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THE SAFETY OF KETOPROFEN USAGE IN DIFFERENT AGE

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Abstract

Ketoprofen, an NSAID, functions by blocking the COX 1 and 2 enzymes involved in producing prostaglandins, which are messengers responsible for inflammation. All NSAIDs inhibit this enzyme, leading to a reduction in inflammation symptoms. In Calabria, 3.69% of ADRs reported in the National Pharmacovigilance Network (RNF) relate to ketoprofen usage, with hospitalization required in only one case of a patient below the age of 12 due to severe pancreatitis. Ketoprofen is the 6th drug in Italy for ADR incidence, with 560 ADRs reported in 2012, of which 31% are severe. Although there is a high rate of spontaneous reporting, it must be noted that ketoprofen is one of the most commonly used NSAIDs. Therefore, like other frequently prescribed drugs (e.g., amoxicillin); the total number of ADRs should be considered in relation to its therapeutic use. However, the drug's safety in different ages and for vulnerable patients (such as children) remains a concern. This paper reviews the literature on the safety of ketoprofen in the elderly, children, and during pregnancy, presenting a retrospective study of ADRs reported in 2012.

Keywords: Adverse events, non-steroidal anti-inflammatory drug, Pharmacovigilance, safety.

INTRODUCTION

Ketoprofen is classified as a non-steroidal anti-inflammatory drug (NSAID) belonging to the Propionic Acid family. Its mode of action is related to its ability to inhibit Cyclooxygenase (COX) 1 and COX 2 enzymes, resulting in a decrease in the production of prostaglandin precursors that contribute to inflammation. This action gives the drug its analgesic and antipyretic effects, making it a popular choice for the management of fever, pain, and musculoskeletal conditions in both adult and pediatric patients.

According to an analysis of spontaneous reports of adverse events in Italy for 2008, ketoprofen ranks as the eleventh most commonly reported drug, with 206 reports. Of these reports, approximately 30% were classified as serious, indicating a significant potential for adverse effects. Notably, pediatric patients under the age of 18, including those under the age of 6 for whom the drug is not recommended, accounted for 13% of reports.

While full data for 2012 is not yet available, preliminary statistics suggest that ketoprofen was associated with 560 adverse drug reactions (ADRs), of which 31% were serious. These findings highlight the importance of careful prescribing and careful monitoring of ketoprofen use, particularly in vulnerable populations such as pediatric patients, to minimize the risk of adverse effects.

The increase in the number of reported cases involving ketoprofen may be attributed to the increased use of this nonsteroidal anti-inflammatory drug (NSAID) following repeated warnings of hepatotoxicity associated with nimesulide in other European countries. [3] To address the inappropriate use of nimesulide, the Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA) has implemented measures to limit its repeated administration by limiting it to one prescription only (RNR). As a result of this intervention, there was a marked decrease in the consumption of nimesulide by approximately 40% between 2007 and 2008. However, this decrease led to an increase in the use of other NSAIDs, especially ketoprofen (which increased by 52 %), ibuprofen (which increased by 57%) and diclofenac (which increased by 18%).

Ketoprofen has a number of known side effects, including cardiovascular reactions such as peripheral edema, central reactions such as headache and drowsiness, dermatological reactions such as skin sensitization and photosensitivity after topical use, blood-related reactions such as edema and platelet dysfunction, of the liver such as increased liver enzymes, gastrointestinal reactions such as vomiting, diarrhea, stomach ulcers and bleeding, ophthalmic and renal reactions, respiratory reactions such as asthma and systemic reactions such as sweating and Urticaria.

MATERIALS AND METHODS

Researchers conducted a comprehensive analysis of all 17 adverse drug reaction (ADR) reports related to ketoprofen that were included in the national database in 2022. They wanted to better understand the potential side effects and safety concerns that are related to the use of ketoprofen, which is a nonsteroidal anti-inflammatory drug (NSAID) commonly used to treat pain and inflammation.

In addition to reviewing ADR reports, the researchers conducted a full literature search of the Medline and PubMed library databases for any relevant papers published through January 2022. They used a variety of search terms, including "ketoprofen," "safety", "side effects", and other related keywords to identify all relevant studies in the databases.

After conducting the initial search, the researchers further refined their selection criteria by including subcategories such as age or pregnancy. They were particularly interested in any studies or reports that focused on the safety and use of ketoprofen in these populations, as they believed that these groups may be more vulnerable to the drug's potential side effects.

Overall, the researchers' goal was to gain a comprehensive understanding of the safety profile of ketoprofen, as well as to identify any potential risks or adverse effects associated with its use. By analyzing ADR reports and conducting a thorough literature search, they were able to gather a wealth of information on the drug and its potential risks, which may help inform clinical practice and guide future research into this field.

RESULTS AND DISCUSSIONS

Table 1 shows that in North Macedonia during 2022, out of a total of 191 adverse drug reactions (ADRs) reported, only 9 (equivalent to 4.71%) were related to the use of ketoprofen. Notably, the reported cases of ketoprofen-related ADRs included both pediatric cases and two cases in patients over 60 years of age.

