Drugs 2008; 68 (1): 123-130
0012-6667/08/0001-0123/$53.45/0

Diclofenac Sodium Injection (Dyloject®)
In Postoperative Pain

Paul L. McCormack and *Lesley J. Scott*

Wolters Kluwer Health | Adis, Auckland, New Zealand, an editorial office of Wolters Kluwer Health, Conshohocken, Pennsylvania, USA

Contents

Abstract

▲ A new formulation of the nonselective NSAID diclofenac sodium suitable for intravenous bolus injection has been developed using hydroxypropyl β-cyclodextrin as a solubility enhancer (HPβCD diclofenac).

▲ HPβCD diclofenac intravenous bolus injection was shown to be bioequivalent to the existing parenteral formulation of diclofenac containing propylene glycol and benzyl alcohol as solubilizers (PG-BA diclofenac), which is relatively insoluble and requires slow intravenous infusion over 30 minutes.

▲ Single-dose HPβCD diclofenac 3.75, 9.4, 18.75, 25, 37.5, 50 and 75 mg administered by intravenous bolus injection produced significantly greater responses than placebo for total pain relief (TOTPAR) over 6 hours or pain intensity at 4 hours in the treatment of moderate or severe postoperative dental pain in randomized, double-blind trials. HPβCD diclofenac 37.5 and 75 mg were similar in efficacy to intravenous bolus ketorolac 30 mg.

▲ In a well controlled trial, single-dose HPβCD diclofenac 75 mg intravenous bolus injection was shown to be superior to PG-BA diclofenac 75 mg intravenous infusion with respect to TOTPAR over 4 hours, indicating faster onset of analgesia in the treatment of moderate or severe postoperative dental pain. Both HPβCD diclofenac and PG-BA diclofenac were superior to placebo.

▲ HPβCD diclofenac was generally well tolerated during single-dose treatment of postoperative pain. The tolerability profile was similar to that of PG-BA diclofenac, but with a lower incidence of thrombophlebitis.

Features and properties of diclofenac sodium injection (DIC075V; Dyloject®)	
Indication	
Treatment or prevention of postoperative pain in supervised healthcare settings	
Mechanism of action	
Inhibition of prostaglandin biosynthesis via nonselective inhibition of cyclo-oxygenase isozymes	
Dosage and administration (commonly used in trials assessing the treatment of postoperative dental pain)	
Dose	75 mg as a 2 mL solution
Route	Intravenous bolus
Frequency	Single dose
Pharmacokinetic properties (single-dose 75 mg/2 mL intravenous bolus injection in healthy adults)	
Mean area under the plasma concentration-time curve from time zero to infinity	4420 ng • h/mL
Mean maximum plasma concentration (C_{max})	21 524 ng/mL
Median time to C_{max}	≤3 minutes
Mean elimination half-life	1.17 hours
Most frequent treatment-related adverse events (in clinical trials of single-dose treatment of postoperative pain)	
Thrombophlebitis, headache, rash, nausea, dizziness, fatigue, post-procedural haemorrhage, infusion-related reactions	

Acute pain, such as moderate to severe postoperative pain, is normally managed with opioids, local anaesthetics or NSAIDs.[1] Opioid analgesics have long been the primary pharmacotherapy for moderate to severe pain after surgery, but are associated with a number of adverse effects, such as respiratory depression, sedation, nausea and vomiting, pruritus, urinary retention and ileus.[1-3] Nonselective NSAIDs are effective analgesics and have been used instead of opioids, or adjunctively to reduce opioid consumption, with the aim of reducing opioid-related adverse effects. Parenteral formulations are often preferred when patients cannot tolerate or are unable to take oral medications, or require rapid onset of analgesia.[4]

