The safety of ketoprofen in different ages

Claudia Carbone, Pierandrea Rende, Pasquale Comberiati, Domenico Carnovale, Maria Mammì, Giovambattista De Sarro

Department of Science of Health, School of Medicine, University of Catanzaro and Pharmacovigilance's Centre Calabria Region, University Hospital Mater Domini, Catanzaro, Italy

ABSTRACT

Ketoprofen is a non-steroidal anti-inflammatory drug (NSAID), which acts by blocking cyclooxygenase (COX 1 and 2), an enzyme involved in the production of prostaglandins, messengers in the development of inflammation. All NSAIDs reduce signs of inflammation by blocking this enzyme and therefore prostaglandin production. In Calabria, 3.69% of adverse drug reactions (ADRs) reported in the National Network of Pharmacovigilance concerns the use of ketoprofen; only in one case in which the patient was under the age of 12 years, hospitalization was required for severe episode of pancreatitis. In Italy, Ketoprofen is the 6th drug for ADRs incidence (560 ADRs in the year 2012, of which, 31% are severe). Despite the high rate of spontaneous reporting, it must be considered that ketoprofen is one of the most used NSAIDs; therefore, as it happens for other commonly used drugs (eg, amoxicillin), the total number of ADRs should be related to the therapeutic use. However, it remains the problem of fragile patients (eg, children) and the safety of the drug in different ages. This paper presents a retrospective study on 2012 ADRs reviewing literature on the safety of ketoprofen in the elderly, children, and during pregnancy.

Key words: Adverse events, non-steroidal anti-inflammatory drug, pharmacovigilance, safety

INTRODUCTION

Ketoprofen is a non-steroidal anti-inflammatory drug (NSAID) belonging to the family of propionics derived from arylcarboxylic acid with analgesic and antipyretic effects. It works by inhibiting cyclooxygenase 1 and 2 (COX 1 and COX 2) enzymes reversibly, which decreases the production of pro-inflammatory prostaglandin precursors. It is widely used in the management of inflammatory and musculoskeletal conditions, pain, and fever in children and adults.[1]

From analysis of spontaneous reports of adverse events for the year 2008 in Italy, ketoprofen is the eleventh busiest with 206 reports of which about 30% are serious. A total of 13% of the reports were in charge of pediatric patients (age below 18 years), even in the range of age (<6 years) in which drug is off-label.[2] Data for the year 2012 are not completely available; however, preliminary statistics indicate that ketoprofen was involved in 560 ADRs of which 31% were serious (personal data).

The increase in reports of ketoprofen is due to an increase in the use of this NSAID after repeated warnings of hepatotoxicity in other European countries in relation to nimesulide.[3] The Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA) has taken action to reduce the inappropriate use of nimesulide limiting its repeatable dispensing from recipe

Access this article online	
Quick Response Code:	Website: www.jpharmacol.com
	DOI: 10.4103/0976-500X.120967

Address for correspondence:
Giovambattista De Sarro, Department of Science of Health, School of Medicine, University of Catanzaro, Via T. Campanella, 115; 88100 Catanzaro, Italy.
E-mail: desarro@unicz.it

to recipe not repeatable (RNR). The sharp reduction in the consumption of this drug between 2007 and 2008 by approximately 40% resulted in an increase in the use of other NSAIDs, in particular ketoprofen (+52%), ibuprofen (+57%), and diclofenac (+18 %).

The known adverse events of ketoprofen include: cardiovascular reactions (peripheral edema), central (headache, drowsiness, etc.), dermatological (skin sensitization and photosensitization after topical use), blood (edema, platelet dysfunction, etc.), liver (increased liver enzymes), gastrointestinal (vomiting, diarrhea, ulcers, and bleeding in the stomach, etc.), ophthalmic, renal, respiratory (asthma), systemic (sweating, hives, etc.).

