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ON THE ROLE OF α_1-ACID GLYCOPROTEIN IN LIGNOCAINE ACCUMULATION FOLLOWING MYOCARDIAL INFARCTION

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1 Blood plasma and free lignocaine concentrations have been measured 12 h after beginning a constant infusion of 2 mg/min and again at the end of the infusion (36–72 h) in five patients with myocardial infarction (MI) and compared with five control patients who did not develop objective evidence of MI.

2 In MI patients, total plasma concentration rose significantly between 12 h and the end of infusion. Because of an increase in α_1 acid glycoprotein (AAG) plasma binding increased, so that free drug concentrations did not change. The rise in whole blood concentration was less than that in plasma as a result of drug redistribution out of red cells due to enhanced binding.

3 In control patients, neither blood nor plasma concentrations changed with time and plasma binding remained constant. Free drug concentrations, however, rose slightly.

4 The concentrations of GX and MEGX remained unchanged in all patients, but the ratio of lignocaine/MEGX concentrations fell in controls but rose in MI patients.

5 Pharmacokinetic modelling suggested that at least some of the rise in blood lignocaine concentration was due to reduced clearance resulting from enhanced plasma binding.

6 We conclude that the rise in AAG following MI is responsible for increased plasma binding and drug redistribution within blood. These changes, together with a reduction in lignocaine clearance, can explain much of the phenomenon of lignocaine accumulation in MI.

Introduction

While the original observation of Prescott *et al.* (1976) that total plasma lignocaine concentrations accumulate during a constant infusion in patients with myocardial infarction has been amply confirmed (Lelorier *et al.*, 1977; Routledge *et al.*, 1980b; Bax *et al.*, 1980) its mechanism remains obscure. Because lignocaine is normally a high clearance drug (Stenson *et al.*, 1971) both reduced hepatic blood flow and intrinsic clearance could contribute to its accumulation (Wilkinson & Shand, 1975). More recently we have shown that the plasma binding of lignocaine also increases following infarction (Routledge *et al.*, 1980b) as a result of a rise in its major binding protein, α_1 acid glycoprotein, AAG (Routledge *et al.*, 1980a). Thus all of the determinants of lignocaine clearance (hepatic blood flow, intrinsic clearance and plasma drug binding) may potentially be involved.

All of the previously quoted studies have confined themselves to estimates of plasma lignocaine. However, it is well recognised that conclusions concerning drug clearance can only be made on the basis of whole blood concentrations (Rowland, 1972) because drug in red cells is potentially available for elimination. In the present study, we have therefore measured whole blood, plasma and free drug concentrations during lignocaine infusions in patients with confirmed myocardial infarction compared with a group of control patients admitted with chest pain who did not develop objective signs of infarction.

Methods

Patients

The subjects of the present study were ten patients admitted to the Duke University Medical Center Coronary Care Unit (CCU) with chest pain who were

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given prophylactic lignocaine therapy. Five of these patients subsequently developed objective signs of myocardial infarction (Q waves and/or a myocardial creatinine phosphokinase band), while the others did not (controls). None of the patients had evidence of pre-existing renal or hepatic failure, and all of them recovered after an uncomplicated clinical course. All patients received a laxative (methyl cellulose) while in the coronary care unit and sublingual GTN when necessary. No other drugs were given apart from to control patient No. 3 who was a known hypertensive and continued to receive propranolol, hydralazine, frusemide and digoxin. Three of the patients with myocardial infarction and one control patient had mild (Killip Class II) heart failure.

Lignocaine regimens

Each patient received a priming dose of 75 mg lignocaine hydrochloride over 2 min followed by 150 mg over the next 18 min, either as a constant infusion or as 3, 50 mg injections. Both loading regimens were followed by a constant infusion of 2 mg/min throughout the study period.

