Dose-response relationships in clinical pharmacology
L Lasagna, S Erill, C A Naranjo, editors

DOSE RESPONSE RELATIONSHIPS IN TOXICOLOGY

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INTRODUCTION

There must always be some relationship between dose and toxicity, and its expression depends on the mechanisms involved and on the adverse effect as a function of drug concentration and time. In practice this relationship is complex and at times it may appear to be non-existent. Drugs and chemicals produce toxic effects by many different mechanisms in diverse settings including normal therapeutic use, drug abuse, acute overdosage, accidental poisoning and occupational exposure. When drugs are given under ideal controlled conditions, dose-toxicity correlations can usually be established readily for a restricted range of adverse effects and indeed, such studies form an essential part of the early clinical investigation of new drugs and clinical trials. Even with very old drugs useful new guidelines can be produced by critical review of clinical experience (1). However, in the rough and tumble of routine clinical practice matters are not so simple because of the heterogeneity of the patient population and multiple confounding and predisposing factors. Doctors are not good at recognising drug toxicity and it may be difficult to attribute an adverse event to a particular agent with any degree of certainty (2). The normal therapeutic range of drug dosage is very narrow and the wider spectrum of acute toxic effects can only be studied in cases of overdosage or poisoning.

DOSE-RESPONSE IN RELATION TO MECHANISMS OF TOXICITY

Dose Response Curves

The mechanism by which a drug produces an adverse effect is an important determinant of the dose-toxicity relationship. In many cases toxicity can be directly related to the concentration of active agent at specific receptor sites and irrespective of the biochemical mechanisms, the pattern of response is then likely to resemble the familiar quantal pharmacodynamic dose-effect curve. As the dose increases a succession of different toxic effects may appear, and each is superimposed with its own dose-response pattern (Figure 1). The relative positions and slopes of the curves for therapeutic and toxic effects may differ greatly according to

individual factors and clinical circumstances, and these differences represent individual variation in susceptibility to toxicity. "Type A" adverse reactions such as an exaggerated therapeutic response (3)

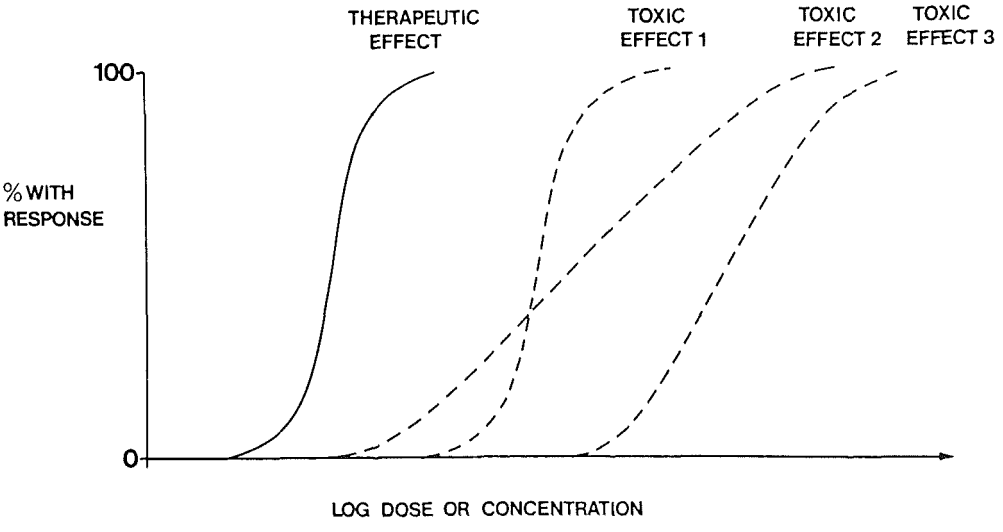

Fig. 1. Hypothetical dose-response curves for therapeutic and different toxic effects. The relative positions of these curves in an individual determine susceptibility to toxicity in relation to the dose required for therapeutic effects.

will occur when the curve for this primary effect is moved to the left. In predisposed or particularly susceptible individuals the toxicity curves are also displaced to the left and adverse effects may appear within the normal dose range. The therapeutic index becomes smaller as the toxicity curves approach the curve for the therapeutic effect. The dose-effect relationship between systemic exposure to teniposide, objective therapeutic action and severe gastrointestinal toxicity may be cited as an example of this type of response (4).

