Occasional Survey

Variability in Response to Drugs*

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British Medical Journal, 1974, 4, 91-94

Summary

Variability in the response to drugs is due to three principal components—the disease, the responsiveness of tissues, and the concentration of the drug at its site of action (as reflected by its plasma concentration). The relative contributions of these components will differ not only for different drugs but also for different effects of the same drug. Rational drug therapy depends on knowledge of all three factors.

Introduction

One of the major problems encountered in modern therapeutics is the enormous variability among individuals in their response to drugs. Thus most clinicians find that when a group of patients receive the same drug dosage some gain a therapeutic effect, others develop toxicity, and others derive no benefit at all. This variability (or variance) in response to drugs appears to be due to three principal components—the disease being treated, the responsiveness of the tissues to the drug, and the concentration of the drug at its site of action as reflected by its plasma concentration. The relative contributions vary with different drugs (see fig. 1). For some drugs (drug A) the three components contribute equally. For others (drugs B and C) one or two components may predominate. Moreover, the relative contributions of these three components may even be dissimilar for different effects of the same drug. The scientific use of drugs in clinical practice depends on knowledge of these factors.

Influence of Disease

The relative contribution of disease to the total variability in response probably depends on two factors, the aetiology and pathogenesis of the disease and its severity. Many disorders—once regarded as single entities have now been shown to represent the sum of a number of diseases, each with a different aetiology or pathogenesis and each requiring a specific form of therapy. For example, in the nephrotic syndrome due to glomerulonephritis the patients with established glomerular changes are unlikely to derive benefit from steroid treatment, whereas those with minimal glomerular lesions have a good chance of prompt remission if given steroids.¹ Studies on the biochemistry of depressive dis-

orders show that patients with endogenous depression may fall into one of two populations,² one with a reduced turnover of noradrenaline in the central nervous system as the causative lesion ("noradrenaline depression") and the other with a reduced turnover of 5-hydroxytryptamine ("5-hydroxytryptamine depression"). Nortriptyline (a tricyclic antidepressant) blocks the "uptake" of noradrenaline at pre-synaptic adrenergic nerve endings³ and thus increases the effective concentration of catecholamine in the synaptic cleft. Treatment with nortriptyline would therefore be expected to benefit only patients with noradrenaline depression since the drug has little influence on 5-hydroxytryptamine "re-uptake." One reason for the variability in the antidepressant response to nortriptyline might therefore be the fact that endogenous depression does not represent a single homogeneous diagnostic entity.²

The severity of a disease also plays an important part in determining the response to drug administration. Severity may be expressed (as in hypertension) either by the magnitude of a measured variable or by the presence of some complication, and both these expressions of severity can be important in determining drug responsiveness. Thus the fall in diastolic blood pressure after thiazide diuretics, chlorthalidone, or spironolactone is positively related to the pretreatment diastolic arterial pressure and is greater in patients with higher pressures.⁴ By contrast, the rapid intravenous administration of diazoxide appears to be highly effective in reducing arterial pressure in hypertensive patients who have entered the accelerated phase⁵ but is less effective in those with chronic hypertension.⁶

Tissue Responsiveness

There is increasing circumstantial evidence to indicate that for some drugs at least tissue responsiveness is also an important component of the total variability in response. For example, appreciable interindividual differences are known to exist in the pupillary response to the mydriatic phenylephrine,⁷ which by virtue of its mode of administration and duration of effect cannot be attributed to differences in its fate after entering the body. The nature of such differences in tissue responsiveness is not clear. Animal studies⁸ indicate that the affinities of receptors for particular agonist and antagonist drugs are constant within and between species. Interindividual differences in the responsiveness to mydriatics, therefore, are unlikely to be due to differences in the receptors themselves but may be due to differences in the highly complex events interposed between receptor stimulation and drug response. Thus variability in the degree of phenylephrine mydriasis appears to be determined predominantly by the underlying levels of parasympathetic and sympathetic tone, which are under genetic control.⁷ Hereditary resistance to coumarin anticoagulants^{9,10} may possibly be due to differences in drug receptors but could be due to differences

