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INTRODUCTION
Cutaneous drug reactions are also denominated “drug eruptions,” “drug allergies” and “dermatitis medicamentosa.” Such reactions have been addressed in dermatology textbooks for less than 25 years. Unfortunately, the occurrence of this dermatosis is underestimated, especially by many clinicians who have no knowledge of its cause and pathogenesis or even its existence. These reactions have multiple clinical aspects ranging from an innocent, single lesion to the generalized form, which, at times, may be fatal.

In the present day, one may observe progressive growth in availability, use and abuse of allopathic drugs, and, concurrently, of drug eruptions. These may involve other organs or systems (kidney, liver, gastrointestinal tract, hematopoietic system and central nervous system), leading to great complications and, every so often, to the death of the patient.

DEFINITION AND INCIDENCE
Cutaneous drug reactions are defined as pleomorphic, recurrent, mucocutaneous affections, with variable pruritus, which may or may not be accompanied by generalized symptoms and with cutaneous lesions of variable types and configurations, resulting from the use of distinct classes of drugs, through any administration route.

They are well known in human medical pathology, where incidence is estimated to be of three per one thousand in dermatological ambulatories and of two to three percent of hospitalized patients. The teaching hospital of the Faculdade de Medicina – Universidade de São Paulo, Brazil, determines an incidence of 1.14% given 166 cases among the 14,561 human patients, out of which 120 were women. In veterinary medicine, the highest incidence involves equines (4.1% of dermatologic cases in Cornell University Clinic), followed by canines and felines, where the last two correspond, respectively, to 2% and 1.6% of all dermatological cases in North American teaching hospitals. Except for occasional reports, there are no solid studies that determine incidence of drug eruptions in South America or in Europe.

CAUSE AND PATHOGENESIS
Cutaneous drug reactions that reflect upon the skin may result from the administration of drugs orally, parenterally, percutaneously or via inhalation. Any drug or immunizer may lead to drug eruption. In humans, atopic and SLE patients seem to be predisposed.

For teaching purposes, drug reactions may be divided into two major groups: predictable or expected reactions and unpredictable or idiosyncratic reactions. The first group includes the dose-dependent forms of the disorder that maintain strict relation to the action of the drug, although inconsistent with the desired effect (e.g. alopecia secondary to cytotoxic substances, cutaneous atrophy and telangiectasia after the use of corticosteroids; intense somnolence with the use of anti-histamines). In the second group, reactions are dose-dependent, relating to hereditarily-determined susceptibility (intolerance) or to an individual immunologic response.

Intolerance reactions develop from doses which would normally be non-toxic to other individuals. It is seen, for example, in a small contingent of human patients treated with quinine that manifest ear humming even when used in small doses.

Cutaneous drug eruptions may also be classified as developing from allergic and non-allergic means. Among non-allergic reactions are “overdose and collateral effects;” “ecological disturbances and biotrophism;” “drug interactions;” “Herxheimer-Jarisch reaction;” “complement activation;” “histamine release;” “photochemical reactions;” “effects over cutaneous pigmentation” and “tumor induction.” Many of these have been evidenced in veterinary medicine (“overdose”; diamidine in high concentrations; “ecological disturbances;” wide-range antibiotics and skin microbial population changes; “biotrophism”; corticoids and demodicosis, “drug interactions”; griseofulvin and barbiturates, “complement activation;”

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urticaria and radiographic contrasts).

In this second form of classification, great importance is given to the so-called allergic reactions, which involve the four types of immune mechanisms: IgE dependent (type I), cytotoxic (type II), mediated by immune-complexes (type III) and cell-mediated reactions (type IV). Certain drugs act as complete antigens whilst others act as haptons. Routinely, one may characterize facts that suggest the allergic pathogenic mechanism of development:

- they are reactions which are different from the pharmacological effect of the drug
- one drug may produce different types of eruptions
- different drugs may produce the same kind of eruption
- during physical examination, many reactions are similar to cutaneous allergies
- usually there is a previous period of sensitization
- re-exposure to the drug will produce eruption within a shorter period
- hypersensitivity is life-long

Many drug eruptions are due to enzymatic anomalies, leading to non-detoxification of drugs, accumulations of metabolites and binding of protein-reactive metabolites that induce immune response.

In the present time, dermatological textbooks present tables where the main forms of cutaneous eruptions are grouped according to the different classes of drugs, immunizers, shampoos, contrast media etc, which greatly facilitate the work of the veterinarian clinician in establishing the conclusive diagnosis, when one suspects of a cutaneous drug reaction.

The following table depicts some of the documented cutaneous drug reaction–inducing drugs:

<table>
<thead>
<tr>
<th>Eruption</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urticaria</td>
<td>Ivermectin, cyclosporine, vaccines, bacterins, radiographic or tomographic contrast media, penicillins, ampicillins, cephalosporins, ciprofloxacin</td>
</tr>
<tr>
<td>Erythroderma</td>
<td>Sulfonamides, itraconazole, benzoyl peroxide, povidone-iodine, lincomycin</td>
</tr>
<tr>
<td>Vesicobullous</td>
<td>Sulfonamides, ampicillin, penicillin, cephalosporins, diethylcarbamazine, hydralazine, cimetidine</td>
</tr>
<tr>
<td>Reactions to local injections</td>
<td>Corticosteroids, ivermectin, vaccines, fipronil, sulfonamides</td>
</tr>
<tr>
<td>Maculopapular</td>
<td>Cyclosporine, flumethasone</td>
</tr>
<tr>
<td>Fixed drug eruption</td>
<td>Clemastine, 5 flucytosine</td>
</tr>
<tr>
<td>Lichenoid</td>
<td>Cyclosporine, flumethasone</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>Chloramphenicol, antiparasitic worm medicine, vaccines, sulfonamides</td>
</tr>
<tr>
<td>Ulceration</td>
<td>Moxidectin</td>
</tr>
<tr>
<td>Erythema multiforme</td>
<td>Sulfonamides, levamisole, ciprofloxacin, cephalaxins, gentamicin, penicillin, neomycin</td>
</tr>
</tbody>
</table>

