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Safety of a Novel Parenteral Formulation of Diclofenac after Major Orthopedic or Abdominal/Pelvic Surgery in a Population Including Anticoagulated, Elderly or Renally Insufficient Patients: An Open-Label, Multiday, Repeated Dose Clinical Trial

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Abstract

Objective. Decisions to use or avoid nonsteroidal anti-inflammatory drugs (NSAIDs) for postsurgical pain are often influenced by concerns about bleeding and renal adverse effects. The objective of this study was to evaluate the safety of a novel parenteral NSAID, hydroxypropyl-β-cyclodextrin (HPβCD) diclofenac, in a large postsurgical patient population, with particular focus on bleeding and renal effects.

Methods. This was a large open-label study in adult patients with acute moderate-to-severe pain following major surgery. Patients received ≥2 days of continuous treatment with HPβCD diclofenac, administered as a small-volume bolus injection every 6 hours. Few exclusion criteria were applied in order to reflect surgical patient populations commonly managed in clinical practice. Adverse events (AEs) were recorded throughout the study. The incidences of bleeding- and renal-related AEs were examined in patient subpopulations with known risk factors for NSAID-induced complications: advanced age, pre-existing renal insufficiency, concomitant anticoagulant use, prolonged exposure, elevated dosage, and major surgeries.

Results. Of the total 971 patients studied, 38% were ≥65 years old (12% >75 years), 62% received concomitant anticoagulants, and 6% had pre-existing renal insufficiency. HPβCD diclofenac was well tolerated by the patient population. AE rates are presented by risk factor to enable clinicians to better describe renal- or bleeding-related AEs.

Conclusions. In addition to its previously demonstrated efficacy, this study provides evidence of HPβCD diclofenac's safety in a large postsurgical population including anticoagulated, elderly or renally insufficient patients. Because study exclusion criteria were minimal, these findings may be broadly generalizable to populations commonly treated in clinical practice.

Key Words. Acute Pain; Analgesia; Renal; NSAID; Bleeding

Introduction

The use of multimodal analgesia, employing a combination of opioid and non-opioid drugs, is considered the current standard of care for the control of acute postoperative pain [1–3]. Nonsteroidal anti-inflammatory drugs (NSAIDs) have been shown to reduce the total requirement for opioid analgesics and thus reduce the impact of opioid-induced side effects, such as somnolence, nausea, vomiting, ileus, and urinary retention, which can slow recovery and readiness for discharge [4–6]. Injectable NSAIDs offer the promise of a rapid onset of action, and the nonsteroidal anti-inflammatory mechanism of action can be especially beneficial following surgical procedures. Side effects associated with the NSAID class include gastrointestinal (GI), hepatic, bleeding, and renal complications [7–11]. In light of these risks, precautions are advised when prescribing or administering NSAIDs in individuals perceived to be at greater risk, such as the elderly, individuals with pre-existing renal or hepatic insufficiency, or patients taking anticoagulants [12–14]. Until recently, ketorolac was the only intravenous (IV) NSAID available to U.S. clinicians. Use of ketorolac, however, has been limited because of concern regarding associated bleeding and renal failure, particularly in elderly patients. Anticoagulation is now a routine part of postoperative care, but the antiplatelet effects of ketorolac and, more recently, ibuprofen are relative or absolute contraindications to the use of either injectable NSAIDs in anticoagulated patients [13,15]. For patients not anticoagulated postoperatively, caution is also advised since NSAIDs have been shown to interfere with the antiplatelet effects of aspirin [16,17].

For over 30 years, the NSAID diclofenac sodium has demonstrated efficacy and safety in many acutely and chronically painful conditions [18–20]. One of the most commonly used NSAIDs worldwide, it is available in oral, IV, suppository, topical, and transdermal formulations. A new formulation of IV diclofenac has recently been developed in the U.S. that allows this molecule to be administered as a small-volume (1 mL) IV bolus rather than as a slower or higher volume infusion, as is required for other IV NSAIDs and IV acetaminophen [15,21–23]. For example, a formulation of diclofenac sodium not available in the U.S. (Voltarol®, Novartis, Surrey, UK) requires a 100- to 500-mL infusion over 30–120 minutes for the treatment of postsurgical pain [22], IV ibuprofen requires infusion of at least 100 mL over no less than 30 minutes [15], and IV acetaminophen requires infusion of 100 mL of drug solution over 15 minutes [23]. The new diclofenac formulation investigated in the current study employs a proprietary solubilizing agent, hydroxypropyl-β-cyclodextrin (HPβCD), which allows the insoluble diclofenac compound to be put into a small volume of solution that releases diclofenac immediately upon injection [24], thus allowing for rapid onset of action.

Recent clinical trials have demonstrated that both single and repeated doses of IV HPβCD diclofenac, either alone or in combination with opioid analgesics, are efficacious and well tolerated by patients with moderate and severe postoperative pain [25–27]. This novel diclofenac formulation has also been found to have minimal effects on platelet aggregation in healthy volunteers, in contrast with the markedly disruptive effects of injected ketorolac or oral aspirin [28]. The current study was designed to evaluate the safety of repeated dose IV HPβCD diclofenac in a large and inclusive population of patients with acute pain of moderate-to-severe intensity following major orthopedic or abdominal/pelvic surgery undergoing routine care that in many instances included postoperative anticoagulation. This study had a particular focus on bleeding and renal adverse events (AEs) based on clinical concerns regarding these potential complications.

