Value of patch tests in clindamycin-related drug eruptions

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Summary

Background. Patch tests help to confirm the aetiology of the cutaneous adverse drug reactions involving delayed hypersensitivity mechanisms, but the results vary with the pattern of skin reaction and the culprit drug.

Objectives. To analyse the results of patch tests in patients with cutaneous adverse drug reactions imputable to clindamycin and assess their contribution to the diagnosis.

Patients and methods. Between 2005 and 2009, we studied patients with delayed cutaneous adverse drug reactions following administration of clindamycin, usually associated with other drugs. After resolution of the cutaneous adverse drug reaction, patch tests were performed with a series of antibiotics, including pure clindamycin 10% in petrolatum.

Results. We studied 30 patients (23 females and 7 males) aged 33–86 years (mean 59.97 years) with generalized maculopapular exanthema where clindamycin was among the highly suspected drugs. Two patients had a previous positive involuntary rechallenge. Patch tests with clindamycin were positive in 9 of 30 patients (30%). More than 50 control patients patch tested with clindamycin were negative.

Discussion. We considered the positive patch tests results with clindamycin, in the 9 patients with maculopapular exantema, to be specific, versus the negative results observed in the control group. Although the sensitivity is low (30%), they confirmed the responsibility of this antibiotic in cutaneous adverse drug reactions in which, with only chronological criteria, it was not possible to conclude on the culprit drug.

Key words: clindamycin; cutaneous adverse drug reaction; drug hypersensitivity; maculopapular exanthema; patch tests.

Clindamycin, a synthetic antibiotic from the class of lincomycins, is a bacteriostatic agent inhibiting bacterial protein synthesis, and is used in the treatment of infections caused by anaerobic and aerobic Gram-positive bacteria, some protozoa (*Toxoplasma gondii*, *Plasmodium falciparum*, *Babesia* spp.) and fungi (*Pneumocystis jiroveci*) (1–3).

Side effects include: diarrhoea, pseudomembranous colitis, metallic taste, transitory increase in serum of aminotransferases, granulocytopenia, thrombocytopenia, and rash (4). Cutaneous adverse drug reactions to clindamycin are usually considered to be rare, but in publications they are reported to occur in <1% up to 10.5% of treated patients (2). The majority of these reactions are macular and maculopapular exanthema, although the Stevens–Johnson syndrome and, more recently, several cases of acute generalized exanthematous pustulosis have been associated with clindamycin (4–9).

Skin tests, and particularly patch tests, have become popular in the diagnosis of cutaneous adverse drug reactions, allowing the identification or confirmation of

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the aetiological agent in some cases. Nevertheless, patch test reactivity is highly variable, depending mainly on the clinical characteristics of the cutaneous adverse drug reaction and on the culprit drug (10).

In this study, we analysed patch tests results in patients with drug reactions attributable to clindamycin, with the purpose of evaluating their contribution to the aetiological diagnosis.

Patients and Methods

Between 2005 and 2009, in the Dermatology Department of the Coimbra University Hospital, we studied 30 patients with delayed cutaneous reactions associated with clindamycin (Fig. 1).

The clinical characteristics of the drug eruption, the time elapsed between drug introduction and initiation of the rash, the infections that motivated treatment, the concomitant drugs used and the treatment were evaluated.

Patch tests were performed 6–12 weeks after complete resolution of the drug eruption. Tests were applied on the upper back, in Finn Chambers® on Scanpor®, and the readings were performed on D2 and D3 or D4, according to the guidelines of the International Contact Dermatitis Research Group. Only + or stronger reactions were considered.

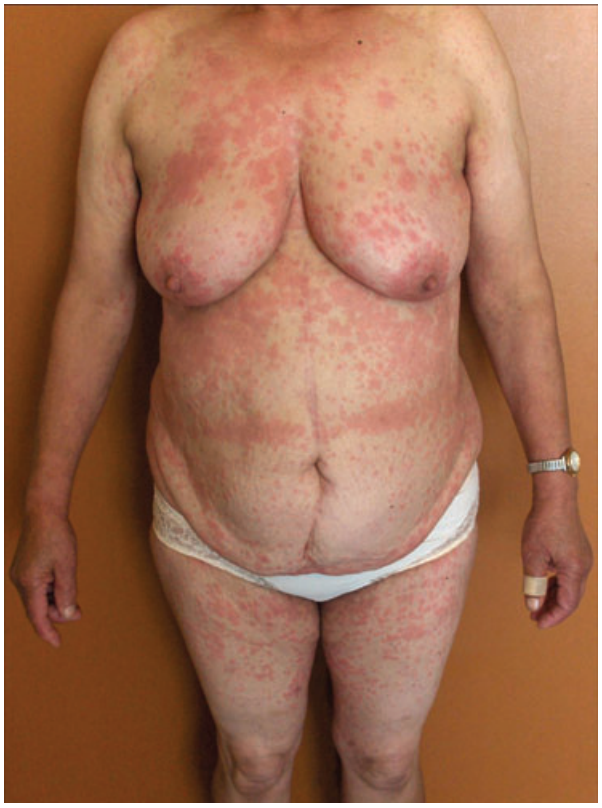

Fig. 1. Maculopapular exanthema induced by clindamycin.

