A GUIDE to DRUG ERUPTIONS

THE FILE OF ADVERSE REACTIONS TO THE SKIN

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The Guide to Drug Eruptions

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Foreword

The main purpose of the Guide in its third edition remains the same, i.e. to provide the practising dermatologist with easily accessible data on adverse reactions related to the skin. Yearly supplements, covering important new adverse reactions reported in the literature, are supplied free of charge to keep the Guide up to date until the next edition appears. In this way the Guide might be regarded as providing a data service in its field. Those who are not yet on our mailing list should send their names and addresses on the enclosed card to the File; they will then receive regularly every new edition in addition to the supplements.

In the second edition a tentative start was made by the File to act as a communication centre for suspected new adverse reactions and unexpected beneficial ones induced by drugs. In this edition of the Guide such suspected reactions are now included, the only criterium being that these reactions must have been reported from at least two different sources. Observation in daily practice has been the major, if not the sole source of recognition of adverse reactions and unexpected beneficial effects of drugs. Rare reactions may be defined as those which occur in fewer than 0,1% of patients treated with a drug, those which occur only after prolonged administration, only after a long lapse of time or only in a particular group of patients. These are unlikely to be detected during pre-marketing studies. Usually they are detected by astute clinicians and later confirmed by similar observations by their collegues. It has been the unexpected adverse reaction which has received until now the major attention. However the unexpected beneficial effect of a drug deserves the same attention. In this respect it might be remembered that the drug thalidomide, a now classical example of the unexpected hazards of pharmacotherapy, is now used for the treatment of leprosy reactions; more recently, a beneficial effect of this drug has been observed in discoid lupus erythematosus.

Foreword

By communicating reports both on suspected adverse reactions and on unexpected beneficial effects of drugs related to the skin, the File may be able to shorten the interval between the moment when suspicion arises and that when reasonably firm conclusions are possible as to a causal relationship. For this purpose a reporting form is enclosed. Personal data will be eliminated before the information is used. Only in this way we do feel free to make the reports available to all participants. By sending a report to the File, the participant will automatically receive a copy of reports and data of similar suspected reactions, if recorded in the File. These reports and data may freely be used for publication. Since the Guide is intended as a handbook for use when searching for the offending drug in connection with a drug eruption, theoretical considerations are given low priority.

W. Bruinsma

Types of adverse reactions to drugs

Overdosage

It is not always possible to control the dose of a drug accurately. The manifestations of overdosage are reasonably consistent for specific drugs and are similar in most persons. Usually the symptoms of overdosage are an exaggeration of the pharmacological action of the drug. Haemorrhage resulting from an overdosage of anticoagulants is a common example. Overdosage effects can be observed in patients receiving the usual doses. This can be due to different rates of absorption, metabolism or excretion of the drug. Especially in the geriatric patient overdosage is likely to occur for those drugs that remain active in the body until secreted by the kidney. Renal function diminishes with increasing age. At 65 years of age there is a reduction of about 30% in glomerular filtration and tubular function. Symptoms of overdosage of such drugs as digitalis and oral hypoglycaemic agents may be a serious hazard in some elderly patients.

In liver disease there may be a failure to metabolize a drug and in this case the action of any drug metabolized by the liver may be enhanced and prolonged. Morphine should not be given at all – or only in small doses – to patients with hepatic deficiency, as normal doses may precipitate coma in these patients. Paraldehyde is an additional example of a drug for which there is an increased susceptibility in liver disease.

Interaction of drugs is another phenomenon which may give overdosage effects in a number of ways. Many drugs compete for the same binding sites of plasma proteins. If, for instance, a patient needing anticoagulant therapy is well controlled on a daily dose of warfarin and is given phenylbutazone or acetylsalicylic acid, both of which have a stronger affinity for the plasma proteins, the warfarin may be displaced from its bound form and serious bleeding may ensue.

Drugs may inhibit or stimulate metabolic enzymes. Phenobarbital has been shown to stimulate such enzymes. Not only is the speed of metabolic breakdown of phenobarbital itself increased, but the metabolism of many other drugs handled by the same enzyme systems is accelerated, with consequent alteration in the action of drugs. Interference with excretion is another example of the way drugs may interact. The effect of probenecid in reducing penicillin excretion by the kidney is well known.

