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## COMMUNICATIONS

In communications with more than one author, an asterisk (*) denotes the one who presented the work.

### CSF plasma ratios of propranolol and pindolol in man

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(Introduced by P. TURNER)

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Although some β-adrenoceptor antagonists have been shown to be effective in the treatment of a variety of central nervous system disorders such as schizophrenia, anxiety, tremor (Conway, Greenwood & Middlemass, 1978), it is not resolved whether their mechanism of action is centrally or peripherally mediated. Both propranolol and pindolol are known to produce central effects in man such as sleep disturbances, visual and tactile hallucinations (Prichard & Gillam, 1964; Stephen, 1966; Shaw & England, 1977) and propranolol has been shown to be concentrated in brain tissue in animals and man whereas the more water soluble atenolol was present in extremely low concentrations (Day, Hemsworth & Street, 1977; Myers, Lewis, Reid & Dollery, 1975).

We previously reported cerebrospinal fluid (CSF)/plasma ratios for propranolol in 15 patients (Taylor, Carroll & Turner, 1978), and have now extended this to 24 patients treated with propranolol, seven with pindolol and five with atenolol, the drugs being used as anxiolytics before routine lumbar puncture. Samples were obtained 1, 2 or 3 h after a single dose of 80 mg propranolol and 3 h after a single dose of 160 mg. In 9 patients 40 mg or 80 mg propranolol was administered twice daily for a minimum of 48 h; samples were taken 3 h following the last dose. A mean CSF/plasma ratio of 0.067 was obtained for the lipophilic drug propranolol. This ratio appeared independent of the time after administration.

Six patients received 5 mg or 10 mg pindolol twice daily for a minimum of 48 h. Samples of CSF and plasma were collected 3 h after the last dose in five patients and 16 h in one patient. A mean CSF/plasma ratio of 0.445 was obtained for pindolol, a moderately lipid soluble drug.

In five patients who received 100 mg atenolol twice daily for 3 days, the concentration of this hydrophilic drug in the CSF was found to be independent of plasma concentration and constant at about 0.2 μg/ml.

Plasma protein binding in nine patients taking propranolol and in six taking pindolol was measured using equilibrium dialysis at 37°C. Means of 89.9% and 60.0% were found for the binding of propranolol and pindolol respectively. Atenolol is only about 3% bound to plasma proteins (Barber, Hawksworth, Kitteringham, Peterson, Petrie & Swann, 1978).

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## Metformin: absorption and disposition in healthy subjects and in diabetic patients


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Description of the kinetics of metformin may help to identify risk factors for the development of biguanide-associated lactic acidosis.

Using g.l.c. (Lennard, Casey, Tucker & Woods, 1978), we have measured metformin concentrations in body fluids of three groups of subjects: Group I—four young healthy males given single doses of 0.25 g i.v., 0.5 g and 1.5 g p.o. as Glucophage® tablets, in a cross-over design; Group II—four newly diagnosed diabetic patients given a single 1.0 g oral dose followed by 0.5 g twice daily; Group III—eight diabetic patients given a single 1.0 g oral dose.

After i.v. injection (Group I), 79% ± 5% (s.d.) of the dose was recovered in the urine as unchanged drug after 72 h, with over 95% of this appearing within 8 h. None was found in faecal samples collected up to 5 days. Plasma data collected up to 12 h indicated a mean 'terminal' $T_{1/2}$ of 3.1 h (2–5.5 h) but urinary excretion rate data collected up to 60 h showed a mean 'terminal' $T_{1/2}$ of 14.2 h (11.0–19.9 h). After single doses (Groups I–III) peak plasma metformin concentrations and urinary excretion rates were observed between 1–3 h. In Group I subjects mean ± s.d. 72 h urinary recoveries of metformin were significantly ($P < 0.05$) lower after the 1.5 g dose compared to the 0.5 g dose (38% ± 7% *v.* 50% ± 12%). Corresponding mean ± s.d. faecal recoveries were higher (33% ± 14% *v.* 27% ± 11%). In Group II and III subjects urinary recoveries were 38% ± 7% and 33% ± 8%, respectively. Oral bioavailability mean ± s.d. estimated from plasma and urine data (Group I) was 64% ± 13% and 63% ± 14%, respectively (0.5 g) and 54% ± 22% and 48% ± 6%, respectively (1.5 g). Agreement between observed peak plasma metformin concentrations on days 7 and 14 of continuous treatment and those predicted from single dose data was excellent (Group II). However, trough concentrations were 95% higher than predicted reflecting the existence of an additional elimination phase undetected from 24 h single dose plasma data. On combining data from Groups I–III a linear correlation was found between the renal clearances of metformin and creatinine ($r = 0.85$; $P < 0.001$). Clearances of the latter ranged between 47–179 ml/min. Correlation between total oral clearance, a more important predictor of accumulation, and creatinine clearance was less good ($r = 0.66$; $P < 0.05$) owing largely to inter-subject variability in absorbed dose.

Sirtori, Franceschini, Galli-Kienle, Cighetti, Galli, Bondioli & Conti (1978) have suggested that the rapid elimination of metformin helps to explain a lower incidence of lactic acidosis compared to that seen with phenformin. Although our findings also indicate that

most of the absorbed dose is quickly excreted, a small fraction is cleared at a much slower rate. The significance of this for accumulation of the drug and the fate of the 20% of the dose unaccounted for after i.v. injection remain to be resolved. In patients with moderate renal impairment we suggest that creatinine clearance is not a reliable indicator of potential metformin accumulation.

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## Indomethacin in rheumatoid arthritis. Comparison of oral and rectal administration

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Indomethacin is an effective drug in rheumatoid arthritis and is often given by suppository at night. Huskisson, Taylor, Burston, Chuter & Dudley Hart (1970) compared oral and rectal administration of indomethacin 100 mg at night but only gave each preparation for one dose at a time. We have given indomethacin 100 mg at night (22.00 h) to thirteen hospital inpatients with definite or classical rheumatoid arthritis. After a 5 day period of placebo treatment each patient received in random order, the oral or rectal preparation for 7 days each using a double-blind, double-dummy cross-over technique. Each patient was assessed on 3 days at both 09.00 h and 14.00 h at the end of each period, using analogue pain score, digital joint size, articular index, grip strength, duration of morning stiffness, overall and comparative global assessment. Paracetamol was allowed as additional therapy and the number of tablets used in each period was counted. Indomethacin plasma concentrations were measured by gas liquid chromatography at 09.00 h on each assessment day and at 09.00, 11.00, 14.00 and 16.00 h on the final assessment day.

Significant improvements in clinical assessments after both oral and rectal indomethacin were seen, compared to the control value, except for digital joint size (Table 1) and these improvements were maintained at 14.00 on both treatment schedules. There were however no significant differences in the clinical assessments between the two routes of administration. The total number of side effects elicited was similar in both periods (seventeen in the oral period, eleven in the suppository period). However headache occurred more commonly in the oral (on nine occasions) than in the rectal period (on two occasions). Diarrhoea was noted on four occasions in the rectal period. The area under the plasma indomethacin concentration versus time curve (from 11 to 18 h) was $1758 \pm 187$ ng/ml × h during the oral treatment period and $1699 \pm 243$ ng/ml × h during suppository treatment ($P > 0.1$). Oral indomethacin 100 mg at night is as effective as the suppository and easier to administer.

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**Table 1** Indomethacin oral and suppository study (09.00 results)

| | *Control* | *Oral* | *Suppository* |
|---|---|---|---|
| Duration of morning stiffness (median) | 2.0 | 4.3* | 4.0* |
| Paracetamol tablets consumed/week (mean ± s.e. mean) | 24.9 ± 4.0 | 17.2* ± 4.0 | 18.8* ± 4.4 |
| Articular index (median) | 11.5 | 4.6* | 3.7* |
| Grip strength (median) (mm/Hg) | 88.0 | 146.3* | 137.3* |
| Pain score (median) max 5 | 3.2 | 1.3* | 1.3* |
| Digital joint size (median) (mm) | 569.0 | 567.3 | 573.6 |
| Mean ± s.e. mean plasma indomethacin (ng/ml) | — | 220.9 ± 28.9 | 200.3 ± 27.4 |
| Mean ± s.e. mean indomethacin plasma half-life (h) | — | 5.26 ± 0.67 | 6.31 ± 0.71 |

* $P < 0.01$ compared to control value.

## Factors influencing the dose of oral aminophylline

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Consecutive medical in-patients who were expected to benefit from oral aminophylline were treated with a controlled-release formulation, following a protocol which conformed with the manufacturer's dose recommendations. They received aminophylline 225 mg 12-hourly for 3 days, followed by 450 mg 12-hourly for 3 days provided there was no evidence of toxicity at the lower dose. Peak (3 h after dosing) and trough (12 h after dosing) plasma theophylline concentrations were measured at each dose level by both HPLC and enzyme multiplied immunoassay methods, results with the two assays showing good agreement (Eppel, Oliver, Smith, Mackay & Ramsay, 1978). Evidence of aminophylline toxicity was sought in a standard manner and without knowledge of the plasma theophylline concentration. Non-parametric statistical methods were used. The investigation was discontinued after 16 patients had entered because eight showed toxic symptoms (nausea and vomiting in seven, acute confusional state in one). In the 16 patients the primary diagnoses were chronic bronchitis (8), asthma (3) and left ventricular failure (5). There was a sevenfold variation between patients in both peak (4–28 μg/ml) and trough (3–23 μg/ml) plasma theophylline concentrations during treatment with aminophylline 450 mg daily. Theophylline concentrations were significantly lower in cigarette smokers ($P < 0.05$) and frequent drinkers (>1 alcoholic drink per day, $P < 0.02$), and higher in those with left ventricular failure ($P < 0.02$). These variables could not be separated statistically. There was a significant positive correlation between age and plasma theophylline concentration ($r_s = +0.84$, $P < 0.001$). This correlation was significant in non-smokers, infrequent drinkers and patients without left ventricular failure. Patients with toxicity had higher peak (20.8 μg/ml *v* 9.1 μg/ml, $P < 0.02$) and trough (18.0 μg/ml *v* 6.9 μg/ml, $P < 0.002$) plasma theophylline concentrations, but there was a large overlap between toxic and non-toxic measurements. Side-effects were observed with plasma theophylline concentrations well within the therapeutic range (5–20 μg/ml). Of five cigarette smokers none were toxic, whereas seven of eight non-smokers suffered toxicity ($P < 0.01$). Some method of dose adjustment is essential if aminophylline is to be prescribed safely. Toxic and therapeutic ranges of plasma theophylline are less clearly separated than the literature would suggest.

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## The effect of age and smoking on theophylline kinetics

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The rate of elimination of some metabolised drugs is reduced in the elderly (Crooks, O'Malley & Stevenson, 1976). Changes in smoking habit with age may contribute to observed differences in rate of metabolism (Vestal, Norris, Tobin, Cohen, Shock & Andres, 1975). In addition, it has been considered that drug absorption may be altered in old age but with the exception of digoxin (Cusack, Horgan, Kelly, Lavan, Noel & O'Malley, 1978) no age-dependant change has been observed.

To investigate further such aspects of age-related drug kinetics single dose studies of theophylline pharmacokinetics have been performed. Subjects were five young (age 21–30 years) and six elderly (age 67–86 years) non-smokers and eight young (age 20–33 years) and six elderly (age 67–79 years) cigarette smokers. Non-smokers received theophylline 125 mg orally and intravenously on separate occasions while smokers were given 125 mg theophylline intravenously. Plasma theophylline concentrations, drawn at intervals up to 32 h, were measured by HPLC.

**Table 1** Theophylline pharmacokinetics in young and elderly smokers and non-smokers

| | | $T_{\frac{1}{2}}$ (h) | $V_d$ area ($l\ kg^{-1}$) | Cl ($ml\ min^{-1}\ kg^{-1}$) |
|---|---|---|---|---|
| Young | Non-smokers | 7.6 ± 0.6 | 0.30 ± 0.03 | 0.46 ± 0.05 |
| | Smokers | 5.9*** ± 0.3 | 0.36 ± 0.03 | 0.72** ± 0.06 |
| Elderly | Non-smokers | 8.0 ± 0.2 | 0.36 ± 0.06 | 0.51 ± 0.08 |
| | Smokers | 5.9**** ± 0.3 | 0.36 ± 0.04 | 0.71* ± 0.06 |

* $P = 0.07$, ** $P < 0.02$, *** $P < 0.01$, **** $P < 0.001$.
Significance levels refer to differences between non-smokers and smokers for each age group using Student's $t$-test for unpaired data. Values are mean ± s.e. mean.

