Dyloject®, a novel injectable diclofenac solubilised with cyclodextrin: Reduced incidence of thrombophlebitis compared to injectable diclofenac solubilised with polyethylene glycol and benzyl alcohol

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Summary

Background: Thrombophlebitis is a common complication of a widely used formulation of injectable diclofenac that employs propylene glycol and benzyl alcohol (PG—BA) as solvents. Initial studies of Dyloject®, a novel injectable diclofenac solubilised with hydroxypropyl-β-cyclodextrin (HPβCD), suggested that this complication occurred less frequently and with lower severity with the newer formulation.

Methods: We conducted a safety analysis of seven single-dose clinical trials that enrolled 531 patients receiving either a rapid intravenous (IV) bolus of Dyloject® or a 30 min IV infusion of PG—BA diclofenac.

Results: The incidence of thrombophlebitis observed as an adverse event following Dyloject® treatment was 1.2% (5 of 423) versus 6.5% (7 of 108) following PG—BA diclofenac (p < 0.01). In a subset of clinical studies that included an observer-rated thrombophlebitis assessment, the incidence of mild irritation was similar for both products (5.4% for Dyloject® and 4.9% for PG—BA diclofenac). Differences between the formulations were most evident in the higher incidence of moderate to severe thrombophlebitis after PG—BA diclofenac (2.4% incidence) compared to Dyloject® (0% incidence).

Conclusion: HPβCD, the solubilising agent in Dyloject®, may be less irritating and result in less clinical thrombophlebitis than the cosolvents propylene glycol and benzyl alcohol used in PG—BA diclofenac.
1. Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are routinely used for postoperative pain control and are administered either alone or in combination as part of a multimodal analgesic regimen. Evidence-based clinical practice guidelines for acute pain control have consistently recommended NSAIDs unless specifically contraindicated on medical grounds [1–3]. When used in conjunction with opioids as part of a multimodal analgesia for the management of moderate-to-severe postoperative pain, NSAIDs allow for a reduction in opioid dosage requirements and a corresponding diminution in opioid side effects including nausea and vomiting [4–6].

Diclofenac is one of the most widely used NSAIDs due to its favourable efficacy, safety and tolerability profiles. Diclofenac has significant analgesic and anti-inflammatory properties and in vitro testing has demonstrated equivalent potency for inhibition of COX-1 and COX-2 isoforms [7,8]. Recent reviews conducted by U.S. and European governmental and regulatory agencies have concluded that the benefit-to-risk ratio for this ‘‘nonselective’’ NSAID is favourable during short-term use [9–10].

Diclofenac is an effective and well-tolerated treatment for postoperative pain [11] although its poor solubility characteristics have limited the development of an optimal parenteral formulation. The originally marketed injectable diclofenac (PG—BA diclofenac; marketed as ‘‘Voltarol®’’ in the United Kingdom) requires reconstitution, buffering and dilution prior to each dose, and must be administered as a slow infusion over a minimum of 30 min [12]. An ongoing concern with this dosage form has been the frequent occurrence of thrombophlebitis following intravenous (IV) administration, which has been attributed to the excipients used in the earlier marketed diclofenac product [13].

Dyloject® (75 mg/2 ml) is a novel injectable diclofenac sodium recently approved in the United Kingdom for the treatment or prevention of acute postoperative pain. Dyloject® can be administered as a rapid IV bolus injection that produces peak plasma concentrations within 3 min [14]. In two separate double-blind, placebo-controlled trials in patients undergoing third-molar extraction, IV Dyloject® 75 mg provided more pain relief than either IV PG—BA diclofenac 75 mg [15] or IV ketorolac 30 mg [16].

The novel formulation of Dyloject® was developed to improve the overall solubility characteristics of parenteral diclofenac by employing hydroxypropyl beta-cyclodextrin (HPβCD) as a solubility enhancer. HPβCD is a cyclic carbohydrate derivative that is pharmacologically inert, well tolerated, and used previously to enhance the solubility of otherwise poorly soluble active ingredients in pharmaceutical products [17,18].

In a recently reported controlled trial, Dyloject® was observed to have a lower incidence and severity of thrombophlebitis and minimal vein irritation compared to PG—BA diclofenac [15].

To better estimate and compare the incidence of thrombophlebitis for Dyloject® compared to the previously marketed parenteral diclofenac formulation PG—BA diclofenac, we performed a pooled safety analysis of data from the Dyloject® clinical development program.

