KETOROLAC TROMETHAMINE IN CLINICAL POST OPERATIVE PAIN MANAGEMENT IN DENTISTRY

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INTRODUCTION

A number of dental procedures cause acute post procedural pain, making effective pain management for all patients an essential component of dental practice. Achieving adequate and safe pain relief may be more challenging in some patient populations, such as those with substance abuse or chronic pain disorders. However, pain following certain dental procedures can be anticipated, which provides dentists an opportunity to thoughtfully plan and optimize the management of acute pain.[1]

Factors contributing to the occurrence of postoperative dental pain are complex, but many are related to the inflammatory process that is initiated by surgical trauma.[2] Injury to the tissues during surgical procedure results in the release of chemical mediators of inflammation.[2] Some of these mediators (histamine, prostaglandins, acetylcholine and bradykinin) evoke pain and cause hyperalgesia, which is characterized by decreased pain threshold and increased sensitivity to suprathreshold stimuli. The prostaglandins have been demonstrated to act, at least in part, by the latter mechanism.[2]

Since the introduction of acetylsalicylic acid in the nineteenth century, Non Steroidal Anti-Inflammatory Drugs (NSAIDs) have become widely used in the treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis for their pain-relieving and anti-inflammatory properties. Given the large and growing numbers of patients affected by the above diseases, NSAID use by both prescription and over-the-counter, is now very common. Although the efficacy of newer NSAIDs is well-established, their widespread use has prompted concerns over safety, particularly gastrointestinal (GI). The mechanism of action of NSAIDs involves the inhibition of cyclooxygenase (COX), a key enzyme in the inflammation cascade.[3]

CYCLOOXYGENASE EXISTS AS TWO ISOENZYMES[3]

- **COX-1:** a constitutive enzyme responsible for the formation of prostacyclin and protective and repair functions in the gastric mucosa.[3]
- **COX-2:** an inducible enzyme responsible for the generation of inflammatory mediators in response to inflammatory stimuli.[3]

The two isoforms of the enzyme have quite different biological properties and functions. Inhibition of COX-1 is responsible for the potentially serious adverse effects of the NSAIDs. NSAIDs have varying degrees of specificity for the two isoforms of cyclooxygenase but in recent years there has been a concerted effort to develop COX-2 specific agents in an attempt to avoid the GI tolerability problems that can be manifest during long-term use of NSAIDs.[3]

With a large number of drugs available commercially for pain management, this review article is aimed at highlighting the potential analgesic and anti-inflammatory properties of Ketorolac Tromethamine over the other drugs, in short term management of moderate to severe pain.

A search of the literature was conducted by using the Pubmed search engine and Google Scholar. Articles were selected for inclusion on the basis of relevance and significance to the topic. This article provides the current status about the newer forms of this drug and their clinical efficacy in detail.

HISTORICAL BACKGROUND

Ketorolac Tromethamine was discovered in 1989 by Syntex Corp. It was approved by FDA on 30th November, 1989 as the first injectable NSAID. The tablet form of ketorolac was approved by FDA in 1991. The ophthalmic (i.e., eye-drop) form was approved by FDA on 9 November 1992 and was introduced by Allergan under license from Syntex. An intranasal formulation of ketorolac tromethamine was approved by FDA on 14 May 2010 and introduced as a Nasal Spray by Daiichi Sankyo for short-term management of moderate to moderately severe pain requiring analgesia at the opioid level.

CLINICAL PHARMACOLOGY

Ketorolac is a Non Steroidal Anti-Inflammatory Drug and is a non selective COX inhibitor. It is a pyrrolo pyrrole derivative (Fig 1). Ketorolac is a potent

analgesic and has moderate anti-inflammatory and antipyretic activity.[4] The chemical structure of ketorolac is related to indomethacin, rather than the ibuprofen class of anti-inflammatory agents.[4] In post operative pain it has equalled the efficacy of morphine, but does not interact with opioid receptors and is free of opioid side effects.[5] This is the first NSAID for which the sole indication is for the treatment of pain, and not for treatment of rheumatoid arthritis and osteoarthritis.[4]

Ketorolac blocks the pathway for prostaglandin synthesis by inhibiting the cyclooxygenase enzyme that metabolizes arachadonic acid and blocks pain by a peripheral mechanism.[5]

After oral administration ketorolac tromethamine dissociates to pure ketorolac molecule in the bloodstream. Ketorolac is absorbed completely after oral and intramuscular administration. Onset of analgesia after administration of 10 mg of oral dosage occurs in 20 – 30 minutes. Peak absorption into the bloodstream occurs in 1 hour and peak analgesia occurs in 3 hours.[4]

It highly binds to plasma protein and 60% is excreted unchanged in urine. Major metabolic pathway is glucuronidation i.e.. liver enzymes metabolize the drug by conjugation with glucuronic acid, to produce inactive products, which are excreted in urine by renal mechanisms.[5] It is lipophilic, hence

