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Spontaneous reporting of Stevens-Johnson syndrome and toxic epidermal necrolysis associated with antiepileptic drugs

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Abstract. – OBJECTIVE: To assess the association between Stevens-Johnson syndrome (SJS)/ toxic epidermal necrolysis (TEN) and antiepileptics including the most recently authorized drugs.

METHODS: In the Spanish Pharmacovigilance database, we searched for spontaneous reports of SJS or TEN associated with antiepileptic drugs and analysed: a) reporting odds ratio (ROR), b) age and gender of the patient, c) evolution, d) latency and recovery periods and e) presence or absence of other suspected drugs.

RESULTS: A total of 84 reports of SJS and 80 of TEN related to 9 antiepileptic drugs were studied. Reports were mainly associated with phenytoin (SJS: 28; TEN: 43), lamotrigine (SJS: 37; TEN: 20) and carbamazepine (SJS: 14; TEN: 16). Other antiepileptic drugs involved were: valproate, phenobarbital, oxcarbazepine, levetiracetam, primidone and gabapentin. Patients were of a median age of 40 [1-87] and 57.3% of them were women. Cases related to phenytoin were more common in older men and to lamotrigine in younger women. The latency period of SJS and TEN did not exceed the first month of treatment and, in most of the analysed reports, the outcome was recovery.

CONCLUSIONS: Our observations support the association of SJS or TEN with phenytoin, carbamazepine, valproate or phenobarbital and enlighten the role of lamotrigine and others such as oxcarbazepine or levetiracetam.

Key Words:
Stevens-Johnson syndrome, Toxic epidermal necrolysis, Antiepileptic drugs, Spontaneous reporting.

Introduction

Nearly 3% of hospital inpatients develop cutaneous adverse drug reactions (ADR)[1], Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) being the most severe syndromes. These ADR have a very low annual occurence, 1-6 cases per 1 million of population, and are clinically characterized by warning signs such as fever and malaise, followed by the rapid onset of erythematous lesions that progress to extensive blistering and epidermal detachment, accompanied by mucosal erosions, slight elevation of hepatic enzymes and digestive and respiratory disorders[2-4]. SJS and TEN are mainly differentiated by the severity and the percentage of body surface area damaged which is < 10% in SJS, > 30% in TEN and between 10-30% in SJS/TEN overlap[5,6].

It is estimated that medications cause 30-50% of cases of SJS and up to 80% of TEN cases in adults[7]. Drugs associated with the development of SJS/TEN include sulfonamides, antiepileptics, non-steroidal antiinflammatory drugs (NSAIDs) and allopurinol[8-11]. Among these pharmacological groups, antiepileptic drugs are authorized for several therapeutic indications and are highly prescribed. The aim of our study was to assess the association between SJS/TEN and antiepileptics, including the most recently authorized drugs, based on the information provided by the spontaneous reporting of suspected ADR.

Methods

Using the Spanish Pharmacovigilance database (FEDRA, Farmacovigilancia Española Datos de Reacciones Adversas) we selected the spontaneous reports of SJS or TEN associated with drugs that fulfil all the following criteria: (1) Reporting date: from 01/01/1980 to 30/09/2009, (2) Type of report: spontaneous reporting from health professionals or drug companies, (3) ADR defined by the preferred terms of MedDRA®, Medical Dictionary for Drug Regulatory Activities, a standardised dictionary of medical terminology, developed under the auspices of the International Conference of Harmonisation *(MedDRA MSSO, Brussels, Belgium)*: "Stevens-Johnson syndrome" or "toxic epidermal necrolysis", (4) Suspected drugs, by themselves or by interaction with other drugs, included

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in the N03 Group (antiepileptic drugs) of the Anatomical Therapeutical Chemical (ATC) Classification *(Norwegian Institute of Public Health, WHO Collaborating Centre For Drug Statistics Methodology, Oslo, Norway).*

In the obtained reports, we calculated the frequency of each ADR (SJS or TEN), for each antiepileptic drug, and analysed: (1) reporting odds ratio (ROR) and the 95% confidence interval (95% CI), by constructing a 2 × 2 contingency table for each antiepileptic drug, (2) age and gender of the patient, (3) evolution, classified as recovered, not recovered, recovered with consequences, in recovery, unknown and *exitus*, (4) latency (interval of time between the beginning of the treatment and the onset of the adverse reaction) and recovery (interval of time between the withdrawal of the treatment and the end of the adverse reaction) periods of both ADR, and (5) presence or absence of other suspected drugs in the treatment received by the patient.

