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Comparison of Reporting of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in Association with Selective COX-2 Inhibitors

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Abstract

Background: Stevens-Johnson syndrome and toxic epidermal necrolysis are closely related severe acute life-threatening, drug-induced skin disorders. The US FDA Adverse Events Reporting System (AERS) has received reports of Stevens-Johnson syndrome and toxic epidermal necrolysis associated with the use of the recently introduced selective cyclo-oxygenase (COX)-2 inhibitor NSAIDs, two of which are also sulfonamides.

Objective: The objective of this study is to review cases of Stevens-Johnson syndrome and toxic epidermal necrolysis reported to the FDA associated with the use of the selective COX-2 inhibitor NSAIDs celecoxib, rofecoxib and valdecoxib, and to compare reporting rates of the two conditions associated with these drugs to each other, meloxicam (an oxicam NSAID that came on the US market at a similar time) and the background incidence rate.

Methods: We reviewed all US cases of Stevens-Johnson syndrome and toxic epidermal necrolysis reported to the FDA AERS database associated with the use of celecoxib, rofecoxib, valdecoxib and meloxicam since these agents were first marketed. We utilised AERS and drug use data to calculate reporting rates for each drug after the first 2 years of marketing. We obtained the background rate from the medical literature.

Results: Up to the end of March 2004, there were 63 cases of Stevens-Johnson syndrome/toxic epidermal necrolysis reported with valdecoxib use, 43 with celecoxib, 17 with rofecoxib (the non-sulfonamide coxib) and none for meloxicam. In the first 2 years of marketing the reporting rate for Stevens-Johnson syndrome/toxic epidermal necrolysis with valdecoxib was 49 cases per million person-years of use, 6 cases per million person-years for celecoxib and 3 cases per million person-years for rofecoxib. The reporting rates for the sulfonamide coxibs were substantially higher than the background rate of 1.9 cases per million population per year, with the valdecoxib rate being 8–9 times that of celecoxib and approximately 25 times that of the background rate.

Conclusion: There is a strong association between Stevens-Johnson syndrome/toxic epidermal necrolysis and the use of the sulfonamide COX-2 inhibitors, particularly valdecoxib. Physicians should be aware of the possibility of this

serious life-threatening event when prescribing these drugs and advise patients to discontinue use at the earliest possible sign or symptom.

Background

Stevens-Johnson syndrome and toxic epidermal necrolysis are closely related severe acute blistering skin disorders that are usually the result of an adverse drug reaction. They are characterised by blister formation with detachment of the epidermis from between 10% to 30% of the body surface area for Stevens-Johnson syndrome and ≥30% for toxic epidermal necrolysis.[1] The mortality rate ranges from 5% to 30%[2,3] and survivors may experience severe disability, including blindness and disfigurement. Stevens-Johnson syndrome and toxic epidermal necrolysis are rare diseases with an estimated annual incidence in industrialised countries of 1–2 cases per million population.[4] Sulfonamides, particularly antibacterial sulfonamides, are among the most common causes of Stevens-Johnson syndrome and toxic epidermal necrolysis, as are NSAIDs.[5]

A sub-group of NSAIDs, the selective cyclo-oxygenase (COX)-2 inhibitors or 'coxibs', were developed in the belief that they would be safer than non-COX-2 selective NSAIDs, particularly in regard to gastrointestinal adverse effects.[6-8] Until September 2004, there were three coxibs on the US market (figure 1), two of which were sulfonamides (celecoxib and valdecoxib) and the third, rofecoxib, was a methylsulfone and contained a sulfonyl moiety. These three coxibs were all launched in the US within the last six years: celecoxib in January 1999, rofecoxib in May 1999 and valdecoxib in February 2002. On 30 September 2004, rofecoxib was voluntarily withdrawn from the US market by its manufacturer because of safety concerns that were unrelated to Stevens-Johnson syndrome or toxic epidermal necrolysis.[9] The marketing of valdecoxib was suspended in the US on 7 April 2005, after the submission of this paper.[10]

Meloxicam, a preferential COX-2 inhibitor NSAID of the 'oxicam' subgroup, was approved for use in the US on 14 April 2000 for treatment of osteoarthritis. Other members of the oxicam subgroup have also been associated with Stevens-Johnson syndrome and toxic epidermal necrolysis.[11]

