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Peri-operative administration of rectal diclofenac sodium. The effect on renal function in patients undergoing minor orthopaedic surgery

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Summary

In a randomized, double-blind study, we administered placebo and diclofenac sodium 100 mg suppositories 1 h pre-operatively and on the first post-operative morning to 22 adult patients undergoing minor orthopaedic surgery. A standardized post-operative intravenous fluid regimen was instituted until oral fluids were tolerated. Renal function was assessed pre-operatively, and on the first and second post-operative days by the measurement of urine output, creatinine, urea, sodium, potassium and NAG (N-acetyl-b-D-glucosaminidase) levels and serum creatinine, urea, sodium and potassium concentrations. On the first post-operative day, the diclofenac group demonstrated a reduced urinary sodium excretion. On the second post-operative day, a reduced urinary NAG/creatinine ratio was observed in the diclofenac group when compared to placebo. We conclude that peri-operative administration of diclofenac causes changes in renal function consistent with prostaglandin inhibition on the first post-operative day but had no lasting adverse effects in this group of patients. Our results reinforce the need for caution when administering this drug in the context of pre-existing renal impairment.

Keywords: ANALGESICS, diclofenac pethidine; KIDNEY, function, nephrotoxicity; TOXICITY, renal; ENZYMES, lysosomal, N-acetyl-b-D-glucosaminidase.

Introduction

Diclofenac sodium, a phenylacetic acid derivative, is a non-steroidal, anti-inflammatory drug (NSAID) which strongly inhibits prostaglandin biosynthesis [1]. It has been shown to have an opioid sparing effect following orthopaedic and abdominal surgery [2] and its use reduces wound oedema, tenderness, and improves ambulation [3]. Peri-operative fasting, activation of the stress response and disturbances of fluid balance during surgery may compromise renal perfusion. Clinically, endogenous production of prostaglandins play an important role in maintaining renal perfusion. If NSAIDs are administered, they could potentially block the renal arteriolar vasodilatory effects of prostaglandins and impair renal function [4].

The present study was designed to assess the renal effects of the peri-operative administration of diclofenac sodium 100 mg suppositories in adult patients undergoing minor orthopaedic surgery.

Methods

We studied 22 adult male patients (ASA classes I and II) undergoing elective minor orthopaedic surgery such as removal of metal implants, and tendon transfer in

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a randomized double-blind, placebo controlled study. Patients with respiratory, cardiac, hepatic or renal insufficiency, a history of peptic ulcer disease or allergy to aspirin, diclofenac or other prostaglandin inhibiting compounds, were excluded. None of the patients were concurrently receiving NSAID medication. The study was approved by the Faculty of Medicine Ethics Committee (The University of Hong Kong) and written, informed consent was obtained from all patients.

Each patient was premedicated with temazepam 20 mg by mouth 1 h before operation and received a blinded suppository containing either diclofenac (100 mg) ($n=11$) or placebo ($n=11$). A second suppository was administered at 0800 hours on the first post-operative day. Immediately prior to induction an isotonic intravenous (i.v.) crystalloid infusion (Hartmann's solution) was started and continued at 1.5 mL kg^{-1} h^{-1} until the patient could tolerate oral fluids post-operatively. Anaesthesia was induced with propofol 2 mg kg^{-1} and fentanyl 1 μg kg^{-1}. Thereafter, anaesthesia was maintained with the patient breathing spontaneously 65% nitrous oxide and 1–2% isoflurane via the Brain laryngeal mask, supplemented by increments of fentanyl as indicated. After the operation intramuscular (i.m.) pethidine 1 mg kg^{-1} was administered for supplementary analgesia if required.

A bulked 24 h urine sample was collected on the day before surgery and during the first and second post-operative days to determine the following variables: urea and creatinine clearance (mL min^{-1}), urine output (mL min^{-1}) and sodium and potassium excretion (μmol L^{-1}). Blood samples were taken for daily measurement of urea, creatinine, sodium, potassium and pH. A preservative-free 10 mL-urine sample was also collected during each 24 h period and stored at −20°C to await colorimetric batch analysis for NAG activity [5]. Statistical significance ($P<0.05$) was determined for inter-group differences using unpaired *t*-test and repeated measures analysis of variance with Neuman–Keuls *post hoc* comparison using the computer interactive statistics program CSS:Statistica™ V.3.1 (Statsoft, Tulsa, OK, USA). Ninety-five per cent confidence intervals were calculated for all significant and nearly significant values using Student's *t*-distribution tables [6].

Results

Twenty-two patients completed the study but one set of results was withdrawn from analysis because the urine samples were accidentally discarded. There was no significant difference between the two groups in relation to age, body weight, duration of surgery or surgical blood loss (Table 1). All patients were tolerating oral fluids within a few hours following surgery and soon had i.v. administration discontinued. Pre-operative measurement of the chosen indices of renal function demonstrated no significant difference between the two groups (Table 2).