Blood sampling and assay

Blood samples (10 ml) were obtained through a non-heparinised cannula or by separate venepuncture 12 h after beginning lignocaine and again at the end of therapy which lasted for 36–72 h. Blood samples were transferred to an all-glass tube (with a teflon screw cap) containing 10 U/ml heparin. This collection method has been shown not to interfere with either the assay of lignocaine or the determination of its plasma binding (Stargel *et al.*, 1979).

Blood and plasma (1 ml) were assayed for lignocaine and its metabolites glycylxylidide (GX) and monoethylglycylxylidide (MEGX) by the high performance liquid chromatographic method of Nation *et al.* (1979).

Plasma lignocaine binding was estimated by equilibrium dialysis at pH 7.4 and 37°C after spiking with [^{3}H]-lignocaine as described by Routledge *et al.* (1980a). Free lignocaine concentration was calculated as plasma concentration × the fraction of free drug determined by dialysis.

AAG concentrations were estimated by an immunodiffusion method (Mancini *et al.*, 1965).

Pharmacokinetic modelling

The apparent clearance of lignocaine from blood (Cl_B) was calculated as

$$Cl_B = \frac{I}{C_B} \quad (1)$$

where I is the infusion rate and C_B lignocaine blood concentration.

The effects of plasma binding changes was assessed using the venous equilibration model of hepatic drug clearance (Rowland *et al.*, 1973), modified to account for altered binding in blood (Shand *et al.*, 1976) according to which whole blood clearance.

$$Cl_B = Q\left(\frac{Cl_i' f_B}{Q + Cl_i' f_B}\right) \quad (2)$$

in which Q is liver blood flow Cl_i' is the intrinsic clearance of free drug and f_B is the fraction of free drug in blood which was calculated as

$$f_B = f_p \div B/P \quad (3)$$

in which f_p is the fraction of free drug in plasma and B/P the blood/plasma concentration ratio.

To model the effects of altered f_p on Cl_B alone, Cl_i' was calculated from the 12 h data for $Cl_B \cdot f_B$ at the end of the infusion was used to calculate the predicted value for Cl_B using equation (2).

Statistical methods

The changes in the various parameters seen with time were analysed using a paired *t*-test and a *P* value less than 5% was considered significant.

Table 1 Comparison of parameters obtained after 12 h and at the end of maintenance infusion of lignocaine (2 mg/min) in patients with myocardial infarction (MI) and controls (mean ± s.d.).

	MI		*Control*	
	12 h	*End*	*12 h*	*End*
Blood concentration (B) (μg/ml)	2.32 ± 1.14	3.11 ± 0.71*	2.37 ± 0.42	2.51 ± 0.18
Plasma concentration (P) (μg/ml)	3.20 ± 1.10	4.81 ± 0.84*	2.80 ± 0.38	2.99 ± 0.20
B/P	0.70 ± 0.07	0.64 ± 0.05*	0.85 ± 0.08	0.84 ± 0.05
% free drug	0.26 ± 0.05	0.20 ± 0.04*	0.31 ± 0.03	0.33 ± 0.05
Free concentration (F) (μg/ml)	0.81 ± 0.26	0.94 ± 0.14	0.87 ± 0.12	1.00 ± 0.15*
AAG	126 ± 38	166 ± 40*	91 ± 20	93 ± 19

* significantly different from 12 h value, $P < 0.05$.

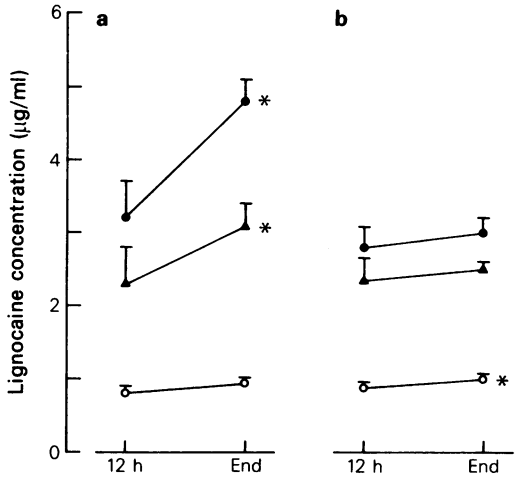

Figure 1 Changes in blood (▲), plasma (●) and free (○) lignocaine concentrations between 12 h and the end of a constant infusion of 2 mg/min of lignocaine in (a) myocardial infarction patients and (b) controls. *denotes a statistically significant difference between the value of the end of infusion and that at 12 h.

