaction.

Data are expressed as mean (SD or (range)). Using a statistical software program (SPSS), Student's t test and two-tailed Mann–Whitney U test were used as appropriate. $P < 0.05$ was considered significant. We estimated the sample size before the study. Power was set at 0.8. A retrospective analysis of piritramide consumption during PCA with a bolus dose of 1.5 mg ml^{-1} in 120 patients revealed mean piritramide consumption of 22.2 (10.3) mg, 24 h after operation. These values were normally distributed. Based on clinical experience with a PCA piritramide bolus dose of 1 mg ml^{-1} in a small number of patients, we expected a difference in opioid consumption of approximately 30%. Using a one-tailed t test ($\alpha = 0.05$; $\beta = 0.20$) the estimated sample size was 27 per group.

Results

There was no significant difference in age, sex, weight, surgical procedure, duration of surgery or dose of fentanyl administered during surgery between groups (Table 1). The maximum total amount of incremental piritramide administered in the recovery room was 15 mg.

Mean piritramide consumption by PCA differed significantly between groups at 24 h and 72 h after surgery. Patients

Table 2 Mean (SD) piritramide consumption, PCA doses and demands at 24 h and 72 h; duration of PCA, VAS scores for pain (at rest and on movement) and pain relief. The 95% confidence intervals for the differences are shown for data which showed no significant differences between groups

	Bolus 0.75 mg (n=30)	Bolus 1.5 mg (n=30)	P
Total piritramide 24 h (mg)	11.4 (5.8)	22.5 (18.3)	0.001
Total piritramide 24 h incremental dose (mg)	15.5 (10.8)	27.1 (19.9)	0.008
Piritramide (µg kg^{-1} h^{-1})	7.5 (5.14)	14.1 (9.57)	0.002
Piritramide + incremental dose (µg kg^{-1} h^{-1})	9.0 (6.85)	15.4 (10.39)	0.007
No. of boluses (24 h)	15 (7.4)	15 (11.4)	[−3.0, 5.4]
No. of demands (24 h)	17 (8.2)	16 (9.0)	[−3.5, 5.8]
Total piritramide 72 h (mg)	24.5 (17.5)	49.1 (33.1)	<0.001
No. of boluses (72 h)	33 (23.3)	33 (22.1)	[−10.3, 11.1]
No. of demands (72 h)	36 (26.0)	36 (16.4)	[−11.0, 12.9]
Duration of PCA (days)	3 (0.9)	3 (1.0)	[−0.7, 0.3]
VAS at rest (mm)	43.7 (18.3)	41.0 (20.1)	[−7.3, 12.6]
VAS on movement (mm)	66.4 (21.8)	73.3 (16.0)	[−16.9, 3.1]
Pain relief VAS (mm)	70.0 (24.2)	68.6 (14.8)	[−9.4, 12.2]

Table 3 Verbal and visual scoring after operation. No significant differences

	Bolus 0.75 mg (n=30)	Bolus 1.5 mg (n=30)
Pain		
None	1	2
Slight	12	11
Moderate	13	13
Severe	4	3
Unbearable	0	1
Satisfaction		
Extremely satisfied	8	12
Satisfied	14	14
Moderately satisfied	5	3
Dissatisfied	3	1
Nausea		
None	22	18
Moderate	4	5
Severe	4	7
Vomiting	7	5
Pruritus		
None	30	28
Mild	0	2
Severe	0	0
Sedation		
Awake	3	2
Drowsy	10	9
Sleeping	17	19

in the 0.75-mg bolus group consumed approximately 50% less piritramide than patients in the 1.50-mg bolus group (Table 2). The overall number of successfully delivered doses and the ratio between the number of successfully delivered doses to the total number of attempts was not different between groups (Table 2). There were no significant differences between groups in VAS pain and VAS pain relief scores (Table 2), VRS scores for pain (at rest and on movement), nausea, sedation, pruritus or satisfaction (Table 3). There was excellent (Pearson $r > 0.94$) agreement between verbal and visual pain scores. There were no

signs of respiratory depression; the minimum ventilatory frequency recorded was 10 bpm.