Methods

Study Subjects

The study protocol and informed consent were reviewed and approved by each site's participating Institutional Review Board prior to subject enrollment. After providing written consent, subjects were screened at 52 sites, with 51 sites enrolling ≥1 subject. Key inclusion criteria were age 18–85 years and the expectation that within 3 weeks following the screening evaluation, the patient would undergo abdominal (laparoscopic or non-laparoscopic), orthopedic, abdominal/pelvic, or any other surgery that would qualify for ≥2 days of scheduled parenterally administered NSAIDs.

Subjects were excluded if they had a history or evidence of significant cardiovascular, respiratory, renal, hepatic, or other GI disease, or a psychiatric disorder that would make study participation unacceptably risky. Other key exclusion criteria were a history of coronary artery bypass graft surgery, hepatic insufficiency at screening (serum bilirubin >2.5 mg/dL), prothrombin time (PT) >20% above the upper limit of normal, significant renal insufficiency at screening (serum creatinine >1.9 mg/dL), warfarin treatment ≤1 week prior to surgery (or the expectation that warfarin treatment would begin before last study drug dose), intraoperative IV NSAID use, known or suspected drug or alcohol abuse, allergy or hypersensitivity to diclofenac, other NSAIDS, or any of the excipients of the study drug preparation, and pregnancy or lactation. Qualifying individuals with serum creatinine >1.1 mg/dL

(women) or >1.3 mg/dL (men) but less than 1.9 mg/dL at screening were identified as having mild renal insufficiency but were not excluded from entry into the clinical trial.

Study Design and Procedures

This was a multicenter, open-label, repeated dose, multiple-day, single-arm safety study. Administration of HPβCD diclofenac, given as an IV bolus, began in the immediate postoperative period, as soon as the patient was stable following surgery according to the study site's usual practice. The study drug was administered every 6 hours (±15 minutes) as the primary postoperative analgesic until the subject was either completely transitioned to oral analgesics, discharged from the institution, received treatment for 5 days, or was discontinued from the study. Most patients (65%) received 37.5 mg doses of HPβCD diclofenac, and dosage was not reduced for elderly patients or for those with hepatic or renal impairment. Based on pharmacokinetic data [29] as well as efficacy findings from a multiple-day, randomized, controlled trial [30], patients ≥95 kg (35%) received 50 mg HPβCD diclofenac in order to maintain equivalent exposure and efficacy. Excepted from this dosage adjustment were subjects ≥95 kg with >1 NSAID-related risk factor. The 37.5-mg dose was administered as a 1.0-mL IV bolus and the 50-mg dose as a 1.33-mL IV bolus.

Opioids or other standard postoperative analgesics (except for other NSAIDs or controlled-release opioids) were allowed on an as-needed basis to supplement the primary analgesic effects of IV HPβCD diclofenac and were given according to the institution's standard of care. Concomitant treatment with commonly used drugs with anticoagulant properties was permitted during the study. Coumadin/warfarin was not permitted during co-administration of the study drug but was allowed to be given beginning on the last day of study drug administration.

Subjects were considered to have completed the study if they received ≥8 consecutive doses of diclofenac (≥2 days of continuous treatment) and completed all follow-up requirements (in-clinic follow-up 10 days following last study drug dose and follow-up telephone call 30–37 days following last dose).

Assessments

Clinical laboratory tests (hematology, biochemistry, urinalysis) and 12-lead electrocardiography were completed at screening, baseline (immediately prior to beginning treatment), and discharge/early termination. For laboratory analyses, baseline values were defined as the most recent value obtained postoperatively and prior to first dose of study drug. Vital signs were collected at screening, baseline, discharge/early termination, and upon follow-up. Physical examinations were conducted at screening and upon follow-up.

AEs

AEs were recorded from the signing of the informed consent through the follow-up telephone call and were followed through resolution or to 30 days following administration of the last dose of study drug, whichever occurred first. Treatment-emergent AEs were defined as those that first occurred or worsened in severity during the course of the study, regardless of their relationship to study drug. The relationship of AEs to treatment was defined by investigators as "not related," "unlikely," "suspected," or "probable," and AEs classified as "treatment-related" were those categorized by the investigator as having a "suspected" or "probable" relationship to study drug.

Bleeding-Related AEs

Events categorized as bleeding-related AEs were those classified by the investigator as a clinically relevant bleeding-related AE. Changes in laboratory values such as prolonged PT, prolonged activated partial thromboplastin time, international normalized ratio increase, and hematocrit decrease in a given patient were not classified as bleeding-related AEs unless the investigator also recorded an event that was significant enough to be coded as a clinical AE according to Medical Dictionary for Regulatory Activities (MedDRA) conventions in the same individual. Postoperative anemia was not classified as a bleeding-related AE unless the clinical investigator classified the anemic event as likely being caused by the study drug vs an expected outcome of the surgical procedure. Bleeding-related AEs included the following verbatim descriptions recorded by clinical investigators, regardless of the investigator's classification of likelihood of the AE being caused by HPβCD diclofenac: rectal hemorrhage, hemorrhagic anemia, small foul-smelling hematoma inferior to surgical site, anal hemorrhage, ecchymosis bilateral forearms at injection site, vaginal hemorrhage, blood loss from surgical incision, hematoma posterior to left colon at surgical site, postoperative wound bleeding, excessive blood drainage at level of left knee at surgical incision, GI bleeding at the level of surgical anastomosis, upper GI bleeding, acute blood loss anemia, blood emesis, hematuria, superficial clot at IV site, infected left hip hematoma, hematochezia, and hematoma right knee.

