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Rectal indomethacin reduces postoperative pain and morphine use after cardiac surgery

Purpose: To evaluate the combination of rectal indomethacin with patient controlled intravenous morphine analgesia (PCA) on postoperative pain relief and opioid use after cardiac surgery.

Methods: With institutional ethics approval, 57 consenting adults undergoing elective aortocoronary bypass surgery were randomly assigned preoperatively in a double-blind fashion to receive either placebo (n = 26) or indomethacin 100 mg suppositories (n = 31), 2-3 hr postoperatively, and 12 hr later. Both groups utilized PCA morphine. Pain scores in the two treatment groups were assessed on a 10-cm visual analogue scale (VAS) (at rest and with cough) at 4, 6, 12, 18 and 24 hr after initial dosing, and were analyzed through a 2 × 5 repeated measures of variance. The 24 hr analgesic consumption, 12 and 24 hr chest tube blood loss, and time to tracheal extubation were also recorded, and compared for the two treatment arms through Student's t test on independent samples.

Results: Postoperative morphine consumption in the first 24 hr was 38% less in the indomethacin group (22.40 ± 12.55 mg) than the placebo group (35.99 ± 25.84 mg), P= 0.019. Pain scores, measured with a VAS, were 26% to 66% lower in the indomethacin *vs* placebo group at rest (P=0.006), but not with cough, for all times assessed. There was no difference in blood loss (at 12 hr) or time to tracheal extubation for both groups.

Conclusion: The combination of indomethacin with morphine after cardiac surgery results in reduced postoperative pain scores and opioid use without an increase in side effects.

Objectif : Évaluer l'action combinée d'indométhacine rectale et d'analgésie contrôlée par le patient (ACP) avec de la morphine intraveineuse sur la douleur postopératoire et l'usage d'opioïde en cardiochirurgie.

Méthode : Ayant obtenu l'approbation du comité d'éthique de l'hôpital, 57 adultes consentants qui devaient subir un pontage aortocoronarien électif ont été répartis au hasard avant l'opération afin de recevoir en double insu, soit un placebo (n = 26), soit de l'indométhacine (n = 31) en suppositoires de 100 mg, 2-3 h après l'opération et 12 h plus tard. Tous ont utilisé de la morphine pour l'ACP. Les scores de douleur ont été évalués à l'aide d'une échelle visuelle analogue (EVA) de 10 cm (au repos et lors de la toux) à 4, 6, 12, 18 et 24 h après le dosage initial et analysés selon un plan 2 × 5 de mesures répétées de la variance. La consommation d'analgésique à 24 h, la perte sanguine au drain thoracique à 12 et 24 h et le moment de l'extubation endotrachéale ont été notés et comparés d'un groupe à l'autre par le test t de Student sur des échantillons indépendants.

Résultats : La demande postopératoire de morphine des 24 premières h a été de 38 % moindre avec l'indométhacine (22,40 ± 12,55 mg) qu'avec le placebo (35,99 ± 25,84 mg), P = 0,019. Les scores de douleur de l'EVA ont été de 26 % à 66 % plus faibles pour l'indométhacine *vs* le placebo, au repos (P = 0,006), non lors de la toux, et ce, pour tous les temps de mesures. La perte sanguine a été semblable dans les deux groupes (à 12 h) ainsi que le temps total d'intubation.

Conclusion : Administrée après une intervention cardiaque, la combinaison d'indométhacine et de morphine a réduit les douleurs et l'usage d'opioïdes sans augmenter les effets secondaires.

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Portions of this paper were presented at the annual meeting of the Society of Cardiovascular Anesthesiologists, in Seattle, April, 1998.

