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A Pooled Analysis Evaluating Renal Safety in Placebo- and Active Comparator-Controlled Phase III Trials of Multiple-Dose Injectable HPβCD-Diclofenac in Subjects with Acute Postoperative Pain

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Abstract

Objective. While injectable nonsteroidal anti-inflammatory drugs (NSAIDs) are a key component of postoperative multimodal analgesia, renal safety concerns may limit use in some patients. This study examined the renal safety of injectable HPβCD-diclofenac when given for ≤ 5 days following orthopedic or abdominal/pelvic surgery.

Methods. Pooled analysis of data from two randomized, placebo- and active comparator–controlled phase III trials in 608 total patients was conducted. Renal safety was assessed by examining treatment-emergent adverse events (AEs) and postoperative blood urea nitrogen (BUN) and serum creatinine shifts.

Results. There were three renal AEs each in the HPβCD-diclofenac (n = 318 patients) and placebo (n = 148 patients) groups, and two renal AEs in the ketorolac group (n = 142 patients). No significant difference in renal AE risk was detected for patients receiving HPβCD-diclofenac (RR: 1.40 [0.15,13.3]; *P* = 0.75) or ketorolac (RR: 2.08 [0.19,22.7]; *P* = 0.56)

versus placebo. All renal AEs were mild or moderate in severity, and a single renal AE (acute renal failure in a patient receiving HPβCD-diclofenac) was treatment-related. One incidence of postoperative shift to high (> upper limit of normal) serum creatinine occurred in the HPβCD-diclofenac group (n = 2 in the ketorolac group). Mean changes in serum creatinine or BUN did not differ significantly between patients receiving HPβCD-diclofenac and placebo.

Conclusions. While this analysis examined relatively brief exposure typical for parenterally administered analgesics in the postoperative setting in patients with largely normal renal function, the results suggest that HPβCD-diclofenac use for acute postoperative pain may not be associated with added renal safety risks over placebo in this patient population.

Key Words. Acute Pain; NSAID; Pain Management; Safety; Diclofenac; Renal

Introduction

A multimodal approach to analgesia makes use of a combination of opioid and nonopioid analgesics, such as the nonsteroidal anti-inflammatory drugs (NSAIDs), and can be used to effectively manage postsurgical pain [1,2]. While beneficial in terms of their ability to provide analgesia and reduce opioid intake, there are general safety concerns associated with NSAID use, including risks of bleeding and hepatic, cardiovascular, and renal complications [3–6]. Potential adverse renal effects with NSAID use are of particular concern in patients with conditions that may compromise renal blood flow, including pre-existing renal disease, blood loss, and heart failure, as well as patients with risk factors such as advanced age, which can be associated with decreased renal function [3,7]. Caution is therefore generally advised when prescribing NSAIDs to individuals with or at risk of developing renal impairment [8–11]. Patient age and renal status are also important considerations in the context of surgery. Advanced age and pre-existing renal impairment have been identified as risk factors for acute postoperative renal failure [12], as have procedures involving significant blood loss or large fluid shifts [13]. As a result, particular consideration must be given to the postoperative analgesia regimen used in these at-risk patients.

Diclofenac sodium is a nonselective NSAID with an established efficacy and tolerability profile, and it is used to treat a number of painful conditions, including acute pain following surgery [14–16]. HPβCD-diclofenac (Dyloject™) is a formulation of diclofenac solubilized with hydroxypropyl-β-cyclodextrin (HPβCD) that does not require dilution and allows for rapid administration as a low-volume bolus injection and immediate release of diclofenac upon injection [17]. In contrast, a previous IV formulation of diclofenac (Voltarol®, formulated with benzyl alcohol and propylene glycol) requires dilution and infusion over 30–120 minutes [18,19]. The efficacy and overall safety of HPβCD-diclofenac have been demonstrated in clinical trials examining both single- and repeated-dose regimens for the treatment of acute postsurgical pain [20–26]. In particular, two randomized, placebo- and active comparator–controlled studies have demonstrated repeated-dose HPβCD-diclofenac's efficacy for the management of moderate-to-severe postsurgical pain, alone or in combination with opioids [21,22].

Given the importance of understanding the potential renal risks associated with any NSAID, the objective of the current evaluation was to investigate renal safety in patients receiving IV HPβCD-diclofenac for ≤ 5 days for the management of acute moderate-to-severe postoperative pain. While a previous open-label safety study examined renal adverse events (AEs) with repeated-dose HPβCD-diclofenac [25], it did not include patients receiving placebo or an active comparator. In the present study, pooled data from two randomized, double-blind, multicenter, multiple treatment-arm, repeated-dose phase III HPβCD-diclofenac trials were analyzed to assess renal safety in a diverse yet well-characterized postsurgical patient population.

