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Ferner, Robin; Aronson, Jeffrey

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R E Ferner[1,2], J K Aronson[1,3]

[1] West Midlands Centre for Adverse Drug Reactions, City Hospital, Birmingham, B18 7QH, UK

[2] Institute of Clinical Sciences, University of Birmingham, UK

[3] Centre for Evidence Based Medicine, Nuffield Department of Primary Care Health Sciences, Oxford, UK

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Address for correspondence:

Professor R E Ferner

West Midlands Centre for Adverse Drug Reactions

City Hospital

Birmingham

B18 7QH

UK

r.e.ferner@bham.ac.uk

Abstract

The pharmacological effects of a drug depend on its concentration at the site of action, and therefore on the concentration in blood and on the dose. The relationship between the concentration or dose and the corresponding effect can usually be represented mathematically as a rectangular hyperbola; when effect is plotted against log concentration or log dose, the curve is sigmoidal.

Inevitably, the effect size and the doses causing benefit and harm will differ among individuals, since they are biological phenomena: some are more likely than others to suffer harm at any given dose. Some harmful effects can occur at much lower doses than those used in therapeutics; that is, the log dose–response curve for harm lies far to the left of the log dose–response curve for benefit. Those who suffer such reactions are *hypersusceptible.* When the dose–response curves for harm and therapeutic effect are in the same range, dose cannot separate the harmful effects from the therapeutic effects, and adverse reactions are *collateral*. *Toxic* effects occur when harmful doses are above the doses needed for benefit.

In this review we consider factors that influence a subject's susceptibility to adverse drug reactions. Determinants of susceptibility include **I**mmunological, **G**enetic, demographic (**A**ge and **S**ex), **P**hysiological and **E**xogenous factors (drug–drug interactions, for example), and **D**iseases and disorders such as renal failure, giving the mnemonic **I GASPED**. Some susceptibility factors are discrete (for example, 'all-or-none') and some are continuous; susceptibility can therefore be discrete or continuous; and the factors can interact to determine a person's overall susceptibility to harm.

Introduction

Some patients become ill from a dose of a drug which in other patients has no discernible effect; some patients die from exposure to drugs that are safe and effective in other patients.

There are in effect two distinct types of adverse drug reaction (ADR): those that will affect all patients, but which occur at different doses in different patients; and those that will affect some patients, but not all, however large a dose is administered. The response in affected patients will necessarily depend on dose; it is a misconception that immunological reactions such as anaphylaxis [[1]] are unrelated to dose, although the dose-dependence may not be evident within the therapeutic dose range.

In this review we consider the factors that influence the susceptibility of subjects to ADRs. Our review derives primarily from a lecture at the British Pharmacological Society's *Pharmacology 2018* meeting and updates a review of the harms from medicines.[[2]]

The dose of the drug

The premise on which this review is based is that all pharmacological effects are related to the concentration of a pharmacological agent at its site or sites of action, whether the action is beneficial or detrimental. We have discussed the reasons for this, and its consequences, elsewhere.[[3,4]] The concentration at the site of action is related, in turn, to the dose administered. Since the dose is usually known, while the concentration at the site of action may be difficult or impossible to measure, it is often convenient to discuss dose–response rather than concentration–response.

The key developments in the history of ideas about dose-responsiveness date from early in the 20th century, although there is a prehistory.[[5]] The cumulative dose of salicylate at which patients with rheumatic disease demonstrated symptoms and signs of toxicity was established before the First World War.[[6]] AJ Clark used the data to draw a sigmoid log dose–response curve[Figures 1 and 2,].[[7]]

{Figures 1 and 2 near here}

The therapeutic dose of salicylate was limited by toxicity. In Hanzlik's practice, 'the salicylate is given in doses of from 10 to 20 grains every hour until symptoms of intoxication begin to appear.' [[6]] Dosing to toxicity has been largely abandoned outside oncology.[Reference to Professor Martin's paper] While toxic ADRs are important, harm can occur with therapeutic doses rather than toxic doses.[[8]] For example, constipation is a

collateral adverse reaction to opioid analgesia, and is expected to accompany the therapeutic action. Where the dose–response curve for a significant ADR approaches a maximum at concentrations lower than those used in treating disease, we have characterized it as indicating hypersusceptibility to the adverse effect in comparison with the therapeutic effect. Most such ADRs affect only a small subset of the treated population—the drug would be of limited clinical value if it often caused significant harm before any benefit was realized.

