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Failure of 'therapeutic' doses of β-adrenoceptor antagonists to alter the disposition of tolbutamide and lignocaine

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1 The effects of separate 1 week pre-treatments with each of the β-adrenoceptor antagonists, propranolol (80 mg every 12 h), metoprolol (100 mg every 12 h) and atenolol (50 mg once daily), on the disposition of a single i.v. dose of tolbutamide were studied in six healthy volunteers. In addition, the effects of a 1 week pre-treatment with metoprolol (100 mg every 12 h) and atenolol (50 mg once daily) on the disposition of orally and i.v. administered lignocaine were determined in seven healthy subjects.
2 Tolbutamide clearance, half-life, volume of distribution and plasma protein binding were not altered by the β-adrenoceptor blocker pre-treatments. Similarly, neither metoprolol nor atenolol had a significant effect on the systemic clearance, apparent oral clearance or other dispositional parameters of lignocaine. 'Therapeutic' plasma concentrations of the β-adrenoceptor blockers were confirmed on each study day.
3 It is concluded that the inhibition of oxidative drug metabolism previously reported for lipophilic β-adrenoceptor blockers may be selective for different forms of cytochrome P450 and possible concentration-dependent.

Keywords oxidative drug metabolism β-adrenoreceptor antagonists tolbutamide lignocaine drug disposition

Introduction

A strong correlation between the lipophilicity of a series of β-adrenoceptor antagonists and their ability to inhibit the metabolism of lignocaine by rat liver microsomes has recently been demonstrated (Deacon *et al.*, 1981). Thus, *in vitro* the most lipid soluble β-adrenoceptor blocker propranolol inhibited lignocaine metabolism to the greatest extent while atenolol, the most polar β-adrenoceptor blocker, had no effect on lignocaine metabolism. Metoprolol, a β-adrenoceptor blocker of moderate lipophilicity, had an effect on lignocaine metabolism intermediate between that of propranolol and atenolol. Consistent with these effects *in vitro*, there is some evidence that certain β-adrenoceptor blockers may be inhibitors of oxidative drug metabolism in man. Propranolol co-administration has been shown to inhibit the elimination of antipyrine (Greenblatt *et al.*, 1978; Bax *et al.*, 1981), chlorpromazine (Peet *et al.*, 1980), lignocaine (Ochs *et al.*, 1980; Conrad *et al.*, 1983) and theophylline (Conrad & Nyman, 1980). Similarly, metoprolol has been reported to reduce the clearance of antipyrine (Bax *et al.*, 1981) and lignocaine (Conrad *et al.*, 1983), although the reduction in the clearances of these drugs was generally only approximately half that following propranolol pretreatment. In contrast, atenolol administration had minimal (Daneshmend & Roberts, 1982) or no effect (Tucker *et al.*, 1982) on antipyrine clearance in normal volunteers.

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To define further the extent of the inhibitory effect of β-adrenoceptor blockers on oxidative drug metabolism in man, we have determined the effect of propranolol, metoprolol and atenolol on the metabolism of tolbutamide, the clearance of which is determined by one oxidative pathway. In addition, we have investigated the effect of metoprolol and atenolol on the disposition of orally and i.v. administered lignocaine to assess the relative importance of changes in haemodynamic factors and drug metabolising enzyme activity due to these β-adrenoceptor blockers.

Methods

Subjects for both the tolbutamide and lignocaine studies were healthy as determined by medical history, physical examination and biochemical and haematological parameters. No medications, other than those required for the studies, were taken for 1 week before or during the studies. Written informed consent was obtained from each subject and the studies were approved by the Clinical Investigation and Drug and Therapeutics Advisory Committees of Flinders Medical Centre.