Cumulation

Cumulative effects may occur after prolonged administration of some drugs. The effects are insidious, as for instance the bluish discoloration of argyria in patients using silver-containing nose-drops. Another example is hypervitaminosis A, manifested by thinning, coarsening and loss of hair.

Pharmacological side effects

Pharmacological side effects are a result of unwanted but usually known pharmacological actions of drugs. Cytostatic drugs used to control cell division will in a similar manner produce alopecia. Sweating may be increased in patients using tricyclic antidepressants as a result of the autonomic activity of these drugs.

Idiosyncrasy, intolerance

In idiosyncrasy the patient reacts with a qualitatively abnormal response only present in these people and not dependent on immunological mechanisms. In intolerance the characteristic effects of the drug are produced by an abnormally small dose. For may drugs it has been shown that these types of reaction are a result of differences in enzymatic constitution.

Quantitative differences are the basis of drug intolerance, whereas qualitative differences are the cause of idiosyncrasies. A classical example is haemolytic anaemia in patients with glucose 6-phosphate dehydrogenase deficiency when treated with the antimalarial drug primaquine. Primaquine inhibits glucose 6-phosphate dehydrogenase which is needed to maintain cell integrity. This enzyme is present in reduced amount in the red cells of individuals susceptible to haemolytic anaemia caused by primaquine.

Genetic factors have been shown to determine important differences in the metabolism of isoniazid. Studies of plasma levels of the drug after intravenous administration of a standard dose

revealed that two separate types of response could be distinguished. Some people achieve high and others low plasma levels. The distribution of these plasma levels is bimodal, i.e. they fall into two clearly distinct groups. These differences in plasma levels are due to differences in the speed of acetylation and inactivation of isoniazid. Slow inactivation of isoniazid is an autosomal recessive trait. In Caucasian and Negro populations the genetic character which determines slow acetylation, the 'slow' allele, is three times more frequent than the 'rapid' allele. In the Japanese these proportions are almost exactly reversed.

Enzyme defects or differences are of great importance as examples of a phenomenon which probably influences in some degree the response to all drugs. These enzyme defects or differences are largely inherited. The inheritance of the abibility to respond to a drug may be determined by one kind of gene (i.e. monofactorial) or by a group of genes. In monofactorial inheritance there are two separate groups in the type of response as a result of the fact that one mutant gene is the decisive factor. Until now human data on multifactorial inheritance of drug responses are scarce. Multifactorial-based enzyme differences may be partly responsible for the types of response at both ends of a normal distribution curve. No doubt this new branch of medicine, pharmacogenetics, concerned with the way in which individuals react to particular drugs, will be of great importance.

Ecological imbalance

Reducing the flora of one species of microorganisms can result in the overgrowth of another. Moniliasis in the mouth and anogenital region after oral therapy with broad spectrum antibiotics is a common example.

Exacerbation of existing latent or overt disease

Examples of this type of reaction are the precipitation of clinical porphyria by barbiturates and the exacerbation of dermatitis herpetiformis after potassium iodide-containing expectorants. Inducement of systemic lupus erythematodes by some drugs may also belong in this category. A more or less identical situation exists in drugs affecting the defence mechanism. Corticosteroid therapy may enhance pyogenic infection.

Jarisch-Herxheimer reaction

This type of reaction is a result of administration of a drug highly

effective in the treatment of an existing infection. The release of toxic substances, due to the destruction of the sensitive microorganisms, causes exacerbation of existing lesions or the development of new ones. The reaction is a frequent phenomenon in patients with early syphilis treated with penicillin. It should be borne in mind that a macular rash after penicillin may be due to this type of reaction.

Hypersensitivity reactions

These types of reactions occur if a patient is given a drug to which he has developed an allergic sensitivity. Drugs may act as complete antigens if they incorporate proteins or polysaccharides. Most drugs, due to the small size of the molecule, are incomplete antigens or haptens. They or their metabolites may, however, be bound to proteins: the modified protein which results from this combination is treated in the body as a foreign protein or antigen, and hence antibody formation occurs. Except for penicillin and some suphonamides the haptenic determinants for most drugs have not yet been identified. Drugs are bound in different ways to different proteins. In this way several types of antibodies may be found in drug hypersensitivity. Accordingly there is a great diversity in types of allergic reactions to one single drug and the same individual may even experience different types of reaction to the same drug.

