



Allergologia et immunopathologia

www.elsevier.es/ai



RESEARCH LETTERS

Successful desensitisation to ceftriaxone in a patient with doxycycline resistant Lyme disease

To the Editor:

Lyme disease is due to infection with a spirochete, *Borrelia burgdorferi*. It is transmitted from host to host by the *Ixodes* or deer tick. Approximately 20000 cases of Lyme disease are reported every year in the United States. Each of the three stages of the disease is associated with specific clinical features: early localised infection (with erythema migrans, fever, malaise, fatigue, headache and myalgias); early disseminated infection (days or weeks later, with neurological, musculoskeletal or cardiovascular symptoms, and multiple erythema migrans lesions); and late disseminated infection (with articular involvement)¹. Lyme disease is mainly a clinical diagnosis and laboratory results may or may not support it. Antibiotic therapy is curative in most patients. The treatment of choice includes doxycycline or amoxicillin, cefuroxime axetil or erythromycin. However, severe or neurological disease with parenchymal involvement requires intravenous treatment with ceftriaxone or penicillin G¹.

The authors present the case of a 60 year old woman, with Lyme disease with neurological involvement in which first doxycycline treatment had failed. Third generation cephalosporins are currently the most effective treatment because of their very low minimum bactericidal concentration (MBC $\leq 0.4 \mu\text{g/mL}$ for ceftriaxone) and have been shown to be effective in penicillin and tetracycline failures². Alternative treatment with ceftriaxone 1 g/day intravenous (iv) for thirty days was started.

On the 8th day, the patient referred itching which evolved into a rash on the palms, feet and neck, resolving spontaneously after the iv infusion was stopped. Treatment was re-started the day after and by the 16th day, she developed immediate pharyngeal, plantar and palmar pruritus, cutaneous rash, nausea and abdominal cramps with no other symptoms or signs. Emergency treatment for anaphylaxis was performed, with intramuscular epinephrine, systemic corticosteroids and antihistamines.

The patient was referred to our Allergy Division for study and management, as no alternative drug was appropriate at this point. According to the *European Network for Drug Allergy* (ENDA) group recommendations³, cutaneous testing (prick and intradermal tests) were not reasonable as the patient was critically ill, and immediate treatment for neurological Lyme disease was mandatory.

The patient began a desensitisation protocol to ceftriaxone starting with 0.001 mg on the first day, with 10 fold increase every 20 minutes; 1 mg as the first dose on the second, 100 mg as the first dose on the third and 1000 mg thereafter until the end of the treatment (Tables I and II). The total dose (1 g/day) was achieved on the third day of treatment, after an eleven step protocol, without any adverse reactions.

The study of hypersensitivity drug reactions is based on a thorough clinical history, skin testing, in some cases (i.e. β -lactams) determination of drug specific IgE and provocation tests. According to the publication of Brockow et al.³, cutaneous testing should not be performed in the acute phase of reac-

Table 1 Solution preparation

Base solution: 1000 mg in 10 mL distilled water \rightarrow 100 mg/mL			
Solution	Quantity (mL)	Distilled water (mL)	Final solution
100 mg/mL	0.1	0.9	10 mg/mL
10 mg/mL	0.1	0.9	1 mg/mL
1 mg/mL	0.1	0.9	0.1 mg/mL
0.1 mg/mL	0.1	0.9	0.01 mg/mL
0.01 mg/mL	0.1	0.9	0.001 mg/mL

Table 2 Desensitisation protocol

Day	Concentration (mg/mL)	Quantity (mL)	Time	Dose (mg)	Cumulative Dose
1	0.001	1	20 min	0.001	1.111 mg
	0.01	1		0.01	
	0.1	1		0.1	
	1	1		1	
2	10	0.1	20 min	1	66 mg
		0.5		5	
		1		10	
		5		50	
3	100	1	20 min	100	900 mg
		2.5		250	
		5.5		550	
4-30	100	10		1000	1000 mg

tion, due to its inherent risks, and an interval of at least 4 weeks should be respected until cutaneous testing is performed.

When available, drug specific IgE should be determined, since it is of great value for diagnostic purposes in the work up of drug allergy. However, in our centre the only available specific IgEs are for amoxicillin, penicilloyl G, penicilloyl V, ampicillin and cefaclor (Phadia® catalogue), so, no specific IgE to ceftriaxone was determined in this patient, although it would have been of great importance.