MATERIALS AND METHODS

All 17 ADRs reports regarding ketoprofen as suspected drug included in the national database in 2012 were analyzed. The Medline and PubMed library databases were searched for papers published until June 2013 for related side effects and papers reporting the safety and use of ketoprofen. Searches were initially conducted to identify all studies extracted from the database using Ketoprofen and safety as keywords. Then papers were selected considering as sub searches age or pregnancy.

RESULTS AND DISCUSSION

Considering the reports of ADRs in Calabria in 2012 (461 ADRs), only 17 (3.69%) were related to ketoprofen [Table 1], including ADRs in children and two in patients older than 65 years.

Most reports were due to the granular pharmaceutical form for oral solution/administration, with the exception of the three cases highlighted in the summary table below [Table 2], including an injectable formulation, a transdermal formulation, and a mouthwash.

In 9 cases, the ADRs were reported by hospital physicians, in 4 cases by pharmacists, in 3 by the general practitioners, and in 1 case by medical specialists.

Table 1: Clinical settings in which ketoprofen should be used with caution and those in which the use of ketoprofen is contraindicated

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 Erythematous';
who are aged 65 years or older;
who are planning to become pregnant or who have problems in 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 in any other excipients present in the medication;
showing signs of an allergic reaction including: a rash, swallowing or breathing problems, swelling of lips, face, throat, or tongue;
who have or have ever had an ulcer or bleed in your stomach or intestine (gut);
who have severe heart and/or liver or kidney problems;
who have or have ever passed blood in stools or inflammation at the back passage (anus or rectum);
who are pregnant;
aged below 12 years.

Table 2: ADRs of ketoprofen in Calabria in 2012

Age (years)	Gender	Source	ADR	Therapeutic indication
37	F	Pharmacist	Bronchospasm	Pain acute
59	M	Hospital doctor	Urticaria	Headache
39	F	Pharmacist	Increased blood pressure, panic attacks	Dysmenorrhea-menstrual pain
39	F	Pharmacist	Urticaria	Back pain
72	M	Hospital doctor	Acute RF	Dental treatment NAS
42	F	General practitioner	Gastric hemorrhage	Headache
76	F	Hospital doctor	Heartburn	Pain
34	F	Hospital doctor	Generalized joint pain	Headache
56	F	Hospital doctor	Drooling	Headache*
23	M	Hospital doctor	Eyelid edema	Tonsillitis§
32	M	Specialist	Tachycardia	Headache
29	M	Hospital doctor	Urticaria	Headache
42	M	Hospital doctor	Allergic urticaria	Headache
52	F	Pharmacist	Tingling, head pain, tachycardia, tingling of the lips	Generalized pain
67	F	General practitioner	Constipation	Joint pain spread
74	F	General practitioner	Allergic dermatitis	Knee pain°
11	M	Hospital doctor	Pancreatitis	Toothache-Toothache

RF=Renal failure. *ketoprofen fl, injectable formulation; § ketoprofen mouthwash; °ketoprofen medicated plaster.

The most frequent reaction was urticaria (5 ADRs).

Of the 17 cases, the therapeutic indication observed in 7 cases (41.2%) was for the treatment of headache, in 6 cases (35.3%) for acute painful symptomatology, in 2 cases (11.8%) for the treatment of toothache; in the remainder of the cases, one for tonsillitis (5.9%) and one for knee pain (5.9%).

The gender distribution of the patients is 7 men and 10 women, mean age 46 years (exceptions are only one patient aged below 12 years and 2 patients older than 65 years).

Only one ADR was considered as serious:

- An 11-year-old child was treated for toothache for a week with ketoprofen 80 mg/die (granules for oral solution) and required hospitalization for pancreatitis.

Starting from ADRs in Calabria, we reviewed the use and safety of this drug, especially in fragile categories (children, elderly, and pregnant women).

We have found it interesting to evaluate, through the study of literature, the use and safety of ketoprofen in classes of patients considered to be more fragile as children, pregnant, and the elderly. In fact, we consider that the under reporting in such fragile population might be due to the knowledge that ketoprofen might be used without indication (off-label).

