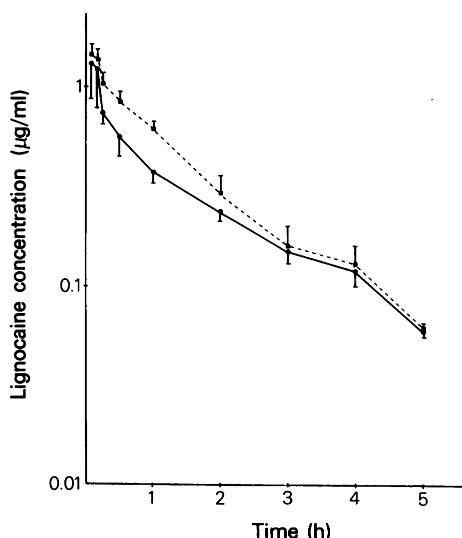

Figure 2 A significant correlation between the plasma and saliva levels of lignocaine was found after a single 100 mg intravenous injection of 100 mg lignocaine. y = 0.14 + 1.20 x, r = 0.78, P<0.001, n = 77.

markedly affected by the degree of ionization in the organism (Paxton, 1979). The pKa value of lignocaine is 7.86 (Newton & Kluza, 1978), and, therefore, due to the slightly acidic pH of saliva (about 7.0) relative to plasma (about 7.4), the concentrations of the weak basic compounds, like lignocaine, in saliva will be higher than in plasma (Danhof & Breimer, 1978).

In one unpublished preliminary study (n = 3, see Danhof & Breimer, 1978) the mean salivary/plasma ratio was 1.78±0.39 (range 1.45–2.21). In this study we found that this ratio is dependent on the time sequence after the drug administration. For at least 3 h after the intravenous drug injection the levels in saliva and plasma were comparable. Therefore, in the elimination phase of lignocaine the salivary samples might be clinically useful in the monitoring of lignocaine therapy. However, due to physiological determinants, there are great interindividual differences in the plasma levels of this agent, and, furthermore, age and diseases have a prominent effect on the pharmacokinetics and pharmacodynamics of lignocaine (Benowitz & Meister, 1978; Paxton, 1979). In addition, there are some limitations in our study: despite the standard stimulus used, saliva pH may have varied both intra- and interindividually, free drug concentrations in plasma were not determined, and the study was performed under ideal conditions in healthy volunteers. In a clinical situation during lignocaine infusion, the saliva/plasma ratio of lignocaine concentrations will differ from that found in this study after a single intravenous injection. Thus, in our opinion, the measurement of lignocaine concentrations in saliva for the determination of clinical drug effect needs further clinical studies, especially during a continuous intravenous infusion.

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6β-HYDROXYCORTISOL EXCRETION IN RELATION TO POLYMORPHIC *N*-OXIDATION OF SPARTEINE

6β-Hydroxycortisol is a minor metabolite of cortisol produced by the microsomal mixed-function oxidases (Frantz *et al.*, 1961). Measurement of urinary 6β-hydroxycortisol excretion provides a simple non-invasive technique for investigating enzyme induction in man (Ohnhaus & Park, 1979). There is now direct evidence for multiple forms of cytochrome P-450 in man (Boobis *et al.*, 1981), but it is not known

which form(s) is responsible for the 6β-hydroxylation of cortisol.

Sparteine, an antiarrhythmic and oxytocic drug, exhibits polymorphism of its metabolism. Two distinct phenotypes, 'metabolizers' and 'non-metabolizers' of sparteine can be observed. In population studies it was observed that some subjects had a gross impairment of sparteine metabolism as these subjects excreted only traces of the sparteine metabolites and more than 90% of the dose as unchanged drug in urine. These subjects were designated as 'non-metabolizers'. The frequency of the 'non-metabolizers' phenotype of sparteine occurs in about 5% of the German population. It was demonstrated that the metabolism of sparteine is determined by two allelic genes at a single gene locus, whereby 'non-metabolizers' are homozygous for an autosomal recessive gene (Dengler & Eichelbaum, 1977; Eichelbaum *et al.*, 1979). The metabolites of sparteine have been identified as 2- and 5-dehydrosparteines. Studies carried out by Spiteller & Spiteller (1979) have demonstrated that these dehydro-metabolites are probably formed from sparteine N_1-oxide which rearranges under the loss of water to 2- and 5-dehydrosparteine. Alternatively, these two dehydrosparteine metabolites could also be formed by dehydration of 2-hydroxysparteine. Based on the results of their experimental data, Spiteller & Spiteller (1978) favour *N*-oxidation as a primary metabolic reaction in sparteine metabolism. Studies with rat liver microsomes and isolated perfused rat livers have shown that sparteine metabolism occurs in a cytochrome P-450 dependent reaction (Dengler & Eichelbaum, 1977). Therefore it is quite likely that in subjects with defective metabolism of sparteine one form of cytochrome P-450 is functionally absent or inadequate.

