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Drug Eruptions

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Are there any findings and observations in the field on drug eruptions since our last international congress in Tokyo [35]?

Worldwide the consumption of drugs is still very high. Therefore we have always to reckon with their cutaneous side effects. Many of these only appear some time after official registration of a new drug. For this reason the importance of the so-called "postmarketing drug surveillance" – for the protection of the patient – is constantly increasing [4, 13, 14, 16, 26, 33, 36, 37, 65, 78].

This surveillance is mainly based on three procedures:

1. So-called "monitored release," that is registration which includes special conditions
2. Foundation of national and international registration centers for adverse drug reactions
3. Comprehensive "drug monitoring"

We are all aware of the fact that drugs with numerous adverse cutaneous reactions are on the market. They include, e.g., beta-lactam antibiotics, sulfonamides, cotrimoxazole, cytostatics, certain drugs affecting the CNS such as hydantoins and carbamazepine, captopril, and allopurinol. As an example, Fig. 1 shows a bullous eruption due to cotrimoxazole. On the other hand there are drugs which are known to have a good cutaneous tolerance, such as digitalis and the benzodiazepines. In most drugs the percentage of cutaneous side effects is between 0.5% and 2%. Below 0.1% cutaneous tolerance is considered to be excellent. Above 3%–5% it is poor [37]. Let us now discuss *pathogenesis* of drug eruptions. In this field our knowledge has not significantly increased during the past 5 years. We definitely know that immunological mechanisms are involved in drug exanthemas. This includes all known immunological reactions (type I–IV, autoimmune phenomena). In other cases drug eruptions occur on a nonimmunological basis, e.g., the so-called pseudoallergy with nonspecific release of inflammatory mediators. To a certain extent thrombocytic anomalies are involved. In several cases of drug eruption, however, the triggering mechanisms are unknown [5, 6, 31, 33, 36, 51, 58, 59, 64, 74, 78]. In the field of *diagnosis* of drug eruptions, progress has only been modest since the Tokyo meeting in 1982. With the exception of penicillin, no new reliable drug test solutions for *cutaneous tests* have been developed. For the elucidation of drug eruptions the skin tests are therefore still unreliable.

Trustworthy *in vitro tests* have not increased in number. Generally accepted are only the radioallergosorbent test (RAST) and the lymphocyte transformation test. Reliable results, however, can only be obtained for a limited number of drugs. Available on the market is, e.g., only a RAST test for penicillin, adrenocorticotrophic hormone (ACTH), and three insulins [5–7, 14, 36, 51, 58, 72, 77]. In the past few years, efforts have been made toward further progress in the field of diagnosis. For example, the RAST test is now available for about 30 additional drugs: half-synthetic penicillins, ampicillins, cephalosporins, tetracyclines, sulfonamides, trimethoprim, pyrazo-



Fig. 1. Bullous eruption due to cotrimoxazole



Fig. 2. Maculopapular rash due to amoxicillin

lones, salicylates, and flavonoids. At the present time, however, these tests are only carried out in specialized immunological centers, and they are still in a preliminary state [72, 73, 77].

Caroline Geczy and collaborators have furthermore developed a simplified *in vitro* test for the determination of cell-mediated allergy: the so-called *procoagulation test* [23]. Sensitized lymphocytes of patients decrease blood coagulation time *in vitro*, after addition of the allergen. The reaction is based on the release of a thromboplastin-like, so-called procoagulation factor. This new *in vitro* test is very specific, technically simple, and very promising. But so far it has only proved reliable in the diagnosis of tuberculin, mumps, nickel, and penicillin allergies. Therefore it still lacks general recognition [2, 23, 57]. In the absence of new generally accepted skin and *in vitro* tests for the diagnosis of drug eruptions, a careful anamnesis and – if justifiable – a reexposition test are still of great importance [33].

What is new in the *clinical field* of drug eruptions? I will focus in this article on a few important drugs and drug groups. Let us first discuss the *antiinfectious drugs*. Worldwide the number of beta-lactam antibiotics is increasing. New cephalosporins and half-synthesized penicillins and ampicillins are constantly appearing on the market. They fight predominantly problematical germs. As an example, Table 1 presents the antibiotics newly registered in Switzerland between 1980 and 1986. The beta-lactam antibiotics predominate. Therefore we always have to be prepared for the frequent cutaneous side effects of the beta-lactam antibiotics, above all maculopapular rashes (Fig. 2). Also known are pruritus, urticaria, fixed drug eruptions, erythema multiforme-like exanthema, Stevens-Johnson and Lyell's syndrome, vasculitis, and elastolysis [1, 14, 17, 18, 36, 42–44, 52, 53, 56, 60, 62, 63, 66, 67, 78]. Of the remaining antibiotics, only *minocycline* will be mentioned here, since it is often used in the treat-