Accepted for publication April 27, 1999

IN the past decade, the American Association of Critical Care Nurses has ranked pain management after cardiac surgery as a high priority.[1] Inadequate postoperative analgesia has been recognized as a universal problem and is considered unacceptable.[1,2] Currently, opioids remain the mainstay of postoperative pain management after major surgery.[3] Although the use of opioids can provide excellent analgesia, the doses necessary to provide effective pain relief may lead to undesirable side effects such as respiratory depression, sedation and nausea.[4]

Non-steroidal anti-inflammatory drugs (NSAIDs) are potent analgesics[4,5] but are inadequate for postoperative analgesia after major surgery when used alone.[3,5] However, NSAIDs in conjunction with opioids for postoperative analgesia have been shown to improve pain scores and reduce opioid consumption.[2,3,6–10] This combination of drugs has been termed balanced analgesia.[3] The combination of indomethacin with morphine has been studied in patients after thoracic, abdominal and orthopedic surgery,[2,11,12] but not after cardiac surgery. Anecdotal reports at our institution have indicated that the combination of rectal indomethacin and parenteral opioid is associated with superior analgesia after cardiac surgery. The choice of indomethacin, administered rectally, was made on the basis of its well studied physiological properties, good absorption, easy and convenient (q12h) administration, and relative inexpensiveness.[13]

The standard postoperative analgesia technique used in many institutions for cardiac surgery does not involve the use of NSAIDs. Through a prospective, randomized, double-blind trial, comparing indomethacin with placebo, as an adjunct to morphine analgesia, we recorded the effects of indomethacin on morphine use and analgesia after cardiac surgery. The difference in postoperative blood loss, time to tracheal extubation and vital capacity (VC) between the indomethacin and placebo groups was also recorded and evaluated.

Patients and methods

With institutional ethics approval and written, informed consent, 122 adult patients scheduled to undergo elective aortocoronary bypass (ACB) surgery were enrolled in this trial. Patients were excluded from participating if one or more of the following existed: (i) previous history of peptic ulcer disease or gastrointestinal bleeding; (ii) hepatic or renal insufficiency; (iii) insulin dependent diabetes mellitus due to risk of diabetic nephropathy; (iv) known allergy or sensitivity to ASA or NSAIDs; (v) use of ASA in the five days preceding surgery; (vi) gastro-epiploic artery conduit; (vii) weight < 60 kg; (viii) inability to operate the patient controlled analgesia (PCA) device; and (ix) language barrier.

Patients enrolled in the study were instructed on PCA use and reporting of pain on a visual analogue scale (VAS). A standard 10-cm VAS was used, where one end of the scale represented no pain (0 cm), and the other end the most severe pain imaginable (10 cm), the distance in centimeters being taken as the pain score.

Preoperatively, all patients received a standard premedication of 1-2 mg lorazepam *sl*, or 1-3 mg of midazolam *im*, or 5-20 mg diazepam *po*. Anesthesia was induced with 10-15 $\mu g \cdot kg^{-1}$ fentanyl, midazolam, pancuronium, and either propofol or thiopental. Anesthesia was maintained by halothane or isoflurane in a 50% oxygen and air mixture. Supplemental doses of vecuronium were used for muscle relaxation as required. Additional fentanyl was given up to a maximum of 15 $\mu g \cdot kg^{-1}$ for the operative period. Tranexamic Acid 5-10 mg *iv* was given prior to skin incision only to patients considered to be at higher risk for bleeding. Patients were given heparin for systemic anticoagulation prior to cardiopulmonary bypass. Systemic anticoagulation was reversed after separation from cardiopulmonary bypass with protamine. Any residual muscle relaxation was reversed with neostigmine and glycopyrrolate.

After transfer to the cardiovascular intensive care unit (CVICU) with the trachea intubated, patients were assessed over two to three hours for blood loss and creatinine levels. Patients with evidence of renal dysfunction, defined as serum creatinine levels higher than the upper limit of the normal range for their age and gender, and chest tube drainage > 100 $ml \cdot hr^{-1}$, were excluded from the study at this stage. Sixty-seven patients continued in the study; all excluded patients were due to excessive chest tube blood loss. Patients continuing in the study were randomized in a double-blind fashion to one of two groups. The indomethacin group, Group (I), received a 100 mg indomethacin suppository two to three hours after surgery and again 12 hr later for the 24 hr study period. The placebo group, Group (P), received an identical appearing placebo suppository according to the same regimen. The randomization procedure was carried out by the pharmacy department by the sequential selection of previously randomized envelopes containing the study drugs.