Tolbutamide study

Protocol Subjects were six male volunteers, aged 19–25 years, weight 76–94 kg. All subjects were non-smokers. The study consisted of four phases, each of which involved the administration of tolbutamide (Rastinon) by i.v. infusion (500 mg over 10 min). During the first phase of the study (T phase) tolbutamide alone was administered. Subsequently tolbutamide was administered on three separate occasions; after a 1 week pre-treatment period with each of the β-adrenoceptor blockers atenolol (Tenormin, 50 mg once daily), metoprolol (Betaloc, 100 mg every 12 h) and propranolol (Inderal, 80 mg every 12 h) (TA, TM and TP phases, respectively). On each study day the β-adrenoceptor blocker dose was administered immediately prior to the tolbutamide infusion and treatment with the β-adrenoceptor blockers was continued until blood sampling was completed after the separate tolbutamide infusions. The control phase was not randomised to ensure safety of tolbutamide administration but thereafter the order of the β-adrenoceptor blocker pre-treatments was randomised. The tolbutamide infusions for the TA, TM and TP phases were separated by at least 2 weeks.

Blood samples (10 ml) were collected through an indwelling cannula inserted into a vein of the forearm opposite to that of the infusion site, before and at 5, 10, 15, 30, 45 min and 1, 2, 4, 6, 8, 24, 28 and 32 h after each infusion. Plasma was separated and stored at −20°C until assayed.

Analytical Plasma concentrations of tolbutamide were measured by a specific high performance liquid chromatographic (h.p.l.c.) method (Nation *et al.*, 1978) and tolbutamide plasma protein binding was determined by equilibrium dialysis (Miners *et al.*, 1982).

Plasma atenolol concentrations were determined by a specific h.p.l.c. method (Gillilan & Mason, 1983).

Similarly, a h.p.l.c. procedure was developed which allowed the quantitation of both propranolol and metoprolol. To 1 ml of plasma (sample or standard) were added 0.1 ml of internal standard (metoprolol, 10 μg/ml or propranolol, 2.5 μg/ml), 0.1 ml of 2 M NaOH and 5 ml of diethylether. The solution was vortex mixed for 2 min and then centrifuged at 1500 *g* for 3 min. The aqueous layer was frozen in acetone-dry ice and the organic phase decanted into a nipple tube containing 0.1 ml of 0.05 M H_2SO_4. After vortex mixing for 2 min phases were separated by centrifugation (1500 *g* for 3 min) and 0.05 ml of the aqueous layer was injected into the chromatograph. Unknown concentrations were determined by comparison of peak height ratios with those of the calibration curves in the range 10–500 μg/l. The chromatograph used was fitted with a μ-Bondapak phenyl column (Waters Associates) and operated at ambient temperature. Quantitation was achieved with a Spectra Physics model 970 fluorescence detector using an excitation wavelength of 230 nm and a 295 nm cut-off emission filter. The mobile phase was sodium acetate (10 mM, pH 7.0)–methanol (43:57) at a flow rate of 2.0 ml/min. Under these conditions metoprolol and propranolol chromatographed with retention times at 3.75 and 7.5 min, respectively. The limit of sensitivity for both compounds was 10 μg/l and the mean intra-assay coefficients of variation (mean ± s.e. mean) for propranolol and metoprolol were 3.6 ± 0.9% (n = 6) and 2.9 ± 0.5% (n = 10), respectively.

Lignocaine study

Protocol Seven subjects participated in the study; four males aged 20–31 years, weight 64–82 kg, and three females aged 20–34 years, weight 52–72 kg. Two subjects (one male and one female) were smokers. All subjects were studied on three pairs of consecutive study days, before (L phase) and after separate 1 week pre-treatments with each of the β-

adrenoceptor blockers atenolol (LA phase) and metoprolol (LM phase). A single oral dose of lignocaine hydrochloride (200 mg) in hard gelatin capsules was administered on 1 day and on the other day lignocaine hydrochloride was infused i.v. over 2 min. The i.v. dose was 100 mg lignocaine base for subjects over 65 kg body weight and 75 mg for the others. In all cases, lignocaine was administered after an overnight fast. The order of dosing with oral and i.v. lignocaine was randomised on each occasion. The doses of atenolol and metoprolol were the same as those described above (tolbutamide study) and the order of pre-treatments with the β-adrenoceptor blockers was randomised. Once again the control lignocaine study was not randomised for safety reasons. Atenolol and metoprolol were taken in the hour preceding lignocaine administration. Dosing of β-adrenoceptor blockers was continued until the second lignocaine study day had been completed. Each pair of study days was separated by at least 2 weeks.

