SHORT COMMUNICATION

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Serious Skin Reactions and Selective COX-2 Inhibitors

A Case Series From Prescription-Event Monitoring In England

Deborah Layton,[1,2] *Vanessa Marshall*,[1,2] *Andrew Boshier*,[1,2] *Peter Friedmann*[3] and *Saad AW Shakir*[1,2]

1 Drug Safety Research Unit, Bursledon Hall, Southampton, UK
2 University of Portsmouth, Portsmouth, UK
3 Dermatopharmacology Unit, Southampton General Hospital, Southampton, UK

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Abstract

Background: The erythema multiforme (EM) spectrum of bullous eruptions (toxic epidermal necrolysis [TEN] and Stevens-Johnson syndrome [SJS]) are rare and serious skin reactions that have been reported for cyclo-oxygenase (COX)-2 selective inhibitors. Our objectives were to identify and describe cases of serious skin reactions reported during postmarketing studies of COX-2 selective inhibitors.

Methods: A retrospective review of information from reports of serious skin reactions reported during prescription-event monitoring (PEM) studies of rofecoxib, celecoxib, etoricoxib and valdecoxib conducted in England since 1999. Exposure data were derived from dispensed prescriptions written by primary care physicians for each study drug. Outcome data were derived from questionnaires posted to prescribers at least 9 months after the date of the first prescription for

each patient (valdecoxib data collection ongoing at the time of this study). Reports of EM, exfoliative dermatitis, SJS, TEN and symptoms associated with EM (EM syndrome) were identified from the PEM database. Additional data on diagnosis, relevant risk factors and management were requested for each case from the prescriber. A causality assessment was undertaken by a Drug Safety Research Unit research fellow and referred for expert review to a consultant dermatologist.

Results: Nine cases of serious skin reactions and two cases of symptoms associated with EM (EM syndrome) were identified. No reports of TEN were recorded. Six skin reaction questionnaires were returned. Of the nine cases of serious skin reactions, four cases (all SJS; one for each COX-2 selective inhibitor studied) were assessed as possibly related to use of the study drug (for combined cohorts: incidence risk 0.008%, 4 of 52 644 patients; rate 0.019 per 1000 patient-months of treatment). These four cases (two male, two female; age range 54–64 years) occurred within 2 weeks of starting treatment; the patient prescribed rofecoxib had reported risk factors (history of allergy, adverse reaction [asthma] to ibuprofen). The two cases from the EM syndrome search (one female, 35 years; one male, 80 years) occurred within 2 weeks of starting treatment; both were assessed as possibly related to use of celecoxib but considered suggestive of angio-oedema/urticaria and hypersensitivity reactions.

Conclusions: This case series provides useful and complementary information to other published studies about serious skin reactions reported during treatment with COX-2 selective inhibitors. The crude incidence of cases of SJS possibly related to the use of a COX-2 selective inhibitor in this case series is very low (0.008% for all four cohorts combined). Prescribers and patients should be aware of the severe and life-threatening risk of EM potentially associated with NSAIDs, including COX-2 selective inhibitors.

1. Background

NSAIDs are not only associated with serious gastrointestinal (GI) events, but also other potentially life-threatening adverse effects including skin reactions.[1] The erythema multiforme (EM) spectrum of bullous eruptions (toxic epidermal necrolysis [TEN] and Stevens-Johnson syndrome [SJS]) has been reported for selective cyclo-oxygenase (COX)-2 inhibitor NSAIDs.[2,3] In particular, valdecoxib (now withdrawn) and its pro-drug parecoxib are associated with an increased rate of such skin reactions (reporting rate 7–8 cases per million patients, based on spontaneous reporting data).[4] The occurrence of these cases appears unpredictable, occurring in patients with and without a history of sulfa allergy, after both short- and long-term use, with the majority of reactions occurring within the first 2 weeks of starting treatment.[4-6]