All patients received standard postoperative analgesia of 2-4 mg morphine *iv* as required for pain relief. The relief of anxiety and agitation was treated with midazolam intravenously. Prior to extubation, intravenous morphine was administered by the nursing staff for analgesia to patients exhibiting signs of tachy-

cardia, hypertension, grimace, sweating, or indicating that they were having pain. Once the patients were awake, normothermic, and hemodynamically stable with satisfactory arterial blood gases (pH 7.32-7.48, PO_2 80 with $FiO_2 \leq .60$ while receiving 5 cm H_2O continuous positive airway pressure for 30 min), extubation of the trachea was performed. All patients received a PCA device to administer supplementary doses of morphine. The PCA device was programmed to provide a bolus dose of 1.5 mg morphine with a lockout time of seven minutes, and a four hour limit dosage of 30 mg morphine.

Patients were studied for 24 hr. Total morphine consumption for the 24 hr was recorded. Pain scores were recorded both at rest and with cough at 4, 6, 12, 18 and 24 hr after initial dosing. Pain scores were recorded with cough as a measure of dynamic pain. Vital capacity via spirometry was recorded at 6, 12 and 18 hr postoperatively. Chest tube loss was recorded at 12 and 24 hr, and time to extubation was also recorded during the study period.

The primary measure (dependent variable) of treatment efficacy was the VAS. Deviations from normal gaussian distribution were treated by standard transformation of the VAS. The two treatment arms, placebo and indomethacin, and five time points of measurement were analyzed in a repeated measures analysis of variance (RANOVA).

The alpha for the interaction F ratio was set at 0.05 and the desired power to 0.80 for a population size of 60 patients enabling the detection of a medium size effect (f=0.20).[14]

The data for benzodiazepine premedication, intraoperative and postoperative midazolam administration, intraoperative fentanyl use, morphine use in the CVICU before initiation of PCA, 24 hr morphine consumption, blood loss, VC, time to tracheal extubation, and serum creatinine concentration were compared for the two treatment arms using Student's t test on independent samples. A P value < 0.05 was considered significant.

Results

One hundred and twenty-two patients consented and enrolled in the study preoperatively. However, before receiving either indomethacin or placebo suppositories, 55 patients were excluded due to postoperative blood loss exceeding 100 $ml \cdot hr^{-1}$ in the first three hours after surgery. A further 10 patients were excluded from analysis due to inadvertent premedication with morphine. Analysis of data with and without these 10 patients yielded similar results. After these exclusions, 57 patients remained for analysis; 31 patients in the indomethacin group and 26 in the placebo group. The groups were similar in respect to number, age, sex and surgical procedure and technique (Table I). Both the indomethacin and placebo groups received similar preoperative medications with no difference in the total amount administered to each group (Table II). There was no difference in the total amount of intraoperative and postoperative midazolam administered to the indomethacin and placebo groups (Table II). Further, no difference in the intraoperative fentanyl use was found between the indomethacin and placebo groups (Table II). There was no difference between groups with the amount of morphine administered in the CVICU before PCA

TABLE I Clinical Characteristics of Patients

	Indomethacin (n = 31)	*Placebo (n=26)*
Median Age (yr)	62.2 ± 9.5	59.4 ± 9.4
Range of Age (yr)	43 - 75	41 - 76
Sex (male/female)	25 / 6	20 / 6
Type of Surgery *(n)*		
ACB x 1	1	0
ACB x 2	6	7
ACB x 3	15	11
ACB x 4	9	8
Type of Surgical Procedure *(n)*		
Saphenous Vein (SV) only	1	2
Left Internal Mammary Artery (LIMA) only	1	0
LIMA & SV	26	18
LIMA & Right Internal Mammary Artery (RIMA)	1	2
LIMA & Radial Artery	2	4

Values are mean ± SD or number. P:NS

TABLE II Medication use for the Indomethacin and Placebo groups

	Indomethacin (n = 31) mg	*Placebo (n = 26) mg*
Preoperative		
Lorazepam	0.29 ± 0.69	0.42 ± 0.81
Diazepam	1.42 ± 4.30	0.58 ± 2.94
Midazolam	0.29 ± 0.78	0.04 ± 0.20
Intraoperative		
Fentanyl	0.93 ± 0.42	0.90 ± 0.33
Midazolam	8.26 ± 4.31	7.96 ± 4.54
Postoperative (CVICU)		
Midazolam	2.32 ± 3.10	2.12 ± 2.57
Morphine prior to PCA	9.17 ± 6.16	13.04 ± 8.43

Values are mean ± SD. P:NS

was started (Table II). No major postoperative complications were reported in either group.

