PHARMACOKINETIC BASIS OF VARIABILITY IN DRUG RESPONSE A study of tolbutamide in models of disease

P du SOUICH, AB KOBUSCH, L LETARTE, S ERILL Department of Pharmacology, Faculty of Medicine, University of Montreal, P.O. Box 6128, Station "A", Quebec H3C 3J7 (Canada)

It is commonly acknowledged that pharmacokinetics accounts for most of the variability in drug response. The pioneering work of and coworkers clearly established that interspecies variability in metabolism and, therefore, in the time course of plasma concentration of drugs was responsible for differences in biological effect (1-4) A variety of other studies, among which those dealing with phenytoin (5), succinylcholine (6), warfarin (7) and pentazocine (8) in man are exceedingly good examples, contributed to establish the concept that for the vast majority of drugs the effect achieved at a given time after administration is a function of the amount of drug in the plasma. In this chapter, we will summarily review the main factors that can for differences in blood levels of drugs between individuals, and will also discuss some data that suggest that pharmacological responses may sometimes be rather complex and that through the interplay of body conditions, drug effects and regulatory mechanisms, pharmacokinetic changes may not always predict modifications in the overall response to drugs.

BASIS OF PHARMACOKINETIC VARIABILITY

Few data are available about interspecies differences in the oral absorption of drugs. Actinomycin C (9) and 6-azauridine (10) provide documented examples of variations of drug effects between experimental animals and man that can be explained by differences in oral availability, and cyclamate illustrates a curious drug interaction whereby oral absorption of lincomycin is facilitated in some laboratory animals (11) and inhibited in man (12). On the other hand, the effects of pharmaceutical formulation on the absorption of drugs are easily elicited, and a host of information is available on the effects of physiological factors, disease and other drugs on the rate and extent of oral absorption of drugs.

Interspecies and interindividual variability in the distribution of drugs in the body or in one of its determinants, the degree of binding to plasma proteins, are also documented. Sulfonamides (13) and penicillins (14) offer good examples of interspecies differences in drug-protein binding and phenytoin (15) and tolbutamide (16) on the one hand, and propranolol (17) on the other illustrate the comparatively narrow variability in the plasma protein binding of acidic drugs in man compared with the larger interindividual differences in the fraction of basic drugs in plasma, accounted by changes in alpha acid glycoprotein, its main carrier.

Changes in the rate or pathways of biotransformation have always been credited as a major cause of variability in drug response. Phenylbutazone offers one of the most striking examples. Protection against glycerol-induced inflammation in the rabbit's eye requires 100 mg/kg every 8 hours whereas antiinflammatory effects in man are achieved by 5-10 mg/kg daily. This marked difference in dosage reflects the biological half life of 3 hours in rabbit compared to 70 hours in man, since the plasma concentration required for the antiinflammatory response in both species is the same, 100-150 µg/ml (18).

Interindividual differences in drug metabolism in normal man are largely determined by inheritance, as demonstrated by studies with several drugs in fraternal and identical twins (19). This genetic control is apparent when there exists a polymorphism. The neuromuscular blockade induced by succinylcholine lasts only a few minutes in the vast majority of subjects, but persists more than 2 hours in individuals that have inherited a variant of the enzyme that metabolizes this drug in the plasma (20). The bimodal distribution of isoniazid concentrations in plasma in normal volunteers or in patients treated with this drug is well known, and it has been shown to be related to the incidence of adverse to the therapeutic response in some of tuberculosis (21). More recently, a number genetic polymorphisms in oxidative drug metabolism have been They may help to identify a percentage of population who are at considerable risk of adverse effects from the usual doses of many drugs (22).

Finally, changes in drug excretion, either by the kidney or through the bile, undoubtedly exist, but they are difficult to elicit due to the confounding effect of differences in drug metabolism. However, when drugs such as barbital, that are not much metabolized in any species, are studied clear interspecies differences are apparent (23). On the other hand, changes in the biliary excretion of indomethacin and its conjugates seem to play a major role in the varying sensitivity to intestinal lesions induced by this drug in different species (24).

