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

COMMUNICATIONS

Urinary dopamine, noradrenaline, adrenaline and sodium relationships in hypertensive and normotensive Chinese with or without a family history of hypertension

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The lack of a positive relationship between sodium (Na) intake and renal dopamine (DA) production has been implicated in the pathogenesis of hypertension in certain ethnic groups (Critchley *et al.*, 1989) but little is known of the mechanism of this relationship or the role of other catecholamines in natriuresis. However, there is evidence that Na loading suppresses urinary noradrenaline (NOR) output while enhancing that of DA and this effect is less marked in some hypertensive subjects (Castellano *et al.*, 1986; Gill *et al.*, 1987).

Fifty-nine normotensive Chinese (Group X: 21M/38F, 43 ± 15 years, 157 ± 8 cm, 55 ± 9 kg) and 30 normotensive Chinese who had one or more first degree relatives with hypertension (Group Y: 5M/25F, 48 ± 7 years, 156 ± 7 cm, 55 ± 7 kg) were studied. They all had BP below 140/90 mm Hg and were compared with 14 hypertensive Chinese (Group Z: 4M/10F, 45 ± 9 years, 159 ± 1 cm, 64 ± 7 kg) with systolic (S) BP > 160 mm Hg and/or diastolic (D) BP > 95 mm Hg. A 24 h urine collection taken when on their normal diet but no medications, was assayed for DA, NOR and adrenaline (ADR) by h.p.l.c. with electrochemical detection. Urinary sodium (Na) and potassium (K) were measured by indirect ion-selective electrodes. Twenty-four h urine creatinine output was used as an index of the completeness of the collections. Data are expressed as means ± s.d. and the 24 h outputs given in Table 1.

There was a significant correlation between urinary Na and DA in group X ($r = 0.42$, $P < 0.01$), but not in groups Y, Z or Y + Z combined. Na also correlated significantly with NOR in group X ($r = 0.39$, $P < 0.01$), but not in groups Y, or Y + Z combined. There was a consistent and very significant correlation ($P < 0.02$ to < 0.001) between urinary DA and NOR in all groups ($r = 0.46$, in X; $r = 0.44$ in Y; $r = 0.74$ in Z; $r = 0.51$ in Y + Z) but not between DA and ADR. Our findings regarding the Na–DA relationships in Chinese are similar to those reported in Caucasians and Japanese normotensive/hypertensive subjects. The strong positive correlation between DA and NOR may suggest a noradrenergic component in the Na–DA mechanism or conversion of extra-neuronal renal DA to NOR.

Table 1

	SBP (mm Hg)	*DBP (mm Hg)*	*Na (mmol)*	*K (mmol)*	*DA (nmol)*	*NOR (nmol)*	*ADR (nmol)*
Group X ($n = 59$)	105 ± 12	70 ± 8	129 ± 50	37 ± 14	1461 ± 602	169 ± 68	36 ± 33
Group Y ($n = 30$)	104 ± 9	69 ± 8	134 ± 34	40 ± 15	1540 ± 470	172 ± 58	33 ± 40
Group Z ($n = 14$)	163 ± 13	101 ± 5	157 ± 70	45 ± 13	1593 ± 348	191 ± 53	28 ± 18

Castellano, M. *et al.* (1986). *J. cardiovasc. Pharmac.*, **8** (suppl. 5), S116.
Critchley, J. A. J. H. *et al.* (1989). *Eur. J. clin. Pharmac.*, **37**, 559.
Gill, J. R. *et al.* (1987). *Hypertension*, **11**, 312.

Use of an *in vitro* lymphocyte cytotoxicity assay to assess the effects of carbamazepine (CBZ), phenytoin (DPH) and oxcarbazepine (OXCZ) in carbamazepine-hypersensitive patients