**SYMPTOMS AND LESIONS**

Cutaneous drug reactions may potentially mimic any dermatosis, ranging from a *venenata dermatitis* to an extensively burnt patient. Generally, prodrome is of three weeks. Some authors claim that there are extreme cases where the patient may manifest symptoms after months of exposure, especially in cases of cutaneous atrophic vasculitis or vaccine reactions. In cases resulting from the application immunizers or of corticoids this period may be of months. Manifestations pertaining to the tegument vary with the species involved.

<table>
<thead>
<tr>
<th>Species</th>
<th>Reaction Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>Urticaria, angioderma, fixed pigmentary erythema</td>
</tr>
<tr>
<td>Canine</td>
<td>Pruritus, excoriation, maculopapular eruptions, erythema multiforme, erythroderma</td>
</tr>
<tr>
<td>Feline</td>
<td>Pruritus, erosions, ulcerations</td>
</tr>
</tbody>
</table>

Lesion types involve all forms of primary cutaneous lesions: changes in color and thickness, formation of...
vesicles or bullae, tissue loss and repair and development of solid formations.

There is apparently no sex predisposition with animals as opposed to humans, where females seem to be predisposed. Animals of any age may be affected, although it seems to be more common with adults. Among races in the USA, Poodles, Yorshires, Bichon Frisés, Maltese terriers, Schnauzers, Old English Sheepdogs, Greyhounds and Fox Terriers seem to be at greater risk.

Out of all forms of cutaneous drug reactions, some are a lot more severe, leading at times to death. Among these one may point out the Stevens-Johnson Syndrome (bullous or “major” erythema multiforme) and the Lyell Syndrome (toxic epidermal necrolysis). Such events demand early diagnosis and immediate treatment.

Besides the cutaneous lesions, which are at times unnoticed in fur-covered areas (maculopapular eruptions: morbilliform, scarlet or ruboeiform; erythema multiforme “minor”), severe or evolved cases may lead to generalized symptoms such as intense prostration, pyrexia, anorexia, dehydration, muscular and articular pain, loss of sight, intense cutaneous sensibility, lethargy and depression.

In humans, strange occurrences were conveyed such as hirsutism (spironolactone, androgens, minoxidil), gingival hyperplasia (cyclosporine, nifedipine, hidantoine) and pseudolymphoma (hidantoine, captopril, enalapril, allopurinol, fluoxetine). Therefore, one must be alert to bizarre dermatologic manifestations, since the veterinary therapeutic arsenal increases rapidly and, with it, the possibility of new reaction pattern inductions.

DIAGNOSIS

It is difficult to confirm the diagnosis of cutaneous drug eruptions given the lack of specific laboratory testing. Routinely, the clinician takes into account patient history, insisting upon the characterization of drug type, immunizers, prophylactic drugs, shampoo, vitamin complexes; in previous exposure to the same drug or of drugs of the same class. Information is complemented by complete physical examination, with emphasis upon the dermatologic examination, as well as laboratory testing such as complete blood count and biochemistry (liver and renal functions, electrolytes). Histopathological exam is helpful, ruling out other diagnostic possibilities and/or confirming the diagnosis via the histological findings (dermatitis: perivascular, interface, intraepidermal vesiculopustular, subepidermal vesicular, interstitial, panniculitis, vasculitis). Some syndromes (erythema multiforme “major” and “minor”) have very typical histopathologic aspects.

Other immunological methods of diagnosis in vivo and in vitro already tested (assays of: basophil degranulation, lymphocytic blastogenesis, lymphocytic toxicity; intradermal testing and serological – RAST) have proven themselves unsatisfactory given the great number of false-negative as well as false-positive results and for the necessity of causal drug re-exposure.

Henceforth, besides the broad anamnesis, careful physical and dermatologic exams and of histopathologic exam executed by a trained dermatopathologist, one may only turn to the method of “rechallenging”. Nevertheless, such method is rarely used because of the risks implied, ethical problems involved and the owner’s lack of compliance regarding the procedure.

Another diagnostic method that has been discussed is the score criterion for the implication of drugs in the development of drug eruptions, adapted to the veterinary medicine through the proposal of the French committee for the pharmacological investigation. However, there is no conclusive result concerning its viability in the present time.

Prognosis varies according to the type of cutaneous reaction, ranging from guarded (erythema multiforme – EM) to poor (Stevens-Johnson Syndrome – SJS or Lyell Syndrome – TEN). In human dermatology the mortality rate varies among less than 1% (EM) and 5% (SJS) to more than 40% (TEN). It is considered that lethality increases proportionally to aging and increase in area of epidermal detachment.

TREATMENT

Treatment is very much based on expectation after any drug not deemed vital is suspended. In the presence of severe oral lesions (SJS, TEN), intravenous fluid-therapy, parenteral nutrition and non-aggressive topical therapy is instituted. Corticosteroids are not always indicated, especially when prescribed 48 hours after initial signs are observed, but few are those that take the risk of not using them.

Intravenous human immunoglobulins* (IVIG) have been successfully used in cases of feline erythema multiforme. These would act through the blockage of macrophage FC receptors, inhibition of complement activity, modulation in cytokine synthesis and action in T and B lymphocyte function and neutralization of autoantibodies.

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Sandoglobulin – Sandoz Pharmaceuticals. NJ (EUA).

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