The time-course of administration

A second factor that influences the risk of adverse drug reactions is the time-course of exposure in relation to the reaction. This is partly because cumulative dose is a function of time, and the cumulative dose determines the risk of some ADRs. For example, the risk of delayed anthracycline-induced cardiomyopathy increases with cumulative dose.[9]

The rate of change of drug concentration can also be important. Examples are the development of flushing and wheeze with rapid infusion of acetylcysteine.[10]

Susceptibility factors related to the patient

Dose–response and time-course represent aspects of the drug and its administration. Susceptibility characterizes the contribution of patient factors to the risk of an ADR. The interactions between dose, time-course, and susceptibility can help clinicians understand, predict, and mitigate ADRs. 'The major interacting factors influencing the response of the host to the drug' were set out a 1958 review of untoward reactions to penicillin. The factors in the 'responding system' included, for example, age, sex, hereditary factors, and the 'presence or stage of pathological conditions.'[11]

Immunological factors

Gell & Coombs classified immunological reactions into four types, each of which can be associated with ADRs. Immediate (Type I) hypersensitivity reactions, in which antigen binds to specific IgE, result in the degranulation of mast cells and the release of histamine, bradykinin, and other mediators that cause the potentially fatal clinical syndrome of airways compromise, hypovolaemia, and cardiovascular collapse. Anaphylaxis to β-lactam antibiotics is an example. In the earliest reported case, a reaction to 15 000 units benzylpenicillin injected intramuscularly in a soldier previously sensitized by dermal application, the reaction was milder and of shorter duration after a further injection of 100 units subcutaneously; oral administration of benzylpenicillin produced desensitization.[12] As far back as 1909, Anderson & Rosenau demonstrated that there was a minimum sensitizing dose of horse serum globulins in the guinea pig [13]; recent studies in patients

sensitized to trinitrophenol showed a clear relation between the dose of trinitrophenol–bovine serum albumin and the intensity of the anaphylactic response.[14]

Haemolytic anaemia provides an example of a drug-induced Type II immunological reaction mediated by IgG. The drug can act as a hapten covalently bound to proteins on the red cell membrane, as happens with penicillin; or can induce a Coombs' test positive haemolytic anaemia by suppressing immune regulation, as happens with the checkpoint inhibitors nivolumab, pembrolizumab, and ipilimumab.[15] The proportion of patients who develop a positive Coombs' test with the antihypertensive drug α-methyldopa increases with increasing dose.[16]

Serum sickness—fever, urticaria, and joint pain following injection of foreign protein—was first delineated in 1905 in patients treated with horse serum containing antibody against diphtheria, used for passive immunization.[17] This Type III immunological reaction is the consequence of circulating immune complexes. It can occur with modern biological therapy such as rituximab, a murine–human chimeric monoclonal antibody directed against the B cell surface marker CD20.[18]

Delayed-type (Type IV) immunological reactions are cell-mediated. The proportion of subjects sensitized by the chemical dinitrochlorobenzene, which induces delayed-type hypersensitivity, increases as the sensitizing dose increases [Figure 3a]; and in sensitized individuals, the size of dermal response depends on the dose used to elicit it.[Figure 3b [19]] There appears to be a predisposition to being sensitized by topical allergens: patients with positive patch tests to many allergens are more easily sensitized to dinitrochlorobenzene than patients with no positive patch tests.[20]

{Figures 3a and 3b near here]

Genetic factors

Genetic factors can determine the pharmacokinetics of drugs. It was established in the 1940s that the hydrolysis of atropine by rabbit serum was determined by a gene called As; hydrolysis was faster in homozygotes than heterozygotes, and absent if the As gene was absent.[21] Prolonged apnoea from respiratory muscle paralysis in patients given the muscle relaxant succinylcholine (suxamethonium) is also genetically determined. In homozygous normal subjects, the drug is rapidly metabolized by an enzyme, butyrylcholinesterase, whose activity is impaired in those with prolonged apnoea and in their families.[22] The duration of apnoea depends on the dose in both normal and abnormal subjects, but in the

latter the dose-response curve is shifted far to the left [Figure 4].[23] The ClinVar database now lists 118 genetic variants of butyrylcholinesterase, of which three-quarters are pathogenic or likely to be pathogenic.[24]