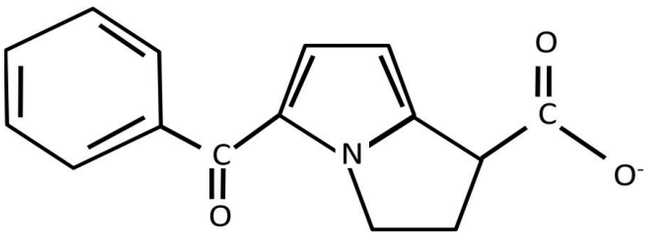

Fig 1: Chemical structure of Ketorolac tromethamine

[(+/-)-5(benzoyl)-2,3-dihydro-1N-pyrrolizine-1-carboxylic acid tris hydroxymethylaminomethane salt]

it crosses the lipid bilayer cell membrane. The plasma T1/2 is 4-5 hours. Those patients who are 70 years of age or older eliminate the drug at a slower rate (half life: 6-7 hours) and may require dose reductions.[4]

USES OF KETOROLAC TROMETHAMINE

It provides symptomatic relief from moderate to severe postoperative pain associated with dental procedures like gingival soft tissue grafting, flap surgery, extractions, biopsy. It is also used for relief from pain of abdominal, gynaecologic, orthopaedic, urologic, ophthalmic origin and cancer pain. It is to be used for short duration of 3-5 days, due to it COX-1 mediated side effects.[2]

ADVERSE EFFECTS

The risk of serious gastrointestinal (GI) toxicity and inhibition of platelet function has limited its use.[10] The major adverse reactions of Ketorolac tromethamine are the damaging effects on gastric mucosa resulting in erosions, ulcers and gastrointestinal bleeding. Ketorolac tromethamine induces gastric damage by a dual insult mechanism. Ketorolac tromethamine is an acidic substance that can damage the GIT even in the absence of hydrochloric acid by changing the permeability of cell membranes allowing a back diffusion of hydrogen ions. This weak acid remains unionized in the stomach, but the resulting lipophilic nature of Ketorolac tromethamine

Table 1: Routes of drug administration and dosage

S. no.	Route of administration	Dosage	Characteristics
1	Oral [6]	10-20 mg 6 hourly	Most common route of Ketorolac administration. Available in Dispersible and delayed release tablet form.
2	Intramuscular (IM) & Intravenous (IV) [6]	15-30 mg every 4-6 hours (max 90mg/day)	Used as an alternative to opioids, ketorolac has proven to provide effective analgesia without the side effects associated with opioids
3	Intranasal route [7]	15.75 mg per spray (2 sprays 8 hourly). (1spray 8 hourly for adults >65 years)	Lack of sedation secondary to lack of CNS activity. Clearance from the nasal cavity without deposition in the lungs. Avoids the oral route, benefiting patients who are nauseated or are unable to take oral medications. Avoids the need for IM injections or intravenous access.
4	Opthalmic solution [6]	0.4 % and 0.5 %	Adjunct to steroids for ocular pain and burning after cataract and refractive surgeries
5	Oral rinse [6]	0.01 %, 0.05 %, 0.1%	Used in patients with progressive alveolar bone loss.
6	Transdermal patches [6]	30 mg	To avoid invasive drug therapy such as injections and to eliminate frequent dosing regimen with oral administration.
7	Bucco adhesive films [6,8]	30 mg	Film delivers drug to the site of application, has acceptable pH and 85-90% drug release.
8	Dentifrice [9]	0.15% and 1.0%	1% dentifrice provides equivalent levels of ketorolac to the gingival tissue as the 0.1% oral rinse. Less systemic exposure Preferred vehicle for administration of Ketorolac in treatment of periodontitis.

allows an accumulation in gastric mucosal cells. Once inside these cells, the higher pH of the intracellular environment causes Ketorolac tromethamine to dissociate and become trapped in the cells. The permeability of the mucosal cell membrane is thus altered, and the accumulation of hydrogen ions causes mucosal cell damage. This gastric damage is a result of the primary insult of acidic substances. The inhibition of prostaglandin biosynthesis in the GIT prevents the prostaglandins from exerting their protective mechanism on gastric mucosa and thus Ketorolac tromethamine induces gastric damage through this secondary insult mechanism.[11] When Ketorolac is given by the nasal route, adverse effects may include nasal discomfort, rhinalgia, increased lacrimation, irritation in throat, rashes, rhinitis.[7]

On administration of ketorolac by parenteral route the reported incidence rates of adverse events in the central nervous system and gastrointestinal tract were 23% and 13% respectively.[12] Other, less common side effects include pain at the injection site, renal impairment, elevated hepatocellular enzyme levels, prolonged bleeding, purpura, edema, fever and exacerbation of asthma.[12]