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CBZ-induced hypersensitivity reactions are associated with a great deal of morbidity and occasional mortality. Shear *et al.* (1988) by using lymphocytes from patients hypersensitive to DPH, phenobarbitone (PB) and CBZ as cellular targets for oxidative drug metabolites generated by an *in vitro* murine hepatic microsomal system, were able to distinguish between these patients and suitable controls. We have used a modified version of this assay in CBZ-hypersensitive patients to (1) confirm previous findings by Shear *et al.* (1988); (2) assess cross-reactivity with DPH and OXCZ; and (3) exclude a non-specific chemical sensitivity of patient lymphocytes by exposing them to synthesised reactive metabolites (dapsone hydroxylamine [DDS-NOH] and amodiaquine quinoneimine [AQQI]). Seven patients (mean age 34.4 years; range 16–78, four males and three females) were identified as being hypersensitive to CBZ. Sixteen controls were used: five patients currently taking CBZ and 11 normal healthy volunteers (mean age 32.8 years;

range 21–74; 13 males and three females). The study was approved by the local ethics committee. Lymphocytes from patients and controls were exposed to the compounds as previously described (Riley *et al.*, 1989). Results are expressed as increase in cell death above the baseline (Table I). The results indicate that (1) CBZ-hypersensitive patients can be distinguished from controls using this assay; (2) in this patient group there was no evidence of cross-reactivity to DPH or OXCZ; (3) the difference between patients and controls is not due to a non-specific chemical sensitivity of patient cells.

Table 1

	Patients			*Controls*		
Drug	n	*Mean*	*95% C.I.*	n	*Mean*	*95% C.I.*
CBZ	7	7.4	5.8–9.5*	16	2.5	1.5–3.3*
DPH	7	3.7	2.3–4.8	14	3.0	0–4.7
OXCZ	7	9.6	5.6–14.8	13	7.1	5.1–8.6
DDS-NOH	6	13.2	7.5–18.9	21	14.2	11.5–17.4
AQQI	6	10.5	5.7–19.4	8	7.9	4.1–11.5

*indicates a significant difference between patient and control groups, $p < 0.001$ (analysis of variance)

Riley, R. J. *et al.* (1989). *Br. J. clin. Pharmac.*, **28**, 482.

Shear, N. H. *et al.* (1988). *J. clin. Invest.*. **82**, 1826.

Oral cimetidine premedication—clinical onset of three preparations

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Cimetidine 200–400 mg in standard tablet form results in therapeutic blood levels 45–90 min later (Keating *et al.*, 1978). The aim of this study was to compare clinical onset and blood concentrations for elixir (E), chewable (C) and swallowed (S) tablets. Following ethics committee approval informed consent was obtained from 137 healthy patients for elective gynaecological surgery. Exclusion criteria included dyspepsia, drugs altering gastric motility/secretion and body weight > 82 kg. Three treatment groups received temazepam 20 mg and 400 mg cimetidine 30–120 min preoperatively (36 patients each group). A control group (N) of 29 patients received temazepam 20 mg only. Gastric contents were aspirated as soon as possible after induction of anaesthesia. Preoperative venous blood samples taken 0, 30, 45, 60, 75 and 90 min after cimetidine administration from 10 patients in each treatment group and were analysed for cimetidine by h.p.l.c. Data were analysed by ANOVA Kruskal Wallis ANOVA and χ^2 tests as appropriate. The groups were comparable for age, weight and time from cimetidine administration to gastric aspiration. At least one patient in each treatment group had a gastric pH < 2.5 and/or gastric aspirate > 25 ml, when measured 0–60, 61–90 or 91 min following cimetidine administration, with no difference between the three groups.

Therapeutic plasma levels were obtained more rapidly after cimetidine elixir. However none of the three preparations ensured safe gastric pH or volume within 60 min of administration.

Table 1 Gastric pH/volume and plasma cimetidine concentrations, mean (95% confidence interval)

	n	*Control (N)*	*Elixir (E)*	*Swallowed (S)*	*Chewable (C)*
Gastric pH	36	1.7 (1.3–2.2)	4.7*** (4.0–5.5)	5.5*** (4.7–6.3)	5.0*** (4.3–5.8)
Gastric volume (ml)	36	24.7 (19.3–30.1)	23.0 (15.6–30.5)	19.1** (11.4–26.7)	18.3** (12.0–24.5)
Plasma cimetidine at 30 min (s.d.) (ng ml^{-1})	10		1153‡ (702)	288 (361)	500 (445)
C_{max} (ng mg^{-1})	10		1421 (888–1955)	1632 (1075–2189)	1283 (1028–1537)
t_{max} (min)	10		49.5† (32.7–66.3)	78.0 (65.8–90.2)	75.0 (59.8–90.2)

** $P = 0.01$; *** $P = 0.001$ compared with N; † $P < 0.05$; ‡ $P < 0.01$ between Groups E, S and C.

Keating, P. J. *et al.* (1978), *Br. J. Anaesth.*, **50**, 1247.