Desensitisation for drug allergy is the induction of temporary clinical unresponsiveness to drug antigens. The main purpose of developing rapid desensitisation protocols for the treatment of drug hypersensitivity is to provide essential medications to patients avoiding severe reactions⁴. The administration of small doses of a drug until achieving the full therapeutic dose can be safely performed in allergic patients, allowing the treatment of severe diseases. These procedures should only be performed in the hospital setting and by fully trained medical personnel. There has been increasing interest in developing more rapid desensitisation protocols to antibiotics, mainly β -lactams, regarding its essential role in a wide number of infections, like syphilis in pregnant women.

There are several protocols for intravenous cephalosporin desensitisation, which range from hours to 14 days. A typical protocol for desensitisation to intravenous penicillin or cephalosporins starts at 1/10000 to 1/100 target dose, doubling the dose every 15-20 minutes, until reaching the full therapeutic dose⁵.

Because this patient was seriously ill, it was decided to proceed with a drug desensitisation protocol with close observation and monitoring of the patient, starting with a very small initial dose (0.001 mg) of ceftriaxone. The total dose (1 g/day) was achieved after 3 days and effective treatment was completed until total recovery of the patient (30 days).

Although more recent and rapid desensitisation protocols to cephalosporins are described in literature, the authors applied a 3-day protocol, because of the severity of the illness, and the patient could have more risks with a faster protocol.

No work up study was done to confirm the drug allergy diagnosis since the patient missed the scheduled appointment. However, the clinical history and the response to drug withdrawal clearly points to the diagnosis of drug allergy.

References

1. Bratton RL, Whiteside JW, Hovan MJ, Edwards FD. Diagnosis and treatment of Lyme disease. *Mayo Clin Proc.* 2008;83(5):566-71.
2. Johnson RC, Kodner C, Russell M. In vitro and in vivo susceptibility of the Lyme disease spirochete, *Borrelia burgdorferi*, to four antimicrobial agents. *Antimicrob Agents Chemother.* 1987;31:164-7.
3. Brockow K, Romano A, Blanca M, Ring J, Pichler W, Demoly P. General considerations for skin test procedures in the diagnosis of drug hypersensitivity. *Allergy.* 2002;57(1):45-51.
4. Castells M. Desensitization for drug allergy. *Curr Opin Allergy Clin Immunol.* 2006;6:476-81.
5. Win P, Brown H, Zankar A, Hussain I. Rapid intravenous cephalosporin desensitization. *J Allergy Clin Immunol.* 2005;116: 225-8.

Linda Graça Cruz*, Josefina Rodrigues,
Carmen Botelho, Edite Rio and Maria Graça Castel-Branco
Hospital S. João, Porto, Portugal

*Corresponding author.

E-mail: linda.cruz4@gmail.com (L.G. Cruz)

Exanthematic reaction to pseudoephedrine

To the Editor:

Pseudoephedrine is a sympathomimetic drug widely used in over-the-counter anti-catarrrhal preparations. Despite its widespread use, cutaneous adverse effects are rare, and generally not life-threatening.

A 30-year-old Caucasian woman presented with a generalised, maculopapular, pruriginous dermatitis with facial oedema, malaise and fever (Fig. 1). During the five days preceding the emergence of the cutaneous lesions, the patient had been taking Actifed® (pseudoephedrine and triprolidine) for rhinorrhea and nasal congestion with no other accompanying symptoms. She denied previous intake of this drug.

Physical examination revealed a generalised, maculopapular dermatitis, sparing the distal extremities and mucous membranes, with facial oedema. Tympanic temperature was 38 °C. No peripheral lymph nodes were palpable and hepatosplenomegaly was absent.

Laboratory tests revealed slight neutrophilia (7.7×10^9 cells/L) without leucocytosis and elevated C-reactive protein levels in blood (21.2 mg/dL). *Mycoplasma pneumonia*, Epstein Barr, Cytomegalovirus, B and C hepatitis, HIV-1 and HIV-2 serologies were negative. Antistreptolysin titter was negative. Chest radiography showed clear lung fields.

Histopathological examination revealed vacuolar degeneration of the basal layer, oedema and haemorrhage of the papillary dermis and mixed perivascular inflammatory infiltrate.

The patient's condition was successfully managed with oral prednisolone.

Patch tests performed with Actifed® as it is and with pseudoephedrine sulphate (1% pet) were both positive (++). Portuguese standard series, ephedrine (1% pet) and phenylephrine (1% aq) were negative. We were unable to test for triprolidine. Testing pseudoephedrine sulphate (1% pet) elicited no reactions in five healthy controls.



Figure 1. On admission: generalized, maculopapular, pruriginous dermatitis