Today's Treatment

Clinical pharmacology

Adverse reactions to drugs

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Adverse drug reactions (defined as unintended effects of substances used in the prevention, diagnosis, or treatment of disease) are common. They are responsible for 3-5% of hospital admissions, occur in 10-20% of hospital inpatients, and have recently been reported in 40% of patients receiving drugs in general practice.[1]

Thompson and I[2] have suggested that adverse reactions and interactions can usually be logically and clinically divided (see table 1) into those that form part of a drug's *normal* pharmacological actions (type A: augmented), and those that represent a *novel* response (type B: bizarre).

TABLE I—*Classification of adverse drug reactions*

Features	Type A	Type B
Pharmacology	Augmented	Bizarre
Predictable	Yes	No
Dose-dependent	Yes	No
Morbidity	High	Low
Mortality	Low	High

Type A (augmented) reactions

Type A reactions (table I) are the results of qualitatively normal, but quantitatively abnormal, pharmacological effects of drugs. They may be due not only to the primary (or intended) pharmacological property of a compound, but also to its other effects—for instance, the anticholinergic actions of tricyclic antidepressants causing tachycardia, dryness of the mouth, and blurring of vision. Such reactions are usually predictable and dose-dependent; and although they may be common, they are rarely life-threatening.

Type A reactions occur in individuals lying at the extremes of dose-response curves for pharmacological effects. Individuals at one end will show frank toxicity, while those at the other will be therapeutic failures (a form of adverse reaction). There are three causes for this type of response.

PHARMACEUTICAL

Differences in pharmaceutical formulation can give rise to substantial alterations in the quantity of drug that is "available" to reach its site of action. As a consequence, most Western countries (including Britain) now have strict regulations governing drug content, release rate, and bioavailability. New formulations are carefully scrutinised by regulatory authorities —for example, the Committee on Safety of Medicines—and claims by pharmaceutical companies that their branded products are superior to cheaper generic equivalents are now unfounded.

PHARMACOKINETIC

Individual differences in absorption, distribution, and elimination result in differences in drug concentrations at the site of action. Enhanced absorption, or impaired elimination, cause an increase in plasma and tissue concentrations and may precipitate type A toxicity. Conversely, impaired absorption or accelerated elimination may result in therapeutic failure. Pharmacokinetic variability is therefore an important and common cause of type A reactions.

Bioavailability—the fraction of an oral dose reaching the systemic circulation—is determined not only by the extent of absorption across the gut wall, but also by the extent of "presystemic" (also called "first-pass") metabolism in the gut wall and liver during the absorptive period.[3] Variability in gastrointestinal absorption may also occur as a result of altered motility or in mucosal disease.[4] Variability in presystemic metabolism occurs with tricyclic antidepressants, some opiates, and neuroleptics (table II), and with many beta-blockers (table III). With such drugs, type A reactions will occur commonly unless their dosages are carefully tailored to individual responses.

The most common pharmacokinetic cause for type A reactions is variability in the rate of elimination. The elimination of drugs excreted unchanged by the kidney is directly proportional to renal function.[5] Patients with impaired renal function (including the elderly) are therefore particularly liable

TABLE II—*Adverse reactions to drugs acting on the central nervous system*

Group	Type A	Type B
Anticonvulsants*	Sedation, ataxia, enzyme induction	Pseudolymphoma,† rashes, porphyria
Antidepressants	Sedation, anticholinergic effects, sensitivity to pressor amines	Hepatotoxicity
Anxiolytics/ hypnotics	Sedation, withdrawal effects	Hepatotoxicity‡
Levodopa	Nausea, vomiting, dyskinesia, psychoses	Haemolytic anaemia
Opiates	Sedation, confusion, nausea, vomiting, respiratory depression	
Neuroleptics	Sedation, confusion, extrapyramidal reactions, hypotension, tardive dyskinesia	Hepatotoxicity§

* Phenytoin, phenobarbitone, carbamazepine.
† Phenytoin
‡ Especially chlordiazepoxide.
§ Especially chlorpromazine.

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to develop type A reactions when given doses designed for healthy young adults. This especially includes digoxin and atenolol (table III), aminoglycosides (table IV), and cimetidine (table V). Adverse effects to these drugs can largely be avoided if their dosages are tailored to individuals' renal function. Many drugs are eliminated by metabolism to inactive products that are then excreted. Two common pathways of biotransformation —microsomal oxidation and acetylation—vary widely in their rate of metabolism. Individual differences are due to both genetic and environmental influences,[6 7] and are compounded by liver disease and (in some instances) cardiac and renal failure. Drugs undergoing elimination primarily by microsomal oxidation included anticonvulsants, antidepressants, most anxiolytics/hypnotics, and most neuroleptics (table II); some beta-antagonists, oral anticoagulants, and theophylline (table III); some oral hypoglycaemics (table VI); and some non-steroidal anti-inflammatory drugs and H_1-antagonists (table V). For all these drugs, variability among patients is so great that it is now unacceptable to prescribe "fixed" or "standard" doses on a chronic basis without adjustments tailored to individual responses. For some drugs, the use of plasma concentrations to monitor treatment can also make an important contribution in preventing toxicity, and this may be expected to become increasingly important in the future.