Renal-Related AEs

Events categorized as renal-related AEs were renal effects classified by the investigator as having a clinical consequence. Changes in laboratory values such as increased blood creatinine, decreased renal creatinine clearance, and increased blood urea in a given patient were not classified as a renal AE unless the investigator also noted subsequent clinical sequelae that could be coded within recognized MedDRA conventions in the same individual. Renal-related AEs included the following verbatim descriptions recorded by clinical investigators regardless of the investigator's classification of likelihood of the AE being caused by HPβCD diclofenac: decreased urine output, acute renal failure, renal failure, renal tubular necrosis, acute renal

insufficiency, oliguria, azotemia, and anuria. For the purpose of this report, events identified as "acute renal failure" and "renal failure" have all been termed "acute renal failure," given the fact that all such instances were reversed once the underlying precipitating factors were addressed and that no patient underwent dialysis.

Patient Global Evaluation of Treatment Efficacy

An overall global efficacy evaluation of treatment was obtained from the patient at the time of study discharge or early termination. Patients were asked to rate their treatment experience as "Excellent," "Very good," "Good," "Fair," or "Poor."

Statistical Analysis

The study sample size was set at 1,000 to ensure that approximately 850 patients would receive ≥8 consecutive doses over 42 hours and be available for evaluation. All descriptive statistical analyses were performed using the SAS® Statistical Software System (SAS Institute, Inc., Cary, NC, USA). For continuous variables, data were summarized by sample size, mean, standard deviation, median, minimum, and maximum. For categorical or ordinal variables, data were summarized as frequency counts and percentages. Missing data were treated as a separate category in the categorical data summaries. No imputation methods were applied to missing safety or patient global evaluation data.

For AE rates in subject groups of particular interest (e.g., ≥65 years old vs <65 years old), 95% confidence intervals were calculated, and distributions were compared using chi-square or Fisher's exact tests based on expected data cell counts. If ≥20% of cells had an expected count of <5, then the Fisher's exact result was reported.

Results

Demographics/Characteristics

In total, 1,171 patients were screened, 1,050 were enrolled, and 971 received HPβCD diclofenac and were included in the safety population analysis (Figure 1). For the 79 patients who were enrolled but did not receive the study drug, the most common reasons were patient withdrawal of consent (N = 32), cancellation of surgery (N = 13), complications occurring after informed consent and before the time of initiation of study drug (N = 8), and the use of prohibited medication (N = 8).

Table 1 provides demographics for the 971 treated patients. Mean age was 58.8 years, with a significant proportion of patients ≥65 (38%) and >75 (12%) years old. Most subjects underwent major surgical procedures (e.g., total knee or total hip replacement, open hysterectomy, laparotomy), and 85% of patients studied received HPβCD diclofenac for 2–3 days following surgery. Over 60% of the patients studied also received concomitant anticoagulants for routine prophylaxis against deep

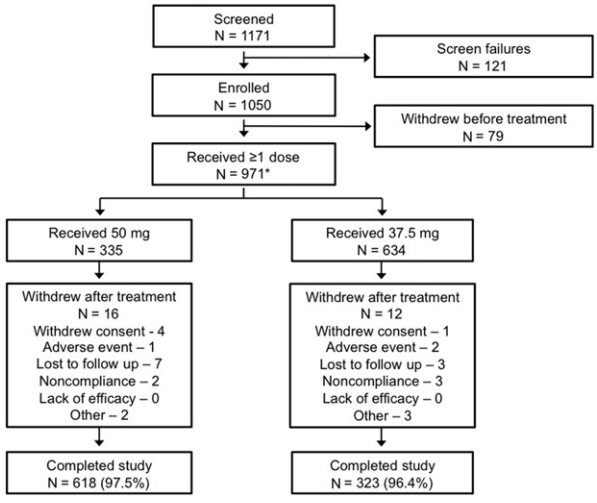

Figure 1 Study subject disposition. A total of 971 subjects received ≥1 dose of intravenous (IV) HPβCD diclofenac for acute postoperative pain, and were included in the safety analysis. In total, 943 (97.1%) subjects received ≥8 doses of study drug and completed the study. *N = 2 patients received 18.75 mg dosage in error (both completed study).

venous thrombosis (DVT), with 7.8% of patients receiving heparin and 51.3% receiving low molecular weight heparin. Warfarin use on the last day of treatment was permitted and was identified in 13.8% of study patients. In addition, many patients remained on low-dose aspirin (81 mg to 325 mg/QD) or clopidogrel for cardiac prophylaxis (40.0%). Patients with mild pre-existing renal impairment were not excluded from the study, and a total of 57 patients (5.9%) with mild renal impairment were evaluated.

