Clinical commentary

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Lacosamide-induced rash

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ABSTRACT – Cutaneous eruptions and hypersensitivity represent frequently reported side effects of anti-seizure medications. However, these side-effects have rarely been previously reported for lacosamide, a newer-generation anti-seizure medication with a novel mechanism of action. Here, we report a case of diffuse skin eruption in a patient with history of epilepsy soon after initiation of lacosamide. The rash resolved after discontinuation of lacosamide and use of antihistamines and steroids. We also review the information on drug hypersensitivity syndrome.

Key words: lacosamide, allergic, rash

Lacosamide (LCM) is a new-generation anti-seizure medication (ASM) that has a unique mechanism of action, enhancing the slow inactivation of the voltage-gated sodium channel. LCM has been studied in three pivotal placebo-controlled trials and was found to have some side effects including double vision, nausea, headache, and dizziness (Abou-Khalil, 2009). Skin reactions were reported in three patients in the placebo group and one patient in the effective drug group in the pivotal trials (Zaccara *et al*., 2013), while post-marketing experience with hundreds of thousands of individuals on LCM worldwide has yielded reports of only rare cases of rash without detailed documentation. In this report, we document a skin eruption related to LCM that was reversible upon discontinuation of LCM and treatment with steroids and antihistamines. This should alert physicians to this potential adverse event as they counsel their patients upon initiating LCM.

Case report

A 36-year-old woman reported a history of epilepsy since the age of 14. Her first seizure consisted of loss of consciousness, falling, jerking, and salivating with the eyes rolled up. Postictally, she had an intense headache and was somnolent. An EEG was performed revealing normal findings. Valproic acid was started and she did not have seizures for two years. Valproic acid treatment was therefore stopped with no seizure recurrence for eight years, while off medications. At age 24, she had another seizure, and since then, her episodes started to recur at a frequency of once a year, always while menstruating.

She received lamotrigine, but developed a skin eruption. When lamotrigine treatment was stopped, she had two seizures in one day. She had also tried treatment with topiramate, however, this exacerbated her co-morbid migraine headaches according to her report, as well as zonisamide, but this was

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stopped due to her depression. She then received levetiracetam for three years during which time she had an uneventful pregnancy with a healthy newborn. Although she was seizure-free on levetiracetam, she reported depression and "aggressiveness".

At that stage, we recommended initiation of LCM. The patient received 50 mg twice a day for a week without any side effects. Two days after, she increased the dose to 100 mg orally, twice a day, and she started to notice a skin eruption characterised by erythematous papules (*figure 1*). The patient was not taking any concomitant medications, and she denied any exposure to new articles of clothing or new cosmetic agents. The diffuse pruritic skin eruption was symmetric; involving her trunk and the extremities. It spared her oral, ocular, and genital mucosa. Three days after reaching a dose of 100 mg, twice a day, she stopped the LCM treatment and returned to levetiracetam treatment at 500 mg, twice a day. She also started taking diphenhydramine, which helped slightly with regards to her itching. However, the eruption continued to worsen, and 24 hours after discontinuing LCM, she noticed significant erythema of her lesions. The skin eruption developed into darkly erythematous papules, coalescing into plaques with areas of central oedema which appeared as focal grey patches within the juicy plaques (*figure 2*). She presented to the emergency room where her liver function tests and complete blood count showed normal values. She continued to receive her diphenhydramine but also received one intravenous dose of steroids, and started to improve gradually. By one week, her skin eruption improved significantly and two weeks later, the lesions resolved almost completely. The patient was lost to follow-up afterwards. No additional tests, such as histological analysis, HLA typing, or viral serology for human herpesvirus (HHV) 6 and 7, or pathological assessment of her lesions or HLA profiling, were performed.

Discussion

Adverse drug reactions represent a common complication of medical therapy that occurs in 5-15% of patients on any medication. Of those, 2-10% are cutaneous side effects that range broadly in severity (Błaszczyk *et al*., 2013). Phenytoin, for example, results in severe cutaneous reactions in 2.3-4.5 per 10,000 and carbamazepine in 1-4.1 per 10,000 (Tennis and Stern, 1997). The relative risk of cutaneous drug reaction is 15% for phenobarbital, 11% for carbamazepine, 13% for phenytoin, and <5% for oxcarbazepine (Roujeau, 2005; Błaszczyk *et al*., 2013). In a 20-year study of ASM adverse effects in a single centre, 95% of the skin reactions were associated with four medications: carbamazepine, phenytoin, lamotrigine, and oxcarbazepine (Błaszczyk *et al*., 2013). Moreover, the cross-reactivity between the aromatic ASMs reached 40-70% (Sierra *et al*., 2005).

