



## URTICÁRIA DE CONTACTO INDUZIDA POR FÁRMACOS

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**RESUMO** – A dermatite de contacto inclui qualquer reacção inflamatória da pele, secundária a contacto direto ou indireto entre esta e agentes agressores. A expressão clínica mais comum é o eczema, ou outros padrões resultantes de reacções retardadas, mas reacções imediatas como a urticária de contacto podem também ocorrer. O espectro de manifestações clínicas por urticária de contacto é amplo. Na sua forma mais limitada, manifesta-se por urticária localizada à área de contacto entre o alérgeno e a pele ou mucosa, e nos casos de apresentações mais exuberantes, podem surgir lesões urticariformes generalizadas, angioedema, ou mesmo anafilaxia. Em teoria, todos os fármacos tópicos podem ser responsáveis por urticária de contacto, e vários fármacos foram já descritos como indutores. As moléculas implicadas podem ser os princípios ativos ou os excipientes, por via de mecanismos imunológicos ou não. Os autores apresentam uma revisão dos diferentes fármacos descritos na urticária de contacto, dando ênfase à urticária de contacto das mucosas e em contexto profissional.

**PALAVRAS-CHAVE** – Anafilaxia/induzida quimicamente; Dermatite Alérgica de Contacto; Dermatite de Contacto; Hipersensibilidade a Medicamentos; Urticária/induzida quimicamente.

## CONTACT URTICARIA INDUCED BY DRUGS

**ABSTRACT** – Contact dermatitis includes any inflammatory skin reaction due to direct or indirect skin contact with noxious agents. The main clinical expression is eczema and other delayed reactions, but immediate reactions, namely contact urticaria, can also occur. Contact urticaria has a broad range of clinical manifestations. The limited form is restricted to the area of contact between the allergen and the skin or mucosa, but more severe presentations include generalized urticaria lesions, angioedema and even anaphylaxis. All topical drugs can theoretically precipitate contact urticaria. The culprit may be either the active compound or the excipients, and the mechanisms of the immediate reactions can be both immune-mediated (IgE-dependent) and non-immune-mediated. The authors present an overview of the different drugs reported to induce contact urticaria, emphasizing the specific contexts of mucosal exposure and contact urticaria induced by drugs in occupational settings.

**KEY-WORDS** – Anaphylaxis/chemically induced; Dermatitis, Contact; Dermatitis, Allergic Contact; Drug Hypersensitivity; Urticaria/chemically induced.

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## 1. INTRODUCTION

Contact dermatitis includes any inflammatory skin reaction due to direct or indirect skin contact with noxious agents. The main clinical expression is eczema, but other delayed reactions can occur (lichenoid, sarcoidal, and lymphomatous reactions, purpura and erythema multiform-like reactions); as well as immediate reactions, namely contact urticaria (CU) or protein-contact dermatitis.<sup>1,2</sup>

CU is not rare, particularly among atopic individuals; however, prevalence data are limited because the disease often remains undiagnosed due to the mildness of symptoms.<sup>3</sup> Contact urticaria syndrome (CUS) is classified according to clinical severity: stage 1) urticaria localized to the area of contact with the offending drug; stage 2) generalized urticaria; stage 3) urticaria with associated systemic symptoms; and stage 4) anaphylaxis.<sup>4,5</sup>

A CU reaction occurs within minutes to 1 hour after cutaneous or mucosal exposure to a substance, and clears completely within hours, and no residual signs. Proteins (molecular weight 10,000 to several hundred thousand) and chemicals (molecular weights below 1,000) can both trigger CUS.<sup>1</sup> Virtually any topical drug can induce an immediate reaction, but most cases have been described with topical antibiotics, NSAIDs and anesthetics, and more recently, with antiseptics such as chlorhexidine (Table 1). Published reports of CU induced by other drugs represent relatively exceptional cases.

Drugs intended for systemic use (oral or i.v.) can also cause immediate cutaneous contact symptoms upon direct contact

or airborne exposure.<sup>6-9</sup> Immediate symptoms have been described with oral drugs, generally initiated during their transient passage in the mouth before swallowing, inducing local symptoms with edema of the lips, oral and oropharyngeal mucosae; and such cases can progress to systemic urticaria.

