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Review

The use of diclofenac sodium in urological practice: A structural and neurochemical based review

Mahmut Ulubay[a,*], Kıymet Kübra Yurt[b], Arife Ahsen Kaplan[b], Mustafa Kemal Atilla[c]

[a] Urology Clinic, Gazi Hospital, Samsun, Turkey
[b] Department of Histology and Embryology, Medical Faculty, Ondokuz Mayıs University, Samsun, Turkey
[c] Urology Clinic, Samsun Training and Research Hospital, Samsun, Turkey

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ABSTRACT

Diclofenac sodium (DS) is a non-steroidal anti-inflammatory drug with antipyretic and analgesic effects. It is mainly found in the form of sodium salt. The mechanism of action of DS operates by way of cyclooxygenase (COX) inhibition. The physiological effect of this substance derives from a decrease in prostaglandin production. DS is a benzeneacetic acid derivative with anti-inflammatory properties. As a non-steroidal anti-inflammatory drug (NSAID), DS binds to both forms of COX (COX-1 and COX-2) and inhibits the conversion of arachidonic acid into pro-inflammatory prostaglandins by means of chelation. At the same time, this agent is also able to inhibit tumor angiogenesis, in which COX-2 is involved. DS is effective in overcoming pain and inflammation when it inhibits COX-2, but gastrointestinal side effects appear when it inhibits COX-1. In this review, we have focused on chemical structure and pharmacokinetic properties and renal effects of DS in light of current knowledge. Additionally, use of diclofenac nanoparticles were also discussed.

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1. Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most widely prescribed pharmaceutical agents in the world and these drugs are commercially in sodium or potassium salt form. Additionally, NSAIDs are divided into two categories as COX-2 inhibitors and that preserve cyclooxygenase (COX-1) and non-selective NSAIDs. Diclofenac is considered as a non-selective NSAID, which is associated with serious adverse effects such as renal dysfunction and gastric ulcers (Harirforoosh et al., 2016). Their anti-inflammatory effects occur through the inhibition of the cyclooxygenase (COX) enzymes. In addition, this drug has a structure of the phenylacetic acid with analgesic, anti-inflammatory and antipyretic properties. It inhibits COX-2 with higher potency compared to COX-1 (Altman et al., 2015; Warner et al.,

Abbreviations: NSAIDs, non steroidal anti-inflammatory drugs; COX, cyclooxygenase; PGs, prostaglandins; AA, arachidonic acid; LO, lipoxygenase; TXA2, thromboxane A2; DS, diclofenac sodium; PLA, poly lactic acid; poly D,L glycolide, PLG; poly lactide-co-glycolide, PLGA.

* Corresponding author.
E-mail address: mulubay61@hotmail.com (M. Ulubay).

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1999). In addition, its adverse effect is associated with the renal damage and gastrointestinal damage (Warner et al., 1999). On the other hands, when the drugs encapsulated into polymer-based nanoparticles, a significant reduction in renal and gastrointestinal side effects were reported (Italia et al., 2007, 2009). In this context, recently, the polymeric nanoparticles in the drug formulation and the nanonization of selected drugs in pharmacology will become increasingly important. In this context, in particular, use of nanoparticles such as poly (lactic acid) (PLA), poly (D, L glycolide) (PLG), and poly (lactide-co-glycolide) (PLGA), which have high rate of hydrolysis, tissue compability and low toxicity, is important in the pharmacology. The efficiency of nanoparticle formulation in eliminating the potential side effects of diclofenac sodium (DS) is associated with orally administrated (Liu et al., 2010).

Main purpose of this review focused on use of the DS in the urogenital diseases and polymer based nanoparticle formulation of the DS as a novel treatment approach. Additionally, the chemical structure and features of the NSAIDs were mentioned in the discussing the current approaches.

2. Pharmacokinetic properties of DS

DS is eliminated through urinary and biliary excretion; DS and its metabolites are excreted in the urine after the biotransformation to sulphate metabolites and glucoroconjugated (Davies and Anderson, 1997). Approximately, while 35% of the dose is conjugated in the bile, 65% of the dose of diclofenac is excreted in the urine (Altman et al., 2015).