Results

The changes in the measured parameters with time are shown in Table 1. Whole blood, plasma and free lignocaine concentrations at 12 h and the end of the infusion (E) are compared in control and myocardial infarction patients in Figure 1. In control patients, neither whole blood or plasma levels changed significantly, but free drug concentration rose consistently, although the average change was small (15.2 ± 8.9%). In contrast, patients with myocardial infarction showed an increase in plasma concentrations, but not free drug concentrations. While whole blood concentration rose significantly, the increase was smaller than that in total plasma concentration (mean ± s.d., 0.8 ± 0.65 *v* 1.6 ± 0.88 μg/ml, $P < 0.001$). The discrepancy between the changes in whole blood and plasma concentrations was reflected in a reduction in the blood/plasma concentration ratio (B/P) at the end of the infusion in myocardial infarction patients, which was associated with a decrease in % free drug and an increase in AAG (Table 1).

In order to assess how much the increase in plasma binding alone might affect blood lignocaine clearance, the 12 h free intrinsic clearance was calculated for each patient, using the venous equilibration model (see **Methods**). Using this value, the whole blood clearance predicted at the end of the infusion was calculated using the observed value for binding in blood (Table 2). While there was a tendency for the observed clearance to be lower than that predicted in patients with myocardial infarction, the difference was not significant. Interestingly, in the control patients the observed blood clearance at the end of the infusion was significantly lower than the predicted value ($P < 0.05$).

The changes in lignocaine metabolites (GX and MEGX) are shown in Table 3. Blood and plasma GX concentrations did not change significantly in either patient group. Blood and plasma MEGX concentrations rose uniformly in control patients (though the change was not statistically significant), but not in patients with myocardial infarction. The ratio of lignocaine/MEGX concentrations in whole blood and plasma is illustrated in Figure 2. This ratio increased with time in patients with infarcts, but decreased in controls, the difference in the changes being significant ($P < 0.02$).

Discussion

Before discussing the effects of myocardial infarction, the kinetics of the drug in the control group should be addressed, especially with regard to the

Table 2 Patient details and predicted (Pred) and observed (Obs) effects of increased plasma binding on lignocaine whole blood clearance (Cl_B) at the end of infusion.

MI patients	*Age (years)*	*Sex*	*Weight (kg)*	*Presence of heart failure*	*Admission BP (mmHg)*	Cl_B *predicted*	Cl_B *observed*
1	43	M	77.7	+	126/82	1.05	0.67
2	54	M	78.8	+	130/80	0.62	0.44
3	64	F	75.5	+	150/66	0.42	0.44
4	38	M	82.8	0	110/70	0.93	0.67
5	79	M	72.9	0	148/90	0.61	0.66
Control patients							
1	64	M	75.0	0	160/80	0.86	0.75
2	52	F	49.0	0	92/64	0.72	0.69
3	61	M	72.0	+	190/98	0.68	0.62
4	45	M	81.6	0	132/98	0.77	0.69
5	53	M	79.4	0	140/100	0.88	0.70

Table 3 Changes (mean ± s.d.) in GX and MEGX concentrations during a lignocaine infusion in patients with MI and controls.