Use of ketoprofen in children

Ketoprofen has been widely used in the management of inflammatory and musculoskeletal conditions, pain, and fever in children and adults. It crosses the blood-brain barrier and therefore it has the potential to cause central analgesic effects. The pediatric use of ketoprofen has been investigated for the treatment of pain and fever, peri- and post-operative pain, and inflammatory pain conditions.[4]

Kokki[4] showed that drug exposure after a single intravenous dose is similar in children and adults and thus similar mg/kg bodyweight dosing may be used in children and adults. Ketoprofen has been investigated in children for the treatment of pain and fever, peri- and post-operative pain, and inflammatory pain conditions. Analgesic efficacy was similar with intravenous, intramuscular, or rectal routes of administration, but the oral administration just before surgery, was inferior to the intravenous administration in this setting. Most of the adverse events reported were mild and transient, and were similar to those observed with other NSAIDs. Long-term tolerability has not been yet fully established.[4]

Kokki *et al*.[5] studied 220 children in the age range 1 to 7 years, inclusive, who underwent adenoidectomy and investigated post-operative analgesic effect of low dose of ketoprofen (0.3 mg kg^{-1}) without any further adverse effects or peri-operative bleeding. For adenoidectomy, intravenous ketoprofen provided superior post-operative analgesic efficacy compared with placebo. Most frequent side effects were nausea and vomiting, which were observed in 13% of patients.

Celebi *et al*.[6] compared efficacy and side effects of ketoprofen, acetaminophen, and ibuprofen in 301 children, between 6 months and 14 years of age, presented to emergency room of 3 medical centers with the complaint of fever. The three drugs were similar in terms of efficacy, adverse effects, and compliance. The incidence of early vomiting in the ketoprofen group was 13.2%, similar to the data reported by Kokki *et al*.[7]

Salonen *et al*.[8] realized a prospective, longitudinal study in 102 children undergoing tonsillectomy to determine the safety and efficacy of ketoprofen in pain treatment after surgery. The main problem after tonsillectomy is the significant pain that may last 9 days or longer after surgery. Ketoprofen combined with paracetamol/codeine seems to provide sufficient analgesia.

Ruperto *et al*.[9] conducted a study in 97 children aged 6 to 12 years, inclusive, with sore throat, which confirmed that paracetamol or ketoprofen, administered as a single oral dose, is a safe and effective treatment in children and it can be used without any special risks of analgesic drugs also in primary care.

Messeri *et al*.[10] compared the analgesic effect of ketoprofen and acetaminophen in 85 children between the ages of 6 to 14 years, inclusive, who had minor surgical procedures and found that the analgesic effect of ketoprofen started earlier and lasted longer. No side effects related to the treatment were noted.

Sturkenboom *et al*.[11] realized a retrospective cohort study (2000-2005) to provide an overview of drug use in children in three European countries: Italy, UK, and Netherlands. Ketoprofen was among the most prescribed drugs in Italy and in the UK. In the latter country, users were 86/1000, of whom 16 were between the ages of 2 and 11 years, inclusive, and 70 between 12 and 18 years, inclusive; in Italy, users were 362/1000, of whom 8 with less than 2 years and 354 between 2 and 11 years, inclusive. This confirms that the use of ketoprofen in Italy is greater than in other countries, even in the age in which it is contraindicated (off-label use).

In conclusion, from this data it seems that the use of ketoprofen in children might represent a safe and efficacious alternative, however, the under reporting in this age range must be reconsidered and attention must be paid to this off-label use.

Use of ketoprofen in pregnancy

There are no controlled data in human pregnancy about the use of ketoprofen.[12] Animal studies failed to reveal evidence of embryotoxicity or teratogenicity except at doses which

produced a significant maternal toxicity.[13] When ketoprofen is used late in pregnancy, it may cause premature closure of the ductus arteriosus and may prolong labor and delivery.[13] Ketoprofen is only recommended for use during pregnancy when benefits outweigh the risks. Ketoprofen has to be avoided in the last trimester of pregnancy and should not be used in the first two trimesters unless the potential benefit to the patient outweighs the potential risk to the fetus.