2. Materials and methods

All single-dose clinical trials from the Dyloject® clinical development program that were completed as of 1 June 2007 were included in this pooled safety analysis. Study sites for each of the clinical trials received Ethics Committee approval prior to study initiation and all studies were conducted in compliance with the Declaration of Helsinki. Table 1 provides a description of each of the clinical trials. Other IV medications (e.g., antiemetics) were not restricted. The incidence of thrombophlebitis was assessed in patients receiving either Dyloject® as a rapid IV bolus injection or PG—BA diclofenac administered as a slow (≥30 min) IV infusion. The primary analysis examined doses of PG—BA diclofenac within a therapeutic dose range anticipated as being appropriate for most patients: 25, 37.5, 50, and 75 mg. In the secondary analysis all doses of Dyloject® (3.75, 9.4, 18.75 25, 37.5, 50, and 75 mg) were included.

Two separate endpoints were used to assess the overall incidence of thrombophlebitis: (1) spontaneously recorded adverse events and (2) categorically graded ordinal ratings of venous irritation based on a previously described thrombophlebitis assessment scale [19]. The numbers of patients reporting thrombophlebitis for each treatment were obtained from the adverse event reports for each trial. Thrombophlebitis adverse event reports were obtained by searching the adverse events database for the Medical Dictionary for Regulatory Activities (MedDRA) preferred term ‘‘thrombophlebitis.’’ Adverse events from studies using the COSTART dictionary were recoded using MedDRA.

A subset of clinical trials were designed and conducted incorporating a 6-point observer-rated thrombophlebitis assessment (0 = no reaction,
### Table 1: Clinical studies evaluating the incidence of thrombophlebitis with Dyloject® and PG—BA diclofenac.

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Study description</th>
<th>Dyloject® treatment, dose, and number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>FARMOVY19/94</td>
<td>Phase 1, single centre, open label, randomised, 3-way crossover, PK study</td>
<td>Dyloject® 75 mg (6)</td>
</tr>
<tr>
<td>FARMOVY27/97</td>
<td>Phase 1, single centre, open label, randomised, 3-way crossover, PK study</td>
<td>Dyloject® 75 mg (27); PG—BA diclofenac 75 mg (26)</td>
</tr>
<tr>
<td>SAD21085</td>
<td>Phase 2/3, randomised, double-blind, single-dose, parallel group, placebo-controlled, dental pain efficacy study</td>
<td>Dyloject® 25 mg (6); Dyloject® 50 mg (73); PG—BA diclofenac 75 mg (73)</td>
</tr>
<tr>
<td>FARMOVY27/97</td>
<td>Phase 1, single centre, analytically blind, randomised, 4-way crossover, placebo-controlled, PK study</td>
<td>Dyloject® 75 mg (8); PG—BA diclofenac 75 mg (8)</td>
</tr>
<tr>
<td>DFC-003</td>
<td>Phase 1, single centre, analytically blind, randomised, 4-way crossover, placebo-controlled PK study</td>
<td>Dyloject® 37.5 mg (23); PG—BA diclofenac 75 mg (24)</td>
</tr>
<tr>
<td>DFC-001</td>
<td>Phase 2/3, randomised, double-blind, single-dose, parallel group, placebo and comparator controlled, dental pain efficacy study</td>
<td>Dyloject® 75 mg (53); PG—BA diclofenac 75 mg (50)</td>
</tr>
<tr>
<td>DFC-002b</td>
<td>Phase 2/3, randomised, double-blind, single-dose, parallel group, placebo and comparator controlled, dental pain efficacy study</td>
<td>Dyloject® 37.5 mg (53); PG—BA diclofenac 75 mg (51)</td>
</tr>
</tbody>
</table>

### 3. Results

Seven single-dose Dyloject® clinical studies were available in which this drug was administered as an IV bolus injection. In four of these studies, PG—BA diclofenac was administered as a 30-min IV infusion. Of the seven studies, four were pharmacokinetic studies in healthy volunteers and three were efficacy and safety trials in patients undergoing molar extraction. Table 1 presents an overview of the seven clinical studies.

