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ORIGINAL REPORT

Large Scale Safety Study of Ketoprofen 25 mg (Toprec®) in Febrile and Painful Conditions

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SUMMARY

Objective — To assess the safety, tolerability and efficacy of low-dose ketoprofen (75–150 mg daily for 5 to 15 days) in a general practice setting.

Design — Open label, non-controlled study of ketoprofen 25 mg tablets in the treatment of pain in ENT diseases, dysmenorrhoea, and musculoskeletal disorders.

Setting — General practice, 600 investigators

Subjects — Four thousand and sixty-eight patients, aged 13–93 years, mean 42.3 years, 1009 with ENT diseases (mean age 38.8 (13–83) years, 53% female), 978 with dysmenorrhoea (mean age 30.3 (13–60) years, 100% female), 2081 with musculoskeletal disorders (mean age 49.6 (16–93) years, 54% female).

Main outcome measures — Occurrence of adverse events, on patient and physician evaluation; dose and duration of treatment prescribed/taken (diary); global evaluation of efficacy by patient and physician.

Result — Twenty-two patients were lost to follow-up (<1%); dose effectively taken was lower than prescribed (3.3 versus 3.6 tablets/day); treatment was stopped prematurely in 3.3% of patients because of adverse events, in 17.1% because of early success of therapy. Gastrointestinal adverse events (AE) were the most frequent (76%) of AE), occurring in 10% of patients. They were more frequent in patients with musculoskeletal pain, who were older and had more associated diseases. Five patients were hospitalized, two for preplanned hospitalizations, the others for one asthma attack, one worsening of low back pain, and one angina attack, none attributed to treatment by the GP. None of the AE was life-threatening. Identified risk factors for AE were age and previous medical history, especially of gastrointestinal disorders.

Conclusions — Good quality large scale studies with little or no loss to follow-up can be done in a general practice setting. At the dose used, ketoprofen was generally well tolerated, and used at a lower dose than prescribed, it was not associated with severe or new side-effects. The results of this study could justify its use in self-medication in these indications.

KEY WORDS — ketoprofen; postmarketing cohort study; NSAIDS; analgesics; risk factors; adverse events

INTRODUCTION

Low doses of NSAIDs have shown consistent analgesic activity with little anti-inflammatory activity, and less risk of severe side-effects,[1–4] justifying the self-medication use of some of them.

Ketoprofen is a propionic acid derivative non-steroidal anti-inflammatory drug (NSAID), widely used in many countries in rheumatic and non-rheumatic conditions, since 1973. Its usual anti-inflammatory dose is from 150 to 300 mg/day, and its usual side-effects are those of all NSAIDs, i.e. predominantly gastrointestinal disorders including GI bleeding, renal failure, and a risk of asthma exacerbation.

Toprec® is a new 25 mg dosage form of ketoprofen, which has, at an average daily dose of 75 mg to 150 mg, essentially analgesic and

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antipyretic properties and is assumed to have little or no anti-inflammatory effects. Its safety profile should therefore be similar to that of other low dose NSAIDs.

The objective of the present study was therefore to evaluate the safety (and efficacy) of Toprec® in general practice as a symptomatic treatment of painful and/or febrile conditions in patients needing at least 5 days of treatment, a typical setting for the utilization of this type of product.

DESIGN AND METHODS

Study design

The study was a prospective non-comparative open-label multicentre cohort study of at least 5 days' treatment with ketoprofen 75 to 150 mg daily for relief of pain or fever.

General description of study

After identification of inclusion criteria, and obtaining informed signed patient consent, patients were given their treatment, and asked to return within 24 h of the end of treatment. They were asked to fill in a diary indicating dose taken each day, associated medication, any event occurring, and comments. In addition, there was an evaluation by the physician at the second visit.

Number of sites/patients

Six hundred investigators were recruited. They were selected from the general population of physicians in general practice. The aim for each investigator was to include eight patients, for an overall number of between 4000 and 5000 patients, of which half were to have a musculoskeletal disorder, one quarter an ENT condition, and the last quarter dysmenorrhoea.