Discussion

Numerous randomized control studies have been published evaluating efficacy, side effects and patient satisfaction with PCA.[1] However, only few studies have evaluated the efficacy of low bolus doses of opioid.[4,5] In this study piritramide was chosen as the opioid for PCA. Lack of haemodynamic effects and less side effects reported in early work[6] may make piritramide more suitable for postoperative pain control compared with other potent opioids. Its relative analgesic potency compared with morphine is approximately 0.7. I.m. bolus injections of 7.5–15 mg are considered to be adequate for approximately 4–6 h. Although the majority of PCA studies were conducted with morphine as the opioid (bolus dose 1–2 mg), there are some data on the use of piritramide in PCA (bolus 2 mg).[6,7]

In our study, a 50% reduction in opioid bolus dose was associated with almost 50% reduction in opioid consumption during postoperative PCA. Hourly consumption of piritramide in the 1.5-mg bolus group (14 μg kg^{-1} h^{-1}) corresponded well with piritramide consumption of 12 μg ml^{-1} h^{-1} in 50 general surgical patients[7] but was significantly less than values reported by Lehmann *et al.*[6] in surgical patients (30 μg kg^{-1} h^{-1}) and after thoracotomy (29 μg kg^{-1} h^{-1}).[8] Despite markedly reduced opioid consumption in the 0.75-mg bolus group (7 μg ml^{-1} kg^{-1}), we found no significant difference in pain, pain relief, side effects or patient satisfaction. This is in marked contrast with the results of other investigators who concluded that small bolus doses (morphine 0.5 mg) failed to achieve adequate analgesia.[4,5] Differences in opioid consumption observed in our study cannot be explained solely by pharmacodynamic and pharmacokinetic factors. Indeed, if pharmacological reasons were responsible for the differences in piritramide consumption, a lower number of demand doses in the 1.5-mg bolus group might be expected. However, the number of bolus doses given was the same in both groups. The ratio between the number of successfully delivered doses to the total number of attempts was the same in both groups. It is interesting to speculate on possible pharmacological reasons for our findings. Although not supported by the literature, piritramide may have a much longer half-life than commonly supposed. Piritramide is usually described as a pure opioid agonist but this raises the question as to whether it has partial agonist properties with a ceiling effect.

The efficacy of PCA implies pharmacological and non-pharmacological variables.[3] Our results indicate that non-pharmacological variables may have a stronger impact on the efficacy of PCA than assumed previously. A placebo-controlled clinical study could clarify this issue. Previous studies have reported conflicting results for possible correlations between personal traits and postoperative pain relief.

The possibility of self-control seems to play a major role in the success of PCA. The impression of being able to control events, when applied to painful phenomena, can have positive consequences, even if the control response as such is not actually applied (i.e. the simple fact of having the PCA pump at one's bedside can already have positive effects). It was shown that anxiety and locus of control were correlated significantly with postoperative pain.[9] Reynaert and colleagues reported a difference in efficacy in PCA between patients with internal and external health loci of control.[10] In our study, the health locus of control was not assessed. Anxiety and social support were important predictors of postoperative pain and PCA use in orthopaedic patients.[2] Our study found no correlation between preoperative anxiety and postoperative VAS for pain and pain relief (data not shown). However, the questionnaire used in our study did not differentiate between state anxiety related to the situation of hospitalization and surgery, and trait anxiety as a stable factor over time in the individual.

Mean VAS pain scores in our study indicated that patients did not use PCA to achieve complete analgesia. Nevertheless, patient satisfaction was high in both groups. A meta-analysis of 15 randomized PCA studies showed that PCA was associated with only a small improvement in pain relief but with a large increase in patient satisfaction[1]. Factors other than pain relief are assumed to be associated with patient satisfaction. Indeed, pain intensity, patients' perceptions of support, expectations of recovery, preoperative anxiety and postoperative depression were significantly correlated with the degree of dissatisfaction with PCA in patients undergoing hysterectomy.[11] Our data showed considerable inter-individual variability in pain scores and analgesic requirements. This is in agreement with published data. Tamsen and colleagues found that patients receiving PCA had up to four-fold variation in analgesic requirements.[12] A PCA regimen with a small bolus dose in combination with a short lockout time improves individual titration of analgesia and takes into account the large inter-individual variance in analgesic requirements.

In our study, the use of a low bolus dose had no influence on the occurrence of side effects. Approximately 60% of patients in both groups felt drowsy or sedated. No PCA-related complications such as respiratory depression or oversedation were observed. The incidence of complications associated with PCA in a survey of 1122 patients appeared to be rather low (approximately 0.7%). However, PCA methods involving infusion in addition to intermittent boluses were associated with a higher incidence of complications compared with those using intermittent bolus doses alone.[13]

We conclude that a PCA regimen with a bolus dose of piritramide 0.75 mg and a lockout time of 5 min was effective in the treatment of postoperative pain, but did not reduce the occurrence of side effects. Further investigations are warranted to re-evaluate the minimal effective bolus dose in PCA.

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