A review of ketorolac as a prehospital analgesic

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Abstract

Non-steroidal anti-inflammatory drugs (NSAIDs) can be used as part of a multimodal approach to managing acute pain. Administering NSAIDs by intramuscular (IM) or intravenous (IV) injection allows them to be used in patients who are nil-by-mouth, who cannot swallow, and to allow a more rapid onset compared to the oral route. Current paramedic practice in the UK does not generally allow for the use of an NSAID given by IM or IV injection for acute pain. While paramedics may administer paracetamol and morphine intravenously, the only option for an NSAID is oral ibuprofen, or rarely oral naproxen or rectal diclofenac. Ketorolac is an NSAID, which can be administered by IV or IM injection. It is an effective analgesic agent when used alone, or in conjunction with other agents as part of a multimodal approach to analgesia. This article reviews the evidence from peer-reviewed papers and current clinical guidelines surrounding the safety and efficacy of ketorolac as an analgesic agent for acute pain, and discusses its potential use in UK paramedic practice.

Key words

● Ketorolac ● NSAID ● Non-steroidal ● Analgesia ● Pain

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Ketorolac was developed by the company Syntex, which gained Food and Drug Administration (FDA) approval for the drug, under the trade name Toradol, in November 1989 (Gupta and Devaraj, 2013; Stolberg, 2016). Ketorolac was the first injectable non-steroidal anti-inflammatory drug (NSAID) to gain FDA approval, with oral, ophthalmic and nasal preparations being approved in 1991, 1992 and 2010 respectively (Gupta and Devaraj, 2013).

In the UK, ketorolac is licensed for the short-term management of moderate-to-severe acute postoperative pain and, as such, its use for other causes of pain would be off-label. However, this is not a barrier to its use, as many of the drugs used routinely in prehospital care are also being used for off-label indications. The Medicine and Healthcare products Regulatory Agency (MHRA) (2007) has advised that treatment with ketorolac should only be initiated in hospitals. However, this advice was not meant to specifically exclude its use in the prehospital setting for a patient en route to hospital. It was concluded by MHRA Pharmacovigilance Service that owing to the relatively slow onset of action, ketorolac was less suitable for general prehospital use (Penny [MHRA Pharmacovigilance Service Team Manager], personal communication). In relation to current prehospital practice, the addition of ketorolac to prehospital care guidelines would provide paramedics with an intravenous (IV) or intramuscular (IM) NSAID. This would provide various prehospital analgesic options acting at various points of the pain pathway, facilitating the provision of effective multimodal analgesia.

Pharmacology

Ketorolac is an NSAID, which has its action through the inhibition of prostaglandin synthesis. As an NSAID, ketorolac inhibits the action of the cyclooxygenase enzymes (COX-1 and COX-2), which metabolise arachidonic acid to prostaglandins and thromboxane A2. NSAIDs are therefore considered to be highly effective for prostaglandin-mediated pathologies causing pain and inflammation including trauma (Curtis and Morrell, 2006; Bartkus, 2011; Gadsden, 2012). Ketorolac has also been shown both clinically and in vitro to inhibit stretch-induced ureteral contractility associated with renal colic when passing kidney stones, making it particularly useful for colicky pain (Wood et al, 2000; Wen et al, 2008). Ketorolac can be administered by various routes, but the IM and IV routes are most common. These routes would produce a more rapid rise in serum concentration and bioavailability compared to the oral route. This would be beneficial in the acute pain setting, and would also be useful for patients destined for emergency surgery who need to be kept nil by mouth.

Speed of onset

Published guidance states that the onset of action for ketorolac can be slower than other IV analgesics, such as morphine. It is likely that the time to onset is around 30 minutes with the peak effect occurring between 45 and 60 minutes (Wood et al, 2000; Bledsoe and Myers, 2003). This is one reason ketorolac may be considered less suitable for use in the prehospital setting.

However, in regions where transport times to hospital are prolonged, or where there is an element of prolonged field care such as during mountain rescue operations, this is unlikely to be a valid reason to deny patients an IV or IM NSAID. Furthermore, IM morphine is currently used in mountain rescue operations in the UK, and this has demonstrated a comparable onset time to IM ketorolac (Rice et al, 1991). This suggests that ketorolac may also be useful in this area of practice. It may however make ketorolac a less valuable intervention in more urban ambulance services where transport times are less than 30 minutes.