As weak acids, NSAIDs are excreted in small amounts into human breast milk with little risk for adverse effects in the suckling infant.[14]

Llanas *et al*.[15] reported of 11 neonates from 7 pregnancies, which were admitted because of ketoprofen-suspected adverse effects, where ketoprofen was administered to their mothers before delivery. It was reported that 10/11 neonates had renal dysfunction and in 3 cases it was lethal; 2 of the 11 developed cardiopulmonary complications and in 1 case it was lethal. Ketoprofen plasma concentration was found to be high in the first few hours of life in 3/6 patients.

A number of studies in which pregnancy outcome has been documented in the offspring of women treated during early pregnancy with various NSAIDs have been published.[16-19]

Based on these studies, it is not thought that NSAIDs are serious teratogens, but they may be associated with low risks for certain congenital malformations and possibly miscarriage. Despite the demonstrated lack of substantial teratogenic risk following first trimester exposure to NSAIDs, a number of risks have been documented when fetal exposure occurs later in pregnancy. Premature closure of the fetal ductus arteriosus with resultant pulmonary hypertension has been noted in association with the use of NSAIDs in the third trimester. Renal dysgenesis leading to oligohydramnios has been observed during the latter pregnancy period due to the exposure to indomethacin, ibuprofen, naproxen, ketoprofen, nimesulide, and piroxicam.[19]

Use of ketoprofen in the elderly

Elderly patients are at higher risk for side effects from medications.[20] Aging changes pharmacodynamics and pharmacokinetics of drugs affecting choice, dosage, and frequency of administration of several drugs.[21] Although life expectancy is gradually increasing in Western countries, the elderly continue to be excluded from participating in clinical trials. The drugs are mainly tested in subjects below 65 years old, but then are often used in elderly patients with multiple concomitant diseases.[22]

The NSAIDs are often used in the elderly and may induce side effects. Safety of ketoprofen in the elderly was investigated by Le Loet.[23] He has monitored the safety profile of ketoprofen in 19.880 patients older than 60 years of age, demonstrating good efficacy and tolerability. Side effects were observed in 15.3% of patients. The most frequent side effects were related to the gastrointestinal tract (13.5% of total patients — ulcer and malena in 0.03%) and skin side effects in 0.7%.

Schattenkirchner has assessed the safety profile of ketoprofen over a 12-month treatment period in 823 patients aged ≥65 years (mean age: 72 years) with osteoarthritis or rheumatoid arthritis. At the end of the study, 302 patients (36.7%) had withdrawn from treatment for various reasons, including adverse reactions, inefficacy, and improvement, or had been lost to follow-up. A total of 314 patients (38.2%) experienced at least one adverse event during the study. Most side effects involved the digestive system (232 patients; 28.2%), the central nervous system (33 patients; 4.0%), or the cardiovascular system (26 patients; 3.2%); gastrointestinal adverse events like ulceration and bleeding (14 patients; 1.7%).[24]

An adverse reaction can cause a disease that if not diagnosed as ADRs may lead to the use of a second drug to treat the disease. Prescribing cascade begins when an ADR is misinterpreted as a new clinical condition. The addition of a new drug puts the patient at risk of developing more adverse events related to the treatment, which was instead superfluous.[25]

The elderly have an increased risk of developing iatrogenic pathologies often higher and more severe than in younger individuals. Drugs at risk of potentially serious reactions in the elderly are often the ones usually prescribed for treatment of chronic diseases. An example of interaction among drugs in the elderly in polytherapy is that of the Triple Whammy (TW): the interaction between angiotensin-converting enzyme inhibitors (or Angiotensin II Inhibitors — Angiotensin II Receptor Blockers), diuretics, and NSAIDs/cox-2 inhibitors, which is characterized by RF. A prospective cohort study has been conducted on the entire population of Ferrara province to analyze patients aged ≥65 years in treatment with the drugs under study. A record linkage with the archive of admissions at the provincial level (SDO) was made and hospitalizations due to TW between 2009 and the first half of 2011 were evaluated, indicating that there is a risk of TW in the population treated with the Anatomical Therapeutic Chemical classification of drugs classes C09, C03, and M01.[26]