Safety

Table 2 presents the most common treatment-emergent AEs in the study population (occurring in ≥5% of subjects). Treatment-emergent AEs were defined as those that occurred or became worse in severity at any time following the first dose of HPβCD diclofenac regardless of relationship to the study drug. Also presented in Table 2 are treatment-related AEs, which were AEs that occurred in >1 patient and were considered by the clinical investigator to be "suspected" or "probably" related to the administration of the study drug rather than the result of a pre-existing medical condition, common postsurgical sequelae (mild-to-moderate anemia, nausea, vomiting, hypotension, etc.) or an unrelated complication that occurred during or after the surgical procedure. In total, 823 (84.8%) patients reported a treatment-emergent AE, and 85 (8.8%) reported a treatment-related AE considered by the clinical investigator as "suspected" or "probably" related to the administration of HPβCD diclofenac. Tables 3 and 4 present treatment-emergent and

Table 1 Demographics and clinical characteristics of study patient population

Demographic Parameter	Total N = 971*; N (%)
Age (years)	
<65	604 (62.2)
65–75	250 (25.7)
>75	117 (12.0)
Mean (SD)	58.8 (13.4)
Median (range)	60 (18–87)
Gender	
Male	354 (36.5)
Female	617 (63.5)
Dose received (mg)	
37.5	634 (65.3)
50	335 (34.5)
18.75 (in error)	2 (0.2)
Length of exposure to study drug (days)	
1	41 (4.2)
2	607 (62.5)
3	220 (22.7)
4–5	103 (10.6)
Mean (SD)	2.4 (0.8)
Median (range)	2.0 (1–5)
Surgical procedure performed	
Orthopedic	676 (69.6)
Total knee replacement	450 (46.3)
Total hip replacement	137 (14.1)
Other†	89 (9.2)
Abdominal/pelvic	293 (30.2)
Gynecologic/genitourinary‡	152 (15.6)
Abdominal§	141 (14.5)
Other	2 (0.2)
Renal function at enrollment	
Renal impairment¶	57 (5.9)
Normal renal function	914 (94.1)
Concomitant anticoagulant use	
Receiving concomitant DVT anticoagulant	602 (62.0)
Heparin	76 (7.8)
LMWH	498 (51.3)
Warfarin**	134 (13.8)
Aspirin/clopidogrel	388 (40.0)
Not receiving concomitant DVT anticoagulant	369 (38.0)

* 51 study sites; highest enrolling sites had 124 (12.8% of total), 87 (9.0%), and 80 (8.2%) subjects, respectively.
† Includes spinal fusion, rotator cuff repair, laminectomy, fracture repair, discectomy, and other, unspecified.
‡ Includes abdominal hysterectomy, other operations of the female genital organs, vaginal hysterectomy, and operations of the male genital organs.
§ Includes laparotomy, incision, excision, and anastomosis of the intestine, partial gastrectomy, gastroenterostomy without gastrectomy, operations of the gallbladder and biliary tract, operations of the pancreas, vagotomy, and other, unspecified.
¶ Serum creatinine >1.1 mg/dL (women) >1.3 mg/dL (men) or urine creatinine >300 mg/dL.
** Beginning on the last day of study drug administration.
DVT = deep venous thrombosis; LMWH = low molecular weight heparin; SD = standard deviation.

treatment-related bleeding- and renal-related AEs that occurred during the study period.

Bleeding-Related AEs

Thirty-two patients (3.3%) reported an AE that was described by the investigator as a clinical bleeding-related event (Table 3). In addition, 218 (22.5%) patients reported postoperative anemia of mild-to-moderate severity. Of these 218 incidences of postoperative anemia, none were considered related to study drug by the clinical investigator responsible (Table 3). Table 5 presents the incidence of bleeding-related AEs in various well-recognized at-risk patient population categories, such as the elderly, those using concomitant anticoagulants, patients subject to prolonged duration of dosing or elevated NSAID dosage, and patients undergoing major surgical procedures. With respect to surgical procedure, the incidence of bleeding-related AEs was 5.7% (N = 8/141) in patients receiving HPβCD diclofenac following major abdominal surgery vs 1.3% (N = 2/152) in those who received HPβCD diclofenac following gynecological or genitourinary procedures ($P = 0.053$). In addition, no significant differences in bleeding-related AE incidence were observed between specific orthopedic procedures (e.g., total knee vs total hip replacement) or when comparing orthopedic and abdominal/pelvic surgeries (Table 5). Other subpopulations with various risk factors for NSAID-induced bleeding complications (concomitant anticoagulant use, elevated HPβCD diclofenac dosage, prolonged drug exposure) were also examined with respect to bleeding-related AE rates. There were no significant differences in the incidence of bleeding-related AEs between patients with and without any of these risk factors.

Renal-Related AEs

Renal-related AEs reported over the course of the study are presented in Table 4. The risk of renal failure associated with NSAID use is another well-recognized clinical concern with regard to postsurgical patient populations. Thus, reports of acute renal failure and decreased urinary output were of particular interest in this study, and the effect of HPβCD diclofenac on the incidence of these renal AEs was closely evaluated within numerous patient subpopulations with and without recognized risk factors for NSAID-induced renal failure, including patients with prior history of compromised renal function, advanced age, surgery ≥2 hours in duration, >2 days NSAID exposure, elevated NSAID dosage, and major surgical procedures (Table 6).