CHANGES IN KINETICS AND DRUG EFFECTS

The concept that pharmacological effects at a given time are a function of the amount of drug in the plasma, although recognized as a kind of simplification, has proved most useful to understand many drug effects and dose-response relationships (25, However, in spite that most drugs are developed for use in disease states, very little is known about the relationship between plasma concentration and pharmacological response under these circumstances. Pharmacokinetics are often altered pathological conditions, but disease could also modify receptor sensitivity or other factors involved in the ultimate response. This may particularly be the case of mediate pharmacological effects such as the hypoglycemic response to sulfonylureas. In this context, a study was undertaken in order to evaluate whether experimentally-induced disease states, namely anemia, hypoproteinemia and renal failure, would influence the relationship between tolbutamide concentrations in the blood and hypoglycemic response in the rabbit.

Material and methods

Male New Zeland white rabbits (2-3.1 kg) were used throughout the study. They were maintained on Purina pellets and water at libitum in individual, well ventilated, metabolic cages at least for 10 days before any experimental work was undertaken. Seven groups of rabbits were formed: A) control animals (n = 5); B) animals with moderate anemia (n = 5), 1 hour before the experiment, 35 mL of blood were drawn, the red cells were removed and the plasma plus 0.9% NaCl to complete the 35 mL reinjected;

C) animals with severe anemia (n = 4), 48 and 1 hour before the experiment 35 mL of blood were withdrawn and replaced as in B; D) animals with moderate anemia and renal failure (n = 4), rabbits received 2 mg/kg i.v. of uranyl nitrate 7 days before, and then were treated as in B; E) animals with moderate hypoproteinemia (n = 8), 1 hour before the experiment 35 mL of blood were drawn, the plasma removed and the red cells plus 0.9% NaCl to complete the 35 mL reinjected; F) animals with severe hypoproteinemia (n = 7), 48 and 1 hour before the experiment 35 mL of blood were drawn and then replaced as in E; G) animals with moderate hypoproteinemia and renal failure (n = 5), rabbits received 2 mg/kg i.v. of uranyl nitrate 7 days before, and then treated as in E.

All animals were kept fasting for the 12 hours prior to the beginning of the experiment. At time 0, they received 100 mg/kg i.v. of sodium tolbutamide. This is a standard dose for eliciting hypoglycemia with this drug in the rabbit (27, 28) and was found in a series of preliminary experiments to conform to linear, first order kinetics. Blood samples (1.5 mL) were drawn at -5, 40, 50, 60, 70, 90, 150, 180, 240 and 360 minutes. An additional blood sample was drawn at 70 minutes to measure tolbutamide binding to blood cells and proteins (control for anemic rabbits, groups B, C and D) or only to plasma proteins (control for groups E, hypoproteinemic rabbits. F and G). Both these determinations were carried out in the control Finally, 2 mL of blood were collected at time 0 to measure creatinine and plasma proteins. For the control group (A) tolbutamide kinetics were estimated in total blood as control for anemic rabbits, and in plasma as control for rabbits with hypoproteinemia.

Tolbutamide in total blood or plasma was assayed by HPLC. Briefly, to 0.25 mL of blood or plasma were added 1.5 mL of deionized water, 0.7 mL of 20% trichloroacetic acid and 0.02 mL of a solution containing the internal standard (chlorpropamide, 0.6 mg/mL), and the mixture was extracted with 10 mL of ethyl ether. After centrifugation the supernatant was evaporated to dryness at $40\,^{\circ}$ C. The residue was redissolved in 1.5 mL of the mobile phase and an aliquot of 0.1 mL was injected into the HPLC. The mobile phase was methanol: water + acetic acid (pH = 3.3)

(55/45). The absorbance was measured in a 441 Detector (Waters Associates) at 228 nm using a cadmium lamp.