An *in vitro* model for studying suxamethonium-induced muscle damage—preliminary results

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Suxamethonium chloride (sux) is associated with muscle damage as shown by a rise in serum creatine kinase (CK). The determinants of this damage are unknown but calcium-induced membrane phospholipid degradation has been suggested (McLoughlin *et al.*, 1988). An *in vitro* isolated muscle preparation using the biventer cervicis muscle of the chick to produce Sux-induced muscle damage is described. It is intended that this preparation should serve as a model for investigating the action of chemical inhibitors on this damage.

One day old chicks were sacrificed in an ether chamber and the biventer cervices muscles removed by careful dissection. The muscles were mounted in organ baths containing 6 ml bicarbonate-buffered Krebs solution and gassed using a 95% oxygen and 5% carbon dioxide mixture and was maintained in a thermostatically-controlled water bath at 37° C. After stabilization, media were exchanged and stored for analyses of baseline ($t0$) CK output. Each preparation then received 30 min exposure from $t0$ to $t30$ to one of four treatments: 1) 50 mM sux solution (S), 2) 3% halothane alone (H), 3) sux + 3% halothane (S + H), and 4) a control group incubated in Krebs solution without intervention (C). Following the treatment period, the medium in each bath was replaced at 30 min intervals for a further 60 min. Specimens were taken at 30 ($t30$), 60 ($t60$) and 90 ($t90$) min and stored for CK analysis. Statistical significance of the results was tested by analysis of variance and $P < 0.05$ considered significant.

Muscle preparations with a baseline CK output of greater than 50 u l^{-1} were removed from analysis as they were felt to have incurred significant damage on dissection. The results (Table 1) showed that CK output remained constant or tended to decrease throughout the study period in the S, H and C groups. Significant increases in CK output occurred in the S + H group at 30, 60 and 90 min ($P < 0.05$). Peak output occurred at 60 min. These results confirm the previously reported occurrence of significant muscle damage following concomitant exposure to sux and H (Innes & Stromme, 1973). Limited studies (5 preparations) using chlorpromazine (Ch) 100 μM solution suggested attenuation of rise in CK in S + H treated specimens.

Table 1 CK: Mean maximum percentage rise

	S	*H*	*C*	*S + H*	*Ch*
	−8.8	+6.0	−2.5	+155	+10.4
n	15	15	18	22	5

Innes, R. K. R. & Stromme, J. H. (1973). *Br. J. Anaesth.*, **45**, 185.

McLoughlin, C. C. *et al.* (1988). *Anaesthesia*, **43**, 565.

Placebo controlled trial of remoxipride in the prevention of relapse in chronic schizophrenia

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Remoxipride (R), a selective dopamine (D_2)-receptor antagonist (Ögren *et al.*, 1984), was assessed for relapse prevention, tolerability and safety in 39 chronic schizophrenic in-patients, in a 24 week double-blind placebo (Pl) controlled trial. After a 4 week Pl washout, 19 patients were randomised to R (150 to 300 mg daily) and 20 to Pl. Assessments by the Brief Psychiatric (BPRS), Krawiecka and Wing Ward Behaviour Rating Scales, the Andreasen Scale for Negative Symptoms and a Clinical Global Impression (CGI) scale were carried out at admission (AD), baseline (BL), 4, 8, 16 and 24 weeks. Compliance was assessed by measurement of R plasma concentration. Relapse was defined as moderate deterioration on CGI.

The mean (s.d.) age of the patients was 54.2 (11.5) years, 26 were male, and the mean (s.d.) duration of illness was 30.4 (9.8) years. The groups were similar in age, duration and severity of illness and previous response to neuroleptic treatment. All patients were valid for safety and intention to treat analyses. Three patients were withdrawn from the main efficacy analyses, one in the R group because of an intercurrent illness (enlarged prostate), and two in the Pl group (one patient withdrew consent, one at the request of the patient's consultant).