On each study day a cannula was inserted into a forearm vein for blood sampling. Blood samples (10 ml) were collected before and at 10, 20, 30, 45 min, and 1, 1.5, 2, 3, 4, 6 and 8 h after lignocaine administration.

Analytical

Plasma lignocaine concentrations were determined by a specific gas–liquid chromatographic procedure employing nitrogen–phosphorous detection (Wing *et al.*, 1984).

Analysis of results

The following parameters were estimated from the tolbutamide and lignocaine plasma concentrations in each individual study. Area under the plasma concentration–time curve (AUC) was determined by the trapezoidal rule with extrapolation to infinity. Elimination half-life ($t_{½,z}$) was calculated from the slope of the terminal portion of the concentration–time curve by linear least squares regression and volume of distribution at steady state (V_{ss}) by the model-independent procedure of Benet & Galeazzi (1979). The systemic clearance of tolbutamide and lignocaine were determined as,

$$CL = D \text{ (i.v.)}/\text{AUC (i.v.)} \times \text{B.W.}$$

where B.W. is the body weight in kg. For the oral dosing studies lignocaine apparent oral clearance was calculated as,

$$CL_o = D \text{ (oral)}/\text{AUC (oral)} \times \text{B.W.}$$

The oral bioavailability of lignocaine (expressed as a percentage of the dose) was calculated as,

$$F = \frac{D \text{ (i.v.)} \times \text{AUC (oral)}}{D \text{ (oral)} \times \text{AUC (i.v.)}} \times 100.$$

The factors required for the conversion of plasma concentrations of propranolol, metoprolol and atenolol (Table 4) from μg/l to S.I. units (nmol/l) are 3.86, 3.74 and 3.75, respectively.

All results are expressed as mean ± s.e. mean. For each parameter differences between all study phases were compared by repeated measures analysis of variance. Atenolol and metoprolol plasma concentrations during the intravenous and oral phases of the LA and LM studies were compared by paired Student's *t*-test. Values of $P < 0.05$ were considered significant. Using the mean control phase values for tolbutamide CL and lignocaine CL and Cl_o and the appropriate residual mean squares from analysis of variance and assuming that the effect of each β-adrenoceptor blocker would be similar, the power of each study was calculated (Winer, 1971).

Results

The effect of subacute atenolol, metoprolol and propranolol treatment on tolbutamide disposition is summarised in Table 1 and individual and mean data for tolbutamide CL are shown in Figure 1. Data presented here demonstrate that none of these β-adrenoceptor blockers had a significant effect on tolbutamide CL, $t_{½,z}$ or V_{ss}. The calculated probability of demonstrating a 20% change in tolbutamide CL by any of the three β-adrenoceptor blockers was > 0.99 at the 1% level. At comparable times (2, 10 and 24 h) after the commencement of the tolbutamide infusion in each of the study phases, there was no difference in tolbutamide free fraction (Table 2). Tolbutamide free fractions 10 h and 24 h after the infusion in each study phase were, however, significantly lower ($P < 0.05$) than at 2 h after the infusion, confirming the previously reported concentration dependence of tolbutamide protein binding (Miners *et al.*,1982).