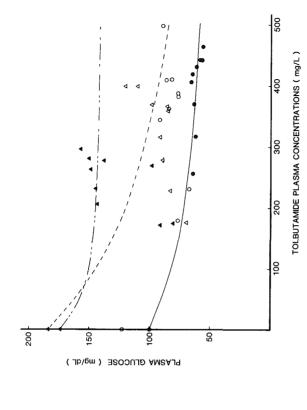
Tolbutamide binding to plasma proteins alone or to plasma proteins and formed elements of the blood was estimated ultrafiltration using ultrafiltracones (Centriflo, Lexington, Ma.). Briefly, the cones were soaked distilled water for 60 minutes and then centrifuged at 1000 rpm for 15 minutes to remove the water. Plasma or blood (1.5 ml) was loaded into the cones and centrifuged at 1000 rpm for 15 minutes. Protein content was determined in the plasma or blood and in the ultrafiltrate. The sample was discarded when more than 1% of the amount of protein in plasma or blood was recovered in the ultrafiltrate. A preliminary study confirmed that the binding of tolbutamide to the cones was negligible.

Plasma creatinine was measured by electrophoresis using a routine clinical technique. Finally, plasma glucose was determined by means of a glucose oxidase/peroxidase kit (Fisher Scientific Ltd).

Tolbutamide pharmacokinetic parameters were estimated assuming that tolbutamide distribution and elimination are first order processes. Apparent total body clearance (Cl) of tolbutamide and apparent volume of distribution at steady state (Vss) were calculated using noncompartimental methods based on the statistical moment theory (30). Lowering of blood glucose was considered the ultimate effect of tolbutamide, the relationship between plasma glucose levels and tolbutamide concentration in the plasma being expressed as a hyperbolic function, based on the \mathbf{E}_{max} model (31). The correlations between plasma glucose levels and plasma tolbutamide concentrations were calculated by means of least squares non-linear regression analysis using a NONLIN program (32).

Comparison of results in the control group with those of the experimental groups was carried out by a one way analysis of variance for parallel groups. Statistical differences were derived from Dunnett's distribution table (33). The minimal level of significance was set at p = 0.05.

In control animals, values of plasma glucose after tolbutamide administration correlated with total blood or plasma tolbutamide





•), in rabbits with mild (o) or seve-

Figure 2. Changes in mean plasma glucose plasma concentrations in control animals

concentrations function of tolbutamide

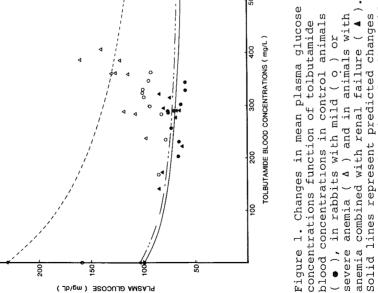
dicted changes in plasma glucose function

of tolbutamide.

failure

(A). Solid lines represent pre-

with hypoproteinemia combined with renal re hypoproteinemia (A) and in animals



concentration (r = 0.8254; p < 0.05 and r = 0.7582, p = 0.05 respectively) but these correlations were not apparent in animals with anemia, hypoproteinemia or any of these conditions associated with renal failure (figs 1 and 2).

Replacement of large volumes of total blood by plasma led to a marked decrease in the hematocrit, without affecting total protein or albumin concentrations. The i.v. injection of 2 mg/kg uranyl nitrate was followed by a marked increase of plasma creatinine, indicating the development of acute renal failure.