Diclofenac is a highly effective and well tolerated nonselective NSAID recommended for use in the treatment of acute and chronic painful and inflammatory conditions.[5,6] The currently available parenteral formulation of diclofenac sodium (Voltarol® ampoules)[1] contains propylene glycol and benzyl alcohol as solubilizers (hereafter termed PG-BA diclofenac), but is still relatively insoluble. For intravenous use in postoperative pain, PG-BA diclofenac requires reconstitution for each patient, dilution to ≥100 mL, buffering and slow infusion over ≥30 minutes to minimize irritation. Despite these limitations, PG-BA diclofenac is used extensively as a result of its proven efficacy.[7]

A new formulation of diclofenac suitable for intravenous bolus injection (Dyloject®) has been developed by complexing diclofenac sodium with hydroxypropyl β-cyclodextrin as a solubility enhancer (hereafter termed HPβCD diclofenac). Although HPβCD diclofenac is being developed for both intramuscular and intravenous use in various acute forms of pain (see section 7), this review focuses on the intravenous use of HPβCD diclofenac in moderate or severe postoperative pain, an indication for which clinical efficacy data are available.

1. Pharmacodynamic Profile

The pharmacodynamic properties of diclofenac have been well characterized[5,8,9] and are essentially unaffected by the formulation or route of administration. Therefore, only a brief overview of the important, relevant pharmacodynamic properties of diclofenac is included in this section.

- Diclofenac, a phenylacetic acid derivative, is an NSAID with analgesic and antipyretic activity.[5,8,9] It is a potent inhibitor of prostaglandin and thromboxane synthesis via inhibition of the cyclo-oxygenase (COX) enzyme and is nonselective in that it inhibits both COX-1 and COX-2 isozymes.[10]

- Diclofenac is active in a variety of animal models of inflammation, pain and fever, and displays analgesic activity similar to that of indomethacin and piroxicam, and greater than that of aspirin (acetylsalicylic acid) and ibuprofen.[5]

- Animal and *in vitro* studies indicate that diclofenac, like all nonselective NSAIDs, has the potential to cause gastric ulceration by inhibiting prostaglandins involved in protection of the gastrointestinal mucosa.[5,8] Diclofenac may also prolong bleeding by inhibiting platelet thromboxane A_2 synthesis, resulting in inhibition of platelet aggregation.[5,8]

- However, controlled clinical studies in healthy subjects show that therapeutic dosages of diclofenac produce less gastrointestinal damage and bleeding than aspirin, indomethacin or naproxen, and have little effect on platelet aggregation or bleeding time.[5,8]

- Diclofenac may also cause renal impairment by inhibiting renal prostaglandins. Oral diclofenac ≥3 mg/kg in rats inhibited chlorthalidone-induced water and electrolyte excretion in a dose-independent manner,[9] although single-dose oral administration of diclofenac 50 mg in rheumatic patients with normal renal function had no significant effect on uric acid excretion.[5]

1 The use of trade names is for product identification purposes only and does not imply endorsement.

2. Pharmacokinetic Profile

The pharmacokinetic properties of HPβCD diclofenac relative to those of PG-BA diclofenac have been assessed in a phase I, randomized, four-way crossover study in healthy fasted adults (n = 22 analysed).[11] Subjects sequentially received single-dose HPβCD diclofenac 75 mg/2 mL by intravenous bolus injection and intramuscular (deep intragluteal) injection, and single-dose PG-BA diclofenac 75 mg/3 mL by intravenous infusion over 30 minutes and intramuscular injection, with ≥5-day washout periods between treatments. The study is unpublished and available as data on file with the manufacturer.[11]