Neither atenolol nor metoprolol pre-treatment had any effect on lignocaine CL, CL_o, $t_{½,z}$, V_{ss} or oral bioavailability (Table 3, Figure 2). The calculated probability of demonstrating a 20% change in lignocaine CL by either atenolol or metoprolol was > 0.99 at the 5% level and > 0.90 at the 1% level; likewise, for a 30% change in lignocaine CL_o the calculated

Table 1 Effect of atenolol, metoprolol and propranolol pre-treatments on tolbutamide disposition

Study phase	CL (ml min^{-1} kg^{-1})	$t_{½,z}$ (h)	V_{ss} (l/kg)
T	0.147 ± 0.013	9.52 ± 0.97	0.116 ± 0.004
TA	0.140 ± 0.013	9.44 ± 0.94	0.111 ± 0.005
TM	0.145 ± 0.015	10.03 ± 1.16	0.119 ± 0.005
TP	0.140 ± 0.016	9.83 ± 1.08	0.112 ± 0.003

Results expressed as mean ± s.e.

probability was > 0.94 at the 5% level and > 0.74 at the 1% level.

For the tolbutamide study atenolol, metoprolol and propranolol plasma concentrations were determined in the pre-dose, 2, 8 and 24 h samples of the TA, TM and TP phases, respectively, and after both oral and i.v. lignocaine dosing atenolol (LA phase) and metoprolol (LM phase) concentrations were measured in the pre-dose, 2 and 8 h samples (Table 4). There was no significant difference in atenolol and metoprolol concentrations at comparable times during the i.v. and oral phases of the LA and LM studies.

Discussion

This study has investigated the effect of several β-adrenoceptor blockers on the disposition of the model drugs tolbutamide and lignocaine. Data presented here demonstrate that pretreatment with either atenolol, metoprolol or propranolol in doses commonly administered clinically had no effect on the clearance of tolbutamide and that lignocaine disposition was similarly unaffected by either atenolol or metoprolol pre-treatment. Each study was sufficiently powerful to detect clinically relevant differences in tolbutamide and lignocaine dispositional parameters. It could be argued that, as neither study was completely randomised, factors associated with the control phase may have exerted a consistent conditioning effect on subsequent responses. This possibility is acknowledged but would seem unlikely since there is no evidence to indicate that either tolbutamide or lignocaine alter their own clearance or will change the inhibitory or inducing effects of interacting drugs.

Tolbutamide was chosen as a model drug since it undergoes almost quantitative conversion to hydroxytolbutamide by the hepatic mixed function oxidase system (Nelson & O'Reilly, 1961; Thomas & Ikeda, 1966). Since tolbutamide clearance is limited by hepatic metabolic capacity ('low clearance' drug), the lack of effect of any of the β-adrenoceptor blockers on tolbutamide systemic clearance indicates that these agents do not inhibit the enzyme(s) responsible for tolbutamide metabolism. Although lignocaine is also eliminated primarily

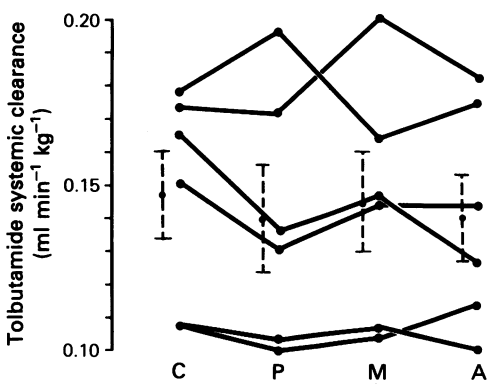

Figure 1 Individual tolbutamide systemic clearances in control (C) and propranolol (P), metoprolol (M) and atenolol (A) pretreatment phases. Group mean ± s.e. mean in each study phase shown as dashed line.

Table 2 Effect of atenolol, metoprolol and propranolol on tolbutamide plasma protein binding

Study phase	Tolbutamide free fraction × 100 2 h*	10 h	24 h
T	5.67 ± 0.14	5.27* ± 0.10	5.30** ± 0.08
TA	5.72 ± 0.16	5.31** ± 0.09	5.26** ± 0.09
TM	5.63 ± 0.12	5.32** ± 0.12	5.17** ± 0.07
TP	5.53 ± 0.10	5.33** ± 0.09	5.22** ± 0.10

