1.1. Ibuprofen and Stevens Johnson Syndrome/Toxic Epidermal Necrolysis

Introduction

Ibuprofen (Brufen®, Nurofen®, Advil®, Spidifen®) is a propionic acid NSAID, widely used for the treatment of inflammatory disorders and as an analgesic. *Its indications include rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, tendonitis, burstis, pain after surgery or dental procedures, primary dysmenorrhoea, flu-like symptoms, tooth ache, headache, arthralgia and myalgia* [1,2].
In lower doses (200 mg and 400 mg) ibuprofen is available over-the-counter (OTC). In 2008, ibuprofen was prescribed in over 800.000 patients [3], however because its OTC availability, ibuprofen use may be significantly higher.
Stevens Johnson's syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are overlapping severe predominantly cutaneous syndromes mostly caused by drug hypersensitivity. Symptoms consist of bullous conditions and epidermal detachment affecting 10-20 percent of skin surface (SJS) to over 30% (TEN). Typically, mucosal surfaces are involved, whereas after remission ophthalmic lesions may develop progressively, leading to visual impairment. These conditions are mostly accompanied by fever, whereas, especially in TEN organs may be affected. Mortality ranges from 1-2 percent in mild SJS to over 25 percent for TEN [4].

Given the absence of SJS/TEN in most SmPCs [1,2,6-14] and the severity of this reaction and the OTC availability of ibuprofen, ibuprofen- related SJS/TEN is addressed in this quarterly report. Three reports, including two recent cases and an overview of the literature on this subject are presented.

Reports

On January 7, 2010 the database of the Netherlands Pharmacovigilance Centre Lareb contained two reports (Table 1) concerning Stevens Johnson Syndrome and one case of Toxic Epidermal Necrolysis associated with ibuprofen use.

Table 1. Reports of SJS and TEN associated with the use of ibuprofen.

Patient, Number, Sex, Age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug Outcome
A 91273 M, 12	ibuprofen flu-like symptoms 200 mg	not reported	Stevens Johnson Syndrome Corneal lesion	8 days discontinued recovered with sequel, corneal transplantation due to severely impaired vision
B 104512 F, 81	ibuprofen pain 200 mg	not reported	Toxic Epidermal Necrolysis	days death
C 51479 M,52	ibuprofen gout diclofenac gout 200mg	not reported	Stevens Johnson Syndrome	one day (ibuprofen), 5.5 weeks diclofenac discontinued one week prior to onset recovering

In the last six months, Lareb received two reports of SJS/TEN associated with ibuprofen use in an over-the-counter available dose (200mg). In both cases this condition resulted in either death or

far-reaching disability (blindness), needing further surgical treatment. Case A, reported by the father of the patient involved is well documented. Patient recovered partially and awaits corneal transplantation. Case B, reported by an internist, concerns an 81-year aged female with limited medical history (osteoarthritis and hypertension) who incidentally used ibuprofen after an uncomplicated fall. No concomitant medication was reported. Despite extensive immunosuppressive and supportive therapy, patient died during hospital admission.
Case C concerns a 52-year-old man who developed SJS one day after start of ibuprofen after a four and a half week period of diclofenac use. Given this short latency, a role for diclofenac or one of its metabolite may well be plausible.
The database of the Netherlands Pharmacovigilance Centre Lareb does not contain reports of SJS/TEN associated with other propionic acid derivates or reports in which erythema multiforme major (EEM), a condition previously considered to form part of the SJS/TEN spectre is mentioned.

Other sources of information

SmPC

Information on SJS and TEN in SmPCs for ibuprofen containing products is limited. Only in the SmPC for Spidifen®, these conditions are mentioned [4]. The Nurofen® SmPC mentions erythema multiforme [2], a condition previously considered to be part of the SJS/TEN spectre, however now generally regarded as a separate entity. However, it gives no information on SJS/TEN. In all other products information is limited to “skin rashes like urticaria, exanthema which can be both pruritic and non-pruritic” or “generalised hypersensitivity reactions” [6-14].