There were 20 total reports of acute renal failure (N = 10) or decreased urinary output (N = 10), occurring in 19 patients. Patients undergoing orthopedic procedures were found to exhibit acute renal failure or decreased urinary output at a rate of 1.5–4.5% depending on the specific procedure, but the differences in incidence between patients undergoing hip, knee, or orthopedic procedures were not statistically significant (Table 6). Within the abdominal/pelvic surgery group, six patients

Table 2 Summary of treatment-emergent and treatment-related adverse events in the study population

	Treatment-Emergent Events (N = 971 Total Subjects)		Treatment-Related Event (N = 971 Total Subjects)	
Adverse Event*	N	%	N	%
Nausea	361	37.2	6	0.6
Postoperative anemia	218	22.5	0	0.0
Constipation	181	18.6	0	0.0
Insomnia	130	13.4	0	0.0
Pruritus	125	12.9	3	0.3
Vomiting	83	8.5	2	0.2
Blood CPK increase	63	6.5	11	1.1
Hypotension	60	6.2	0	0.0
Pyrexia	58	6.0	0	0.0
Headache	56	5.8	1	0.1
Infusion site pain	50	5.1	33	3.4
Dizziness	49	5.0	0	0.0
Dyspepsia	36	3.7	5	0.5
Blood creatinine increase	10	1.0	4	0.4
Urine output decreased	10	1.0	2	0.2
Acute renal failure†	10	1.0	6	0.6
Abnormal liver function test	6	0.6	4	0.4
Infusion site thrombosis	6	0.6	2	0.2
Infusion site irritation	2	0.2	2	0.2

* Occurring in ≥5% of the study population, regardless of relation to HPβCD diclofenac (treatment-emergent) and/or considered by the investigator as "suspected" or "probably" caused by HPβCD diclofenac in >1 individual (treatment-related).
† Includes reports of "acute renal failure" and "renal failure." All such events were reversed once the underlying precipitating factors were addressed and no patient underwent dialysis.
CPK = creatine phosphokinase; HPβCD = hydroxypropyl-β-cyclodextrin.

reported acute renal failure or decreased urinary output, all of whom underwent abdominal procedures (vs none in patients undergoing gynecological/genitourinary procedures; $P = 0.012$).

Patients experiencing acute renal failure or decreased urinary output were also examined in relation to duration of surgery and presurgical renal function. Patients undergoing procedures ≥2 hours in length were shown to be at a

Table 3 Treatment-emergent and treatment-related bleeding-related adverse events and postoperative anemia in the study population

	Treatment-Emergent Events (N = 971 Total Subjects)		Treatment-Related Events (N = 971 Total Subjects)	
Adverse Event*	N	%	N	%
Postoperative anemia	218	22.5	0	0.0
Incision site hemorrhage	7	0.7	0	0.0
Postprocedural hemorrhage	4	0.4	0	0.0
Hemorrhagic anemia	3	0.3	0	0.0
Hematochezia	3	0.3	0	0.0
Wound hemorrhage	3	0.3	0	0.0
Hematoma	2	0.2	0	0.0
Incision site hematoma	2	0.2	0	0.0
Upper GI hemorrhage	1	0.1	1	0.1
Anal hemorrhage	1	0.1	1	0.1

* Occurring in >1 individual, regardless of relation to HPβCD diclofenac (treatment-emergent), and/or considered by the investigator as "suspected" or "probably" caused by HPβCD diclofenac in ≥1 individual (treatment-related).
GI = gastrointestinal; HPβCD = hydroxypropyl-β-cyclodextrin.

Table 4 Treatment-emergent and treatment-related significant renal adverse events in the study population

	Treatment-Emergent Events (N = 971 total subjects)		Treatment-Related Events (N = 971 Total Subjects)	
Adverse Event*	N	%	N	%
Urine output decreased	10	1.0	2	0.2
Acute renal failure†	10	1.0	6	0.6
Oliguria	2	0.2	1	0.1
Blood urea increased	2	0.2	1	0.1
Anuria	1	0.1	1	0.1
Azotemia	1	0.1	1	0.1
Renal tubular necrosis	1	0.1	1	0.1

* Occurring in >1 individual, regardless of relation to HPβCD diclofenac (treatment-emergent), and/or considered by the investigator as "suspected" or "probably" caused by HPβCD diclofenac in ≥1 individual (treatment-related).
† Includes reports of "acute renal failure" and "renal failure." All such events were reversed once the underlying precipitating factors were addressed and no patient underwent dialysis.
HPβCD = hydroxypropyl-β-cyclodextrin.

significantly greater risk of experiencing one of these AEs than those undergoing procedures <2 hours in duration ($P = 0.003$; Table 6). Taken in isolation, the incidence of acute renal failure was 2.4% (N = 5/215) in patients who underwent procedures ≥2 hours long and 0.7% (N = 5/756) in those who underwent shorter procedures. There were no significant differences in the incidences of renal-related AEs of particular interest based on duration of

Table 5 Incidence of bleeding-related adverse events in at-risk postsurgical patient populations