Shortly after marketing of the coxibs, the US FDA began receiving reports of Stevens-Johnson syndrome and toxic epidermal necrolysis occurring in association with their use, which led to the strengthening of the product labelling of celecoxib and valdecoxib within the first year of marketing. For celecoxib postmarketing reports of Stevens-Johnson syndrome and toxic epidermal necrolysis were added to the adverse events section of the product label and for valdecoxib a warning was added and a 'Dear Healthcare Professional' letter was issued.[12,13] However, the agency continued to receive reports, which led to further strengthening of the label on 9 December 2004, with the addition of a boxed warning for Stevens-Johnson syndrome and toxic epidermal necrolysis.

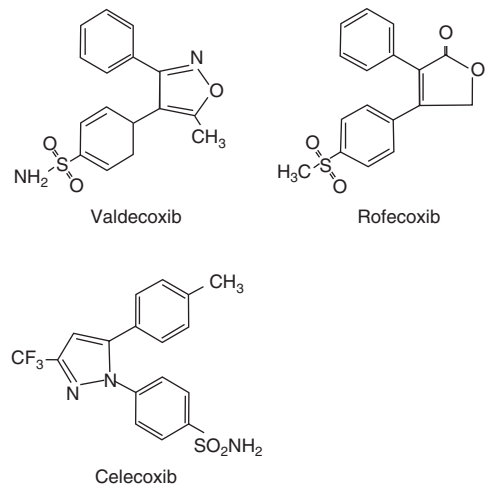

Fig. 1. Chemical structure of selective cyclo-oxygenase inhibitors valdecoxib, celecoxib and rofecoxib.

Objective

The objective of this study is to review cases of Stevens-Johnson syndrome and toxic epidermal necrolysis associated with use of the selective COX-2 inhibitors celecoxib, rofecoxib and valdecoxib that have been reported to the FDA. We also compare reporting rates of Stevens-Johnson syndrome and toxic epidermal necrolysis associated with these drugs to each other and to meloxicam in the first 2 years of marketing and to the background incidence rate.

Methods

We searched the FDA Adverse Event Reporting System (AERS) database for domestic (US) cases of Stevens-Johnson syndrome and toxic epidermal necrolysis associated with the use of celecoxib, rofecoxib, valdecoxib and meloxicam from their initial marketing to the end of March 2004. AERS is a computerised database of adverse events reported to the FDA in association with medication use. It is a passive surveillance system in which consumers and healthcare practitioners report adverse events on a voluntary basis, either directly or through the manufacturer of the particular drug product. It is an ongoing reporting system, containing reports dating back to 1969.

We reviewed case reports manually to remove duplicates, confirm the diagnosis and extract demographic and other pertinent data such as dose, duration of therapy and time to onset of the reaction. Additionally, we contacted individual manufacturers to ensure that the agency had received all reports in the relevant time period. Cases were classified as definite Stevens-Johnson syndrome or toxic epidermal necrolysis if they were so designated by the reporter and/or if the diagnosis had been made by a dermatologist, the diagnosis was confirmed by biopsy, the patient died and there was an autopsy diagnosis, or there was an adequate clinical description of blisters over >10% of the body surface with involvement of mucous membranes at one or more sites. Possible cases were so designated if they were reported as possible cases and there was insufficient information provided to classify them as definite.

We calculated reporting rates by dividing the number of definite US cases of Stevens-Johnson syndrome and toxic epidermal necrolysis associated with each drug by the estimated total person-years of exposure for the first 2 years of marketing. We estimated person-years of drug exposure by multiplying the total estimated number of dispensed prescriptions for each drug by the average duration of each prescription in days and dividing the product by 365, to convert days to years. We obtained estimates of the total number of prescriptions sold in the US for all four drugs since marketing began until March 2004, using the IMS Health National Prescription Audit *Plus*™ (NPA *Plus*™) database. This database measures the number of projected total prescriptions dispensed in the US based on a sample of approximately 22 000 retail pharmacies, including chain, independent, food stores, mail order and long-term care facilities. We obtained information on mean duration of prescriptions for all four drugs from the IMS Health National Disease and Therapeutic Index™ (NDTI™), which surveys treatment patterns and diseases encountered during patient visits at office-based medical practices in the continental US. We also used a combination of NPA™ and NDTI™ data to examine the age and sex distribution of coxib users in the US in 2003 and compared the results with the cases.