	Blood		*Plasma*	
	12 h	*End*	*12 h*	*End*
GX concentration (μg/ml)				
MI	0.21 ± 0.07	0.23 ± 0.06	0.44 ± 0.23	0.41 ± 0.31
Control	0.34 ± 0.27	0.46 ± 0.51	0.34 ± 0.17	0.37 ± 0.20
MEGX concentration (μg/ml)				
MI	0.39 ± 0.13	0.38 ± 0.06	0.37 ± 0.09	0.35 ± 0.13
Control	0.35 ± 0.20	0.55 ± 0.33	0.35 ± 0.27	0.59 ± 0.46

achieving of steady state. It is now recognized that, even in normal volunteers, the kinetics of lignocaine are non-linear. Thus Ochs *et al.* (1980) have recently shown that the plasma clearance of lidocaine during a continuous infusion (averaging 603 ml/min) is about 50% of that following a single i.v. dose. This is consistent with our observed value of 576 ml/min in control patients and raises the question of how long it might take to reach steady state. Unfortunately Ochs *et al.* (1980) did not report drug half-life after discontinuing the infusion which apparently reached steady state by 8 h, but did note that the half-life was greatly prolonged. Given that the half-life might be prolonged two-fold (to say 3 or 4 h) then 12 h should have been sufficient time to establish steady state in our control patients. This is supported by the observation that neither blood nor plasma concentrations changed between 12 h and the end of an infusion lasting 36–60 h. Interestingly, free drug concentrations rose uniformly in all controls despite the fact that neither plasma binding nor B/P changed significantly. Thus none of the determinants of free drug concentration changed consistently. In a previous study four of six controls had an increase in free drug concentration (Routledge *et al.*, 1980b). End-product inhibition has been raised as an explanation for the non-linear kinetics of lignocaine. In the present study GX levels remained stable, but both blood and plasma MEGX concentration rose so that the ratio of lignocaine to MEGX fell significantly by the end of the infusion in the controls. This continued rise in MEGX is consistent with a longer half-life than the parent drug. Whether this resulted in a reduced drug clearance is unclear, but in view of these findings we feel that the steady state seen for plasma and blood concentrations should be termed apparent.

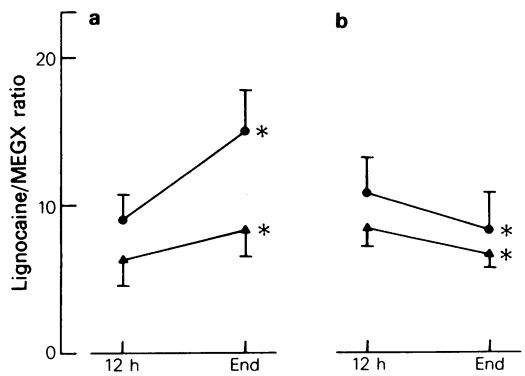

Figure 2 Changes in the ratio of lignocaine concentration to its metabolite (MEGX) between 12 h and the end of a constant infusion of lignocaine (2 mg/min) in (a) myocardial infarction patients and (b) control patients. *denotes a statistically significant difference between the end of the infusion and 12 h.

In contrast to the situation in control patients, both blood and plasma concentration increased significantly following infarction, as did plasma lignocaine binding and AAG. Further, the changes in plasma binding are entirely consistent with the increase in AAG. The major objective of the present study was to gauge how much the alteration in plasma binding might contribute to the changes seen in circulating drug concentrations. The reduction in the B/P concentration ratio is certainly consistent with a redistribution of drug out of red cells and perhaps leucocytes as a result of enhanced plasma binding. This redistribution of lignocaine would contribute to the rise in plasma concentrations and also explains why whole blood concentrations rose less (47%) than those in plasma (61%). Most importantly, enhanced binding was responsible for the fact that free drug concentration did not rise significantly despite the rise in both blood and plasma concentration.