A total of 531 patients from the seven clinical trials were assessed in the primary analysis. This analysis considered only patients who received doses of Dyloject® anticipated to be of therapeutic relevance, i.e., 25 mg and higher. Four hundred and twenty-three patients (80%) received Dyloject® at these doses and 108 patients (20%) received PG—BA diclofenac. The Dyloject® group had 215 males and 208 females. The PG—BA diclofenac group had 67 males and 41 females. The mean (S.D.) age and body weight of persons receiving Dyloject® were 24.7 (5.49) years and 71.8 (14.65) kg, versus 25.2 (7.01) years and 72.6 (11.51) kg for persons receiving PG—BA diclofenac.

Twelve instances of thrombophlebitis were reported as adverse events in patients who received Dyloject® doses of 25 mg or greater, or PG—BA diclofenac. The incidence of thrombophlebitis following Dyloject® treatment was 1.2% (5/423) while the incidence of thrombophlebitis following PG—BA diclofenac treatment was 6.5% (7/108) (p < 0.01). Among the five subjects who developed thrombophlebitis with Dyloject®, four events were mild and one event was moderate in intensity. Among the seven persons reporting thrombophlebitis with
Table 2  Results of thrombophlebitis assessment (0–5 scale) at 8 h following dosing.

<table>
<thead>
<tr>
<th></th>
<th>Dyloject®</th>
<th>PG–BA diclofenac</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>202</td>
<td>82</td>
</tr>
<tr>
<td>Number (%) of persons reporting Grade 1 thrombophlebitis</td>
<td>11 (5.4%)</td>
<td>4 (4.9%)</td>
</tr>
<tr>
<td>95% C.I.</td>
<td>[2.8%, 9.5%]</td>
<td>[1.3%, 12.0%]</td>
</tr>
<tr>
<td>Number (%) of persons reporting Grade 2 thrombophlebitis</td>
<td>0 (0.0%)</td>
<td>2 (2.4%)</td>
</tr>
<tr>
<td>95% C.I.</td>
<td>[0.0%, 1.8%]</td>
<td>[0.3%, 8.5%]</td>
</tr>
</tbody>
</table>

See text for detailed description of thrombophlebitis rating scale. Confidence intervals were calculated using GraphPad software to implement the exact method of Clopper and Pearson [50], which is based on a relationship between the F distribution and the binomial distribution.

PG–BA diclofenac, five events were mild and two events were moderate in intensity.

In four clinical studies (DFC-PL1, DFC-001, DFC-002, and DFC-003) a specific thrombophlebitis assessment was performed 8 h following dosing. In these four studies a total of 202 subjects received Dyloject® at doses of 25 mg or greater and 82 received PG–BA diclofenac. The proportion of these subjects with venous tenderness alone (‘Grade 1’) was similar for both products (5.4% [11/202] for Dyloject® versus 4.9% [4/82] for PG–BA diclofenac), but none of the subjects given Dyloject® had more severe reactions (≥ Grade 2) compared to 2.4% (2/82) of those who received PG–BA diclofenac (Table 2). The confidence intervals for these proportions overlapped, indicating a lack of statistical significance.

A secondary analysis that included all patients (N = 576) and all doses (3.75, 9.4, 18.75, 25, 37.5, 50, and 75 mg) in the Dyloject® clinical development database was performed. The results were consistent with the primary analysis. The number of patients reporting thrombophlebitis as an adverse event was 0.86% (5/576) for patients receiving Dyloject® and 6.5% (7/108) for patients receiving PG–BA diclofenac (p = 0.0007).

An analysis of the four studies that included the specific thrombophlebitis assessment 8 h post-dosing was performed on the 355 patients receiving Dyloject® at any dose and the 82 patients receiving PG–BA diclofenac. Confirming our primary analysis, the incidence of tenderness along the vein (Grade 1) in this secondary analysis was similar for both products (19/355 [5.4%] Dyloject® versus 4/82 [4.9%] PG–BA diclofenac). However, more severe reactions (≥ Grade 2) were absent for Dyloject® compared to 2.4% for PG–BA diclofenac. These differences did not achieve statistical significance.

4. Discussion

Diclofenac is a nonselective NSAID that has been used clinically in various formulations for over 30 years. Currently, diclofenac sodium for injection is available in most countries throughout the world and has established itself as an appropriate therapeutic choice for a variety of acutely painful conditions. Diclofenac sodium for injection has been used preoperatively and perioperatively to pre-empt pain following orthopaedic surgery [21], major abdominal surgery [22,23], gynaecologic surgery [24], dental surgery [25,26], day-case laparoscopy [27], and in children undergoing herniotomy or orchidopexy [28]. In many randomised, controlled trials, diclofenac sodium for injection has been shown to be safe and effective for the treatment of acute pain. Diclofenac sodium injection has been evaluated for the relief of acute pain after orthopaedic surgery [21,29–33], abdominal surgery [34,35], dental surgery [25,36–39], caesarean section [40], laparoscopic tubal ligation [41], laparoscopic cholecystectomy [42,43], as well as in the treatment of renal [44], and ureteric colic [45].