{Figure 4 near here}

Pharmacodynamic differences can also be genetically determined. For example, aspirin-exacerbated respiratory disease (asthma, nasal polyps, and aspirin sensitivity: Samter's triad) was recognized to be familial in the 1950s; it is associated with genetic abnormalities, usually in the production or action of cysteinyl leukotrienes.[25] Another pharmacodynamic susceptibility recognized in the 1950s was haemolytic anaemia with oxidizing agents. The resistance of haemoglobin in red blood cells to oxidation depends on the function of glucose-6-phospate dehydrogenase, the key enzyme in the generation of reduced glutathione.[26] Over 300 enzyme variants from G6PD AACHEN to G6PD ZHITOMIR are now recognized.[27] The extent of haemolysis depends on both the enzyme variant and the dose of oxidizing agent.

Genetic and immunological susceptibility interact through human lymphocyte-associated antigens. For example, Genetic and immunological susceptibility interact through human lymphocyte-associated antigens. For example, the demonstration that abacavir binds to and alters the antigen coded for by HLA-B*5701, so that it alters the repertoire of peptides recognized by the receptor, which now reacts to peptides previously recognized as self, and causes an immune response and tissue damage. This helps to explain the observation that serious cutaneous adverse reactions to abacavir are much commoner in subjects with that genotype.[28,29]

Age

Some ADRs are more common in infants and children, who have immature physiological systems, and others are increased in the elderly with failing physiological systems and increasing frailty and co-morbidity. The classical example in neonates is 'grey baby syndrome.' In this syndrome, high concentrations of chloramphenicol accumulate as a result of poorly developed hepatic metabolism.[30] The high chloramphenicol concentration causes cardiovascular collapse.

A further difficulty in children is that the range of agents is smaller than the range licensed for use in adults, and it is therefore common to use preparations untested in children. A study of children admitted to hospital showed that adverse reactions were more

likely to occur with unlicensed and off-label medicines than licensed medicines (relative risk 1.67; 95% CI 1.38, 2.02; $P < 0.001$).[31]

Some ADRs occur more often in older people than younger adults. For example, in cross-sectional studies of French and Icelandic populations, the risk of drug-induced liver injury increased four-fold from ages 15–29 to age over 70.[32] Part of the explanation could be that different populations are exposed to causative agents, such as co-amoxiclav, to different extents. However, difference in exposure is not the entire explanation: the risk of liver injury with flucloxacillin was 25 times higher in those aged 70–79 than in those aged 18–49 [33]; and age and dosage were independent risk factors for statin-induced liver injury in a Chinese cohort.[34] More generally, a model based on data from 1408 inpatients identified age as a major predictor of preventable harm from medicines,[35] as did several other models.[36 37]

Responses to drugs can differ qualitatively with age. A good example is the difference in ADRs to the dopamine antagonist metoclopramide. The risk of acute dystonic–dyskinetic reactions was more than thirty times greater in those below the age of 20 years than those above the age of 65 years; parkinsonism was significantly commoner in those aged over 65 years than in those below 65.[38] The difference may be due to the change in the balance between dopamine D1 and D2 receptors with age.

Reduced renal function and altered body composition in older people can cause marked changes in drug disposition, which probably contribute to higher rates of hospital admission for ADRs.[39] Two important sequelae to physical and mental frailty are falls (and their consequence—femoral fractures) and delirium. Falls are associated with prescription of hypnotics and sedatives;[40] although benzodiazepines are particularly incriminated, the regular use of a non-benzodiazepine hypnotic ('z-drug') increased the relative risk of falls four-fold in a longitudinal study of nursing home residents.[41] In another study, older adults who continued taking drugs that were believed to increase the risk of falls were ten times more likely to suffer falls than older adults who stopped taking such drugs.[42] Opioid analgesics, benzodiazepines, anticholinergic drugs, and other commonly used medicines, often cause delirium in older people.[39,43].