Contraindications and side-effects

Ketorolac has been favourably reviewed as having a better side-effect profile when compared with opiates used in severe pain (Rainer et al, 2000). In fact, it was suggested that it may become the analgesia of choice for many emergencies (Jelinek, 2000). A comparison of the common side-effects seen with paracetamol, NSAIDs and opiates is presented in *Table 1*.

There are a number of contraindications to the use of ketorolac (*Table 2*)—many of these being common to all NSAIDs. Contraindications such as active bleeding, increased anticoagulant and asthma are caused by the inhibition of COX, the subsequent antiplatelet effects, and increased leukotriene levels; as such, this would be similar with the use of any other NSAID. It is important to note however that ketorolac does have an increased risk of causing gastrointestinal bleeding with prolonged use in comparison with other NSAIDs. In a prehospital setting, this is unlikely to be a significant issue in relation to a single dose. It is also important to remember that by using ketorolac, the expectation would be a decreased opiate requirement and, therefore, a reduced opiate side-effect burden.

Ketorolac in clinical practice

Ketorolac has been demonstrated to be an effective analgesic in various circumstances. Some examples include the following:

- Renal colic (Wood et al, 2000)
- Spinal surgery (Munro et al, 2002)
- Migraine (Taggart et al, 2013)
- Musculoskeletal pain (Turturro et al, 1995).

Ketorolac is widely considered one of the most effective analgesic agents for renal and biliary colic (Wood et al, 2000; Alonso-Serra and Wesley, 2003; Bledsoe and Myers, 2003). Furthermore, it has been specifically advocated for use in traumatic injuries—both in the prehospital (Butler et al, 2000) and in-hospital setting (Gadsden, 2012). In cases of colicky or traumatic pain, ketorolac can be used as a sole agent, or preferably as an adjunct to other analgesia such as opiates (Bledsoe and Myers, 2003; Bartkus, 2011).

In UK prehospital care, ketorolac could be used as the preferred first-line analgesic for patients with renal, ureteric and biliary colic. It could also be a first-line treatment alongside paracetamol and morphine for traumatic limb injuries.

Internationally, ketorolac is commonly used during the prehospital phase to provide analgesia for adult patients and, in America, is considered a common part of paramedics' scope of practice (Vincent and Williams, 2010; Beck, 2015; Phrampus and Paris, 2016). Ketorolac is also used as a battlefield analgesic by American and UK armed forces (Butler et al, 2000; Shackelford et al, 2015; Buckenmaier and Mahoney, 2016), and its use has been advocated in the mountain rescue and wilderness setting (Ellerton et al, 2014; Russell et al, 2014). However, it is not currently widely used in UK prehospital care. *Table 2* provides a summary of ketorolac in the prehospital setting, and could provide the basis for a patient group directive.

Benefits in UK prehospital care

Ketorolac is currently unavailable to the majority of UK paramedics. However, by some, it is viewed as a useful analgesia adjunct when provided by doctors working in prehospital care (Salkin, 2002). Ketorolac is simple to administer, and the same preparation can be given intravenously or via the IM route. It is most commonly supplied as 1 ml of colourless (or slightly yellow) liquid of 30 mg ketorolac trometamol, in an amber glass ampoule. These ampoules do not need special

Table 1. Comparison of uses and side-effect profiles

	Utility	Common side effects
Opiates	Analgesic, antidiarrhoeal and antitussive activity	Cardiovascular, respiratory and central nervous system depression
Paracetamol	Analgesic and anti-pyretic activity	Hepatotoxicity and renal impairment in overdose
NSAIDs	Analgesic, anti-inflammatory and anti-pyretic activity	Dose dependent hepatic and renal impairment Bronchospasm in ~20% of asthmatics Platelet inhibition

