

## Adverse drug reactions caused by ketorolac off-label use in Italy

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As a result of many reports of serious adverse reactions, above all at a gastrointestinal level, and of some fatal cases, the safety profile of ketorolac has been under investigation for several years. In 2002 the Italian Ministry of Health decided to limit the therapeutic indications of this drug to the short-term treatment of acute post-surgery pain of a mild-serious degree and to the treatment of renal colic pain. Also the regimen of delivery of ketorolac-based medicines was modified from repeatable to non-repeatable prescription. In 2005 also the European Medicines Agency (EMA) analyzed the safety profile of different NSAIDs and documented scientific evidence of higher gastrointestinal risk in patients treated with ketorolac, as compared to users of other NSAIDs, mainly in countries with a widespread off-label use of this drug. EMA concluded that the benefit/risk profile of ketorolac is positive only for short-term use in authorized therapeutic indications (post-surgery pain and renal colic) and the treatment should be started in hospital. Accordingly, the Italian Medicines Agency (AIFA) has started an information campaign among physicians, to ensure an appropriate use of the drug.

The aim of this study was to evaluate the adverse drug reactions (ADRs) related to ketorolac according to both on- and off-label use. All the suspected cases recorded in the Italian pharmacovigilance database up to November 2014 and associated with ketorolac were retrieved. Individual case evaluation based on duration of treatment, dose or route of administration was conducted in order to identify the off-label use of ketorolac. Moreover, an analysis of the inappropriate use of ketorolac and the number of hospitalizations, which could potentially be ascribed to such inappropriate use, was conducted using Caserta local health unit record linkage database ('Arianna database'), covering a population of around 1 million persons, from 2002 to 2013.

Up to November 2014, 847 reports of ADRs related to ketorolac use were retrieved in RNF. Of these reports 292 (35%) were certainly related to an off-label use of ketorolac. In 51% of cases the reaction was reported as serious and this percentage rose to 57% for intramuscular use. We noted that the duration of treatment exceeded the maximum authorized treatment time both for intramuscular administration (47% of reports above 2 days limit) and oral administration (34% of reports above 5 days). As regarding the intravenous route only 19% of ADR reports were above the authorized treatment time. Alternative routes of administration are indicated in RNF, such as sublingual and subcutaneous. Besides, we noticed a higher incidence of serious cases in off-label rather than in on-label use. Gastrointestinal ulcers, hemorrhagic events, renal impairments and liver damages are more frequently reported with off-label use of ketorolac. The analysis of Arianna database showed that among 61,910 patients treated with ketorolac during the study period, the treatment was off-label for indication of use in 35,489 cases (57%) and for duration of treatment in 2,240 cases (4%). Patients were hospitalized for upper gastrointestinal bleeding in 81 cases. This study showed that the off-label use of ketorolac is widespread in our country. The seriousness of ADR reports increased, especially in case of prolonged duration of treatment. These findings led AIFA to send a dear doctor letter to healthcare professionals on April 2015, in order to sensitize physicians to ketorolac use at the minimum effective dose for the shortest possible time. Serious adverse reactions could be avoided if physicians are aware of this risk.