TABLE III—*Adverse effects of cardiovascular drugs and respiratory drugs*

Group	Type A	Type B
Beta-agonists	Tachycardia, tremor	
Beta-antagonists	Bradycardia, hypotension, heart failure, bronchospasm	Rashes, oculocutaneous syndrome*
Cardiac glycosides	Nausea, vomiting, arrhythmias	Gynaecomastia
Diuretics (potassium sparing)	Hyperkalaemia	
Inhaled steroids	Candidiasis, adrenal suppressions	
Methyldopa	Sedation, hypotension	Hepatotoxicity, fever
Oral anticoagulants	Haemorrhage, resistance	Rashes†
Theophylline	Nausea, vomiting, tachycardia	
Thiazide and loop diuretics	Hypokalaemia, gout	Vasculitis, thrombocytopenia

* Practolol.
† Phenindione, only rarely with warfarin.

TABLE IV—*Adverse reactions to some antimicrobial drugs*

Group	Type A	Type B
Aminoglycosides	Ototoxicity, nephrotoxicity*	Rashes
Cephalosporins	Nephrotoxicity*	Rashes
Isoniazid	Peripheral neuropathy	Hepatotoxicity
Penicillins	Diarrhoea, convulsions	Anaphylaxis, rashes
Sulphonamides	Diarrhoea, enzyme inhibition†	Agranulocytosis, rashes
Tetracyclines	Uraemia, tooth deformities	Photosensitivity,‡ Fanconi syndrome

* Especially in combination with frusemide.
† Sulphamethoxazole.
‡ Demethylchlortetracycline.

PHARMACODYNAMIC

Despite the importance of pharmacokinetic variability, at least part of the individual susceptibility to drugs is due to altered target organ sensitivity. Although this has been inadequately studied, both changes in receptors (density and affinity) and alterations in homoeostatic mechanisms are probably concerned. Altered target organ response accounts for much of the variation in response to warfarin[8] and for the rare condition of hereditary resistance.[9] Differences in oestrogen and progestogen receptor density appear to be a major determinant of the response to endocrine treatment in breast cancer.[10] A reduction in the gain of homoeostatic processes accounts for the precipitation of heart failure or bronchospasm with beta-antagonists (table II). Impaired homoeostasis in the elderly is a common cause of postural hypotension with neuroleptics (table II) and loop diuretics (table III), as well as hypothermia with many central nervous system depressant drugs.

TABLE V—*Adverse reactions to miscellaneous drugs*

Group	Type A	Type B
Non-steroidal, anti-inflammatory	Gastric erosions, dyspepsia	Asthma, hepatotoxicity, bone marrow suppression
Paracetamol	Hepatotoxicity	Anaphylaxis
H_1 antagonists	Sedation, confusion	Photosensitivity
H_2 antagonists	Confusion, enzyme inhibition	
Topical steroids	Skin atrophy, rosacea, adrenal suppression	

The specific type A reactions shown in tables II to VI are those that are most often observed with commonly prescribed drugs. The drugs shown in table II are, with the exception of levodopa, central nervous system depressants (causing sedation, loss of concentration, and confusion) to which the elderly are particularly vulnerable. These adverse effects summate either when two (or more) of this group are prescribed together, or if the patient takes alcohol. Although tolerance to the central sedative effects of these drugs occurs, appropriate advice about driving, operating heavy machinery, or drinking should be given to patients who are starting treatment.

Alkylating cytotoxic drugs (table VI) are mutagenic, and many have been shown to be carcinogenic in animals. Some have been shown to be carcinogenic in man, and they probably all possess this feature. In treating malignant disease such risks are clearly justified, but the use of alkylating cytotoxic drugs for non-malignant conditions clearly warrants careful consideration.

TABLE VI—*Adverse reactions to drugs with metabolic and endocrine effects*

Group	Type A	Type B
Carbimazole	Myxoedema	Agranulocytosis
Cytotoxics	Bone-marrow suppression, carcinogenicity	
Insulin	Hypoglycaemia	Haemolytic anaemia
Oral contraceptives	Withdrawal bleeding, break-through bleeding, thromboembolism	Prophyria, hepatotoxicity
Oral hypoglycaemics	Hypoglycaemia	Alcohol flushing*

* Chlorpropamide.

All non-steroidal anti-inflammatory drugs produce dyspepsia and some loss of blood (usually slight) from the gastrointestinal tract. They may also cause acute gastric erosions. Whether these drugs produce peptic ulceration, or cause massive haemorrhage and perforation in pre-existing ulcers, is still disputed. Despite this, it is wiser to avoid such drugs in patients with known duodenal or gastric ulcers unless clinical circumstances suggest that the possible risk is outweighed by the likely benefits. Sedation and confusion are common adverse effects of H_1-antagonists; confusion may also occur with H_2-antagonists, particularly in the elderly and others with reduced renal function.

