TOXIC EPIDERMAL NECROLYSIS AND CLARITHROMYCIN

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ABSTRACT

Toxic epidermal necrolysis almost always occurs after taking a medication. Despite spectacular clinical signs, it is mainly diagnosed with pathologic techniques. The identification of a drug as the cause for the immune related cytotoxic reaction can be difficult if the molecule is not generally known to be a classical cause of this reaction. The present study describes a female patient who rapidly developed a severe bullous skin disease after taking clarithromycin for tonsillitis. The case illustrates the process involved in attributing causality to a molecule using an established imputability assessment framework.

***Key Words**: Toxic epidermal necrolysis, clarithromycin, causality, macrolide*

Although rare, the unforeseen effects of medication are potentially dangerous and even life-threatening, so they must be documented in order to assess their frequency and circumstances of occurrence.[1,2] Toxic epidermal necrolysis (TEN) is a severe bullous skin disease inducing massive epidermal peeling with painful ulceration of all mucosal tissue. It rapidly extends and may cover the whole cutaneous-mucosal surface.

Although it is rare, with an estimates incidence of one case per million inhabitants per year, it is fatal in approximately 30 % of cases.[1] In 90 % of cases it is triggered by an immuno-cytotoxic reaction to medication.[2,3,4] The most frequently incriminated molecules are anticonvulsants, non steroidal anti inflammatory drugs, allopurinol, and sulfonamide antibiotics.[5,6] Other antibiotics known to induce this syndrome are the aminopenicillins, the cephalosporins and the quinolones, while macrolides were thought to induce a specific allergic cutaneous reaction rather than TEN. A number of years ago an amendment was made to the pharmaceutical dictionary (VIDAL, 2001) mentioning the possible but exceptional occurrence of TEN with macrolides. We report a case in which clarithromycin (Naxy®), a semi-synthetic derivative of erythromycin A, triggered TEN.

Case report

While suffering from fever accompanied by laryngo-pharyngeal pain and diffuse myalgia, a 29-year-old woman without significant past medical history consulted her general practitioner. Tonsillitis was diagnosed and 10 days of treatment were given with clarithromycin (Naxy 250®), paracetamol (Doliprane 500®), acetylsalicylic acid (Aspegic 1000®) and erdosteine (Vectrine®). Treatment commenced on the day of diagnosis, except for the aspirin which the patient did not use. The patient had previously received antibiotics on several occasions for upper respiratory tract infections, particularly the macrolide roxithromycin (Rulid®).

Forty-eight hours after commencing treatment, a pruritic vesicular rash appeared on her face and thighs. Her general practitioner discontinued the clarithromycin and replaced it with amoxicillin (Clamoxyl®). Her state worsened during the night with the appearance of bullous lesions on her abdomen and a fever of 40^{o} C. She was hospitalized the following day and Stevens-Johnson syndrome was diagnosed die to the presence of peeling of the ocular, buccal, and vulvo-vaginal muscosa. On day 4, the peeling affected 70% of the body surface, and severe involvement of all mucosal tissue required her to be transferred to a specialized burn unit. Intensive

care was provided and included antibiotics (Vancomycin, Vancocine®, Gentamycin, Gentalline®, doxycyclin, doxicline®) for a cutaneous staphylococcal superinfection and pneumonia of the right lung. The patient also received paracetamol for several days owing to the persistence of fever. All complementary tests pointed to a diagnosis of TEN, particularly a skin biopsy that evidenced sub-epidermal bullous peeling accompanied by numerous necrotic keratinocytes and negative immunofluorescence.

All bacteriological tests including search for mycoplasma and staphylococci were negative. No hypereosinophilia was found. The patient remained in hospital for one month with satisfactory re-epithelilization occurring in over 10 days. After one year, sequelae included dyschromic scars that persist on her skin and ophthalmologic lesions with decreased visual acuity, diffuse keratitis and a palpebral symblepharon.

DISCUSSION

For many years TEN was attributed to particularly slow acetylating genotypes, leading to the accumulation of toxic metabolites or to immune mechanisms involving reactive metabolites behaving as highly immunogenic haptenes. At present, several studies[7,8,9] point to the role of T lymphocytes directly reacting with a molecule and triggering the synthesis of cytokines, leading to the apoptosis of the keratinocytes and to epidermal necrolysis.

Particular profiles favour the occurrence of TEN although the precise mechanism remains unknown.[3-4, 7-9] These include HIV infection, systemic lupus erythematesus, radiotherapy, bone marrow allograft and certain immunologic phenotypes such as HLA B12 and HLA DR4.[1] However, these factors were not relevant in this patient. The clinical presentation was characteristic of TEN except that the onset of clinical signs was faster after exposure than is usually described (7 to 21 days).