Methods

Both clinical trials included in the pooled analysis were registered with clinicaltrials.gov (trial identifiers NCT00448110 and NCT00507026). Following Institutional Review Board (IRB) approval, all patients provided IRB-approved written informed consent. Detailed methods are provided in Gan et al., 2012 [21] and Daniels et al., 2013 [22].

Patients

For the studies included in the analysis, patients ≥ 18 years of age were screened for inclusion if they were scheduled to undergo an abdominal/pelvic or orthopedic procedure within 2 (abdominal/pelvic) or 3 (orthopedic) weeks and were expected to require IV analgesia for the management of moderate-to-severe pain following their procedure. The key postsurgical inclusion criterion was the presence of moderate-to-severe pain, defined as pain intensity ≥ 50 mm on a 0–100 mm visual analog scale, within 6 hours of surgery completion (Table S1). The upper age limit for inclusion was 65 years for abdominal/pelvic surgery patients and 85 years for orthopedic surgery patients. Females of childbearing age were required to have a negative pregnancy test at screening and be using an approved method of contraception. Patients were excluded from either study if they had a history of uncontrolled chronic disease (e.g., gastric erosion/ulceration or bleeding, renal impairment, or cardiac failure) that would disqualify them from study participation, require hospitalization within a month of study participation, or render participation inadvisable in the opinion of the study site investigator; recent history (≤ 6 months) of cardiovascular events; known allergy to

diclofenac, NSAIDs, morphine, anesthetics, or any of the excipients of the study preparation; clinically significant lab or electrocardiography (ECG) result at baseline or screening; or had taken monoamine oxidase inhibitors, tryptophan, carbamazepine, or valproate ≤ 2 weeks prior to taking the study drug. Patients were also excluded from the respective studies if they had taken aspirin (except for antiplatelet cardiac protection), other NSAIDs, or other common centrally or peripherally acting analgesic drugs, centrally acting adjuvants, major and minor tranquilizers, or antihistamines ≤ 24 hours prior to study drug administration, with the exception of medications administered during the procedure. Long-acting NSAIDs or COX-2 inhibitors were to be discontinued 3 days prior to surgery. The abdominal/pelvic surgery study [21] excluded patients with renal impairment at baseline, while the orthopedic surgery study [22] included patients with mild or moderate renal impairment. In this analysis, mild renal impairment at baseline was defined as serum creatinine greater than the upper limit of normal (ULN) to 1.5 × ULN. Moderate impairment was defined as serum creatinine > 1.5 to 3 × ULN, in line with serum creatinine-based guidelines for assessing acute kidney injury (AKI) [27]. Patients with severe renal impairment at baseline were not enrolled in either study.

Study Design and Outcomes

Studies included in this analysis were identified based on their similar design, patient populations, duration of treatment, and endpoints. Both studies were phase III trials with a randomized, double-blind, multicenter, placebo- and active comparator–controlled design, and are the only two studies comparing repeated-dose HPβCD-diclofenac to placebo and the active comparator ketorolac in the postsurgical setting. In both studies, a computer-generated random number code was used to randomly assign patients meeting inclusion criteria to receive either HPβCD-diclofenac, ketorolac tromethamine, or placebo. Clinicians and patients were blinded to treatment group assignment. Dose levels of individual study treatments, however, were not blinded in the orthopedic surgery study. In the abdominal/pelvic surgery study, patients received 18.75 mg or 37.5 mg HPβCD-diclofenac based on the randomization protocol, 30 mg ketorolac, or placebo. In the orthopedic surgery study, patients received either 18.75 mg, 37.5 mg, or 50 mg HPβCD-diclofenac based on the presence of defined risk factors. The 18.75 mg dose was given to patients weighing < 50 kg; aged ≥ 65 years; or with NSAID-related GI risk factors, hepatic impairment, or renal impairment (i.e., high-risk patients). The 50 mg dose was given to patients ≥ 95 kg with no predefined risk factors. There was similar dose adjustment for ketorolac in orthopedic surgery patients, with a standard dose of 30 mg for a maximum of 120 mg/day given to patients < 65 years of age and patients without renal insufficiency based on labeled guidelines, and a dose of 15 mg for a maximum of 60 mg/day given to high-risk patients [8].