Inclusion criteria

- Indifferent sex
- Age above 18
- Not hospitalized
- One of the following disorders: (1) musculoskeletal pain; (2) dysmenorrhoea; (3) ENT condition (otitis, sinusitis, tonsillitis)

The disease was to be painful but of a short expected duration (especially for the musculoskeletal disorders), so that treatment would last at least 5 days but not exceed 15 days.

Non-inclusion criteria

- Known allergy to ketoprofen or other NSAID
- Gastroduodenal ulcer
- Severe hepatic or renal insufficiency
- Pregnancy or lactation
- Usual treatment with aspirin or other NSAID
- Concomitant treatment with high dose methotrexate (cancer therapy)

These criteria correspond to Summary of Product Characteristics contra-indications.

Treatment

- Dose: recommended dosage was one 25-mg tablet three times a day, but the investigator was allowed to prescribe up to six tablets per day
- Duration: 5 to 15 days
- Treatment units were provided by the sponsor (Rhône-Poulenc-Rorer)

All other treatments including aspirin and other NSAIDs were allowed, except as indicated above. The patient had instructions to note all treatments in the diary.

Evaluation

Safety. Recording of adverse events (AEs): AEs were either new events occurring during the study, or significant changes in pre-existing conditions. They were recorded (1) during the study, by the patients in a diary and (2) at the end of the study, by the investigator, from the diary and by questioning the patient.

At the end of the study, the investigator also questioned the patients about any associated therapy since inclusion and evaluated the severity and relationship to the study medication of all events.

Severity was assessed according to the following scale: **mild**: event noted by the patient, but not affecting daily activities and functions; **moderate**: uncomfortable event, impairing daily activities, but without danger for the health and **severe**: event considerably interfering with daily functioning or putting the patient's health at risk.

Causality was graded as follows: **unknown**: the event was attributed neither to the treatment under study, nor to any other factor, for lack of

information; **unrelated**: there was no temporal association with the treatment under study, and the event was clearly related to other medication or diseases; **possible**: there was a possible temporal relationship with the treatment under study, and a correspondence to the usual side-effects of the drug or class, although it could also have been due to other factors such as disease state or other medication; **probable**: there was a plausible temporal relationship with the treatment under study, the event corresponded to the usual side-effects of the drug or class, and there was no other reasonable cause; **highly probable**: in addition, the event occurred just after treatment administration, resolved after treatment discontinuation, or reoccurred after readministration.

Efficacy. Evaluation of the efficacy was not the primary objective of the study. However, at the final visit the investigator had to fill in a Clinical Global Impression (CGI) score, which integrates both efficacy and tolerability.

Treatment dose and duration. Daily use and duration of treatment as used by the patient was assessed from the patient diaries and completed by the counting of returned tablets. These were compared to the initial prescription.

Ethics and quality assurance

The study was performed in accordance with Good Clinical Practices and the French law. It was approved by the CCPPRB (Review Board) in Colmar (France). Written informed consent was obtained from all patients.

Statistical methods

Adverse events were analysed in different ways.

Descriptive approach. Adverse events were described and classified according to the system-organ involved. They were evaluated globally and by event category. They were also evaluated by patient group, severity, relationship to the study medication, and measures taken. Incidences were compared by the chi-squared test, with a preset 5% alpha risk. The Bonferroni correction was applied to multiple comparisons.

Evaluation of risk factors. The potential role of some 'risk factors' was also evaluated, namely (1) history of gastroduodenal ulcers, hiatal hernia, GI bleeding; (2) concomitant diseases, such as cardiac, renal or hepatic insufficiency; (3) concomitant therapy with drugs whose official labelling mentions warnings in case of co-prescription with ketoprofen or other NSAIDs. According to the case, the chi-square or Fischer's exact test were used.

Additional analysis by logistic regression. Several variables (age, sex, indication for treatment, dose and duration of therapy, concomitant therapies) were analysed by multiple logistic regression in order to determine their prognostic value with regard to the occurrence of adverse events.