Statistical Analysis

We studied the main features of the cases of SJS or TEN separately and carried out comparisons between them by Chi-squared test for qualitative variables and *t*-test for quantitative variables. Data mining and statistical analysis of the reports were performed with SPSS for Windows (IBM SPSS Statistics 19.0, Armonk, NY, USA). $p < 0.05$ was considered statistically significant.

Results

A total of 84 reports of SJS and 80 of TEN associated with 9 antiepileptic drugs were found. Table I shows the frequency and the disproportionality analysis of the most frequently involved antiepileptic drugs: phenytoin, lamotrigine, carbamazepine, valproate and phenobarbital. Other antiepileptic drugs less frequently reported were: oxcarbazepine (SJS, 1; TEN, 2), levetiracetam (SJS, 1; TEN, 1), gabapentin (SJS, 1) and primidone (TEN, 1).

The age and gender of the patients affected by SJS versus TEN associated with antiepileptic drugs, considered as a group, are summarized in Table II. There were no differences in the median age of patients. However, a different distribution of the age groups was observed by comparing SJS versus TEN; SJS was less frequent than TEN in adult and elderly patients. By studying the reports on all the antiepileptic drugs together, no difference (p=0.5) was found in the distribution by gender between SJS and TEN (Table II). On the other hand, the comparison between antiepileptic drugs (Table III) showed that patients with SJS associated with phenytoin were significantly ($p < 0.01$) older than patients with SJS associated with other antiepileptic drugs. In addition, TEN related to phenytoin was significantly ($p < 0.01$) less frequent in women. However, TEN cases associated with lamotrigine were significantly ($p < 0.01$) more frequent in women and in younger patients than TEN cases associated with other antiepileptic drugs.

The latency period of SJS and TEN did not exceed the first month of treatment (Table II). In most of the analysed reports the outcome was recovery although some cases of SJS or TEN evolved to *exitus*. Furthermore, some of the analysed reports included more than one suspected drug; the mean of suspected drugs included in the TEN reports being higher ($p < 0.05$) than in SJS reports. The percentages of the reports of SJS or TEN associated with one antiepileptic drug alone are presented in Figure 1. In all cases associated with valproate there were other concomitant suspected drugs.

Table I. Disproportionality analysis for antiepileptic drugs with n > 6 reports of SJS or TEN.

Drug	n	SJS [ROR* (95% CI)]	n	TEN [ROR (95% CI)]	Total reports
Phenytoin	28	31.5 (21.0-47.0)	43	51.4 (36.6-72.1)	532
Lamotrigine	37	48.3 (34.6-67.4)	20	24.6 (15.4-39.3)	392
Carbamazepine	14	10.2 (5.9-17.6)	16	11.5 (7.0-19.3)	743
Valproate	10	10.2 (5.9-17.6)	8	10.5 (5.2-21.4)	393
Phenobarbital	2	–	8	23.4 (11.4-48.0)	181

ROR: reporting odds ratio.

Table II. Main features of cases of SJS or TEN associated with antiepileptic drugs.

	SJS (n = 84)	TEN (n = 80)	p (TEN vs SJS)
Age, median [range]	40 (1-82)	40.5 (3-87)	0.2
Age groups, n (%)			< 0.05
Child (2-11 years)	15 (17.9)	7 (8.8)	
Adolescent (12-17 years)	10 (11.9)	4 (5)	
Adult (18-65 years)	43 (51.2)	52 (65)	
Elderly (> 65 years)	14 (16.7)	15 (18.8)	
Unknown	2 (2.4)	2 (2.5)	
Gender, n (%)			0.5
Female	50 (59.5)	44 (55)	
Male	32 (38.1)	35 (43.8)	
Unknown	2 (2.4)	1 (1.3)	
Latency days, mean ± SEM (n)	19.4 ± 1.6 (69)	22.3 ± 2.3 (64)	0.4
Outcome, n (%)			< 0.05
Recovered	63 (75)	43 (53.8)	
Not recovered	7 (8.3)	12 (15)	
Recovered with consequences	4 (4.8)	6 (7.5)	
In recovery	–	2 (2.5)	
Unknown	6 (7.1)	5 (6.3)	
Exitus	4 (4.8)	12 (15)	
Recovery days, mean ± SEM (n)	15.9 ± 2.0 (55)	27.7 ± 4.4 (48)	0.1
Suspected drugs, mean ± SEM (n)	1.3 ± 0.1 (22)	2.1 ± 0.1 (38)	< 0.05