Study medication was given as an IV bolus injection, with the first dose given ≤ 6 hours following completion of the surgical procedure and subsequent doses given every 6 hours until discharge or withdrawal/discontinuation. Abdominal/pelvic surgery patients were observed for at least 48 hours following first study drug dose and for up to 5 days. Orthopedic surgery patients were observed for at least 24 hours, and for up to 5 days. Rescue medication (bolus IV morphine) was available to patients upon request, up to once every 3 hours after the first dose of study drug. If rescue medication did not provide adequate analgesia, the patient was withdrawn from the study and given pain medication in accordance with the investigator's usual practice.

Safety Assessments

General safety was assessed by physical examination, laboratory testing, vital sign testing, 12-lead ECG, and physician evaluation of injection site thrombophlebitis and wound healing. AEs were recorded from baseline through the 30-day follow-up period in the abdominal/pelvic surgery study, and from screening through the 30–37 day follow-up period in the orthopedic surgery study. Renal AEs, as assessed by study site investigators, were coded in accordance with the Medical Dictionary for Regulatory Activities (MedDRA) preferred term and by System Organ Class (SOC), and the observations reported herein likewise employ the MedDRA nomenclature. AEs were graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events v.3.0 (CTCAE) [28]. If a severity rating for a particular AE was not defined in the CTCAE, severity was rated as mild (subject was aware of sign or symptom, but easily tolerated), moderate (enough discomfort to cause interference with usual activities), severe (incapacitating, with inability to work or do usual activities), or life-threatening (immediate risk of death from the event as it occurred). Clinical laboratory measurements, including blood urea nitrogen (BUN) and serum creatinine, were obtained at screening, 24 hours post-first study drug dose, and at discharge/early termination. Additional clinical laboratory measurements were obtained at 5–9 days post-first study drug dose in the abdominal/pelvic surgery population. Shifts in laboratory values were defined in reference to baseline values and were calculated for individual subjects for whom data were available. Laboratory shifts are presented as treatment group mean (standard deviation [SD]). In order to identify potential incidences of postoperative AKI, absolute changes in serum creatinine levels from baseline were retrospectively assessed for all patients.

Statistical Analysis

Both studies included in this analysis were powered to detect a clinically significant difference in each study's respective primary efficacy measure [21,22]. Analysis was performed on the pooled safety population for both studies using software from SAS (Cary, NC, USA) version 9.1 or later. Only treatment-emergent renal AEs (AEs first occurring or worsening in severity during the study period) were analyzed. AE incidences were evaluated for all treatment groups, and relative risks (RRs) of experiencing an

AE for active treatments versus placebo were calculated where appropriate. RRs are presented as RR [95% confidence interval (CI)]. To further examine differences across treatment groups, *P* values were calculated from ANOVA for numerical variables and Cochran–Mantel–Haenszel test for categorical variables. A P value < 0.05 was defined as statistically significant.

Results

Patient Characteristics

The pooled population included 608 patients (n = 318 HPβCD-diclofenac, n = 142 ketorolac, n = 148 placebo) who underwent an abdominal/pelvic or orthopedic procedure and met all inclusion criteria. The abdominal/pelvic surgery study contributed 54.4%, 57.7%, and 51.4% of patients in the HPβCD-diclofenac, ketorolac, and placebo groups, respectively. There were no significant differences across treatment groups with respect to patient age, sex, weight, procedure type or duration, or baseline renal function (Table 1). For any given treatment group, the majority of patients were female, and though the study allowed for administration for up to 5 days, > 75% of patients received study treatment for ≤ 2 days (≤ 8 doses). The proportions of patients receiving 1–6, 7–8, and > 8 doses of study medication were similar for the HPβCD-diclofenac and