All patients were tested with the European baseline series of allergens, a series of systemic antibiotics (Chemotechnique® Diagnostics, Vellinge, Sweden), and pure clindamycin at 10% in petrolatum, as usually recommended for performing patch testing with other antibiotics (10). Clindamycin was initially supplied by the pharmaceutical industry and prepared at our laboratory and, more recently, was obtained from Chemotechnique® Diagnostics. Additionally, the powder from capsules of two commercial preparations of clindamycin (Dalacin C® and Clindamycin Atral®) were diluted in pet. so that the final concentration of clindamycin in the peparation was 10%. In individual cases, drugs administered concomitantly with clindamycin that were not part of the drug series from Chemotechnique® Diagnostics [e.g. other antibiotics and non-steroidal anti-inflammatory drugs (NSAIDs)] were also prepared at 10% pet., with either pure products supplied by the pharmaceutical industry (cefazolin and cefoxitin) or commercial preparations, namely vancomycin (Vancomycin Labesfal®) and levofloxacin (Tarivid®).

Pure clindamycin at 10% pet. and prepared from commercial preparations was also tested in 42 controls with cutaneous adverse drug reactions attributed to other antibiotics and in nine patients exposed to clindamycin without cutaneous adverse drug reactions.

Results

A total of 30 patients (23 females and 7 males) with ages ranging from 33 to 86 years (59.97 ± 13.21 years) were included in the study.

They had suffered from a variety of infections (27 with severe erysipelas, 1 with osteomyelitis, and 2 with dental abscesses), and had therefore been treated with oral clindamycin (150–300 mg every 6–8 h) and with other antibiotics in 29 cases, namely cefazolin or cefoxitin in 26, clarithromycin in 1, levofloxacin in 1, and vancomycin in 1; 2 had been treated with NSAIDs.

They all developed a generalized, pruriginous, maculopapular exanthema that began 2–12 days (mean 7.9 ± 2.2 days) after the introduction of clindamycin. Two patients with recurring erysipelas developed a similar maculopapular exanthema within 48 h of the administration of clindamycin and a different cephalosporin.

Patients were treated with topical steroids, oral antihistamines and, in 15 patients, also oral corticosteroids. Clindamycin was stopped in all patients

Table 1. Clinical data of patients subjected to patch testing

Patient no.	Age (years)/sex	Type of infection	Drugs used	Start of maculopapular exanthema (days)	Systemic corticosteroid therapy
1	66/M	Erysipelas	Cly + Cefx	10	Yes
2	72/F	Erysipelas	Cly + Cefx	10	—
3	66/F	Erysipelas	Cly + Cefz	10	Yes
4	71/F	Erysipelas	Cly + Levo	9	—
5	76/F	Erysipelas	Cly + Cefa	9	Yes
6	43/F	Erysipelas	Cly + Cefx/Cefz	9	Yes
7	59/F	Erysipelas	Cly + Cefa/Ceftz	8	Yes
8	79/F	Erysipelas	Cly + Cefz	10	—
9	53/M	Erysipelas	Cly + Cefz	8	Yes
10	66/F	Erysipelas	Cly + Cefa	7	Yes
11	52/F	Erysipelas	Cly + Cefx/Cefa	9	Yes
12	52/F	Erysipelas	Cly + Cefx	7	Yes
13	67/F	Erysipelas	Cly + Cefx	8	Yes
14	61/F	Erysipelas	Cly + Cefa	9	—
15	75/M	Erysipelas	Cly + Cefx	8	—
16	55/F	Erysipelas	Cly + Cefx	3	Yes
17	70/F	Erysipelas	Cly + Cefz	7	—
18	40/M	Erysipelas	Cly + Cefz	5	—
19	59/F	Erysipelas	Cly + Cefz	8	—
20	86/F	Erysipelas	Cly + Cefx	8	Yes
21	69/F	Osteomyelitis	Cly + Vanc + Te	10	—
22	62/F	Erysipelas	Cly + Cefx	9	—
23	53/M	Erysipelas	Cly + Cefx	8	Yes
24	62/F	Erysipelas	Cly + Cefz	7	—
25	33/F	Dental abscess	Cly + Clar	2	—
26	45/F	Dental abscess	Cly + Nim	12	Yes
27	60/M	Erysipelas	Cly + Cefx	4	Yes
28	69/F	Erysipelas	Cly + Cefz	8	—
29	45/F	Erysipelas	Cly + Cefx	7	—
30	33/M	Erysipelas	Cly + Cefz	8	—
	Mean = 59.97± 13.21 years 23F/7M	Erysipelas: 27 Osteomyelitis: 1 Dental abscess: 2		Mean = 7.9 ± 2.2 days	Total = 15