It is necessary to conclude by presenting the safety profile of NSAIDs evaluated by Lapeyre-Mestre *et al*.[27] Eight oral NSAIDs (aceclofenac, diclofenac, ketoprofen, meloxicam, naproxen, nimesulide, piroxicam, and tenoxicam) were evaluated using data reported through French pharmacovigilance system from 2002 to 2006, focusing on the reported rates of serious ADRs in the following system organ classes: gastrointestinal, hepatic, cutaneous, renal, and cardiovascular. Ketoprofen was associated with the highest

cumulative reported rate of serious ADRs (0.78 cases per million defined daily doses). Most frequently reported serious ADRs were cutaneous, followed by gastrointestinal, hepatic, renal, and rarely, cardiovascular events. Most frequent serious ADRs reported with the selected oral NSAIDs are cutaneous, followed by gastrointestinal, hepatic, and renal events. The utmost risks for serious gastrointestinal, hepatic, cutaneous, and renal adverse events were linked, respectively, with ketoprofen, nimesulide, meloxicam, and tenoxicam compared with the other NSAIDs.

With the increase of cases of serious side effects related to the use of ketoprofen, several bodies of sanitary control at European level have taken steps to limit access to the drug (e.g., in Italy, now the medical NOT repeatable prescription — RNR is required), or even in some cases it has been withdrawn from the market (e.g., in Spain and Finland). Although today, ketoprofen is considered a safer medication over nimesulide, we still need to have some thorough understanding of its uses, doses, and bounds, to avoid an underestimation of the risks or abuse done in good faith and not jeopardize their own health.

ACKNOWLEDGMENTS

The Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA) is kindly acknowledged for its financial and technical support.