	Bleeding-Related Adverse Events			
Postsurgical Patient Population	N	%	95% CI	*P*
Total (N = 971)	32	3.3	2.26–4.62	
Age (years)				
<65 (N = 604)	19	3.1	1.90–4.87	NS*
65–75 (N = 250)	11	4.4	2.22–7.74	
>75 (N = 117)	2	1.7	0.21–6.04	
Concomitant anticoagulant use				
With anticoagulants (N = 602)	22	3.7	2.30–5.48	NS
Without anticoagulants (N = 369)	10	2.7	1.31–4.93	
Duration of dosing (days)				
1–2 (N = 648)	21	3.2	2.02–4.91	NS
3–5 (N = 323)	11	3.4	1.71–6.01	
Dose received				
Normal dose (37.5 mg; N = 634)	22	3.5	2.19–5.21	NS
High dose (50 mg; N = 355)	10	3.0	1.44–5.42	
Type of surgery				
Orthopedic (N = 676)	22	3.3	2.05–4.89	
Total knee replacement (N = 450)	10	2.2	1.07–4.05	NS†
Total hip replacement (N = 137)	7	5.1	2.08–10.24	
Other orthopedic (N = 89)	5	5.6	1.85–12.63	
Abdominal/pelvic (N = 293)	10	3.4	1.65–6.19	
Gynecological/genitourinary (N = 152)	2	1.3	0.16–4.67	NS‡
Abdominal (N = 141)	8	5.7	2.48–10.87	

* NS = nonsignificant differences between age groups.
† Total knee vs total hip vs other orthopedic.
‡ Abdominal vs gynecological/genitourinary.
CI = confidence interval; NS = Non-significant difference between groups.

Table 6 Incidence of acute renal failure and decreased urinary output adverse events in at-risk postsurgical populations

Postsurgical patient population	Acute renal failure or decreased urinary output adverse events			
	N	%	95% CI	*P*
Total (N = 971)				
Acute renal failure*	10[†]	1.0	0.50–1.89	
Decreased urinary output	10	1.0	0.50–1.89	
Renal function at enrollment[‡]				
Renal impairment (N = 57)	5	8.8	2.91–19.30	0.004
Normal renal function (N = 914)	14	1.5	0.84–2.56	
Age (years)				
<65 (N = 604)	6	1.0	0.37–2.15	NS[§]
65–75 (N = 250)	7	2.8	1.38–5.68	
>75 (N = 117)	6	5.1	1.90–10.83	0.007[¶]
Duration of surgery (hours)				
<2 (N = 756)	9	1.2	0.55–2.25	0.003
≥2 (N = 215)	10	4.7	2.25–8.39	
Duration of dosing (days)				
1–2 (N = 648)	12	1.9	0.96–3.21	NS
3–5 (N = 323)	7	2.2	0.88–4.41	
Dose received				
Normal dose (37.5 mg; N = 634)	16	2.5	1.45–4.07	NS
High dose (50 mg; N = 335)	3	0.9	0.19–2.59	
Type of surgery				
Orthopedic (N = 676)				
Total knee replacement (N = 450)	7	1.6	0.63–3.18	NS
Total hip replacement (N = 137)	2	1.5	0.18–5.17	
Other orthopedic (N = 89)	4	4.5	1.24–11.11	
Abdominal/pelvic (N = 293)				
Gynecological/genitourinary (N = 152)	0	0.0	0.0–2.4	0.012
Abdominal (N = 141)	6	4.3	1.58–9.03	

* Includes reports of "acute renal failure" and "renal failure." All such events were reversed once the underlying precipitating factors were addressed and no patient underwent dialysis.
[†] One patient reported renal failure and decreased urinary output.
[‡] Renal impairment = serum creatinine >1.1 mg/dL (women), >1.3 mg/dL (men); or urine creatinine >300 mg/dL.
[§] Nonsignificant difference, <65 years old vs 65–75 years old.
[¶] Subjects >75 years old vs subjects <65 years old.
CI = confidence interval; NS = Non-significant difference between groups.

HPβCD diclofenac exposure (1–2 days vs >2 days) or the dose received (37.5 mg vs 50 mg/dose; Table 6).

In the 19 patients experiencing acute renal failure or decreased urinary output, treatment consisted of the administration of fluids (including transfusion in two patients in whom anemia was present), diuretics and discontinuation of HPβCD diclofenac. None of the patients studied underwent dialysis as treatment for renal failure. For patients experiencing an episode of acute renal failure, the median duration for this AE was 3.5 days (range 2–10 days; data for eight patients for which timing of onset and resolution data were available). Seven of the 10 patients who experienced acute renal failure (70%) also experienced an episode of hypotension preceding the acute renal failure event (Table 7). The three remaining acute renal failure patients, who did not experience a preceding hypotensive event, were identified as having renal insufficiency prior to surgery and treatment with study drug. Patients with mild pre-existing renal impairment experienced a significantly greater incidence of acute renal failure or decreased urinary output than those with no pre-existing renal impairment (8.8% [N = 5/57 patients] vs 1.5% [N = 14/917]; $P = 0.004$), and acute renal failure occurred in 3.5% (N = 2/57) of patients with elevated serum creatinine levels prior to surgery but 0.9% (N = 8/ 914) of those with normal presurgical serum creatinine levels.