Whilst there appears to be some pattern with relation to time, a multitude of other risk factors for EM have been proposed, including genotypic differences in metabolising drugs and unusual immune responses.[1,7] The biological mechanisms underlying drug-induced SJS/TEN clearly involve the generation of drug-reactive T lymphocytes, with a predominance in CD4+ and CD8+ subsets within the dermis and epidermis.[1] Epidermal keratinocytes are found to express large amounts of the ligand for

Table I. Summary characteristics of prescription-event monitoring cohorts of rofecoxib, celecoxib, etoricoxib and valdecoxib

Drug	Rofecoxib	Celecoxib	Etoricoxib	Valdecoxib
Prescription collection dates	Jul 1999–Nov 1999	May 2000–Dec 2000	May 2002–Mar 2003	Jan 2003–Sep 2004
Green form send dates	Jan 2000–Aug 2000	Nov 2000–Oct 2001	Mar 2003–Oct 2003	April 2004–ongoing
Response rate (%)	35.2	40.0	42.7	38.3 [to 30 April 2005]
Size of cohort (n)	15 268	17 458	12 665	7253 [to 30 April 2005]

CD95 (fas); a member of the so-called 'death receptor family'. It is thought that the expression of fas-ligand is a result of an interaction with the effector T lymphocytes; the result is that the epidermal cells undergo large-scale apoptosis, which results in blisters.[8]

Current classification schemes recognise SJS as being a milder form of TEN, with an overlap of the two also possible. The clinical presentations of SJS and TEN have been described in detail elsewhere.[9] The mortality rate from SJS/TEN is 20–30%, often due to secondary complications (infections or pulmonary involvement) or multi-organ failure and sepsis.[7] TEN is almost always drug-related, whereas infections and drugs have been implicated in cases of SJS. The incidence of TEN and SJS is estimated at 0.4–1.3 cases and 1–7 cases per million person-years, respectively, in the general population.[1]

The Drug Safety Research Unit (DSRU) monitors the safety of newly marketed drugs during their immediate postmarketing period in England, using the noninterventional observational cohort technique of prescription-event monitoring (PEM).[10] PEM uses a systematic approach to data collection and is conducted in accordance with international ethical guidelines. Data are collected on patients prescribed a drug in 'real world' clinical practice. As part of its monitoring programme, the DSRU has carried out individual PEM studies of three COX-2 selective inhibitors, with a fourth study currently underway (see table I).

For these PEM studies, exposure data were derived from dispensed prescriptions for each study drug written by primary care physicians (general practitioners [GPs]). Outcome data were derived from simple questionnaires (green forms) posted to GPs at least 9 months after the date of the first prescription for each patient. These questionnaires requested information on demographic data and details of any significant events that may have occurred in the patients' medical history since the day the study drug was started. Each cohort comprises those patients for whom a completed green form has been returned to the DSRU.

Our objectives were to identify and describe cases of serious skin reactions reported during postmarketing studies of rofecoxib, celecoxib, valdecoxib and etoricoxib in response to a request from the European Medicines Agency.

2. Methods

2.1 Identification of Cases

We searched the PEM database for cases where any one of the four higher level event terms, EM, TEN, SJS and exfoliative dermatitis, had been reported on green forms during the three completed studies of rofecoxib, celecoxib and etoricoxib, and the ongoing valdecoxib study.

2.2 Follow-Up

Using a specially designed serious skin reaction questionnaire for this case series, further details on drug exposure and outcome data, plus information on diagnosis[11] (including laboratory results), relevant risk factors and management[7,12] were requested from the prescriber for each identified case (see table II for summary).

Table II. Summary of information requested on the serious skin reaction follow-up questionnaire used in this case series

Use of the drug in the month prior to the event
The daily dose of the drug at the time of the event
Time to onset of the event
A description of the event, including prodromal symptoms (e.g. sore throat, headache, fever), presence (or absence) of target lesions/blisters/pustules, ocular-, oral- or genital mucosal membrane involvement
An indication of how diagnosis was made (skin biopsy, histology), percentage body surface area involvement (<10%, 10–30%, >30%) with requests for copies of relevant laboratory tests and/or investigations
Use of other medications that are known to cause skin reactions, in the month before, or at the time of the event (antibacterials, imidazole antifungals, anticonvulsants, other NSAIDs, paracetamol [acetaminophen], allopurinol, cytotoxics or other medications, such as prescribed over the counter drugs, herbal medicines and supplements)
Previous history of allergy, adverse reactions to drugs, tested as HIV-positive, rheumatoid arthritis, systemic lupus erythematosus, ulcerative colitis or other relevant past medical history
Recent (<1 month) history of pregnancy, radiotherapy, viral infection, bacterial infection or malignancies
Whether the drug was stopped because of the event
Outcome (resolution, sequelae and death if relevant)