Results expressed as mean ± s.e. mean.
*Time after commencement of tolbutamide infusion
**Compared to value at 2 h in same phase, $P < 0.05$

Table 3 Effect of atenolol and metoprolol pretreatments on the disposition of i.v. and orally administered lignocaine

Study phase	*CL* *(ml min^{-1} kg^{-1})*	*CL_o* *(ml min^{-1} kg^{-1})*	*$T_{½,z}$* *(h)*	*V_{ss}* *(l/kg)*	F *(%)*
L i.v.	10.84 ± 1.41	—	1.78 ± 0.21	1.58 ± 0.19	—
L oral	—	45.00 ± 7.99	1.71 ± 0.19	—	29.1 ± 5.2
LA i.v.	10.16 ± 0.98	—	1.77 ± 0.15	1.52 ± 0.13	—
LA oral	—	47.18 ± 7.17	1.94 ± 0.10	—	23.9 ± 3.9
LM i.v.	9.33 ± 0.99	—	1.98 ± 0.21	1.56 ± 0.18	—
LM oral	—	44.51 ± 9.60	1.93 ± 0.11	—	28.2 ± 6.3

Results expressed as mean ± s.e. mean

by oxidative metabolism (Keenaghan & Boyes, 1972) it is a high hepatic clearance drug and thus systemic clearance is limited by hepatic blood flow. Potential interactions between β-adrenoceptor blockers and lignocaine may involve effects on both hepatic blood flow and drug metabolising enzyme activity and thus to define such interactions fully lignocaine was administered by both the i.v. and oral routes in the same subject. In this study lignocaine CL, CL_o and oral bioavailability were all unaltered by the atenolol and metoprolol pre-treatments.

In dogs a 23% decrease in lignocaine systemic clearance following propranolol administration was shown to be entirely due to the haemodynamic effects of propranolol reducing liver blood flow, there being no change in hepatic extraction (Branch *et al.*, 1973). A finding in man consistent with this observation is that in normal volunteers co-administration of propranolol during continuous infusion of lignocaine increased mean steady state lignocaine plasma concentrations by 30% (Ochs *et al.*, 1980). More recently, Conrad *et al.* (1983) reported that lignocaine CL was decreased 31% by metoprolol pre-treatment and 47% by propranolol pre-treatment. In particular, the change due to propranolol is greater than that expected by the reduction in hepatic blood flow usually observed with β-adrenoceptor blockade and suggests an additional substantial contribution from reduced extraction. Propranolol was not administered with lignocaine in the present study. In the present study there was no significant difference in lignocaine CL between the control phase and either of the β-adrenoceptor blocker pre-treatment phases. Although the mean values were lower in both pre-