RESULTS

Patient population

Four thousand and sixty-eight patients were included in this study: 1009 had ENT disorders, 978 dysmenorrhoea, and 2081 musculoskeletal pain.

The characteristics of the 4068 patients analysed are presented in Table 1. Patients in the musculoskeletal pain (MSP) group were older than in the two other groups, and within this group, women were older (mean 53 years old) than men (mean 46 years old, $p < 0.01$).

Premature study termination, lost to follow-up

Nine hundred and seventy patients stopped treatment before the prescribed duration had elapsed: 716 (17.6%) because of treatment efficacy, 74 (1.8%) because of inefficacy, and 158 (3.8%) for adverse events. Twenty-two patients (0.5%) were lost to follow-up. Their distribution according to diagnostic group is shown in Table 2.

Risk factors

There were more patients with a previous history of gastrointestinal disorders, of current use of medication increasing gastrointestinal risk, or of concomitant disease in the group with MSP than in the ENT or dysmenorrhoea patient group (Table 3).

Duration and dose of treatment (Table 1)

The median duration of prescribed treatment was 8 days overall, which was the same as the median

Table 1 — Characteristics of the patients in the study

	ENT	Dysmenorrhoea	MS pain
Number of patients	1009	978	2081
Mean age (range)	38.8 (13–83)	30.3 (13–60)	49.7 (16–93)
Female sex (%)	52.9	100	53.6
Indication	Tonsillitis 50% Sinusitis 39% Otitis media 10%		Osteoarthritis 50% Trauma 25% Tendinitis 23%
Mean daily dose			
Prescribed	3.7 tablets*	3.6 tablets*	3.6 tablets*
taken	3.4 tablets*	3.1 tablets*	3.3 tablets*
Median duration of treatment	7 days	5 days	10 days

ENT, ear nose or throat conditions; MS pain, musculoskeletal pain.
*Tablets were 25 mg.

Table 2 — Reasons for premature treatment discontinuation: number of patients (% of patient group)

	ENT	Dysmenorrhoea	MS pain	All
Early improvement	193 (19%)	236 (24%)	287 (14%)	716 (18%)
Inefficacy	13 (1.3%)	9 (1%)	52 (2.5%)	74 (2%)
AE	32 (3.2%)	14 (1.5%)	112 (5.5%)	158 (4%)
LFU	5 (0.5%)	8 (0.8%)	9 (0.4%)	22 (0.5%)

ENT, ear nose or throat conditions; MS pain, musculoskeletal pain; AE, adverse event; LFU, lost to follow-up.

Table 3 — Distribution of risk factors: number of patients with one, two, or three factors for gastrointestinal adverse events

	ENT	Dysmenorrhoea	MS pain	All
None	961 (95%)	965 (99%)	1829 (88%)	3755 (92%)
One	43 (4%)	12 (1%)	219 (11%)	274 (7%)
Two	4	1	29 (1%)	34
Three	1		4	5

ENT, ear nose or throat conditions; MS pain, musculoskeletal pain.

duration of reported treatment. Treatment was longer for patients with MS pain (10 days), than for those with ENT conditions (7 days), or dysmenorrhoea (5 days).

The mean prescribed dose was 3.6 tablets/days, i.e. 90 mg/day, and the mean reported dose was 3.25 tablets/day, i.e. 81 mg/day. The mean cumulated use of the drug was 34 tablets (850 mg) in MS pain patients, 24 (600 mg) in ENT patients, and 18 (450 mg) in dysmenorrhoea patients ($p < 0.01$, MS versus ENT, D, and D versus ENT).