- HPβCD diclofenac was bioequivalent to PG-BA diclofenac after both intravenous and intramuscular administration, since the 90% confidence intervals for the mean area under the plasma concentration-time curve for the time period from zero to infinity (AUC_∞) and from zero to the last time point with a concentration at or above the limit of quantification (AUC_t) were all within the 80–125% limits.[11]
- The mean AUC_∞ values for HPβCD diclofenac and PG-BA diclofenac were 4420 and 4055 ng • h/mL after intravenous administration, and 4304 and 3932 ng • h/mL after intramuscular administration.[11] The respective mean AUC_t values were 4363 and 3970 ng • h/mL after intravenous administration, and 4237 and 3754 ng • h/mL after intramuscular administration.[11]
- Parenteral administration of diclofenac avoids the first-pass metabolism observed with orally administered diclofenac, whereby only about 60% of the orally administered drug reaches the systemic circulation in unchanged form.[5,8]
- After intramuscular administration, mean maximum plasma concentration (C_{max}) values of 2569 and 1541 ng/mL were attained after median times (t_{max}) of 38.5 and 47.5 minutes for HPβCD diclofenac and PG-BA diclofenac.[11] Following intravenous administration, a C_{max} of 21 524 ng/mL (including one aberrant value, approximately 10-fold higher than expected) for HPβCD diclofenac was attained at a median t_{max} of 3 minutes (first assessment point) and a C_{max} of 5668 ng/mL for PG-BA was attained at a t_{max} of 30 minutes (duration of the infusion).[11]
- Diclofenac is highly bound (99.7%) to serum proteins, mainly albumin, and has a volume of distribution of about 0.12–0.17 L/kg in healthy subjects.[5,8]
- Diclofenac is eliminated principally by metabolism and subsequent urinary and biliary excretion of glucuronide and sulphate conjugates of the metabolites.[8] The mean elimination half-life ($t_{1/2}$) of HPβCD diclofenac was 1.17 hours after both intravenous bolus and intramuscular injection, while that for PG-BA diclofenac was 1.23 hours after intravenous infusion and 1.71 hours after intramuscular injection.[11]

3. Therapeutic Efficacy

The therapeutic efficacy of single-dose HPβCD diclofenac intravenous bolus injection in treating postoperative dental pain has been assessed in three randomized, double-blind, double-dummy, placebo-controlled, parallel-group trials. One of the studies has been published in full;[7] one has been published in abstract form[12] and is supplemented by data on file with the manufacturer;[13] while one is unpublished.[14]

One phase II trial (n = 269) was a comparison of three different doses of HPβCD diclofenac (25, 50 and 75 mg) with placebo; each administered as a single-dose intravenous bolus injection.[14]

Another phase II trial was a dose-ranging study (HPβCD diclofenac 3.75, 9.4, 18.75, 37.5 and 75 mg) [n = 51 per group] and comparison with ketorolac (ketorolac tromethamine) 30 mg (n = 47) and placebo (n = 51) in which all study medications were administered as single-dose intravenous 2 mL bolus injections.[12,13]

The fully published trial was a phase II/III comparison between single-dose HPβCD diclofenac 75 mg/2 mL intravenous bolus injection (n = 53), PG-BA diclofenac 75 mg administered by intravenous infusion over 30 minutes (n = 50) and placebo (n = 52).[7] The primary objectives of the phase II/III study were to assess the superiority of HPβCD

diclofenac over placebo and the noninferiority of HPβCD diclofenac to PG-BA diclofenac.[7]

Patients in all studies were adults, aged ≥18 years, undergoing extraction of one or more fully or partially impacted third molars requiring bone removal who experienced moderate or severe pain (categorical [using a 4-point scale: none, mild, moderate and severe] and ≥50 mm on a 100 mm visual analogue scale [VAS]) within 6 hours of completion of surgery.[7,12,13]

The primary efficacy endpoint in the trial comparing three doses of HPβCD diclofenac with placebo was the mean pain intensity at 4 hours assessed either by 100 mm VAS or 4-point categorical score (0 = none, 1 = mild, 2 = moderate and 3 = severe). Primary endpoints in the other two trials were mean total pain relief (TOTPAR) assessed by 100 mm VAS over the interval 0–6 hours (TOTPAR6) [dose-ranging study][12,13] or 0–4 hours (TOTPAR4) [phase II/III study][7] after study drug administration in the intent-to-treat populations.