It should also be realized that drugs are never 100% pure chemicals. Besides the active ingredient there are the substances generally considered inactive used as a vehiculum, in addition to the coating, flavouring and colouring components. It has been shown for instance that the colouring constituents of capsules may produce urticaria and fixed eruptions. In the different stages of manufacture of the drug, traces of chemicals reminiscent of this process cannot always be eliminated. Instability of the drug is another factor that renders the 100% pure drug an ideal which is difficult if not impossible to attain. These factors should be kept in mind, especially in hypersensitivity reactions where a minimal amount of antigen is sufficient to elicit a reaction. A large proportion of allergic reactions to penicillins, especially in the past, have been due to protein contaminants.

Hypersensitivity reactions to hormones like corticotrophin, insulin and the corticosteroids are mainly a result of trace amounts of foreign substances.

One or more of the following criteria may be used to assess the

probability that an adverse reaction is allergic in nature:
1. Circulating or cellular bound antibodies may be demonstrated.
2. The reaction occurs after a sensitizing period of administration. Although the amount of antigen is important in causing sensitization, minimal doses may thereafter induce the reaction.
3. After recovery the same reaction can as a rule be precipitated again by a single test dose.
4. The reaction conforms to a known allergic pattern, as for instance urticaria, anaphylaxis, exanthema. The reaction is different from those which would be expected on the basis of the pharmacological action of the drug.

There is a great variation in the period of sensitization. Drugs tolerated for years may suddenly give a severe reaction. In others the same drug may give a reaction within a few days of the initial administration.

The incidence of allergic drug reactions increases with age. No doubt this can be explained by the greater exposure rate to different drugs in older people. However, it is known that pathologically changed proteins have a greater potential for producing allergic reactions than have normal proteins. Changed proteins are relatively more frequent in the older age groups. These changed proteins in combination with a drug as hapten could be part of the explanation for the greater incidence of allergic drug reactions as age advances. Another explanation may lie in differences in the metabolism of drugs. Frequently there exists in the elderly a decreased abibility to metabolize drugs.

Pathologically changed proteins are also present in autoimmune diseases and temporarily in various illnesses. Similarly it is known that drug eruptions tend to occur more frequently in ill people than in persons treated with the same drug as controls. Sometimes reexposure to a drug will not elicit anew a drug eruption.

These phenomena could be due to the temporary presence of these abnormal proteins. Drug eruptions are more frequent in females than in males. It still has to be determined whether this is a result of the generally higher consumption of drugs by females or reflects a similar situation.

Although genetic factors in various allergic phenomena have been established, there is as yet no evidence for a genetic determination in drug allergy. However, the possibility that the underlying mechanisms of hypersensitivity reactions to drugs are genetically determined must be borne in mind.

Mainly as a result of investigations in penicillin allergy, some of the basic immunological mechanisms for different clinical hypersensitivity reactions have been elucidated. As has been mentioned, most drugs are incomplete antigens or haptens. The binding of the hapten to the large molecule of proteins, polypeptides or amino acids must be strong and the antigenic determinants of the hapten must be retained if antibody formation is to take place. As a result of this binding, termed covalent binding, the complete antigen may possess one antigenic determinant and in other instances two or even more antigenic determinants. Antibodies which possess more than one binding site to bind the corresponding antibody are formed only to antigens with more than one antigenic determinant. These antibodies with several binding sites can combine later with antigens with more than one antigenic determinant to form a sort of network. It is this type of reaction that is the basis of hypersensitivity reactions.

Antigens with only one antigenic determinant may occupy the antibody combining site and thus prevent the bridging of two or more molecules. In this case, although an immunological reaction takes place, there is no hypersensitivity reaction. Similarly, in patients where antibodies are found, the administration of the particular drug is not necessarily followed by a clinical reaction.

Although antibodies can only be produced when the hapten is bound to a large molecular carrier, the hapten itself or molecules very closely related to it may conjugate with the binding sites of the antibody. If the free hapten molecule possesses only one antigenic determinant, they may in the same way prevent the bridging of the antibody molecules. Usually different types of antigens and antibodies are formed at the same time and the ultimate clinical reaction depends on the ratio between these different types of antigens, antibodies and haptens. Frequently, in drug allergies a powerful built-in protective mechanism exists in the fact that an excess of monovalent antigens contributes to the blockade of polyvalent antibodies.

