Fatal Toxic Epidermal Necrosis: Responsibility of Diacerein? A Controversy

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Toxic epidermal necrosis (TEN) is a life-threatening condition induced by a large variety of drugs, most often anticonvulsants, nonsteroidal anti-inflammatory drugs (NSAIDs) and sulphonamides; reports involving other drugs are available. We report the first case in which diacerein, an anthraquinone derivative recently introduced for rheumatological diseases, has been considered as a possible culprit.

A 71-year-old woman was referred for acute, rapidly progressing, widespread mucocutaneous lesions accompanied with major vital signs. She had had joint pains of mechanical origin mainly located in the hips, wrists and shoulders for which she had been continuously treated with diacerein for 3 months before the occurrence of cutaneous lesions with a daily dose of 100 mg. Other recent drug intakes included oral spiramycin for dental abscess stopped 3 weeks before the cutaneous accident; she denied any NSAID intake during the preceding 3 months. Long-duration medications included flunitrazepam and lormetazepam, both of them introduced at least 2 years before and well tolerated. The mucocutaneous lesions developed suddenly with multiple mucous erosions, a generalized, macular, dark red exanthema, fever at 40°C and major general alteration. Nikolsky’s sign quickly appeared whereas diffuse blistering progressed to exfoliation in large sheets of more than 80% of her body surface over 48 h. The histological picture was typical of TEN with necrosis of the whole epidermis, dermo-epidermal cleavage and minor inflammatory infiltrate in the upper dermis. Direct immunofluorescence and a serological test for mycoplasma were negative. She presented two deleterious factors in TEN, lymphopenia and hyperglycaemia, and in spite of supportive care, she rapidly worsened with respiratory distress syndrome and bronchial mucosa exfoliation. She eventually died of lung sepsis 10 days after the beginning of the eruption.

We consider that this case of fatal TEN might have been induced by diacerein. The diagnosis of TEN can hardly be questioned since all clinical and histological data were typical of this rare condition. Although flunitrazepam and lormetazepam should also be regarded as culprits, the role of diacerein was considered since it was the only recently introduced drug received by the patient when the TEN occurred; particularly, extensive investigations failed to demonstrate any recent NSAID intake. Spiramycin, a rare but possible TEN-inducing drug, had been stopped 3 weeks earlier, a time lapse theoretically inconsistent with its involvement given its short half-life (6–8 h). By contrast, in our patient, a free interval longer than the usual 2–3 weeks after the beginning of a continuous treatment, although rare, is not an exclusion criterion [1]; this unusual interval can be connected with the unusual delay of efficacy of the drug which is about 45 days [2].

Diacerein is an original molecule supposed to exhibit an anti-IL1 activity, without influencing the cyclo-oxygenase activity. It shows no frank structural homology with NSAIDs. Serious cutaneous side-effects have not been reported to date. A comprehensive survey of its cutaneous side-effects is advocated.

References

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Reply

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The onset of Lyell’s syndrome (toxic epidermal necrolysis) in a 71-year-old woman, reported in the ‘Letter to Dermatology’ by Dereure et al. [Dermatology 1998;196:431] gave rise to investigations by the French Agency for the Evaluation of Medicinal Products, the Pharmacovigilance Regional Center in Montpellier and Laboratoires NEGMA of all of whom reached the conclusion of dubious intrinsic imputability (assessed according to the French method).

It is difficult to establish with certainty a cause-effect relationship between a drug taken by a patient and the occurrence of a clinical event, and any appraisal is based on intrinsic semiological and chronological criteria, and on extrinsic criteria (bibliographical data).

Diacerein which has been on the market in France since September 1994 for the indication ‘symptomatic treatment of the functional symptoms of osteoarthritis’ is an antiosteoarthritic drug and is distinct from the class of NSAID both in terms of its chemical structure and its mechanism of action which differs from that of NSAID insofar as it does not act through the inhibition of cyclo-oxygenase and prostaglandins.

Furthermore, the chemical structure of diacerein which belongs to the family of anthraquinones is not related to that of any of the compounds known to date to have been responsible for causing Lyell’s syndrome.

In the clinical case described, the time between onset of the event and intake of the drug does not in our view seem to incriminate diacerein.

Data in the literature concerning the onset of Lyell’s syndrome mention a characteristic delay of 1–3 weeks between dosing with the drug and appearance of the reaction [1].
Furthermore, Roujeau et al. [2] specified that in the case of substances for prolonged use (months or years), the iatrogenic effect with respect to the onset of Lyell’s syndrome usually occurred during the first 2 months of treatment.

However, in the case referred to, the event occurred 3 months after the initiation of diacerein therapy.

The authors tried to explain that this time lag, by comparison with the usual delay, was due to the delayed onset of action of diacerein. It is important to emphasize in this respect that although the expected therapeutic effect is triggered as soon as the drug therapy is initiated, it only becomes statistically significant vis-à-vis the functional symptoms of osteoarthritis (pain, functional limitations) after 30–45 days, while the adverse effects appear early and are those expected for the chemical class of anthraquinones, both in terms of their type and their time to onset.

Finally, the numerous clinical studies undertaken using diacerein which lasted for periods ranging from 3 months to 3 years and involved more than 5,000 osteoarthritic patients, together with data from the Thalès Permanent Epidemiological Observatory concerning prescriptions of diacerein in 1,904 patients between July and December 1995 and 1,811 patients between January and June 1996, did not provide evidence of any serious adverse events related to the use of this product. Similarly, between September 1994 and June 1997, approximately 2.7 million diacerein prescriptions were recorded representing 153 million days of treatment.

References


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