Secondary endpoints in the dose-ranging and phase II/III studies included 100 mm VAS and categorical (5-point scale: none, a little, some, a lot and complete) TOTPAR over other time intervals (e.g. 0–2 [TOTPAR2], 0–8 [TOTPAR8] or 0–24 hours [TOTPAR24]), various other measures of pain intensity or pain relief, time to first request for rescue medication and patient global evaluation assessed on a 5-point categorical scale (poor, fair, good, very good and excellent).[7,12,13]

- Mean pain intensity at 4 hours was significantly ($p < 0.05$) less in patients receiving single-dose HPβCD diclofenac 25, 50 and 75 mg than in placebo recipients according to both 100 mm VAS (33.3, 38.1, 28.8 vs 51.6) and categorical measures (1.49, 1.64, 1.33 vs 2.05).[14] There were no significant differences in pain intensity scores between the three doses of HPβCD diclofenac.[14]

- In the dose-ranging study, pain relief with HPβCD diclofenac 3.75, 9.4, 18.75, 37.5 and 75 mg was significantly greater than with placebo according to mean TOTPAR6 (primary endpoint) [figure 1].[13] HPβCD diclofenac 37.5 and 75 mg displayed similar efficacy to intravenous ketorolac 30 mg.[12,13]

- Total pain relief with HPβCD diclofenac 18.75, 37.5 and 75 mg was significantly ($p < 0.001$) greater than with placebo over all time intervals from TOTPAR2 to TOTPAR24.[13] HPβCD diclofenac

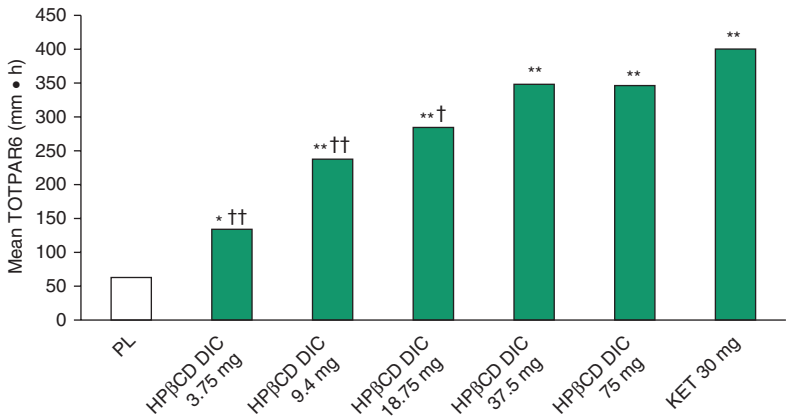

Fig. 1. Comparative efficacy of intravenous bolus hydroxypropyl β-cyclodextrin-complexed diclofenac (HPβCD DIC) in relieving postoperative dental pain. Mean total pain relief scores over the period from 0 to 6 hours after study drug administration (TOTPAR6) [primary endpoint] assessed on a 100 mm visual analogue scale (VAS) in a randomized, double-blind, double-dummy, placebo-controlled, parallel-group study.[12,13] Adult patients, aged 18–43 years, with moderate or severe pain (≥50 mm on a 100 mm VAS) following third molar extraction received single-dose treatment with HPβCD DIC 3.75, 9.4, 18.75, 37.5 or 75 mg (n = 51 per group), ketorolac (KET) 30 mg (n = 47) or placebo (PL) [n = 51], all administered as intravenous 2 mL bolus injections. * $p < 0.05$, ** $p < 0.0001$ vs PL; † $p < 0.01$, †† $p < 0.0001$ vs KET.

3.75 mg was not significantly different from placebo for TOTPAR8, TOTPAR10, TOTPAR12 and TOTPAR24, while HPβCD diclofenac 9.4 mg was not significantly different from placebo for TOTPAR24.[13] Similar response patterns were observed for other secondary measures of pain relief.