Dose-Toxicity Thresholds

With some forms of toxicity, there is a more clearly defined dose threshold. For example, in overdosage paracetamol may cause hepatic necrosis through its conversion to a reactive intermediate metabolite which is normally removed by conjugation with glutathione. Liver damage does not occur until glutathione is depleted by 70 to 80% and this critical point represents the threshold for toxicity. The

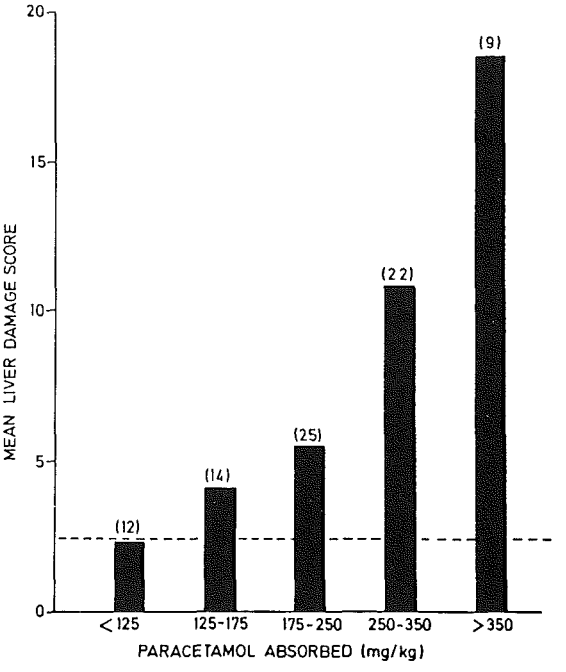

Fig. 2. The single acute threshold dose for paracetamol hepatotoxicity in man. The dashed line represents the upper normal limit for the liver damage score and the number of patients is given above each column. Reproduced with permission from reference 5.

single acute threshold dose of paracetamol which produces hepatic necrosis in man is about 150 mg/kg and the incidence and severity of liver damage increase steeply above 250 mg/kg (Figure 2) (5). Dose thresholds may be expected with other agents which produce similar glutathione-dependent toxicity.

Lack of Correlation between Dose and Toxicity

A whole range of uncommon and apparently sporadic toxic effects cannot be related to dose. These "Type B" reactions (3) include immunological toxicity and such events as drug induced retroperitoneal fibrosis, blood dyscrasias, acute dystonic reactions and benign intracranial hypertension. Allergic and hypersensitivity reactions are conditioned by the immunological status of the individual, and are usually unpredictable and unrelated to dose. A major reaction may be provoked by a very small dose in a previously sensitised individual. For example, amidopyrine may stimulate the formation of

antibodies to leucocytes and subsequent ingestion of a small dose may then cause massive leucoagglutination with rapid disappearance of these cells from the peripheral blood (6). Presumably in reactions such as these, there is extreme displacement of the toxicity curve to the left and for practical purposes there is no dose-response relationship. Other forms of immunological toxicity such as vasculitis and serum sickness also depend on individual sensitivity and there is no clear dose dependence. In some cases there may even be a negative dose-toxicity relationship. Thus in prescription event monitoring of enalapril, dizziness and hypotension occurred more often with very low (2.5 mg) than with higher doses (10 to 30 mg). This paradox was attributed to the selective use of low doses in highly susceptible frail elderly patients with cardiac failure (7).