Discussion

In our study, the three antiepileptic drugs most frequently associated with reports of SJS or TEN were phenytoin, lamotrigine and carbamazepine; our results for phenytoin and carbamazepine being in agreement with some previous studies[8,9,12]. Lamotrigine was the second most frequent antiepileptic drug involved in our observations whereas in the SCAR (Severe Cutaneous Adverse Reaction) study[8], carried out from 1989 to 1993, there were no cases associated with lamotrigine. In the EuroSCAR (European Severe Cutaneous Adverse Reaction) study[9], conducted from 1997 to 2001, only fourteen cases were associated with lamotrigine. Some cases of SJS or TEN associated with lamotrigine have been published[13-15] and one previous Spanish study in pediatric patients found that lamotrigine was frequently related to SJS or TEN[16]. In Spain, lamotrigine was authorized in 1993 and our work, although only including reports from the Spanish population, covers the period of time from that year to 2009. This, and perhaps a wider prescription of the drug, could explain this high number of cases related to lamotrigine.

In addition, we found reports of SJS or TEN associated with more recently authorized antiepileptic drugs such as, oxcarbazepine, levetiracetam, primidone and gabapentin that were

Table III. Age and gender differences between antiepileptic drugs in the analysed reports.

	SJS		TEN		SJS		TEN	
Drug	Age median (range)	p*	Age median (range)	p	Female sex n (%)	p	Female sex n (%)	p
Phenytoin	59 (9-81)	< 0.01	54 (10-80)	0.1	16 (57.1)	0.7	15 (34.9)	< 0.01
Lamotrigine	25 (2-82)	0.1	34.5 (3-87)	< 0.01	23 (62.2)	0.6	17 (85)	< 0.01
Carbamazepine	21.5 (3-78)	0.5	58.5 (14-85)	0.1	7 (50)	0.4	10 (62.5)	0.3
Valproate	11.5 (2-43)	0.1	33.5 (10-55)	0.2	4 (40)	0.6	5 (62.5)	0.7
Phenobarbital	11 (3-19)	–	55.1 (21-76)	0.2	1 (50)	–	3 (42.8)	0.7

*p values were calculated for each antiepileptic drug versus the others taken as a group.