TABLE I : Mean (+ SE) value of the hematocrit total protein and creatinine in plasma in rabbits with anemia and renal failure (F)

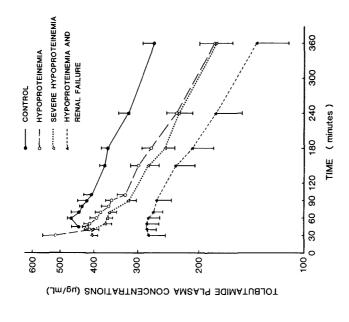
Control (n = 5)	Anemia (n = 5)	Severe anemia (n = 4)	Anemia and RF (n = 4)
40 <u>+</u> 1	28 <u>+</u> 2 ^a	19 <u>+</u> 1 ^b	31 <u>+</u> 3 ^a
5.52 <u>+</u> 0.26	5.02 <u>+</u> 0.10	5.15 <u>+</u> 0.24	5.20 <u>+</u> 0.33
3.34 <u>+</u> 0.07	3.34 <u>+</u> 0.08	3.33 <u>+</u> 0.13	3.10 <u>+</u> 0.22
-	-	-	1.61 <u>+</u> 0.11
-	-	-	9.19 <u>+</u> 0.88 ^c
	$(n = 5)$ 40 ± 1 5.52 ± 0.26	$(n = 5)$ $(n = 5)$ 40 ± 1 28 ± 2^{a} 5.52 ± 0.26 5.02 ± 0.10	$(n = 5)$ $(n = 5)$ anemia $(n = 4)$ 40 ± 1 28 ± 2^a 19 ± 1^b

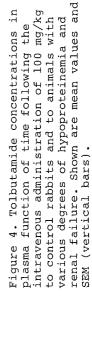
a : p < 0.01 compared to control values

Tolbutamide concentrations in whole blood did not significantly change in animals with anemia but tended to be lower in those with renal failure (fig 3). A statistically significant increase in the blood clearance of tolbutamide was detected in this group. Although the correlation between blood levels of the drug and effect observed in control animals could no longer be

b : p < 0.001 compared to control values

c : p < 0.001 compared to before RF





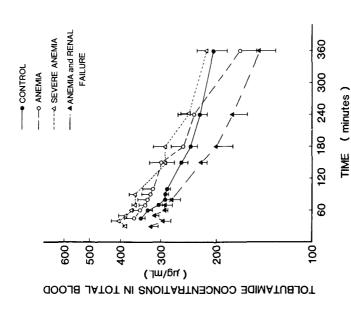


Figure 3. Tolbutamide concentrations in total blood function of time following the intravenous administration of 100 mg/kg to control rabbits and to animals with various degrees of anemia and renal failure. Shown are mean values and SEM (vertical bars)

detected in rabbits with anemia, without or with renal failure, the peak hypoglycemic effect, i.e. the maximal percentage change in plasma glucose with reference to baseline values, was not altered in any of these groups.

TABLE II : Kinetic parameters of tolbutamide and changes in blood glucose after administration of 100 mg/kg i.v. tolbutamide to rabbits with anemia and renal failure (RF). (Mean + SE)

	Control (n = 5)	Anemia (n = 5)	Severe anemia (n = 4)	Anemia and RF (n = 4)
AUMC (g min ² /mL)	138 <u>+</u> 27	84 <u>+</u> 24	121 <u>+</u> 30	61 <u>+</u> 14
Cl (mL/min/kg)	0.50 <u>+</u> 0.07	0.66 <u>+</u> 0.10	0.49 <u>+</u> 0.05	0.78 <u>+</u> 0.11 ^a
Vss (mL/kg)	296 <u>+</u> 14	286 <u>+</u> 28	255 <u>+</u> 7	317 <u>+</u> 17
fb (%)	38 <u>+</u> 2	36 <u>+</u> 11	30 <u>+</u> 3	40 + 4
Baseline plasma glucose (mg/dL)	99 <u>+</u> 10	158 <u>+</u> 23	231 <u>+</u> 32 ^a	104 <u>+</u> 10
Minimal plasma glucose (mg/dL)	54 <u>+</u> 4	74 <u>+</u> 8	100 ± 27	60 <u>+</u> 14

a : p < 0.05 compared to control values

AUMC : Area under tolbutamide first moment curve Cl : Tolbutamide apparent total body clearance