The Time Factor

Most adverse drug effects occur within the first few days or weeks of starting treatment. The duration of exposure is always important and in some cases toxicity correlates better with the area under the plasma concentration time curve (sometimes referred to as "dose intensity") than dose or plasma concentrations (8). There may also be circadian rhythms in susceptibility to toxicity (9). Both dose and duration of therapy are important in the development of drug-induced auto-immune disease such as systemic lupus erythematosus. Similarly, the appearance of IgG antibodies to red cells and the development of auto-immune haemolytic anaemia in patients taking alpha-methyldopa depends on dose and the length of treatment (10). Progressive, irreversible organ damage may occur insidiously with continuous use of a drug over a period of many years, and in conditions such as the practolol oculo-cutaneous syndrome, alcoholic cirrhosis and analgesic nephropathy, the cumulative dose may be the relevant factor (11). Timing may be more important than dose in teratogenicity. Thalidomide caused phocomelia in a small proportion of women when it was taken between the third and eighth weeks of pregnancy, but if a single dose was taken on the 40th day the incidence was virtually 100% (12).

PHARMACOKINETIC FACTORS

Pharmacokinetic factors have a profound effect on dose-toxicity relationships because for a given dose, drug concentrations may vary greatly according to individual differences in absorption, distrib-

ution, metabolism and excretion. For this reason, toxicity is usually related much more closely to drug concentrations than to dose (13). This is an important principle in therapeutic drug monitoring but there is considerable individual variation in plasma concentrations associated with toxicity (14).

Absorption

The rate and extent of absorption depends on the drug, its formulation, the mode of administration and multiple individual factors. Toxicity is most likely to occur when fast drug input produces high rapidly rising concentrations. Bolus intravenous injection is by far the most dangerous method of administration and it is a common cause of toxicity (15). The whole dose is delivered immediately into the pulmonary circulation, and concentrations are initially very high in well perfused central organs such as the heart and brain. Oral absorption is fastest when a quickly dissolving product is taken fasting under conditions which promote rapid gastric emptying. Slow release formulations are supposed to extend absorption and minimise the risk of adverse effects. However, with these products dose-dumping may occur, food has a variable effect on absorption and differences in bioavailability may cause toxicity when brands are switched (16).

Distribution

There is normally relatively little individual variation in drug distribution and plasma protein binding. However, the volume of drug distribution is reduced in patients with circulatory failure and poor peripheral perfusion. Thus for a given dose, concentrations are higher, and toxicity is more likely, in central well perfused tissues such as the myocardium and brain (17). Effects are thought to be related to the concentration of free unbound drug and reduced plasma protein binding is probably more important with acidic than basic drugs. Binding is reduced in patients with hypoalbuminaemia and uraemia, and this may predispose to toxicity. The plasma protein binding of drugs is concentration dependent, and there may be a disproportionate increase in the free fraction following overdosage.

Drug metabolism

Drug metabolism is probably the most important single factor influencing dose-toxicity relationships. The capacity for drug metabolism depends on multiple individual, environmental and genetic factors and there is often enormous variation between individuals.

These factors have a direct bearing on dose-toxicity relationships.

Individual variation. There may be 30 to 40 fold differences in the metabolic clearance of some drugs as judged by steady state plasma concentrations in patients receiving the same dose, and this is equivalent to a correspondingly wide range in effective dose (18). In addition, drugs which have a high hepatic extraction ratio are subject to extensive first pass loss after oral administration and their clearance is highly dependent on hepatic blood flow. Small individual differences in first pass loss result in very large differences in the amount absorbed intact and hence the effective dose (19). First pass loss is decreased in patients with liver disease and the elderly (20) and this may predispose to toxicity.

Genetic factors. Genetic polymorphism is an important cause of individual variation in drug metabolism (18). For a given dose, poor metabolisers are exposed to much higher drug concentrations for a longer period than extensive metabolisers and the dose-toxicity curves are displaced to the left (21). Thus auto-immune reactions are more frequent in slow than fast acetylators of hydralazine (22) while peripheral neuritis and hepatotoxicity occurred mostly in poor hydroxylators of perhexiline (18).