Table 1 Study population demographics

	HPβCD-diclofenac (n = 318)	Ketorolac (n = 142)	Placebo (n = 148)	*P* values*
Age (years), mean (SD)	48.9 (14.1)	48.0 (14.7)	48.6 (14.1)	0.81
Age group				
18–50 years, n (%)	176 (55.3%)	79 (55.6%)	89 (60.1%)	0.70
> 50–65 years, n (%)	102 (32.1%)	49 (34.5%)	41 (27.7%)	
> 65 years, n (%)	40 (12.6%)	14 (9.9%)	18 (12.2%)	
Sex				
Male, n (%)	85 (26.7%)	35 (24.6%)	41 (27.7%)	0.83
Female, n (%)	233 (73.3%)	107 (75.4%)	107 (72.3%)	
Weight (kg), mean (SD)	86.0 (20.2)	85.5 (21.9)	84.8 (21.2)	0.83
Procedure type†				
Abdominal/pelvic, n (%)	173 (54.4%)	82 (57.7%)	76 (51.4%)	0.55
Orthopedic, n (%)	145 (45.6%)	60 (42.3%)	72 (48.6%)	
Procedure duration (h), mean (SD)	1.17 (0.69)	1.13 (0.65)	1.19 (0.71)	0.76
Doses received, mean (SD)	7.3 (3.4)	7.5 (3.5)	6.2 (3.7)	–
Dose number group				
1–6 doses, n (%)	101 (31.8%)	43 (30.3%)	71 (48.0%)	–
7–8 doses, n (%)	150 (47.2%)	67 (47.2%)	53 (35.8%)	
> 8 doses, n (%)	67 (21.1%)	32 (22.5%)	24 (16.2%)	
Total dose received (mg), mean (SD)	226.7 (138.7)	206.6 (92.1)	0.0 (0.0)	–
Baseline renal function‡				
Normal, n (%)	304 (95.6%)	137 (96.5%)	139 (93.9%)	0.42
Mild impairment, n (%)	10 (3.1%)	2 (1.4%)	8 (5.4%)	
Moderate impairment, n (%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	
Missing, n (%)	3 (0.9%)	3 (2.1%)	1 (0.7%)	
Number of doses of rescue medication				
0 doses, n (%)	85 (26.7%)	45 (31.7%)	10 (6.8%)	
1–3 doses, n (%)	144 (45.2%)	51 (35.9%)	44 (29.7%)	
4–6 doses, n (%)	48 (15.1%)	17 (12.0%)	44 (29.7%)	
> 6 doses, n (%)	41 (12.9%)	29 (20.4%)	50 (33.8%)	

*From ANOVA for numerical variables and Cochran–Mantel–Haenszel test for categorical variables.
†Most common procedures (> 5% of subjects in all treatment groups): abdominal hysterectomy, abdominal surgery, bunionectomy/foot bone, inguinal hernia repair, knee replacement, vaginal hysterectomy, other.
‡Mild renal impairment defined as screening creatinine > ULN to 1.5 × ULN; moderate renal impairment defined as screening creatinine > 1.5 × ULN.

ketorolac groups (1–6 doses: 31.8% vs 30.3%; 7–8 doses: 47.2% vs 47.2%; > 8 doses: 21.1% vs 22.5%). Most patients in the pooled population had normal baseline renal function (95.6%, 96.5%, and 93.9% in the HPβCD-diclofenac, ketorolac, and placebo groups, respectively). In total, 20 patients, all of whom underwent an orthopedic procedure, had mild renal impairment at baseline (n = 10/318 [3.1%] in the HPβCD-diclofenac group; n = 2/142 [1.4%] in the ketorolac group; n = 8/148 [5.4%] in the placebo group). In addition, one patient in the HPβCD-diclofenac group (0.3%) had moderate baseline renal impairment. When comparing the individual studies included in the pooled analysis, similar numbers of patients aged 50–65 years were contributed by each study. In line with the study inclusion criteria, however, all patients aged ≥ 65 years were patients who were enrolled in the orthopedic surgery study (Table S1). The majority of patients in the abdominal/pelvic surgery study received 7–8 doses of study medication, while in the orthopedic surgery study, most patients received either 1–6 or > 8 doses.

Renal Adverse Events

In total, eight renal AEs occurred in 6 patients in the pooled population (Table 2). Renal AEs occurred in 0.9% (n = 3/318) of patients receiving HPβCD-diclofenac, 1.4% (n = 2/142) of patients receiving ketorolac, and 0.7% (n = 1/148) of patients receiving placebo. There was one reported incidence each of hematuria, oliguria, and acute renal failure in the HPβCD-diclofenac group, two incidences of oliguria in the ketorolac group, and one incidence each of nephrolithiasis, acute renal failure, and renal tubular necrosis in the placebo group. No significant difference in renal AE risk was detected for either HPβCD-diclofenac (RR: 1.40 [0.15, 13.3]; $P = 0.75$) or the active comparator ketorolac (RR: 2.08 [0.19, 22.7]; $P = 0.56$) as compared with placebo.

Of the eight renal AEs occurring in the pooled population, all were resolved (laboratory values, clinical signs, or symptoms related to the event normalized/returned to baseline) and none required dialysis. Four renal AEs were judged to be mild, while four were moderate in severity (Table 3). Two of the moderate renal AEs were in patients who received HPβCD-diclofenac (hematuria, oliguria). The other two moderate renal AEs (acute renal failure, renal tubular necrosis) occurred in a single patient in the placebo group, a 62-year-old female who underwent total knee replacement surgery and also experienced nephrolithiasis, which was judged to be mild in severity. The patient's acute renal failure was considered secondary to a postoperative hypotensive event and was resolved.