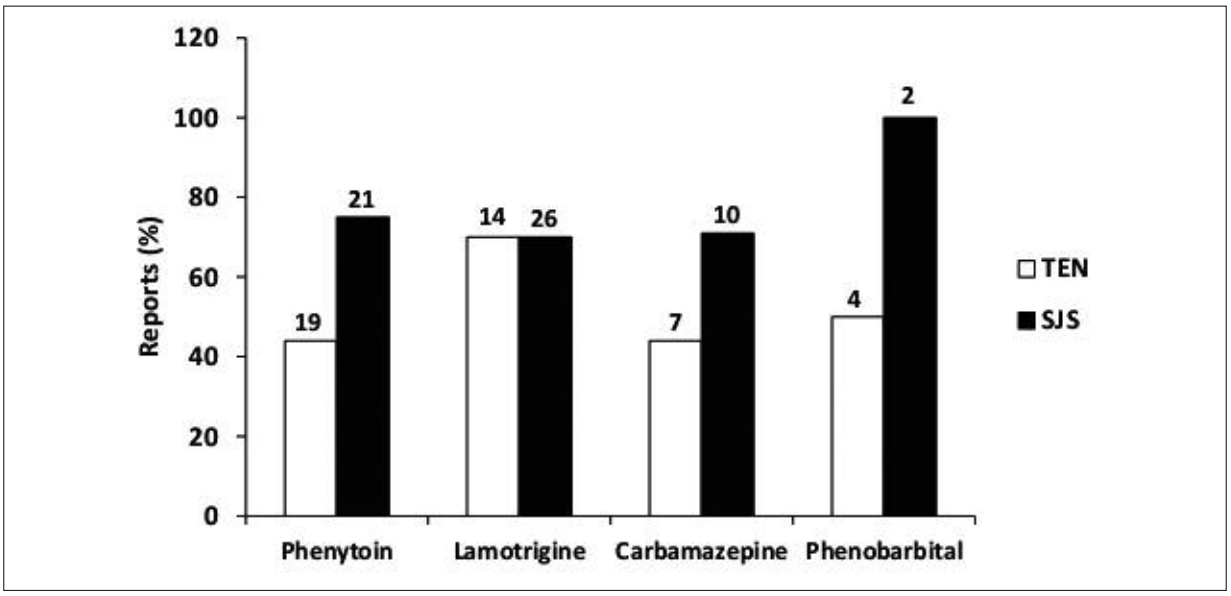

Figure 1. Reports (%) of SJS and TEN associated with one antiepileptic drug alone [numbers over the bars represent the number of cases].

not related to severe cutaneous ADR in the previous above-mentioned studies[7,8], although isolated cases associated with some of these antiepileptics have been reported[17-21]. Oxcarbazepine and levetiracetam are the most recently marketed, but gabapentin was authorized the same year as lamotrigine and the number of reports related to gabapentin was lower than that related to lamotrigine. This difference seems not to be based on differences in consumption because, according to the report published by the Spanish Health Agency of Medicines and Medical Devices[22], from 2000 to 2006 the consumption of gabapentin in Spain was higher than the consumption of lamotrigine.

The mechanism action of lamotrigine to induce SJS or TEN is under debate. Lamotrigine is predominantly metabolized in the liver by glucuronidation and the genetic alteration of this process, with a lower clearance of lamotrigine, has been proposed as a potential mechanism involved in the development of some TEN cases[23]. Furthermore, lamotrigine has an aromatic amine structure and this type of antiepileptic drugs has been more commonly related than others to the development of some hypersensitivity disorders, such as SJS and TEN[12,24-26]. However, gabapentin is a non-aromatic antiepileptic drug and is excreted primarily unchanged and, hence, the production of toxic metabolites with this drug is very low. On the other hand, carbamazepine, phenytoin and phenobarbital are metabolized in a high proportion (90-100%)[23,27]. These pharmacokinetic differences could partially explain differences between antiepileptic drugs in the induction of severe cutaneous ADR.

Valproate was the fourth most frequently antiepileptic drug related to cases of SJS or TEN in our study, although it was always in combination with other antiepileptic drugs such as lamotrigine, phenytoin or carbamazepine and it is difficult to establish the partial contribution of each drug in the development of the ADR. Some potential consequences of the interaction between valproic acid and lamotrigine have been previously described[28,29]. Valproic acid interacts with the metabolism of lamotrigine by inhibiting its glucuronidation[27] that secondarily induces the increase in the oxidative process and the production of toxic metabolites, that could trigger cutaneous ADR[30,31].

In the analysed reports, SJS and TEN were developed more frequently in women than men and the median age of patients affected was nearly 40 years, in agreement with the observations of previous studies[8,9,32,33]. These features were common to all antiepileptic drugs analysed apart from the cases associated with phenytoin, which were more frequent in men, and the cases associated with lamotrigine, more common in younger women. These age and gender differences could simply reflect differences in the prescription and

consumption of the antiepileptic drugs. Consumption data by age and gender have not been published but lamotrigine monotherapy at doses lower than 300 mg per day is considered one of the safest antiepileptic treatments in women of childbearing potential[34]. Phenytoin has a narrow therapeutic range and exhibits saturable kinetics with therapeutic doses[35] and its prescription can be lowered in children, young women and elderly patients.

Latency period to develop SJS or TEN was under 4 weeks, this period being within the interval of 1-8 weeks described in the EuroSCAR study[9]. Recovery period was almost 2 weeks in the cases of SJS and 3 weeks in the cases of TEN, certainly in relation with the severity in the TEN cases. Most of the reports included 1 or 2 suspected drugs, TEN reports being those that included a higher number of concomitant drugs, perhaps due to a tendency by the reporters to collect and enclose more information about concomitant medications in the most severe cases.

Conclusions

Our observations are in line with those identified in previous studies, providing information on the features of cases and suggesting associations with more recently authorized drugs within the group of antiepileptic drugs studied.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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