Toxic metabolic activation. Toxicity may be caused by active metabolites rather than the parent drug. In such circumstances the consequences depend on the relative activities of the pathways of toxic metabolic activation and parallel non-toxic routes of elimination. The extent of metabolic activation of paracetamol is indicated by the proportion of a dose which is excreted in the urine as glutathione-derived cysteine and mercapturic acid conjugates. On this basis, production of the potentially hepatotoxic metabolite of paracetamol varies as much as 60 fold in healthy young adults in different countries while there is only a 2 to 3 fold difference in the major pathways of elimination by glucuronide and sulphate conjugation (23). The hepatotoxicity of paracetamol depends on the balance between the rates of formation of the reactive metabolite and synthesis of glutathione, and all other things being equal, this marked individual variation in metabolic activation indicates corresponding variation in the dose required to produce liver damage.

Saturation of drug metabolism. Within the therapeutic dose range, most drugs are eliminated at a rate proportional to their concentration (first order kinetics). However, drug metabolising enzymes

may become saturated or essential co-factors depleted. Elimination may then become zero order with removal of only a fixed maximum amount in unit time. This has an important effect on dose-toxicity relationships because a small increase in dose results in a disproportionately large increase in drug concentrations and effects. The metabolism of drugs such as salicylate and diphenylhydantoin may become saturated with therapeutic doses (24). The elimination of ethanol is also zero order and this explains why sudden incapacity can overtake those who take just one drink too many.

Cumulation. The time taken to reach steady state after starting treatment or changing the dose of a drug is about 4 times the half life. Drugs which are eliminated very slowly are particularly dangerous because during chronic administration concentrations may increase gradually over a period of weeks or even months. Dose-toxicity relationships may therefore be obscured. Late onset toxicity with very persistent drugs such as amiodarone (25) may be related to the progressive increase in the amount of drug in the body. Cumulation is a particular problem with long acting drugs in the elderly in whom drug metabolism is often impaired and very variable. Benoxaprofen had a long half life and this was prolonged even further in the elderly. Indeed, some patients were virtually unable to eliminate the drug (26). Chronic therapy in such patients would inevitably result in progressive cumulation of benoxaprofen over months, and this could explain the delayed fatal toxicity in frail elderly women.

Renal excretion

There is usually less individual variation in the renal clearance than the metabolism of drugs. However, the renal clearance of some weak acidic and basic drugs is strongly pH-dependent and changes in the urine pH can influence the toxicity of drugs such as salicylate and methotrexate (27).

OTHER FACTORS INFLUENCING DOSE-TOXICITY RELATIONSHIPS

Many other factors modify toxicity in clinical practice. Some adverse effects cannot be demonstrated in the absence of predisposing conditions. Thus non-selective ß-adrenergic blocking drugs do not normally cause significant bronchoconstriction without pre-existing pulmonary disease and in short term use the non-steroidal anti-inflammatory drugs are not overtly nephrotoxic in healthy young adults unless renal blood flow is already compromised (28).

Body weight

Paediatric doses are usually adjusted according to body weight or surface area. In adults, most drugs are prescribed in fixed doses and the actual dose/Kg body weight may vary 2 or 3 fold. Toxicity may occur from this simple cause alone (29).

Formulation

The uncontrolled release of irritant drugs in the gastrointestinal tract may cause local mucosal injury if stasis occurs. Thus tetracycline and emepronium can cause lower oesophageal damage, aspirin is notorious for its gastrotoxicity and enteric coated potassium chloride caused small intestinal ulceration and stenosis. Such toxicity depends more on formulation and gastrointestinal transit than dose, and it can be minimised by better dosage form design (30).