Table 1. Newly regis
1980 and 1986, with t

Cephalosporins
Cefadroxil
Cefazedon
Cefoperazon
Cefotaxim
Cefotiam
Cefroxadin
Cefsulodin
Ceftriaxon
Cefotetan
Ceforanid
Ceftazidin
Moxalactam

Table 2. Quinolone:

Cinoxacin
Ciprofloxacin
Enoxacin
Nalidixinic acid
Norfloxacin
Ofloxacin
Oxolinic acid
Pefloxacin
Pipemidinic acid
Rosoxacin
Cutaneous side eff
Maculopapular
Anaphylactic re
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Table 1. Newly registered antibiotics in Switzerland between 1980 and 1986, with the beta-lactam antibiotics predominating

Cephalosporins	Penicillins
Cefadroxil	Azlocillin
Cefazedon	Mecillinam
Cefoperazon	Mezlocillin
Cefotaxim	Piperacillin
Cefotiam	Pivmecillinam
Cefroxadin	Other beta-lactam antibiotics
Cefsulodin	Amoxicillin + clavulanic acid
Ceftriaxon	Imipenem + cilastatin
Cefotetan	Other antibiotics
Ceforanid	Clavulanic acid
Ceftazidim	Netilmicin
Moxalactam	Iosamycin

Table 2. Quinolones and their cutaneous side effects

Cinoxacin
Ciprofloxacin
Enoxacin
Nalidixinic acid
Norfloxacin
Ofloxacin
Oxolinic acid
Pefloxacin
Pipemidinic acid
Rosoxacin
Cutaneous side effects
Maculopapular exanthema
Anaphylactic reactions
Photosensitization and photo-onycholysis

ment of acne. As a dermatological peculiarity – after long-term treatment – minocycline may cause blue-gray to brown spotted cutaneous hyperpigmentation. These skin pigmentations were first described by Basler. The pigmentation is generally found on the lower legs and on the feet. In addition it can appear on other, especially sunlight-exposed, regions of the body, e.g., on the face. The pigment deposits are generally located within macrophages and consist of complexes of iron, melanin, calcium, and a drug metabolite [11, 24, 41, 55].

A newer group of chemotherapeutic drugs with a wide antibacterial spectral range are the *quinolones*. They are also known under the name of gyrase inhibitors. Some of the most important representatives of this drug group are shown in Table 2. The quinolones are considered to belong to those drugs which are well tolerated. The following cutaneous side effects are known: maculopapular rashes, anaphylactic reactions, and mainly photosensitization including photo-onycholysis (Fig. 3) [10, 53, 76].

In the past few years, the antimalarial *Fansidar* has caused quite a lot of attention among experts. Mainly American tourists traveling to the tropics have suffered from severe cutaneous symptoms similar to Stevens-Johnson and Lyell's syndromes after



Fig. 3. Photosensitization due to nalidixic acid



Fig. 4. Severe Stevens-Johnson syndrome due to Fansidar

prophylactic consumption of the drug (Fig. 4). Several patients have died. Worldwide more than a 100 cases with severe cutaneous side effects have been reported [9, 27, 47]. Since withdrawal of the drug has not yet been considered, the following precautions must be taken when Fansidar is prescribed:

1. Prophylactic and therapeutic prescription are only indicated if the locally predominant malaria germ is resistant to other drugs.
2. Always exclude sulfonamide incompatibility

3. No combination
4. At the first sign ately

Finally in the group virostatics. Important in the treatment of

Another important drug is zidovudine (Retrovir), which reduces the mortality of these modern drugs. They have good tolerance. They cause urticaria, macular rash, and are more dangerous.

Another new group is the cytostatics (Tegretol, A (Sandimmun). In some others a gastrointestinal side effects [34, 36, 37]. Important antihypertensive drugs both block the renin-angiotensin system.

Their numerous side effects include severe maculopapular rash. They are mostly oral. A neonatal test can also be done. A great extent by the occurrence of hepatitis, Lyell's syndrome.

Enalapril (Renin Inhibitor) is essentially a cross-reactant. As side effects occur in a group of cardiovascular effects: facial redness, pruritis, urticaria, etc. With nifedipine given.