The rate parameters and extent of absorption for non-smokers were similar in both age groups as were values for volume of distribution, elimination half-life and plasma clearance. The comparison between non-smokers and smokers in respective age groups in Table 1 shows that clearance was significantly greater and half-life significantly shorter in young smokers. Although half-life values were significantly shorter in elderly smokers the increase in clearance did not reach significance because of the scatter of values in non-smokers.

It is concluded that theophylline absorption and other kinetic parameters are unchanged in old age. The more rapid elimination in young smokers indicates an effect of enzyme induction. The data are also suggestive of increased elimination in elderly smokers. Studies examining the effect of age on drug metabolism should take account of other factors, such as smoking habits, which may vary with age.

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## Altered lymphocyte β-adrenoceptor function in the elderly

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The number of specific binding sites in human lymphocytes for the β-receptor antagonist (−)-dihydroalprenolol is diminished in old age (Shocken & Roth, 1977). It is difficult, however, to gauge the significance of this finding since a maximum physiological response may be obtained when fewer than 1% of the total number of β-receptors are occupied (Levitski, 1976). We have, therefore, examined the rate of production of cyclic AMP in response to the specific β-agonist isoprenaline in lymphocytes from young and old subjects.

The groups consisted of six male geriatric patients aged from 61–81 years and six young male volunteers aged from 18–22 years. No subject included in the study was receiving any significant medication.

Lymphocytes were isolated by centrifugation of defibrinated whole venous blood on a ficoll-hypaque gradient (density 1.076) and aliquots of $10^6$ cells were incubated with a range of isoprenaline concentrations ($10^{-8}$ M to $10^{-4}$ M). Incubations were carried out in the presence of $5 \times 10^{-3}$ M theophylline at 37°C for 15 min. The cells were lysed and the extract deproteinized with TCA which was then removed by ether washing. Cyclic AMP was measured by a protein binding assay. Response was expressed as increase over baseline value (pmol per $10^6$ cells).

The mean increase over baseline for the young subjects was 2.0 pmol/$10^6$ cells at a concentration of $10^{-8}$ M isoprenaline and rose to a maximum (11.3 pmol/$10^6$ cells) at $10^{-5}$ M isoprenaline. In the elderly subjects the mean concentration of cAMP at $10^{-8}$ M isoprenaline showed no increase over baseline while a maximum (5.4 pmol/$10^6$ cells) was observed at $10^{-4}$ M isoprenaline. The increase in cAMP in both young and old was a linear function of the log concentration of isoprenaline between $10^{-8}$ M and $10^{-6}$ M isoprenaline. Covariance analysis of these linear portions showed no significant difference in slopes, but there was a significant difference in elevation ($P < 0.01$) with the line for the elderly displaced to the right.

These findings support the suggestion that altered receptor function plays a role in the changed responsiveness to drugs observed in the elderly. In particular, they are consistent with the observation of Shand, Vestal & Woods (1978) of a decreased cardiac responsiveness to isoprenaline in the elderly.

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## Propranolol kinetics in hyperthyroidism

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In a previous study, the rate of elimination of oral propranolol was not found to differ significantly between a group of patients with hyperthyroidism and another group with hypothyroidism (Bell, Russell, Nelson, Kelly & McDevitt, 1977). In apparent contrast, Feely, Crooks & Stevenson (1978) have reported that the mean plasma steady state propranolol level was significantly increased when hyperthyroid patients became euthyroid following surgery. We have investigated the effect of hyperthyroidism on propranolol kinetics following intravenous and oral administration of single doses.

Following an overnight fast, six female hyperthyroid patients, mean age 37 years (range 26–55 years) received propranolol 100 mg orally and 20 mg intravenously over 10 min on different occasions separated by at least 24 h. The order of administration was randomised. Through an indwelling venous cannula, 10 ml blood samples were collected before and at, 1, 2, 3, 4, 5, 6, and 8 h following the oral dose, and before, immediately after and at 0.5, 1, 2, 3, 4 and 6 h following the intravenous dose. Plasma was stored frozen until assayed by fluorimetry or by gas liquid chromatography. The study was repeated in each patient when she became euthyroid, following treatment.

The results are shown in Table 1. During hyperthyroidism, the mean elimination half-lives of propranolol were shorter after both oral and intravenous administration, although the differences did not achieve significance. Similarly, allowing for the increase in mean body weight with treatment, the mean apparent volume of distribution was larger in the hyperthyroid state, though not significantly so ($P > 0.2$). These effects, however, appear to be compounded in the significant increase in mean clearance found during hyperthyroidism ($20.8 \pm 2.5$ ml$^{-1}$ min$^{-1}$ kg$^{-1}$ compared to $11.7 \pm 1.7$ ml$^{-1}$ min$^{-1}$ kg$^{-1}$; $P < 0.05$).

Thus the clearance of propranolol appears to be increased in hyperthyroidism. The results of the present study are consistent with the previous findings (Bell *et al.*, 1977; Feely *et al.*, 1978).

**Table 1** Kinetic parameters for propranolol in six hyperthyroid patients before and after treatment

| *Parameter* | *Hyperthyroid* | *Euthyroid* |
|---|---|---|
| $T_{\frac{1}{2}}$ oral (h) | $3.20 \pm 0.54$ | $4.06 \pm 0.70$ |
| $T_{\frac{1}{2}}$ intravenous (h) | $2.55 \pm 0.33$ | $3.54 \pm 0.65$ |
| $V_d$ (l/kg) | $4.8 \pm 0.4$ | $3.8 \pm 0.5$ |
| Clearance* (ml$^{-1}$ min$^{-1}$ kg$^{-1}$) | $20.8 \pm 2.5$ | $11.7 \pm 1.7$ |

Results are mean of six patients ± s.e. mean.
* $P < 0.05$.

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FEELY, J., CROOKS, J. & STEVENSON, I.H. (1978). Alterations in plasma propranolol steady-state. *Clin. Pharmac. Ther.*, **22**, 112–113.

## Altered pharmacokinetics of propranolol in hyperthyroidism

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The plasma clearance of single doses of antipyrine (Crooks, Hedley, MacNee & Stevenson, 1973) and of other drugs (for review see Eichelbaum, 1976) is known to be increased in hyperthyroidism. Plasma propranolol steady-state concentrations are low in hyperthyroid patients and increase with correction of the condition suggesting an increased elimination of propranolol in hyperthyroidism (Feely, Crooks & Stevenson, 1978). This study reports on the pharmacokinetics of single doses of propranolol during chronic therapy.

Plasma propranolol was determined as previously by a specific gas liquid chromatographic method in five hyperthyroid patients receiving chronic treatment with propranolol (mean 368 mg/day) both when hyperthyroid and again when euthyroid. In addition the clearance and distribution of propranolol were studied following an infusion of [$^{14}$C]-propranolol (approximately 10 μCi–0.1 mg/kg) given to three of these patients when hyperthyroid and again when euthyroid.

During chronic treatment with propranolol, the levels at the beginning and at the end of a dosage interval were similar indicating that steady state had been achieved and the area under the plasma drug concentration $v$ time curve (AUC) during a dosing interval increased significantly ($P < 0.05$) from 405 ng ml$^{-1}$ h$^{-1}$ when hyperthyroid to 778 ng ml$^{-1}$ h$^{-1}$ when euthyroid. The results from the [$^{14}$C]-propranolol study, analysed by a non-linear least square regression computer program, suggest that an increased volume of distribution at steady-state makes a major contribution to the lower plasma propranolol steady-state concentrations seen in hyperthyroid patients. A decrease in the extent of plasma protein binding of propranolol found in this study may be one factor in this increased volume of distribution of propranolol.

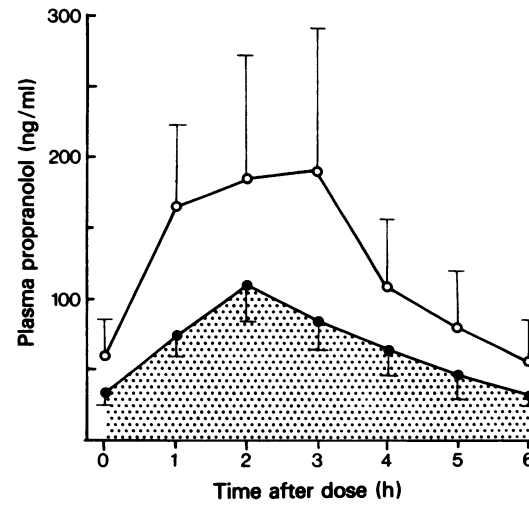


**Figure 1** Mean ± s.e. mean plasma propranolol concentrations during a dosage interval in five patients when hyperthyroid (●, AUC 405 ng ml$^{-1}$ h$^{-1}$) and again when euthyroid (○, AUC 778 ng ml$^{-1}$ h$^{-1}$). The difference between the AUCs was significant, $P < 0.05$.

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FEELY, J., CROOKS, J. & STEVENSON, I.H. (1978). Alterations in plasma propranolol steady state concentration in thyroid disorders. *Clin. Pharmac. Ther.*, **23**, 112–113.

## Plasma catecholamines and the acute effects of oral L-dopa in Parkinsonian patients

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Previous studies of catecholamine levels following L-dopa administration in Parkinsonian patients have employed a fluorimetric assay. We have used the more sensitive catechol-*O*-methyl transferase radioenzymatic method (Da Prada & Zurcher, 1976) to profile changes in plasma dopamine, noradrenaline and adrenaline and a modification of this method to assay L-dopa. These results have been related to alterations in both autonomic function and neurological disability. Six Parkinsonian patients were studied (five treated, one untreated). L-Dopa therapy was stopped for 48 h and then either 500 mg oral L-dopa or placebo was administered, employing a double blind randomised cross-over design, with a 48 h washout period between the two study days. Blood was taken for assay of plasma catecholamines and measurements of supine and erect blood pressure, heart rate and neurological disability were made at corresponding time intervals. Plasma L-dopa and dopamine attained peak levels within 4 h and then declined with half-lives of 1.74 $\pm$ 0.15 s.e. mean and 2.11 $\pm$ 0.24 s.e. mean h respectively. There was no rise in plasma noradrenaline or adrenaline. Indeed there was a significant fall in plasma noradrenaline (0.80 $\pm$ 0.24 s.e. mean to 0.36 $\pm$ 0.10 s.e. mean ng/ml, $P < 0.05$). This was maximal at 1 h. There was also a statistically significant fall in both supine and erect mean blood pressure following L-dopa ($P < 0.05$). Disability improved significantly after L-dopa and showed a close correlation with plasma dopamine ($r = 0.787$).

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## Amitriptyline overdosage: plasma concentrations and clinical features

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Poisoning with tricyclic antidepressant drugs is a common cause of admission to hospital and has a considerable morbidity. Diagnosis and prediction of the severity of the overdose can sometimes be difficult. In these cases measurement of the plasma antidepressant concentration may be useful.

The present study is based on the detailed follow-up by personal observation or questionaire of 28 cases of amitriptyline poisoning where the presence of significant amounts of other drugs was excluded. Blood samples were obtained within the first 24 h of ingestion, not more than 6 h after the time of maximum severity of symptoms. Plasma concentration of amitriptyline and its main active metabolite, nortriptyline, were measured using a specific and sensitive gas chromatographic procedure (Dawling & Braithwaite, 1978). Nineteen of the patients were female and nine male and their ages ranged between 11 and 75 years (mean 36 years). The plasma concentration of amitriptyline plus nortriptyline ranged between 267 and 3670 μg/l (median 990 μg/l). The ratio of amitriptyline to nortriptyline plasma concentration ranged between 0.8 and 18.9 (median ratio, 3.2). Table 1 shows the relationship between clinical features of the overdose and the plasma drug concentration recorded. Patients whose combined plasma drug concentrations were above 1000 μg/l had a higher incidence of severe complications, (convulsions, cardiovascular complications, prolonged coma or respiratory depression) than those with plasma drug concentrations below this figure ($P < 0.005$). All patients with plasma amitriptyline plus nortriptyline concentrations above 1300 μg/l developed one or more serious complications.