Selected individual case reports were assessed for causality and classified by a DSRU research fellow as either 'probable', 'possible', 'unlikely', 'conditional' (awaiting further information) or 'unassessable',[13] and were also referred to a consultant dermatologist for confirmation.

A physician might have reported a group of symptoms over a period of time without a subsequent diagnosis; therefore, we conducted a search on the DSRU database for other potential cases for which at least two pre-identified event terms relating to symptoms associated with EM were reported on the green forms. Of these, at least one had to be from the skin system organ class. In the context of this study, this search will be referred to as the 'EM syndrome' search (table III). Eligible cases identified through this search were followed up for additional information using the skin reaction questionnaire. Event terms relating to other bullous skin reactions were reviewed in order to detect possible misclassification (see footnote in table III).

3. Results

Nine cases of serious skin reactions were identified, along with two cases from the EM syndrome search. All 11 cases are summarised in table IV, ranked in order of causality assessment. No reports of TEN were recorded. Six serious skin reaction questionnaires were returned (response rate 54.5%; case numbers: 1, 3, 5, 6, 7, 8), of which additional information to that provided on the green form was available for five.

Of the nine cases of serious skin reactions, four cases (all SJS; one for each drug studied) were assessed as possibly related to use of the drug (for

Table III. Drug Safety Research Unit (DSRU) dictionary event terms associated with serious bullous skin eruptions to be included for an 'erythema multiforme syndrome' search[a]

Body system organ class	Lower term[b]
Skin	Dry skin, blister, erythema, erythema multiforme, dermatitis exfoliative, erythroderma, fixed eruption, purpura, rash, skin unspecified,[c] Stevens-Johnson syndrome, ulcer skin
Immunological	Allergy
Eye	Corneal oedema, eye trivial, eye unspecified,[c] ulcer corneal
Respiratory	Respiratory unspecified[c]
Alimentary	Stomatitis, ulcer mouth, ulcer rectal, hepatic failure, hepatitis, jaundice, liver function test abnormal, hepatic unspecified[c]
Haemopoietic	Anaemia, blood unspecified,[c] bone marrow abnormal, eosinophilia, hypereosinophilic syndrome, leucocytosis, lymphocytosis, neutrophilia, leucopenia, neutropenia, anaemia aplastic, thrombocytopenia
General	Laboratory test abnormal, multi-organ failure

a Bullous skin reactions reviewed for possible misclassification: pemphigoid, pemphigus, malignancies of the skin, collagen vascular disease, bacterial infections e.g. *Staphylococcus,* scalded skin syndrome, mechano-bullous eruptions, acute pustular psoriasis, acute generalised exanthematic pustulosis, Kawasaki's disease, toxic shock syndrome, vasculitis, epidermolysis bullosa, fixed drug eruption, photosensitivity reaction, lichenoid drug eruption, pustular eruption, urticaria/angio-oedema.

b Doctor summary terms (not shown) mapping to these lower level terms were reviewed for inclusion/exclusion by a consultant dermatologist.

c Unspecified: event for which no lower level or higher level DSRU dictionary term currently exists.

