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Phenobarbital-induced DiHS and ceftriaxone hypersensitivity reaction: a case of multiple drug allergy

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Key words

Anticonvulsivant drugs, DiHS, Multiple drug hypersensitivity

Summary

Patients with DiHS show an increased risk of sensitization to multiple drugs. We report a case of a young woman who developed cutaneous rash, lymphoadenopathy, malaise and fever after the introduction of phenobarbitale. Because of these symptoms, she was treated with ceftriaxone and she experienced a severe flare-up of the cutaneous and general reaction. Allergological work-up, by cutaneous and lymphocyte transformation test, confirmed a double sensitization to phenobarbital and ceftriaxone. In conclusion, the high risk of DiHS during anticonvulsive therapy should suggest caution in using additional drugs, because of an increased risk of multiple reactions.

Drug-induced Hypersensitivity Syndrome (DiHS) is a life-threatening systemic reaction characterized by cutaneous rash, fever, lymphoadenopaty, internal organ involvement and leukocytosis with eosinophilia. Anticonvulsive drugs are among the most frequent causative agents (1). Patients with DiHS show an increased risk of sensitization to multiple drugs (2,3).

A 30- year-old woman treated with sodium valproate for six years because of a post-traumatic epileptic syndrome, added phenobarbital on therapy. After three weeks she developed cutaneous rash, lymphadenopathy, malaise and fever. The persistence of this clinical picture despite the discontinuation of phenobarbital, induced to start antibiotic therapy with ceftriaxone. After a few doses the patient developed a flare-up of the cutaneous rash, with labial angioedema and a worsening of her general condition, giving to the hospitalization. The laboratory findings showed leucocytosis with eosinophylia and an increase of transaminases (ALT 123 U/l, AST 65 U/l). An allergological consultation suggested the hypothesis of a drug hypersensitivity reaction induced by phenobarbital, with a subsequent sensitization to ceftriaxone. Therefore, antibiotic therapy was stopped. The clinical recovery was very slow.

Four months later, the patient was submitted to the allergological investigations:

- Patch test for anticonvulsive drugs and beta-lactams antibiotics (phenobarbital, carbamazepine, phenytoin, sodium valproate, ceftriaxone, ceftazidime, cefotaxime, penicillin, ampicillin, amoxicillin)
- Cutaneous allergological test for ceftriaxone and phenobarbital (prick and intradermal test – i.d.)
- Lymphocyte Transformation Test (LTT) for phenobarbital, ceftriaxone, cefotaxime, ceftazidime, penicillin G.

The results confirmed a positive late reaction to phenobarbital (positive patch-test, negative prick and intradermal test) and ceftriaxone (positive patch test and i.d. 2 mg/ml at 24 h reading). LTT was positive for both the drugs, at a higher level of Stimulation Index (S.I.) for ceftriaxone (tab. 1). Among the other beta-lactams, LTT was positive for cefotaxime confirming the possible cross-reactivity between these two cephalosporins.

The three diagnostic methods showed a different sensitivity for the drugs investigated. Particularly, intradermal test showed a lower sensitivity than patch test and LTT for phenobarbital, while results were concordant for ceftriaxone (4,5).

At our knowledge, this case is the first report of multiple drug hypersensitivity with involvement of phenobarbital and ceftriaxone, confirmed by in vivo and in vitro tests. This is an example of sensitization to different drugs administered sequentially, responsible of a paradoxical worsening of clinical symptoms of DiHS, despite the withdrawal of the first causative drug.

The drug-induced massive T-cell activation, occurring in case of DiHS, can increase the risk of hypersensitivity reactions to drugs different from the eliciting one (3). For its clinical features DiHS may be often mistaken for severe infectious diseases and unnecessary antibiotic therapy may be started, with a risk of developing multiple drug reaction. As a practical consequence, we should keep in mind that in case of a clinical picture suggesting a DiHS, particularly frequent in patients on anticonvulsive therapy, empirical treatment with antibiotics should be avoided.

Table 1 - Results of the allergological test

DRUG	PATCH (48/72 h)	LTT - S.I.	I.D (24 h)
Phenobarbitale 30%	+++	11.6	Neg
Carbamazepine 1%	Neg.	n.p.	n.p.
Phenitoin 30%	Neg.	n.p.	n.p.
Sodium valproate 30%	Neg.	n.p.	n.p.
Ceftriaxone 25%	+	46	POS
Ceftazidime 25%	Neg.	0.6	n.p.
Cefotaxime 25%	Neg.	31	n.p.
Penicillin 5%	Neg.	0.8	n.p.
Ampicillin 20%	Neg.	n.p.	n.p.
Amoxicillin 20%	Neg.	n.p.	n.p.

LTT = Lymphocyte Transformation Test S.I. =Stimulation Index
I.D. = intradermal test n.p.= not performed

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Erratum corrige

On the top of the page 90 of the issue n. 3-2008 there was an error: Vol 40, N 2, 90-103, 2008 is wrong and the correct version is the following: **Vol 40, N 3, 90-103, 2008**