Safety of Oral Paracetamol – Analysis of Data from a Spontaneous Reporting System in Poland

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INTRODUCTION

Paracetamol (acetaminophen), an active metabolite of phenacetin, is probably the most popular over-the-counter antipyretic and analgesic used in Poland. First introduced to the market in 1878 in Germany, it was quickly displaced by phenacetin and aspirin, but attracted new attention in the late 1940s when David Lester and Leon Greenberg found that paracetamol is a major acetanilide metabolite responsible for its analgesic properties and did not cause methemoglobinemia [1]. Squibb introduced paracetamol to the American pharmaceutical market in 1950 under the name Trigesic, then Apamid by Ames (Dome) in 1952 and Tylenol by McNeil in 1955 were introduced [2]. Now paracetamol is sold in almost every country worldwide with annual production exceeding 15,000 tons [3].

Paracetamol has analgesic and antipyretic properties comparable to those of aspirin and other non-steroid anti-inflammatory drugs (NSAIDs), but its peripheral anti-inflammatory activity is very limited. The action mechanism is not completely understood. The drug inhibits cyclooxygenase type 2 (COX-2) and its metabolites e.g. NAPQI and acts as an agonist of TRPA1-receptors in the spinal cord, which suppresses the pain transduction [4,5].
Paracetamol is commonly used for the relief of headaches and other minor pains and is a major active ingredient in numerous cold preparations.

Adverse effects of paracetamol are rare, but hypersensitivity including skin rash may occur. There have been reports of blood dyscrasias including, thrombocytopenia, neutropenia, pancytopenia, leukopenia and agranulocytosis, but these were not necessarily related to paracetamol [6,7].

Post-marketing surveillance using tools such as data mining of spontaneous (passive) reports and the investigation of case reports to identify adverse drug reactions are very important in drug safety monitoring.

PPF HASCO-LEK S.A. manufactures medicinal products with paracetamol in the form of tablets (Paracetamol HASCO coated tablets 500 mg) and oral suspension (Paracetamol HASCO oral suspension 120 mg/5 ml). These medicinal products have been available on the Polish pharmaceutical market from November 2000. The manufacturer, as the Marketing Authorisation Holder (MAH), has a pharmacovigilance system at their 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 SA cooperates closely with the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products based in Warsaw, which is the National Monitoring Center in Poland. The monitoring actions aim to detect new drug adverse reactions and interactions as well as groups of patients with more frequently occurring 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 to any pharmaceutical product to assess its safety to ensure patient health and this is the rationale of our study.

METHODS

This study identified new, unknown adverse effects of oral paracetamol and the analysed the safety of oral paracetamol produced by Hasco-Lek, Poland (Paracetamol HASCO coated tablets 500 mg, Paracetamol HASCO oral suspension 120 mg/5 ml).

We analyzed sales volume and data obtained from monitoring spontaneous reports on adverse effects of paracetamol HASCO coated tablets 500 mg and paracetamol HASCO oral suspension 120 mg/5 mL collected by the manufacturer (PPF Hasco-Lek S.A. Wroclaw, Poland) and National Monitoring Center in Warsaw in the period between November 2000 and June 2012. The Polish system is based on written reports voluntary submitted by healthcare professionals.

RESULTS

A total of 45,694 units of paracetamol HASCO coated tablets 500 mg and 6,048,289 units of the oral suspension (120 mg/5 mL) produced by PPF HASCO-LEK S.A. Wroclaw, Poland were marketed during the period for which data were analyzed.

There were 4 spontaneous reports regarding these medications registered in Poland in the period analyzed:

1. A 67-year old woman received 500 mg of paracetamol during post-operative pain management. A rash and itching were observed shortly afterwards.

2. A 21-month old boy weighing 12kg developed generalised oedema of his soft tissues including his eyes, face and trunk (angioedema or Quincke's oedema) after the boy had been given paracetamol HASCO oral suspension (7.5 mL of suspension i.e. 180 mg; 15 mg/kg) for fever on the third day of chickenpox. The oedema responded well to steroid treatment.