- The median times to rescue medication for recipients of HPβCD diclofenac 3.75, 9.4, 18.75, 37.5 and 75 mg were 3.0, 4.0, 4.1, 6.2 and 6.0 hours, respectively, compared with 1.2 hours for placebo and >8 hours for ketorolac.[13]
- The proportions of patients receiving HPβCD diclofenac 3.75, 9.4, 18.75, 37.5 or 75 mg who rated their global evaluation of treatment as 'very good' or 'excellent' were 18%, 39%, 41%, 61% and 57%, respectively, compared with 66% of ketorolac recipients and 4% of placebo recipients.[13]
- In the phase II/III trial, both HPβCD diclofenac and PG-BA diclofenac were superior to placebo ($p < 0.001$) with respect to mean TOTPAR4 (primary endpoint) [figure 2] and all other measures of efficacy.[7] The treatment difference between HPβCD diclofenac and PG-BA diclofenac for TOTPAR4 was 34.4 mm • h (95% CI 1.6, 67.1), indicating not only noninferiority of HPβCD diclofenac relative to PG-BA diclofenac (since the lower limit of the two-sided 95% confidence interval was greater than the predefined noninferiority limit of −60 mm • h), but statistical superiority of HPβCD diclofenac over PG-BA diclofenac (since the two-sided 95% confidence interval did not include the point of no difference [zero]).[7]
- HPβCD diclofenac was superior ($p < 0.01$) to PG-BA diclofenac for TOTPAR2, indicating a faster onset of analgesic effect with HPβCD diclofenac, but there were no statistically significant differences between the formulations for TOTPAR6 and TOTPAR8.[7] With respect to pain intensity difference and pain relief scores, HPβCD diclofenac was also superior to PG-BA diclofenac at 15 (both $p < 0.0001$) and 30 minutes ($p < 0.01$ and $p = 0.0001$) after drug administration, but not at 45 and 60 minutes.[7]
- The proportions of patients reporting a 30% reduction in pain intensity at 15 minutes with HPβCD diclofenac and PG-BA diclofenac were 52% versus 21% ($p < 0.01$), but the proportions at 1 hour were similar (93% vs 92%).[7]
- The median time to rescue medication was similar for both diclofenac formulations at approximately 6.5 hours compared with approximately 1 hour for placebo.[7]
- The proportions of patients rating their global evaluation of treatment as 'good', 'very good' or 'excellent' were 98% and 92% for HPβCD diclofenac and PG-BA diclofenac recipients (both $p < 0.001$ vs placebo) compared with 10% for placebo recipients.[7]

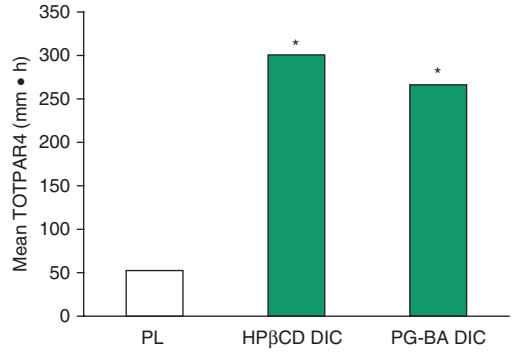

Fig. 2. Comparative efficacy of intravenous bolus hydroxypropyl β-cyclodextrin-complexed diclofenac (HPβCD DIC) and slow intravenous infusion of diclofenac formulated with propylene glycol and benzyl alcohol (PG-BA DIC) in the treatment of postoperative dental pain. Mean total pain relief scores over the period from 0 to 4 hours after study drug administration (TOTPAR4) [primary endpoint] assessed on a 100 mm visual analogue scale (VAS) in a randomized, double-blind, double-dummy, placebo-controlled, parallel-group study.[7] Adult patients, aged 18–44 years, with moderate or severe pain (≥50 mm on a 100 mm VAS) following third molar extraction received single-dose treatment with HPβCD DIC 75 mg (n = 53) by intravenous bolus injection, PG-BA DIC 75 mg by intravenous infusion over 30 minutes (n = 50) or placebo (PL) [n = 52]. * $p < 0.001$ vs PL.

