
GENERAL

**SAFETY OF ORAL IBUPROFEN – ANALYSIS OF DATA
FROM THE SPONTANEOUS REPORTING SYSTEM IN POLAND****ERNEST KUCHAR^{1*}, STANISŁAW HAN², KATARZYNA KARŁOWICZ-BODALSKA²,
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Abstract: Ibuprofen is a popular over-the-counter, non-steroidal anti-inflammatory medication, frequently used for the relief of fever, headaches, menstrual and other minor pains as well as a major active ingredient in numerous cold preparations. We analyzed sales volume and data obtained from the monitoring of spontaneous reports on the adverse effects of IBUM soft capsules, IBUM Forte soft capsules, and IBUM oral suspension 100 mg/5 mL collected by the manufacturer (PPF HASCO-LEK S.A. Wrocław, Poland) and National Monitoring Center in Warszawa in the period between October 2002 and June 2012. A total of 19,644,797 units of IBUM soft capsules 200 mg, 5,678,164 units of IBUM Forte soft capsules 400 mg and 4,333,325 units of IBUM oral suspension 100 mg/5 mL (29,656,286 units altogether) produced by PPF HASCO-LEK S.A. Wrocław, Poland were marketed during the period analyzed. There were 5 spontaneous reports regarding these medications registered in Poland in the period analyzed. Forms of oral ibuprofen are very safe medication rarely causing adverse effects; nevertheless, the existing spontaneous monitoring system of adverse effects in Poland is not sensitive enough to detect all adverse effects and needs improvement.

Keywords: pharmacoepidemiology, drug safety, pharmacovigilance, NSAID, adverse event

Abbreviations: COX – cyclooxygenase, FDA – Food and Drug Administration, NSAID – non-steroidal anti-inflammatory drug, OTC – over-the-counter

Ibuprofen, a propionic acid derivate, is a non-steroidal anti-inflammatory medication (NSAID) frequently used for the relief of fever, headaches, menstrual and other minor pains.

Patented in 1966, it was launched as a treatment in Great Britain by Boots Group in 1969 as Brufen (1). The patent's expiration in 1985 brought many generic drugs to the market.

At present, ibuprofen is one of the most widely used analgesics, anti-pyretics and anti-inflammatory drugs. It probably ranks after aspirin and paracetamol on the non-prescription over-the-counter (OTC) sale, although the patterns of use of these analgesics vary considerably from country to country (2).

Ibuprofen is a non-selective cyclooxygenase enzyme (COX) inhibitor, which inhibits COX-1 iso-

form responsible for physiologic action and COX-2 isoenzyme stimulated by the inflammation process. The COX enzyme catalyses the conversion of arachidonic acid to messenger molecules in the inflammation process: prostaglandins and thromboxane (2).

The most common adverse effects of oral ibuprofen are: dizziness, epigastric pain and heartburn. Adverse reactions such as nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, hematemesis, ulcerative stomatitis, gastritis exacerbation of colitis and Crohn's disease have also been reported following ibuprofen administration. Adverse effects such as pancreatitis, hypersensitivity reactions and various type of rashes have also been reported very rarely. Data from epidemiological sources and from a large

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number of controlled clinical trials performed in comparison with the newer coxib class of NSAIDs has shown that ibuprofen is amongst the NSAIDs with the lowest risk of serious gastrointestinal events (i.e., peptic ulcer bleeds etc.) (3).

Post-marketing surveillance using tools such as the data mining of spontaneous (passive) reports and the investigation of case reports to identify adverse drug reactions are very important in drug safety monitoring. Spontaneous reporting of suspected Adverse Drug Reactions (ADR) is well established as the most effective method of discovering possible new adverse reactions after medicinal products have received market approval.

PPF HASCO-LEK S.A. manufactures medicinal products with ibuprofen in the form of soft capsules (IBUM soft capsules 200 mg, IBUM Forte soft capsules 400 mg) as well as oral suspension (IBUM oral suspension 100 mg/5 mL). IBUM medicinal products have been on the Polish pharmaceutical market since October 2002. The manufacturer, as the Marketing Authorization Holder (MAH), has a pharmacovigilance system at his disposal, which is based on current EU legislation. As part of the pharmacovigilance system, the MAH monitors spontaneous reporting i.e., adverse reaction reports submitted by healthcare professionals and patients or their carers and world literature. PPF HASCO-LEK S.A. works closely with the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products based in Warszawa, which is the National Monitoring Centre in Poland. For new drugs, the monitoring actions aim to detect adverse reactions and interactions as well as groups of patients with a more frequent occurrence of adverse reactions.