When exposure occurs through mucosa or through skin wounds, CU onset is usually more rapid than via normal skin, probably due to an easier access of the offending drug to dermal mast cells. Moreover, mucosa exposure is more frequently associated with systemic symptoms, including anaphylaxis, which can be life-threatening.<sup>10,11</sup>

## 2. PATHOGENESIS

Drugs intended for skin application are usually small reactive compounds that can easily penetrate the epidermis, and eventually reach the dermis, where they can activate the mechanisms responsible for immediate symptoms. Drugs can induce both immune-mediated and non-immune-mediated CUS, the latter being more frequent.<sup>12</sup>

In case of non-immunologic mechanisms, drugs directly interfere with cutaneous mast cells and induce non-specific degranulation, or may interfere with other neurologic and vascular mediators (prostaglandins/leukotrienes, PAF, substance P or other neuropeptides), resulting in increased vascular permeability, vasodilation, dermal edema and pruritus. The mechanisms of non-immune-mediated, drug-induced immediate contact reactions have not been precisely studied for most drugs, but causal mechanisms have been identified in

**Table 1 - Main drugs causing contact urticaria syndrome.**

ANTIBIOTICS	NSAIDS	ANTISEPTICS, PRESERVATIVES	MISCELLANEOUS	
Penicillin, mezlocillin	Acetylsalicylic acid	Chlorhexidine	Capsaicin	Corticosteroids
Ampicillin, amoxicillin	Diclofenac	Povidone iodine	Nicotinic acid esters	Cisplatin
Cephalosporins	Ketoprofen	Formaldehyde	Chloroform	Mechlorethamine
Rifampicin, rifamycin	Etofenamate	2-phenoxyethanol	Dimethylsulfoxide	Phenothiazides
Chloramphenicol	Pyrazolones	Benzoic acid	Tar extracts	Chlorpromazine
Gentamicin, neomycin	Metamizole	Sorbic acid	Tincture of benzoin	Levopromazine
Streptomycin	Aminophenazone	Chlorocresol	Dinitrochlorobenzene	Benzoyl peroxide
Bacitracin	Prophylphenazone/ascein	<b>Perfumes</b>	Diphenylcyclopropenone	Donezepil
Levofloxacin	<b>Anti-histamines</b>	Cinnamic aldehyde	Pentamidine isethionate	Guanidinium salts
Sodium fusidate	Promethazine	Balsam of Peru	Pilocarpine	Lindane
Virginiamycin	<b>Local anesthetics</b>		Cyclopentolate hydrochloride	Uranium salts
Iodochlorhydroxyquin	Benzocaine/ tetracaine		Carboxymethylcellulose sodium	Guar gum
Polymyxin B	Lidocaine			Ethylene oxide

**Table 2 - Contact urticaria mechanisms.**

Non-IgE dependent mechanism	Proposed and demonstrated* mechanisms	Drug-specific IgE dependent mechanism (Drug-specific IgE identified)
Etofenamate, diclofenac, ketoprofen, acetylsalicylic acid and other topical NSAIDs	Imbalance between prostaglandins and leukotrienes	Betalactam antibiotics
Benzoic acid and sorbic acid	Prostaglandin D2 release*	Bacitracin
Capsaicin	Release of substance P from nerve endings	Chlorhexidine
Rifamycin	-	Topical anesthetics
Cannabis	-	NSAID
Local anesthetics	-	Formaldehyde
Perfumes	-	

particular cases, including the example of capsaicin, which releases substance P from nerve endings<sup>4</sup> (Table 2).