4. Pharmacoeconomic Considerations

- HPβCD diclofenac intravenous bolus injection was projected to be cost-saving relative to PG-BA diclofenac intravenous infusion for the treatment of postoperative pain according to a cost-minimization analysis conducted in the UK (published as an abstract plus poster), with the respective per-patient total mean treatment costs being £28.65 and

£80.08.[15] The decision-analytic model assumed a 50% lower incidence of thrombophlebitis with HPβCD diclofenac compared with PG-BA diclofenac.

- Although the predicted acquisition cost per patient of HPβCD diclofenac was markedly higher than that for PG-BA diclofenac (£12.19 vs £1.69), this was more than offset by lower per-patient costs for drug administration (£10.40 vs £51.19), consumables (£1.40 vs £16.72), rescue medication (£2.48 vs £6.14) and the treatment of adverse events (£2.19 vs £4.35).[15] One-way sensitivity analysis indicated that the results were sensitive to the costs for staff time and consumables.

5. Tolerability

- Worldwide use of various formulations in a number of different indications over several decades has demonstrated that diclofenac is generally well tolerated, with an adverse event profile better than that of aspirin or indomethacin and similar to that of ibuprofen, naproxen or ketoprofen.[5,16]
- The most common adverse events, predominantly assessed during medium- to long-term use of diclofenac in inflammatory rheumatic diseases, are gastrointestinal events (e.g. gastric upset or discomfort), CNS symptoms (e.g. headache or dizziness), and allergic and local, mostly cutaneous, reactions (e.g. rash or pruritis).[5] Although gastrointestinal effects are the most frequent adverse events, peptic ulceration and gastrointestinal bleeding are relatively uncommon events.[5]
- In the two clinical efficacy trials discussed in section 3 that reported tolerability results,[7,13] there were no drug-related serious or significant adverse events and there were no withdrawals as a result of adverse events following single-dose administration of HPβCD diclofenac. There were no unexpected adverse effects and most were of mild or moderate severity.
- The most frequent events in the dose-ranging study that were considered possibly related to HPβCD diclofenac therapy were headache, dizziness, nausea and infusion-site burning.[13]
- The most common treatment-related adverse events with an incidence >1% in HPβCD diclofenac recipients in the phase II/III study were thrombophlebitis, headache, rash, nausea, fatigue, post-procedural haemorrhage and infusion-related reactions (figure 3).[7]
- The nature and pattern of adverse events with HPβCD diclofenac in these two clinical trials were similar to those with ketorolac and PG-BA diclofenac,[7,13] except that the incidence of thrombophlebitis (descriptive analysis only) in PG-BA diclofenac recipients was twice that in HPβCD diclofenac recipients (figure 3).[7]
- Pooled data from this phase II/III study and all previous studies comparing the two formulations show that thrombophlebitis was significantly more frequent with PG-BA diclofenac (n = 108) than with HPβCD diclofenac (n = 322) [6.5% vs 1.6%; $p < 0.01$].[7]

6. Dosage and Administration

HPβCD diclofenac 75 mg is marketed as a solution in a 2 mL vial ready for immediate injection. HPβCD diclofenac 75 mg/2 mL administered by intravenous bolus injection or deep intragluteal injection was the most commonly used standard dose in clinical studies (section 3).[7,11] Moreover, the formulation was shown to be bioequivalent to the currently available PG-BA diclofenac intravenous formulation (Voltarol® ampoules) for which the recommended dose is 75 mg by either the intravenous (infusion) or intramuscular route, with repeat dosing up to a maximum daily dose of 150 mg.[17]

7. Diclofenac Sodium Injection (Dyloject®): Current Status

HPβCD diclofenac was granted marketing authorization from the UK Medicines and Healthcare Products Regulatory Agency in October 2007 and has subsequently been launched in the UK.[18] Additional marketing applications are to be filed through the mutual recognition process in a number of EU countries. An application for marketing approval is to be filed in the US, where phase III clinical trials are ongoing. The primary indication for intravenous