Vss : Predicted tolbutamide apparent volume of distribution at steady

state

b : Tolbutamide free fraction in total blood

Total plasma proteins, and indeed albumin, decreased in rabbits with severe hypoproteinemia, without any significant change in the hematocrit. The group of animals with moderate hypoproteinemia treated with 2 mg/kg uranyl nitrate showed an important increase in plasma creatinine and also a decrease in the hematocrit. In this group, total plasma proteins and albumin decreased only marginally.

TABLE III : Mean (+ SE) values of the hematocrit, total proteins and creatinine from plasma in rabbits with hypoproteinemia (HP) and renal failure (RF)

	Control (n = 5)	HP (n = 8)	Severe HP (n = 7)	HP & RF (n = '5)
Hematocrit	40 + 1	41 ± 1	37 <u>+</u> 3	29 <u>+</u> 2 ^b
Total proteins (g/dL)	5.52 <u>+</u> 0.26	4.79 <u>+</u> 0.21	4.50 ± 0.12 ^b	5.36 <u>+</u> 0.30
Albumin (g/dL)	3.34 <u>+</u> 0.07	3.27 <u>+</u> 0.16	2.90 ± 0.09 ^a	3.16 <u>+</u> 0.17
Creatinine before RF	-	-	-	0.99 <u>+</u> 0.09
Creatinine after RF	-	-		12.92 <u>+</u> 1.32 ^c

a : p < 0.05 compared to control values

Tolbutamide plasma concentrations increased significantly in all three groups of rabbits with hypoproteinemia, the decrease being most pronounced in those with moderate hypoproteinemia and renal failure (fig 4). AUMCs were reduced in all three groups, and a statistically significant increase in the plasma clearance of tolbutamide was detected in animals with severe hypoproteinemia or with hypoproteinemia and renal failure. In this latter group, an increase in the free fraction of tolbutamide in plasma, associated with an increase in the volume of distribution at steady state, was also apparent. As in the case of animals with anemia, the peak response to tolbutamide was not substantially altered.

b : p < 0.01 compared to control values

c : p < 0.01 compared to before RF

TABLE IV : Kinetic parameters of tolbutamide and changes in blood glucose after 'he administration of 100 mg/kg i.v. tolbutamide to rabbits with hypoproteinemia (HP) and renal failure (RF) (Mean \pm SE)

Control (n = 5)	HP (n = 8)	Severe HP (n = 7)	HP & RF (n = 5)
178 <u>+</u> 34	75 <u>+</u> 19 ^a	81 <u>+</u> 24	68 <u>+</u> 25 ^a
0.38 ± 0.04	0.58 <u>+</u> 0.08 ^a	0.64 ± 0.07 ^a	0.87 <u>+</u> 0.17 ^a
219 <u>+</u> 5	218 <u>+</u> 19	258 <u>+</u> 12	335 <u>+</u> 31 ^a
29 <u>+</u> 2	24 + 2	25 <u>+</u> 1	42 <u>+</u> 2 ^a
99 <u>+</u> 10	125 <u>+</u> 6	183 ± 23	174 <u>+</u> 35 ^a
54 <u>+</u> 4	72 <u>+</u> 9	79 <u>+</u> 11	98 <u>+</u> 11
	(n = 5) 178 ± 34 0.38 ± 0.04 219 ± 5 29 ± 2 99 ± 10	$(n = 5) (n = 8)$ $178 \pm 34 75 \pm 19^{a}$ $0.38 \pm 0.04 0.58 \pm 0.08^{a}$ $219 \pm 5 218 \pm 19$ $29 \pm 2 24 \pm 2$ $99 \pm 10 125 \pm 6$	$ (n = 5) \qquad (n = 8) \qquad (n = 7) $ $ 178 \pm 34 \qquad 75 \pm 19^{a} \qquad 81 \pm 24 $ $ 0.38 \pm 0.04 \qquad 0.58 \pm 0.08^{a} \qquad 0.64 \pm 0.07^{a} $ $ 219 \pm 5 \qquad 218 \pm 19 \qquad 258 \pm 12 $ $ 29 \pm 2 \qquad 24 \pm 2 \qquad 25 \pm 1 $ $ 99 \pm 10 \qquad 125 \pm 6 \qquad 183 \pm 23 $