Age

The young and the elderly are particularly vulnerable to toxicity. There may be qualitative differences in response and the metabolism and renal excretion of drugs may be impaired at the extremes of age (31,32). Thus chloramphenicol may cause the grey baby syndrome in neonates (33), children born to mothers who take diazepam may be hypotonic, hypothermic and fail to feed properly (the "floppy baby syndrome") (34), and Reye's syndrome (which is probably a manifestation of subacute salicylate intoxication) occurs almost exclusively in children and young teenagers (35). The elderly often have multiple pathology and organ failure with dietary deficiencies, and they are less well able to compensate for drug effects than younger people. They are also prescribed more drugs. Thus the elderly (especially females) are at considerably increased risk of serious blood dyscrasias induced by phenylbutazone (36), they suffer more persistent dose dependent sedation after taking flurazepam (37), and they are more sensitive to warfarin than younger subjects (38).

Sex

In virtually all reports, the incidence of adverse drug reactions has been greater in females than in males (39). This may be due in part to the greater use of drugs by women and their disproportionate representation in the elderly population.

Diet and nutrition

Diet and nutrition influence toxicity in animals but there is little relevant information in man. Poor diet may predispose to drug-induced vitamin deficiencies and it has variable effects on drug metabolism (40).

Immunological state

Many "Type B" adverse reactions depend on immunological status. Drugs, their metabolites, impurities, excipients, solvents, diluents and dyes may all stimulate the formation of antibodies and sensitise some individuals in an unpredictable manner (41). A history of a previous major reaction to a drug must be taken as a serious warning and immunological reactions are more likely in atopic patients. Toxicity may be associated with human lymphocyte antigens (HLA), as for example the increased incidence of systemic lupus erythematosus in type DR4 patients taking hydralazine (42).

Disease

Disease may profoundly influence dose-toxicity relationships. Examples include greater narcotic-induced respiratory depression in patients with chronic lung disease, precipitation of heart failure in cardiac patients by ß-adrenergic blocking and non-steroidal anti-inflammatory drugs, and succinylcholine-induced hyperkalaemia with arrhythmias in patients with neuromuscular disease (43). Many pathological conditions alter drug disposition. Distribution, metabolism and excretion are likely to be abnormal in patients with cardiac, hepatic and renal disease, and in the latter, retention of active drug metabolites may predispose to adverse reactions (44).

Tolerance

Continuous administration of drugs such as glyceryl trinitrate and narcotic analgesics may result in the rapid development of tolerance with a corresponding resistance to some toxic effects.

Genetic predisposition

Apart from effects on drug metabolism, genetic factors may predispose to toxicity in other ways. Examples include the effects of corticosteroids on intraocular pressure, sensitivity to drug-induced haemolysis in patients with glucose-6-phosphate dehydrogenase deficiency and malignant hyperthermia during anaesthesia (45).

Drug interactions

Polypharmacy is almost universal, and drug interactions are a common cause of toxicity.

DRUG OVERDOSAGE AND POISONING

Toxicity is related to dose in a more obvious and dramatic way in acute drug overdosage and poisoning. Signs of intoxication usually appear rapidly, and there are often multiple effects on different organ systems. In most cases the severity of intoxication is

directly related to the amount absorbed but dose-toxicity relationships can be modified by a host of factors. With drugs such as barbiturates, anticonvulsants, tricyclic antidepressants, ethanol, theophylline and salicylate, the effects and time course of intoxication correlate reasonably well with plasma concentrations (13). Nevertheless, there is considerable individual variation and published lists of "toxic" and "lethal" doses are often very misleading. Delayed or persistent toxicity (as in paracetamol, paraquat and organophosphate poisoning) may not be related to concentrations or amounts in the body at the time. However, plasma concentrations during the initial phase of intoxication can be a useful guide to the dose absorbed and prognosis (5).

Factors influencing dose-toxicity relationships in drug overdosage

Dose absorbed versus dose allegedly taken. Self-poisoners are notoriously unreliable historians. The dose is often exaggerated and there are often major discrepancies between the amount claimed to have been taken and subsequent toxicity. The only way to estimate the dose absorbed is to measure the plasma concentrations.