Multi-morbidity, the simultaneous occurrence of several morbid conditions, increases the risk that the pharmacokinetics or effect of one or more medicines is altered by the presence of disease. It also makes polypharmacy more likely, and that increases the risk of drug–drug

interactions. The number of possible two-way interactions* increases from 1 with 2 drugs to 10 with 5 drugs, to 45 with 10 drugs, to 105 with 15 drugs [Figure 5].

{Figure 5 near here}

Sex

Some adverse drug reactions are limited to one sex for biological reasons. For example, clear-cell carcinoma of the vagina, a delayed consequence of exposure to diethylstilboestrol *in utero*,[44] can only occur in women. A contemporary example is the risk of abnormal vaginal bleeding in women treated with anticoagulants. This is a particular problem with direct-acting oral anticoagulants.[45] In one analysis, this 'occurred frequently (9–15/100 [patient-years]) and significantly more often in women of reproductive age receiving edoxaban compared with women receiving warfarin.' [46]

Many studies show that, for ADRs that occur in both men and women, the risk is generally higher in women. For example, in a review of studies of ADRs causing or occurring during admission to hospital, 8/15 studies identified female sex as a risk factor, and no trial identified an increased risk in males.[37] In an analysis of 48 cohort studies of newly marketed drugs used in general practice the overall age-standardized relative risk of an ADR being recorded was 1.6 (95% CI 1.5 1.7) in women.[47] This may be partly due to the use of standard doses unrelated to body size, since women are on average smaller than men. Some ADRs are twice as common in women as in men. In the case of the potentially fatal arrhythmia *torsade de pointes*, one factor is the sex difference in repolarization of heart muscle, reflected in a longer corrected QT interval in women at baseline.[48] Database studies suggest that cough with angiotensin-converting enzyme (ACE) inhibitors is approximately twice as common in women as in men, although angioedema from ACE-inhibitors, whose pathogenesis is likely to be similar, is reported 30% more frequently in men.[49]

Physiological changes

Pregnancy has a marked influence on body composition and physiological function, and hence on drug disposition. It also exposes the unborn fetus to potentially harmful concentrations of maternal drugs. Wilson noted that the susceptibility of the conceptus to teratogens depended on genotype, the developmental stage at the time of exposure, and the

* ${}_nC_2 = n!/(n-2)!2! = n(n-1)/2$

dose of the teratogen.[50] The relationship between dose and response was clearly shown in Himalayan rabbits exposed to thalidomide, in whom the incidence of defects in leg bones, malformation of the digits, and sternal synostosis were all dose-related.[51] The degradation of a transcription factor called SALL4 has been implicated in the harm caused by thalidomide, which resembles the Duane Radial Ray Syndrome that results from loss-of-function mutations in the gene coding for SALL4.[52] There are mutations in the zinc-finger domain of murine SALL4 that protect it from the action of thalidomide, and explain why mice are not susceptible to thalidomide embryopathy.

Circadian rhythm influences both the disposition of drugs and their effects. In one study, unfractionated heparin was given at constant rate by infusion pump. The activated partial thromboplastin time and Factor Xa inhibition assay nevertheless showed peak values (towards midnight) 40% higher than trough values (towards 07.00 hours).[53] In healthy male volunteers, the clearance of an intravenous dose of 20 mg methylprednisolone given at 08.00 h was substantially slower than the clearance of an identical dose given at 16.00 h.[54] Both sex and genetics substantially influence chronopharmacology, at least in mice.[55] It is also possible that the menstrual cycle influences drug metabolism and hence the risk of ADRs. The activity of drug-metabolizing enzymes CYP1A2, CYP2A6, and NAT2 differed significantly between the early and late follicular phase in women of childbearing age, as assessed by caffeine metabolism.[56] However, since caffeine metabolite ratios were used to determine enzyme activity, the results for the three enzymes were not independent.

Exogenous factors

Environmental factors and exposure to foodstuffs and interacting medicines are likely to influence the risk of ADRs to drugs.