Cutaneous adverse drug reactions associated with ASMs may take the form of a number of related

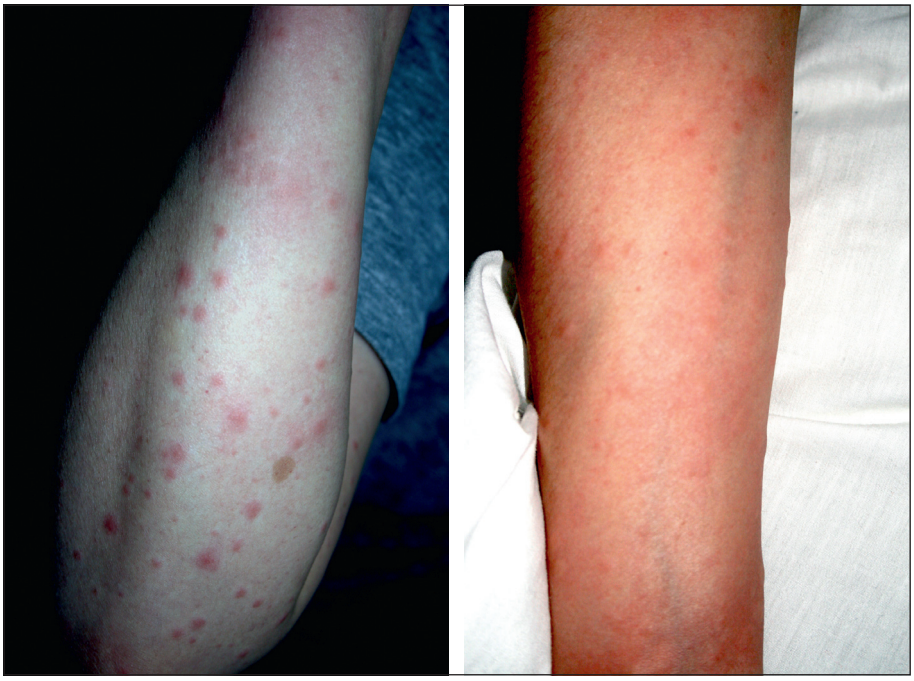

Figure 1. Early stage of eruption showing erythematous papules on the patient's right forearm (left) and leg.

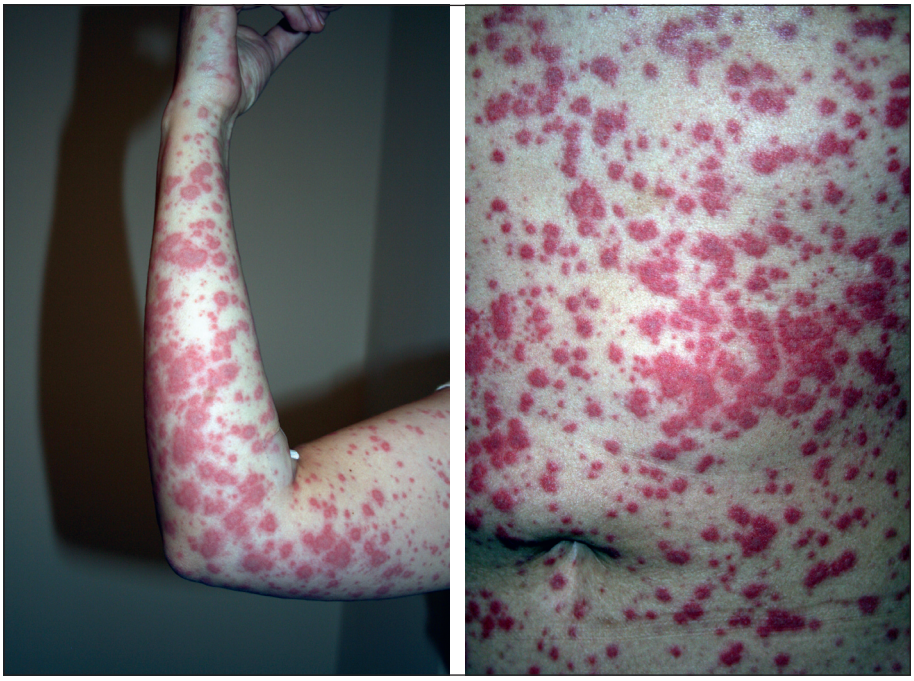

Figure 2. Dark erythematous papules and plaques with central oedema on the patient's right arm (left) and abdomen.