Table 1

	Total BPRS scores *Medians (semi-interquartile range)*		
	AD	*BL*	*LR*
Remoxipride	16 (7)	14.5 (14)	10 (17)*
Placebo	11 (9)	13 (11)	22 (16)

* Different from Pl, $P = 0.03$ (Change from BL different from Pl, $P = 0.016$) (Wilcoxon)

In the R group 11 patients completed the 24 weeks treatment without relapse compared with three in the Pl group ($P = 0.008$). The CGI showed six of the R patients were moderately improved compared with one Pl patient ($P = 0.04$) at the last rating (LR). The total BPRS scores are shown in Table 1.

R was well tolerated. At the last rating the most common treatment-emergent adverse effects were: sleep problems (4 R, 7 Pl), difficulty concentrating (7 Pl), depressed mood (3 R), poor appetite (3 R) and irritability (3 Pl). Akathisia (mild) was seen in one patient in each group. Mild hypo-/akinesia and dyskinesia were recorded in one patient in the Pl group.

R was significantly better than Pl in preventing relapse in these chronic schizophrenic patients and was well tolerated.

Ögren, S. O. *et al.* (1984). *Eur. J. Pharmac.*, **102**, 459.

Multiple sub-types of the NPY receptor in adult ventricular cardiomyocytes

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It has been previously shown that in ventricular cardiomyocytes neuropeptide Y (NPY) decreases isoprenaline-stimulated accumulation of cAMP (Millar *et al.*, 1988) and contractile response (Piper *et al.*, 1989). The finding that contractile response was more sensitive than the accumulation of cAMP to NPY indicated that the peptide may act through multiple signalling systems. The aim of this study was to test the hypothesis that NPY interacts with ion channels in its modulation of the contractile response.

Ventricular cardiomyocytes were isolated from adult Wistar rats (200–250 g) or guinea pigs (300–350 g) and resuspended in a modified Tyrode solution containing adenosine deaminase (5u ml^{-1}). NPY attenuated the increase in the contractile response induced by isoprenaline (10^{-7} M) in a dose-dependent manner and the IC_{50} value was 4×10^{-9} M. In the presence of 4-aminopyridine (4-AP, 0.5 mM), which is selective for the transient outward potassium ($i_{to}K^+$) current, the inhibitory effect of NPY (10^{-7} M) was completely abolished, whereas the positive contractile response to isoprenaline was unaffected. Like NPY, the non-selective muscarinic receptor agonist, oxotremorine (10^{-7} M) and the selective A_1-receptor antagonist (-)-N^6-phenylisopropyladenosine (PIA) attenuated the contractile effect of isoprenaline (10^{-7} M). 4-AP did not influence the effect of PIA, but the inhibitory effect of oxotremorine was reduced by 61%. Thus, the inhibitory effect of PIA and oxotremorine differs in mechanism from that of NPY. The inhibitory action of all three agents could be abolished by treating the cells with pertussis toxin (1 g ml^{-1}, 37° C, 6 h). NPY (10^{-7} M) did not significantly influence the basal contractile response in rat cardiomyocytes: in the presence of 4-AP, however, the contractile response was stimulated in a dose-dependent manner and the EC_{50} was 2×10^{-9} M NPY. This effect could be abolished using verapamil (10^{-8} M) but not by pretreatment with pertussis toxin. In guinea pig cardiomyocytes, NPY (10^{-7} M) increased the contractile response in the absence of 4-AP by 39% and this effect was blocked by verapamil (10^{-8} M).

From these results we propose the existence of two or three subtypes of the NPY receptor on the ventricular cardiomyocyte of the adult rat, one linked to adenylate cyclase, a second to the $i_{to}K^+$ current (which could be the same as the first one) and a third to a L-Ca^{2+} channel. In ventricular cells from the guinea pig heart, NPY only activates the L-Ca^{2+} channel to induce a positive contractile response.

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Millar, B. C. *et al.* (1988). *Naunyn-Schmied. Arch. Pharmac.*, **338**, 426.

Piper, H. M. *et al.* (1989). *Naunyn-Schmied. Arch. Pharmac.*, **340**, 333.