Drugs can also be specifically recognized by IgE on mast cells, basophils, and eventually by Langerhans cells, and other skin dendritic cells. In these cases, drugs likely act as haptens and combine with proteins (human serum albumin or other serum or skin proteins) prior to IgE recognition (Table 2).<sup>13</sup> IgE recognition on mast cells and basophils can trigger a sequence of signaling events that result in cell degranulation, and release of histamine, cytokines, and other pre-formed mediators, or else activate phospholipase A, to release arachidonic acid for pro-inflammatory pathway.<sup>4</sup>

IgE-dependent CU that is induced by drugs or other agents, is usually more severe than CU induced by non-immunologic reactions, often extending beyond the application area, and being associated with facial angioedema, oropharyngeal edema or conjunctivitis; and with systemic symptoms such as cough, bronchospasm, dyspnea, abdominal cramps and, in some cases, anaphylaxis with bradycardia and hypotension.<sup>4</sup>

It is important to underline that both immediate and delayed hypersensitivity mechanisms may be concomitantly involved for a single agent, as in chlorocresol, an excipient of corticosteroid creams, or as in occupational airborne disinfectants.<sup>6</sup>

### 3. CU FROM TOPICAL DRUGS APPLIED ON THE SKIN

Many topical drugs used either on normal or damaged skin cause CUS. Both the active ingredient and a component of the vehicle can be responsible, and most represent a non-immunological reaction induced by perfumes or preservatives.<sup>5,14,15</sup>

Some of these immediate reactions manifest only as transient erythema and tingling, or as pruritus without wheals, usually resolving in less than 30-60 minutes. Therefore, they are not usually the subject of publication or more detailed study.

#### 3.1. Topical antibiotics

CU in response to topical antibiotics is not frequent, but although only a few cases have been described they can be severe. Most published cases of CU or more severe immediate reactions from topical antibiotics are rather old, similarly to those induced by bacitracin and polymyxin B,<sup>16</sup> rifamycin,<sup>8,17</sup> chloramphenicol, gentamycin, streptomycin, neomycin<sup>18</sup> and viginiamycin.<sup>4</sup> Nevertheless, a recent case reported CUS with severe systemic symptoms in a 16 year-old boy, following the use of sodium fusidate applied to skin with abrasions.<sup>9</sup>

Topical antibiotics are often used on skin with barrier defects, or even on open wounds or ulcers. This may favor sensitization and/or the effector reaction, due to easier access of the drug to the dermis. Also, in infected or wounded skin, previous activation of the innate immune system by pathogens and their pathogen-associated molecular patterns (PAMP), by inflammatory molecules and by danger-associated molecular patterns (DAMPs), may additionally facilitate a specific immune response that exacerbates the urticarial reaction.

#### 3.2. Topical antihistamines and NSAIDs

Immediate reactions have been described with topical antihistamines such as promethazine; and with topical NSAIDs such as acetylsalicylic, metamizol and other pyrazolone compounds,<sup>4,19,20</sup> diclofenac,<sup>21</sup> etofenamate<sup>22</sup> and ketoprofen<sup>23</sup>; and other drugs such as aescin.<sup>24</sup> However, those reports were mostly isolated cases, dating back to the 1990s.

#### 3.3. Topical anesthetics

Local anesthetics applied on normal skin have been described as a cause of CU, namely benzocaine cream<sup>18</sup> and especially creams containing lidocaine. Contrasting with its low capacity to induce delayed hypersensitivity reactions,<sup>25</sup> lidocaine has caused CU in a hemorrhoidal cream<sup>7</sup>; in a combination of lidocaine and tetracaine (7% each)<sup>26</sup>; and in EMLA<sup>®</sup>

cream, an eutectic mixture of lidocaine and prilocaine at 2.5% each.<sup>25</sup>

### 3.4. Topical antiseptics

Topical antiseptics such as povidone iodine<sup>27,28</sup> and chlorhexidine<sup>29,30</sup> are particularly involved in immediate reactions when applied to surgical or other open wounds, or to the mucosa.

## 4. CONTACT URTICARIA FROM MUCOSAL EXPOSURE TO DRUGS

Exposure through mucosa is often associated with more rapid onset of reaction and more severe symptoms, even upon very discrete exposure to the offending drug.