The safety of diclofenac injection has also been well established. However, despite the extensive clinical efficacy and safety profile, its use is often limited in many clinical settings due to the pain associated with intramuscular (IM) injection or the cumbersomeness and preparation time required for reconstitution and administration IV.

Diclofenac is a benzeneacetic acid derivative, designated chemically as 2-[(2,6-dichlorophenyl) amino] benzeneacetic acid, monosodium salt, with a molecular weight of 318.14. Diclofenac is freely soluble in methanol, soluble in ethanol, and practically insoluble in chloroform and in dilute acid. It is minimally soluble in water. To overcome the limited aqueous solubility of diclofenac, the currently marketed diclofenac sodium (PG–BA diclofenac) employs propylene glycol and benzyl alcohol as solvents. Both of these agents are known vascular irritants and cause pain on injection [46,47]. The current PG–BA diclofenac labelling therefore recommends fresh reconstitution and dilution of each dose in a minimum volume of 100 mL, and infusion IV over a period of 30 min to 2 h [12]. The
Diclofenac solubilised with cyclodextrin

importance of correct dilution and buffering prior to IV administration is highlighted by the observation that improper dilution is associated with an increased incidence of venous thrombosis close to the IV injection site [13]. The PG—BA diclofenac formulation also contains sodium metabisulfite.

Dyloject®, a novel diclofenac sodium formulation, utilises HPβCD to solubilise diclofenac in a small volume (2 ml), and is stable at room temperature for at least 2 years. No reconstitution is required prior to use. Dyloject® recently received marketing authorization in the United Kingdom, is currently under review in several other European countries, and is in Phase 3 clinical development in the United States. This formulation of soluble diclofenac is administered directly as either an IV bolus or by IM injection. Dyloject® contains neither the organic cosolvents nor sodium metabisulfite used in PG—BA diclofenac that may lead to local irritation or allergic reactions. Dyloject® can be administered IV in less than 60 s as a rapid bolus, resulting in rapid pain relief [15,16].

HPβCD is a well recognised excipient, which is nontoxic and minimally irritating to veins. HPβCD has been employed to enhance the solubility of the marketed antifungal product itraconazole [17], and a novel formulation of the anaesthetic propofol now under development [18].

During early formulation development it was hypothesised that the use of HPβCD in Dyloject® would permit bolus IV injection, eliminate the necessity for the slow IV infusion necessary for PG—BA diclofenac, consequent earlier and greater peak diclofenac plasma concentrations and a more rapid onset of analgesia. Additionally, it was thought that the avoidance of irritating solvents such as propylene glycol and benzyl alcohol might decrease the incidence and/or severity of thrombophlebitis associated with IV diclofenac administration. Subsequent clinical studies have confirmed these hypotheses. Dyloject®’s rapid onset of analgesia has been reported in two separate double-blind, randomised controlled trials in postoperative pain [15,16]. The present results of an aggregate analysis of seven clinical trials strengthen previous isolated observations of a lower incidence of thrombophlebitis with Dyloject® compared to PG—BA diclofenac.

The results of this analysis may have significant pharmacoeconomic and safety implications. A recent analysis reported cost savings for Dyloject® relative to PG—BA diclofenac from both the reduced need for treatment of thrombophlebitis and the time saved by avoiding need for reconstitution prior to each dose [48]. Moreover, an ongoing NHS patient safety initiative discourages the use of products that require mixing and reconstitution when ready-to-use alternatives are available [49]. In addition to the benefits of Dyloject® with respect to thrombophlebitis, its potential cost and safety advantages require additional investigation.

Conflict of interest

Funding for four of the studies included in this review was exclusively provided by Javelin Pharmaceuticals, Inc. (Javelin). All authors were employed by Javelin at the time this manuscript was created. As Javelin employees, the authors had financial interest in the subject matter, materials, equipment, or devices discussed in this manuscript. However, the investigators who conducted the studies had no financial interests in Javelin beyond reimbursement of the costs of the investigation.

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References