Perhaps the most critical question is whether enhanced plasma binding could produce the rise in whole blood concentration by reducing lignocaine clearance. We cannot give a definitive answer because hepatic blood flow was not measured, but pharmacokinetic modelling suggests that altered plasma binding could affect lignocaine clearance, because during a prolonged infusion the putative hepatic extraction falls in the intermediate range. Thus a fall in blood clearance from an average of 854 to 726 ml/min in the myocardial infarct patients was predicted on the basis of enhanced binding in blood alone. Although observed and predicted values were

not significantly different the average observed value was certainly lower (576 ml/min). This raises the question of whether another factor(s) may be involved, and possibilities include a further fall in intrinsic clearance and/or liver blood flow.

It also seems likely that some degree of extravascular drug redistribution would occur as the result of enhanced plasma binding, thereby reducing the apparent volume of distribution. While such an effect would not alter steady-state concentrations which depend only on drug clearance, the changes seen during lignocaine accumulation occur continuously for at least 48 h. Under these circumstances any contribution of a decreased volume of distribution would depend on the relative time course of the changes in redistribution and drug clearance. This is clearly a most complex situation that will require further experimental data before its resolution. However, the present data do suggest that two effects of enhanced binding (intravascular drug redistribution and reduced clearance) contribute to lignocaine accumulation following myocardial infarction.

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References

BAX, N.D.S., TUCKER, G.T. & WOODS, H.F. (1980). Lignocane and indocyanine green kinetics in patients following myocardial infarction. *Br. J. clin. Pharmac.*, **10**, 353–361.

LE LORIER, J., GRENON, D. & LATOUR, Y. (1977). Pharmacokinetics of lidocaine after prolonged intravenous infusions in uncomplicated myocardial infarction. *Ann. Int. Med.*, **87**, 700–702.

MANCINI, G., CARBONARA, A.O. & HEREMANS, J.F. (1965). Immunochemical quantitation of antigens by single radioimmunodiffusion. *Immunochemistry*, **2**, 235–254.

NATION, R.L., PENG, G.W. & CHIOU, W.L. (1979). High-performance liquid chromatographic method for the simultaneous determination of lidocaine and its *N*-dealkylated metabolites in plasma. *J. Chromatog.*, **162**, 566–473.

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.

PRESCOTT, L.F., ADJEPON-YAMOAH, K.K. & TALBOT, R.G. (1976). Impaired lignocaine metabolism in patients with myocardial infarction and cardiac failure. *Br. med. J.*, **1**, 939–941.

ROUTLEDGE, P.A., BARCHOWSKY, A., BJORNSSON, T.D., KITCHELL, B.B. & SHAND, D.G. (1980a). Lidocaine plasma protein binding. *Clin. Pharmac. Ther.*, **27**, 347–351.

ROUTLEDGE, P.A., STARGEL, W.W., WAGNER, G.S. & SHAND, D.G. (1980b). Increased α_1-acid glycoprotein and lidocaine disposition in myocardial infarction. *Ann. Int. Med.*, **93**, 701–704.

ROWLAND, M. (1972). Influence of route of administration on drug availability. *J. pharm. Sci.*, **61**, 70–74.

ROWLAND, M., BENET, L.Z. & GRAHAM, G. (1973). Clearance concepts in pharmacokinetics. *J. Pharmacokin. Biopharm.*, **1**, 123–136.

SHAND, D.G., COTHAM, R.H. & WILKINSON, G.R. (1976). Perfusion-limited effects of plasma drug binding on hepatic drug extraction. *Life Sci.*, **19**, 125–130.

STARGEL, W.W., ROE, C.R., ROUTLEDGE, P.A. & SHAND, D.G. (1979). Importance of blood-collection tubes in plasma lidocaine determination. *Clin. Chem.*, **25**, 617–619.

STENSON, R.E., CONSTANTINO, R.T. & HARRISON, D.C. (1971). Interrelationships of hepatic blood flow, cardiac output and blood levels of lidocaine in man. *Circulation*, **43**, 205–212.

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

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