Literature

Four case reports describing ibuprofen related SJS/TEN have been published. Beside dermal symptoms, all patients (two, nine and ten-year old girls, a nineteen-year old female and a 44-year old male patient) experienced concomitant liver involvement, ranging from acute vanishing bile duct syndrome to acute hepatitis [15].
Furthermore *Mockenhaupt et al.* found in a case control study (scar database German, French, Italian and Portugese data between 1989 and 2005) an increased risk of SJS and TEN for ibuprofen (RR 4.3 [95% CI 1.2-25]), the highest risk of the non-oxicam, non-specific NSAIDS [16].
More recently *Dore and Salisbury* found fifteen cases of SJS/TEN or Erythema multiforme in children using ibuprofen, either as monotherapy (n=5) or in combination with azithromycin (n=6) or with other drugs (phenytoin (n=2), clarithromycin (n=1), cefixime (n=1) and clarithromycin (n=1) [17]. Ibuprofen as monotherapy or in combinations with these drugs accounted for 47% of the 32 cases of SJS/TEN and EM presented in this descriptive study of patients younger than fifteen years admitted to a tertiary care centre for burn lesions.
In other studies like the pooled analysis by *Levi et al*, which used combined SCAR and Euroscar data, and the database study by Mockenhaupt et al no such overrepresentation of ibuprofen was encountered [18;19].

Databases

Due to the limited number of reports of this association in the Lareb database, the reporting odds ratio (ROR) could not be calculated for SJS and TEN separately.
The number of reports and the ROR for the association between ibuprofen and SJS/TEN in the WHO database of the Uppsala Monitoring Centre are presented in Table 2.

Table 2. Reporting odds ratios of ibuprofen and SJS and ibuprofen and TEN in the WHO Pharmacovigilance database.

Drug and ADR	Number of reports	ROR (95% CI)
Ibuprofen and SJS	273	2.34 (2.07-2.64)
Ibuprofen and TEN	124	3.04 (2.55-3.64)

On April 18th, the Eudravigilance database contained 187 reports of Stevens Johnson Syndrome associated with use of ibuprofen, leading to seven deaths. Ages ranged from one to 85 years. Fifty-four persons were younger than sixteen years.

On April 18th, the Eudravigilance database contained 145 reports of toxic epidermal necrolysis associated with use of ibuprofen, leading to 17 deaths. Ages ranged from two to 93 years. Fifty persons were younger than sixteen years.

Prescription data

The number of patients using ibuprofen in the Netherlands is shown in table 3.

Table 3. Number of ibuprofen users in the Netherlands between 2005 and 2008 [3]

Drug	2005	2006	2007	2008
ibuprofen	848,546	835,030	838,320	823,800

Mechanism

Besides classical mechanisms which are postulated in the pathogenesis of SJS/TEN leading to keratinocyte injury leading to SJS/TEN, it is suggested that ibuprofen might be involved through non-COX dependent effects on apoptosis, leading to development of SJS/TEN [17].

Discussion

Stevens Johnson Syndrome and Toxic Epidermal Necrolysis associated with ibuprofen use have been reported three times to Lareb. Findings in literature on this association are contradictory. Although based on only one study, children may be at particular risk given a large percentage of ibuprofen users in the study by *Dore en Salisbury* [17]. These findings are reflected by a high prevalence of SJS/TEN in children in the findings in the Eudravigilance database in which children younger than fifteen accounted for 29 percent (SJS) and 35 percent (TEN). This numbers must be seen with some caution, since in clinical practice the distinction between SJS/TEN and EEM is not always clear and because of a relatively high background incidence of SJS/TEN secondary to infections in this age group. More generally, NSAIDs associated SJS/TEN is particularly prone to protopathic bias, since these drugs can be used to prodromal symptoms of an NSAID-independent SJS/TEN.

All cases presented to Lareb are medically confirmed and well documented. These cases must however be seen with caution. In one case (Case C), the short latency is not typical for SJS/TEN. This can be due to previous sensitisation during prior ibuprofen use, but casts doubt on the causality between ibuprofen use and the reaction in this specific report, especially due to prior use of diclofenac. In case B ibuprofen was used intermittently in a patient with plausible use of co medication given a medical history of hypertension and arthrosis. Given the chronic indication and age of the patient involved yearlong use of this drugs can be expected, which would make a causal relation with these drug less typical as well.

Despite all shortcomings of this quarterly report, attention for this association is needed given ibuprofen's over-the-counter availability, the possibly increased risk in children and the at best very implicit mentioning of SJS/TEN in the vast majority of ibuprofen SMPCs.

Conclusion

More information on ibuprofen related SJS/TEN is needed. Further attention for a possibly increased risk for SJS/TEN in children may be warranted.

- More information on this association is needed to determine whether the SmPC of ibuprofen or its OTC status must be changed.

References
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This signal has been raised on September 2010. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbgmeb.nl/cbg/en/default.htm or the responsible marketing authorization holder(s).