Table 1. Patient characteristics and operative data in the diclofenac and placebo groups

	Diclofenac ($n=11$)	Placebo ($n=10$)	*P* value
Age (years)	45.6 (19.0)	33.5 (9.5)	0.96
Weight (kg)	64.9 (12.7)	63.3 (11.5)	0.72
Blood loss (mL)	117 (31.2)	155 (65.0)	0.10
Surgical duration (h)	1.1 (0.5)	1.8 (1.6)	0.19

Data are presented as mean (SD).

Following surgery there was no significant change in serum or urine indices from pre-operative values, nor was there any difference between the two treatment groups in relation to urea clearance and potassium excretion. On the first post-operative day, there was a reduction in sodium excretion in the diclofenac group, which returned towards pre-operative levels on day 2. The decline in sodium excretion was not demonstrated in the placebo group. One patient receiving placebo had a marked increase in potassium excretion on day 1, but there was no statistical difference in potassium excretion between the groups. On the second post-operative day, there was a significant rise in the NAG/creatinine ratio in the placebo group with no change in the diclofenac group (Table 2).

Discussion

Our results show an increase in the NAG/creatinine ratio in the placebo group with no change in the diclofenac group.

Urinary N-acetyl-b-D-glucosaminidase (NAG) is a sensitive indicator of proximal renal tubular injury, and elevated urinary NAG excretion has been demonstrated during active renal disease and post-operatively [7]. NAG enzymuria has been shown to

Table 2. Group data for assessment of renal function in the diclofenac and placebo groups

	Diclofenac	Placebo	*P* value
Urine output (mL min^{-1})			
pre-operative	1.01 (0.27)	0.87 (0.28)	0.26
post-operative day 1	0.78 (0.38) (0.1–1.47)	1.19 (0.56) (0.17–2.21)	0.06
post-operative day 2	1.11 (0.58)	1.58 (0.70)	0.11
Urea clearance (mL min^{-1})			
pre-operative	40 (11)	53 (20)	0.11
post-operative day 1	42 (22)	72 (57)	0.15
post-operative day 2	58 (17)	61 (21)	0.72
Creatinine clearance (mL min^{-1})			
pre-operative	87 (23)	94 (23)	0.53
post-operative day 1	81 (31) (24.9–137.1)	113 (40) (39.8–186.2)	0.07
post-operative day 2	103 (31)	120 (43)	0.39
Sodium excretion (μmol min^{-1})			
pre-operative	101 (32)	108 (39)	0.65
post-operative day 1	58 (33) (−1.7–117.7)	128 (91) (−38–294)	0.03
post-operative day 2	88 (49)	120 (65)	0.24
Fractional sodium excretion (%)			
pre-operative	1.05 (0.96)	0.83 (0.20)	0.24
post-operative day 1	0.5 (0.25)	0.79 (0.35)	0.57
post-operative day 2	0.61 (0.23)	0.75 (0.27)	0.53
Potassium excretion (μmol min^{-1})			
pre-operative	25 (6)	23 (10)	0.57
post-operative day 1	23 (9)	50 (64)	0.20
post-operative day 2	27 (14)	23 (12)	0.53
Fractional potassium excretion (%)			
pre-operative	6.78 (1.46)	7.0 (5.35)	0.96
post-operative day 1	7.16 (1.64)	12.5 (18.5)	0.14
post-operative day 2	6.47 (1.8)	5.3 (3.07)	0.75
NAG/creatinine ratio			
pre-operative	0.80 (0.41)	0.62 (0.25)	0.27
post-operative day 1	0.81 (0.26)	0.98 (0.88)	0.50
post-operative day 2	0.76 (0.24) (0.33–1.19)	1.20 (0.58) (0.14–2.26)	0.03

Data are presented as mean (SD) (95% confidence intervals).

occur prior to any other measurable renal functional change and, as such, has been successfully used as a sensitive tool for identifying potentially nephrotoxic drugs [8], early renal allograft rejection [9], peri-operative renal function in patients with chronic renal disease [10], and as a predictor of diabetic nephropathy [11]. To account for the variation in urine flow, enzyme activity is divided by creatinine concentration and presented as the urinary NAG/creatinine ratio (Table 2). Whilst a post-operative rise in enzyme activity was observed in the placebo group, no such rise occurred in the patients receiving diclofenac. This implies that any peri-operative proximal renal tubular damage was not attributable to the drug. A normal NAG/creatinine ratio is any value less than 1.0 in our laboratory [12] and we were therefore unable to compute the power of the study.

Renal prostaglandins normally suppress the renal vasoconstrictor effects of angiotensin, noradrenaline, and vasopressin, increase urinary sodium excretion [13] and blunt the hydraulic conductivity response of collecting tubules to vasopressin [14]. Inhibition of prostaglandin effect by diclofenac, therefore, accounts for the reduction in creatinine clearance, urine output and urinary sodium excretion found in the treated patients in this study. The changes were similar to those reported by Power and colleagues [15]. Although statistical significance was not attained because of the relatively small study groups and wide variability in urine output, sodium and creatinine data, our results may be clinically important. We feel that this emphasizes the need for attention to careful peri-operative fluid balance in all patients receiving NSAIDs even though significant deterioration in renal function is much more likely to occur in the context of pre-existing renal impairment or long-term administration.

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