*Based on the inaugural lecture of the Ruth and Lionel Jacobson Professor of Clinical Pharmacology delivered at the University of Newcastle upon Tyne on 22 January 1974.

in clotting factor synthesis or to differences in vitamin K concentrations in the liver.¹¹

The abnormal drug responses seen in glucose-6-phosphate dehydrogenase (G-6-PD) deficiency,¹² hereditary methaemoglobinemia,¹³ porphyria,¹⁴ and malignant hyperpyrexia of anaesthesia¹⁵ are also instances in which alterations in tissue responsiveness may contribute to the total variability in response to drugs. This component will be particularly prominent in those populations in whom these abnormal gene frequencies—for example, G-6-PD deficiency—are high, and international collaboration to determine the incidence of adverse drug reactions may give important clues to the existence of such genes.

Plasma Concentration

During multiple-dose therapy the plasma concentration of a drug reaches a "steady state" when the amount of drug eliminated daily equals the daily dose.¹⁶ At this time equilibrium is established between the concentration of free drug in plasma and the concentration at its site of action. Most methods of determining plasma concentrations of drugs measure both the fraction bound to protein and the "free" (unbound) fraction. Normal people, however, show only relatively minor interindividual differences in the degree of protein binding,¹⁷ so that the total drug concentration in the plasma at steady state is a *reflection* of the concentration at its site of action. The pharmacological effect of a reversibly acting drug is a function of the concentration at its site of action, and interindividual differences in plasma concentration might therefore be an important component in the variability of response to some drugs (see fig. 1).

FIG. 1—Relative contributions to total variability in response to three hypothetical drugs A, B, and C.

The steady-state plasma concentration of a drug during multiple dosing depends on (a) the dose, (b) the dosage interval, (c) the extent to which dose given by mouth reaches the general circulation, and (d) the rate of elimination of the drug.¹⁸ The dose and dosage interval are decided in theory by the prescribing doctor, though in practice the patient usually has the final say. The elimination rate of a drug is determined by a combination of physiological and biochemical factors which are under the control of genetic, environmental, and pathological influences; decreasing rates of drug elimination lead to higher steady-state plasma levels.

Drug elimination occurs by renal excretion of unchanged drug, by metabolism to derivatives which are usually (but not invariably) pharmacologically inactive, or by a combination of the two. The relation between dose and plasma level of drugs eliminated primarily by the kidneys is linear and shows little variability between individual adult patients with normal renal function. When renal impairment is present, however, toxic plasma levels may be encountered if conventional doses are used, and the concept of adjusting antibiotic dosage in the light of plasma levels is widely acknow-

ledged.¹⁹ Metabolism of drugs can occur by a variety of differing pathways. Two in particular—acetylation and oxidation—are subject to wide interindividual variability. Acetylation, the metabolic pathway by which many sulphonamides²⁰ (including sulphadimidine and sulphamethoxazole), isoniazid,²¹ dapsone,²² and phenelzine²³ are inactivated, is under polygenic control, with the gene for slow inactivation (acetylation) being autosomally recessive.²⁴ The proportion of rapid acetylators in the population varies in different parts of the world (see fig. 2), being highest (95%) among Eskimos²⁵ and lowest (32%) among Swedes.²⁶ Acetylator status has been shown to influence noticeably the therapeutic effects²⁷ and the toxicity of phenelzine²³ and of intermittent treatment with isoniazid.^{28, 29}

FIG. 2—Percentage prevalence of rapid acetylators in various populations of the world.

Hepatic microsomal drug oxidation is under polygenic control,³¹ but unlike acetylation it does not appear possible at present to characterize patients according to their oxidator status.³⁰ Drugs which are metabolized by this route include phenytoin,³¹ nortriptyline,³² amitriptyline,³³ phenylbutazone,³⁴ and warfarin.³⁵ Patients receiving these drugs show wide interindividual differences in plasma levels. Thus for phenytoin plasma concentrations may range from 4 to 40 $\mu\text{g/ml}$ in patients taking 300 mg daily,³⁶ while for nortriptyline steady-state levels of 10 to 300 ng/ml have been observed in patients receiving 75 mg daily.³⁷ It has been established that for some drugs differences in plasma concentrations account for much of the variability in response. Among these digoxin, phenytoin, and nortriptyline predominate.