Pain scores measured with a VAS were consistently lower in the indomethacin than in the placebo group at rest for 4, 6, 12, 18 and 24 hr (P=0.006) (Figure 1). The patients in both groups were not awake and alert enough in the first few hours after surgery to comply with measurement of pain scores. Therefore, the 0 and 2 hour measurements were excluded due to insufficient data. Furthermore, since a number of pain scores were not recorded at 24 hr due to patient transfer from the CVICU to the ward, only 27 patients were analyzed in the full 2 x 5 RANOVA. When the 24 hr measure was dropped from the RANOVA the sample size in the 2 x 4 RANOVA increased to 43. This statistical analysis confirmed the treatment effect (P= 0.005) on pain scores at rest in the indomethacin group.

At rest, the pain scores at 4, 6 and 18 hr for the indomethacin group were approximately 60% less than for the placebo group. At 12 and 24 hr, the pain scores of the indomethacin group were only 30% less than the placebo group. Indomethacin consistently produced lower pain scores than placebo (Figure 1). The time effect (P=0.013) demonstrated that pain scores generally decreased with time in both groups.

With cough, pain scores at 4, 6, 12, 18 and 24 hr for the indomethacin group were 9% to 23% lower than for the placebo group. These differences did not reach statistical significance (Figure 2). Postoperative morphine use in the first 24 hr was less in the indomethacin group (22.40 ± 12.55 mg) than in the placebo group (35.99 ± 25.84 mg), P=0.019.

All of the study subjects had their chest tubes removed by 20 hr into the study period. There was no difference in blood loss (12 hr postoperatively) for the indomethacin (494 ± 200 ml) and placebo (495 ± 239 ml) groups. Also, there was no difference in time to tracheal extubation between the indomethacin and placebo groups (430 ± 188 vs. 418 ± 216 min). The analysis of respiratory function revealed that vital capacity was 31%, 22% and 13% higher in the indomethacin than in the placebo group for 6, 12 and 18 hr respectively but these differences did not reach statistical significance.

None of the study subjects (either group) developed postoperative renal dysfunction. Postoperatively at 24 hr, a moderate reduction in serum creatinine concentration was observed in both the indomethacin (100.6 ± 17.2 to 84.7 ± 14.5 $\mu mol \cdot l^{-1}$) and placebo groups (106.8 ± 15.8 to 89.8 ± 12.0 $\mu mol \cdot l^{-1}$) (P:NS). There was no difference between groups with respect to the total dose of dimenhydrinate used for nausea during the study period.

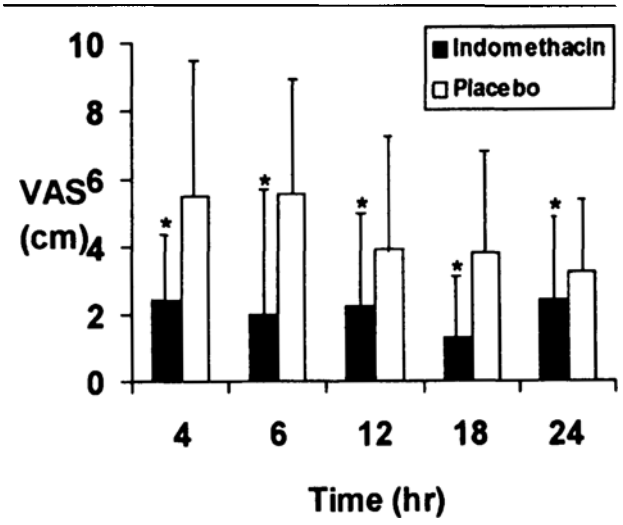

FIGURE 1 Postoperative Pain Scores at Rest (n=27). Scores were measured with a visual analog scale (0-10 cm; 0: no pain, 10: worst possible pain). Pain scores are expressed as the mean ± SD for each group. *P=0.006 compared with placebo.