Type B (bizarre) reactions

Type B reactions are bizarre, qualitatively abnormal (table I) effects, which are apparently unrelated to a drug's normal pharmacology. Again, there are three basic causes.

PHARMACEUTICAL

By-products of chemical synthesis—for instance aspiryl anhydride—or in-vitro degradation products, such as tetracyclines and penicillins, may give rise to toxic effects that have no relation to a drug's known pharmacological properties. Similarly the additives, excipients, colorisers, and binders that make up a pharmaceutical product—for example, lactose, glutein, tartrazine—may themselves cause toxicity, or may react with the drug itself to yield toxic derivatives such as carboxymethylcellulose and penicillin).

PHARMACOKINETIC

Individual differences in the overall rate and extent of absorption, distribution, and elimination results in changes in the intensity of a drug's effects which, as we have seen, are important causes of type A reactions. It is theoretically possible, however, that the toxicity of some compounds is mediated via the formation of unusual, or novel, metabolites. There is evidence that the hepatotoxicity of methyldopa and isoniazid (tables III and IV) may be due to this process. It has also been suggested that the formation of electrophilic drug metabolites, which can bind covalently to tissue macromolecules, may result in the production of complete antigens or autoantibodies,[11] but at present there is no convincing example of such a mechanism at work.

PHARMACODYNAMIC

Some type B reactions are due to genetic abnormalities which result in altered target organ responses.[2] These include haemolysis with oxidant drugs—for instance, sulphonamides, 8-aminoquinolines—in individuals with red cell glucose-6-phosphate dehydrogenase deficiency or certain haemoglobinopathies; the precipitation of acute porphyria with enzyme-inducing agents; malignant hyperpyrexia with inhalational anaesthetics and muscle relaxants; and periodic paralysis with drugs that alter some potassium.

Many type B reactions in tables II-VI appear to have an immunological basis. Nevertheless, not all immunological reactions are of type B, for in those instances where a drug is antigenic per se—for instance, antisera, polypeptides—the development of immunological effects is predictably type A.

Conclusions

The "augmented-bizarre" classification of adverse reactions used in this article is intended to provide a logical framework to the understanding, diagnosis, and management of drug toxicity. In some instances it must be accepted that due to our ignorance of the pharmacology of certain drugs, some apparent type B reactions will in the future need reallocation. In clinical practice, however, most type A reactions are preventable by careful dosage titration; they produce a clinical picture that is an extension of their normal pharmacological actions; and they can usually be managed either by appropriate adjustment of the dosage, by substitution of a more selective agent, or by giving an additional drug to antagonise unwanted effects. In contrast type B reactions are often (though not invariably) unpredictable and usually require complete withdrawal of the offending drug.

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MATERIA NON MEDICA

London packaged

Having previously fought shy of package tours we were initially less than enthusiastic when our local BBC radio station announced their plans for a "London weekend." However, the enthusiasm of our children rapidly overcame our own inhibitions—a visit to the metropolis from the "border city" being a comparative rarity other than for professional reasons.

Our application was accepted and we set off by coach at 7 am on a beautiful autumn Saturday. The journey was surprisingly quick and comfortable and on arrival in London we immediately set off for the obligatory sight-seeing tour. Nevertheless, despite several years of undergraduate study in London it was surprising how many of the places of interest pointed out I was seeing for the first time. "My Fair Lady" was the evening show and we enjoyed the splendid revival as much if not more than the original version at Drury Lane several years ago. What luxury to be transported from hotel to theatre door by coach and to find the coach waiting outside after the show, double-parked in the Strand—do tour operators have an understanding with traffic wardens?

A quick visit to St Paul's and Westminster on Sunday morning and on to Buckingham Palace in time to see the changing of the guard. Then followed a chance to explore the vessels moored at St Katherine's dock under the care of the Maritime Trust, with the added attraction of the costumes from the television series *The Onedin Line* on display. Into the coach again to Greenwich for the afternoon to savour the flavour of ships under sail in the *Cutty Sark* and to marvel how Sir Francis Chichester could possibly have survived his historic journey in a vessel the size of *Gipsy Moth IV*. Sunday evening saw us at the Albert Hall for the rare opportunity to hear the sparkling melodies of the Strauss family authentically played by the Vienna Symphony Orchestra. It would not have mattered if maestro Sawallisch had been taken ill during the performance—our 9-year-old son in any case conducted the entire concert with his right index finger.

There was no way of escaping the Oxford Street stores on Monday morning but adequate compensation in the afternoon was an opportunity to enjoy the treasures of Windsor minus the weekend crowds. Time here to revel not only in the splendour of the Waterloo Chamber but also to take note of the historic minutiae such as the carefully preserved bullet which killed Nelson at Trafalgar. The journey home was equally comfortable. We arrived home tired but with no regrets, a revised opinion of packages and even more enthusiastic supporters of our local radio station. There was also unanimous agreement that at £40 a head this must have been the bargain of an inflationary year.—R H SALTER (consultant physician, Carlisle).