DIGOXIN

Theoretically plasma levels of digoxin are predictable from a knowledge of the daily dose and the patient's renal function.¹⁸ In practice differences in bioavailability^{38, 39} and digoxin content⁴⁰ of different preparations together with rapid fluctuations in renal function—often make such predictions unreliable. Various workers⁴¹⁻⁴⁴ have established that toxicity is likely to occur at plasma levels above 2 ng/ml and is unlikely to occur at those below this. The value of 2 ng/ml, however, can never be expected to represent a sharp cut-off point between non-toxic and toxic levels because plasma concentrations of digoxin represent only one component (albeit the most important) in determining drug responsiveness. Despite this limitation measurements of plasma digoxin are a valuable guide to the diagnosis of toxicity.

PHENYTOIN

Several studies⁴⁵⁻⁴⁷ have shown that optimal therapeutic results in the treatment of grand mal epilepsy with phenytoin

are achieved at plasma concentrations between 10 and 20 $\mu\text{g/ml}$. Below this level seizure control may be poor and above this level toxicity occurs, but it appears that most patients whose plasma levels lie in the therapeutic range show good control. A few do not,⁴⁷ which again reflects the role of other components in the total variability in response, and non-responding patients of this type will require additional antiepileptic drug therapy. The real value of measuring plasma levels of phenytoin is therefore in determining whether non-responsiveness is due to the low levels of phenytoin requiring an increase in dose or to resistance and requiring additional drug therapy. Measurements of plasma phenytoin concentrations can also be of value in diagnosing toxicity when the clinical diagnosis is not clear.

Dosage adjustments of phenytoin in the light of plasma concentrations have to be performed with care since this drug shows "non-linear" kinetics.^{48,49} Thus doubling the daily dosage can increase plasma concentrations fourfold to sixfold and thereby change plasma concentrations from sub-therapeutic to toxic levels. This phenomenon appears to be due to saturation of metabolism, and small increments in daily dosage (50 to 100 mg) are mandatory. Moreover, some of the individual differences in plasma levels of phenytoin result from the failure of patients to take the dose prescribed. If this is suspected it may be beneficial to admit them to hospital and to measure their plasma concentrations during a period of controlled drug intake. If failure of medication is confirmed many patients will respond to a tactful explanation of its cause.

NORTRIPTYLINE

The therapeutic effect of nortriptyline in the treatment of endogenous depression occurs only at plasma concentrations of 50 to 140 ng/ml.⁵⁰ At levels above and below this a therapeutic effect is not observed. Though the explanation for the failure of response at high levels is not clear its significance is apparent;³ only measurements of plasma concentrations will enable the doctor to decide whether to decrease or increase the dose. Dosage adjustment with nortriptyline is simpler than with phenytoin because its kinetics are linear and a twofold increase in the daily dose will result in a precise twofold increase in plasma level.⁵¹ Once again, however, not all patients in the therapeutic range respond and it has been suggested that the non-responders are suffering from a 5-hydroxytryptamine depression which would more readily benefit from either electric convulsion therapy or treatment with a potent inhibitor of 5-hydroxytryptamine uptake.³

OTHER DRUGS

Limited information at present available indicates that variability in response to salicylates,⁵² phenylbutazone,⁵³ lignocaine,^{54,55} procainamide,⁵⁶ quinidine,⁵⁷ hydralazine,⁵⁸ and theophylline⁵⁹ might be reduced and therapeutic efficacy enhanced by dosage adjustments in the light of plasma concentrations. One drug for which plasma level determinations appear to be of little value is warfarin.⁶⁰ Thus in a group of patients receiving warfarin sufficient to maintain good control (thrombotest value 5-8%) a tenfold (0.04 to 0.4 mg/kg) range in daily dosage was required, and this was associated with a fivefold (0.6 to 3.1 $\mu\text{g/ml}$) range in plasma warfarin levels. Warfarin is therefore a drug for which the wide variability in response is due predominantly to differences in tissue sensitivity, and dosage adjustments on the basis of plasma concentrations instead of anticoagulant control would be dangerous.