Our experience suggests that measurement of plasma concentrations of amitriptyline and other tricyclic antidepressants is potentially useful in two circumstances: (1) where diagnosis is difficult because of either unusual symptoms or uncertain patient history and (2) in severe poisoning in order to indicate the likely duration of toxic effects. In interpreting the

**Table 1** Combined plasma amitriptyline and nortriptyline concentrations in twenty-eight adult patients with amitriptyline overdose

| *Clinical feature* | *Median (μg/l)* | *Range (μg/l)* | *Clinical feature* | *Median (μg/l)* | *Range (μg/l)* | P* |
|---|---|---|---|---|---|---|
| Convulsions | 1420 | 571–3670 | No convulsions | 865 | 267–3600 | >0.05 (NS) |
| Coma lasting >24 h | 1420 | 560–3670 | Coma lasting <24 h | 770 | 267–1389 | <0.02 |
| Respiratory depression requiring artificial ventilation | 1420 | 560–3670 | Spontaneous respiration | 773 | 267–2000 | <0.02 |
| Cardiovascular complications** | 1405 | 773–3670 | No cardiovascular complications | 817 | 267–3660 | <0.05 |
| Severe poisoning*** | 1340 | 560–3670 | Mild poisoning | 665 | 267–1250 | <0.02 |

* Mann Whitney U-test (two-tailed).
** Hypotension, arrhythmia or conduction disturbance.
*** Defined as the presence of one or more of the symptoms listed above.

results for an individual patient, attention should be paid to the timing of the blood sample, the possible effects of other drugs which may also have been ingested and preceding events such as respiratory arrest.

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## The acute and chronic effects of oxprenolol on ambulatory blood pressure and heart rate in essential hypertension

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A 24 h intra-arterial blood pressure (BP) recording was carried out on an out-patient basis in 20 untreated patients with essential hypertension, using the 'Oxford' recording system (Millar-Craig, Hawes & Whittington, 1978). The recording was continued for a second 24 h period when treatment with oxprenolol 80 mgs t.d.s. was commenced. Treatment was then adjusted in the clinic to produce satisfactory BP control (mean daily oxprenolol dosage 344 mg). No placebo control period was used. Each patient was restudied after an average of 14 weeks chronic treatment. Data analysis, using a hybrid computer system (Cashman, Stott & Millar-Craig, 1979), allowed calculation of hourly pressures and heart rates. During the acute treatment period there was a reduction in daytime heart rate ($P < 0.01$), but no reduction in BP. Chronic treatment was associated with a reduction in daytime systolic and diastolic BP ($P < 0.01$), but had little effect during the night-time or early morning. Heart rate changes were similar to those observed during the acute treatment period. Reanalysis of the data relative to the time of waking showed that the antihypertensive effect observed during chronic treatment commenced 1 h after waking. It is concluded that in ambulatory patients chronic treatment with oxprenolol reduces daytime blood pressure. A reduction in daytime heart rate occurs during both acute and chronic treatment. Neither acute nor chronic treatment have much effect on either night-time BP or heart rate.

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## Tiamenidine, a centrally acting antihypertensive drug in essential hypertension

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We have investigated the hypotensive effect, pharmacokinetic properties and side effects of tiamenidine (2-chloro-4 methyl-3-(2'-imidazoline-2'-yl) amino thiopene hydrochloride), a clonidine like substance (Lindner & Kaiser, 1974).

Six male mild essential hypertensives, aged 43–57 years received a single oral dose of tiamenidine 1 mg, followed by a chronic dosing (0.2 mg three times a day for 3 days and 0.4 mg three times a day for 3 days) and a 2 day withdrawal period. Blood pressure and heart rate were measured supine and after 3 min standing. Plasma noradrenaline (NA) was measured radio-enzymatically (Henry, Starman, Johnson & Williams, 1975) and urinary catecholamines fluorimetrically. Plasma tiamenidine was measured by radioimmunoassay at different time intervals after a single oral dose of tiamenidine 1 mg.

Tiamenidine 1 mg orally induced a maximal fall in blood pressure after 4 h, from 153.2 ± 6.5/102.7 ± 3.4 mm Hg to 104.2 ± 5.1/71.8 ± 4.8 mm Hg (mean ± s.e. mean) lying and from 151.0 ± 8.4/108.0 ± 5.9 to 102.7 ± 8.2/78.2 ± 6.5 mm Hg standing ($P < 0.001$). Heart rate fell from 71.8 ± 5.3 to 67.3 ± 7.1 lying ($P < 0.05$) while on standing heart rate did not change. Concomitantly, plasma NA fell from 0.52 ± 0.05 ng/ml to 0.25 ± 0.04 ng/ml after 2 h and to 0.29 ± 0.09 ng/ml after 6 h ($P < 0.05$). Sedation, measured by visual analogue scales, was not very marked. Salivary flow (measured as g/min, by change in weight of pre-weighed dental cotton rolls) was reduced by 70% after 2 h. Peak plasma concentrations of 1.3–2.7 ng/ml were observed between 0.5–2.4 h with a half-life of 2.3–5 h after an oral dose of tiamenidine 1 mg. On chronic dosing, blood pressure fell by 15 mm Hg on tiamenidine 0.2 mg three times a day and by 20 mm Hg on 0.4 mm Hg three times a day. Urine NA fell from 53.75 ± 5.7 to 35.84 μg/g creatinine during treatment with tiamenidine. Urinary catecholamine levels did not exceed the pretreatment ones on withdrawal. There was no evidence of overshoot of blood pressure on withdrawal of tiamenidine.

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## Sotalol in the management of hypertension complicating pregnancy

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The administration to pregnant ewes of sotalol, a β-adrenoceptor antagonist with low lipid solubility, did not produce evidence of β-adrenoceptor blockade in the fetus: this was in contrast to the observed effects of propanolol and oxprenolol and suggested that sotalol did not cross the placental barrier (Truelove, Van Petten & Willes, 1973). To evaluate this possibility in humans, we have used sotalol to treat hypertension in 12 pregnant women. The study was approved by the ethical committee. Therapy was commenced with sotalol 200 mg orally each day prior to 32 weeks gestation and the dose increased as necessary to reduce blood pressure below 140/90 mmHg. Blood pressure was measured using a London School of Hygiene sphygmomanometer.

Umbilical cord blood, maternal blood and, where possible, amniotic fluid were collected at delivery. If a mother elected to breast feed, sotalol was continued post-partum and samples of breast milk obtained simultaneously with maternal blood samples. Blood and amniotic fluid specimens were centrifuged and all specimens were stored at −20°C until assayed by a spectrophotofluorimetric method modified from Garrett & Schnelle (1971).

Prior to treatment, the mean gestational age was 22.8 ± 1.9 weeks (range 10–31 weeks) and mean ± s.e. mean arterial pressure was 114.9 ± 3.1 mmHg. With a mean sotalol dose of 400.0 mg daily (range 200–800 mg), mean arterial pressure fell to 102.5 ± 4.5 mmHg.

Delivery occurred at mean gestational age of 37.7 ± 0.7 weeks: there were two spontaneous preterm labours in patients with pre-disposing factors other than hypertension. Twelve infants were liveborn with a mean weight of 2.8 ± 0.1 kg, and eight of them had no significant neonatal problems. Two of the other four died from severe congenital abnormalities, one had perinatal asphyxia and one mild transient hypoglycaemia.

At delivery, the mean umbilical cord plasma sotalol concentration was 1.7 ± 0.3 μg/ml which was similar to the mean maternal plasma levels of 1.8 ± 0.3 μg/ml. The maternal:fetal ratio was 1:1.05 (range 0.4–2.0). The mean amniotic fluid sotalol concentration in six patients was 7.0 ± 2.7 μg/ml.

In the five mothers who were breast feeding, simultaneous specimens of milk and blood were obtained on 20 separate occasions. The mean sotalol concentration in milk was 10.5 ± 1.1 μg/ml (range 4.8 to 20.2 μg/ml) compared to a mean plasma concentration of 2.3 ± 0.3 μg/ml—a plasma:milk ratio of 1:5.4 (range 2.2 to 8.8).

Thus sotalol reduced arterial hypertension in these patients but did cross the human placental barrier. The presence in the fetal circulation of sotalol concentrations similar to those in the mother would indicate that it offers no advantages over other β-adrenoceptor antagonists and its long elimination half-life (Brown, Carruthers, Kelly, McDevitt & Shanks, 1976) may be a disadvantage. The high concentrations of drug in breast milk, if repeated throughout each 24 h period, could result in the neonate ingesting pharmacologically active amounts of sotalol.

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## Effect of cimetidine on gastric pH in women undergoing elective Caesarean section

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Aspiration of acid gastric contents is a recognised hazard of obstetric anaesthesia. The risk is reduced by the preoperative administration of alkalis, but these often nauseate patients and are unreliable in their action. It would seem that the $H_2$ inhibitor cimetidine would offer a possible solution in this situation. This is a report of the administration of 200 mg intravenously approximately 60 min before operation in ten patients with a comparison with 16 untreated controls. Before embarking on the study we confirmed that it would have no influence on uterine tone or foetal heart rate (Dundee, McGowan & Moore, 1979) and no effect on cardiac output in adults.

**Table 1** Findings in fasting patients undergoing elective Caesarean section under general anaesthesia. Cimetidine (200 mg) was given intravenously to one group approximately 1 h before operation

| | *Control* | *Cimetidine (200 mg)* |
|---|---|---|
| *n* | 16 | 10 |
| Average duration of operation (min) | 60 | 58 |
| *At intubation* | | |
| pH over 2.5 | 2(1) | 10 |
| Average pH | 2.07 | 5.13 |
| Volume (ml) | 19.3 | 14.4 |
| *End of operation* | | |
| pH over 2.5 | 3(1) | 7(3) |
| Average pH | 2.36 | 6.27 |
| Volume (ml) | 11.2 | 3.3 |

pH difference—$P < 0.001$.
The figure in brackets indicates the number of patients in whom no aspirate was obtained.

The study was carried out in mothers at term who were expected to deliver normal healthy infants of equivalent gestation. Following a routine atropine-thiopentone-suxamethonium induction and tracheal intubation a gastric tube was passed and the volume and pH of aspirated contents noted. The results in Table 1 show that cimetidine is effective in reducing gastric acidity, although, as expected, it has no significant effect on gastric emptying.

The well-being of the neonate was comparable in the cimetidine and control groups. This drug is worthy of further study.

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## Cimetidine increases the action of warfarin in man

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The therapeutic combination of cimetidine and warfarin while unusual is not incompatible and an interaction could prove particularly undesirable. Previous studies in the rat (Leslie & Walker, 1971) reported no interaction between cimetidine and a wide variety of drugs including warfarin, although interactions with warfarin in man have recently been reported (Flind, 1978). We have studied the effects of cimetidine on the kinetics and dynamics of warfarin in man.

Seven healthy volunteers (four female, three male, aged 24–54 years) participated in the study. A daily dose of racemic warfarin was determined, for each volunteer, to prolong the prothrombin time (P.T.) by 3–5 s and this dose was continued throughout the study. After 2 weeks on warfarin alone cimetidine 200 mg three times daily and 400 mg at night was added for 3 weeks, followed by a final period when warfarin alone was given for a further 2 weeks. The P.T. was monitored regularly and plasma stored deep frozen for subsequent measurement of plasma warfarin concentration by gas chromatography (Kaiser & Martin, 1974), plasma protein binding of warfarin by equilibrium dialysis, and the prothrombin times by the standard one stage technique.

Cimetidine significantly ($P < 0.05$) prolonged the P.T. from 19.4 $\pm$ 0.6 s (mean $\pm$ s.e. mean) to 22.9 $\pm$ 1.4 s. When cimetidine was discontinued the P.T. fell significantly ($P < 0.01$) to 18.2 $\pm$ 1.1 s. Likewise, cimetidine produced a significant ($P < 0.02$) increase in plasma warfarin concentration from 0.96 $\pm$ 0.11 μg/ml to 1.76 $\pm$ 0.19 μg/ml; and when cimetidine was discontinued warfarin concentration fell significantly ($P < 0.02$) to 1.20 $\pm$ 0.15 μg/ml. Plasma protein binding of warfarin did not alter significantly during the study.

The interaction was investigated further in man and rat. Warfarin and antipyrine clearances were determined after single doses of each in four volunteers before and after cimetidine 400 mg four times a day for 2 weeks. Antipyrine in plasma was measured by radioimmunoassay (Chang, Wood, Dixon, Conney, Anderson, Eiseman & Alvares, 1976). Warfarin clearance decreased significantly ($P < 0.05$) from 3.40 $\pm$ 0.12 ml/min to 2.50 $\pm$ 0.26 ml/min and antipyrine clearance fell significantly ($P < 0.005$) from 34.49 $\pm$ 2.36 ml/min to 27.03 $\pm$ 2.77 ml/min after cimetidine. In the male Wistar rat cimetidine in doses from 30 to 120 mg/kg given by intraperitoneal injection 30 min before pentobarbitone increased significantly ($P < 0.001$) the sleeping time in a dose related manner. Saline controls 98 $\pm$ 9 min; cimetidine 120 mg/kg 410 $\pm$ 21 min. The waking concentrations of pentobarbitone in plasma were not significantly different. Zoxazolamine paralysis times were likewise prolonged from 229 $\pm$ 38 min with saline to 395 $\pm$ 39 min with cimetidine 120 mg/kg ($P < 0.05$).