Age. In accidental poisoning in young children, the amounts taken are usually small and serious toxicity is rare. Infants are particularly sensitive to agents which cause methaemoglobinaemia because of the ease of oxidation of foetal haemoglobin (46). Young children are more susceptible than adults to the metabolic toxicity of salicylate, but more resistant to the hepatotoxicity of paracetamol (47). The elderly recover from poisoning more slowly than healthy young adults. Complications are more frequent and the mortality is greater.

Pre-existing disease. Underlying pathology is another important adverse factor. Complications such as pneumonia and pulmonary oedema are more serious in patients with pre-existing lung disease, patients with cardiac failure are more susceptible to myocardial depressants, drug elimination is impaired in patients with hepatic or renal disease and the latter are more vulnerable to the nephrotoxicity of non-steroidal anti-inflammatory drugs.

Multiple overdosage. Some 40 to 50% of patients take multiple drugs in overdosage and ethanol is often taken as well. This obviously complicates any dose-toxicity assessment, and toxicity curves are usually shifted to the left (48).

Rate of absorption. Drugs taken in overdose can be absorbed surprisingly quickly and the onset of toxicity is correspondingly

rapid. Thus ingestion of preparations containing d-propoxyphene can result in fatal cardio-respiratory arrest in a matter of minutes (49). The outcome of poisoning may therefore depend on whether absorption is rapid if the drug is taken fasting, or slow if it is taken after a big meal. Overdosage of sustained release products may result in prolonged toxicity.

Previous therapeutic use. If cumulative drugs such as lithium and phenobarbitone have previously been taken regularly for therapeutic purposes, there will already be an amount in the body equivalent to a full loading dose. An acute overdose therefore adds substantially to this and is more likely to produce toxicity than the same overdose in a patient not previously taking the drug (50).

Tolerance. Tolerance is an important mechanism of protection against the toxicity of many drugs and poisons. It may develop with regular heavy use of central nervous system depressants such as ethanol, barbiturates, benzodiazepines and narcotic analgesics. In such circumstances an overdose which would normally cause coma may have relatively little effect (13). Recovery from acute intoxication with long acting benzodiazepines such as diazepam, nitrazepam and flurazepam depends on the development of acute tolerance (51). Thus healthy young adults recover overnight after major overdosage of these drugs and by the time consciousness is regained only a very small fraction of the dose will have been eliminated. The ability to develop acute tolerance is apparently impaired in the elderly, as recovery is much slower and they often remain depressed, drowsy and apathetic for days.

Duration of exposure. Most self-poisoning results from a single acute overdose, but prolonged exposure (e.g. carbon monoxide poisoning and therapeutic intoxication) has an important bearing on dose toxicity relationships and outcome. Prolonged exposure to high concentrations of lithium or carbon monoxide may result in irreversible cerebral damage while morbidity and mortality are much greater in chronic therapeutic salicylate intoxication than after a single acute overdose (52).

Drug metabolism and elimination. The disposition of drugs is often grossly abnormal in poisoned patients (53). Drug metabolism usually determines the rate of recovery (54) and it is critical for toxicity caused by metabolic activation. Elimination kinetics are often non-linear in severely poisoned patients with a slow initial fall in concentrations followed by an increasingly rapid decline

during recovery. This may be due to saturation of drug metabolism, but other possible causes include slow continuing absorption, low cardiac output with reduced hepatic and renal blood flow, hypothermia, and induction of drug metabolising enzymes (13). Saturation of first pass metabolism of high clearance drugs during absorption of an overdose will result in a major increase in bioavailability and toxicity. Complete saturation of the metabolism of a drug such as diphenylhydantoin results in prolonged intoxication followed by sudden rapid recovery as elimination kinetics change from zero to first order. The plasma half life of salicylate at toxic levels is more than 30 hours because of saturation of its glycine conjugation but this reduces to about 3 hours at low therapeutic concentrations. In contrast, there is enormous capacity for the glucuronide conjugation of paracetamol, and saturation only occurs at exceptionally high concentrations (55). Induction or inhibition of drug metabolising enzymes may have important effects on toxicity caused by metabolic activation but this is difficult to prove in man.