Thus, since both cortisol and sparteine are metabolized via a cytochrome P-450 dependent reaction, it was of interest to see whether or not the impaired metabolism of sparteine also extends to the 6β-hydroxylation of cortisol. In 26 subjects who have been phenotyped according to their ability to metabolize sparteine the urinary excretion of 6β-hydroxycortisol was determined. Details of the phenotyping procedure have been described previously (Eichelbaum *et al.*, 1979). In the original description of our phenotyping procedures subjects with a metabolic ratio of >180 were designated as 'non-metabolizers' and subjects with a metabolic ratio below 180 as 'metabolizers'. In the initial description of the method, the same extraction efficiency of sparteine and its dehydro-metabolites was assumed. With the synthetic dehydrosparteines, which recently became available, the yield of the extraction for the metabolites was found to be only 50% of the parent drug. In addition, adsorption of the dehydro-metabolites to the gaschromatographic column support was observed at low concentrations of these metabolites. By using a different brand of column support (Applied Science Laboratories) these difficulties could be avoided. Furthermore, urine samples from poor metabolizers were concentrated 10 times. As a result of these changes in methodology, lower metabolite concentrations could be detected. Therefore, subjects who were previously defined as 'non-metabolizers' are now designated as 'poor metabolizers' since in these subjects traces of the 2-dehydro-metabolite could be detected. Thus, the sparteine to dehydrosparteine metabolic ratio values are now lower than previously reported. Subjects with a metabolic ratio >20 were designated as 'poor metabolizers' and subjects with a metabolic ratio <20 as 'metabolizers'. Urinary 6β-hydroxycortisol was measured by radioimmunoassay (Park, 1978). chloroform extractable urinary 17-hydroxycorticosteroids spectrophotometrically (Sanghvi *et al.*, 1973) and the results from these measurement are shown in Table 1. From the table it can be seen that there is no difference in 6β-hydroxycortisol excretion between the metabolizers and poor metabolizers of sparteine, indicating that different forms of cytochrome P-450 are responsible for cortisol 6β-hydroxylation and sparteine oxidation, and that the two biotransformations are controlled by different enzyme systems. The values obtained for 6β-hydroxycortisol excretion and the 17-hydroxycorticosteroid concentrations were similar to those obtained in previous studies (Park, 1981).

In recent studies it was shown that the metabolism of sparteine is closely related to the metabolism of debrisoquine. Poor metabolizers of sparteine were poor debrisoquine hydroxylators (Bertilsson *et al.*, 1980a, b; Inaba *et al.*, 1980; Eichelbaum *et al*, 1982); as for sparteine, a genetic polymorphism of the hydroxylation of debrisoquine has been demonstrated (Maghoub *et al.*)

This indicates that the metabolism of sparteine and debrisoquine is controlled by similar if not identical genetic factors. However, the metabolism of antipyrine, which is quite frequently used as a 'model drug' in clinical pharmacological studies, is not related to sparteine or debrisoquine metabolism. Thus, antipyrine metabolism seems to be carried out by different enzyme systems (Bertilsson *et al.*, 1980; Danhof *et al.*, 1981; Eichelbaum *et al.*, submitted for publication).

Although poor metabolizers of sparteine exhibit a normal antipyrine and cortisol metabolism they are, nevertheless, deficient in an oxidative reaction in drug metabolism, thus demonstrating that care should be exercised in extrapolating data obtained from so-called 'model drugs'.