The conjunctiva has been the exposure site for localized or generalized urticaria or even anaphylaxis induced by eye drops, i.e. levofloxacin and mydriatic cyclopentolate hydrochloride eye drops.<sup>31-33</sup>

The oral mucosa has been the exposure site for cases of CU induced by anesthetic gels containing lidocaine and guar gum in the excipient<sup>34</sup>; by chlorhexidine used in dental endodontic procedures,<sup>30</sup> mouth washes<sup>10</sup> and toothpastes<sup>35</sup>; and also by formaldehyde used in dental procedures.<sup>36</sup>

Exposure of the vaginal mucosa to chlorhexidine<sup>29</sup> or povidone iodine<sup>37</sup> during gynecological procedures has been associated with generalized urticaria. Chlorhexidine has also been involved in CU after the insertion of central catheters or intra-urethral catheters soaked in this antiseptic, namely Instillagel<sup>®</sup>, which contains both chlorhexidine and lidocaine.<sup>38</sup>

Perioperative urticaria or anaphylaxis can also be a presentation of CU, mainly by contact with latex or ethylene oxide used for the disinfection of material (masks),<sup>38</sup> but also by the antiseptics chlorhexidine and povidone iodine,<sup>21</sup> or by the antibiotics rifamycin and bacitracin used for surgical wound disinfection.<sup>29</sup>

## 5. CONTACT URTICARIA FROM DRUGS IN OCCUPATIONAL SETTINGS

Occupational CU from drugs occurs mainly in nurses who prepare injectable drugs, and in nurses and other caregivers who are required to crush and handle tablets.<sup>39</sup> CU in the pharmaceutical industry is rare, as most drugs are produced in closed circuits involving little or no contact with the worker.<sup>5</sup> The main allergen associated with CU among the health care population is latex, although the incidence has declined significantly in recent years by improving latex production and through the use of powder-free gloves.<sup>3</sup>

Frequent chronic hand eczema in nurses, due to irritation, delayed allergy, or atopic dermatitis, consequently with a disturbed skin barrier, may contribute to enhanced drug penetration through the epidermis and thereby easier access

of potential allergens to dermal mast cells. Continuous hand exposure to drugs recognized by IgE can also induce immediate vesicular reactions; as in protein contact dermatitis, this can contribute significantly to aggravation and persistence of chronic hand eczema in this occupational setting.<sup>40</sup>

Nurses with occupational CU mostly complain of transient hand edema or swelling in association with pruritus or paresthesia. Lesions on the face, neck and forearms can also occur, eventually with generalization of urticaria and systemic symptoms (cough, dyspnea, asthma, rhinorrhea or abdominal cramps), particularly upon airborne exposure to volatile substances or powders of the drug.<sup>41</sup>

The drugs primarily associated with occupational CU are the antibiotics, particularly penicillin, ampicillin, amoxicillin and the cephalosporins.<sup>38,42,43</sup> Apart from antibiotics, other drug-induced cases of CU have been reported in health care workers, namely with chlorhexidine, donepezil, and cisplatin.<sup>34,44,45</sup>

## 6. DIAGNOSIS OF IMMEDIATE SYMPTOMS INDUCED BY DRUGS

The diagnosis of CU induced by drugs is based mainly on clinical history, which requires very precise data on the timing of events (drug exposure and initiation of symptoms), and the localization of lesions (initial localization and progression).

When urticaria is preceded by exposure to multiple drugs (topical and systemic), it is extremely important to perform complementary tests in order to achieve a precise diagnosis, and to enable the culprit drug to be avoided in future. When the patient has been exposed to a single drug, complementary tests may be important to confirm the etiology, evaluate cross-reactivity to related chemicals,<sup>46</sup> to identify a safe alternative drug and, eventually, to appreciate the participation of drug-specific IgE.

The development of urticaria or anaphylaxis preoperatively is often incorrectly attributed to systemic drugs, as they are the main cause of urticaria in these settings (neuromuscular blockers, antibiotics, anesthetics, opiates, analgesics such as metamizol or radiocontrast media).<sup>11,29</sup> However, topical drugs can be the cause, as shown in a recent study where chlorhexidine represented 5% of all perioperative anaphylaxis cases.<sup>29</sup>

To prevent avoidable cases of severe reactions during skin testing, the study of such patients should begin with open epicutaneous tests in normal skin, and occlusive patch tests on the forearms with immediate readings (20-30 minutes). If negative, they should be followed by skin prick tests, and eventually, by intracutaneous tests (Fig. 1). These tests should be performed in settings where there is easy access to resuscitation measures, since generalization of urticaria from skin testing, or even anaphylaxis<sup>36,38</sup> can occur, particularly in the study of severe CU or anaphylactic reactions. When organs other than skin are involved, it is important to begin testing with a diluted