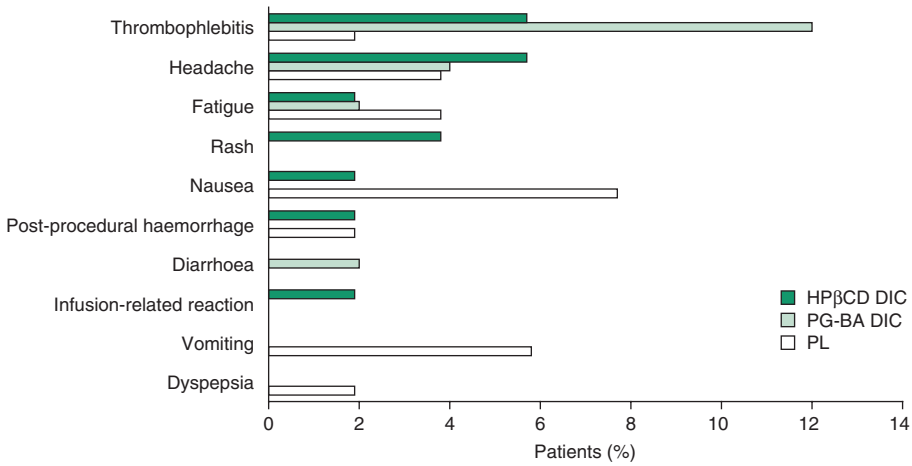

Fig. 3. Comparative tolerability profiles of hydroxypropyl β-cyclodextrin-complexed diclofenac (HPβCD DIC) and diclofenac formulated with propylene glycol and benzyl alcohol (PG-BA DIC). Percentage of patients in each treatment group reporting treatment-related adverse events with an incidence >1% (descriptive analysis only) in a randomized, double-blind, parallel-group trial in which patients experiencing moderate or severe postoperative dental pain received single-dose treatment with HPβCD DIC 75 mg intravenous bolus injection (n = 53), PG-BA DIC 75 mg intravenous infusion over 30 minutes (n = 50) or placebo (PL) [n = 52]. Empty bars indicate an incidence of zero percent.[7]

bolus injection is postoperative pain in supervised healthcare settings, while those for intramuscular administration include renal colic, exacerbations of osteoarthritis and rheumatoid arthritis, acute back pain, acute gout, acute trauma and fractures, and postoperative pain.

HPβCD diclofenac has shown clinical efficacy in the treatment of moderate or severe postoperative dental pain in three randomized, double-blind, placebo-controlled trials. The analgesic efficacy of HPβCD diclofenac was superior to placebo and similar to that of ketorolac and PG-BA diclofenac, but had a faster onset of analgesic effect than PG-BA diclofenac. HPβCD diclofenac was generally well tolerated and had a lower incidence of thrombophlebitis than PG-BA diclofenac.

The convenience associated with bolus injection of a pre-prepared formulation results in time and cost savings with HPβCD diclofenac compared with the conventional formulation. These improvements, combined with the faster onset of analgesia and improved tolerability, confer distinct advantages on this new formulation.

Acknowledgements and Disclosures

The manuscript was reviewed by: **H. Breivik**, Department of Anaesthesiology, Faculty Division Rikshospitalet, University of Oslo, Oslo, Norway; **S. Strassels**, Division of Pharmacy Practice, University of Texas at Austin, Austin, Texas, USA.

The preparation of this review was not supported by any external funding. During the peer review process, the manufacturer of the agent under review was also offered an opportunity to comment on this article. Changes resulting from comments received were made on the basis of scientific and editorial merit.