Cimetidine appears to increase the anticoagulant effect of warfarin by inhibition of drug metabolism and care should be taken in concomitant therapy.

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## Effects of buffered aspirin and salicylate on the bio-electric potential difference across the human buccal mucosa

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The potential difference (P.D.) across the gastric mucosa has been used as an index of the integrity of the gastric mucosal barrier in animals and in man (Chvasta & Cooke, 1972; Bowen, Krause & Ivey, 1977). Agents such as ethanol, aspirin and bile salts damage the mucosal barrier resulting in increases in luminal sodium ion concentration, back-diffusion of hydrogen ion, and a reduction of the mucosal P.D. (Davenport, 1964). The basic similarities in the responses of the buccal and gastric mucosal P.D. may enable changes in the buccal P.D. to be used to measure functional mucosal damage caused by drugs or other agents (Huston, 1978). The present study was designed to investigate the response of the buccal mucosa to aspirin and salicylate.

Subjects of either sex (18–60 years) did not take any aspirin-like compounds within 1 week of the study. Buccal mucosal P.D. was measured with a silver-silver chloride probe and skin electrode (Huston, 1978). After a 3 min control period the subject held 20 ml of the test solution in the mouth for 3 min, the mouth was rinsed with 100 ml deionised water and buccal P.D. measured for a further 3 min.

Aspirin powder B.P. (600 mg suspended in 20 ml deionised water; pH 2.6) reduced the buccal P.D. from a resting value of $-44 \pm 4$ mV (mean ± s.e. mean; $n = 5$) to $-18 \pm 4$ mV ($P < 0.01$). Likewise, a solution of two soluble aspirin tablets B.P. (600 mg in 20 ml deionised water; pH 4.6) caused a comparable fall in buccal P.D. ($\Delta 19 \pm 3$ mV; $n = 11$). The fall with soluble aspirin (300 mg and 1200 mg) was $\Delta 4 \pm 2$ mV ($n = 5$) and $\Delta 15 \pm 2$ mV ($n = 5$) respectively. Two proprietary formulations of soluble aspirin and codeine caused comparable changes in buccal P.D. However, when the aspirin powder or soluble aspirin tablets were buffered to pH 7.0–7.5 with sodium bicarbonate solution (5% w/v), there was no significant fall in buccal P.D. Sodium salicylate (1200 mg in 20 ml deionised water; pH 4.4) likewise decreased buccal P.D. (from $-54 \pm 5$ mV to $-29 \pm 5$ mV; $P < 0.01$), an effect which was not apparent when the solution was buffered to pH 7.2. In control experiments, saline solutions buffered between pH 2.0–7.0 with citric acid and sodium bicarbonate had no effect on buccal P.D.

These experiments indicate that as with the human gastric mucosa (Bowen *et al.*, 1977) aspirin and salicylate can reduce human buccal mucosal P.D., which may reflect a topical irritant action. These P.D. changes appear to depend on the concentration of free $H^+$ ions available for diffusion, since buffering with sodium bicarbonate abolished this action as is seen with the human gastric mucosa (Bowen *et al.*, 1977). The abolition of the buccal P.D. change thus suggests a reduction in the direct topical irritant action of aspirin in buffered solutions. However, the buffering capacity of such formulations must take into account the gastric acidity in the stomach. Furthermore, since the direct topical action of aspirin-like compounds is only one of several factors promoting the formation of erosions and ulcers (Whittle, 1977), such formulation would not necessarily produce an aspirin-like derivative devoid of gastro-intestinal irritancy.

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## Uric acid excretion related to pharmacokinetics of frusemide

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The proposed mechanism for diuretic-induced uric acid retention is either competition for active tubular secretion between drug and uric acid (Mudge, 1975), or reduced renal clearance of uric acid secondary to extracellular fluid volume contraction (Steele, 1977). An increase in uric acid excretion immediately following diuretic administration and subsequent retention of uric acid favoured the latter, and suggested that homeostatic sodium-conserving mechanisms might be responsible (Roberts, Homeida, Roberts & Bogie, 1978). Such mechanisms are known to affect the relationship between plasma frusemide level and sodium excretion rate as diuresis proceeds (Branch, Roberts, Homeida & Levine, 1977).

The aim of this study was to examine the time course of the changes in urate clearance in response to frusemide and to relate them to pharmacokinetic measurements and sodium excretion.

Five healthy male subjects aged 20 to 29 years received an intravenous infusion of 80 mg frusemide over 60 min. Venous blood samples and urine were collected before the infusion, then at intervals of 10 min for 2 h and every 15 min for one further hour. Urine was subsequently collected until the end of 24 h. Plasma and urine frusemide levels were measured by the methods previously used (Branch *et al.*, 1977). Urine sodium, potassium and uric acid and plasma uric acid were measured using automated methods.

The peak plasma frusemide level and peak frusemide excretion rate occurred at the end of the frusemide infusion (60 min). They subsequently declined with half lives of 28 and 33 min respectively. Peak sodium excretion rate occurred at 30 min. There was a rise in urate clearance from $8.0 \pm 1.8$ ml/min to $17.6 \pm 2.0$ ml/min (mean ± s.e. mean) ($P < 0.05$) 20 min after the start of the infusion of frusemide. Urate clearance subsequently declined and fell below the baseline values. The relationships between the plasma frusemide and both sodium excretion rate and uric acid clearance demonstrated hysteresis so that excretion of uric acid and sodium was greater for a given frusemide level in the early part of the diuresis compared to the later part. Plasma uric acid rose from $0.34 \pm 0.4$ mmol/l to $0.37 \pm 0.4$ mmol/l at 3 h ($P < 0.05$).

The study has confirmed an early uricosuric response to frusemide. The simultaneous occurrence of uricosuria and maximal frusemide excretion makes competition for tubular secretion an unlikely mechanism for urate retention. It is postulated that the hysteresis in the relationship between plasma frusemide level and sodium excretion rate is due to stimulation of homeostatic sodium conserving mechanisms and that these mechanisms also effect changes in uric acid clearance.

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# Use of a linear variable differential transformer to measure compliance of human hand veins *in situ*

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For the investigation of direct drug effects and drug interactions on single human veins *in situ* two main methods are currently used. One is the venoconstriction test (Sicuteri, del Bianco, Fanciullacci & Franchi, 1964). Pressure in a dorsal vein of the hand is measured before and after local infusion of a drug producing venospasm. A computerized version of this test has been described (del Bianco & Sicuteri, 1978). The other important method relies on the measurement of venous diameter at a constant pressure. In its original version described by Nachev, Collier & Robinson (1971) an optical method is used. The subject is resting in a flat supine position. An arm is placed on a support sloping upwards at an angle of 30° from the horizontal, thus allowing complete emptying of superficial veins. A stereomicroscope is focused on a marked spot on the vein and refocused after inflation to 45 mm Hg of a sphygmomanometer cuff placed on the upper arm. The difference between the two positions of the microscope is a measure of the diameter of the studied vein under a congestion pressure of 45 mm Hg.

The latter method was used in particular for the assessment of the venoconstrictor action of dihydroergotamine after oral or local i.v. administration as well as to study its mode of action on human veins (Aellig, 1974).

Modifications have been developed with the aim to record venous diameter with an electromechanic device. Aminu & Vere (1972) used a small capacitor with one plate resting on a superficial hand vein, and the other on the skin beside the vein. White & Udwadia (1975) placed an arm of a displacement transducer over a marked spot on the vein. With both modifications a standardized pressure was used as in the original method.

A new, relatively simple variant for recording venous diameter at a given congestion pressure has been developed. It is based on a linear variable differential transformer. This is an arrangement of three identical coils of which the central one is energized by an alternating current (Schaevitz, 1947). The device is mounted with the aid of a small tripod directly on the back of the hand, thereby reducing the influence of hand movements. A light core weighing 0.5 g is placed over the summit of the vein under investigation. This core alters the voltage generated in the outer coils, and the changes are proportional to its displacement. As the device can be exactly calibrated, it allows the direct registration of the venous diameter at the chosen congestion pressure. This method has been used to establish dose-response curves for the venoconstrictor effects of various agents such as noradrenaline, adrenaline, 5-hydroxytryptamine, ergotamine and dihydroergotamine. Our first experience suggests that this rather simple method may prove to be useful for interaction studies with various agonists and antagonists on human hand veins *in situ*.

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## Pre and postsynaptic α-receptor agonists and the rate of release of noradrenaline in man

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α-Methylnoradrenaline (MNA) and phenylephrine (PE) possess predominantly pre- and post-synaptic α agonist properties *in vitro* (Langer, 1979). An improved index of the rate of release of noradrenaline (NAR) may be obtained by correcting endogenous plasma noradrenaline (NA) for individual values of clearance (Fitzgerald, Hossmann, Hamilton, Reid, Davies & Dollery, 1979). We have studied the effect of infusions of MNA and PE on NAR in man.

MNA, PE and saline placebo were each infused whilst the subjects spent 10 min supine and 5 min sitting, standing and submaximally exercising. The infusions were performed at subpressor and mildly pressor rates of MNA; Δ systolic BP + (5.65 ± 0.8 mm Hg) and PE + (5.82 ± 0.76 mm Hg). Plasma NA was measured radioenzymatically (Henry, Starman, Johnson & Williams, 1975). Clearance was derived from steady state plasma concentrations during an hour long infusion of (−)-NA (0.05 μg $kg^{-1}$ $min^{-1}$).

Plasma NA did not differ from placebo during subpressor or pressor infusions of MNA or PE during physiological activation of the sympathetic system (Table 1). There was a wide interindividual difference in NA clearance (15.8–2.25 l/min) which contributed to the range of supine plasma NA (0.3–2.1 nM). Despite this, the delta increases of plasma NA on change of posture and on exercise did not differ between individuals during the infusions. NAR was not altered from placebo values during MNA or PE infusions.

No evidence was found of a reduction in sympathetic activity by peripheral presynaptic α receptor agonism in man.

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**Table 1** Mean values of plasma noradrenaline (± s.e. mean) in five normotensive individuals. Methylnoradrenaline, phenylephrine and saline placebo infusions were maintained while the subjects changed posture and exercised

| | *Plasma noradrenaline (nM)* | | | | | |
|---|---|---|---|---|---|---|
| | *Methylnoradrenaline* | | *Phenylephrine* | | *Placebo* | |
| | *Subpressor* | *Pressor* | *Subpressor* | *Pressor* | (1) | (2) |
| Supine | 0.88 ± 0.39 | 1.29 ± 0.53 | 1.23 ± 0.33 | 0.9 ± 0.34 | 0.87 ± 0.32 | 1.45 ± 0.6 |
| Sitting | 1.47 ± 0.55 | 2.15 ± 0.86 | 2.22 ± 0.72 | 1.72 ± 0.6 | 1.47 ± 0.55 | 2.15 ± 0.86 |
| Standing | 3.08 ± 0.5 | 2.29 ± 0.5 | 3.79 ± 1.27 | 3.52 ± 0.81 | 2.20 ± 0.74 | 2.99 ± 0.8 |
| Exercise | 5.99 ± 1.4 | 8.08 ± 2.26 | 7.58 ± 2.9 | 7.46 ± 1.65 | 6.46 ± 1.06 | 7.18 ± 1.65 |

## Interaction of desipramine and ciclazindol with adrenergic mechanisms in the human iris

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Tricyclic antidepressants have a dual effect on the adrenergic synapse: they block the uptake of noradrenaline and tyramine into presynaptic terminals, and, at somewhat higher concentrations, block postsynaptic α-adrenoceptors (Westfall, 1973). It has been reported that the tricyclic antidepressant amitriptyline reduces the size of the dilator response of the pupil to tyramine (Szabadi, Besson & Bradshaw, 1975). It is not known, however, whether this effect is due entirely to the blockade of tyramine uptake, or whether it also reflects the blockade of α-adrenoceptors. In

the present experiments, we compared the effects of desipramine and ciclazindol on the dilator response of the pupil to tyramine, an indirectly acting sympathomimetic amine, and methoxamine, a directly acting α-adrenoceptor stimulant with no affinity for uptake mechanisms (Trendelenburg, Maxwell & Pluchino, 1970).