Cefa, cefaclor; Cefx, cefoxitin; Cefz, cefazolin; Ceftz, ceftazidime; Clar, clarithromycin; Cly, clindamycin; Levo, levofloxacin; Nim, nimesulide; Te, tenoxicam; Vanc, vancomycin; F, female; M, male.

and, eventually, so were other antibiotics with the same degree of imputability. In patients observed in more recent years, after the beginning of the maculopapular exanthema, the cephalosporin introduced concomitantly with clindamycin was continued, with no delay in the resolution of the rash. When still needed, the antibiotics were replaced by levofloxacin or clarithromycin. For patient details, see Table 1.

In 9 of the 30 patients studied (30%), we observed positive patch test reactions (+ or ++) to clindamycin, with reactivities of similar intensity with either the pure powder or the powder of the commercial capsules (Fig. 2). One patient had a simultaneous positive reaction to cefoxitin 10% pet. (Fig. 3). There were no reactions to other antibiotics or drugs used concomitantly with clindamycin, and none of the controls reacted to clindamycin preparations.

In 10 patients (33.3%), there was reactivity to allergens of the European baseline series, mainly to nickel sulfate (4 patients, 13.3%) and the topical drug-related allergens *Myroxylon pereirae* (4), fragrance mixes I and II (3), lanolin (wool alcohols) (2), thimerosal (2), and caine mix (2), reflecting the high number of patients with leg ulcers or chronic venous insufficiency who developed erysipelas of the lower limbs (Table 2).

Discussion

Patch testing can be a useful complementary diagnostic method in the study of cutaneous adverse drug reactions, particularly when there is suspicion of the involvement

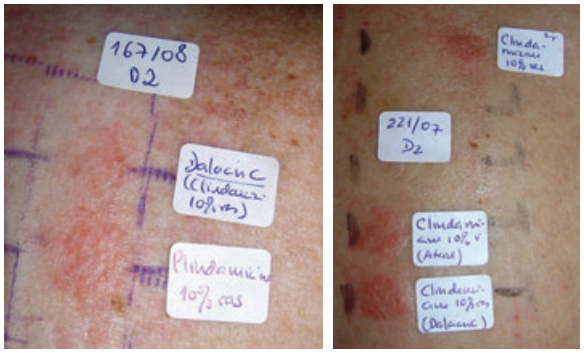

Fig. 2. Positive reactions to clindamycin, both pure powder and the powder of the commercial capsules (Dalacin C® and Clindamycin Atral®), prepared at 10% pet.

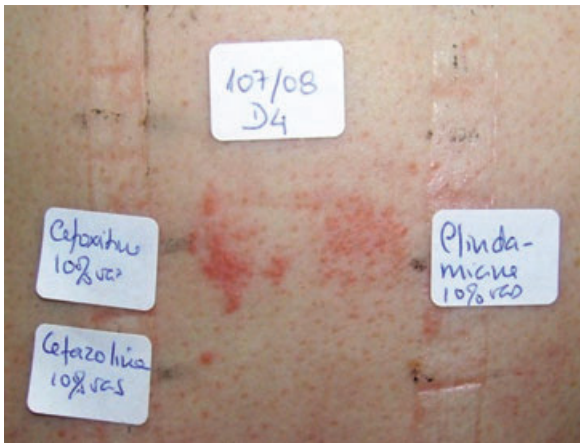

Fig. 3. Positive reaction to cefoxitin and clindamycin in patient 24.

of a delayed hypersensitivity reaction, namely in maculopapular exanthema, drug rash with eosinophilia and systemic symptoms (DRESS) (11), acute generalized exanthematous pustulosis, fixed drug eruption and, eventually, also in Stevens–Johnson syndrome/toxic epidermal necrolysis (12). In these delayed cutaneous adverse drug reactions, patch test reactivity varies according to the tested drug and the clinical pattern of the cutaneous adverse drug reaction, being higher in cases of maculopapular exanthema and with some drugs, such as β-lactam antibiotics and carbamazepine (11, 13). However, patch test reactivity in these cutaneous adverse drug reactions is significantly inferior to that in allergic contact dermatitis, the paradigm of a delayed hypersensitivity skin immune reaction. There are several possible reasons for false-negative reactions: the allergen might be a metabolite of the drug that is not produced from skin application, the concentration or the vehicle for patch testing might be inadequate, or simultaneous factors needed to trigger the reaction may not be present, namely a concomitant drug or an acute viral infection.