A single reported renal AE, acute renal failure in a patient in the low-dose (18.75 mg) HPβCD-diclofenac treatment group, was suspected of being related to the study drug (Table 3). This was also the only renal AE in the population that was judged to be a serious AE (SAE). This patient underwent total hip replacement surgery and had a number of characteristics suggesting an increased risk of postoperative renal complications, including advanced age (81 years), obesity (BMI = 31.5 kg/m^2), a history of hypertension and cardiovascular disease, mild preoperative renal insufficiency, as well as intraoperative vasopressor and diuretic use. In addition, this AE was preceded by a hypotensive event and the patient had increases in serum creatinine and BUN from baseline (Table 4). The patient's acute renal failure was resolved following blood transfusion and discontinuation of valsartan, furosemide, and HPβCD-diclofenac.

Table 4 summarizes key characteristics of all patients who experienced ≥ 1 renal AE during the study period. All patients in the HPβCD-diclofenac and placebo groups experiencing a renal AE were > 50 years of age (including two patients > 65 years old), and all but one underwent an orthopedic procedure. Conversely, both incidences of oliguria in the ketorolac group occurred in patients < 50 years old who underwent an abdominal/pelvic procedure. Both incidences of acute renal failure

Table 2 Renal adverse events in the study population

	HPβCD-diclofenac (n = 318)	Ketorolac (n = 142)	Placebo (n = 148)
Number of renal events	3	2	3
Patients with ≥ 1 treatment-emergent renal AE, n (%):	3 (0.9%)	2 (1.4%)	1 (0.7%)
Relative risk vs placebo (95% CI)	1.40 (0.15, 13.3)	2.08 (0.19, 22.7)	–
P values*	0.75	0.56	–
Renal disorders by preferred term, n (%)			
Hematuria	1 (0.3%)	0 (0.0%)	0 (0.0%)
Nephrolithiasis	0 (0.0%)	0 (0.0%)	1 (0.7%)
Oliguria	1 (0.3%)	2 (1.4%)	0 (0.0%)
Renal failure acute	1 (0.3%)	0 (0.0%)	1 (0.7%)
Renal tubular necrosis	0 (0.0%)	0 (0.0%)	1 (0.7%)

*From Cochran–Mantel–Haenszel test comparing treatment and placebo.
AE = adverse event; CI = confidence interval of risk ratio.

Table 3 Severity of renal adverse events in the study population and relationship to treatment

	HPβCD-diclofenac (n = 318)	Ketorolac (n = 142)	Placebo (n = 148)
Renal AEs by severity, n (%)*:			
Mild	1 (0.3%)	2 (1.4%)	1 (0.7%)
Moderate	2 (0.6%)	0 (0.0%)	2 (1.4%)
Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)
Renal AEs by relationship to treatment, n (%):			
Not related to treatment	2 (0.6%)	2 (1.4%)	3 (2.0%)
Treatment-related†	1 (0.3%)	0 (0.0%)	0 (0.0%)

*According to severity defined by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events v.3.0 (CTCAE) or if severity was not defined in the CTCAE, as follows: mild AE: subject aware of sign or symptom but easily tolerated; moderate AE: enough discomfort to cause interference with usual activities; severe AE: incapacitating, with inability to work or do usual activities.
†One incidence of acute renal failure was suspected of being treatment-related by study investigator.
AE = adverse event.

were associated with shifts in serum creatinine levels exceeding the Kidney Disease Improving Global Outcomes (KDIGO)-defined threshold for stage 1 AKI of 26.5 μmol/L (equal to 0.3 mg/dL) [27]. The patient in the placebo group who experienced three renal AEs did not have a history of renal impairment, but had a hypotensive event following surgery, as well as shifts from normal to high values for both serum creatinine and BUN (Table 4). No dose-response relationship for the incidence of renal AEs and increasing doses of HPβCD-diclofenac was apparent, though the number of patients receiving HPβCD-diclofenac experiencing a renal AE was limited.

