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Case Report

Fatal hypersensitivity reaction to an oral spray of flurbiprofen: a case report

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SUMMARY

What is known and objective: **Safety of the anti-inflammatory drug flurbiprofen is comparable with that of other non-steroidal anti-inflammatory drugs of the propionic acid class, which are commonly associated with gastrointestinal and renal side effects. Here we report a case of a fatal hypersensitivity reaction to an oral spray of flurbiprofen taken for sore throat.**

Case summary: **A 29-year-old man came to the emergency care unit reporting sore throat with an intense burning sensation associated with fever. Pharyngotonsillitis was diagnosed, and local treatment with oral flurbiprofen spray was prescribed. Immediately after using the spray, the patient experienced a severe reaction characterized by serious dyspnoea, followed by death. The cause of death was heart failure with acute asphyxia from oedema of the glottis. The cause of death was concluded to be hypersensitivity to flurbiprofen spray.**

What is new and conclusion: **Oral propionic acid derivatives have been associated with a relatively high frequency of allergic reactions. However, allergy to flurbiprofen has rarely been documented. Scientific literature reports two relevant cases of hypersensitivity reaction to flurbiprofen: in one case, a patient presented with a maculopapular rash 48 h after having taken oral flurbiprofen followed by angio-oedema and hypotension. In another case, a single oral dose of flurbiprofen caused itching and swelling around the eyes, redness and increased lacrimation. We describe, for the first time, a fatal case of hypersensitivity reaction to flurbiprofen oral spray. Hypersensitivity reactions to flurbiprofen are infrequent; however, health professionals should be aware of potential adverse reactions, even during topical administration as oral spray.**

WHAT IS KNOWN AND OBJECTIVE

Flurbiprofen, a phenylalkanoic acid derivative, is a chiral non-steroidal anti-inflammatory drug (NSAID) of the 2-arylpropionic acid class. Although it presents a chiral centre, with the S-(+)-enantiomer possessing most of the beneficial anti-inflammatory activity, both enantiomers may have analgesic activity and all flurbiprofen preparations to date are marketed as the racemate.[1,2] It is also an antipyretic, analgesic agent advocated for use in rheumatoid arthritis, degenerative joint disease, ankylosing spondylitis and similar conditions. Absorption of flurbiprofen is rapid and almost complete when administered orally.[1] In a number of pharmacological studies, it has been shown to be a potent and effective drug in the treatment of inflammatory conditions, including rheumatoid diseases.[3] Its systemic administration was approved by the United States Food and Drug Administration (US FDA) in 1988 for the treatment of rheumatoid arthritis and osteoarthritis. The drug is also used to treat the inflammatory affections of the oral cavity, pharynx and larynx.[4] Like other NSAIDs, flurbiprofen is commonly associated with side effects related to the gastrointestinal and renal systems. Reported adverse reactions include contact dermatitis,[5] delayed hypersensitivity[6] and cutaneous vasculitis.[7] Furthermore, a rare case of myocarditis due to hypersensitivity reaction caused by oral flurbiprofen has been also reported.[8] The global safety of flurbiprofen is comparable with that of ibuprofen and naproxen, and its gastrointestinal tolerance is considered better than that of aspirin and comparable with that of indomethacin, ibuprofen and naproxen.[3] Here we report a case of hypersensitivity reaction to flurbiprofen oral spray whose outcome was fatal.

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CASE SUMMARY

A 29-year-old man reported symptoms including tiredness, rhinorrhoea and sneezing for a month. At a later stage, the man reported sore throat with an intense burning sensation associated with fever (37·5 °C). For this reason, he went to the emergency medical care and pharyngotonsillitis was diagnosed. On the basis of the mild clinical symptoms, the physician suggested a local treatment with oral flurbiprofen spray plus, only if necessary, paracetamol suppositories and the antibiotic clarithromycin for oral use. The man went back home where he took only flurbiprofen, and immediately after using the oral spray, an acute and unexpected severe reaction characterized by dyspnoea occurred. He died before reaching medical assistance.

A post-mortem examination was performed. The external examination showed an intense congestion in the brachiocephalic area and subungual cyanosis of both hands and feet. Dissection highlighted no traumatic lesions; however, considerable oropharyngeal hyperaemia and hyperplasia of the tonsils and of the lymphoid tissue at the basis of the tongue were evident. The

pharynx mucosa was whitish, gelatinous and thickened; the volume of the uvula was doubled and the opening of the epiglottis constricted (diameter 0·5 cm). The larynx mucosa was also hyperaemic and oedematous; no alterations were found in the vocal cords. Paratracheal, parabronchial and parahilar lymphonodes were bilaterally hyperplastic. The trachea, bronchial airways and lungs showed pronounced oedema and congestion. The histological examination of small fragments extracted from the organs during autopsy showed oedema of the brain, chronic inflammation of the glottis, uvula and trachea, lymphoid hyperplasia and tonsil oedema.

The patient had no past history of allergies to food or drugs. The cause of death was heart failure with acute asphyxia from oedema of the glottis. Because no other drugs were taken, the concluding cause of death was hypersensitivity to flurbiprofen spray.

WHAT IS NEW AND CONCLUSION

Oral propionic acid derivatives have been associated with a relatively high frequency of allergic reactions, indicating a possible class effect. A case/non-case study from an Italian spontaneous reporting database seems to confirm the hypothesis that propionic acid derivatives are at a higher risk of inducing allergies compared with other non-steroidal anti-inflammatory drug classes.[9] Furthermore, a study in children showed that a large proportion of reactions associated with ibuprofen were based on an allergic mechanism.[10] However, true allergy to flurbiprofen has rarely been documented. A case of a patient who developed a maculopapular rash 48 h after beginning oral therapy with flurbiprofen, followed by angio-oedema and hypotension 2 days later, has been reported. Patch tests with flurbiprofen were positive 48 and 72 h after application. The clinical and allergic features of this case strongly suggest a type IV hypersensitivity-mediated local reaction.[6] More recently, another case of a hypersensitivity reaction to a single oral dose of flurbiprofen, characterized by itching and swelling around the eyes, redness and increased lacrimation, has been described.[4]

In our case, it was concluded that flurbiprofen was associated with death because of the temporal relationship between the use of the drug and the onset of respiratory symptoms, the absence of other major diseases or identified causative factors and other explanations for hypersensitivity reaction.

It is well known that spray formulations enhance absorption and bioavailability of flurbiprofen due to increased solubility and dissolution rate of the drug.[11,12] Therefore, the rapid onset of the reaction, in the case here reported, could have been due to the rapid absorption of the drug.

According to the Naranjo algorithm[13] (score 6 for this case), the causality relationship between the adverse reaction and the administration of the suspected drug was considered as probable.

In conclusion, hypersensitivity reactions to the anti-inflammatory drug flurbiprofen are rare; however, health professionals should be aware of potential adverse reactions to this drug, even when using topical administration such as a spray.

The above case report has been described according to the International Society for Pharmacoepidemiology and International Society of Pharmacovigilance's Guidelines for submitting adverse event reports for publication.[14]

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