The character of the side effects of darone have been only recently registered. Pigmentation are

Table 3. Immunomodulators

Drugs
Cyclosporin A (Sandimmun)
Interferon
Levamisole
Thymus "hormone" e.g., thymopoietin
Transfer factor
Diethylthiocarbamate
Bestatin

3. No combination with chloroquine
4. At the first sign of a cutaneous symptom, Fansidar should be stopped immediately

Finally in the group of anti-infectious agents mention should be made of some modern *virostatics*. Important representatives are *acyclovir* and *vidarabine*, which are applied in the treatment of severe herpes infections.

Another important new virustatic drugs is 3'-azido-3'-deoxythymidine or *zidovudine* (Retrovir), which has been recently registered in several countries. Retrovir reduces the mortality in advanced case of AIDS disease. Our clinical experience with these modern drugs is still modest. In spite of the high efficacy they appear to have a good tolerance. The following cutaneous side effects have been observed: pruritus, urticaria, macular rash, and alopecia. Bone marrow depression and kidney damage are more dangerous.

Another new group of drugs are the so-called *immunomodulators*. They are related to the cytostatics (Table 3). Presently the most important representative is *cyclosporine A* (Sandimmun). In many patients it may cause a reversible hypertrichosis (80%) and in some others a gingival hyperplasia (28%) (Figs. 5 and 6). There are also some other side effects [34, 36, 37, 46]. Let us come to the group of *cardiovascular drugs*. The important antihypertensive agents *captopril* and *enalapril* were discussed in Tokyo. They both block the renin-angiotensin system.

Their numerous cutaneous side effects are well known today, especially the intensive maculopapular rashes associated with fever, pruritus, and glossitis (10%–12%). They are mostly of pseudoallergic origin (Figs. 7 and 8). Nevertheless their epicutaneous test can also be positive. Nowadays these remarkable rashes can be avoided to a great extent by a lower dosage of the drug. Captopril may also be responsible for the occurrence of lichenoid, pityriasis rosea- and LE-like exanthema, aphthous stomatitis, Lyell's syndrome, pemphigus, and lymphadenopathy [49].

Enalapril (Reniten) seems to be better tolerated than captopril. There is not necessarily a cross-reaction between these two drugs. They can be interexchanged as soon as side effects occur [8, 28, 35, 61]. The *calcium-antagonists* form an important new group of cardiovascular drugs (Table 4). So far they have shown few cutaneous side effects: facial redness and tumefaction, heat sensation, and pain in the legs. Less often pruritus, urticaria, macular and fixed exanthema, and lymphadenopathy are noticed. With nifedipine gingiva hyperplasia is also seen [36, 54].

The characteristic photosensitization and dark facial discoloration due to *amiodarone* have been well known in Europe for many years. Since amiodarone has been only recently registered in the United States, American reports about lipofuscin hyperpigmentation are becoming increasingly numerous (Figs. 9 and 10) [70].

Table 3. Immunomodulators and their cutaneous side effects

Drugs	Side effects
Cyclosporin A (Sandimmun)	Hypertrichosis Gingiva hyperplasia
Interferon	Pruritus
Levamisole	Urticaria
Thymus "hormone"	+ angioedema
e.g., thymopoietin pentapeptide	Diverse exanthema
Transfer factor	Stomatitis
Diethylthiocarbamat (DTC)	Diffuse alopecia
Bestatin	Kaposi's sarcoma



Fig. 5. Hypertrichosis due to cyclosporine A



Fig. 6. Gingiva hyperplasia due to cyclosporine A



Fig. 7. Maculopapular rash due to captopril



Fig. 8. Maculopapular rash due to captopril

Table 4. Calcium antagonists

Diltiazem	Nisoldipine
Fendilin	Tiapamil
Nicardipine	Verapamil
Nifedipine	etc



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Fig. 9. Hyperpigmentation due to amiodarone ("pseudocyanosis")