Renal Laboratory Measures

In order to further investigate the potential effects of IV HPβCD-diclofenac on renal function, shifts in BUN and serum creatinine were examined. Given that high BUN or serum creatinine levels are typically used as indicators of impaired renal function, shifts from low or normal baseline BUN or serum creatinine levels to high levels following surgery and treatment with study drug were of particular interest. Overall, shifts to high BUN or serum creatinine were uncommon. For BUN, three such shifts occurred, two in patients receiving ketorolac and one in a patient receiving placebo. With respect to serum creatinine, there was one shift to high (> ULN) each in the HPβCD-diclofenac and placebo groups, and two such shifts in the ketorolac group (Table S2). The patient in the HPβCD-diclofenac group and one patient in the ketorolac group had equal baseline serum creatinine values (88.4 μmol/L). These two patients also had an equal increase in serum creatinine above baseline (17.68 μmol/L), which was below the 26.5 μmol/L KDIGO threshold for stage 1 AKI. Both of these patients were female, for whom the normal serum creatinine range was 53.04 μmol/L–97.24 μmol/L. The second patient in the ketorolac group with a shift to high serum creatinine had a baseline value of 114.92 μmol/L and a 26.52 μmol/L increase in this measure, which was slightly above the 26.5 μmol/L threshold for AKI [27], but no renal AEs. This patient was male (normal serum creatinine range 61.88 μmol/L–114.92 μmol/L). Finally, the female patient in the placebo group had a baseline serum creatinine value of 88.4 μmol/L, with a 159.12 μmol/L increase from baseline (maximum value 247.52 μmol/L), and had a recorded AE of acute renal failure (Table 4). All shifts to high BUN or serum creatinine occurred in patients > 50 years of age, and all but one occurred in patients who underwent procedures as part of the orthopedic surgery study. Overall, a total of seven patients in the pooled population had an absolute change in serum creatinine from baseline that exceeded the KDIGO threshold for AKI. Aside from the two patients with recorded AEs of acute renal failure described in Table 4, no other patients with an increase in serum creatinine ≥ 26.5 μmol/L had a renal AE during the study period, and notably, three of the seven had an overall increase of 26.52 μmol/L, which exceeds the KDIGO threshold by 0.02 μmol/L (Table S3). No patients required dialysis, and serum creatinine values returned to normal ranges upon correction of underlying factors such as hypovolemia.

In addition to defined directional shifts, mean changes in BUN and serum creatinine levels were also examined across treatment groups. In general, mean changes in renal lab values were negative; i.e., postsurgical values were lower than screening values (Table S4). For the overall study population, the mean change in BUN in the HPβCD-diclofenac group did not differ significantly from the mean change in patients receiving placebo (–1.47 ± 1.60 vs –1.80 ± 1.72 mmol/L; $P = 0.067$), while the mean change in BUN was significantly different (less negative) in patients receiving ketorolac as compared with placebo (–1.12 ± 1.75 mmol/L; $P = 0.002$). With respect to serum creatinine levels, there were no significant differences between the mean change vs placebo (–3.11 ± 19.23 μmol/L) in either the HPβCD-diclofenac (–4.61 ± 11.02 μmol/L; $P = 0.32$) or ketorolac (–0.83 ± 10.61 μmol/L; $P = 0.24$) group.

Table 4 Characteristics of patients with ≥ 1 renal adverse event

Patient	Renal AE	Treatment	Number of doses	Procedure type	Suspected of being related to treatment? (Y/N)	Age (yrs)/sex	Renal impairment at screening? (Y/N)*	AE preceded by hypotensive event? (Y/N)	Blood urea nitrogen (μmol/L)				Serum creatinine (μmol/L)			
									Shift to high? (Y/N) †	Baseline‡	Final§	Change	Shift to high? (Y/N) †	Baseline‡	Final§	Change
04-007	Hematuria	HPβCD-diclofenac 18.75 mg	>8	Orthopedic	N	78/M	N	N	N	6.43	5.71	–0.72	N	97.24	97.24	0
12-018	Oliguria	HPβCD-diclofenac37.5 mg	1–6	Abdominal/ pelvic	N	57/F	N	N	N	3.57	2.50	–1.07	N	79.56	44.20	–35.36
04-033	Renal failure acute#	HPβCD-diclofenac 18.75 mg	7–8	Orthopedic	Y	81/M	Y	Y	N	9.64	12.50	2.86	N	123.76	185.64	61.88
12-026	Oliguria	Ketorolac	7–8	Abdominal/ pelvic	N	49/F	N	N	N	6.43	4.28	–2.15	N	61.88	61.88	0
12-054	Oliguria	Ketorolac	1–6	Abdominal/ pelvic	N	37/M	N	N	N	4.28	5.71	1.43	N	79.56	79.56	0
04-042	Renal failure acute&, renal tubular necrosis, nephrolithiasis	Placebo	1–6	Orthopedic	N	62/F	N	Y	Y	7.85	9.28	1.43	Y	88.40	247.52	159.12

*Mild renal impairment defined as screening creatinine > upper limit of normal (ULN) to 1.5 × ULN; moderate renal impairment defined as screening creatinine > 1.5 × ULN.
†Shift from normal or low value at screening to a high value (> ULN).
‡Measurement at day –14 to day –2 pre-surgery (abdominal/pelvic surgery) or day –21 to day –2 (orthopedic surgery).
§Postoperative (24 h, early discharge/termination, or 5–9 days [abdominal/pelvic surgery patients only]).
#Identified based on increase in serum creatinine to 2.7 mg/dL and increase in BUN to 40 mg/dL.
&Identified based on increase in serum creatinine to 2.5 mg/dL.

