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SHORT COMMUNICATION

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Drug reexposure in children with severe mucocutaneous reactions

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Abstract
In pediatric patients, severe cutaneous adverse reactions (SCARs) frequently occur in the course of acute illnesses, mostly infections, which are usually treated with antibiotics or analgesics. The drug provocation test (DPT) is contraindicated in such situations, due to the risk of triggering a new severe reaction. As a consequence, lifelong avoidance is recommended. However, causation is uncertain in most cases. The dilemma arises when avoiding the drug is not harmless for the patient. We have attended three patients who were referred to our pediatric allergy unit with a history of SCAR related in time to simultaneous use of paracetamol and ibuprofen. Medical records and images of the patients were reviewed with the assistance of a dermatologist, and alternative diagnoses were considered in both cases. The ALDEN score for implicated drugs was calculated. After considering a high probability of ibuprofen tolerance and obtaining informed consent from the patients, we performed a sequential allergy workup including *in vitro* tests, skin tests, and finally DPT in two of the patients, confirming ibuprofen tolerance. In conclusion, although generally contraindicated, DPT may be considered for some useful drugs after careful evaluation of the risk-benefit balance, preceded by a sequential study including *in vitro* and skin tests.

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Introduction

Pediatric allergy units attend a large number of patients with suspected drug hypersensitivity. Most of the suspected reactions are mild, and can be discarded after a drug provocation test (DPT) with the culprit drug. This has a strong positive impact on the quality of life and future healthcare of these patients. Much less frequently, the suspicion of hypersensitivity emerges from the occurrence of a severe cutaneous adverse reaction (SCAR) such as Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN). DPT is contraindicated in these cases due to the risk of triggering a new severe reaction. Therefore, drugs implicated in severe skin or systemic reactions are considered dangerous for the patient, and lifelong avoidance is recommended.[1] This can be a serious drawback when such drugs are very frequently needed or regarded as the first-choice treatment for the patient, and no equally effective alternatives are available.

In pediatric patients, SCARs frequently occur in the course of acute illnesses, mostly infections, which are usually treated with antibiotics or analgesics, making it difficult to discern whether the reaction was related to the administered drugs or the ongoing disease.[2] Paracetamol and ibuprofen are the two most commonly used analgesic and antipyretic drugs in pediatrics. When both are involved in SCAR, the dilemma of recommending their lifelong avoidance arises, with the need to resort to other second-line drugs for the symptomatic treatment of fever or pain, with the added issue of possible cross-reactivity with other nonsteroidal anti-inflammatory drugs.[3] We attended three patients who were referred to our pediatric allergy unit with a history of SCAR related in time to paracetamol and ibuprofen use. These patients and their relatives signed the consent for review and anonymized publication of their clinical data.

Case Reports

The main data of these three patients are shown in Table 1. All three of them had received metamizol during hospitalization, with no observed adverse effects. Medical records and images of the patients were reviewed in our pediatric allergy unit with the assistance of a dermatologist, and alternative diagnoses were considered in two of the cases (Table 1). The ALDEN score, an algorithm specifically designed to evaluate the causality of drugs involved in SJS and TEN,[4] was calculated (Table 1). After this evaluation, it was considered that these patients would have a high probability of tolerating, at least, ibuprofen. Given that the performance of DPT, the definitive test to verify tolerance, is considered contraindicated in patients with SCAR in the main international clinical guidelines, a formal consultation with the Clinical Ethics Committee of the Alicante University General Hospital was made. The committee raised no objections to request appropriate informed consent to carry out a sequential allergy workup including *in vitro* tests, skin tests and, finally, DPT. The families consented, and all tests were performed between 3 and 12 months after the index reaction (Table 1). The lymphocyte transformation test was performed with increasing concentrations of paracetamol and ibuprofen, and the stimulation index was calculated. The patch tests were performed with 10% paracetamol and 10% ibuprofen in petrolatum. The patches were applied for 48 h to the upper back and read at the time of patch removal and again 48 h later (96 h from patch placement). The prick test (5 mg/ml) and intradermal test (0.1 mg/ml) with ibuprofen were followed by immediate (15 min) and delayed (48–72 h) readings. After obtaining negative results with these tests, Patient 1 tolerated DPT with increasing single doses of ibuprofen, with weekly administration and observation intervals (5 mg, 20 mg, 100 mg, and 400 mg). After that, a course of 400 mg of ibuprofen was administered every 8 h for 2 days (6 doses in total), which was also tolerated. In Patient 3, a similar DPT was performed, though some doses had to be repeated due to mild oral discomfort (small canker sores, mild lip edema), which the patient had already suffered occasionally before DPT and did not reappear, with a final tolerated dose of 300 mg repeated at 12 h (2 doses). Patients 1 and 3 have subsequently taken ibuprofen as a symptomatic treatment, with good tolerance. In Patient 2, the decision was made to not perform DPT due to the presence of severe corneal sequelae with visual impairment.