References

1. White PF. The role of non-opioid analgesic techniques in the management of pain after ambulatory surgery. Anesth Analg 2002; 94: 577-85
2. Filos KS, Lehmann KA. Current concepts and practice in postoperative pain management: need for a change? Eur Surg Res 1999; 31 (2): 97-107
3. Wheeler M, Oderda GM, Ashburn MA, et al. Adverse events associated with postoperative opioid analgesia: a systematic review. J Pain 2002 Jun; 3 (3): 159-80
4. National Pharmaceutical Council. Pain: current understanding of assessment, management, and treatments [online]. Available from URL: http://www.npcnow.org/resources/PDFs/painmonograph.pdf [Accessed 2007 Jun 5]

5. Todd PA, Sorkin EM. Diclofenac sodium: a reappraisal of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy. Drugs 1988 Mar; 35 (3): 244-85
6. Barden J, Edwards J, Moore RA, et al. Single dose oral diclofenac for postoperative pain. Cochrane Database Syst Rev 2004; (2): CD004768
7. Leeson RM, Harrison S, Ernst CC, et al. Dyloject, a novel injectable diclofenac formulation, offers greater safety and efficacy than Voltarol for postoperative dental pain. Reg Anesth Pain Med 2007 Jul-Aug; 32 (4): 303-10
8. Brogden RN, Heel RC, Pakes GE, et al. Diclofenac sodium: a review of its pharmacological properties and therapeutic use in rheumatic diseases and pain of varying origin. Drugs 1980 Jul; 20 (1): 24-48
9. Maier R, Menasse R, Riesterer L, et al. The pharmacology of diclofenac sodium (Voltarol). Rheumatol Rehabil 1979; Suppl. 2: 11-21
10. Chandrasekharan NV, Dai H, Roos KLT, et al. COX-3, a cyclooxygenase-1 variant inhibited by acetaminophen and other analgesic/antipyretic drugs: cloning, structure, and expression. Proc Natl Acad Sci U S A 2002 Oct 15; 99 (21): 13926-31
11. Javelin Pharmaceuticals Inc. A phase 1, randomized, analytically blind, fasted, single-dose, four-way crossover study of the bioavailability of one dose level of parenteral DIC075V (diclofenac sodium 75 mg/2 ml), administered intramuscularly and intravenously, vs. parenteral Voltarol® (diclofenac sodium 75 mg/3 ml) administered intramuscularly and intravenously in healthy adult volunteers. New York: Javelin Pharmaceuticals Inc., 2004. (Data on file)
12. Christensen K, Daniels S, Bandy D, et al. Dyloject™, a novel injectable diclofenac: efficacy of unexpectedly low doses and faster onset than ketorolac [abstract no. 643]. Eur J Pain 2006; 10 Suppl. S1: S168
13. Javelin Pharmaceuticals Inc. A randomized, double-blind, placebo- and comparator-controlled, single-dose, parallel-group comparison of the analgesic efficacy and safety of intravenous DIC075V (diclofenac sodium injection), ketorolac tromethamine and placebo following surgery. New York: Javelin Pharmaceuticals Inc., 2006. (Data on file)
14. Data on file, Javelin Pharmaceuticals Inc., 2007
15. Wallerstein K. A cost minimization analysis of IV bolus versus IV infusion diclofenac in post-operative pain [abstract and poster]. 10th Annual European Congress of the International Society for Pharmacoeconomics and Outcomes Research; 2007 Oct 20-23; Dublin
16. Catalano MA. Worldwide safety experience with diclofenac. Am J Med 1986 Apr 28; 80 (4B): 81-7
17. Novartis Pharmaceuticals UK Ltd. Voltarol ampoules: summary of product characteristics [online]. Available from URL: http://emc.medicines.org.uk [Accessed 2007 May 30]
18. Javelin Pharmaceuticals Inc. Javelin Pharmaceuticals receives marketing authorization approval for Dyloject® in the United Kingdom [media release]. 2007 Oct 31

Correspondence: *Paul L. McCormack*, Wolters Kluwer Health | Adis, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, North Shore 0754, Auckland, New Zealand. E-mail: demail@adis.co.nz