The effects of time and dose on the relative β_1/β_2-receptor antagonism of betaxolol and atenolol

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Betaxolol and atenolol are cardioselective β-adrenoceptor blocking drugs which exhibit selective antagonism of β_1-receptors, and are both recommended for use in once daily dosage. The purpose of the present study was to evaluate the effects of time and dose on the relative β_1- and β_2-receptor antagonism of betaxolol and atenolol. Six normal subjects (mean age 23 years) were given randomised single oral doses of betaxolol 10 mg (B10), 40 mg (B40), 80 mg (B80); atenolol 50 mg (A50), 200 mg (A200); or placebo (PL), at weekly intervals. Measurements of β_1-adrenoceptor blockade (reduction of exercise heart rate) and of β_2-adrenoceptor

blockade (attenuation of isoprenaline responses) were made at baseline, and at 2 h, 4 h, 6 h, 8 h, 24 h after drug ingestion. Dose-ratios were calculated (by comparison with placebo) for the doses of isoprenaline required to increase finger tremor by 100% (IT_{100}), heart rate by 25 beats min^{-1} (IH_{25}) and to decrease DBP by 20 mm Hg (ID_{20}), after each treatment. Mean values for C_{max} and t_{max} were as follows: B10 (33 ng ml^{-1}, 3.7 h), B40 (84 ng ml^{-1}, 4.0 h), B80 (179 ng ml^{-1}, 3.7 h); A50 (261 ng ml^{-1}, 2.7 h), A200 (1369 ng ml^{-1}, 2.0 h). Reduction of exercise heart rate (EHR) occurred in dose-dependent fashion up to a ceiling at B40 (as % reduction *cf.* placebo, at peak and 24 h): B10 16.2 to 10.2%, B40 27.1 to 16.2%, B80 27.0 to 18.7%; A50 20.9 to 9.1%, A200 28.8 to 15.0%. There were also dose-related increases in β_2-adrenoceptor antagonism (IT_{100} dose-ratios, at peak and 24 h): B10 2.1 to 1.2, B40 4.7 to 1.8, B80 6.0 to 4.7; A50 2.0 to 1.2, A200 4.7 to 1.8. There were similar trends for attenuation of heart rate and DBP responses to isoprenaline. Ratios of β_1 : β_2-receptor antagonism were calculated (as % reduction EHR ÷ IT_{100} dose-ratio) to provide an index of β_1-receptor selectivity at peak and 24 h: B10 7.7 to 8.5, B40 5.8 to 6.2, B80 4.5 to 4.0; A50 10.5 to 7.6, A200 6.1 to 8.8. Thus, increasing doses of betaxolol and atenolol were associated with a progressive decline in the degree of selective β_1-adrenoceptor blockade. The selectivity ratio was unchanged with betaxolol after 24 h compared with peak effects. In contrast, ratios for A200 and A50 were comparatively reversed after 24 h. This is due to the relatively greater decline in β_2- and β_1-adrenoceptor antagonism with A200 and A50 respectively. Values for the % decline (from peak to trough) in β_1- and β_2-adrenoceptor blockade were as follows: A50 (β_1 57%, β_2 40%), A200 (β_1 45%, β_2 62%); B10 (β_1 38%, β_2 43%), B40 (β_1 41%, β_2 45%), B80 (β_1 30%, β_2 22%). These findings infer that the use of twice daily low dose atenolol or betaxolol might be of greater benefit in producing effective 24 h blockade of β_1-receptors, without causing significant antagonism of β_2-receptors which occurs with once daily high dose therapy. Further studies are now indicated to assess whether this type of regime might be more preferable for patients with angina pectoris who have coexistent airflow obstruction or peripheral vascular disease.

α- and β-adrenoceptor mediated venous responsiveness of dorsal hand veins in patients with severe heart failure

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Congestive heart failure (CHF) is associated with increased sympathetic and hormonal activation resulting in vasoconstriction and increased venous tone (Zelis & Flaim, 1979). Down regulation of β-adrenoceptors has been demonstrated in the heart but it is not known if comparable changes occur in the peripheral veins. We hypothesized that i) prolonged excessive sympathetic activity will result in decreased sensitivity of α-adrenoceptors to phenylephrine (PE); ii) increased circulating catecholamines may in turn alter β-adrenoceptor mediated venodilatation to isoprenaline (IP).