Discussion

Children with a history of SCAR related in time to drug administration are usually advised to avoid the suspected drug. However, causation is uncertain in most cases. The dilemma arises when avoiding the drug is not harmless for the patient. Firstly, it is important to try verify the reported diagnosis. The diagnosis of SJS and TEN may overlap with other disorders such as erythema multiforme major or mucositis associated with *Mycoplasma pneumoniae* infection, making it very difficult to confirm the implication of drugs in these episodes.[5] Secondly, the ALDEN score may help to determine the probability of causation for any implicated drug.[4] Although DPT is contraindicated due to the risk of recurrence of a severe reaction, it may be contemplated when causation is considered unlikely, and drug avoidance implies disadvantages or risks for the patient after carefully considering the risk–benefit ratio. DPT should be preceded by a sequential study, including *in vitro* tests and skin tests, after obtaining informed consent from the patient and family.[6,7] A similar approach to that described above has been proposed and carried out in patients with DRESS syndrome.[8] There are few reported cases of intentional or unintentional reexposure to the drug involved in SCAR,[7,9-11] and even fewer cases in pediatric patients,[12-14] mostly with satisfactory results. A recent study has shown the ability of high-dose intravenous corticosteroids to reverse the recurrence of symptoms during DPT in patients with SJS and DRESS syndrome, potentially improving the safety of drug rechallenge protocols in these patients.[15]

Conclusion

Although generally contraindicated, DPT may be considered for some useful drugs weakly implicated in SCAR (based on

Table 1 Clinical characteristics of the patients and results of the allergy workup.

Patient	Age (years)/ Sex	Acute episode and hospitalization data		Allergy workup					
		Clinical characteristics	Hospital diagnosis	Revised diagnosis	ALDEN score for implicated drugs	Lymphocyte transformation test	Patch test	Prick and intradermal test	DPT
1	14/M	Fever and upper respiratory tract infection. After 7 days, oral, ocular, and genital mucositis appeared, with minimal skin involvement. Hospitalization for 18 days.	SJS Mycoplasma pneumoniae infection	Possible mycoplasma-associated mucositis	Paracetamol +2 (possible) Ibuprofen -1 (very unlikely) Azithromycin -7 (very unlikely)	Paracetamol (+) (repeated on two occasions) Ibuprofen (−)	Paracetamol (−) Ibuprofen (−)	Ibuprofen (−)	Tolerates ibuprofen
2	2/F	After 3 days with fever, a skin rash and lesions on the oral, ocular, and genital mucosa appeared. Progression of ocular lesions and skin detachment. 45% of the body surface was involved. Hospitalization for 29 days, including 19 days in the PICU.	TEN probably drug related	TEN resulting in visual impairment	Paracetamol +1 (unlikely) Ibuprofen 0 (unlikely)	Paracetamol (−) Ibuprofen (−)	Paracetamol (−) Ibuprofen (−)	Not performed	Not performed
3	10/F	Fever, odynophagia, skin vesicular rash, and lesions on the oral, ocular, and genital mucosa. Hospitalization for 12 days.	SJS	Possible erythema multiforme major	Paracetamol +1 (unlikely) Ibuprofen 0 (unlikely)	Paracetamol (−) Ibuprofen (−)	Paracetamol (−) Ibuprofen (−)	Ibuprofen (−)	Tolerates ibuprofen

DPT: Drug provocation test; F: Female; M: Male; PICU: Pediatric Intensive Care Unit; SJS: Stevens–Johnson syndrome; TEN: Toxic epidermal necrolysis; (+): Positive test result. (−): Negative test result

the revised diagnosis and/or ALDEN score), after adequate evaluation of the risk-benefit balance and the obtainment of informed consent from the patient, preceded by a sequential study including *in vitro* and skin tests.

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