Clinical safety

The incidence and type of adverse events are shown in Table 4, from the 4046 patients who completed the study. Of these, five were admitted to hospital (serious events according to regulations). Two hospital admissions were preplanned, one for an orthopedic operation, the other for cancer chemotherapy. The three other admissions were for: an asthma attack in an asthmatic patient treated for sinusitis with a history of previous uneventful use of NSAIDS including ketoprofen; angina pectoris

Table 4 — Adverse events (AE) in 4068 patients taking ketoprofen 75–150 mg daily

	ENT	Dysmenorrhoea	MS pain	All
Number of patients with at least one AE, and 95% CI*	82/1009 8.1% (6.4–9.8%)	50/978 5.1% (3.7–6.5%)	285/2081 13.7% (12.2–15.2%)	417 10.3% (9.3–11.2%)
Number of AE	104	60	386	550
Gastrointestinal AE	87 in 70 pts 6.9% (5.4–8.5%)	37 in 33 pts 3.4% (2.2–4.5%)	296 in 238 pts 11.4% (10.1–12.8%)	420 in 341 pts 8.4% (7.5–9.2%)
CNS AE	5	12	44	61
Skin AE	4	4	26	34
Other	8	7	20	35

ENT, ear nose or throat conditions; MS pain, musculoskeletal pain.
*$p < 0.01$, MS versus ENT versus dysmenorrhoea.

Table 5 — Severity of side-effects, as assessed by investigators

	Severity		
	Mild	Moderate	Severe
GI AEs	184	186	49
CNS AEs	30	24	7
Skin AEs	20	10	4
Other AES	13	17	3
All AEs	247	237	63

Severity was assessed on a three-degree-scale, according to impact of AE on daily activities.

in a smoking 42-year-old female patient on oral contraceptives, where the hospital discharge summary related the chest pain to oestrogen- and tobacco-related coronary spasm; and severe low back pain (treatment ineffectiveness). None of these events were thought to be related to ketoprofen by the physician.

Five hundred and fifty adverse events were noted in 417 patients. None was unexpected or unlabelled.

The incidence of AE was significantly higher ($p < 0.001$) in patients with MS pain than in the two other groups, and significantly lower in patients with dysmenorrhoea.

As expected, most reported AE concerned the gastrointestinal tract (76% of AEs). Gastralgia (63% of 420 gastrointestinal AE) was the most frequent, followed by nausea and vomiting. Four cases of black stools were reported, by patients with no previous history of digestive disease, or concomitant therapy. Though there was no objective proof of bleeding and no endoscopy was performed, they occurred in a context of gastralgia or diarrhoea, which suggests gastrointestinal bleeding. All cases resolved uneventfully with (three cases) or without stopping therapy. Only one of the cases was rated as severe by the physician. Severity of adverse events, as assessed by the investigators, is given in Table 5. Central nervous system events were mainly vertigo and headache, four of which were judged to be severe. Of the skin events, four were considered severe, three being itching, and the fourth a case of eczema accompanied by asthma. Three allergic events were considered severe: one case of Quincke's oedema in a patient with a known allergic history, and two of asthma (see above).

The average duration of therapy until occurrence of an AE was 3.3 days and was similar in the three groups. The relationship to treatment as assessed by investigators, is shown in Table 6.

Table 6 — Relationship of adverse events with treatment, as assessed by investigators

	Relation to therapy				
	Unknown	None	Possible	Probable	Highly probable
GI AEs	11	11	134	142	121
CNS AEs	12	12	24	9	4
Skin AEs	1	5	16	5	7
Other AEs	5	17	3	5	5
All AEs	29	45	177	161	137