Table 2. Drug monograph for ketorolac

KETOROLAC		
Formulation Most commonly; a glass ampoule containing 30 mg of ketorolac in 1 ml	**Actions** Ketorolac is a non-steroidal anti-inflammatory drug (NSAID) Its analgesic and antipyretic action is through its action blocking the COX enzyme, and inhibition of prostaglandin synthesis	
Indications Adult patients experiencing moderate to severe pain Especially suitable for colic (renal colic, biliary colic, etc)	**Side-effects** Prolonged use can cause gastric irritation Bronchospasm in sensitive individuals Nausea Dyspepsia	
Contraindications Age <18 years. Concurrent use of NSAIDs or Lithium Ischaemic cardiac pain Active gastric ulcer Allergy to ketorolac or its ingredients Third trimester pregnancy or active labour Breastfeeding Active major haemorrhage	**Cautions** Previous gastric ulcer Asthma (especially in the presence of nasal polyps) Renal impairment (see dosing below) Weight <50 kg (see dosing below)	
Additional Information Ketorolac is particularly useful for pain caused by smooth muscle spasm, and therefore works well for colicky pains Ketorolac is also suitable for use in traumatic musculoskeletal injuries		
Dose and administration		
Single dose only		
The dose for ≥65 years old is also suitable for patients with; renal impairment or weight <50 kg		
Age (in years)	**Slow IV**	**IM**
≥65	15 mg	15 mg
18–<65	30 mg	30 mg

precautions for storage, but should not be stored above 30°C or in direct sunlight. It can be given alongside paracetamol and morphine, which are the mainstay of current paramedic pharmacological pain management. While there appears to be no significant pain relief benefit in using ketorolac over oral ibuprofen (Curtis and Morrell, 2006), ketorolac does allow an NSAID to be given parenterally, which may be a significant advantage, such as in patients who are immobilised, vomiting or nil by mouth.

The use of ketorolac can also decrease the amount of opiates required when used as a co-agent. This could potentially lead to fewer patients experiencing the unpleasant side-effects of high-dose opiates. It has also been suggested that ketorolac, when used to treat pain from traumatic injuries may be more cost-effective than opiates while achieving the same level of analgesia (Rainer et al, 2000).

Limitations in UK prehospital care

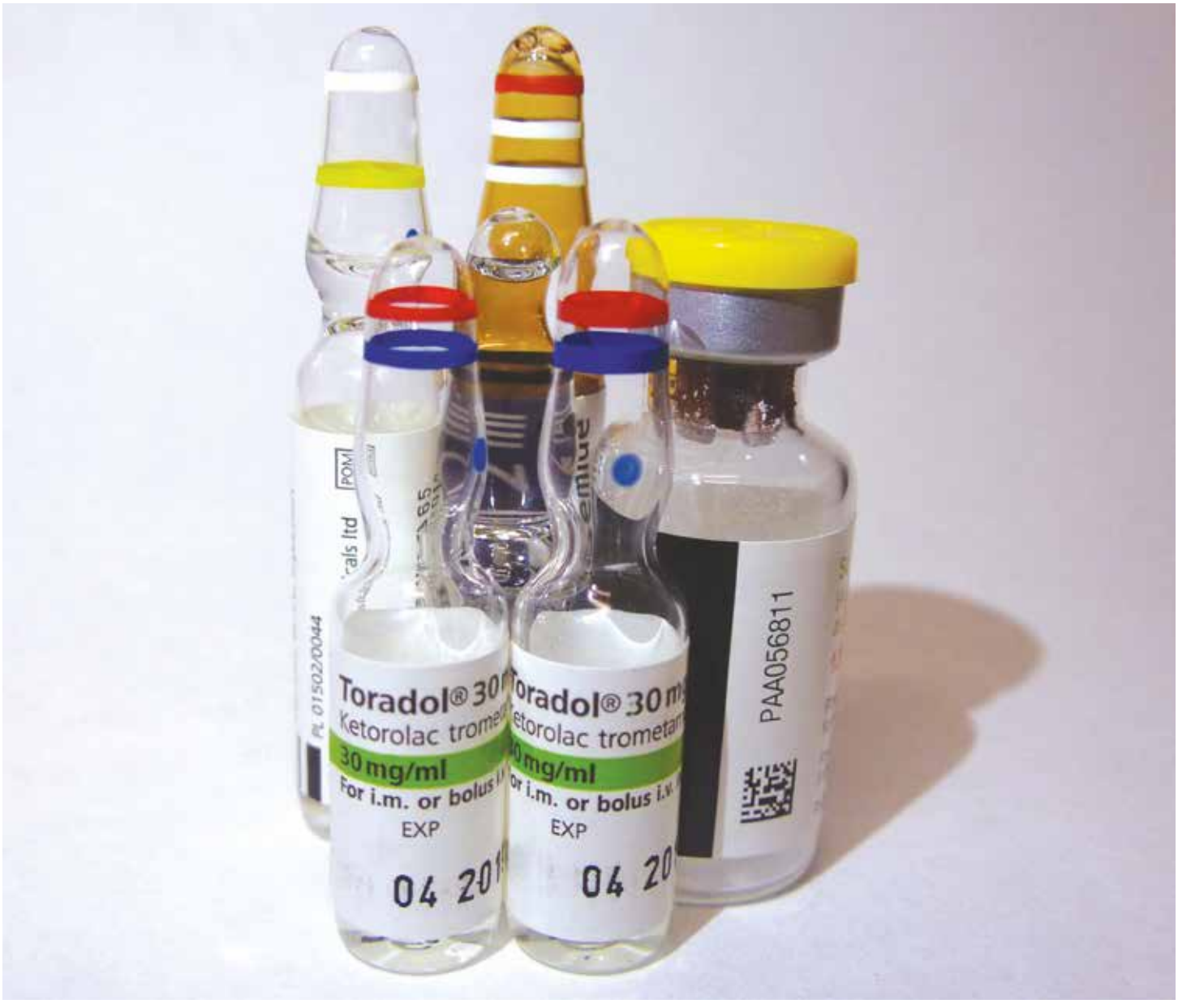
One limitation of NSAIDs is their effect of impairing platelet aggregation. This occurs owing to inhibition of thromboxane A2 synthesis, as a result of COX inhibition by ketorolac. While this antiplatelet action has been highlighted as a reason to avoid ketorolac in trauma, it is likely that the anticoagulant effect is minimal and not clinically significant (Butler et al, 2000). This view is supported by the meta-analysis of 27 studies undertaken by Gobble et al (2014), which concluded that ketorolac provided beneficial analgesia, and did not significantly increase postoperative bleeding. This antiplatelet effect is likely to make ketorolac less suitable in cases of significant polytrauma—although this is not a rigid contraindication.

