QUANTITATIVE STRUCTURE PHARMACOKINETIC ACTIVITY RELATIONSHIPS WITH SOME TETRACYCLINES

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Considerable success has been achieved in QSAR (Hansch 1969). Extension of this approach to quantitative structure pharmacokinetic activity relationships (QSPAR) has been more limited (Notari 1975). We have examined QSPAR in a series of tetracyclines; this analysis enlarges and extends that of Green et al (1976). The relevant parameters (Table 1) were obtained either directly from literature values, or indirectly by analysis of available data.

Table 1. Composite values of pharmacokinetic parameters of some tetracyclines in man

Compound	Partition Coefficient Octanol/ water(pH7.5)	Fraction unbound in Plasma(fu)	Half-life ($t_{\frac{1}{2}}$) hours	Renal clearance (CL_R)L/hr	Non Renal clearance (CL_{NR})L/hr	Volume of distribution (V) litres
Oxytetracycline	0.025	0.690	9.2	5.92	2.54	112.31
Tetracycline	0.036	0.405	9.0	4.41	2.94	95.45
Demethylchlortetracycline	0.050	0.250	14.0	2.12	3.77	118.99
Chlortetracycline	0.13	0.300	5.6	1.93	8.79	86.62
Methacycline	0.43	0.220	11.1	2.73	6.37	145.76
Doxycycline	0.60	0.125	22.0	1.10	1.40	79.37
Minocycline	1.10	0.240	16.0	0.90	7.28	188.86

The fraction of drug unbound in plasma (fu) varies within the series. Log ($^1/_{fu}$), a measure of the affinity of drug for protein, tends to increase linearly with log P (octanol/water), pH 7.5 partition coeff-icient ($r^2 = 0.524$, $P < 0.05$). Elimination half-life ($t_{\frac{1}{2}}$) correlated poorly with degree of plasma binding (1-fu)($r^2 = 0.335$, $P > 0.2$). A more meaningful understanding is gained by separating $t_{\frac{1}{2}}$ into total clearance (CL) and volume of distribution (V), and by further dividing CL into renal clearance (CL_R) and non-renal (hepatic) clearance (CL_{NR}) and by correcting for plasma binding.

A poor correlation exists between V and either P or log P ($r^2 = 0.223$; $P > 0.3$). However, when correcting for differences in fu, a highly significant positive correlation exists between volume of distribution based on unbound drug, and log P ($r^2 = 0.828$, $P<0.001$), indicating that as in plasma, drug binding to tissue components increases with lipopholicity.

Although CL is poorly correlated with lipophilicity, log P ($r^2 = 0.02$, $P > 0.8$), renal clearance (CL_R) is directly proportional to fu ($r^2 = 0.836$, $P<0.001$). When corrected for fu however, the renal clearance based on unbound drug is relatively constant (8.47 L/hr) for all compounds; this value is close to the glomerular filtration rate, implying filtration occurs without further substantial secretion or reabsorption.

No correlation exists between non-renal clearance (CL_{NR}) and log P ($r^2 = 0.187$; $P > 0.4$), but since the value of CL_{NR} is low for all compounds correction for plasma binding must be made to assess events within the liver. The non-renal clearance based on unbound drug ($CLu,_{NR}$) varies; the failure of liphopilicity to account for all this variability ($CLu,_{NR}$ v log P, $r^2 = 0.497$; $P<0.05$) indicates that other factors, possibly steric and ionic, are also largely responsible for differences in efficiency of the liver to handle these tetracyclines.

The present analysis illustrates the need to resolve pharmacokinetic parameters into component parts, before attempting to relate the influence of structural modification on pharmacokinetics.

Green, R., Brown, J.R., Calvert, R.T. (1976) Europ. J. Clin. Pharmacol. 10, 245
Hansch, C. (1969) Accounts Chem. Res. 2, 232
Notari, R.E. (1975) Pharm. Weekblad. 10, 110