Table 7 Selected demographics and clinical characteristics of patients reporting acute renal failure or decreased urinary output

Patient	Renal AE*	Age	Renal-related AE Preceded by Hypotensive Event?	Pre-Existing Renal Insufficiency?
47050	Acute renal failure	84	Y	N
54035	Acute renal failure	84	Y	N
54076	Acute renal failure	84	Y	N
47046	Acute renal failure	81	Y	Y
58069	Acute renal failure	78	Y	N
24012	Acute renal failure	73	N	Y
58031	Acute renal failure	72	N	Y
70009	Acute renal failure	70	Y	N
86004	Acute renal failure	67	N	Y
72027	Acute renal failure	60	Y	N
47046	Decreased urinary output	81	Y	Y
73003	Decreased urinary output	80	N	N
24028	Decreased urinary output	69	Y	Y
47020	Decreased urinary output	69	Y	N
73004	Decreased urinary output	66	N	Y
73007	Decreased urinary output	60	N	N
47039	Decreased urinary output	58	N	N
73011	Decreased urinary output	57	N	N
47009	Decreased urinary output	56	Y	N
73018	Decreased urinary output	23	N	Y

* "Acute renal failure" includes reports of "acute renal failure" and "renal failure." All such events were reversed once the underlying precipitating factors were addressed and no patient underwent dialysis.
AE = adverse events; N = no; Y = yes.

Patients >75 years of age were at a significantly higher risk of developing acute renal failure or decreased urinary output following surgery vs those <65 years old (5.1% [N = 6/117] vs 1.0% [N = 6/604]; $P = 0.007$; Table 6). Incidence in patients 65–75 years old was 2.8% (N = 7/250; not statistically significant vs patients <65 years old). Acute renal failure occurred in 4.3% (N = 5/117) of patients >75 years old vs in 0.6 % (N = 5/854) of patients ≤75 years old. The median age of those experiencing acute renal failure was higher, at 76 years old (range 60–84 years) vs those who experienced a decrease in urinary output (median 63 years, range 23–81 years). In total, the median age of all patients studied who experienced a renal-related AE was 68 years (range 22–84 years), which was higher than the median age of those patients who did not experience a renal-related AE (58.5 years; range 18–87 years).

Patient Global Evaluation of Treatment Efficacy

Of the subjects completing the global efficacy evaluation, 932/958 (97.3%) indicated that their experience with the study medication was "Excellent," "Very good," or "Good," with 839 patients (86.4%) assessing their experience as "Excellent" or "Very good."

Discussion

Development of novel non-opioid-based IV analgesic options that are safe and efficacious for use in the postoperative setting continues to be of great importance. IV NSAIDs often elicit concerns related to the risk of postoperative bleeding and renal failure [7,8,11,12]. Safety concerns frequently lead clinicians to limit the use of these agents and instead to rely upon more frequent or higher opioid dosages, which can lead to serious potential consequences for the postsurgical patient [31–33].

The primary purpose of this large, multicenter clinical study was to characterize the safety of repeated dose IV HPβCD diclofenac in a large population of postsurgical patients, many of whom underwent routine anticoagulation for DVT prophylaxis or cardiac concerns, with a focus on the incidence of bleeding- and renal-related AEs. The intention is to provide data for clinicians to individualize and optimize postoperative analgesic regimens. Thus, the study was designed to include large at-risk cohorts, including the elderly (N = 367 subjects ≥65 years old), those receiving concomitant anticoagulants (N = 602 subjects), as well as individuals with pre-existing mild renal

impairment (N = 57). This study characterizes the safety profile of IV HPβCD diclofenac when administered every 6 hours following major surgery for a 2- to 5-day postoperative recovery period.

The risk of unexpected severe postsurgical bleeding associated with the use of NSAIDs is a well-recognized clinical concern. Because of this, we examined the incidence of bleeding-related AEs in a variety of subpopulations with and without well-recognized risk factors for NSAID-induced complications. Few differences were observed between at-risk patient subpopulations with respect to bleeding-related AEs. In total, 3.3% of all subjects studied reported a bleeding-related AE other than postoperative anemia, while mild-to-moderate postoperative anemia was reported in 22.5% of all participants. Clinical investigators, however, did not consider the anemic event to be caused by HPβCD diclofenac in any of the postsurgical patient situations studied. The incidence of clinically significant bleeding-related AEs, such as GI bleeding, anastomotic hemorrhage, postoperative bleeding from the surgical incision site, hematoma, hematemesis, hematuria, and others, was greater in patients undergoing abdominal surgical procedures (laparotomy, incision, excision, and anastomosis of the intestine, as well as operations of the gallbladder, biliary tract, and pancreas) than those undergoing gynecologic or genitourinary procedures (mostly open hysterectomies), but this difference was not statistically significant. This observed elevation in the incidence of bleeding-related events with abdominal vs gynecologic/genitourinary procedures, however, is consistent with previous evidence indicating an increased incidence of bleeding-related AEs with general surgical procedures vs surgical procedures involving the reproductive organs [34].