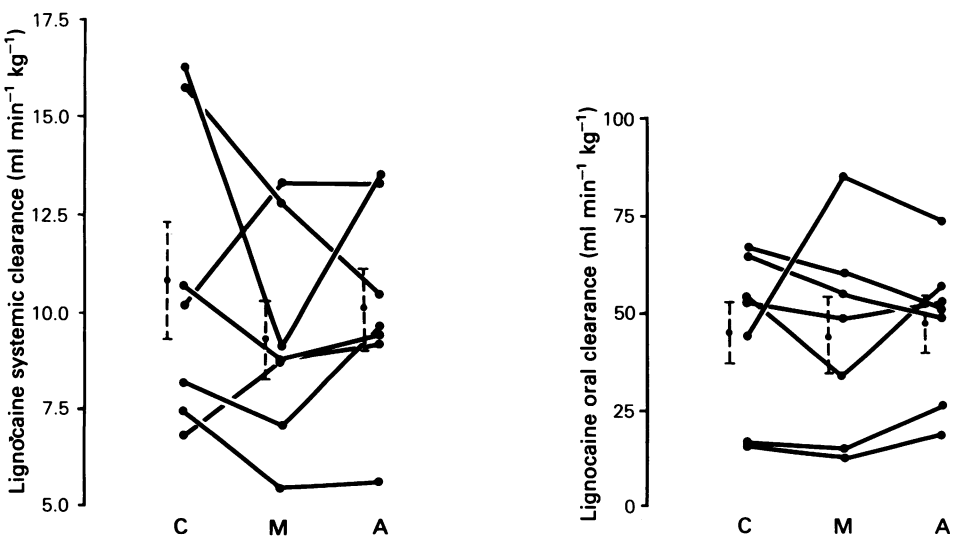

Figure 2 Individual lignocaine systemic clearances and oral clearances in control (C) and metoprolol (M) and atenolol (A) pretreatment phases. Group mean ± s.e. mean in each study phase shown as dashed line.

Table 4 β-adrenoceptor blocker plasma concentrations during tolbutamide and lignocaine studies

β-adrenoceptor blocker/time*	β-adrenoceptor blocker concentration (μg/l)		
	Tolbutamide study	Lignocaine study	
		i.v. phase	oral phase
Atenolol			
pre-dose	27.0 ± 2.0	160.8 ± 28.0	151.3 ± 30.8
2 h	150.3 ± 24.2	183.8 ± 23.1	187.7 ± 18.6
8 h	97.5 ± 15.0	108.4 ± 12.9	121.4 ± 16.6
24 h	84.2 ± 33.2	—	—
Metoprolol			
pre-dose	17.2 ± 3.4	77.4 ± 13.9	71.9 ± 19.7
2 h	74.7 ± 11.4	106.6 ± 22.3	114.9 ± 24.7
8 h	29.7 ± 7.6	42.4 ± 10.4	32.4 ± 8.9
24 h	43.3 ± 12.2	—	—
Propranolol			
pre-dose	14.5 ± 2.0		
2 h	65.0 ± 12.6		
8 h	20.8 ± 1.9		
24 h	39.0 ± 14.4		

*Time of sampling refers to time after tolbutamide/lignocaine dose. For details of β-adrenoceptor blocker administration, see **Methods**.

treatment phases (LA phase 7% reduction, LM phase 14% reduction), there was considerable interindividual variability in response (Figure 2). The extent of β-adrenoceptor blockade achieved in this study was not determined but plasma concentrations of the individual β-adrenoceptor blockers were similar to those observed by others in the presence of significant β-adrenoceptor blockade (Chidsey *et al.*, 1976; Johnsson & Regårdh, 1976; McAinsh, 1977). It should be noted that the results of this study are consistent with those of Parker *et al.* (1983) who failed to show a significant effect of pretreatment with propranolol, metoprolol or nadolol on indocyanine green clearance in healthy volunteers.

Although the absence of any effect of atenolol on lignocaine CL_o in this study is consistent with the lack of inhibition of lignocaine metabolism by atenolol *in vitro*, the lack of effect of metoprolol on lignocaine CL_o is at variance with the *in vitro* data as metoprolol has been reported to reduce the *in vitro* metabolism of lignocaine by rat liver microsomes by approximately 30% (Deacon *et al.*, 1981). It is acknowledged that the power of the present study with respect to CL_o was more limited than for lignocaine CL and small decreases in lignocaine CL_o may not have been detected. However, a factor which may be of relevance is the difference in β-adrenoceptor blocker concentrations used in the *in vitro* study and those achieved in the plasma of subjects during the β-adrenoceptor blocker treatments. The concentrations of β-adrenoceptor blockers used in the *in vitro* study of lignocaine metabolism were 50–100 times greater than the maximum plasma concentrations observed in the present study. Similarly, the concentrations of certain β-adrenoceptor blockers reported to inhibit ethoxyresorufin deethylase and disopyramide dealkylation in rat liver microsomes were 50–350 times greater than peak therapeutic plasma concentrations measured here (Ahokas *et al.*, 1983). Again, it must be acknowledged that β-adrenoceptor blocker plasma concentrations may be considerably lower than those in hepatocytes (Ong *et al.*, 1981). In addition, the putative metabolic inhibitory effect of β-adrenoceptor blockers may not be due to the parent drug but to a covalently bound metabolic intermediate, as suggested for propranolol (Bax *et al.*, 1983). In these cases inhibitory effects may not be reflected in peripheral concentrations of unchanged β-adrenoceptor blocker.