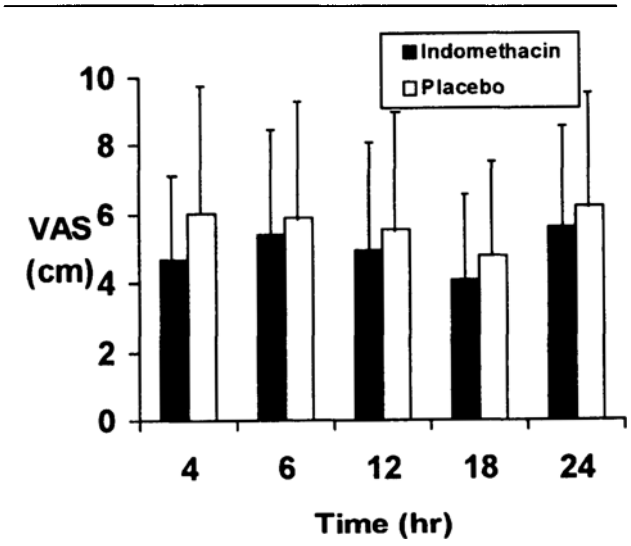

FIGURE 2 Postoperative Pain Scores with Cough (n=23). Scores were measured with a visual analog scale (0-10 cm; 0: no pain, 10: worst possible pain). Pain scores are expressed as the mean ± SD for each group.

Discussion

This study has demonstrated that the combination of indomethacin with morphine to provide analgesia after cardiac surgery, results in reduced pain scores at rest and decreased opioid requirements in the early (24 hr) post-

operative period. Patients given indomethacin suppositories used 38% less morphine than patients given placebo. This opioid sparing effect is in agreement with results reported in previous clinical trials of indomethacin in conjunction with opioids for postoperative analgesia.[10,12,15] Sims *et al.*[15] using a similar analgesic regimen to our study, reported a 44% reduction in morphine use for the indomethacin *vs* placebo group in the first 36 hr after appendectomy. Turner & Gorringe[16] reported a 54% reduction in opioid requirement for the indomethacin group in the first 72 hr after open cholecystectomy. A review by Dahl & Kehlet[3] of NSAID use in lower and upper abdominal surgery, showed a 20-35% reduction in postoperative opioid use in NSAID *vs* placebo groups.

This opioid sparing effect may reduce the incidence of drowsiness and need for antiemetic therapy.[6,17] Parker *et al.* reported that the addition of an NSAID resulted in a more rapid return of gastrointestinal function.[17] A reduction in opioid related side effects may result in decreased postoperative morbidity and shorter recovery time.[18] Sedation, nausea, gastrointestinal function, and recovery time were not assessed in this study.

In the first 24 hr after cardiac surgery, the indomethacin group obtained better analgesia than the placebo group; reporting 26% to 66% lower pain scores at rest (Figure 1). Pain scores with cough, were 9% to 23% lower in the indomethacin group but this was not statistically significant (Figure 2). Decreased pain scores at rest are consistent with the findings of the majority of previous clinical studies for other types of surgery.[6,8–13,15,19] Similar to our study, Reasbeck *et al.* reported a 50% to 71% reduction in pain scores at rest with the rectal indomethacin group in the four postoperative days after major abdominal surgery.[12] The observation of reduced pain scores at rest, but not with cough, is consistent with a study done by Engel on post hysterectomy patients, where there was decreased pain at rest but not with movement, in patients receiving indomethacin.[10]

Optimal pain relief has been shown to reduce the duration of ischemic episodes through reduced myocardial oxygen demand.[20] Superior pain relief using a combination of NSAID and opioid results in decreased heart rate and blood pressure, and hence reduced myocardial oxygen demand in the first 24 hr postoperatively.[20] This may be advantageous to post-cardiac surgery patients, as the majority of these patients will develop biventricular myocardial dysfunction within the first 4-24 hr postoperatively.[21,22] The duration and frequency of postoperative ischemic episodes was not assessed in this study.