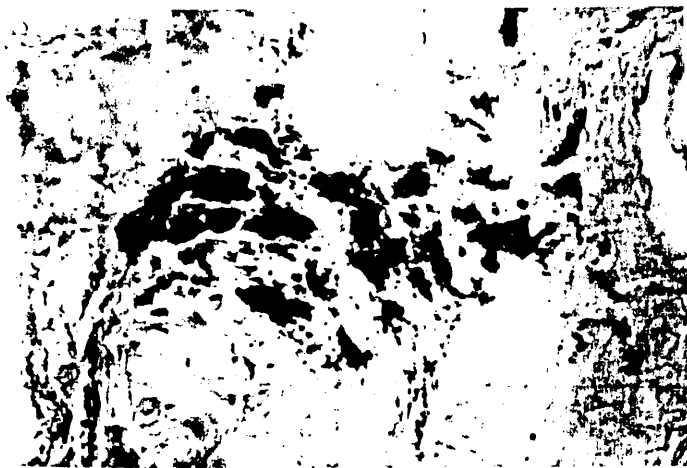


Fig. 10. Lipofuscin deposits in the dermis due to amiodarone

Frequently prescribed newer drugs are the two H_2 -receptor blockers *cimetidine* and *ranitidine*. They are mainly administered in the treatment of patients with gastric complaints. Especially cimetidine may cause various cutaneous side effects: namely dry and itching skin, seborrheic dermatitis, urticaria, Quincke's edema, maculopapular rashes and alopecia. Less often we observe the Stevens-Johnson syndrome, erythema anulare centrifugum, and exacerbation of systemic lupus erythematosus (SLE). Also characteristic is the appearance of painful gynecomastia. Ranitidine

(Zantac) seems to have a more favorable tolerance. Our experience with this newer drug is, however, limited. To date pruritus, urticaria, and maculopapular exanthema as well as gynecomastia have been observed [20, 29, 30, 45, 48, 68, 69].

Let us now discuss the last group of drugs: the *antirheumatics* [38]. The numerous cutaneous side effects of D-penicillamine were reported on 5 years ago. Presently the most important and largest group of modern antirheumatics are the *nonsteroidal anti-*

Table 5. Different groups of nonsteroidal anti-inflammatory drugs

1. <i>Heterocyclic acidic-acid derivatives</i>	2. <i>Propionic acid derivatives</i>
Indomethacin	(Benoxaprofen)
Sulindac	Carprofen
Diclofenac	Fenbufen
Tolmetin	Fenoprofen
(Zomepirac)	Flurbiprofen
	Ibuprofen
2. <i>Anthralinic acid derivatives ("fenamates")</i>	(Indoprofen)
Meclofenaminic acid	Ketoprofen
Mefenaminic acid	Naproxen
Flufenaminic acid	Pirprofen
Nifluminic acid	etc
etc	4. <i>Oxicams</i>
	(Isoxicam)
	Piroximan
	Tenoxicam



Fig. 11. Exanthema due to piroxicam (Felden)



Fig. 12. Photosensitization due to carprofen (Imadyl)

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inflammatory drugs (NSAID). Their efficient antirheumatic action is due to an inhibition of prostaglandin synthesis. According to their structure different groups are distinguished (Table 5). These new drugs have long been considered to be well tolerated and harmless, and have kept this reputation. The reality, however, is different: they are often responsible for dangerous side effects. Not only the gastroenteric system, the liver, and the bone marrow, but also the skin is affected. Toxic as well as allergic mech-



Fig. 13. Severe vasculitis due to naproxen (patient of the Department of Rheumatology of the University of Bern)



Fig. 14. Lyell's syndrome due to isoxicam (patient of Dr. Roujeau, Hôpital Mondor, Paris)

anisms contribute to the appearance of pruriginous rashes and photosensitization (Figs. 11 and 12) [3, 12, 19, 32, 40, 50, 75]. In many cases the drugs have provoked Stevens-Johnson and Lyell's syndromes as well as severe vasculitis (Fig. 13). Great differences in the rate of cutaneous side effects between the particular representatives of this group do not exist (according to the literature it varies from 1.5% to 5%). Only zomepirac (Zomax) and benoxaprofen were exceptions (20%–40%). Hence both were withdrawn from the market [25]. Until now the small group of *oxicams* have also proved to be poorly tolerable to the skin. About 1 year ago the registration of *isoxicam* (Pacyl) had to be withdrawn, mainly on account of severe Stevens-Johnson and Lyell's syndromes, which were predominantly noticed in France (Fig. 14). Some of these cases had fatal developments [22, 71].

These severe rashes may possibly have been due to drug-induced autoimmune reaction. The frequently administered *piroxicam* (Felden) also evokes marked cutaneous side effects: photosensitization and generalized exanthema but also Lyell's syndrome and even pemphigus [49].

Caution must be taken when prescribing modern nonsteroidal-antirheumatics. At the first appearance of side effects the drugs should immediately be cut off [15, 21, 39]. What I have summarized here is but a small selection of the more recent observations from the wide field of drug eruptions. New intensively acting drugs are being developed and registered. Therefore our topic may retain its relevance. For it is almost an eternal truth that a highly potent drug also has various side effects in store.

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