REFERENCES

1. Gallelli L, Colosimo M, Pirritano D, Ferraro M, De Fazio S, Marigliano NM, *et al*. Retrospective evaluation of adverse drug reactions induced by nonsteroidal anti-infiammatory drugs. Clin Drug Investig 2007;27:115-22.
2. GIF 2009: Available from: http:// www.gruppogif.org/ [Last accessed on 2013 Jun 15].
3. Gallelli L, Ferraro M, Mauro GF, De Fazio S, De Sarro G. Nimesulide-induced hepatotoxicity in a previously healthy woman. Clin Drug Investig 2005;25:421-4.
4. Kokki H. Ketoprofen pharmacokinetics, efficacy, and tolerability in pediatric patients. Paediatr Drugs 2010;12:313-29.
5. Kokki H, Nikanne E, Tuovinen K. I.v. intraoperative ketoprofen in small children during adenoidectomy: A dose finding study. Br J Anaesth 1998;81:870-4.
6. Celebi S, Hacimustafaoglu M, Aygun D, Arisoy ES, Karali Y, Akgoz S, *et al*. Antipyretic Effect of Ketoprofen. Indian J Pediatr 2009;76:287-91.
7. Kokki H, Tuomilehto H, Tuovinen K. Pain management after adenoidectomy with ketoprofen: Comparison of rectal and intravenous routes. Br J Anaesth 2000;85:836-40.
8. Salonen A, Kokki H, Nuutinen J. The effect of ketoprofen on recovery after tonsillectomy in children: A 3-week follow-up study. Int J Pediatr Otorhinolaryngol 2002;62:143-50.
9. Ruperto N, Carozzino L, Jamone R, Freschi F, Picollo G, Zera M, *et al*. A randomized, double.blind, placebo-controlled trial of paracetamol and ketoprofen lysine salt for pain control in children with pharyngotonsillitis cared by family pediatricians. Ital J Pediatr 2011;29:37-48.
10. Messeri A, Busoni P, Noccioli B, Murolo S, Ivani G, Grossetti R, *et al*. Analgesic efficacy and tolerability of ketoprofen lysine salt vs paracetamol in common paediatric surgery. A randomized, single blind, parallel, multicentre trial. Paediatr Anaesth 2003;13:574-8.
11. Sturkenboom M, Verhamme K, Nicolosi A, Murray M, Neubert A, Caudri D, *et al*; TEDDY European Network of Excellence. Drug use in children: Cohort study in three European Countries. BMJ 2008;337:a2245.
12. Chambers C, Tutuncu Z, Johnson D, Jones K. Human pregnancy safety for agents used to treat rheumatoid arthritis: Adequacy of available information and strategies for developing post-marketing data. Arthritis Res Ther 2006;8:215-25.
13. Awan AF, Nazir T, Ashraf M, Umer O, Rehman H. Studies of ketoprofen toxicity in avian species. J Basic Appl Sci 2011;7:127-31.
14. Østensen ME. Safety of non-steroidal anti-inflammatory drugs during pregnancy and lactation. Inflammopharmacology 1996;4:31-41.
15. Llanas B, Cavert MH, Apere H, Demarquez JL. Adverse effects of ketoprofen after intrauterine exposure. Value of plasma determination. Arch Pediatr 1996;3:248-53.
16. Ericson K, Kallen BA. Non-steroidal anti-inflammatory drugs in early pregnancy. Reprod Toxicol 2001;15:371-5.
17. Nielsen GL, Sorensen HT, Larsen H, Pedersen L. Risk of adverse birth outcome and miscarriage in pregnant users of nonsteroidal anti-inflammatory drugs: Population based observational study and case-control study. BMJ 2001;322:266-70.
18. Li DK, Liu L, Odoul R. Exposure to non-steroidal anti-inflammatory drugs during pregnancy and risk of miscarriage: Population based cohort study. BMJ 2003;327:368-70.
19. Kaplan BS, Restaino I, Raval DS, Gottlileb RP, Bernstein J. Renal failure in the neonate associated with in utero exposure to non-steroidal anti-inflammatory agents. Pediatr Nephrol 1994;8:700-4.
20. Routledge P, O'Mahony M, Woodhouse K. Adverse drug reactions in elderly patients. Br J Clin Pharmacol 2003;57:121-6.
21. Shi S, Klotz U. Age-related changes in pharmacokinetics. Curr Drug Metab 2011;12:601-10.
22. Rehwagen C. Older people are wrongly excluded from drug trials. BMJ 2005;331:1360.
23. Le Loet X. Safety of ketoprofen in the elderly: A prospective study on 20.000 patients. Scand J Rheumatol Suppl 1989;83:21-7.
24. Schattenkirchner M. Long-term safety of ketoprofen in an elderly population of arthritic patients. Scand J Rheumatol Suppl 1991;91:27-36.
25. Rochon PA, Gurwitz JH. Optimising drug treatment for elderly: The prescribing cascade. BMJ 1997;315:117-23.
26. Barotto M, Benini A, Delfino M, De Togni A, Catapano L, Cellini M, *et al*. Polytherapy and safety. The Triple Whammy case in the elderly: The interaction between NSAIDs, ACE inhibitors, and diuretics. Ricerca e Pratica 2012;28:210-3.
27. Lapeyre-Mestre M, Grolleau S, Montastruc JL. Adverse drug reactions associated with the use of NSAIDs: A case/noncase analysis of spontaneous reports from the French pharmacovigilance database 2002-2006. Fundam Clin Pharmacol 2013;27:223-30.

How to cite this article: Carbone C, Rende P, Comberiati P, Carnovale D, Mammì M, De Sarro G. The safety of ketoprofen in different ages. J Pharmacol Pharmacother 2013;4:99-103.

Source of Support: Nil , **Conflict of Interest:** Nil.