Since no amount of pre-clinical and clinical data is sufficient to conclude the complete safety of a drug, it is necessary to report any adverse reaction of any pharmaceutical product to assess its safety to ensure patient health, which is the rationale of our study.

The identification of new, unknown adverse effects of oral ibuprofen and analysis of the safety of oral ibuprofen marketed by HASCO-LEK (IBUM soft capsules 200 mg, IBUM Forte soft capsules 400 mg, and IBUM oral suspension 100 mg/5 mL).

MATERIALS AND METHODS

We analyzed data obtained from the monitoring of spontaneous reports on adverse effects of IBUM soft capsules, IBUM Forte soft capsules, and IBUM oral suspension 100 mg/5 mL collected by

the manufacturer (PPF HASCO-LEK S.A. Wrocław, Poland) and National Monitoring Centre in Warszawa and sales volumes in the period from October 2002 to June 2012.

RESULTS

A total of 19,644,797 units of IBUM soft capsules 200 mg, 5,678,164 units of IBUM Forte soft capsules 400 mg and 4,333,325 units of IBUM oral suspension 100 mg/5 mL (29,656,286 units altogether) produced by PPF HASCO-LEK S.A. Wrocław, Poland were marketed during the period analyzed.

There were 5 spontaneous reports regarding medications registered in Poland in the period analyzed.

1. An adult male reported a heavy burning sensation in his mouth as well as edema and irritation of the throat after chewing the IBUM Forte capsule, which is not recommended by the manufacturer. The symptoms subsided within about 20 min after gargling with water.
2. A 38-year old male complained of a burning sensation on his tongue after he tasted the IBUM oral suspension to check its taste.
3. An adult female complained of a burning sensation on her tongue after she tasted the IBUM oral suspension to check its taste.

The two above mentioned reports were received shortly after the manufacturer changed the color of the IBUM oral suspension from pink to white, which triggered anxiety in parents of child consumers.

4. A 6-year old girl weighing 24 kg developed generalized itching and a rash, prominently on her buttocks, knees and elbow folds after she had been administered IBUM oral suspension at a daily dose of 30 mL (i.e., 600 mg; 25 mg/kg) for 4 consecutive days. The girl was found to be allergic to the drug.
5. A 4-year old boy weighing 11 kg, developed generalized urticaria (hives) shortly after a single 5 mL dose of the IBUM suspension given for fever. The boy was found to be oversensitive to NSAIDs.

DISCUSSION

Following the thalidomide tragedy in 1961, the WHO pursued measures aiming at the prompt detection and publication of information relating to unknown and poorly understood adverse effects, which, in 1978, contributed to the creation of a

worldwide pharmacovigilance network that now includes more than 130 countries, known as the WHO Programme for International Drug Monitoring with its headquarters in The Uppsala Monitoring Centre, Uppsala, Sweden (4). Therefore, in most countries worldwide, drug-related adverse reactions are monitored in order to increase the safety of pharmacological therapy. A new field of science, called pharmacovigilance, came into being (5). As part of clinical trials preceding the launch of a drug, the most frequent adverse reactions are detected. Due to the number of subjects, very rare adverse effects with a frequency lower than 1 : 10,000 are hardly detectable. Antihistamine drugs used to treat common allergies are ubiquitous remedies administered in millions of patients worldwide annually. With such extensive drug use, extremely rare adverse events, even those < 1 per million, are unavoidable. Detecting these rare events is the issue to be addressed in the studies. Due to practical and financial reasons, active surveillance of millions of patients is not viable, thus pharmacovigilance is based on the analysis of spontaneous reports from healthcare professionals and consumers. The assessment of the frequency of rare adverse events is based on an equation with a numerator – the number of events – and a denominator – the number of therapies. The problem is that not all adverse reactions are reported, which results in decreased sensitivity and difficulties assessing the number of treatments. In practice, the surrogate for the number of therapies is the number of drug packs available on the market. Another issue is the difficulty establishing drug use causality (effect or coincidence), especially in the case of concomitant drug use as discussed in the report analyzed herein. In general, a causal relationship depends upon the nature and amount of evidence supporting an attribution hypothesis, such that “medication X causes adverse effect Y”. X can be a sufficient cause of Y, meaning that X is always followed by Y; or a necessary cause, meaning that Y cannot occur without being preceded by X; or both. These deterministic concepts are not relevant to pharmacovigilance. No drug is a sufficient cause of any adverse effect, and there are no examples of necessary causes either. The trigger for modern pharmacovigilance, thalidomide, has come close to being considered a necessary cause of a congenital defect, phocomelia, but this is not true. Phocomelia is very rare in the absence of thalidomide but does happen; x-irradiation is one example of another cause (6).