In the oral administration of the diclofenac, its systemic absorption is so rapid. The rate of diclofenac absorption is associated with highly soluble potassium salt and pharmaceutical content. However, variable maximum plasma concentration (Cmax) and time to Cmax (Tmax) can be inconsistent with the rate of absorption of diclofenac. In this context, the presence of plasma peaks in plots of diclofenac concentration versus time can be considered (Macia et al., 1995; Reiner et al., 2001; Terhaag et al., 2000). Also, Desjardins et al. (2015) studied on pharmacokinetic properties of low-dose (18- and 35-mg) SoluMatrix diclofenac capsules for the healthy volunteers and suggested that rapid absorption of the diclofenac is measured by Tmax and especially, SoluMatrix diclofenac capsules can be considered as an option for the treatment of osteoarthritis-related pain and acute pain (Desjardins et al., 2015). On the other hand, it has been suggested that individual differences in the gastrointestinal pH may affect the inconsistences in the diclofenac absorption (Laine et al., 2003). Additionally, it has been reported that variety in the timing in gastric emptying and enterohepatic circulation may lead to arise in the inconsistences in the absorption (Chuasuwan et al., 2009; Lotsch et al., 2000). Additionally, while intravenous formulations of diclofenac have been developed for treatment of severe and moderate pain such as perioperative pain. Topical formulations of diclofenac have been formulated as a treatment approaches for different types of localized pain (Goh and Lane, 2014; McCormack and Scott, 2008).

3. Chemical structure and mechanism of diclofenac sodium: pathophysiology of NSAIDs

DS, which is commonly prescribed is a phenyl acetic acid and has partial solubility in the hydrophobic environment because of its feature of weak acid. The structural feature of the molecule is designed as a phenylacetic acid group and a phenyl ring containing two chlorine atoms. The molecule is linked to the COX by rotation of the phenyl ring (Fig. 1) (Altman et al., 2015). In the mechanism of COX and lipoxygenase, the phospholipids of the membrane are hydrolysed and arachidonic acid releases into the cytoplasm by

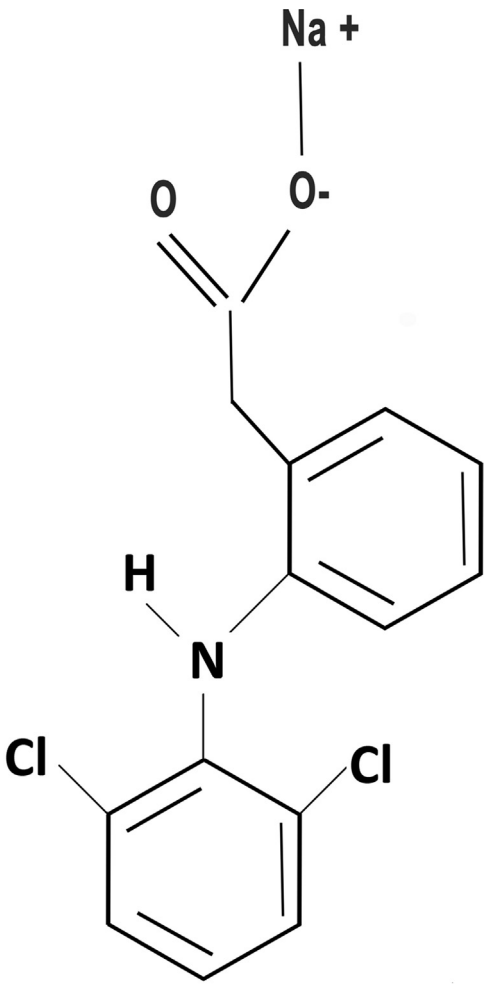

Fig. 1. Chemical structure of diclofenac sodium is given in the schema (Modified from Altman et al., 2015; Cooper and Harirforoosh, 2014).

activation of the phospholipase A2 enzyme. While COX pathway induces the formation of some prostaglandins (PGs) such as PGI_2, PGD_2, PGE_2 $PGF_{2\alpha}$ and thromboxane A_2 (TXA_2), leukotrienes and lipoxins is produced through the lipoxygenase pathway (Howard and Delafontaine, 2004; Vane and Botting, 1998). Especially, COX enzymes play a key role in cardiovascular homeostasis. COX-1 induces the synthesis of TXA_2 in the platelets and leads to platelet aggregation, proliferation in the smooth muscle cells and vasoconstriction. Contrarily, COX-2 induces the synthesis of prostacyclin in the endothelial cells and causes the relaxation in the vascular smooth cells and vasodilatation (Antman et al., 2007). Several prostanoids such as PGE_2 and prostacyclin protects the gastric mucosa against erosive effects of stomach acid. Additionally, the studies demonstrated that PGE_2 and PGI_2 have an important role in cardioprotection by up-regulation of COX-2 (Fig. 2) (FitzGerald et al., 2001; Shinmura et al., 2000).

NSAIDs exhibit anti-inflammatory, analgesic and antipyretic effects by blocking prostaglandin production through the non-selective inhibition of COX isozymes. They also exhibit bacteriostatic effects by inhibiting bacterial DNA synthesis (Dastidar et al., 2000). They play a basic role in the pharmacological treatment of acute and chronic pain. COX-1 and COX-2 have different biological effects. The analgesic effect is primarily associated with COX-2 inhibition, while different side effects emerge with the inhibition of COX-1 and COX-2. All NSAIDs have gastrointestinal and cardiovascular side effects depending on their relative selectivity to COX-1 and COX-2. Since all NSAIDS exhibit their therapeutic