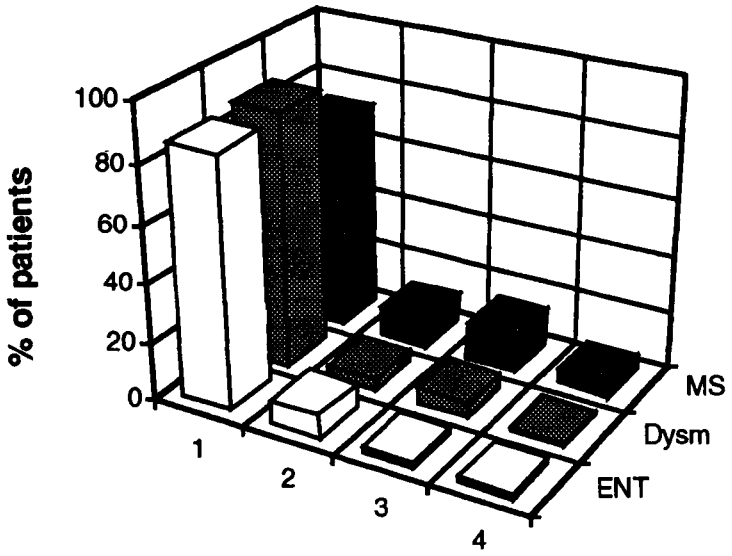

Fig. 1 — Results of Global Clinical Impression. 1, Marked or average therapeutic effect without AE; 2, marked or average therapeutic effect with AE; 3, minor or no therapeutic effect/worsening without AE; 4, minor or no therapeutic effect/worsening with AE. ENT, ear, nose or throat condition; Dysm, dysmenorrhea; MS, musculoskeletal pain

Risk factors

The following factors were found to play a statistically significant role as risk factors for the occurrence of AEs:

- Age ($p < 0.01$)
- Previous history of gastroduodenal ulcer or hiatal hernia ($p < 0.01$)
- Concomitant disease at inclusion, such as gastroduodenal ulcer, renal, hepatic, or cardiac insufficiency ($p = 0.016$)
- Concomitant therapy with treatments where warnings are mentioned in the case of co-prescription with ketoprofen or other NSAIDs ($p < 0.01$)
- Longer duration of therapy ($p < 0.001$)

Sex and daily doses (within the range of doses used) were not significant risk factors in this study.

These results account for the higher incidence of AEs in the MS pain group, where the mean age is higher, mean duration of therapy is longer, and medical history, concomitant diseases and therapy are more frequent.

The additional analysis of risk factors by logistic regression confirmed the role of the indication for therapy, the duration of treatment and the presence of concomitant therapies. In this analysis, age plays a role only for GI AEs.

Efficacy

The analysis of the Global Clinical Impression scores is shown in Fig. 1. The proportion of patients reporting a marked or average effect was lower in the MS pain group, where the conditions are more chronic and perhaps more severe.

DISCUSSION

This study was open-label and non-comparative, destined to test the effects and safety of ketoprofen used in a self-medication-like setting, i.e. in the symptomatic treatment of painful and febrile conditions. It was not used for its anti-inflammatory properties, and it was used at low doses and for short periods of time, conditions that should minimize the risk of severe adverse events. The main risks of this class of products are related to their gastrointestinal side-effects, which are dose-related, and to immunoallergic symptoms, not including asthma exacerbation, which is thought to derive from prostaglandin cyclooxygenase inhibition, and would therefore also be dose-dependent.

The study was designed to maximize the identification and reporting of AE, and gather evidence for risk factors. The inclusion and exclusion

criteria were chosen so that the population studied would be as representative of the intended target population for the drug as possible, conforming to recommendations.[5] The results of this study should represent the worst of what could be expected from the real-life use of the product, especially with a view to self-medication use.

The methodology was designed to minimize loss to follow-up, in order to ensure the reliability and pertinence of the information. This resulted in 22 lost to follow-up (LFU) in a population of more than 4000 patients, i.e. less than 0.5%, while a LFU ratio below 5% is considered an indicator of a good-quality clinical trial.[6]

Patient compliance monitoring showed that the patients took the drug for approximately the length of time the physician had prescribed it, but tended to take a little less than prescribed. Savage *et al.*[7] also found that only 6% of patients on ketoprofen exceeded the recommended maximal maintenance dose (as opposed to, e.g. 12% for diclofenac, or 25% for indomethacin). Keeping to the prescribed doses has two implications: (i) it is probably indicative of drug efficacy. If the drug had not been effective, it can be predicted that patients would tend to take more than prescribed, rather than less; (ii) it is an indicator that the findings of this trial will hold in general use of the drug: since side-effects of NSAIDs are for the most part dose-dependent, it is satisfying that patients tend to take less, rather than more of the drug than prescribed.