Complications of acute drug intoxication. The final outcome often depends on the nature and severity of complications. As with other events in poisoning, there is a certain element of chance. Thus coma or convulsions in an unattended patient may result in respiratory obstruction, inhalation of vomit may cause fatal aspiration pneumonia and metabolic disturbances such as acidosis predispose to malignant cardiac arrhythmias. The development of renal failure after paraquat poisoning almost always indicates a fatal outcome because urinary excretion is the only route for its elimination from the body.

EPIDEMIOLOGICAL CONSIDERATIONS

Dose-toxicity relationships have important epidemiological implications. Safe limits have to be established for occupational and environmental exposure, and for the use of potentially toxic substances as food additives etc. Population studies may be useful to confirm a suspected causal relationship. For example, the role of salicylate in Reye's syndrome has been controversial, but the demonstration of an indisputable dose-response effect is compelling evidence (35). Similarly, there was a clear cut dose-response effect in the Spanish toxic oil syndrome epidemic in 1981 and a striking association with cooking oil contaminated with aniline and fatty acid anilides in the households of affected families (56).

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Discussion - Dose-response relationships in toxicology

L. Lasagna

The average age of the population is increasing in most of the developed countries, which means more people will be afflicted with chronic illness and more people will be chronically taking drugs, not just for days or weeks, but months or years, and obviously people are going to ask what about delayed toxicity. It seems to me that some of the things people are going to be worried about, like cancer, peptic ulcer, heart attacks, can occur as a consequence of a drug as well as in the absence of any drug. We certainly need to get data to subtract out the background noise from what we are recording. I suppose one could try to get epidemiological data on the population as a whole, stratified by age and gender, or one could, I suppose, try to keep track of what the events are in a series of alternative treatments for a given illness, but an effort should be made to keep our perspective and, at the same time, not to lose data.

L.F. Prescott

This is a very difficult problem. Unless the delayed effect is very characteristic or unusual, there is no chance that it will be picked up by existing methods.

R.J. Temple

Although a direct method may not exist, one should always consider the possibility that a clinical observation in a group of patients may lead to specific studies that will uncover an effect. Something like observations in rheumatoid patients treated with aspirin, which led to studies that demonstrated important clinical benefit from the effects of this drug on platelets.

L.F. Prescott

Yes, but we should not forget that in this particular field quite opposite evidence also existed : it was known that the incidence of fatal cardiovascular diseases in analgesic abusers was, in fact, very high. Maybe they were doing other things as well that increased their risk, but a paradoxical situation existed.

D.S. Davies

Can you further comment on the decreased ability to develop acute tolerance exhibited by the elderly?

L.F. Prescott

It seems quite clear that young people recover rapidly from acute intoxication with long-acting benzodiazepines because they develop tolerance overnight. The elderly just do not do this.

D.S. Davies

But, can you be sure that this is pharmacological tolerance? When one reverses a hypoglycemic attack with intravenous glucose in a young person, complete recovery is observed within quite a short time, whereas an old person can take a long time to come round. So perhaps the old brain does not somehow peak up as quickly after the insult has gone.

L.F. Prescott

I think it is pharmacological tolerance. In the elderly people we see the characteristic persistent effects of benzodiazepines.

B.P. du Souich

At any event, pharmacokinetic differences should also be taken into account.

L.F. Prescott

I agree, but the fact remains that a young person can be completely unconscious and the next morning can wake up and still function with virtually the same amount of drug in the brain as the night before. I don't see how one can explain that except by acute tolerance. In the elderly it is probably much more complex.

S. Erill

I just wonder whether the rapid development of tolerance to the REM suppressing effect of anticholinergics and other drugs could be used as a model to quantify age-related differences in the development of tolerance.