Background rates were obtained from the published literature. We calculated 95% confidence intervals for the observed reporting rates based on the application of a Poisson distribution as has been previously described.[14,15]

Results

The results are summarised in table I and table II. Through March 2004, there were 63 definite cases of Stevens-Johnson syndrome/toxic epidermal necrolysis associated with valdecoxib, 43 with celecoxib and 17 with rofecoxib. Table I summarises the characteristics of the cases. There were no cases of either Stevens-Johnson syndrome or toxic epidermal necrolysis for meloxicam from the time of marketing up to July 2004.

Table I. Characteristics of reported US cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) from time of marketing to 31 March 2004

Characteristic	Valdecoxib	Celecoxib	Rofecoxib
Total no. of definite cases	63	43	17
Age			
total no. of cases[a]	41	31	11
range (y)	15–84	24–94	25–91
median (y)	62	62	79
Sex[a] [n (%)]			
female	45 (82)	24 (69)	11 (79)
male	10 (18)	11 (31)	3 (21)
Onset			
total no. of cases[a]	45	22	10
median (d)	7	11	7
Reaction			
SJS	56	31	12
TEN	7	12	5
Indication[a] [n (%)]			
arthritis (OA/RA/DJD)	24 (56)	18 (58)	6 (46)
injury/pain/inflammation/sciatica	17 (40)	9 (29)	5 (38)
fibromyalgia/polymyalgia	1 (2)	2 (6)	0
dysmenorrhoea	1 (2)	0	0
gout	0	1 (3)	1 (8)
multiple sclerosis	0	0	1 (8)
carpal tunnel syndrome	0	1 (3)	0
Dosage			
total no. of cases[a]	37	24	11
range (mg/d)	10–40	100–600	12.5–50
median (mg/d)	20	200	25
Sulfa allergy [n (%)]	18 (29)	9 (21)	1 (6)
Outcome			
hospitalisation	30	23	8
death	4	8	2
other	29	12	7

a Cases with available information for the characteristic.

DJD = degenerative joint disease; **OA** = osteoarthritis; **RA** = rheumatoid arthritis.

The median age of cases for rofecoxib was 79 years compared with 62 years for valdecoxib and celecoxib. Most cases were female, with valdecoxib having the highest proportion of females (82%). The most common indication for prescribing the drug was arthritis (osteoarthritis, rheumatoid arthritis and degenerative joint disease): 56% for valdecoxib, 58% for celecoxib and 46% for rofecoxib. The proportion of cases with pre-existing allergy to sulfa was reported as 29% for valdecoxib, 21% for celecoxib and a single case, 6%, for rofecoxib.

When we compared the characteristics of people for whom the coxibs were prescribed with the characteristics of the cases, we found that a greater proportion of coxib users were female (rofecoxib 56%, celecoxib 58%, valdecoxib 61%), but the proportion was less than that of the cases (table I). The cases were also older than the coxib users: proportion of users >55 years of age were 45% for rofecoxib, 51% for celecoxib and 42% for valdecoxib.

The background incidence rate for Stevens-Johnson syndrome and toxic epidermal necrolysis in

Table II. Reporting rates for Stevens-Johnson syndrome and toxic epidermal necrolysis associated with rofecoxib, celecoxib, valdecoxib and meloxicam use for the first 2 years on market[a]

Drug	Total cases[b] [n (%)]	Deaths	Mean days of therapy[c]	Total dispensed prescriptions[d]	Total person-years exposure	Reporting rate per million person-years[b]	
						Cases[e]	Deaths
Celecoxib	19 (24)	4	30	40 652 000	3 341 260	5.7 (7.2)	1.2
Rofecoxib	7 (11)	2	29	32 344 000	2 569 797	2.7 (4.3)	0.78
Valdecoxib	58 (65)	4	26	16 554 000	1 179 189	49.2 (55.2)	3.4
Meloxicam	0	0	27	3 505 000	259 273	0	0

a Celecoxib January 1999–December 2000; rofecoxib May 1999–April 2001; valdecoxib February 2002–January 2004.