Healthy volunteers, aged between 18 and 30 years, were used. One drop of either of the following solutions was instilled into the conjunctival sac: tyramine hydrochloride (0.072 M, pH 4.0), methoxamine hydrochloride (0.04 M, pH 5.0). Photographs were taken of the eyes every 5 min over a period of 2 h (Sneddon & Turner, 1969). Sessions took place twice weekly over a period of 8 weeks. In Phase I (2 weeks) standard responses were established to the agonists. In Phase II (4 weeks) each subject took either desipramine hydrochloride (100 mg/day) or ciclazindol hydrochloride (100 mg/day) in two divided doses. Phase III (2 weeks) was the recovery phase after the administration of the antidepressant had been discontinued. Comparisons were made within subjects: mean responses for the last 2 weeks of Phase II were compared with those of the last week of Phase I and the last week of Phase III. Blood samples were taken at each session during Phases II and III to determine the plasma levels of the antidepressants.

The resting pupil diameter increased significantly ($P < 0.05$) in seven out of the nine subjects taking desipramine, and in ten out of the eleven subjects taking ciclazindol. In Phase III, the resting pupil size declined towards values obtained during Phase I in both groups.

The size of the response to tyramine was significantly reduced, in Phase II, in six subjects out of seven taking desipramine ($P < 0.05$) and in eight out of eleven subjects taking ciclazindol ($P < 0.01$).

The size of the response to methoxamine was significantly reduced, in Phase II, in all five subjects taking desipramine ($P < 0.001$) and in all six subjects taking ciclazindol ($P < 0.01$).

During the last 2 weeks of Phase II, the mean plasma level (±s.e. mean) of desipramine was 0.66 (±0.09) μM, and that of ciclazindol 5.7 (±0.47) μM.

The antagonism of the pupillary response to methoxamine by the antidepressants suggests that these drugs, in doses used clinically, block α-adrenoceptors, and thus this effect may also contribute to the reduction in the size of the response to tyramine.

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## Pharmacodynamic studies of verapamil after oral and i.v. administration in man

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The useful anti-arrhythmic drug, verapamil, undergoes extensive first-pass metabolism (Schomerus, Spiegelhalder, Stieren & Eichelbaum, 1976), so that the oral dose (*c.*120 mg) is approximately ten times the intravenous dose (*c.*10 mg). Animal work (Neugebauer, 1978) suggests that the metabolites are, for practical purposes, inactive. As a potent calcium-blocker the useful effect of verapamil is to impair conduction in the calcium-dependant cells of the atrioventricular node, which are responsible for the major delay of the PR interval in the conventional electrocardiogram. In view of the stability of the PR interval in resting normal subjects, we have used this measurement in an open uncontrolled study in six subjects to compare the therapeutically useful effect of intravenous and oral verapamil. We have also assessed the effects of the drug on non-invasive measurements of

systolic time intervals in five subjects to determine the possibility of adverse cardiovascular effects.

The PR interval increased significantly in five subjects for 60 min after intravenous verapamil 0.1 mg kg with a slight increase in heart rate; after oral administration of verapamil 120 mg the PR interval was increased significantly between 60 and 180 min with a slight reduction in heart rate. One subject developed Wenckebach type second degree block after both doses of verapamil without change in heart rate. This higher degree of block had a similar time-course to the significant PR interval change in other subjects. In the systolic time intervals, ejection time (LVET) was corrected for heart rate on the basis of data derived from the action of atropine (Burgess, Wadsworth & Warrington, 1979). We have used the PEP/LVET ratio as an inotropic measurement relatively independent of other influences. Intravenous verapamil increased the PEP/LVET ratio significantly at 30 min only; there were no significant changes after the oral dose.

We conclude that the PR interval is a useful and stable measurement to assess the effect of verapamil on atrio-ventricular conduction. The effect for 3 h after the oral dose of 120 mg suggests that this would be a suitable dose interval for a sustained action. The prolongation of PEP/LVET ratio seen after the intravenous dose is the reverse of the change expected from a positive inotropic effect, and might be anticipated from the action of a calcium-blocker on the myocardium. However, the haemodynamic effects of verapamil are complex, a peripheral vasodilator effect tending to decrease PEP/LVET, countering any increase from a direct negative inotropic action and improving left ventricular performance by a reduction in afterload. Vasodilation will also provoke reflex sympathetic stimulation producing a similar effect, this reflex response probably accounting for the increase in heart rate seen after intravenous verapamil in our relatively vagotonic volunteers. It seems reasonable to conclude that verapamil at these doses has little adverse effect on cardiac performance in subjects with normal myocardial function and intact sympathetic reflexes.

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## The effect of spontaneous changes in urinary pH on mexiletine plasma concentrations and excretion during chronic administration to healthy volunteers

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## Cardiac effects of disopyramide and lignocaine assessed by echocardiography

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While invasive studies have shown lignocaine to have little cardiodepressant effect in man after doses used to control cardiac dysrhythmias (Grossman, Cooper & Frieden, 1969), results with disopyramide are conflicting (Vismara, De Marion, Miller, Amsterdam & Mason, 1975; Davies, Marrott & Muir, 1979).

Echocardiography is a potentially useful non-invasive method of assessing the cardiac effects of drugs. Using this technique, we have examined the effects of disopyramide and lignocaine on left ventricular end systolic diameter (ESd) and contractility, as measured by the maximum % systolic shortening (%Δd), under controlled conditions in four healthy male volunteers.

The drugs were given in random order by stepped i.v. bolus plus infusion regimens designed to achieve three successive steady-state plasma drug concentrations within the reported therapeutic ranges (1.5–5 μg/ml for both drugs). Studies with each drug were at least 3 weeks apart.

At each steady-state multiple readings were made of pulse rate, blood pressure, ESd and %Δd and compared with those obtained at the same times during a control isovolumetric infusion of normal saline. Changes in these variables were assessed in relation to plasma drug concentrations measured by g.l.c. Effects of the two drugs were compared using a two-way analysis of variance designed to permit valid comparisons between small groups.

Three subjects completed the lignocaine study and four completed the disopyramide study. The mean ± s.d. plasma concentrations of disopyramide (μg/ml) at the three steady-states were 2.26 ± 0.48, 3.26 ± 0.43 and 4.01 ± 0.45. At these concentrations the mean percentage changes (compared with the control infusion) in ESd were +7% ($P < 0.01$); +13% ($P < 0.01$); +19% ($P < 0.01$); and in %Δd were −16% ($P < 0.01$); −26% ($P < 0.01$); −36% ($P < 0.01$), respectively. These changes were significantly related to plasma drug concentrations (ESd, $r = 0.60$; $P < 0.01$ and %Δd, $r = 0.70$; $P < 0.01$). Percentage changes in estimated cardiac output were −14% ($P < 0.05$), −1% (NS) and −5% ($P < 0.05$) at the three steady-state levels. Both heart rate and blood pressure rose progressively with increasing concentrations.

The mean ±s.d. plasma concentrations of lignocaine (μg/ml) at the three steady-states were 1.58 ± 0.06, 2.96 ± 0.47 and 4.32 ± 0.13. At these concentrations there were no significant changes in ESd, %Δd or blood pressure. At both the second and third steady-states there were significant rises in estimated cardiac output (+8%, $P < 0.05$; +13%, $P < 0.01$) and heart rate (+7%, $P < 0.01$; +12%, $P < 0.01$) (compared with saline controls).

Comparison of results in the three subjects receiving both drugs showed that disopyramide, but not lignocaine, has a significant cardiac depressant effect, although its full extent is not reflected in changes in cardiac output.

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## The individual variation in sensitivity and in pharmacokinetics of thiopentone in a group of young women

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The individual variation in sensitivity to thiopentone can partly be explained by variations in age, sex and diseases (Dundee, 1954; Christensen & Andreasen, 1978). We have studied the pharmacokinetics of thiopentone in eight young women with gynaecological diseases (cf. Table 1), who were given a dose sufficient for the induction of anaesthesia. The patients were premedicated with 1 mg pethidine plus 0.1 mg diazepam/kg body weight and 0.5 mg atropine intramuscularly 0.5–1 h before the induction. One hundred mg suxamethonium was given to facilitate intubation and the anaesthesia was maintained with nitrous oxide and halothane. The same anaesthetist (J.H.C.) gave all the anaesthetics. The concentration of thiopentone was determined by high performance liquid chromatography (Christensen & Andreasen, 1979) and serum levels were followed for about 20 h. The serum concentration curves could be fitted to a three compartment open model assuming elimination from the central compartment only:

**Table 1** The diagnosis and some pharmacokinetic parameters for thiopentone in eight women

| Patient | Age (years) | Body weight (kg) | $V_1$ (l/kg) | $V_2$ (l/kg) | $V_3$ (l/kg) | $Cl_s$ (ml $min^{-1}$ $kg^{-1}$) | $T_{\frac{1}{2}\alpha}$ (min) | $T_{\frac{1}{2}\alpha}$ (min) | $T_{\frac{1}{2}\beta}$ (min) | $k_{1,2}$ ($min^{-1}$) | Diagnosis |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 36 | 64 | 0.068 | 0.142 | 2.246 | 0.63 | 2.7 | 43 | 3148 | 0.145 | Sactosalpinx |
| 2 | 25 | 53 | 0.114 | 0.137 | 0.724 | 2.20 | 2.7 | 29 | 438 | 0.124 | Carcinoma of the uterus |
| 3 | 25 | 62 | 0.178 | 0.220 | 0.796 | 1.99 | 3.8 | 52 | 559 | 0.091 | Sterilisation |
| 4 | 25 | 52 | 0.202 | 0.336 | 0.975 | 4.01 | 3.6 | 46 | 386 | 0.102 | Endometriosis |
| 5 | 23 | 57 | 0.196 | 0.185 | 0.765 | 2.40 | 4.9 | 33 | 407 | 0.057 | Primary sterility |
| 6 | 31 | 56 | 0.128 | 0.235 | 1.674 | 1.55 | 5.8 | 71 | 1325 | 0.063 | Primary sterility |
| 7 | 22 | 72 | 0.216 | 0.150 | 1.939 | 1.34 | 6.9 | 62 | 2346 | 0.037 | Abdominal pain |
| 8 | 25 | 56 | 0.046 | 0.195 | 0.736 | 1.60 | 1.8 | 45 | 593 | 0.247 | Primary sterility |
| Mean | | | 0.143 | 0.195 | 1.238 | 1.96 | 4.0 | 48 | 1150 | 0.108 | |
| ± s.d. | | | 0.064 | 0.066 | 0.616 | 0.99 | 1.7 | 14 | 1052 | 0.066 | |

$$C_s = A.e^{-\pi t} + B.e^{-\alpha t} + C.e^{-\beta t}$$

Some of the pharmacokinetic data are shown in Table 1. A significant correlation ($r = 0.9493$, $<0.01$) was found between the rate constant from $V_1$ to $V_2$ ($k_{12}$) and the concentration in serum from venous blood 20 s after the disappearance of the ciliar reflex. The average value of this serum concentration was 38.6 ± 24.1 μg/ml (s.d.).

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## Effect of low doses of alcohol on the sleep of healthy man

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The effect of alcohol on the sleep of healthy adults has been described by several workers, though the studies have involved few subjects with only single dose ingestions, and the designs have not been amenable to statistical analysis. In doses above 1 g/kg body weight, alcohol reduces REM sleep and may shorten the latency to sleep onset and slow wave sleep (Yules, Freedman & Chandler, 1966; Gresham, 1969; Rundell, Lester, Griffiths & Williams, 1972), but there is little information available on the effects of lower doses.

The subjects were six healthy male volunteers aged between 20 and 31 years. They were familiar with the sleep laboratory and the techniques used in sleep recording, and were required to refrain from napping and undue exercise, and to abstain from caffeine and alcohol on the days which preceded overnight sleep recording. Usual alcohol consumption was moderate, and the subjects were all non-smokers. Details of experimental conditions and recording techniques, and of the analysis of records are described elsewhere (Nicholson & Stone, 1979).

Assessment of each treatment (placebo or alcohol) involved three nights. During the first night the subjects slept at home, retiring at a set time between 23.00 and 23.30 h. They slept in the laboratory for the next two nights, and reported 1.5 h before their usual time to retire. Alcohol (0.16, 0.32 and 0.64 g/kg body weight as a flavoured 18% solution) or placebo (distilled water equal to the volume of the middle alcohol dose) was ingested on the third night. The doses were ingested between 1.0 and 0.5 h before retiring, and provided an estimated peak blood alcohol level not exceeding 20, 40 and 80 mg/100 ml.