a : p < 0.05 compared to control values

AUMC: Area under tolbutamide first moment curve Cl: Tolbutamide apparent total body clearance

Vss : Predicted tolbutamide apparent volume of distribution at steady

state

fp : Tolbutamide free fraction in plasma

Discussion

Although the fall in blood glucose after tolbutamide administration is an indirect effect, mediated by insulin release and perhaps other factors (34), changes in plasma glucose after i.v. administration of tolbutamide to normal animals showed a good correlation with tolbutamide concentrations, measured either in whole blood or in plasma. However, this correlation was no longer apparent in animals with anemia, hypoproteinemia or any of these two conditions associated with renal failure. Probably, more than one factor account for this lack of correlation. On the one hand baseline plasma glucose levels were raised to a varying extent in rabbits with experimentally-induced disease states. These increa-

ses could have been secondary to elevated catecholamine levels in anemia (35) or to a decrease in plasma oncotic pressure and circulating volume in hypoproteinemia (36) or to a combination of both. Altered baseline values of glucose could theoretically influence tolbutamide response since glucose itself induces the release of insulin (37). Other regulatory mechanisms such as glucagon, adrenal steroids, growth hormone, somatostatin, etc may operate in a different manner under these circumstances. Furthermore, the induced changes in hematocrit, plasma protein levels and renal function might have also acted upon regulatory mechanisms. On the other hand, altered tolbutamide kinetics may have contributed to an abnormal course of pharmacological response after the bolus injection of the drug. In view of the many factors that regulate blood glucose levels (35) it is difficult to predict to which extent the course of response to tolbutamide could be modified in the experimentally-induced disease states used in this study and, in some ways, it is not surprising to observe a lack of correlation between tolbutamide concentrations in the blood and effect at the time studied.

The relative insensitivity on the peak hypoglycemic response to changes in tolbutamide kinetics is more difficult to understand. In three of the experimental groups (anemia plus renal failure, severe hypoproteinemia and hypoproteinemia plus renal failure) there was a decrease in tolbutamide concentrations in blood or plasma, reflecting increased tolbutamide total body clearance, that did not result in a decrease in the peak hypoglycemic effect. Tolbutamide is primarily cleared by metabolic transformation in the rabbit (38) and it is interesting to note that actual increases in intrinsic clearance were detected in animals with moderate or severe hypoproteinemia (2.60 + 0.41 and 2.71 + 0.33 mL/min/kg respectively, versus 1.32 + 0.22 mL/min/kg in control animals; p & 0.05 in both cases). Furthermore, increases in the free fraction of tolbutamide may have contributed to the detected increases in total body clearance. Overall, the kinetic changes observed in the present study would have tended to predict a decreased response to tolbutamide. The actual finding of an unaltered drug effect indicates that disease effects on blood glucose regulation, besides those on tolbutamide kinetics should

be taken into account. These divergent findings, compounded with the lack of correlation between blood or plasma concentrations and serial effects in the induced disease states, suggest that the predictability of the magnitude and course of pharmacological effects from kinetic data in pathological conditions should be considered with care, particularly in the case of complex responses.