b Calculations based on the US FDA Adverse Events Reporting System reporting rates and total number of prescriptions dispensed in the US.

c Data source: IMS Health National Disease and Therapeutic Index™; January 1999–January 2004 (extracted September 2004).

d Data source: IMS Health National Prescription Audit *Plus*™; celecoxib and rofecoxib January 1999–April 2001 (extracted February 2003), valdecoxib February 2002– January 2004 (extracted August 2004).

e Numbers in parenthesis include definite and possible cases.

industrialised countries was found to be 1.9 cases per million population annually.[4] The reporting rates for the three coxibs for the first 2 years on the US market are summarised in table II. The rate for valdecoxib was 25–26 times that of the background rate and nine times that for celecoxib. The reporting rate for deaths in the first 2 years of marketing with valdecoxib was approximately three times that of celecoxib and rofecoxib.

Case counts, exposure duration, observed rates and confidence intervals for definite cases of serious skin reactions reported in association with selected COX-2 selective NSAIDs are summarised in table III. Statistical significance is shown by the non-overlapping confidence intervals for the observed rates.

Discussion

To our knowledge, this is the largest series of Stevens-Johnson syndrome/toxic epidermal necrolysis cases associated with the coxibs reported to date. Previous reports have been of single cases or small series of two or three cases.[16-18] Our results indicate that cases of Stevens-Johnson syndrome and toxic epidermal necrolysis were reported with all three coxibs on the US market in the time period under study, but cases with valdecoxib outnumbered those for celecoxib and rofecoxib combined. Cases tended to occur more commonly in elderly women, which is the pattern for Stevens-Johnson syndrome and toxic epidermal necrolysis generally.[19] Median time to onset was between 7 and 11 days, which is in keeping with reports for the onset of this disease.[20] However, there were a few outliers. For valdecoxib, 4 of 45 (9%) patients reported a time to onset of 25–150 days of use. One-third of celecoxib patients had times to onset ranging from 49 days to 18 months. Ten of the 14 rofecoxib cases had information on time to onset and for four this was >9 days; ranging from 23 to 365 days. The median dose for all three coxibs was at the recommended level for most indications, so that the high dose was probably not an important aetiological factor.

Both valdecoxib and celecoxib are sulfa drugs and the product labelling cautions against their use in patients with sulfa allergy. For valdecoxib, 29% of the cases reported sulfa allergy, compared with 21% for celecoxib and a single case (6%) for rofecoxib. The importance of a sulfa allergy as a risk

Table III. Case counts, exposure duration, observed rates and confidence intervals for definite cases of serious skin reactions reported in association with selected cyclo-oxygenase selective NSAIDs and meloxicam

Drug	No. of cases	Exposure duration (person-years)	Observed rate per million person-years (95% CI)[a]
Celecoxib	19	3 341 260	5.7 (3.4, 8.9)
Rofecoxib	7	2 569 797	2.7 (1.1, 5.6)
Valdecoxib	58	1 179 189	49 (34, 59)
Meloxicam	0	259 273	0 (0, 14)

a Based on expectation for a Poisson variable.

factor is not clear. For some patients, it could be a risk factor and certainly a history of sulfa allergy should be a contraindication for use of either of the two sulfonamide coxibs.

The strength of spontaneous reporting systems is that they are a cost-effective method of detecting rare, unexpected adverse reactions to drugs. So they are ideal for detecting a signal like Stevens-Johnson syndrome or toxic epidermal necrolysis, which are rare disorders with an estimated background rate of 1–2 cases per million population per year.[4] However, spontaneous reporting systems are subject to a number of important limitations.[21] Reports may be incomplete, with missing demographic and other data. More importantly, there is usually substantial under-reporting of adverse events.[22] Mittman and colleagues[23] recently examined the problem of under-reporting of toxic epidermal necrolysis in a Canadian population and found that only 4–10% of cases were actually reported. Factors believed to affect the likelihood of reporting include event severity, whether the event is labelled or not, publicity surrounding the event or the drug and secular patterns related to the time of marketing and length of time on the market, among others.[24] These factors often affect reporting to varying extents for different drugs. For this reason reporting rates cannot be equated with incidence rates.