When patient subgroups were examined, patients receiving HPβCD-diclofenac in the normal baseline renal function and 18–50 years subgroups had, on average, significantly larger (more negative) changes in serum creatinine than patients receiving placebo (–4.52 ± 9.99 vs –1.47 ± 18.38 μmol/L [$P = 0.035$] in patients with normal baseline renal function; –4.48 ± 9.71 vs –1.23 ± 11.33 μmol/L [$P = 0.03$] in patients 18–50 years old; Table S3). There were no significant differences between HPβCD-diclofenac and placebo for any other subgroup for either mean BUN or serum creatinine changes. Mean BUN and serum creatinine changes in the ketorolac group also differed significantly from placebo in some patient subgroups. Most notably, the mean change in serum creatinine was positive (i.e., increased serum creatinine) in patients > 65 years old receiving ketorolac, but negative in patients receiving placebo (2.72 ± 15.05 vs –9.95 ± 13.65 μmol/L; $P = 0.03$). No such difference was observed, however, when patients receiving HPβCD-diclofenac were compared with those receiving placebo (–3.32 ± 16.10 μmol/L; $P = 0.15$). In addition, the mean change in BUN was significantly different in patients receiving ketorolac vs placebo in the normal baseline renal function and 18–50 years subgroups (–1.14 ± 1.75 vs –1.66 ± 1.49 mmol/L [$P = 0.02$] in patients with normal baseline renal function; –0.92 ± 1.51 vs –1.51 ± 1.33 mmol/L [$P = 0.02$] in patients 18–50 years old; Table S3). No significant differences between HPβCD-diclofenac and placebo were observed in subgroups defined by surgery type (orthopedic, abdominal/pelvic), though mean change in BUN differed significantly between patients receiving ketorolac and placebo in the orthopedic surgery group (–0.95 ± 1.72 vs –1.80 ± 1.99 mmol/L; $P = 0.013$).

Discussion

The pooled analysis approach used in the present report allowed for a detailed examination of renal safety data from two pivotal phase III trials. While the utility of pooled analyses (versus meta-analysis) can be limited by heterogeneity between studies and inherent study biases [29–31], the studies included were highly amenable to this approach given that they both had a randomized, placebo- and active comparator–controlled design; were similar in terms of drug dosages, dosing schedule, duration of administration, and safety assessments carried out; and were conducted in similar settings, in populations defined by consistent inclusion and exclusion criteria. Further, the two studies analyzed represent the only two randomized controlled studies comparing multiple-dose HPβCD-diclofenac to placebo and the active comparator ketorolac in the postsurgical setting.

Renal complications were relatively uncommon across treatment groups; however, the pooled data suggest that there may be no added renal safety risk associated with the use of IV HPβCD-diclofenac for ≤ 5 days over placebo in the postsurgical setting. Likewise, there was no apparent significant increase in renal AE risk versus placebo among patients receiving ketorolac. Taken together, renal AEs were reported in 6 of 608 patients in the pooled safety population, with 8 total events across treatment groups. Furthermore, all renal AEs were mild or moderate in severity. A single renal AE (acute renal failure in a patient in the HPβCD-diclofenac group, mild in severity) was suspected of being related to the study drug. Importantly, however, review of the patient's case report revealed several pre-existing risk factors for renal complications, including age > 65 years and a history of hypertension, cardiovascular disease, and mild preoperative renal insufficiency. Thus, a number of factors are likely to have contributed to this patient's acute renal failure following surgery.

In light of evidence that renal insufficiency is associated with adverse short- and long-term postsurgical outcomes, including increased mortality risk [32], identifying changes in renal function during the postoperative period is critical. Shifts to high BUN or serum creatinine levels, both used as objective indicators of impaired renal function, were, like renal AEs, relatively uncommon in the pooled postsurgical population examined, with no discernible differences in shift frequency evident between treatment groups. In total, a shift to high serum creatinine was reported for n = 4 patients. It is important to note that in these studies, "high" was defined as exceeding the testing laboratory's ULN. Examination of changes in serum creatinine from baseline in these patients revealed two patients with shifts below the threshold for acute kidney injury, while a third patient had a shift that exceeded the KDIGO-defined threshold by 0.02 μmol/L and had no renal AEs. The fourth patient, who received placebo had an increase in serum creatinine > 150 μmol/L and was identified as having acute renal failure by the study investigator. Considering the entire pooled study population, examination of absolute changes in serum creatinine levels revealed that, using KDIGO criteria, postoperative AKI was relatively uncommon in the study population (7/608 total patients, 2 of whom had a reported renal AE).