Indomethacin, an NSAID, is an inhibitor of prostaglandin synthesis and, thus, has the potential to decrease gastric mucosal integrity, renal blood flow and platelet aggregation. This can lead to complications, including upper gastrointestinal ulcer formation and hemorrhage, renal insufficiency and platelet dysfunction resulting in an increase in postoperative blood loss.[4] However, when used over a short time, in relatively low doses, the potential side effects of NSAIDs are rare.[4] Previous investigators have reported no important gastrointestinal ulceration or hemorrhage with short-term (<48 hr) therapy.[3,4]

Our results showed no deterioration in renal function following the use of NSAIDs. Clinical trials evaluating the effects of NSAID therapy on renal function in healthy patients have previously documented transient, but clinically insignificant increases in creatinine following NSAID use.[5,16,23] Our patients did not exhibit a transient increase in postoperative serum creatinine concentration. Perhaps, this is a result of our stringent exclusion of any patient with a systemic disease process known to have a high incidence of renal involvement. We excluded all insulin dependent diabetics since 40% to 50% of these patients develop diabetic nephropathy.[24] The incidence of acute renal failure following exposure to NSAIDs is uncommon in adults without underlying kidney disease.[23,25] However, patients with hypovolemia, arteriosclerosis, congestive cardiac failure, cirrhosis and renal insufficiency, are at high risk for adverse renal effects if placed on NSAID therapy.[26]

In our study, patients given indomethacin suppositories did not have a difference in postoperative surgical blood loss compared with patients given placebo for the first 12 hr after surgery. However, patients who had higher chest tube blood loss after surgery were not entered into the study. Our finding is in agreement with previous clinical trials of NSAIDs use in conjunction with opioids for postoperative analgesia in non-cardiac surgery.[3,16,17,27]

If patients are properly screened for renal insufficiency, previous history of peptic ulcer disease, hepatic disease, allergy or sensitivity to ASA or NSAIDs, then short-term NSAID use for postoperative analgesia is appropriate.

In conclusion, the benefit of using indomethacin with morphine for balanced analgesia in post cardiac surgery outweighs the minimal risks for carefully selected patients. The use of indomethacin reduces postoperative pain scores and opioid use without producing side effects.

Acknowledgments

The authors would like to thank the nursing staff of the cardiovascular intensive care unit and ward for their help with data collection during the study, and Technilab Inc. for supplying the indomethacin and placebo suppositories, without any financial support. Also, Dr. Bill Wong's review of the manuscript is gratefully acknowledged.

References

1 *Maxam-Moore VA, Wilkie DJ, Woods SL.* Analgesics for cardiac surgery patients in critical care: describing current practice. Am J Crit Care 1994; 3: 31–9.

2 *Moote C.* Efficacy of nonsteroidal anti-inflammatory drugs in the management of postoperative pain. Drugs 1992; 44(Suppl): 14–30.

3 *Dahl JB, Kehlet H.* Non-steroidal anti-inflammatory drugs: rationale for use in severe postoperative pain. Br J Anaesth 1991; 66: 703–12.

4 *Nuutinen LS, Laitinen JO, Salomäki TE.* A risk-benefit appraisal of injectable nsaids in the management of postoperative pain. Drug Safety 1993; 9: 380–93.

5 *Souter AJ, Fredman B, White PF.* Controversies in the perioperative use of nonsteroidal antiinflammatory drugs. Anesth Analg 1994; 79: 1178–90.

6 *Reuben SS, Connelly NR, Lurie S, Klatt M, Gibson CS.* Dose-response of ketorolac as an adjunct to patient-controlled analgesia morphine after spinal surgery. Anesth Analg 1998; 87: 98–102.

7 *Laitinen J, Nuutinen L.* Intravenous diclofenac coupled with PCA fentanyl for pain relief after total hip replacement. Anesthesiology 1992; 76: 194–8.