Spontaneous reporting systems are not designed to assess causality but can highlight associations between particular drugs and adverse events. The exact number of events that constitutes a signal varies with the rarity and seriousness of the event. Stevens-Johnson syndrome and toxic epidermal necrolysis are extremely rare disorders and are almost always drug induced.[5] For these reasons, we believe there is a causal association in our series between valdecoxib use and serious skin reactions.

To minimise the potential biases described previously, we used two other coxibs marketed at about the same time, celecoxib and rofecoxib, as comparators for valdecoxib. We limited comparison to the first 2 years on the market because studies have shown that adverse events are more likely to be reported early in marketing.[24] Because celecoxib is also a sulfonamide and is marketed in the US by the same company as valdecoxib, there was a lower likelihood of reporting differences between these products. We chose meloxicam as a comparator for the coxib group because it is a traditional NSAID with COX-2 selectivity and is used for a similar indication to the coxibs. Also, meloxicam was first marketed in the US in April 2000, in the same general time period as the coxibs. There were no cases reported in AERS associated with meloxicam, perhaps because usage in the US was very low (table II).

Our comparison showed that the reporting rate was higher for both sulfonamide coxibs than for rofecoxib and meloxicam; however, this difference was substantially higher for valdecoxib and even more so when compared with the background rate for Stevens-Johnson syndrome/toxic epidermal necrolysis of 1–2 cases per million population per year.[4] That the reporting rate for Stevens-Johnson syndrome/toxic epidermal necrolysis with valdecoxib was 26 times that for the background incidence rate is notable, given the likely 10-fold under-reporting of this event. The actual incidence is likely to be much higher. The 9-fold difference between valdecoxib and celecoxib suggests that being a sulfonamide does not solely account for this difference.

We are usually hesitant to apply statistical tests to spontaneous reports data as the variance structure of such data is undefined. Nevertheless, because of the magnitude of the signal with valdecoxib, we calculated confidence intervals for the reporting rates. The absence of overlap between the confidence intervals for valdecoxib and the other coxibs supports the idea that valdecoxib is distinctly different from the other coxibs with respect to the risk of Stevens-Johnson syndrome and toxic epidermal necrolysis.

At present there is no satisfactory method for determining who is at greatest risk for developing drug-associated Stevens-Johnson syndrome and toxic epidermal necrolysis and hence of preventing it, short of avoiding drugs altogether. There has been a single study suggesting that early withdrawal of the agent at the first sign of the illness may improve the outcome.[25] Although this intuitively makes

sense, this study needs to be replicated. Even if it is proven correct, its practical application will be limited because it is very difficult to identify the very earliest lesion in a timely manner because of the rapidly progressive nature of this illness and the non-specific features of its prodrome.

Another challenge in the prevention of Stevens-Johnson syndrome and toxic epidermal necrolysis is that very little is known at present about their underlying pathogenetic mechanisms. Thus, a targeted intervention to halt, mitigate or reverse the process after it has been initiated does not currently exist. This remains an area of active research.[26-28] Investigations are underway to try to identify some genetic or other factors that might predispose people to this illness. Chung et al.[28] recently reported finding a strong association in Han Chinese between a genetic marker, the human leucocyte antigen HLA-B*1502 and carbamazepine-induced Stevens-Johnson syndrome. It remains to be seen whether this association will be confirmed by other researchers and in other populations and whether similar markers will be found for other drugs. In the meantime, it is important for physicians prescribing coxibs to be aware of the association of Stevens-Johnson syndrome and toxic epidermal necrolysis with these products and to consider whether the risk is in proportion to the benefit.

Conclusion

Cases of Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported in association with all three US-approved selective COX-2 inhibitor NSAIDs. Reporting rate comparisons showed that Stevens-Johnson syndrome/toxic epidermal necrolysis was reported much more frequently for valdecoxib than for celecoxib and rofecoxib and at a much greater rate than expected (based on the background incidence rate). This association cannot be explained by a history of sulfonamide allergy alone, as celecoxib, also a sulfonamide, had a lower reporting rate than valdecoxib. Physicians should be aware of this serious life-threatening adverse event when prescribing these drugs.

If the benefit is deemed to outweigh the risk and coxibs, particularly valdecoxib, are prescribed, patients should be advised to discontinue the drug at the first possible symptom or sign of Stevens-Johnson syndrome or toxic epidermal necrolysis.

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