CLINICAL EFFICACY

The rational for prophylactic NSAIDs administration is that, the presence of the drug in the tissues at the time of surgery results in blocking of both synthesis and direct effects of prostaglandins, and thereby limiting postoperative pain and other components of surgically induced inflammation. Studies on clinical efficacy of NSAID premedication, however, seem to suggest that postsurgical pain control is strictly related to many factors, such as patient selection, nature of medication, and drug regimen.[13]

Oral Ketorolac is completely absorbed, with a mean peak plasma concentration occurring an average of 44 min after a single 10-mg dose.[14] Ketorolac is strongly (99%) protein bound, with the degree of binding apparently independent of the plasma concentration of the drug.[15] For this reason, an oral loading approximately twice the maintenance dose is administered to minimize the analgesic delay due to ketorolac's two-compartmental characteristics.

Plasma half-life is 4 to 6 hours in the normal adult, and analgesia may be maintained for 6 to 8 hours.[2] Since the maximum concentration of prostaglandins in actively injured tissues occurs simultaneously with the peak intensity of postoperative pain, 3 to 4 hours after injury,[16] the pharmacokinetic properties of ketorolac may have allowed for achieving therapeutic blood levels of the drug which would blunt the biochemical processes leading to pain. Although preoperative ketorolac treatment significantly reduces pain intensity on the day of surgery, the results of a single-dose, parallel-group, double blind study showed that 20 mg ketorolac administered immediately before periodontal surgery was effective for alleviating the early postoperative painful sequelae. However, ketorolac premedication did not either affect delayed pain levels, nor postoperative analgesic use . No disadvantages were noted related to this method of administration.[2] In a study patients who underwent periodontal surgery were given preoperative ketorolac treatment, they experienced low to moderate postoperative pain, even when osseous reduction was involved.[17] There is evidence that pain levels following periodontal surgery are greatest within the immediate 11 hours postoperative period and reach about 25 to 40% after Ketorolac administration.[18]

Gastrointestinal intolerance and adverse CNS manifestations are among the most common side effects seen in NSAID's therapy. A major concern when taking any NSAID is the subsequent effect on platelet aggregation. In a previously reported study where 82% of 115 patients treated with single oral dose of ketorolac had registered no complaints such as gastrointestinal intolerance and adverse CNS manifestations during the postoperative observation period.[14]

Parenteral ketorolac offers an alternative for patients who cannot take medication orally. It does not provide therapeutic blood concentrations more rapidly than the oral form of the drug. Pharmacokinetic studies involving both young and elderly volunteers have demonstrated that the two forms of ketorolac have similar rates and extents of absorption.[12] Furthermore, there is no clinical evidence to support a faster onset of pain relief with the parenteral product, if one assumes that prostaglandin inhibition is the step that limits the absorption rate, a faster effect would not be expected.[12] The clinical trials that were conducted to examine all aspects of parenteral ketorolac established that, IM ketorolac was an effective NSAID analgesic with a suitable risk/benefit profile for the treatment of acute pain states such as renal colic, posttraumatic musculoskeletal pain.[7] Dose-ranging studies conducted during these trials established that IM doses of 15 mg to 30 mg of ketorolac every 6 to 8 hours were safe and effective for short-term (up to 5 days) analgesic use. Clinical experience with IM ketorolac confirmed the safety and efficacy of IM ketorolac as an effective alternative to opioids.[7]

Ketorolac is a potent inhibitor of prostaglandin biosynthesis. PGE2 concentration in GCF was significantly reduced 1 hour after the use of 0.01%, 0.05% or 0.1% KT oral rinse.[19] In a study, patients suffering from chronic periodontitis were treated with 0.1% Ketorolac Tromethamine oral rinse twice daily for 6 months resulted in reduction of PGE_2 in GCF.[20] In another study, the authors reported that topically used ketorolac as oral rinse (0.1%) was clinically effective in treatment of periodontitis. The authors measured the ketorolac concentration in the oral cavity, namely in the gingival crevicular fluid and reported a maximum concentration of about 4.2 mg/ml for the drug after application of 0.1% KT oral rinse for 30 seconds.[21]

CONCLUSION

Ketorolac (KT) is currently administered orally in the form of tablets or as intramuscular injections in multiple divided doses for short term management of post-operative pain. Tablets given orally have few adverse effects such as GI erosions and ulcers, inhibition of platelet function, renal effects. Concept of administration of drug through ophthalmic solution, intranasal solution, dentifrices and mouthrinses have been tested, and found to result in lower incidence of side effects. The newer methods of its administration like microspheres and delayed release tablets, are still in the phase of development. It is highly recommended to make all the formulations of this drug commercially available in an order to provide more specific form of administration and also decrease the occurrence of adverse effects.

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More references are available on request