Hypersensitivity reactions are classified into four types:
Type I – anaphylactic.
Type II – cytotoxic.
Type III – antigen-antibody complexes.
Type IV – delayed cellular.

Type I reactions. The main antibody involved in this reaction is IgE (reagins). Until recently it was only possible to demonstrate the presence of IgE antibodies by intradermal transfer of serum

(the Prausnitz-Küstner reaction). To this class of antibodies specific antisera have been developed in recent years, and by different immunological techniques the presence of these antibodies may now be demonstrated in vitro. Patients with atopic diseases have elevated levels of serum IgE. IgE antibodies have a particular affinity to cell membranes, especially of mast cells and basophils. Cross linkage of two antibody molecules by bivalent antigens on the cell membrane sets in motion an enzyme reacton, which in turn leads to the release from the cell of histamine, heparin and kinins. The cell membrane is not destroyed during the release process. Both anaphylactic reactions and urticaria are the clinical manifestations of this type of reaction. In humans massive release of histamine leads to bronchiolar constriction, localized oedema, often in the laryngeal and glottal region, and vasodilatation with consequent hypotension and shock.

Type II reactions. In type II reactions it is not the antibody which is attached to cell surfaces but the antigen. The antigen-antibody complexes take up complement and the cell is destroyed. Acute haemolytic anaemia and allergic thrombocytopenic reactions are due to this mechanism. The antibodies in this type of reaction are IgG or IgM.

Type III reactions. Type III reactions are a result of soluble antigen-antibody complexes or the formation of these complexes in tissue spaces. Soluble complexes may be formed in antigen excess. Deposition of these complexes, with the uptake of complement, in the blood vessel wall or in basement membranes causes local inflammation. IgG and IgM class of antibodies are involved. Serum sickness and Arthus type reactions are based on this type of process. In serum sickness, antibodies are built up during an incubation period of 5–14 days. The antibody formation is independent of whether the drug has been given only once or continuously. After this period, due to the deposition of antigen-antibody complexes in the blood vessel wall and membranes, one or more of the clinical symptoms of fever, exanthema, urticaria, adenopathy and arthralgia appear. These symtoms may persist for several days or weeks. Vascular lesions of longer duration may result in a chronic arterial inflammation, similar to polyarteritis nodosa. This type of reaction is especially common after continued administration of sulphonamides.

It should be emphasized that this classification is essentially immunological and frequently more than one of these types of

reaction are involved in clinical hypersensitivity. Urticaria usually occurs as an isolated manifestation, but it may be a feature of the serum sickness type of reaction.

Type IV reactions or delayed type of reactions. In the delayed type of allergic reaction no circulating antibodies are found. They are sometimes demonstrable in lymphocytes but not in plasma. The inflammatory process precipitated by a delayed reaction reaches a peak only after 24–28 hours. The infiltrate consists predominantly of mononuclear cells. Next to contact dermatitis, most of the exanthematous eruptions are due to the delayed type of allergy.

Autoimmune-like reactions

The symptomatology of autoimmune-like reactions depends on the target organ involved. In dermatological practice the most frequently seen manifestations are disseminated lupus erythematosus and some types of thrombocytopenic purpura. The possible mechanisms of auto-antibody formation cross the whole spectrum of immunology and different theories are considered. The drug or one of its metabolites may alter auto-antigens so that a normal antibody-producing mechanism no longer recognizes them as 'self'. Drugs may in some way stimulate 'immunocytes' to produce a clone or clones of abnormal but immunologically competent cells. These cells may fail to recognize the auto-antigens as 'self' and subsequently produce auto-antibodies against them. However, it is not known if auto-antibodies are pathogenic and their presence may be the result instead of the cause of tissue changes of a non-allergic type. The circulating antibodies may also be present in concurrence with a state of delayed sensitivity and it may be that this rather than an antigen-antibody reaction is the cause of the lesions.

Conclusion

For many drug eruptions it is not known to which category of the above-mentioned mechanisms, or for that matter of any other mechanism not yet elucidated, they belong. The pathogenesis of toxic epidermal necrolysis, the erythema multiforme-like reactions and the fixed eruptions remain for instance obscure.

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