Table IV. Case report summaries of serious skin reactions reported during prescription-event monitoring studies of cyclo-oxygenase-2 inhibitors (rofecoxib [R], celecoxib [C], etoricoxib [E] and valdecoxib [V])

Case no.	Suspected drug	Prescribing indication	Dose at start of treatment/ dose at event (mg/day)	Age at start of treatment (y); sex	Term reported on green form	Time to onset (days)	% body surface area involved	Admitted to hospital	Use of NSAID <3 months before starting study drug	Concomitant medication	Medical history	Reason for stopping
'Possible' causal relationship												
1	R	NS	12.5/12.5	54; F	SJS	11	DK	No	No	Ethinylestradiol 10mg	GI conditions, atopic conditions (asthma); ADR (lidocaine, ibuprofen – asthma)	Yes
2	C	Cervical spondylosis	NS/200	60; M	SJS and septic shock	4	>30	Yes	No	None	Chronic back pain, duodenal ulcer. Reiter's syndrome	Yes
3	E	RA	40/90	55; M	SJS	3	NS	NS	Yes	Alendronic acid, folic acid, dihydrocodeine, zopiclone, methotrexate, pyridoxine, citalopram	GI conditions	Yes
4	V	NS	10/10	65; F	SJS (or sulphur sensitivity)	8	NS	NS	Yes	Histamine H_2 receptor antagonists/PPI	GI conditions	Yes
'Unlikely' causal relationship												
5	V	OA	20/NS	51; F	Suspected EM	47 (33 days after stopping)	DK	No	Yes	NSAID[a] use <1 month after stopping study drug prior to event	ADR to dextropropoxyphene/ paracetamol (acetaminophen) [lightheaded]	N/A
6	V	OA	20/20	58; M	ED	46 off drug (intermittent therapy)	<10	No	No	Morphine tablets 30mg bd	Chronic back pain Arthritis of knees	N/A
7	C	Mixed RA/ OA	NS/200	74; M	Er	147	>30	No	No	Sulfasalazine	RA	Conflicting information

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Table IV. Contd

Case no.	Suspected drug	Prescribing indication	Dose at start of treatment/ dose at event (mg/day)	Age at start of treatment (y); sex	Term reported on green form	Time to onset (days)	% body surface area involved	Admitted to hospital	Use of NSAID <3 months before starting study drug	Concomitant medication	Medical history	Reason for stopping
8	R	Sciatica	12.5/NS	65; M	EM	212 (164 days after stopping)	DK	No	No	Indapamide	GI conditions, hypertension, rosacea, anxiety/ depression; ADR to diclofenac (dyspepsia) prior to rofecoxib Viral infection (URTI) within 1 month of event	N/A
9	C	OA	200/90	47; F	Skin exfoliation	224	NS	NS	Yes	Dothiepin, anticoagulants/ antiplatelet agents	GI conditions; depression	Yes
'Possible' causal relationship - EM syndrome search												
10	C	Inflammed soft tissue of leg	200/200	35; F	Ulcers in mouth, sore tongue, lips peeled	9	NS	NS	NS	None	GI conditions	Yes
11	C	Painful finger joints	12.5/12.5	80; M	Allergic reaction-swelling lips, puffy eyes and generalised erythematous rash	13	NS	NS	NS	Warfarin	NS	Yes

a Etodoloac for 7 days followed by ibuprofen for 7 days (both 1 month prior to event).

ADR = adverse drug reaction; **bd** = twice daily; **DK** = don't know (GP response); **ED** = exfoliative dermatitis; **EM** = erythema multiforme; **Er** = erythroderma; **F** = female; **GI** = gastrointestinal; **GP** = general practitioner; **M** = male; **N/A** = not applicable; **NS** = not specified within green form questionnaire or follow-up questionnaire; **OA** = osteoarthritis; **PPI** = proton pump inhibitor; **RA** = rheumatoid arthritis; **SJS** = Stevens-Johnson syndrome; **URTI** = upper respiratory tract infection.

combined cohorts: incidence risk 0.008%, 4 of 52 644 patients; rate 0.019 per 1000 patient-months of treatment, 4 of 206 830 patient-months of treatment). These four cases (two male, two female; age range 54–64 years) occurred within 2 weeks of starting treatment (3–11 days). Of these four, only one Yellow Card report (for etoricoxib) was submitted to the Committee on Safety of Medicines (CSM).