Mean changes in serum creatinine and BUN values from baseline were, on average, negative in patients receiving HPβCD-diclofenac (i.e., mean levels did not increase from baseline during treatment), both for the overall population and for the different patient subgroups evaluated. This observation suggests that, by these laboratory measures, renal function did not appear to be adversely affected. It was also observed that patients in the ketorolac group had a significantly different (less negative) mean shift in BUN than patient receiving placebo. While potential causes for this observation were not examined, it is possible that differences in fluid administration, either intra- or postoperatively, may have contributed. It is interesting to note that in some patient subgroups, HPβCD-diclofenac was associated with a significantly greater reduction in serum creatinine levels from baseline than placebo, though, as with the overall treatment groups, the reason for these differences was not investigated. Still, the data suggest

that postoperative renal function was not worsened by receipt of HPβCD-diclofenac versus placebo in any patient subgroup examined. Although mean serum creatinine and BUN levels tended to decrease from baseline in patients in the placebo and ketorolac groups, a notable exception was that ketorolac treatment was associated with a mean increase in serum creatinine in patient patients > 65 years old. It is important to note, however, that while a statistically significant difference was detected between the ketorolac and placebo treatment groups, the number of patients > 65 years old in either group was relatively low. While definitive conclusions about the relative effects of HPβCD-diclofenac, ketorolac, and placebo on postoperative serum creatinine levels in elderly patients cannot be made, this analysis presents promising data suggesting that HPβCD-diclofenac does not lead to increased serum creatinine or BUN versus placebo in this patient group.

The low incidence of acute renal failure observed with HPβCD-diclofenac treatment in the current study compares favorably to reported incidences of postsurgical renal failure from national data sets [12,33]. The observations regarding renal safety of HPβCD-diclofenac in the current analysis also compare favorably with observations from other clinical trials examining diclofenac and other NSAIDs. Acute renal failure and oliguria both occurred in 1/318 patients receiving HPβCD-diclofenac in the pooled population analyzed, similar to the incidences observed in a large phase III HPβCD-diclofenac safety study [25]. Furthermore, renal or urinary AEs have been shown to occur in 5% of patients receiving IV ibuprofen for ≤ 5 days postoperatively [34], and the incidence of oliguria has been described in previous studies to range from 1% to 10% in patients receiving postoperative ketorolac, depending on the administration regimen [35,36].

In the present analysis, use of IV HPβCD-diclofenac for ≤ 5 days postoperatively was not found to be associated with an increased renal safety risk over placebo. This is in agreement with recent meta-analyses indicating that postoperative NSAIDs do not increase the risk of postoperative renal failure or affect renal function in a clinically meaningful way in patients with normal preoperative renal function [37,38]. With respect to patients with pre-existing renal impairment in the current analysis, 1 of 11 patients receiving HPβCD-diclofenac had a renal AE (acute renal failure). While the number of patients with pre-existing renal impairment was low in the population analyzed, this incidence rate is similar to that observed in a large open-label HPβCD-diclofenac safety study [25]. It is advisable to exercise caution when prescribing NSAIDs, including HPβCD-diclofenac, postoperatively in patients with pre-existing renal insufficiency or conditions that can impair renal function or present an added risk of renal impairment, as well as patients at risk of volume depletion. It is also important to note that a large proportion of patients received ≤ 8 doses of HPβCD-diclofenac, and conclusions should be drawn in the context of this acute exposure period.

Taken together, the results of this pooled analysis suggest that HPβCD-diclofenac was not associated with an added risk of adverse effects on renal function over placebo in the surgical population examined and present promising data to guide future studies in larger populations. Given the relatively limited size of the study population and infrequency of renal AEs, the present analysis had limited statistical power to detect differences in renal AE incidences between treatment groups or patient subgroups. In addition, most patients had a relatively short duration of exposure to HPβCD-diclofenac, as is typical for a parenterally administered analgesic in this clinical setting, and the majority of patients in the study population had normal baseline renal function. Thus, larger studies powered to detect differences in renal AE rates, including retrospective analyses of real-world patient populations, to further examine the renal safety of HPβCD-diclofenac in at-risk patient groups, such as patients with pre-existing renal impairment or in patients with longer exposure are warranted. Still, these findings support the current evidence for the safety of HPβCD-diclofenac in postsurgical patients.

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Supplementary data

Supplementary Data may be found online at http://painmedicine.oxfordjournals.org.

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