REFERENCES

- Shannon JA, Earle DP, Brodie BB, Taggart JV, Berliner RW (1944) J Pharmacol Exp Ther 81: 307-330
- Burns JJ, Berger BL, Lief PA, Woolack A, Papper EM, Brodie BB (1955) J Pharmacol Exp Ther 114: 289-298
- Quinn GP, Axelrod J, Brodie BB (1958) Biochem Pharmacol 1: 152-159
- 4. Brodie BB (1962) Clin Pharmacol Ther 3: 374-380
- 5. Kutt H, Winters W, Kokenge R, McDowell F (1964) Arch Neurol (Chicago) 11: 642-648
- 6. Levy G (1967) J Pharm Sci 56: 1687-1688
- 7. Nagashima R, O'Reilly RA, Levy G (1969) Clin Pharmacol Ther 10: 22-35
- Berkowitz BA, Asling JH, Shnider SM, Way EL (1969) Clin Pharmacol Ther 10: 320-328
- 9. Begemann H (1960) Ann NY Acad Sci 89 : 455-467
- 10. Handschumacher RE, Creasey WA, Fink ME, Calabresi P, Welch AD (1962) Cancer Chemother Reports 16: 267-269
- 11. Smith CG, Pontsiaka JW, Schreiber EC (1973) J Int Med Res 1
 : 489-503
- 12. Wagner JG (1968) Symp 5th Nat Meet AphA Academy of Pharmaceutical Sciences pp 53
- 13. Anton AH (1960) J Pharmacol Exp Ther 129 : 282-290
- 14. Rolinson G, Sutherland R (1965) Br J Pharmacol Chemother 25
 : 638-650
- 15. Barth N, Alván G, Borga O, Sjöqvist F (1976) Clin Pharmacokin 1 : 441-452
- 16. Fernández MC, Erill S, Lucena M, Pita E, Pérez-Alférez N (1985) Clin Pharmacokin 10 : 451-455

- 17. Alván G, Bergström K, Borga O, Iselius K, Pedersen N (1983) Eur J Clin Pharmacol 25 : 437-441
- 18. Burns JJ (1968) Ann NY Acad Sci 151: 959-967
- 19. Vesell ES (1978) Hum Genet 1(suppl) : 19-30
- 20. Harris (1964) Proc R Soc Med 57: 503-506
- 21. Mitchison DA (1973) In Davies DS, Prichard BNC (eds) Biological effects of drugs in relation to their plasma concentrations, MacMillan, London, pp 169-182
- 22. Eichelbaum M (1983) In Lamble JW (ed) Drug metabolism and disposition. Elsevier, Amsterdam pp 115-121.
- 23. Williams RT (1967) In Wolstenholme G, Porter R (eds) Drug responses in man, Little Brown, Boston, pp 71-87.
- 24. Duggan DE, Hooke KF, Noll RM, Chiu Kwan K (1975) Biochem Pharmacol 25: 1749-1754.
- 25. Levy G (1966) Clin Pharmacol Ther 7: 362-372.
- 26. Levy G (1983) In Lemberger L, Reidenberg MM (eds). Proceedings of the Second World Conference on Clinical Pharmacology and Therapeutics, Am Soc Pharmacol Exp Ther, Bethesda, pp 1-10
- 27. Bander A, Haussler A, Scholz (1957) Dtsch med Wschr 82: 1557-1564
- 28. Erill S (1969) Arch Int Pharmacodyn 177: 287-289.
- 29. Bauer JD, Ackermann PG, Toro G (1974) Clinical Laboratory Methods, The C.V. Mosby Company, St. Louis
- 30. Gibaldi M, Perrier D (1982) In Swarbrick J (ed) Pharmacokinetics, Marcel Dekker Inc, New York, pp 409-417
- 31. Holford NHG, Sheiner LB (1981) Clin Pharmacokin 6: 429-453
- 32. Metzler CM (1969) NONLIN: A computer program for parameter estimation in nonlinear situations, Technical Report No. 7292/69/7292/005, The Upjohn Company, Kalamazoo.
- 33. Winer BJ (1971) Statistical Principles in Experimental Design, McGraw-Hill, New York, pp 201-204
- 34. Duncan LJP Baird JD (1960) Pharmacol Rev 12 : 91-158
- 35. Felig P (1980) In Bondy PK, Rosenberg (eds) Metabolic Control and Disease, W.B. Saunders, Toronto, pp 276-371
- 36. Guyton AG (1971) Textbook of Medical Physiology, B.W. Saunders, Philadelphia, pp 230-238
- 37. Cerasi E (1975) Q Rev Biophys 8 : 1-41
- 38. Shibaski J, Konishi R, Morishita T, Ueki T (1973) Chem Pharm Bull 21 : 1754-1763