8 *Nissen I, Jensen KA, Öhrström JK.* Indomethacin in the management of postoperative pain. Br J Anaesth 1992; 69: 304–6.

9 *Pavy T, Medley C, Murphy DF.* Effect of indomethacin on pain relief after thoracotomy. Br J Anaesth 1990; 65: 624–7.

10 *Engel C, Lund B, Kristensen SS, Axel C, Nielsen JB.* Indomethacin as an analgesic after hysterectomy. Acta Anaesth Scand 1989; 33: 498–501.

11 *Keenan DJM, Cave K, Langdon L, Lea RE.* Comparative trial of rectal indomethacin and cryoanalgesia for control of early postthoracotomy pain. BMJ 1983; 287: 1335–7.

12 *Reasbeck PG, Rice ML, Reasbeck JC.* Double-blind controlled trial of indomethacin as an adjunct to narcotic analgesia after major abdominal surgery. Lancet 1982; 2: 115–8.

13 *Alván G, Orme M, Bertilsson L, Ekstrand R, Palmér L.* Pharmacokinetics of indomethacin. Clin Pharmacol Ther 1975; 18: 364–73.

14 *Cohen J.* F tests on means in the analysis of variance and covariance. *In*: Statistical Power Analysis for the Behavioral Sciences, Revised ed. New Jersey: Academic Press, 1977: 273–406.

15 *Sims C, Johnson CM, Bergesio R, Delfos SJ, Avraamides EA.* Rectal indomethacin for analgesia after appendectomy in children. Anaesth Intensive Care 1994; 22: 272–5.

16 *Turner GA, Gorringe J.* Indomethacin as adjunct analgesia following open cholecystectomy. Anaesth Intensive Care 1994; 22: 25–9.

17 *Parker RK, Holtmann B, Smith I, White PF.* Use of ketorolac after lower abdominal surgery. Effect on analgesic requirement and surgical outcome. Anesthesiology 1994; 80: 6–12.

18 *Eriksson H, Tenhunen T, Korttila K.* Balanced analgesia improves recovery and outcome after outpatient tubal ligation. Acta Anaesthesiol Scand 1996; 40: 151–5.

19 *Kinsella J, Moffat AC, Patrick JA, Prentice JW, McArdle CS, Kenny GNC.* Ketorolac trometamol for postoperative analgesia after orthopaedic surgery. Br J Anaesth 1992; 69: 19–22.

20 *Beattie WS, Warriner CB, Etches R, et al.* The addition of continuous intravenous infusion of ketorolac to a patient-controlled analgetic morphine regimen reduced postoperative myocardial ischemia in patients undergoing elective total hip or knee arthroplasty. Anesth Analg 1997; 84: 715–22.

21 *Breisblatt WM, Stein KL, Wolfe CJ, et al.* Acute myocardial dysfunction and recovery: a common occurrence after coronary bypass surgery. J Am Coll Cardiol 1990; 15: 1261–9.

22 *Mangano DT.* Biventricular function after myocardial revascularization in humans: deterioration and recovery patterns during the first 24 hours. Anesthesiology 1985; 62: 571–7.

23 *Feldman HI, Kinman JL, Berlin JA, et al.* Parenteral ketorolac: the risk for acute renal failure. Ann Intern Med 1997; 126: 193–9.

24 *Foster DW.* Diabetes mellitus. *In*: Wilson JD, Braunwald E, Isselbacher KJ, et al. (Eds.). Harrison's Principles of Internal Medicine, 14th ed. New York: McGraw-Hill Inc., 1998: 2060–79.

25 *Singh G, Ramey DR, Morfeld D, Fries JF.* Comparative toxicity of non-steroidal anti-inflammatory agents. Pharmacol Ther 1994; 62: 175–91.

26 *Kenny GNC.* Potential renal, haematological and allergic adverse effects associated with nonsteroidal anti-inflammatory drugs. Drugs 1992; 44: 31–7.

27 *Perttunen K, Kalso E, Heinonen J, Salo J.* I.V. Diclofenac in post-thoracotomy pain. Br J Anaesth 1992; 68: 474–80.