Pharmacovigilance in action is essentially Bayesian: a tentative prior probability for a hypothesis becomes modified up or down as further evi-

dence is obtained, to become a posterior probability for new consideration. Such evidence may come from different sources and also the overall view of the data may use different logic. Individual case reports can provide excellent evidence on attribution in one or more specific patients (6)

Among the reported cases, the first one occurred due to medical error connected with the incorrect administration of IBUM Forte soft capsules 400 mg. A soft capsule is a pharmaceutical form, which encloses medicines in a relatively stable shell allowing them to be taken orally. It should be swallowed not chewed by patients. Irritation connected with the drug crushed in the mouth can be connected with a relatively high concentration of the active substance or other ingredient, but it can also be a hypersensitivity reaction to one of the ingredients. Two registered reports from suspicious parents of a burning sensation on the tongue after tasting IBUM oral suspension were received shortly after the manufacturer changed the color of the drug from red to white (a colorant had been removed). The color change could have triggered anxiety in parents, who reported their own taste sensation.

Two reported adverse reactions connected with skin and soft tissue disorders were assessed as hypersensitivity reactions due to ibuprofen use. These cases were non-serious reactions.

Assessment of the occurrence probability of the reported reactions described above after ibuprofen administration shows ibuprofen as a possible cause according to WHO criteria (4).

Ibuprofen rarely causes skin-related adverse reactions, especially fixed drug eruptions (7). However, in the literature there were described either general drug eruption like in one reported case or urticaria in another one. Shelley and Shelley (8) described 4 cases of ibuprofen urticaria, which have been observed in 3 adults and a 14-year old girl. Diaz Jara et al. (9) reported urticaria after 120 mg of ibuprofen administration to 7-year old boy in the treatment of a headache.

According to data from clinical trials, ibuprofen is believed to have a very good clinical safety profile. In large randomized controlled clinical trials in which 83,915 children participated, adverse events were only observed in 79 children among 54,785 treated with ibuprofen. The following was noted: abdominal pain in 4 children, asthma in 44 children, multiforme erythema in 3 children, leucopenia in 8 and gastritis in 20 (10). FDA acknowledge ibuprofen as a very safe NSAID (11).

In the 18-year period, a total of 5,042 adverse event reports were received for ibuprofen from the

USA. Of these, 768 (15.2%) were serious. Clinically significant reports, such as GI bleeding and perforation (71 cases) were infrequent over the 18-year reporting period for the US population, which is estimated at 300 million. Of the 324 serious GI reports received during this 18-year period, death was noted in four, presumably due to GI bleeding. Two decades of post-marketing experience in the United States have established that the reporting frequency of serious GI events remained consistently low during this time, suggesting that ibuprofen, which is available over-the-counter, is well tolerated in the general population (11).

Analyzing all safety signals reported in nearly 10-years of marketing of IBUM drugs in Poland allows us to estimate that oral ibuprofen is a safe medication. But only 5 cases of adverse reactions reported against almost 30 million treatments might be a signal of the low sensitivity of the existing monitoring system. According to the FDA data transferred into the Polish population, few reports of adverse reactions are expected annually. Similarly, in the RxISK electronic database (<https://www.rxisk.org/Default.aspx>) only 20,590 reports were found where ibuprofen was the suspected drug, covering 78,271 reactions. The main reason for the small number of reports received might be due to medical practitioners' poor awareness of the importance of all safety signals, including all well-known and common adverse reactions.

The weakness of this paper is that it is based on passive adverse event reports and its strength is almost 10- years of observation of the entire Polish population.

Forms of oral ibuprofen are very safe rarely causing adverse reactions. The scarce number of safety reports shows that the existing spontaneous monitoring system in Poland seems not to be sensitive enough to detect all adverse effects and needs improvement.

Conflicts of interest

Ernest Kuchar has received funding or honoraria for lectures, conference attendance, or consultancy from a number of pharmaceutical companies including PPF HASCO-LEK S.A. Stanisław Han is the President of the Management Board of PPF HASCO-LEK S.A. Katarzyna Karłowicz-Bodalska is a Research Director in PPF HASCO-LEK S.A. Elżbieta Kuttycka is a Pharmacovigilance Department Manager in PPF HASCO-LEK S.A.

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Received: 26. 08. 2013