As the plasma concentrations of atenolol, metoprolol and propranolol measured in this study are similar to those observed during clinical dosing with these drugs (Chidsey, 1976; Johnsson & Regårdh, 1976; McAinsh, 1977), the findings in the present studies suggest that clinically significant inhibition of tolbutamide metabolism by propranolol, metoprolol or atenolol is unlikely. Similarly, clinically significant inhibition of lignocaine metabolism is unlikely with usual therapeutic doses of metoprolol and atenolol. While the possibility exists that the extent of metabolic inhibition due to

β-adrenoceptor blockers is concentration-dependent, the present data still appear to be at variance with the findings that common therapeutic doses of propranolol reduce the elimination of the low clearance drugs antipyrine, chlorpromazine and theophylline and similarly for the reduction in antipyrine clearance following metoprolol. It should be noted that therapeutic doses of propranolol do not alter the elimination of quinidine (Ochs *et al.*, 1978). As it is accepted that there are multiple forms of cytochrome P450 with different but overlapping substrate specificities, an explanation for these disparate results is that the inhibition of oxidative drug metabolism by lipophilic β-adrenoceptor blockers could be selective for different forms of cytochrome P450. Thus, while propranolol appears to inhibit those enzymes involved in antipyrine, chlorpromazine, lignocaine and theophylline metabolism, it does not affect the form(s) of cytochrome P450 involved in tolbutamide metabolism.

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References

Ahokas, J. T., Davies, C. & Ravenscroft, P. J. (1983). Comparison of β-adrenoceptor antagonists as modulators of drug metabolism. *Clin. exp. Pharmac. Physiol.*, **10**, 678.

Bax, N. D. S., Lennard, M. S. & Tucker, G. T. (1981). Inhibition of antipyrine metabolism by β-adrenoceptor antagonists. *Br. J. clin. Pharmac.*, **12**, 779–784.

Bax, N. D. S., Lennard, M. S., Al-Asady, S., Deacon, C. S., Tucker, G. T. & Woods, H. F. (1983). Inhibition of drug metabolism by β-adrenoreceptor antagonists. *Drugs*, **25** (Suppl. 2), 121–126.

Benet, L. Z. & Galeazzi, R. L. (1979). Noncompartmental determination of the steady-state volume of distribution. *J. pharm. Sci.*, **68**, 1071–1074.

Branch, R. A., Shand, D. G., Wilkinson, G. R. & Nies, A. S. (1973). The reduction of lidocaine clearance by dl-propranolol: an example of hemodynamic drug interaction. *J. Pharmac. exp. Ther.*, **184**, 515–519.

Chidsey, C., Pine, M., Favrot, L., Smith, S., Leonetti, G., Morselli, P. & Zanchetti, A. (1976). The use of drug concentration measurements in studies of the therapeutic response to propranolol. *Postgrad. med. J.*, **52** (Suppl. 4), 26–32.

Conrad, K. A. & Nyman, D. W. (1980). Effects of metoprolol and propranolol on theophylline elimination. *Clin. Pharmac. Ther.*, **28**, 463–468.

Conrad, K. A., Byers, J. M., Finley, P. R. & Burnham, L. (1983). Lidocaine elimination: effects of metoprolol and of propranolol. *Clin. Pharmac. Ther.*, **33**, 133–138.

Daneshmend, T. K. & Roberts, C. J. C. (1982). The short term effects of propranolol, atenolol and labetalol on antipyrine kinetics in normal subjects. *Br. J. clin. Pharmac.*, **13**, 817–820.

Deacon, C. S., Lennard, M. S., Bax, N. D. S., Woods, H. F. & Tucker, G. T. (1981). Inhibition of oxidative drug metabolism by β-adrenoceptor antagonists is related to their lipid solubility. *Br. J. clin. Pharmac.*, **12**, 429–431.