Fourteen patients with severe CHF (55 ± 3 years; LVEF, 13.4% ± 1.5 (s.e. mean)) were studied and compared with eleven age-similar normals (52 ± 2 years). Venous responsiveness was measured in a dorsal hand vein with a linear variable differential transformer (Aellig, 1981). α-adrenoceptor mediated venoconstriction was assessed with graded infusions of PE (2–17,000 ng min^{-1}). The PE concentrations (PE_{50} and PE_{80}) to cause 50% and 80% venoconstriction from maximal 5% dextrose distension at 45 mm Hg were calculated. Veins were then pre-constricted by infusion of PE_{80} dose. β-adrenoceptor mediated venodilatation was assessed with concurrent graded infusions of IP (2–1, 000 ng min^{-1}). The IP concentration (IP_{50}) needed to produce 50% maximal venodilatation (response to infused nitroglycerine, 100 ng min^{-1}) was determined.

Plasma catecholamine levels were significantly elevated in CHF compared with normals (noradrenaline: 4676 ± 234 *vs* 1397 ± 123 pmol l^{-1}, $P < 0.001$; adrenaline: 411 ± 18 *vs* 161 ± 33 pmol l^{-1}, $P < 0.001$). The PE_{50} was significantly increased in severe CHF patients (4685 ± 710 ng min^{-1}) as compared with normals (2176 ± 374 ng min^{-1}, $P < 0.01$). IP_{50} was not significantly different in severe CHF *vs* normals (50 ± 25 *vs* 76 ± 66 ng min^{-1}). There was no significant difference between CHF and normals in the maximal venous distension with either infused dextrose or nitroglycerine.

In summary, the results show evidence of decreased α-adrenoceptor responsiveness of hand veins to PE in severe CHF. However, there was no apparent alteration in responsiveness of β-adrenoceptors to IP despite elevated plasma adrenaline levels. The altered α-adrenoceptor responsiveness may result in modification of the peripheral venoconstrictive response in severe CHF.

Aellig, W. H. (1981). *Br. J. clin. Pharmac.*, **11**, 237.

Zelis, R. & Flaim, S. F. (1979). *Prog. Cardiovasc. Dis.*, **24**, 437.

The effects of chronic dosing on the relative β_1/β_2-receptor antagonism of betaxolol and atenolol

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Selective β_1-adrenoceptor blockade has been shown to be a relative rather than absolute property, in that antagonism of β_2-receptors is a dose-related phenomenon (Lipworth *et al.*, 1989a,b). The degree of β_2-receptor antagonism is the limiting factor for the use of β-adrenoceptor blocking drugs in patients who have coexistent airflow obstruction, peripheral vascular disease and diabetes mellitus. The purpose of this study was to evaluate the effects of chronic-dosing on the relative β_1/β_2-receptor antagonism of betaxolol and atenolol. Nadolol was used for comparison as a reference non-selective β-adrenoceptor antagonist. Six normal subjects were given once daily treatment for 15 days with placebo (PL), betaxolol 10 mg (B10),, 40 mg (B40); atenolol 100 mg (A100); and nadolol 40 mg (N40). Measurements of β_1-adrenoceptor blockade (reduction of exercise heart rate) and of β_2 adrenoceptor blockade (attenuation of isoprenaline responses) were made after the first, eighth and fifteenth doses of each drug. Dose-ratios were calculated (by comparison with placebo) for the doses of isoprenaline required to increase finger tremor by 100% (IT_{100}), heart rate by 25 beats min^{-1} (IH_{25}) and to decrease DBP by 10 mm Hg (ID_{10}), after each treatment. There were appropriate dose-related increases in blood concentrations between B10 and B40 and there was significant drug accumulation between single-dose and steady-state levels. The reduction in exercise heart rate (EHR) with B10 was less in comparison with all other treatments. There were no significant differences in effects on EHR between single and chronic-dosing for any of the treatments (% reduction EHR compared with PL, on days 1 and 15): B10 (18.2, 19.0), B40 (28.6, 26.5); A100 (22.7, 23.1); N40 (26.6, 23.8). Dose-ratios for attenuation of isoprenaline-induced tremor were significantly greater with B40 compared with B10 or A100 (no IT_{100} dose-ratio could be calculated for N40). There were no differences between single and chronic-dosing (IT_{100} dose-ratios on days 1 and 15): B10 (3.0, 2.5), B40 (4.4, 5.3); A100 (4.0, 3.0). Attenuation of the chronotropic response to isoprenaline by N40 was significantly greater than all other treatments, and there were no differences between IH_{25} dose-ratios on days 1 and 15: B10 (2.8, 3.6), B40 (5.1, 5.8); A100 (3.6, 3.6); N40 (19.0, 17.4). There were similar trends for DBP responses. Thus, despite drug accumulation after chronic-dosing, there was no evidence of any increase in either β_1- or β_2-receptor antagonism at steady-state in comparison with after single-dosing. These results infer that the degree of β_2-receptor antagonism at steady-state may be reliably predicted from the single-dose effects of treatment with cardioselective β-adrenoceptor blocking drugs.