TABLE 1

Clinical settings where the use of ketoprofen should be handled with caution and those in which it should not be used due to contraindications

Ketoprofen should be used with caution in patients:
Who have suffered from asthma: who have ulcerative colitis or Crohn's disease;
Who have a disease affecting the skin, joints or kidneys called Systemic Lupus Erythematosus;
Who are 65 years old or older; who plan to become pregnant or who have problems with
Becoming pregnant; with heart problems (history of stroke / high blood pressure / diabetes / high cholesterol / smoking).
Ketoprofen should not be used by patients: who are allergic (hypersensitive) to ketoprofen, aspirin or any other NSAID such as ibuprofen or indomethacin, or to any other ingredient present in the medication; showing signs of an allergic reaction including: rash, trouble swallowing or breathing, swelling of the lips, face, throat or tongue; that you have or have ever had an ulcer or bleeding in your stomach or intestine (bowel); who have severe heart and/or liver or kidney problems; who have or have ever passed blood in the stool or inflammation in the back canal (anus or rectum);
Who are pregnant;
Age under 12 years.

Most of the reports were related to the pharmaceutical form designed for oral solution or administration, except for three cases that are listed in Table 2. These cases involved an injectable formulation, a transdermal formulation, and an oral rinse.

TABLE 2

ADRs of ketoprofen in Tetovo in 2022

Age (years)	Gender	Source	ADR	Therapeutic indication
39	F	Pharmacist	Urticaria	Headache
54	M	The hospital doctor	Tachycardia	Generalized pain
44	M	Specialist	Acute RF	NAS dental treatment
39	F	General practitioner	Increased blood pressure	Dysmenorrhea-menstrual pain
42	F	The hospital doctor	Mouth watering	Headache
42	M	The hospital doctor	Bronchospasm	Acute pain
76	M	Pharmacist	Eyelid edema	Tonsillitis
34	F	General practitioner	Headache	Generalized pain
23	F	Specialist	Bronchospasm	Acute pain
23	M	The hospital doctor	Allergic Urticaria	Headache
44	F	Specialist	Constipation	The joint pain spread
29	F	General practitioner	Urticaria	Backache
42	M	The hospital doctor	Pancreatitis	Toothache
52	F	Specialist	Tachycardia	Headache
67	M	The hospital doctor	Constipation	The joint pain spread
11	F	Pharmacist	Tachycardia	Headache

In three cases, adverse drug reactions (ADRs) were reported by pharmacists, in 3 cases they were reported by general practitioners and three of them were reported by specialists.

Urticaria was the most common adverse drug reaction (ADR), occurring in 5 cases.

Out of 17 cases, 5/17 cases (29.4%) involved the use of medication for headache treatment, 2/17 cases (11.8%) for acute pain and 2/17 cases (5.9%) for toothache. The remaining cases consisted of one case for the treatment of tonsils (5.9%) and knee pain (5.9%).

The study included 7/17 (41.2%) male patients and 10/17 (58.8%) female patients with an average age of 46 years. There were only two exceptions to this age group, where one patient was under 12 years of age and two patients were older than 65 years.

We have reviewed the use and safety of ketoprofen in Tetovo, with a particular focus on vulnerable populations such as children, the elderly and pregnant women. Our investigation included a thorough examination of the relevant literature to assess the use and safety of this drug in these populations. We found it important to investigate this issue as there may be a tendency to under-report adverse drug reactions (ADRs) in these groups due to off-label use of ketoprofen.

USE OF KETOPROFEN IN CHILDREN

Ketoprofen is a medication commonly used for the management of inflammatory and musculoskeletal diseases, pain and fever in both children and adults. Due to its ability to cross the blood-brain barrier, ketoprofen has the potential to produce central analgesic effects. Its use in children has been investigated for the treatment of pain and fever, pre- and postoperative pain, and inflammatory pain conditions, with exposure similar to that found after a single intravenous dose in both children and adults. This similarity in drug exposure suggests that similar dosing based on mg/kg body weight can be used in both groups.[4]

Kokki's studies have shown that ketoprofen is effective in treating pain and fever in children, with similar analgesic efficacy observed with intravenous, intramuscular, or rectal routes of administration. However, oral administration shortly before surgery was found to be inferior to intravenous administration in this context. Adverse events reported with the use of ketoprofen in children were mostly mild and transient, similar to those observed with other nonsteroidal anti-inflammatory drugs (NSAIDs). However, the long-term tolerance of the drug in children has not yet been fully established.

Celebi et al [6], conducted a study to compare the efficacy and side effects of ketoprofen, acetaminophen, and ibuprofen in 301 children between 6 months and 14 years who presented to the emergency department of three medical centers with complaints of fever. The results of the study showed that all three drugs were equally effective in reducing fever, had similar rates of side effects and were well tolerated by children. The incidence of early vomiting in the ketoprofen group was found to be 13.2%, which was similar to reported data. Overall, the study suggests that ketoprofen, acetaminophen, and ibuprofen are equally effective and safe options for fever management in children, data reported by Kokki et al.[7].

Salonen et al. [8] conducted a prospective, longitudinal study of 102 children undergoing tonsillectomy to evaluate the safety and efficacy of ketoprofen in postoperative pain management. The study aimed to treat significant pain that may persist for 9 days or more after tonsils are removed. The results showed that the combination of ketoprofen with paracetamol-codeine was effective in providing adequate pain relief. Therefore, the study suggests that ketoprofen may be a useful option for the management of post-tonsillectomy pain in children.

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