There are few studies evaluating the usefulness of patch testing with clindamycin in patients with a

Table 2. Results of patch tests with clindamycin and other allergens

Patient no.	Clindamycin to 10% pet. D2	Clindamycin to 10% pet. D3/D4	Other patch tests
1	—	—	Nickel ++ Caine mix + Methyldibromo glutaronitrile ++ Corticosteroid mix ++ Busedonide +
2	—	—	Thiuram mix ++ Colophonium ++ *Myroxylon pereirae* ++ Fragrance mix I + Mercury ammonium chloride ++ Thimerosal ++ Thiosalicylic acid ++
3	—	—	—
4	—	—	—
5	—	—	—
6	++	++	—
7	—	—	—
8	—	—	—
9	—	—	—
10	—	—	—
11	—	+	—
12	—	—	Nickel ++
13	++	++	—
14	—	—	—
15	—	—	—
16*	+	+	—
17	—	—	*Myroxylon pereirae* +
18	—	—	—
19	—	—	—
20	—	—	—
21	++	++	—
22	—	—	Nickel ++ Thimerosal +
23	—	—	Paraben mix ++ Lanolin ++ Fragrance mix II ++ *Myroxylon pereirae* ++
24*	+	++	Cefoxitin ++ Fragrance mix II ++ Coumarin ++
25	++	++	Nickel ++ *Myroxylon pereirae* ++
26	+	+	—
27	—	—	Caine mix +
28	—	—	Colophonium ++ Lanolin ++
29	—	—	—
30	++	+	—
Total	9/30 (30%)		10/30 (33.3%)

*Maculopapular exanthema upon re-exposure to clindamycin.

clear history of drug hypersensitivity after its systemic administration. In this study, all patients developed maculopapular exanthema with a considerable delay after initiation of clindamycin (mean 7.9 days) in different infections, mostly erysipelas, but almost all patients were using concomitant antibiotics. Positive reactions to clindamycin, with an erythemato-papular or vesicular pattern (+ to ++), both with pure clindamycin at 10% pet. and with powder of the commercial capsules of clindamycin, also at 10% pet., with negative results in over 50 controls, show the highly specific character of this reaction.

However, the sensitivity of the clindamycin patch test is rather low, as only 30% of the patch tests were positive. In this group of patients who used several concomitant drugs for the infections, it may be possible that another drug or the use of combined drugs or, eventually, a concomitant infectious agent may have been important for the development of the maculopapular exanthema observed in these patients.

Nevertheless, we observed higher reactivity to clindamycin in the patch tests than in previously published studies, in which the reactivity varied between 15% and 19%. Lammintausta et al. found positive patch test reactions to clindamycin in 12 of the 63 patients (19%), but the clinical charts of the tested patients were not described in detail (1), and Seitz et al. observed positive test reactions in 15% (5/33) of the patients (14). In this study, at least 4 of the 28 negative results (14.3%) were false-negative results, as oral rechallenge was positive. Also, Notman et al., who used only prick and intradermal skin tests (without assessing patch tests), obtained a negative predictive value of just 68% (2), and suggested that these immediate skin tests were not useful. However, in this study, both immediate and delayed adverse drug reactions were included and, on the other hand, delayed readings of intradermal tests were not performed systematically, which might have changed the results. Actually, two of these patients spontaneously reported late reactions to intradermal testing. Although we did not perform them in this study, intradermal tests with clindamycin with delayed readings, performed when patch test results are negative, might still increase the sensitivity of skin testing in studying cutaneous adverse drug reactions involving T cell-mediated hypersensitivity reactions to clindamycin, as occurs with aminopenicillins (15, 16) Despite the low reactivity (30%) in our study, patch tests were essential to confirm the imputability of clindamycin in these patients. As this antibiotic was considered to seldom cause cutaneous adverse drug reactions (2), we always suspected that the other antibiotic was the cause of the maculopapular exanthema, and in two patients with recurring erysipelas, before performing patch tests, we reused clindamycin associated with another cephalosporin, and patients developed an accelerated maculopapular exanthema.

In contrast to our experience with its systemic use, the broad use of topical clindamycin in acne, even though at a lower concentration (1%), and its use in vaginal cream at 2% has only exceptionally been associated with allergic contact dermatitis, with only five cases being published in the literature (17–21).

In conclusion, before an oral challenge, the reference standard for the diagnosis these drug eruptions, we recommend performing patch tests with clindamycin, a non-invasive technique, as they are safer, are specifically relevant, and can be useful for the diagnosis, even though they may have a low negative predictive value.

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