Lipworth, B. J. *et al.* (1989a). *Br. J. clin. Pharmac.*, **28**, 95.

Lipworth, B. J. *et al.* (1989b). *Eur. J. clin. Pharmac.*, **37**, 297.

Comparative cardiovascular effects of nifedipine and nicardipine in the presence of atenolol

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We have previously detected small differences in the haemodynamic effects of oral nifedipine and nicardipine in healthy volunteers using transthoracic electrical bioimpedance cardiography (TEBC), with nicardipine producing slightly larger increases in stroke volume and ventricular contractility than equivalent doses of nifedipine (Thomas & Smith, 1990). In order to determine whether this difference is maintained or exaggerated in the presence of β-adrenoceptor blockade, a placebo controlled double-blind crossover study was performed in 12 healthy male volunteers to compare the cardiovascular effects of single oral doses of nifedipine (5, 10 and 15 mg) and nicardipine (20 and 30 mg) in the presence of atenolol 100 mg. Haemodynamic measurements were made by TEBC 2 h following drug administration during supine rest, passive tilting (70° head-up), graded bicycle exercise (30–150W), and recovery from exercise.

In the absence of calcium channel blockade, atenolol reduced mean blood pressure, heart rate, and cardiac index, and increased stroke volume, peripheral resistance, pre-ejection period, and ventricular ejection time, particularly during and after exercise. In comparison with atenolol alone, addition of nifedipine or nicardipine reduced peripheral resistance but did not produce significant changes in stroke volume, cardiac output, dZ/dt[max], pre-ejection period (PEP), Ventricular ejection time (VET), PEP/VET, or Heather index at any point in the experiment. Similar reductions in peripheral resistance were produced by nifedipine 10 mg and nicardipine 20 and 30 mg. These apparently equivalent doses of nifedipine and nicardipine had similar effects on stroke volume (Table 1), cardiac index, PEP/VET and Heather index.

Thus the increases in ventricular contractility previously demonstrated in association with nifedipine and nicardipine therapy were not observed in the presence of β-adrenoceptor blockade, and under these conditions no important differences were observed between the cardiovascular effects of these two calcium channel blockers.

Table 1 Effects of atenolol nifedipine (NF), and nicardipine (NC) on TEBC-derived stroke volume index (ml m^{-2}). Mean values (95% confidence intervals)

	Placebo	*Atenolol alone*	*Atenolol + NF 10 mg*	*Atenolol + NC 20 mg*	*Atenolol + NC 30 mg*
Supine	80.3 (79.6–83.8)	79.6 (77.5–84.2)	81.5 (78.6–84.3)	80.4 (77.9–82.9)	80.0 (77.0–82.9)
Tilted	47.8 (45.8–49.9)	54.9 (52.3–57.5)*	53.8 (51.0–56.6)*	56.8 (53.8–59.9)*	54.8 (52.2–57.5)*
Exercise (150W)	75.5 (72.1–79.0)	86.3 (80.4–86.9)*	81.4 (77.3–85.5)	81.7 (78.7–84.8)	82.3 (78.5–86.2)

* $P < 0.05$ *vs* placebo by ANOVA.

Thomas, S. H. L. & Smith, S. E. (1990). *Br. J. clin. Pharmac.*, **28**, 212P.