disorders and range in severity. Like our case, 90% of all drug-induced rashes are benign (Hunziker *et al*., 1997), most commonly taking a form of exanthematous or morbiliform rash without eosinophilia or liver function abnormalities, and disappear over the course of a few days without major health consequences (Błaszczyk *et al*., 2013). Patients typically present with symmetric exanthematous or maculopapular rash that appears between days 4 and 14 of exposure and is associated with pruritus and low-grade fever (Roujeau, 2005). Acute generalised exanthematous pustulosis follows a different time-line, starting within two days of introduction of the offending chemical as multiple small non-follicular pustules that arise on a diffuse oedematous erythematous base, with frequent involvement of mucosal membranes and natural folds of the body (Roujeau, 2005). ASM-induced hypersensitivity constitutes a subclass of drug-induced hypersensitivities. Here, the eruptions are diffuse and can be severe with an associated mortality rate of approximately 10% (Roujeau, 2005). The rash reported herein is far from being a drug reaction with eosinophilia and systemic symptoms (DRESS) which typically presents with a triad of fever, cutaneous rash, and internal organ dysfunction, and is frequently associated with liver enzyme abnormalities. Like our patient, DRESS patients present with diffuse skin eruption, characterised by deeply erythematous papules and plaques. However, the danger of the syndrome lies frequently in the changes in the internal organ functions, with liver enzyme elevation, eosinophilia, gastro-intestinal involvement, and pulmonary manifestations which serve as major contributors to morbidity and mortality (Roujeau, 2005). DRESS was first described after introduction of cyclic hydantoins compounds (Kumari *et al*., 2011), and, after introduction of Dilantin to the market, it was named "Dilantin hypersensitivity" (Kumari *et al*., 2011) and continues to be a well-recognised potential adverse drug reaction.

Finally, among the most severe expressions of drug-induced cutaneous reactions is Stevens-Johnson syndrome, which, unlike a benign "common rash", constitutes a life-threatening condition presenting as fever, sore throat, fatigue, and other flu-like symptoms, followed by mucosal blistering and ulceration, and extensive erythematous skin lesions with desquamation. The related condition, toxic epidermal necrolysis (TEN), is also life-threatening and often includes separation of the dermis from the epidermis, forming bullae and ulceration covering extensive body surfaces and necessitating treatment in burn units.

Despite years of post-marketing experience with LCM and hundreds of thousands of individuals currently being treated with this medication worldwide, a Pubmed search using "lacosamide and rash" and another using "lacosamide and dermatitis" yielded only one post-marketing report of LCM-related rash (Höfler and Trinka, 2013). The rash was not described in detail in that report, but the authors mentioned that it occurred in two subjects in the setting of intra-

venous LCM administration for status epilepticus or seizure clusters, and led to discontinuation of LCM in only one of the two. High doses of LCM, such as those achieved during the intravenous administration, can facilitate development of adverse drug reactions, including rashes. It is worthwhile mentioning that a report of consumption of 7 g of LCM with a serum concentration of 27.7 μg/mL (normal range: 6.6-18.3) in a suicidal attempt yielded cardiac side effects, but no cutaneous eruptions (Malissin *et al*., 2013). Our patient had a history of rash in response to lamotrigine, but any conclusions about cross reactivity of LCM with other ASMs may only be tentative at this stage. In addition, the patient was lost to follow-up, and no additional studies such as histological analysis or serology were performed.

In conclusion, we report a 36-year-old woman with LCM-induced rash after eight days of exposure to medication. In our case, it is highly likely that escalating the daily dose from 50 to 100 mg BID did not *per se* cause the skin eruption, but rather represented a classic delayed response (Roujeau, 2005). Fortunately, our patient did not experience any systemic involvement and was successfully treated by withdrawal of the offending chemical agent and addition of antihistamines and steroids. This finding is consistent with a drug-induced skin eruption. □

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