Total sleep time (TST) was increased by 0.16 g/kg ($P < 0.05$). There were no changes with the higher doses compared with placebo, though TST with 0.64 g/kg was reduced compared with the lower doses. Duration of awake activity was reduced with 0.16

g/kg ($P < 0.05$), and duration of awake activity with 0.64 g/kg was greater than that with 0.16 g/kg ($P < 0.01$). There was a reduction in stage 1 (drowsy) sleep in the first 3 h after sleep onset latency (SOL) with 0.64 g/kg ($P < 0.01$), and in slow wave sleep (stages 3 + 4), in the second 3 h after SOL with 0.32 and 0.64 g/kg. All doses reduced the percentage stage 3 sleep in the first 6 h after SOL, and the two higher doses reduced the percentage stages 3 + 4 in the second 3 h interval.

Small doses of alcohol (0.16 g/kg) may improve sleep with increased TST and reduced awake activity during the whole night, but, though higher doses (up to 0.64 g/kg) may improve sleep during the early part of the night, there is reduced slow wave sleep during the latter part of the night.

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## Effect of sustained release antihistaines on performance in man

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## Double-blind, placebo controlled, cross-over comparison of the sedative and haemodynamic effect of single doses of clonidine and nitrazepam

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The sedative and hypotensive effects of clonidine were studied in comparison with a hypnotic, nitrazepam.

Five healthy male volunteers aged between 26–35 years, received a single oral dose of clonidine 0.3 mg, nitrazepam 20 mg or placebo in double-blind fashion at 09.00 h, with an interval of at leâst 1 week between each treatment in each individual. Blood pressure was measured by Arteriosonde in 10 min intervals, heart rate was estimated from the ECG which was continuously recorded together with the EEG, EOG and EMG for evaluation of the sleep-stages following the standard criteria of Rechtschaffen & Kales (1969). Plasma noradrenaline (NA) was determined at intervals after drug administration by the radioenzymatic method of Henry, Starman, Johnson & Williams (1975).

Clonidine induced a maximal systolic blood pressure fall from 104.8 ± 1.6 to 84.7 ± 1.4 mm Hg (mean ± s.e. mean) and nitrazepam from 102.0 ± 1.9 to 90.3 ± 2.6 mm Hg after 2 h while after placebo blood pressure progressively increased from 102.5 ± 2.9 to 109.6 ± 3.6 mm Hg during the 8 h study. Total sleep time increased from 90.3 ± 25.5 min after placebo to 256.2 ± 21.0 min after clonidine and 281 ± 40.3 min after nitrazepam ($P < 0.01$). Stage I sleep increased from 49.7 ± 11.2 min to 76.9 ± 10.2 min after clonidine and 76.3 ± 25.2 min after nitrazepam ($P < 0.05$), while the highest percent increase of sleep was observed in stage II: 230.7 ± 25.6 min after clonidine, 236.6 ± 35.4 min after nitrazepam compared with only 48.5 ± 15.8 min after placebo ($P < 0.001$). Plasma NA did not change significantly after placebo but fell after nitrazepam from 0.28 ± 0.04 ng/ml to 0.14 ± 0.02 ng/ml after 3 h ($P < 0.05$) and after clonidine from 0.23 ± 0.07 to 0.07 ± 0.02 ng/ml after 4 h ($P < 0.01$).

Clonidine and nitrazepam both induced a hypnotic and a hypotensive effect with some evidence of reduction of sympathetic activity.

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## The action of tolmesoxide on certain cardiovascular measurements in healthy human volunteers

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Tolmesoxide (4,5-dimethoxy-*o*-tolyl methyl sulphoxide) lowers the blood pressure of normotensive and hypertensive rats and cats (Doxey, 1978). In human volunteers an approximately equal degree of dilatation of the forearm arteries and dorsal hand veins was observed following intra-arterial and intravenous infusions of tolmesoxide (Collier, Lorge & Robinson, 1978).

In the present uncontrolled study, tolmesoxide was given to ten healthy volunteers at a dose of 100 mg, firstly by the oral and then by intravenous infusion. These treatments were followed by 200 mg orally. Eight of these volunteers later received 400 mg orally. During each 12 h study period, heart rate was measured from the R–R interval on the electrocardiograph, blood pressure in both the recumbent and standing positions by standard sphygmomanometry and stroke volume was calculated from cardiac impedance measurements obtained from a Minnesota Impedance Cardiograph (Kubicek, Kottke, Ramos, Patterson, Witsoe, Labree, Remole, Layman, Schoering & Garamela, 1974). These parameters were measured at fixed time intervals. An intravenous catheter was inserted into a forearm vein before each study and retained *in situ* for withdrawal of blood samples for assay of plasma tolmesoxide levels.

Slight increases in mean heart rates were measured after the intravenous infusion and 1 h after the two lower oral doses. One hour after the 400 mg dose, the mean heart rate had increased significantly by 12.6% above the mean control level: ($P < 0.01$). A significant reduction ($P < 0.05$) in heart rate occurred 1 h after the infusion.

No significant reductions in recumbent systolic blood pressure were measured after any treatment. Two hours after the intravenous infusion reduction in the recumbent diastolic blood pressure was observed ($P < 0.01$). Mean systolic blood pressures measured standing fell 1 h after the 200 mg dose ($P < 0.05$) and more profound mean reductions in the range of 11–14 mm Hg occurred after the 400 mg dose: these were significantly less than the mean control values ($P < 0.01$).

Statistically significant rises in recumbent blood pressures occurred 12 h after dosing. These changes might have been due to increased arousal at the completion of the experiment.

The mean stroke volume was significantly increased at the 2 h time interval after the intravenous infusion ($P < 0.01$) and the 2 and 3 h time intervals after the 200 mg oral dose ($P < 0.05$) and the 400 mg oral dose ($P < 0.01$): after the latter dose the increase persisted for a further hour. In the context of these changes it was found that plasma tolmesoxide levels reached a maximum 1.5 h after 400 mg of tolmesoxide (the terminal half life was 2.2 h) and that peak plasma levels of the sulphone metabolite (RX 7112) occurred 2 h after the intravenous infusion.

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## Cardiovascular effects of single oral doses of the new β-adrenoceptor blocker SL 75212 in healthy volunteers

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A new β-adrenoceptor blocking agent SL 75212 (±)-1-(isopropylamino)-3-(*p*-(cyclopropyl-methoxy-ethyl)-phenoxy)-2-propanol HCl, was given by mouth to six healthy male volunteers age 21–40 years in doses ranging from 5 to 40 mg in a single dose in a random double-blind manner. A placebo was also given. Studies were performed in each subject at weekly intervals for 5 weeks. Blood was collected for determination of the drug by a gas chromatographic technique (Bianchetti, Ganansia & Morselli, 1979). Cardiovascular indices were evaluated (Åblad, Ervik, Haullgren, Johnsson & Sölvell, 1972) and peak expiratory flow rates were measured with a Wright Peak Flow Meter prior to and from 1 to 23 h after the drug, before and at the end of periods of exercise. At all doses of SL 75212 there was a significant reduction of the tachycardia induced by exercise. With doses of 20 and 40 mg the slowing of the pulse rate, as compared to placebo ($P < 0.01$), was still present at 23 h following administration. Resting heart rate was reduced by doses of 20 mg and 40 mg ($P < 0.01$). Diastolic pressure was not altered. Resting systolic pressure was lowered at 3 h at all dose levels, but at 8 h the difference was only significant (<0.01) for the 20 and 40 mg doses. The post-exercise systolic blood pressures were lowered by the drug at all times (<0.05). This reduction was significant for the 5 mg dose only up to 8 h, and up to 23 h at doses higher than 5 mg. Peak expiratory flow rate did not change. There were no untoward effects. Blood elimination half-life lay between 13 and 21 h. Plasma clearances were in the range 0.32–0.46 l $kg^{-1}$ $h^{-1}$ and the volume of distribution varied from 5.8 to 13 l/kg. Between 3.5 and 8.2% of the drug was recovered from the urine of four subjects. In the other two urinary recovery was up to 16%. There were significant correlations between area under the curve of blood levels: (1) Bl-$AUC_{0-\infty}$ and dose given ($r = 0.925$, $P < 0.001$), (2) peak blood levels and change in post-exercise heart rate ($r = 0.53$, $P < 0.05$), (3) Bl-$AUC_{0-23\,h}$ and AUC of effect on post-exercise heart rate ($r = 0.55$, $P < 0.01$). Thus SL 75212 is a potent long acting β-adrenergic receptor blocking agent.

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## Blood concentrations and pharmacodynamic effects of SL 75212, a new β-adrenoceptor antagonist, after oral and intravenous administration

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SL 75212 (±)-1-(isopropylamino)-3-(*p*-(cyclopropyl-methoxyethyl)-phenoxy)-2-propanol HCl has been shown in animal experiments to be cardioselective and to have low 'first-pass' extraction after oral administration. We have examined the tolerance of SL 75212 intravenously and in a separate experiment have determined the bioavailability of the drug given orally, with particular reference to pharmacodynamic effects.

In the tolerance study, four healthy male volunteers received intravenous dose of SL 75212 up to 70.5 μg/kg. Shortly before each dose was given and at 0.5 h, 1 h and hourly up to 6 h afterwards, the subjects exercised for 3 min on a bicycle ergometer at a workload which had previously been shown to produce a heart rate of at least 150 beats/min during the last 20 s of each period of effort. $FEV_1$ was measured immediately before exercise and peak expiratory flow rate (PEFR) was determined both at rest and during exercise. Blood pressure was recorded during administration of SL 75212, before and immediately after each period of effort. Standard clinical, haematological and biochemical screening examinations were performed at intervals after drug administration.

Intravenous SL 75212 was well tolerated: no unwanted effects were reported, no abnormalities were found in any screening examination and there was no evidence of any effect on respiratory function.

In the bioavailability study, four healthy male volunteers age 21–45 years received single oral and intravenous doses of SL 75212 150 μg/kg 1 week apart and blood samples were obtained during the 48 h after each dose. Urine was collected for 24 h after drug administration. Immediately before each dose and at 2, 4, 6, 8 and 24 h afterwards, the subjects were exercised and their $FEV_1$, PEFR and BP measured as described above in the tolerance study. The concentration of SL 75212 in whole blood and urine was determined by gas-liquid chromatography.

Peak blood concentrations of SL 75212 were seen at between 2 and 3 h after the oral doses; thereafter, the decay curves were indistinguishable for the two routes. Mean elimination half-life (±s.e. mean) was 14.8 ± 1.4 h after intravenous and 14.3 ± 0.7 h after oral administration, with volumes of distribution of 8.7 ± 0.7 l/kg (intravenous) and 9.8 ± 0.3 l/kg (oral), assuming 100% bioavailability.

Comparison of the areas under the blood concentration/time curves from 0.5 to 48 h gave a bioavailability of 89 ± 5%. The amount of unchanged drug excreted in the urine in the first 24 h was 11.6 ± 2.1% (intravenous) and 12.6 ± 2.5% (oral). Similar maximum effects on rest and exercise heart rate and systolic blood pressure were seen 2 h after both routes and there was no significant difference between the effects of intravenous and oral doses at any time. No effect on respiratory function was detected.

Intravenous SL 75212 was well tolerated. We have confirmed the high bioavailability, low 'first-pass loss' and long elimination half-life suggested by earlier studies.

## The action of the new β-adrenoceptor blocker SL 75212 on the metabolic response to insulin-induced hypoglycaemia in man

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The metabolic response to insulin-induced hypoglycaemia was assessed in six healthy volunteers following intravenous injection of saline, propranolol (200 μg/kg), practolol (1000 μg/kg)and SL 75212 (±)-1-(isopropylamino)-3-(*p*-(cyclopropyl-methoxy-ethyl)-phenoxy)-2-propanol HCl (150 μg/kg). Details of the methodology have already been described (Kilborn, Morselli, Saunders & Sönksen, 1979).

Before drug administration, and for 180 min afterwards (120 min after insulin) blood samples were taken for measurement of insulin and growth hormone (radioimmunoassay, Sönksen, 1976) and glucose (glucose oxidase method). Fluorimetric enzymatic assays were used for glycerol (Kreutz, 1962) and free fatty acids (Carruthers & Young, 1973).

Blood glucose was significantly reduced from 70 to 150 min following saline, practolol and SL 75212 and up to 180 min after propranolol, reaching a nadir at 90 min which was similar after all agents (overall mean 1.2 mmol/l). Recovery from hypoglycaemia was significantly slower with propranolol than saline ($P < 0.01$), practolol ($P < 0.05$) or SL 75212 ($P < 0.05$). Practolol and SL 75212 were not significantly different from saline.

Glycerol levels significantly increased from 100 to 180 min after saline but not after the β-adrenoceptor blockers.

Free fatty acids fell after insulin to a similar nadir after all treatments. The rate of recovery towards baseline levels was saline > SL 75 212 > propranolol.