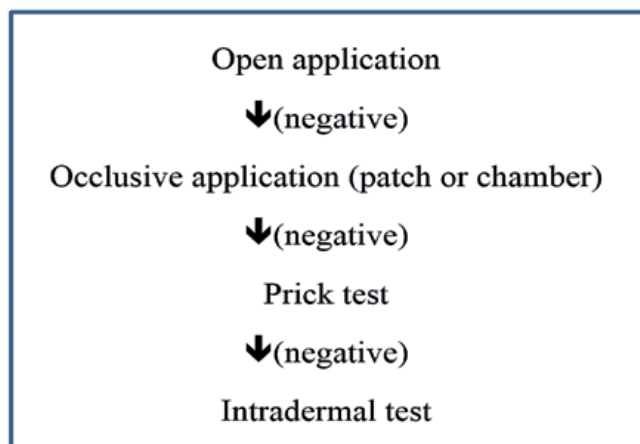


Fig 1 - Contact urticaria diagnosis.

allergen. Nevertheless, there are few standardized drug preparations for skin testing, namely for epicutaneous patch testing, and even fewer for skin prick or intracutaneous testing.

Topical drugs and dressings can be tested as such in open epicutaneous tests, on the volar forearm; subsequently, a lancet puncture can be performed across the material applied to the skin. For prick testing with drugs, sterile dilutions from commercial preparations have to be performed, preferably from i.v. preparations. There is no consensus on the dilutions to be used, but in more severe reactions it is advisable to begin with higher dilutions and to increase the concentration progressively in case of negative tests ( $10^{-3}$ ,  $10^{-2}$ ,  $10^{-1}$ , then pure), or to follow the concentrations recommended by the ESCD<sup>46</sup> and ENDA/EAACI study groups<sup>47</sup> for the assessment of adverse effects of systemic drugs.

Results have always to be compared with the positive control (histamine 10mg/ml) and negative control (saline). According to the guidelines for prick testing, only papular erythematous reactions with a diameter >3mm are considered positive.<sup>46</sup>

The sensitivity of *in vivo* testing is usually higher than *in vitro* tests, but it is important to be aware that some drugs (opioids, non-steroidal anti-inflammatory drugs - NSAIDs) cause non-specific mast cell degranulation and, consequently, false-positive reactions. Therefore, in positive results, particularly with unknown drugs, skin testing in at least 20 control patients is mandatory to confirm the specificity of the positive reaction.

Reagents for specific IgE (*in vitro* test) are commercialized only for a limited number of drugs and excipients potentially involved in CU, namely beta-lactam antibiotics, chlorhexidine, formaldehyde, ethylene oxide and gelatin, and for a few others that can cause urticaria upon systemic exposure.<sup>48,49</sup> BAT (basophil activation tests) evaluation for degranulation of basophils upon *in vitro* exposure to the chemical, and the

increase in basophil expression of CD63 or CD203c evaluated by flow cytometer, can be performed in selected laboratories, but these tests are less specific.<sup>50</sup> Measuring serum tryptase during the acute episode, or within the first 2-4 hours after a stage 3 CUS or anaphylaxis, and comparison with basal values (>24h), is a useful complementary test to document mast cell/basophil degranulation, but does not confirm the etiology of the reaction.<sup>37</sup> Controlled exposure to the suspected drug, or to safe alternative drugs may be advisable when all previous tests were negative.

## 7. CONCLUSIONS

Topical drugs, or occasionally systemic drugs, that come into contact with the skin or mucosa may induce CU, which is often overlooked because some reactions are mild and ignored by patients. Moreover, as such effects are transient, they are seldom present at the time of consultation or at the time of testing, which makes diagnosis difficult. Complementary tests (skin tests with immediate readings and, eventually, *in vitro* tests) are mandatory in certain situations, as precise diagnosis of the culprit drug and identification of safe alternative drugs can be life-saving.

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