In this study, the overall incidence of adverse events was 10.3%. It reached almost 14% in patients treated for musculo-skeletal pain (mostly arthritic or traumatic), who were older, had more previous medical history, more associated treatments, and took the drug for longer than ENT or dysmenorrhoea patients. The latter had only 5% AE, were the youngest overall, and had the shortest treatment duration. This is similar to the frequencies of adverse events with ibuprofen, a widely available OTC NSAID: in large phase IV studies the range of gastrointestinal adverse events ranged from 2% to above 30%. The overall incidence of AEs in more than 45,000 patients was 7% (95%CI 6.7–7.4%).[8] In these studies,[8] the incidence of GI adverse events was 5% (95%CI 4.7–5.3%). This is lower than in the present study, but the authors rightly underline that these studies were not designed primarily to study adverse events. In 26 clinical trials of single-dose ibuprofen (400 mg), there was a 22% incidence of AE, 60% of which were gastrointestinal. In the present study, if one interprets that all four cases of black stools were indeed GI bleeds, the incidence is 0.1% (0.002–0.2%) versus 0.02% (0.01–0.05%) in the phase IV studies of ibuprofen with the same restriction on how GI bleeding was diagnosed.

In case–control studies of the association between gastrointestinal bleeding and various NSAIDS, ketoprofen at anti-inflammatory doses seems to be among the midline NSAIDS, with OR of 2.6,[9] 3.6,[10] 3.1,[11] and 2.4,[7] comparable to drugs such as diclofenac or naproxen, though one study[12] found a higher OR, of 23.7. The OR for ketoprofen is similar or lower than that for aspirin even taken occasionally: 3.1 (95%CI: 2.1–4.8) found by Langman *et al.*,[12] 3.3 (2.1–5.0) by Kaufman *et al.*,[13] 4 (1.9–8.7) by Bégaud *et al.*,[14] and 3.1 (1.8–5.1) by Savage *et al.*[7] (if the aspirin dose was above 300 mg). Studies that tested it found a dose-related risk,[11–13] with an approximate halving of the risk between medium and low-dose NSAIDs. This is also true for ibuprofen, which has a low OR when taken at analgesic doses as is usual, but whose OR is comparable to that of the other NSAIDs when taken at anti-inflammatory doses.[11]

All these reports indicate that ketoprofen at anti-inflammatory doses is as safe as most NSAIDS including aspirin, and therefore should be even safer at low doses.

The incidence of AEs, and especially of gastrointestinal adverse events, is linked to known risk factors such as age, indication for therapy, and duration of therapy, which were also found in most of the above-mentioned studies.

In over 4000 patients, we found no unexpected (i.e. previously unknown) adverse events, which was not an unexpected finding considering the fact that this drug has been in use for a number of years, without any significant safety problems, at much higher doses than those used here.

This study has fulfilled its aims, of demonstrating that in general practice, when used at low doses for analgesia, ketoprofen is safe and apparently effective. The drug was used as prescribed, with no tendency on the patients' part to increase doses or duration of treatment, another harbinger of future safety. The validity of these results is strengthened by the very low number of patients lost to follow-up, which is methodologically satisfactory in this type of study. If ketoprofen 25 mg was used OTC, one could reasonably expect a similar safety profile.

CONCLUSION

This open multicentre study was performed in order to assess the safety and prescription patterns of ketoprofen used as an analgesic at a daily dose usually between 75 mg and 100 mg for 5 to 15 days in general practice. Among more than 4000 patients analysed, overall 10.3% presented one or more adverse events, with a higher incidence in the musculoskeletal pain group (13.8%) than in the ENT conditions group (8.2%) or in the dysmenorrhea group (5.2%). The most frequent AEs concerned the gastrointestinal system, but no serious AE of this nature was reported. Some risk factors were confirmed, such as age, duration of therapy, medical history, concomitant disease and associated medications.

Overall, ketoprofen 25 mg used as an analgesic in general practice can be considered as safe, well tolerated and effective.

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