Of note for these four cases, only the patient prescribed rofecoxib had reported risk factors for a serious skin reaction (history of allergy and ADR [asthma] to ibuprofen); for the etoricoxib case, modulation of the immune system and use of methotrexate could be important; however, these were not recorded as specific risk factors. For the celecoxib case, the rapid onset suggested that the patient had been pre-sensitised in some way but no further information was provided on follow-up. For the valdecoxib case, no follow-up questionnaire was received; however, the case was assessed as possibly-related based on time to onset (8 days) and the event given as the reason for stopping the study drug.

One additional case of erythroderma was reported for celecoxib; this occurred with a delayed onset subsequent to the introduction of sulfasalazine in a 74-year-old male. This case was assessed as unlikely to be related to use of celecoxib based on time to onset; however, the combination of sulfasalazine and celecoxib, which contains a sulfonamide moiety, could be important in this case.

For the remaining four cases of serious skin reactions identified, three were assessed as unlikely to be related to use of the study drugs; for the two valdecoxib cases, one patient had used other NSAIDs within 1 month of the event and no definite final diagnosis had been made, whilst for the other, another cause was likely (fridge fluid). For the rofecoxib case, another cause (viral) was suspected. One other case was not assessed because insufficient information was provided on the green form and no follow-up questionnaire was received.

There was no obvious pattern with regard to prescribing indications between the nine cases. None of these events had a fatal outcome but one patient was hospitalised with serious sequelae.

Two cases identified through the EM syndrome search occurred within 2 weeks of starting celecoxib (9 and 13 days) and resolved after stopping treatment. Although both were assessed as possibly related to the use of celecoxib, the first of these two reported events was more likely to be indicative of an angio-oedema type reaction and the second a hypersensitivity/anaphylactoid-type reaction rather than associated with EM. No further cases were obtained from the search of event terms to identify possible misclassification.

4. Discussion

4.1 Main Findings

This paper describes a series of cases reported during four PEM studies of rofecoxib, celecoxib, etoricoxib and valdecoxib. A causality assessment of 'possible' was recorded for four cases of SJS in this cohort of >52 000 patients (combined risk 0.008%, rate 0.019 per 1000 patient-months of treatment). In no case was the casual association assessed as probable. We acknowledge that variation in risk between drugs is possible. For the purposes of this case series and in view of the very low incidence of these events reported for these drugs, the risk and rate estimates (numerator [one case for each drug assessed as possible] and denominator [number of patients for whom a completed green form was returned to the DSRU, or patient-months of treatment]) is based on all four cohorts combined.

The crude risk is at least 27-fold higher than the upper end of the estimated incidence in the general population,[7] despite possible under-reporting.[14] This signal is important given the size of the PEM

cohorts. PEM has highlighted a similar safety signal amongst 11 316 patients prescribed lamotrigine, in which 12 cases of SJS were confirmed (incidence risk 0.11%; rate 0.1 per 1000 patient-months of treatment), supporting findings of an association between SJS/TEN with this antiepileptic drug.[15]

4.2 Strengths and Limitations

Because SJS and TEN are rare, the most appropriate methodology to study risk factors for such events is probably the case-control or case-registry approach. Mockenhaupt et al.[16] examined data on NSAID use from an international case-control study, a population-based enhanced active surveillance programme in Germany, and data from the US FDA spontaneous reporting scheme. The authors identified some NSAIDs as true risk factors for the development of SJS and TEN, especially early after starting treatment. The risks of SJS/TEN were most apparent in cases exposed to oxicams (piroxicam and tenoxicam) compared with controls (relative risk 34; 95% CI 11, 105); the excess risk estimated as 1 per 100 000 population within 8 weeks after starting treatment.[16] The risk of SJS/TEN were not significantly different between three comparator drugs with differing strengths of association with SJS/TEN (carbamazepine, allopurinol and amoxicillin). Important considerations raised in their study include international variation in the relative frequency of use of NSAIDs, diagnoses, method of reporting and error introduced by under-reporting. There is also evidence of a secular trend of an increasing number of reports to spontaneous reporting schemes by decade.[16]

The strengths of PEM have been described in detail elsewhere.[10] Of particular importance to this case series is that exposure and outcome data were gathered in a similar manner for each drug immediately after their respective launch. The drugs were monitored under general practice conditions in England (all since 1999) and prescribers were asked to report all clinical events without making an assumption of causality; thus, standardising reporting conditions as far as possible. Furthermore, cases were identified according to predefined criteria,[17] and questionnaires that had been specifically designed for this study were sent to the prescriber responsible for each case in an attempt to standardise and increase the quality of data available as well as supplement information reported on the original green form. Causality was assessed using standard criteria[13] and referred for review by an expert dermatologist.