There have been deaths linked to the use of ketorolac, related to the risk of significant gastrointestinal bleeding with long-term use, and also with cases of anaphylaxis. However, the numbers are not such that they indicate ketorolac is significantly more dangerous than other commonly used analgesics. As with all NSAIDs, ketorolac carries a small risk of anaphylaxis (Sánchez-Borges, et al, 2010), which can prove fatal (Oliva et al, 2007; Campobasso et al, 2008). However, ketorolac is not believed to be more allergenic than other related NSAIDs. It is safe to use within the limits of the cautions and contraindications highlighted in *Table 2*.

Ketorolac is not currently one of the medications authorised specifically for paramedic use in the UK, and it is currently a prescription-only medication (POM)—unlike some other NSAIDs. Therefore, for a paramedic to use ketorolac in the UK, they would need to be administering it under a Patient Group Directive on the authorisation of a doctor (England, 2016). One of the benefits of its status as a POM, however, is that it is not a controlled drug (CD) and, as such, is free from the restrictions surrounding carriage and storage of CDs.

Conclusion

Ketorolac is an effective analgesic option for IV or IM administration. It is used in prehospital care internationally in both civilian and military practice.



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Ketorolac is usually administered via intramuscular and intravenous routes, which can be useful in prehospital care

While there are concerns regarding its long-term use and increased risk of gastrointestinal bleeding, these are unlikely to be an issue as a result of a one-off prehospital dose. Equally, many of the other cautions and contraindications for ketorolac are shared by all NSAIDs and UK paramedics are already able to administer ibuprofen.

Concerns related to its variable and sometimes slow onset of action are valid and may make ketorolac a less suitable option for use in prehospital care systems where transport times are less than an hour. Despite this, many UK paramedics work in a system where it takes over an hour from patient assessment to subsequent assessment and management in hospital. This is especially true of those paramedics working where extrication and transport times may be extended; for example, owing to technical rescue or remote locations.

Ketorolac is a useful adjunct to the provision of multimodal analgesia, and it should be considered for inclusion in the armamentarium of paramedics in the UK. **JPP**

Conflict of Interest: None.

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Key Points

- Ketorolac is an injectable NSAID analgesic
- Ketorolac is an effective analgesic when used as a sole agent, or concurrently with paracetamol and morphine
- Ketorolac is used worldwide in prehospital, military and wilderness settings
- The side-effect profile of ketorolac is comparable to that of other NSAIDs

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CPD Reflection Questions

- If ketorolac was introduced into UK practice, what clinical grade of practitioner do you think could safely administer it?
- What are the qualities of an ideal (and imaginary) analgesic agent for the prehospital care of acute pain?
- What other analgesic drugs do you feel would be valuable additions to paramedic practice in the UK?