DISCUSSION - Pharmacokinetic basis of variability in drug responses

L.F. Prescott

It is often stated that most of the variability in drug response has a pharmacokinetic basis. Pharmacokinetic variation is often very impressive, but I am not sure that we have the corresponding clinical data for pharmacodynamic variation.

S. Erill

That is right, and as shown by our data on tolbutamide in animals, it is just possible that pharmacokinetic changes do not automatically result in modifications of the overall effect.

M.M. Reidenberg

To add some quantitative data to the discussion, is it worth mentioning the cases of phenytoin and theophylline. It has been reported that individuals who show nystagmus as the only adverse effect during treatment with phenytoin have blood levels between 18 and 28 µg/ml, whereas in patients with nystagmus and ataxia the levels tend to run to about 30-40 µg/ml, and patients exhibiting nystagmus, ataxia and obvious mental changes all have levels of phenytoin above 40 µg/ml. It is interesting to notice that while individual variation in the rate of metabolism of about 600-700 percent in metabolically normal phenytoin is subjects, the relationship between drug concentration in plasma and intensity of drug effect varies much less. Theophylline again shows enormous interindividual variation in metabolism rate, whereas it has been shown that interindividual variation in the effect of a given concentration in asthmatic patients is only about one hundred percent.

L.F. Prescott

Probably we have paid too much attention to pharmacokinetics and not enough to pharmacodynamics. We should be more concerned with the measurement of drug effects.

O. Pelkonen

Somebody remarked, a number of years ago, that when looking at

pharmacodynamic differences one should look at receptors, because most drugs exert their effects through binding to specific receptors. Since receptors are proteins, and proteins exhibit polymorphisms and variations in structure, we should not expect less variability in drug receptors than in drug metabolizing enzymes or in drug binding plasma proteins.

G.J. Mulder

It is easy to envisage a role for environmental factors in pharmacokinetic variation, but I would like to know whether receptors can be also subject to some type of influences.

S. Erill

It is known that the sensitivity to beta adrenergic agonists and antagonists changes with age. Receptor density and sensitivity can also be modified by hormones and drugs, but I do not know of any external influences other than those.

A.L. de Weck

There are also a number of data on the modulating effect of cimetidine on the activation or induction of human lymphocytes and basophiles, and in this regard the individual variation is about + 50%.

R. Lauwerys

Concerning the influence of genetic factors in pharmacokinetics, I would like to ask the audience whether it is clear that slow acetylators are at greater risk of bladder cancer, compared with fast acetylators, when exposed to aromatic amines.

M.M. Reidenberg

My personal answer is yes. At least as one can take epidemiological information and infer causation with biochemical plausibility, the story on slow acetylation and risk of bladder cancer for people who are exposed to aromatic amines is, in my judgement, reasonably good.

G.J. Mulder

However, in terms of mechanisms, there is not enough data to

sustain that acetylation increases carcinogenesis by aromatic amines. It has been shown that in the case of aminofluorene acetylation certainly increases carcinogenesis in some species whereas in other species one finds that non-acetylated aminofluorene derivatives cause cancer.

H. Vainio

At any event, the initial epidemiological studies on bladder cancer in man are being repeated now in many countries, and we may soon have more data at this respect.