Growth hormone values rose in response to hypoglycaemia. None of the β-adrenoceptor blockers affected this response. Plasma insulin levels were similar in all four studies.

The effects of SL 75212 on the metabolic response to hypoglycaemia were similar to those of practolol and different to those of propranolol.

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# POSTER COMMUNICATIONS

## The spectrofluorimetric estimation and buccal absorption of SL 75212, a novel β-adrenoceptor antagonist

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SL 75212 (1-(isopropylamin)-3-(*p*-(2-cyclopropylmethoxyethyl)-phenoxy)-2-propanol HCl) is a new β-adrenoceptor antagonist which may have advantages over other β-adrenoceptor antagonists in that it is cardioselective without partial agonist activity, has a long half life, and because of low hepatic extraction, high bioavailability. The partitioning of SL 75212 and propranolol into six organic solvents from 0.1 M sodium hydroxide was investigated (Table 1). Their buccal absorption was studied at pHs 5–10 using a method similar to Beckett & Triggs (1967).

**Table 1** Partition coefficients of SL75212 and propranolol in six organic solvents

| *Solvent* | *SL 75212* | *Propranolol* |
|---|---|---|
| *n*-Heptane | 6.0 | 29.9 |
| Benzene | 40.4 | 309.6 |
| Toluene | 19.6 | 169.8 |
| Chloroform | 144.4 | 391.0 |
| Amyl alcohol | 310.2 | 391.0 |
| Ethyl acetate | 2.7 | 3.0 |

SL 75212 demonstrates maximum fluorescence intensity at emission wavelength 300 nm and excitation wavelength 275 nm as compared with propranolol which has maxima at Em 345 nm and Ex 300 nm. The intensity of the fluorescence of propranolol was found to be approximately ten times that of SL 75212. The concentrations of SL 75212 and propranol used were 10 μg/ml and 1 μg/ml respectively, these levels being chosen to give a similar fluorescence intensity. SL 75212 and propranolol were estimated according to the following method. To 3 ml of sample in a quickfit glass tube were added 0.2 ml 10 N NaOH and 12 ml *n*-heptane. Each tube was shaken for 10 min and then centrifuged at 400 *g* for 5 min. Ten ml of the heptane layer was then decanted into a clean tube containing 3 ml of 0.01 M $H_2SO_4$ and the tube shaken and centrifuged as before. The aqueous layer was then removed and SL 75212 and propranolol read in a spectrofluorimeter at the Em and Ex wavelengths given above. Both drugs gave linear plots of fluorescence intensity against concentration over the range measured. The pKas of SL 75212 and propranolol were measured by titration with NaOH and were found to be 9.38 and 9.45 respectively. The disappearance of the drugs from the buccal cavity was lowest at pH 5 and highest at pH 10, the absorption of propranolol always being slightly greater than that of SL 75212.

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## Recovery of propranolol after buccal absorption

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Absorption of drugs through the buccal mucosa has been proposed as an *in vivo* model of passive drug transfer through lipid membranes' (Beckett & Triggs, 1967). Later work has clearly demonstrated that absorbed drugs may be recovered from the buccal mucosa by back-partitioning into freshly introduced buffer solution, which is consistent with the reversibility of the process (Beckett & Pickup, 1975, Temple & Schesmer, 1978, Davis & Johnston, 1979).

Using two trained subjects, we investigated the recovery of 200 μg propranolol absorbed at pH 9.2 during a standard 5 min buccal absorption test, by repeatedly introducing fresh buffer solution for twelve 2 min periods. Recovery was performed in this way at three pH values (5.2, 7.4, 9.0), and also at pH 7.4 after absorption for 1 and for 10 min. The amounts recovered were plotted and the area under the curve taken as the total amount recovered. Mean recovery was 56% at pH 5.2, 49.5% at pH 7.4 and 19% at pH 9.0. Asymptotic values for recovery were calculated, and showed that approximately 90% of the absorbed drug was recoverable when buffers at 5.2 and 7.4 were used, and 26% when buffer at pH 9.0 was used. When drug was absorbed for 1 min and 10 min periods, and recovered at pH 7.4, the absorption appeared to be time-dependent.

Disappearance from the buccal cavity is not synonymous with entry of drug into the systemic circulation, and a clear distinction between them must be made, since considerable amounts of drug may be stored in the tissues; storage in buccal mucosa may explain why in this experiment so little drug was recovered at pH 9.0. A clearer evaluation of the buccal absorption model is required to determine the rate constants for disappearance of drug from the buccal cavity and for entry into the circulation. Attempts have been made to demonstrate the latter (Kates, 1978), but the swallowing of 'absorbed' drug which has back-partitioned into the mouth needs to be excluded to validate the model.

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## Plasma concentrations of oral hypoglycaemic drugs in diabetic clinic patients

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Wide variability in plasma concentrations of tolbutamide and chlorpropamide in diabetic outpatients has recently been reported (Melander, Sartor, Wåhlin, Scherstén & Bitzén, 1978) and it was suggested that there were marked interindividual differences in the disposition of these drugs.

We have measured plasma concentrations of chlorpropamide and tolbutamide by the method of Prescott & Redman (1972) and in addition of metformin by the method of Brohon & Noel (1977) in 243 diabetic clinic patients at routine attendances and obtained information on a number of factors thought likely to influence these concentrations.

The main finding with chlorpropamide was of a strong positive correlation between dose and plasma concentration ($r = 0.81$, $n = 108$, $P < 0.001$) after exclusion of non-compliers (Figure 1). Inter-individual variability was greater in the 50% of the sample on doses above approximately 4 mg $kg^{-1}$ 24 $h^{-1}$ ($F = 3.8$, $P < 0.01$). Metformin dose correlated less strongly with plasma concentration ($r = 0.3$, $n = 82$, $P < 0.01$). With drugs the overall correlation coefficient was not improved either by selection of specific post-dosing sample intervals or by exclusion of patients on concurrent drug therapy.

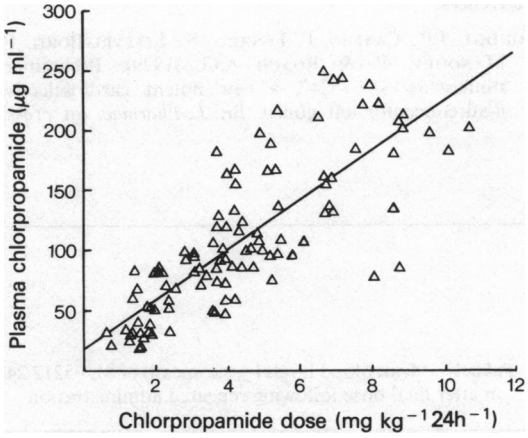


**Figure 1** Plasma concentration of chlorpropamide in relation to 24 h weight-related dose in 108 diabetic outpatients. $r = 0.81$, $n = 108$, $P < 0.001$.

Metformin but not chlorpropamide plasma concentration correlated positively with both age ($r = 0.27$, $P < 0.05$) and serum creatinine ($r = 0.3$, $P < 0.01$).

In 13 patients on tolbutamide a positive correlation was found between dose and plasma concentration ($r = 0.86$, $P < 0.001$) but no relationship existed between plasma tolbutamide and either age or plasma albumin.

These findings suggest that, overall under routine clinic conditions, inter-individual variability in the plasma concentration of chlorpropamide may be less than previously reported, but may increase on higher doses. Differences ar more likely to relate to factors such as metabolic elimination or distribution than to age or renal excretion. In the case of metformin the variability is greater and higher levels may be associated with increasing age and/or impaired renal function.

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## Comparison of the β-adrenoceptor blocking properties and pharmacokinetics of SL 75212 and propranolol in man

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The pharmacological effects and the pharmacokinetics of SL 75212 (±)-1-(isopropylamino)-3-(*p*-(cyclopropylmethoxyethyl)-phenoxy)-2-propanol HCl, a new β-adrenoceptor blocking agent (Boudot, Cavero, Fénard, Lefèvre-Borg, Manoury & Roach, 1979), have been compared to those of propranolol and a placebo in a double-blind trial involving six healthy volunteers.

SL 75212 (20 mg orally) and propranolol (80 mg orally) were equally effective in reducing resting heart rate and exercise-induced tachycardia, but while these effects had completely disappeared after 23 h following propranolol, they were still present up to 48 h with SL 75212. Myocardial contractile force at rest was slightly and transiently diminished by both drugs as indicated by an increase in the PEP/LVET ratio. Plasma renin activity was reduced by both drugs, up to 8 h by propranolol and up to 25 h following SL 75212. Finally propranolol but not SL 75212 produced a reduction in exercise-induced increase in peak expiratory flow rate.

These results demonstrate that in man SL 75212, by oral route, is a potent, at least 4-fold more than propranolol, cardioselective and long-lasting adrenoceptor blocking drug. The pharmacokinetic data fit with these pharmacological findings: thus, SL 75212 has a lower clearance rate than propranolol ($0.28 \pm 0.02$ *v* $1.13 \pm 0.06$ l $h^{-1}$ $kg^{-1}$) and consequently a longer half-life ($12.3 \pm 1.1$ *v* $4.1 \pm 0.6$ h); further-

more SL 75212 is much less subject to liver first-pass metabolism than propranolol as shown by a higher systemic bioavailability value (80.1 *v* 16.0%) and a narrower fluctuation range in the peak blood concentration values.

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## Pharmacokinetics of the new β-adrenoceptor blocker SL 75212 in man after repeated oral administration

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The pharmacokinetics of the β-adrenoceptor blocker SL 75212 (±)-1-(isopropylamino(-3(*p*-(cyclopropylmethoxyethyl)-phenoxy)-2-propanol.HCl. in normal man were studied by Bianchetti, Cadigan, Gomeni, Kilborn, London, Morselli & Pentecost (1979) after single oral doses. We have compared the kinetics after repeated doses to investigate whether the characteristics change.

Nine volunteers entered two studies. In one, 10 mg/day SL 75212 for 1 week was followed by 20 mg/day for a further week. In the second study increasing doses of 20 to 60 mg/day were given for a total of 15 days. Blood levels were measured at intervals throughout and for 96 h afterwards.

Mean blood levels 24 h after the last dose of SL 75212 in both studies are shown in Table 1. There is a good correlation between doses and steady state blood levels. After 4 to 5 days of treatment, levels double those found in a previous single-dose study were reached (8.1 ± 1.4 ng/ml after 10 mg, 15.1 ± 1.1 ng/ml after 20 mg) (Cadigan, Bianchetti, Gomeni, Kilborn, London, Morselli, Pentecost, unpublished). The mean $T_{\frac{1}{2}}$ in the 10 day washout period was 16.4 ± 0.7 h (study 1) and 22.1 ± 2.8 h (study 2). Apparent bioavailability was 76.6 ± 2.5% and 78.0 ± 4.5%. Vd calculated on apparent bioavailability was 7.7 ± 0.6 and 8.8 ± 2.3 l/kg. The blood clearance was 0.33 ± 0.03 and 0.28 ± 0.06 l $h^{-1}$ $kg^{-1}$. None of these values are significantly different from those found in single dose studies (Cadigan *et al.*, unpublished). $T_{\frac{1}{2}}$ did not change with repeated administration, unlike propranolol (Chidsey, Morselli, Bianchetti, Morganti, Leonetti, Zanchetti, 1975). Steady state levels agreed closely with those predicted from single dose studies.

**Table 1** Mean blood levels (± s.e. mean) of SL 75212 24 h after final dose following repeated administration

| *Study* | *Dose (mg)* | *Duration of treatment (days)* | n | *Blood levels (ng/ml)* |
|---|---|---|---|---|
| Study 1 | 10 | 7 | 6 | 16.0 (1.5) |
| | 20 | 7 | 6 | 30.6 (3.5) |
| Study 2 | 20 | 3 | 3 | 25.0 (3.1) |
| | 40 | 3 | 3 | 41.5 (9.1) |
| | 60 | 7 | 3 | 76.3 (19.2) |

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# The effects of the new β-adrenoceptor blocker SL 75212 on the cardiovascular responses to insulin induced hypoglycaemia in man

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The cardiovascular responses to hypoglycaemia are known to be masked by propranolol (Abramson, Arky & Woeber, 1966).