Conclusion

Hence for several drugs routine estimations of plasma concentrations are therapeutically valuable. This number is likely to increase enormously over the next few years and facilities must be made available to meet the demand for a service which carries great potential benefits for patient care. It is equally important, however, to realize that such determinations will provide only part of the answer to the problem of interpatient variability in response to drugs. Disease and tissue responsiveness are also important components of the total variability and for some drugs they will predominate. Much more research is required to delineate the sources of variability in response to drugs. Clinical studies which show a good relationship between plasma concentration and therapeutic response should point the way to the more rational use of drugs and encourage us to perform routine plasma drug level estimations. Studies which fail to show a good relationship between plasma levels and response are, however, equally valuable provided they make us re-examine our preconceived notions of diagnostic homogeneity and encourage us to look at the responsiveness of tissues. In these ways we may improve both our understanding of disease and our ability to treat it.

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Hospital Topics

Emergency Endoscopy after Gastrointestinal Haemorrhage in 50 Patients with Portal Hypertension

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British Medical Journal, 1974, 4, 94-96

Summary

Endoscopy was carried out in 50 patients with oesophageal varices within 24 hours of a major haematemesis or melaena. Sources of bleeding were identified in 42 of the cases and in only 19 patients was bleeding due to oesophageal varices. Bleeding from gastric varices was present in 11 patients, and a variety of acute and chronic lesions made up the remainder. In contrast with previous series haemorrhage from erosive gastric lesions was seen in only five patients and was no more common in 23 patients with alcoholic cirrhosis than in the group as a whole.

Introduction

Emergency endoscopy is a safe and reliable means of diagnosing the source of upper gastrointestinal bleeding.^{1,2} Accurate diagnosis of the bleeding site is particularly important in patients with portal hypertension since reports from Europe and the U.S.A. of emergency endoscopy have shown a high incidence of bleeding from lesions other than oesophageal varices. These have included erosive gastritis, chronic peptic ulcer, and Mallory-Weiss tears.³⁻⁹ There has been no detailed study of patients admitted to a British unit and we describe here the findings in 50 patients with portal hypertension in whom emergency endoscopy was carried out within 24 hours of a major haematemesis or melaena.

Patients and Methods

The 50 patients came from a series of 55 consecutive patients admitted between November 1972 and March 1974. Four patients considered too ill for endoscopy and one violent alcoholic patient were excluded. Thirty-one of the patients were male with a mean age of 50 years (range 20-64) and 19 were female with a mean age of 49 years (range 8-68). Portal hypertension was secondary to chronic liver disease except in two patients with portal vein thrombosis (table I).

TABLE I—Aetiology of Portal Hypertension in 50 Patients

Diagnosis	No of Patients
Cirrhosis:	
Alcoholic	23
Cryptogenic	8
Active chronic hepatitis	8
Primary biliary cirrhosis	6
Wilson's disease	1
Schistosomiasis	1
Extrahepatic portal vein obstruction	2
Budd-Chiari syndrome	1

Emergency endoscopy was carried out within three hours of haematemesis or melaena in 24 of the patients and within 24 hours in the remainder. An end-viewing ACMI 7089P endoscope was used with the patient in the left lateral position. Most patients were examined under sedation with intravenous diazepam (5-25 mg), but in 17 patients with signs of moderate or severe encephalopathy sedation was withheld. In no case was premedication used. A lesion was recorded as the bleeding site if it was seen to be bleeding, if blood clot was adhering to it, or if no other abnormality was seen during the course of a complete examination, which occurred in only four patients.

Results

Oesophageal varices were seen in all the patients, and in 17 cases gastric varices were also present. Oesophageal varices were identified as the sole source of bleeding, however, in only 16

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