The complications were classical, as pneumonia due to the peeling of the bronchial mucosa occurs in about 30 % of cases and ocular sequelae occur in 40 % of cases.[10,11] The diagnosis of TEN due to a medication is quite likely in this case but it is difficult to decide which molecule is to be incriminated since the severity of the symptoms ruled out any attempt at a cutaneous test or re-introduction. We therefore used the drug imputability criteria established by the French pharmacovigilance centers[12] which allowed us to establish a very strong suspicion of clarythromycin (Table 1).

These criteria take into account both the chronology of events from the moment the drug is taken until the appearance of the lesions (intrinsic chronological imputability), the type of clinical sign (intrinsic semiologic imputability) and the data in the literature (extrinsic imputability). Clarithromycin would appear to be the most likely imputable drug since the patient was not taking any medication prior to the appearance of the bullous lesions, apart from a contraceptive pill (which she had taken for ten years); Paracetamol and erdosteine have been re-administered and tolerated since the event (semiologic criterion: S3).Even though TEN symptoms usually occur between days 7 and 21 after exposure to the precipitating molecule, there are rare cases where re-introduction of a molecule previously prescribed has triggered TEN in a much shorter time (< 3 days). For this reason, the previous administration of the macrolide roxithromycin (Rulid®) may be considered as a prior source of sensitisation and would explain the acceleration of the immune response (chronological criterion: C3). The overall intrinsic imputability score (I4) strongly suggests the involvement of clarithromycin.

Finally, although there is very little published on macrolides causing TEN, the rareness of adverse event and the very low degree of involvement of antibiotics in this syndrome would have a limiting effect on the extrinsic imputability score (B1) with respect to the overall causality assessment.

CONCLUSION

TEN is a life-threatening condition causing serious ocular and cutaneous sequelae. A number of drugs are known to induce TEN and the list should include macrolides. Because clarithromycin is widely used it is important to bring the present case to the attention of the medical community so that prescribers can be aware of the risk.

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TABLE 1 Criteria used for imputability

Chronologic criteria (C) / **Intrinsic imputability score**		**Time to appearance of event**						
		Highly suggestive			**Compatibility**			**Incompatibility**
Evolution when drug is curtailed	Suggestive	C3	C3	C1	C3	C2	C1	C0
	Inconclusive	C3	C2	C1	C3	C1	C1	C0
	Non-suggestive	C1	C1	C1	C1	C1	C1	C0
		positive	not made	negative	positive	not made	negative	not made
		Relapse during involuntary re-administration of drug						

Highly suggestive: e.g., anaphylactic shock a few minutes after injection; fetal malformation for which administration of suspect drug coincides with the precise period during which involved organ is formed
Compatibility: eczema-type reaction occurring several days after taking incompatible drug
Incompatibility: fixed pigmented erythema occurring several weeks after taking drug
Inconclusive: regression which is spontaneous or induced by non-specific dermocorticoid anti-histaminic symptomatic treatment, irreversible lesions, insufficient follow- up, drug not curtailed because essential
Non-suggestive absence of regression of reversible type of event or complete regression despite continuation of drug
C0 excluded ; **C1** doubtful ; **C2** plausible ; **C3** probable

TABLE 1 – Cont'd

Semiologic criteria (S) Intrinsic imputability score		**Semiology (**clinical or para-clinical)					
		Evocative of role of drug (and / or highly suggestive factor)			Other semiologic possibilities		
Other explanation not attributable to drug	Absent (after appropriate work-up)	S3	S3	S1	S3	S2	S1
	Possible (present or not sought)	S3	S2	S1	S3	S1	S1
S1 doubtful ; **S2** plausible ; **S3** probable		positive	0	negative	positive	0	negative
		Reliable specific complementary test (0 = test not available)					

Intrinsic imputability score (I)		**Semiologic criterion (S)**		
		S1 doubtful	**S2** plausible	**S3** probable
Chronologic criteria (C)	**C0** excluded	I 0	I 0	I 0
	C1 doubtful	I 1	I 1	I 2
	C2 plausible	I 1	I 2	I 3
	C3 probable	I 3	I 3	I 4

I0 excluded ; **I1** doubtful ; **I2** plausible ; **I3** probable ; **I4** very probable

Extrinsic imputability score (B)

B0	**B1**	**B2**	**B3**
Effect never published in international reference documents, even after exhaustive bibliographic search	Effect not described in international reference works	Not well-known effect published once or twice only, different semiology or similar drug	Well-known effect described in the VIDAL dictionary or in reference works

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