More selective β-adrenoceptor blockers may behave differently (Deacon & Barnett, 1976). SL 75212 is a new β-adrenoceptor blocking drug (Boudot, Cavero, Fénard, Lefèvre-Borg, Manoury & Roach, 1979) having the formula (±)-1-(isopropylamino)-3-(*p*-(cyclopropylmethoxyethyl)-phenoxy)-2-propanolol HCl. We have studied the effects of intravenous propranolol, practolol, SL 75212 and saline on the cardiovascular responses to insulin-induced hypoglycaemia in normal subjects. Six healthy male volunteers fasted overnight received intravenously 50 ml saline and (μg/kg) propranolol (200), practolol (1000) and SL 75212 (150) diluted in 50 ml saline at weekly intervals according to a partial latin square design. The doses were previously shown to be equipotent in inhibiting exercise tachycardia 2 h after administration. An intravenous cannula was inserted into a forearm vein and the subjects rested semi-supine for 1 h before slow intravenous injection of the β-adrenoceptor blocker or saline. Sixty minutes later insulin 0.1 units/kg was given intravenously into a vein in the contralateral forearm. Heart rate and blood pressure were measured before administration of the β-adrenoceptor blocker and for 180 min afterwards (120 min after insulin). Pulse rate was measured by a monitor with digital display and blood pressure by an automatic recorder with external cuff (Arteriosonde 1217, Roche). In saline tested subjects insulin caused a significant increase in pulse rate from 10 to 50 min after insulin. In contrast in subjects given propranolol pulse rate fell within 30 min after insulin and remained depressed for the duration of the study. An increase in pulse rate was seen after insulin following practolol and SL 75212. The maximum effect was observed 30 min after insulin with a mean increase of 17.8 ± 4.33/min following saline, 14.8 ± 5.33/min following SL 75212, 11.5 ± 4.43/min following practolol and a mean decrease of 7.33 ± 4.29/min following propranolol.

Following saline a significant increase in systolic blood pressure was recorded in response to insulin, returning to normal 120 min later. No significant change was observed with the three β-adrenoceptor blockers. Propranolol led to an increase in diastolic blood pressure which differed significantly from saline, practolol and SL 75212 which produced a fall (significant only for saline at 100 min).

Multivariate analysis of all cardiovascular parameters showed a significant difference between propranolol and the other two treatments. The findings are consistent with $\beta_1$ receptor antagonism by practolol and SL 75212 and $\beta_1$ and $\beta_2$ receptor blocking activity of propranolol: thus, selective $\beta_1$ receptor blockers do not interfere with the cardiovascular response to insulin. Also, the effects on the heart rate would be consistent with the presence of cardiac $\beta_2$ receptors.

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# Intestinal metabolism during transport of ethinyl oestradiol across the rat small intestine *in vitro*: the effect of enzyme inducers

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The aim of this study was to investigate whether ethinyl oestradiol (EE) is metabolised during absorption across the small intestine of the rat and to determine the effect of the chronic administration of phenobarbitone or rifampicin on this system.

The everted-sac method, based on that described by Wilson & Wiseman (1954) was used. The animals were untreated or pretreated for 6 days with either phenobarbitone (80 mg/kg, i.p. or rifampicin (100 mg/kg, p.o.). The solution on the mucosal side of the sacs initially contained [$^3$H]-EE (1.0 μg/ml (3.4 μM); 0.08 μCi/ml) in Krebs-Henseleit bicarbonate-buffered saline (pH 7.4). After incubation an aliquot (0.5 ml) of the solutions from the mucosal and serosal sides was extracted with ether (2 ml) for 30 min. Part of the residue (0.25 ml) was acidified (0.2 ml, 20% TCA) and extracted into ether as before. The remainder of the residue was incubated with β-glucuronidase (BDH, low in arylsulphatase), the pH adjusted to 7.4 and the solution re-extracted with ether. The solutions from the mucosal and serosal sides and the ether layers were analysed for total radioactivity by liquid scintillation counting. Further aliquots of the ether layers were subjected to thin layer chromatography in chloroform: methanol (97:3 v/v) on silica gel plates.

The results shown in the table indicate that EE forms an acid extractable metabolite(s) which is hydrolysed by β-glucuronidase to material which is extracted by ether at pH 7.4. This has the same chromatographic mobility as EE. Phenobarbitone and rifampicin stimulate the formation of this metabolite(s).

In control and rifampicin treated animals recovery of radioactivity was incomplete and may indicate the presence of metabolites other than glucuronides; after phenobarbitone pretreatment there was a total recovery of radioactivity which may indicate that metabolism is preferentially stimulated via the glucuronidation pathway.

We thank Dr D.J. Back, Department of Pharmacology, University of Liverpool, for his interest in this project.

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**Table 1** Intestinal metabolism of ethinyl oestradiol

| *Pretreatment* | *% of total [$^3$H] at end of incubation* *Mucosal* | *Serosal* |
|---|---|---|
| | *Before acidification* | |
| None | 42.6 ± 1.6 (39) | 21.9 ± 1.9 (36) |
| Phenobarbitone | 38.8 ± 1.9 (23) | 19.7 ± 1.1 (22) |
| Rifampicin | 31.9 ± 1.5 (29)**† | 14.2 ± 1.0 (28)**†† |
| | *After acidification* | |
| None | 39.9 ± 2.3 (33) | 53.7 ± 3.0 (33) |
| Phenobarbitone | 69.5 ± 2.4 (23)** | 80.6 ± 2.7 (22)** |
| Rifampicin | 61.8 ± 3.1 (28)** | 67.1 ± 3.1 (28)*† |
| | *After β-glucuronidase* | |
| None | 38.8 ± 3.5 (23) | 68.2 ± 4.8 (25) |
| Phenobarbitone | 64.5 ± 3.0 (22)** | 92.5 ± 3.7 (23)** |
| Rifampicin | 50.2 ± 1.8 (28)*†† | 77.0 ± 2.0 (28)† |

All values are given as mean ± s.e. mean with the number of determinations in parentheses. * $P < 0.01$, ** $P < 0.001$, † $P < 0.01$, †† $P < 0.001$ using a non-paired *t*-test. * Refer to differences within groups between treatment and control, † refers to differences within groups between rifampicin and phenobarbitone.

# The binding of thiopentone to serum proteins determined by ultrafiltration and equilibrium dialysis

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The percentual binding of thiopentone to plasma proteins has been determined by ultrafiltration (Brodie, Bernstein & Mark, 1952) and by equilibrium dialysis (Dayton, Perel, Landrau, Brand & Mark, 1967). Results in the literature do differ, and we found no information about the association constants and the number of binding sites on human plasma proteins.

Thiopentone was added to two human sera at a concentration of 10 μg/ml. A series of ultrafiltration experiments were continued over stepwise increased time periods (37°C, pH 7.4 was secured with $CO_2$). A value for the percentual binding of thiopentone was obtained for each step. All those values were higher than values for the binding in the two sera determined by equilibrium dialysis against an equal volume of an isotonic phosphate buffer (37°C, pH 7.4). Extrapolation of the binding curves obtained by ultrafiltration to an estimated point of 'no increase in the concentration of macromolecules' yielded values of the perceptual binding of thiopentone which appeared slightly lower (83.80% and 85.13% respectively) than the values obtained by equilibrium dialysis (86.47% ± 0.68% and 86.23% ± 0.17% respectively).

The percentual binding, with concentrations of thiopentone from 0.4 to 80 μg/ml, was studied by equilibrium dialysis of serum with an albumin concentration of 45 g/l and compared with the binding in a buffer solution with the same ablumin concentration. No significant difference in percentual binding was found. $\bar{\nu}/D_f$ was plotted as a function of $\bar{\nu}$ (Scatchard, 1949) ($\bar{\nu}$ = number of small molecules bound for each large molecule and $D_f$ = molar concentration of unbound small molecules). Association constants and relative number of binding sites on the albumin molecules were calculated assuming two independent classes of binding sites on the albumin molecules were calculated assuming two independent classes of binding sites (Table 1).

The results of experiments with identical thiopentone concentrations (10 μg/ml) and increasing concentrations of albumin (1–8 g/100 ml) were also utilized to calculate $\bar{\upsilon}$ and $\bar{\nu}/D_f$. Plots of $\bar{\nu}/D_f$ as a function of $\bar{\nu}$ resulted in a curve with a positive slope (cf. Shen & Gibaldi 1974). A conclusion of our study thus is that the binding parameters are influenced by the albumin concentration.

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**Table 1** The average number of binding sites of two independent classes per human serum albumin molecule. Concentration of thiopentone from 0.4 to 80 μg/ml. The corresponding association constants are also shown

| *Average number of binding sites per albumin molecule* | *Albumin solution 45 g/l* | *Serum 45 g albumin/l* |
|---|---|---|
| $N_1$ | 0.0012 | 0.00071 |
| $N_2$ | 3.54 | 6.32 |
| *Association constants* ($M^{-1}$) | | |
| $K_1$ | $3.39 \times 10^6$ | $13.3 \times 10^6$ |
| $K_2$ | $2.16 \times 10^3$ | $1.19 \times 10^3$ |

## Spectrofluorometric assay and buccal absorption of LM 5008, a new potential antidepressive drug

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LM 5008 (chemical name 4-(3-indolyl-2-ethyl) piperidine) is a potent inhibitor of 5-HT uptake into central neurones and a potential antidepressive agent (le Fur & Uzan, 1977). We have developed a spectrofluorometric assay procedure to study its buccal absorption characteristics.

The spectrofluorimetric method is as follows. To a 2 ml sample in a glass centrifuge tube were added 0.1 ml 1M sodium hydroxide and 10 ml toluene containing 2% amyl alcohol. Each tube was shaken for 10 min and centrifuged for 10 min. Seven ml of upper solvent layer were transferred to a second centrifuge tube with 2 ml 0.01 M HCl. The tube was shaken and centrifuged as previously. The acidic layer (1.5 ml) was read on an Aminco SPF 125 spectrofluorimeter at maximum excitation and emission wavelengths of 290 and 370 respectively. The method was linear over the range measured (50 ng/ml–5 μg/ml).

The buccal absorption of LM 5008 resembles that of other weak bases such as propranolol (Schurmann & Turner, 1978). The disappearance of drug from the buccal cavity was greatest in alkaline conditions. There is evidence that it is metabolised in man, and further studies are required to determine the influence of urinary pH on the total clearance of active drug and metabolite.

We thank Dr Uzan of Pharmindustrie for supplying LM 5008 for these studies.

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## Plasma naloxone levels in the newborn after intravenous and intramuscular administration

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The reversal of the depressant effects of transplacentally acquired pethidine by the intravenous administration of naloxone at the recommended dose (30–40 μg) is relatively rapid in onset but lasts for less than 1 h (Weiner, Hogg & Rosen, 1977). The duration of action, achieved by the administration of a large (200 μg) intramuscular dose, 24–48 h, is greater than would be expected from simply increasing the dose (Wiener *et al.*, 1977). The present study was carried out to investigate the pharmacokinetics of naloxone in neonates after i.v. and i.m. administration.

Between five and seven capillary blood samples were obtained from each of 12 newborn infants at various intervals over a period of 6 h after injection of either 35 or 70 μg naloxone HCl into the umbilical vein, and from 20 babies for up to 36 h after 200 μg administered intramuscularly. Plasma naloxone was determined by RIA.

Peak plasma levels of 4.0–5.4 ng/ml and 9.2–20.2 ng/ml were observed within 40 min of the i.v. administration of 35 and 70 μg respectively. The concentration then declined exponentially at similar rates in both groups. The mean ± s.e. mean half-life, apparent volume of distribution and plasma clearance was 3.5 ± 0.9 h, 2.20 ± 0.48 l/kg and 0.56 ± 0.20 l $kg^{-1}$ $h^{-1}$ in the 35 μg dose group and 2.6 ± 0.5 h, 1.79 ± 0.30 l/kg and 0.58 ± 0.15 l $kg^{-1}$ $h^{-1}$ in the 70 μg dose group.

The plasma naloxone concentrations observed after the intramuscular dose are shown in Table 1. Peak levels of 11.3–34.7 ng/ml were observed at 0.5–2 h. The logarithm of the concentration *v* time curve was consistently biphasic thereafter with the level declin-

ing rapidly between 1 and 6 h and more slowly from 6–36 h.

The rate of elimination of naloxone in neonates after i.v. administration was approximately one-third of that reported for adults (Ngai, Berkowitz, Yang, Hempstead & Spector, 1977). After i.m. administration plasma levels remained high for at least 36 h. This may account for the longer duration of action of this drug when this route is used.

**Table 1** Naloxone levels in neonates after 200 μg i.m.

| Time (h) | 0.5 | 1 | 2 | 6 | 16–20 | 24–36 |
|---|---|---|---|---|---|---|
| *n* | 13 | 15 | 17 | 16 | 18 | 11 |
| Concentration (ng/ml) | 16.2 | 18.2 | 9.5 | 7.1 | 4.9 | 4.2 |
| s.e. mean | 2.3 | 1.8 | 1.4 | 1.1 | 0.5 | 0.8 |

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