

Dyloject (diclofenac sodium) for post-operative pain

Dyloject (Therabel Pharma) is the first ready-to-use intravenous solution of diclofenac sodium to be licensed in the UK. In this article, the North Central London Formulary and Medicines Management Group looks at the evidence for its efficacy in post-operative pain.

Dyloject (Therabel Pharma) is a relatively new, ready diluted, intravenous solution of diclofenac. The presence of a solubility enhancer, hydroxypropyl β -cyclodextrin, enables Dyloject to be administered as a bolus injection (over 60 seconds).⁴

By contrast, the solubility of diclofenac within the only previously licensed parenteral formulation, Voltarol (Novartis), which contains the solubilisers propylene glycol and benzyl alcohol, is relatively poor, requiring dilution and buffering with sodium bicarbonate prior to intravenous administration. Voltarol is thus given by slow intravenous infusion, over 30 to 120 minutes, to minimise the incidence of thrombophlebitis.⁵

It is thought that timely pre-operative administration of intravenous diclofenac can help achieve a peak plasma concentration to coincide with time of incision, which may improve the quality of recovery after surgery.⁶

Efficacy

The efficacy of Dyloject for post-operative (dental) pain has been assessed in a phase II/III randomised, double-blind, double-dummy, placebo-controlled, parallel-group



An IV bolus can provide faster onset of pain relief than an IV infusion

trial.⁷ The trial included adult patients (n=155) who, following the extraction of one or more impacted third molars, experienced moderate to severe pain (defined using a four-point categorical scale [no pain, mild, moderate, severe] and a score of ≥ 50 mm on a 100mm visual analogue scale [VAS]) within six hours of completion of surgery. Pain was assessed by each patient at: baseline; 15, 30, and 45

minutes after administration of study drug; and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10 and 12 hours after administration of study drug.

The primary objective of this three-arm (1:1:1) study was to assess the superiority of single-dose Dyloject (75mg; bolus) over placebo, and the non-inferiority of Dyloject over Voltarol (75mg; 30-minute infusion). Mean total pain relief (TOTPAR) was assessed by a 100mm VAS over 0–4 hours after drug administration in the intention-to-treat population. Fifty evaluable patients per arm were required to provide 90% power. A non-inferiority margin of 15mm per hour (i.e. 60mm over 4 hours; based on a 30% decline in pain intensity from baseline representing a clinically meaningful reduction) was specified *a priori*.

Secondary efficacy endpoints included: assessment of mean TOTPAR over the 0–4 hour period assessed against the categorical scale; mean TOTPAR over the 0–8 hour period assessed against the VAS and categorical scale; pain intensity; and time to first rescue medication. All patients received an intravenous infusion and bolus of active drug/placebo to maintain blinding.

The mean TOTPAR (in mm hours, \pm standard deviation) after 4 hours for Dyloject, Voltarol and placebo were 300.6 ± 73.6 , 266.2 ± 91.6 and 52.5 ± 88.8 , respectively, providing a (non-inferior) inter-group difference of 34.4 ± 16.7 between Dyloject and Voltarol. With reference to the proportion of patients experiencing a 30% reduction in pain intensity, 52% of Dyloject patients versus 21% Voltarol patients met this endpoint 15 minutes after dosing. There was no difference in this endpoint at 60 minutes after dosing (92.5% versus 92.0%, respectively).

Background

Acute pain associated with surgery is traditionally managed with local anaesthetics, opioids, and non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs are given for moderate to severe pain and can be used instead of opioids or to help reduce the dose of adjunct opioids, thus potentially reducing opioid-related adverse effects.^{1,2}

A recent health technology assessment programme funded by the National

Institute of Health Research investigated the significance of adjunctive selective or non-selective NSAIDs and/or paracetamol therapy with an opioid in the peri-operative period. Preliminary conclusions are that although adjunctive therapy decreased the 24-hour morphine consumption post-surgery, there was no strong evidence that this amounts to a clinically relevant reduction in morphine-related adverse effects.³

Safety

The majority of reported adverse events associated with Dyloject exposure were mild to moderate in severity and were typical of those generally observed following administration of diclofenac. No deaths or serious drug-related adverse effects were reported. No patients discontinued treatment as a result of a treatment-emergent adverse event. Of the adverse events reported, thrombophlebitis was the most common, occurring in 5.7% of patients in the Dyloject group (3/53), 12% in the Voltarol group (6/50), and 1.9% in the placebo group (1/52). This translates into a number needed to harm (NNH) of 26 for Dyloject compared with 10 for Voltarol.

Risk assessment and convenience

The National Patient Safety Agency has reported that of the 24% of medication errors associated with injectable medicines, 73% are a result of administration errors, including preparation.⁸ The availability of a ready-to-use infusion has the potential to reduce workload (preparation and administration) for nursing staff and could assist in reducing the incidence of medication-related errors. Additionally, since Dyloject is administered as a bolus, it can provide a faster onset of pain relief than is possible with Voltarol.

It is important to note that the availability of two very different formulations of intravenous diclofenac on a trust's formulary poses risk management issues, since their administration methods are not interchangeable.

Cost-effectiveness

There is very limited health economic evidence for Dyloject. The relative drug acquisition cost for Dyloject is £4.80 per 75mg vial, versus £1.69 for a Voltarol 75mg vial. One cost minimisation analysis from a UK perspective was identified from a pharmaceutical industry-sponsored

conference abstract.⁹ The authors concluded that, while Dyloject is more expensive, Voltarol results in a greater per-patient mean post-operative treatment cost (£80.08) than Dyloject (£28.65), taking into account factors such as drug administration, consumables, rescue medication and management of adverse events. Equal efficacy was assumed. The Scottish Medicines Consortium accepted Dyloject within NHS Scotland based on these data.¹⁰

Summary

Dyloject has demonstrated non-inferiority in terms of efficacy (pain reduction) when compared with Voltarol in patients undergoing dental extractions. Therapeutic indications within its product licence have been extrapolated from these data.

Since Dyloject does not require buffering, dilution or administration as a slow infusion, as is the case with Voltarol, it has the advantage of convenience as well as meeting the NPSA recommendations to use ready-diluted injectable drugs to help minimise potential administration errors.

However, Dyloject is almost three times more expensive than Voltarol (although such costs will likely be offset by convenience advantages) and a recent review failed to provide evidence of sparing opioid-induced adverse effects.³

In summary, Dyloject represents a therapeutic advance in the delivery of intravenous diclofenac although the exact place in therapy for parenteral NSAIDs remains a matter of conjecture.

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Conflicts of interest: none declared.



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Drug appraisal articles

University College London Hospitals NHS Foundation Trust, Royal Free Hampstead NHS Trust and The Whittington Hospital NHS Trust operate a centralised medication review scheme for assessing formulary applications to their Use of Medicine and Drugs and Therapeutics Committees. A review of selected formulary applications are published regularly in *The British Journal of Clinical Pharmacy*. These reviews are intended to inform readers about the individual merits and limitations of the drugs in question, and to provide examples of in-depth, critical reviewing which can be adapted and used in all areas of evidence-based medicine.