Gillilan, R. B. & Mason, W. D. (1983). Revised hplc determination of atenolol in plasma and urine. *Analytical Letters*, **16**, 941–949.

Greenblatt, D. J., Franke, K. & Huffman, D. H. (1978). Impairment of antipyrine clearance in humans by propranolol. *Circulation*, **57**, 1161–1164.

Johnsson, G. & Regårdh, C. G. (1976). Clinical pharmacokinetics of β-adrenoreceptor blockers. *Drugs*, **11** (Suppl. 1), 111–121.

Keenaghan, J. B. & Boyes, R. N. (1972). The tissue distribution, metabolism and excretion of lidocaine in rats, guinea pigs, dogs and man. *J. Pharmac. exp. Ther.*, **180**, 454–463.

McAinsh, J. (1977). Clinical pharmacokinetics of atenolol. *Postgrad. med. J.*, **53** (Suppl. 3), 74–78.

Miners, J. O., Foenander, T., Wanwimolruk, S., Gallus, A. S. & Birkett, D. J. (1982). The effect of sulphinpyrazone on oxidative drug metabolism in man: inhibition of tolbutamide elimination. *Eur. J. clin. Pharmac.*, **22**, 321–326.

Nation, R. L., Peng, G. W. & Chiou, W. L. (1978). Simple, rapid and micro high pressure liquid chromatographic method for the simultaneous determination of tolbutamide and carboxytolbutamide in plasma. *J. Chromatogr.*, **146**, 121–131.

Nelson, E. & O'Reilly, I. (1961). Kinetics of carboxytolbutamide excretion following tolbutamide and carboxytolbutamide excretion. *J. Pharmac. exp. Ther.*, **132**, 103–109.

Ochs, H. R., Greenblatt, D. J., Woo, E., Franke, K. & Smith, T. W. (1978). Effect of propranolol on pharmacokinetics and acute electrocardiographic changes following intravenous quinidine in humans. *Pharmacology*, **17**, 301–306.

Ochs, H. R., Carstens, G. & Greenblatt, D. J. (1980). Reduction in lidocaine clearance during continuous infusion and by coadministration of propranolol. *New Engl. J. Med.*, **303**, 373–377.

Ong, H., du Souich, P. & Marchand, C. (1981). *In vivo* study of propranolol and metabolites disposition in rat liver. *Drug Metab. Disp.*, **9**, 529–534.

Parker, G., Ene, D., Daneshmend, T. & Roberts, C. (1983). Effects of three beta-blockers on the clearances of indocyanine green and antipyrine. *Second World Conference on Clinical Pharmacology and Therapeutics*, Washington D.C., abstract no. 453.

Peet, M., Middlemass, D. N. & Yates, R. A. (1980).

Pharmacokinetic interaction between propranolol and chlorpromazine in schizophrenic patients. *Lancet*, **ii**, 978.

Thomas, R. C. & Ikeda, G. J. (1966). The metabolic fate of tolbutamide in man and rat. *J. med. Chem.*, **9**, 507–510.

Tucker, G. T., Bax, N. D. S., Lennard, M. S., Crewe, K. & Woods, H. F. (1982). Lack of effect of atenolol on antipyrine clearance. *Br. J. clin. Pharmac.*, **14**, 743–744.

Wilkinson, G. R. & Shand, D. G. (1975). A physiological approach to hepatic drug clearance. *Clin. Pharmac. Ther.*, **18**, 377–390.

Winer, B. J. (1971). *Statistical principles in experimental design* (2nd edition), pp. 220–228. Tokyo: McGraw-Hill, Kagakusha.

Wing, L. M. H., Miners, J. O., Birkett, D. J., Foenander, T., Lillywhite, K. & Wanwimolruk, S. (1984). Lidocaine disposition: sex differences and the effect of cimetidine. *Clin. Pharmac. Ther.*, **35**, 695–701.

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