In animal experiments using the marmoset monkey (*Callithrix jacchus*) it has been shown that cortisol 6β-hydroxylation is not associated with cyto-

Table 1 Urinary 6β-hydroxycortisol, chloroform-extractable 17-hydroxy-corticosteroids and sparteine metabolites in sparteine 'metabolisers' and 'poor-metabolisers' in relation to sparteine metabolism phenotype

Number	*Age (years)*	*Sex*	*Smoking habit*	*6β-OHC (μg/12 h)*	*6β-OHC/ 17-OHCS*	*Sparteine/ dehydrosparteine*
					Metabolisers	
1	29	M	NS	172	2.96	0.44
2	24	M	NS	103	2.82	0.72
3	24	M	S	138	1.33	0.30
4	26	M	NS	173	2.21	1.00
5	23	M	NS	157	3.93	0.74
6	23	M	NS	122	4.02	0.68
7	24	F	NS	107	4.14	0.41
8	25	M	S	88	3.36	0.31
9	30	F	NS	120	4.85	0.55
10	23	M	NS	196	4.08	0.28
11	27	F	NS	109	4.16	0.24
12	23	M	NS	275	4.63	0.49
13	25	M	NS	171	6.04	0.51
Mean±s.d.				148±50	3.73±1.21	
					Poor metabolisers	
1	25	F	S	136	1.68	110.0
2	25	M	S	234	3.27	64.8
3	52	F	NS	195	4.93	64.0
4	18	M	NS	122	4.68	55.2
5	24	M	S	175	4.68	79.3
6	61	F	NS	121	1.69	65.9
7	34	F	S	125	5.20	51.5
8	30	M	S	183	4.24	65.0
9	25	F	NS	242	3.79	49.2
10	28	F	NS	123	6.06	53.9
11	23	M	NS	120	3.08	46.2
12	28	M	NS	178	2.88	83.9
13	24	M	NS	185	5.60	29.9
Mean±s.d.				164±43	3.98±1.40	

NS = nonsmoker, S = smoker

chrome(s) P-450 induced by 3-methylcholanthrene (Challiner *et al.*, 1980, 1981). Thus, although the excretion of urinary 6β-hydroxycortisol is increased by a wide range of enzyme inducing agents in man (Park, 1981), there is still some selectivity in the forms of cytochrome P-450 responsible for its production.

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PHARMACOKINETICS OF NOMIFENSINE AFTER A SINGLE ORAL DOSE

Nomifensine (8-amino-2-methyl-4-phenyl-1,2,3,4,-tetrahydroisoquinoline, Merital, Hoechst) is a clinically effective anti-depressant agent, structurally distinct from the monoamine oxidase inhibitors and tricyclics (Brogden *et al.*, 1979). The pharmacokinetics of the drug in man have been studied by several authors. Heptner *et al.* (1977) administered ^{14}C-labelled nomifensine as a single oral dose. The half-life of elimination of 'total' nomifensine was 1.6 h and of nomifensine was 1.9 h. Other studies, using various dosages of unlabelled drug, have reported the half-life of elimination of nomifensine between 1 and 5 h (Vereczkey *et al.*, 1975; Chamberlain & Hill, 1977; Bailey *et al.*, 1977). These studies have been conducted in healthy male volunteers and little information is available on the kinetics in females. In one healthy female volunteer, the half-life of nomifensine elimination was 2.2 h (Dawling *et al.*, 1980).

The validity of these initial kinetic studies has been questioned due to the observation that nomifensine exists in plasma as both the unconjugated drug and an acid-labile conjugate (Heptner *et al.*, 1978) which is thermally unstable in plasma (Dawling & Braithwaite, 1980; McIntyre *et al.*, 1981a). The method of blood sample collection is then important for a reliable estimation of plasma concentration. This may account for the poor correlation observed between different methods of nomifensine measurement (Chamberlain & Hill, 1977). The present investigation was carried out to reassess nomifensine kinetics in both male and female volunteers. A preliminary report of this work was presented at the World Conference on Clinical Pharmacology and Therapeutics, London, 3–9 August, 1980.

Twelve healthy volunteers of average height and weight (6M, mean age 24.0±2.0 years; 6F mean age 22.3±3.7 years) took part in the study after giving informed consent. None was receiving other psychotropic drugs. One female volunteer was taking an oral contraceptive (Microgynon ED 30, Schering), one male and one female volunteer were smokers. Each volunteer received 100 mg (2 × 50 mg capsules) of nomifensine with 100 ml of water.

Venous blood samples (20 ml) were collected prior to the dose, 8–9 samples were taken from an