For example, patch test responses to piperazine depended on environmental temperature.[57] The authors of a Swedish study concluded that warm weather increased the risk of drug-induced hyponatremia, [58] and 'heat-related' adverse effects of diuretics and some other drugs were twice as frequent in summers affected by heat-waves as in control summers.[59]

Foodstuffs can provoke reactions analogous to those caused by medicines, as is the case with tartrazine in patients with aspirin-exacerbated respiratory disease.[60] Foodstuffs and medicines can have pharmacodynamic interactions, as do ethanol and diazepam;[61] or pharmacokinetic interactions, as happens when mono-amine oxidase inhibitors prevent the breakdown of tyramine from foods such as blue cheese.[62] They can also display

pharmaceutical interactions, as when the absorption of tetracycline is reduced by binding to calcium in milk.[63]

Drug–drug interactions are well established, and an important cause of avoidable ADRs.[64] However, there is the serious difficulty, both in general and in individual patients, that while potential adverse drug reactions are very numerous serious adverse reactions are rare, even when they are known to occur. For example, in one study of elderly Italian patients, the number of potentially important adverse drug reactions was 12578, but only 464 (4%) of these were observed, and even for the most serious potential reactions, only 5% resulted in clinically significant effects.[65] This divergence between theory and clinical observation suggests that the theory needs refinement.

Disease

Disease can affect the absorption, distribution, metabolism, and elimination of drugs.

The effects of renal and hepatic impairment are well known, and *Summaries of Product Characteristics* give advice on dosage adjustment, although not all such advice may be based on good evidence. The effects in liver and renal disease are, for the most part, caused by higher drug concentrations. In the case of liver disease, this can be a result of porta-systemic shunting, which allows orally administered agents to be absorbed without undergoing first-pass hepatic metabolism; or reduced hepatic elimination as a consequence of reduced metabolism or diminished biliary excretion. In kidney disease, the major effect is on renal drug elimination, but some drugs—notably insulin and 25-hydroxycholecalciferol— are affected by a reduction in renal metabolism.

Pharmacodynamic effects of liver failure are most obvious in patients with cirrhosis, who are especially sensitive to sedative drugs. It is postulated that the sensitivity is related to an increase in GABA-ergic tone, perhaps because of circulating endogenous benzodiazepines; this is in keeping with the observation that flumazenil can sometimes lighten hepatic coma. [66].

The influence of other conditions is less well explored. For example, the effects of obesity on drug distribution are of increasing importance as the average body-mass index increases. A recent review of vancomycin dosing noted that no recommendations make adjustment for obesity, despite adjustments for actual body weight, renal function, and other relevant parameters.[67]

The interactions between diseases and the actions of medicines are also important, as is evident, for example, in the hyperglycaemic action of corticosteroids in patients with

diabetes; even local corticosteroid injections cause a transient increase in blood glucose concentration.[68]

Conclusions

The many factors that influence the occurrence of adverse drug reactions can be summarized as **D**ose, **T**ime, and **S**usceptibility (**DoTS**), reflecting properties of the drug, the reaction, and the patient. The factors that alter an individual's susceptibility include **I**mmunological and **G**enetic factors, **A**ge, **S**ex, **P**hysiological changes, **E**xogenous influences, and **D**isease conditions; that is, **I GASPED**. Interactions between these factors help to explain why some patients suffer serious adverse reactions while others are unaffected; and all depend on dose of the drug.

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Legends to figures

Figure 1: Cumulative percentage of patients who have become salicylate-toxic plotted against log dose of salicylate (in grains; 1 grain $\underline{\sim}$ 65 mg) [after references 6 and 7]

Figure 2. Hanzlik's data[6] plotted as a cumulative distribution curve (cumulative percentage versus standard deviation from a mean dose of 186 grains)

Figure 3a. Percentage of subjects sensitized -v- dose of dinitrochlorobenzene on a logarithmic scale [after reference 19]

Figure 3b. Wheal thickness response to topical dinitrochlorobenzene versus dose of dinitrochlorobenzene on a logarithmic scale in subjects sensitized to DNCB [after reference 19]; note that the dose required to provoke a response is two orders of magnitude less than the dose required to sensitize a subject

Figure 4. Duration of apnoea (minutes) -v- dose of suxamethonium in milligrams (log scale) for normal subjects (UU) and those with two abnormal alleles (AA) [after reference 23].

Figure 5: The number of pair-wise interactions of *n* drugs, two at a time.