The limitations of case reports and case series have been well described.[18] Of particular relevance to this study is bias introduced by non-response by prescribers and by variation in quality of additional information supplied retrospectively by prescribers for each case. Of 11 specially designed questionnaires sent to the prescriber for each case, six were returned and useful information was available for five, which was in addition to information obtained during each PEM study. Therefore, some important clinical information, such as percentage of body surface area involvement, is lacking for some cases. An important consideration is that this case series examined information collected retrospectively since 1999 and is dependent on GP prescribers having recorded such information in medical records. Furthermore, of the four cases assessed as possibly related to the use of a COX-2 inhibitor, only one was recorded by the prescriber as having been reported to the CSM via the Yellow Card scheme.

4.3 What Has Been Reported Elsewhere?

In the UK, the examination of Yellow Card data showed that for valdecoxib there have been two reports of SJS;[19] for celecoxib four reports of SJS, 12 reports of EM and two reports of TEN;[20] for rofecoxib, one report of SJS, 11 reports of EM and three reports of TEN;[21] and for etoricoxib, two reports of SJS and one report of EM[22] recorded

since each of the drugs were launched onto the UK market, up to June 2005. A US-based study reported that 63, 43 and 17 definite cases of SJS/TEN with valdecoxib, celecoxib, and rofecoxib use, respectively, were submitted to the US FDA Adverse Events Reporting System up until March 2004.[23] The US reporting rate of definite cases of SJS/TEN for the three COX-2 inhibitors combined was estimated as 0.058 per 1000 patient-months exposed.

This study provides useful information on cases regarding case characteristics, risk factors and demographics. Although the numbers of 'possible' cases in our case series is very small (n = 4), patient characteristics (median age 58 years, 50% female, median time to onset 6 days) are in line with those patients within the aforementioned US study, who tended to be elderly (women) with median time to onset between 7 and 11 days. However, one should be cautious in making comparisons between spontaneous reports and data submitted using PEM, given that spontaneous reporting systems are subject to a number of well known biases affecting both the numerator (number of patients) and the denominator (usage data). The valdecoxib PEM study was not yet complete by the time this study was conducted.

4.4 Addendum

After the study data-lock point of 30 April 2005, one report of exfoliative dermatitis with a maculopapular rash was received for a patient prescribed valdecoxib. This event was assessed as possibly related to valdecoxib based on time to onset (13 days) and a positive dechallenge within days. However, the clinical categorisation of this event is imprecise; the exfoliative dermatitis was described as 'blistered and wet', which is highly compatible with EM and mild TEN; however, the rapid resolution conflicts with this diagnosis.

5. Conclusion

This case series provides useful and complementary information to other published studies about serious skin reactions reported during treatment with COX-2 selective inhibitors. Of nine reports of serious skin reactions received during the four PEM studies of rofecoxib, celecoxib, valdecoxib or etoricoxib, four possible cases of SJS occurred within 2 weeks of starting treatment. The crude incidence risk of cases of SJS in this case series is low (0.008%; rate 0.019 per 1000 patient-months of treatment) for all four cohorts combined, but is still several times higher than the incidence of SJS in the general population. Prescribers and patients should be aware of the severe and life-threatening risk of EM associated with NSAIDs including COX-2 selective inhibitors. However, the choice of an NSAID should be based on a broad range of considerations, such as the overall benefit-risk profile of the individual product.

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Correspondence and offprints: Dr *Saad AW Shakir*, Drug Safety Research Unit, Bursledon Hall, Blundell Lane, Southampton, SO31 1AA, UK.
E-mail: saad.shakir@dsru.org