No statistically significant differences in the incidence of bleeding-related AEs occurred between patients receiving HPβCD diclofenac in addition to anticoagulants for DVT or cardiac prophylaxis vs those not receiving anticoagulants. Likewise, no differences were observed in patients ≥65 years old vs those <65 years old, in patients receiving <2 days of treatment vs those receiving up to 5 days of continuous treatment, or in patients receiving 50 mg HPβCD diclofenac vs those receiving the 37.5-mg dosage.

Although a postsurgical patient population is already at a greater risk for acute renal failure and other renal AEs because of fluid shifts and unstable hemodynamics, multiple-dose IV HPβCD diclofenac was associated with a relatively low incidence of postoperative renal failure in this trial. There was a total of 10 reports of acute renal failure (1.0%) in this study, which is consistent with the 1% incidence reported in national surgical data sets for postoperative acute renal failure in all post surgical patients, not just those also receiving postoperative IV or oral NSAIDs [35,36].

Consistent with data identifying advanced age as an independent risk factor for acute postoperative renal failure [36,37], the incidence of renal-related AEs of greatest interest (acute renal failure, decreased urinary output) increased with age in this study population. This trial demonstrated an increase in the incidence of decreased urinary output and acute renal failure in the most elderly of the patients studied. These renal-related AEs were experienced by 5.1% of patients >75 years of age, while the incidence was 1.0% in those <65 years of age and 2.8% in those 65–75 years old. There was no statistical difference in the incidence of these AEs between patients aged 65–75 and those <65 years old. Taken alone, acute renal failure occurred in 4.3% patients >75 years old vs in 0.6% of patients ≤75 years old. Caution should be used with this and any IV NSAID in an elderly postsurgical patient population.

In addition, this trial demonstrated that patients undergoing surgical procedures ≥2 hours in duration had a higher incidence of acute renal failure or decreased urinary output AEs than those undergoing shorter surgical procedures (<2 hours in total length). The incidence of acute renal failure was 2.4% in those undergoing procedures ≥2 hours in duration vs 0.7% in those undergoing shorter surgeries. This increase in renal AEs may reflect the likelihood of more extensive fluid shifts and corresponding periods of hypotension that can occur more frequently with more extensive surgical procedures that last a longer period of time.

Patients with mild pre-existing renal impairment prior to surgery also experienced a significantly greater incidence of key renal-related AEs in this trial than those with normal presurgical serum creatinine levels. Acute renal failure occurred in 3.5% of patients with elevated serum creatinine levels prior to surgery but only 0.9% of those with normal presurgical serum creatinine levels. With respect to duration of treatment, continuous treatment with HPβCD diclofenac for 2–5 days did not result in a significant increase in renal AEs as compared with incidence in patients treated for only 2 days.

Finally, efficacy of HPβCD diclofenac was assessed using a patient global evaluation, which relied on patient assessment of the treatment experience with the study drug, and 86.4% of patients reported that their experience was “Very Good” or “Excellent.” This basic patient-reported outcome is commonly reported in analgesic and other clinical trials [38], and also is the foundation for many assessments of the quality of health care delivery in general, for example, in the Hospital Consumer Assessment of Healthcare Providers and Systems survey. Recently, however, some have called for closer scrutiny of the complex patient experiences that are contained within this deceptively simple measure [39]. It is important to note that the current study had an open-label, non-comparative design and that the patient global evaluation is an indication of general effectiveness and not statistically driven efficacy.

The current study adds to a growing body of literature regarding the safety of IV HPβCD diclofenac, which includes single- and repeated dose studies. Two

double-blind, randomized, placebo-controlled clinical trials investigated single-dose HPβCD diclofenac following third-molar extraction, finding no treatment-related SAEs and no withdrawals as a result of AEs [25,26]. More recently, two Phase III placebo- and active-controlled efficacy trials have provided additional evidence that repeated dose IV HPβCD diclofenac over multiple days, in addition to providing significant analgesic effect with less total opioid consumption in the postoperative setting, is likewise well tolerated [27].

Conclusions

In conclusion, this study demonstrates that IV HPβCD diclofenac is safe and well tolerated in a large postsurgical patient population with few exclusion criteria, including patients undergoing anticoagulation as a routine standard of postoperative care and those with pre-existing renal insufficiency. The incidence of bleeding-related and renal-related AEs was evaluated in order to provide a context to assess risk vs benefit when selecting among opioid and non-opioid IV analgesics for at-risk patients with a variety of concomitant conditions and medications. As an open-label safety trial without a control group, the present study's assessments of risks are best compared with published observations drawn from large data sets comprised of similar patient groups undergoing comparable operations with or without NSAID use. Finally, while some of the at-risk groups evaluated in this study were limited in terms of size (e.g., patients with pre-existing renal impairment), the data provide evidence for the relative safety of HPβCD diclofenac with respect to different risk groups, as well as identify patients for whom caution would be advisable. Overall, the safety profile of IV HPβCD diclofenac established herein, as well as its analgesic efficacy seen in previous studies [25–27], indicate that this new non-opioid IV diclofenac formulation may play an important role in the management of postoperative pain. Because elevated incidences of relevant renal AEs (acute renal failure, decreased urinary output) were observed in patients >75 years of age as well as those with significant pre-existing renal impairment, caution would be advised, as with any NSAID, with respect to use of HPβCD diclofenac in these patient groups.

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