

Immediate Hypersensitivity to Clindamycin: Rare, But Not Impossible



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Lincomycin, a natural antibiotic isolated from actinobacterium *Streptomyces lincolnensis*, was the first lincosamide launched commercially in 1964. Clindamycin, a semisynthetic derivative of lincomycin (7(S)-chloro-7-deoxylincomycin), was synthesized 3 years later. It quickly superseded the use of lincomycin because it had higher potency, covered a broader spectrum, and was bioavailable orally. The US Federal Drug Administration in 1970, approved its hydrochloride salt for oral administration and the phosphate salt for parenteral, topical, or vaginal administration. Clindamycin is used in the treatment of head and neck, respiratory, bone and soft tissue, abdominal, and pelvic infections caused by Gram-positive bacteria, including strains of methicillin-resistant *Staphylococcus aureus*, most anaerobic bacteria, and certain protozoa. Despite good tolerance, high efficacy, and excellent tissue penetration, the use of clindamycin is usually restricted to patients with severe infections and/or to patients with beta-lactam hypersensitivity due to a 4-fold increase in the risk of *Clostridium difficile*-induced diarrhea and pseudomembranous colitis compared with other classes of antibiotics.^{1,2}

Within a decade of marketing, both immediate and delayed hypersensitivity reactions to clindamycin were reported.³ Early studies in the 1970s reported adverse reactions in 10% of patients⁴; a subsequent study in a cohort of 3896 patients reported a probably more realistic prevalence of only 0.4%.⁵ Most of these adverse reactions are nonimmediate cutaneous reactions: nonsevere maculopapular exanthems that tend to occur after 7 to 10 days from the beginning of the treatment course.² However, despite clindamycin's generally excellent safety record, it can also provoke severe cutaneous adverse reactions such as acute generalized exanthematous pustulosis, toxic epidermal necrolysis, and drug reaction with eosinophilia and systemic symptoms syndrome.^{2,3}

The small number of reported cases of type I hypersensitivity to clindamycin is somewhat surprising considering its widespread

use. Prescribing practices vary between countries and between hospitals. At Guy's and St Thomas' Hospitals (London, UK), one of the largest tertiary hospital trusts in the United Kingdom with approximately 2.5 million patient contacts per year, around 2% of patients received oral and/or intravenous clindamycin in the last year (written communication, C. Szlumper, Msc, Specialist Clinical Pharmacist, Guy's and St Thomas' Hospital, August 2018). In the literature, only 3 cases of anaphylaxis to clindamycin had been reported before 2016.⁶⁻⁸ The case presented in this issue of the journal⁹ underlines the challenges faced by clinicians when diagnosing drug allergy and the progress that is being made in this field. Currently, the diagnosis of clindamycin allergy is made by skin testing (skin prick, intradermal, and patch tests), but, because of the small number of cases, these tests have not been fully validated because both false-positive and false-negative results occur. Basophil activation test (BAT), which confirmed the diagnosis in the case reported, can support the diagnosis of type I allergic reactions due to venom, food, certain neuromuscular agents, radiocontrast media, and antibiotics. In general, BAT has a high specificity (92%) but low sensitivity for antibiotics (40%).¹⁰ It needs to be performed as soon as possible after the reaction due to a negative correlation between the time interval between the reaction and the likelihood of a positive test result. It is not widely available and has as yet not become part of the standard allergy testing armamentarium. Nevertheless, in expert hands, it appears to be of a great value, and Ebo et al⁹ confirm this. We hope that more allergy centers will continue to gain experience with BAT. Subsequent availability of concordant results from robust *in vitro* and *in vivo* tests might hopefully reduce the requirement for drug provocation testing (DPT) in the future. For now, however, DPT remains the criterion standard to confirm the diagnosis of clindamycin allergy. It does carry a risk of acute reactions and is generally not performed in patients with positive skin or *in vitro* test results as in the case reported. As a general principle, DPT should be offered only after balancing the risk-benefit ratio.

Why is clindamycin-induced type I hypersensitivity so rare compared with, for example, beta-lactam antibiotics? This challenging question remains to be answered. Clindamycin is metabolized in the liver, primarily by the cytochrome P450 isoenzyme 3A4 (and 3A5), to the major bioactive metabolites *N*-desmethylclindamycin and clindamycin sulfoxide. The absorption after oral administration is nearly complete (90%), with peak serum concentrations within 45 to 60 minutes. A short intravenous infusion (10-30 minutes) leads to peak serum concentrations almost immediately. After an intramuscular dose, peak concentration is reached within 3 hours. Systemic absorption can occur after topical administration, depending on the surface area covered. Up to 30% of vaginally applied clindamycin

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(ovaules) is systemically absorbed, but only 5% with a vaginal cream. After oral dosage, about 10% is excreted in the urine (active drug and metabolites), about 3.6% in the feces, and the remainder as inactive metabolites.¹ The elimination half-life of active clindamycin is about 3 hours. It is important to consider the pharmacokinetics when speculating about possible immune mechanisms. There is no evidence to suggest that clindamycin is implicated in nonspecific histamine release activity. Moreover, clindamycin appears unable to spontaneously form a covalent bond with a carrier protein; oxidative metabolism to reactive metabolites (haptens) might be required before immune sensitization.¹¹ The positive BAT result in the case reported by Ebo et al⁹ points toward an IgE-dependent mechanism. However, very little is known about the exact allergenic epitopes of clindamycin. The impact of the antibiotic dose and subsequent serum and local concentration of active and inactive metabolites, antigen presentation pathways, and the mediator release profile might all influence the outcome, that is, allergy versus tolerance.

Nonimmediate immune responses triggered by interaction with either major histocompatibility complex products or the T-cell receptors have already been demonstrated for other drugs, such as carbamazepine, allopurinol, and piperacillin/tazobactam.^{2,12,13} The HLA-B*51:01 haplotype appears to be associated with adverse cutaneous reactions to clindamycin in Asian patients.¹² If these novel data are confirmed and an HLA association is found in other populations, then the identification of patients at risk might become possible before the drug is administered. For now, all patients with confirmed immediate or nonimmediate hypersensitivity are advised to avoid clindamycin. As an alternative, desensitization protocols have been reported for both types of reactions.^{14,15} Without any doubt, further collaborative effort is needed to improve diagnosis of drug allergy, particularly in the case of drugs such as clindamycin that rarely cause adverse reactions.

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