3. A 58-year old woman received 2.0 g of paracetamol tablets during post-operative pain management. She complained of itching (without a rash).

4. A 28-year old woman presented with vomiting of blood (hematemesis) after she had taken 4.0 g of paracetamol tablets and 200mg of ketoprofen, an NSAID medication used for menstrual pain. She required hospitalisation. The adverse effect was most likely due to ketoprofen, but a causative relationship with paracetamol cannot be excluded completely.

DISCUSSION

Following the thalidomide tragedy in 1961, the WHO pursued measures aiming at the prompt detection and publication of information relating
Paracetamol is a widely used agent with an excellent safety record and adverse effects are rare. However, in a few patients, skin and respiratory symptoms, immediate urticaria, angioedema, fixed drug reactions and allergic and non-allergic anaphylactic reactions have been reported in both children and adults in association with paracetamol administration [10--12]. Most reactions to paracetamol occur in patients with non-allergic hypersensitivity to NSAIDs. Alternatively, reactions may result from an allergic hypersensitivity to paracetamol, with tolerance of NSAIDs [10]. According to Paracetamol tablets Product Characteristics [13] hypersensitivity and anaphylactic reactions including skin rash may occur very rarely. These were observed in our report in cases 1, 2 and 3 above. There have also been reports of blood dyscrasias including thrombocytopenia and agranulocytosis but these were not necessarily related to paracetamol.

The cases presented did not show any symptoms and signs of dyscrasias. Most reports of adverse reactions to paracetamol relate to overdosing with the drug due to a “narrow therapeutic window”, i.e., a small difference between therapeutic and toxic doses. Chronic hepatic necrosis has been reported in a patient who took daily therapeutic doses of paracetamol for about a year and liver damage has been reported after daily ingestion of excessive amounts for shorter periods. Nephrotoxicity following therapeutic doses of paracetamol is uncommon, but capillary necrosis has been reported after prolonged administration [6].

Angioedema is a known but very rare adverse effect of paracetamol. Panchabhai et al [14] presented a 4-year-old boy with a presumed viral infection who developed an allergic rash and angioedema in relation to paracetamol exposure. After he received 2 doses of syrup paracetamol (15 mg/kg/dose) within an hour, he developed oedema of the lips, along with massive dermal oedema, which initially involved the periorbital region and the face and later spread to the trunk and the limbs. Very similar symptoms were observed in our case. Bousseta et al [10] reported 25 cases of hypersensitivity in children after paracetamol treatment, including a single case of angioedema. An oral challenge to acetylsalicylic acid in this patient caused urticaria

Symptoms of paracetamol overdose in the first 24 h are pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion [13]. Case number 4, a 28-year-old woman presented with vomiting of blood but had no further symptoms of liver damage, so those symptoms should be attributed to ketoprofen, a drug belonging to NSAIDs, well known for their gastrointestinal side effects. The reported symptoms of adverse reactions should thus be regarded as already known.
million therapies may suggest low sensitivity of the existing monitoring system, particularly since the large electronic drug safety RxISK database [https://www.rxisk.org/Default.aspx] also including consumer reports contains 32,671 reports where paracetamol was the suspect drug covering 122,914 reactions of which 19,861 do not specify the patient's country. The database includes 3.9 million reports submitted to the FDA's MedWatch from 1st January 2004 to 31st March 2012. About a third of these reports came from outside the United States and paracetamol-related reports accounted for 1.19% of all the reports.

The under-reporting of adverse effects may result from lack of awareness among medical professionals of the usefulness of any adverse drug-related data, including known and common adverse reactions.

Limitation of the study

The weakness of this paper is that it is based on passive adverse event reports and its strength is an approx. 12-year observation of the entire Polish population.

CONCLUSION

Forms of oral paracetamol are a safe medication rarely causing adverse effects. Only a few cases of known adverse effects were reported in the 12-year observation period after more than 6 million medication units were distributed. However, 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.

REFERENCES