Prediction and optimisation of antihypertensive therapy with enalapril and nifedipine

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Using concentration-effect modelling in individual essential hypertensives we have previously shown that with both enalapril and nifedipine the fitted model parameters for acute and chronic therapy are closely correlated (Donnelly *et al.*, 1988, 1990). In this study the application of this concentration effect modelling technique was evaluated in the prediction of long-term blood pressure response from the first dose response as characterised by an E_{max} model for enalapril and a linear model for nifedipine. The antihypertensive response to a single 20 mg dose of enalapril or nifedipine (Retard) was characterised in 13 and 14 essential hypertensives respectively. The pharmacokinetic-dynamic model parameters were then used to predict long-term response. Predictions were compared with the measured responses after 6 weeks of 20 mg enalapril once daily and 20 mg nifedipine twice daily.

The observed and predicted blood pressure profiles over 12 h were well correlated in all patients who were treated with enalapril. At trough (pre-dose) the observed fall in systolic BP was 18.9 ± 6.8 compared with predicted 17.6 ± 5.8 mm Hg (mean prediction error 1.2 ± 3.4 and correspondingly at 4 h post dose, 37.1 ± 6.8 compared with 37.4 ± 4.8 mm Hg (mean error −0.3 ± 3.7). With nifedipine the mean prediction errors for the 14 patients at trough and 4 h post dosing were −0.4 ± 8.0 and 0.6 ± 10.6 mm Hg respectively. However, whilst the observed and predicted blood pressure profiles were in good agreement in 11 of the 14 patients, in the remaining 3 they were widely discrepant and it was apparent that these discrepancies arose from inappropriate prediction of the pharmacokinetic profiles at steady state.

For both drugs the parameters were used to simulate steady state responses to alternate doses and dose frequencies. With enalapril twice daily dosing significantly increased the trough to peak BP response ratio to 75 ± 5% with 10 mg twice daily compared to 33 ± 16% with 20 mg once daily. Similarly the trough to peak blood pressure response to nifedipine was considerably enhanced by thrice compared with twice daily dosing, the respective trough to peak ratios being 66 ± 9% and 47 ± 9%.

These findings suggest that concentration effect modelling has potential in predicting long-term antihypertensive response especially for enalapril and the technique may also be of particular value for optimising dosage regimens in individual patients.

Donnelly, R. *et al.* (1988). *Hypertension*, **12**, 443.

Donnelly, R. *et al.* (1990). *Hypertension*, **15**, 301.

Cough and enalapril: assessment by spontaneous reporting and visual analogue scale under double-blind conditions

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Persistent dry cough has emerged as an important side-effect of ACE inhibitors, and has been the commonest cause of withdrawal in some series (Yeo & Ramsay, 1990). Its frequency depends greatly on the method of ascertainment (Yeo & Ramsay, 1990). We have assessed the incidence and prevalence of cough related to enalapril by spontaneous reporting, and a visual analogue scale, during a 6-month random double-blind parallel-group study comparing enalapril with nifedipine in 128 patients.

Cough was reported spontaneously by 6.2% (95% CI 0.3–12.1%) of enalapril-treated patients, and by none on nifedipine. After 24 weeks treatment, increases in visual analogue scale (VAS) scores for cough frequency of 8 mm or more were significantly more common for

enalapril than nifedipine (difference 21.5%, 95% CI 7.3–35.7%; $P < 0.025$). Increased cough frequency was present throughout the study consistently in women, but less consistently in men (Table 1). High scores for cough were not related to the dose of enalapril. The data are consistent with those from open clinic-based studies of the incidence and prevalence of enalapril-induced cough. Although cough can be detected after only 8 weeks of treatment by visual analogue scale, the evidence available suggests that it may increase in severity over time, and that even a period of 6 months treatment is too short to evaluate ACE inhibitor-induced cough adequately.

Table 1 Number (and %) of patients with increase in VAS score for cough of 8 mm or more

	Enalapril			*Nifedipine*		
	Women	*Men*	*Total*	*Women*	*Men*	*Total*
8 weeks	10/22[1] (45.5%)	4/33 (12.1%)	14/55 (25.5%)	3/15 (20.0%)	7/33 (21.2%)	10/48 (20.8%)
24 weeks	8/22[2] (36.4%)	9/35 (25.7%)	17/57[2] (29.8%)	2/15 (13.3%)	2/33 (6.1%)	4/48 (8.3%)
Intention to treat	8/25[3] (32.0%)	10/37[4] (27.0%)	18/62[2] (29.0%)	4/26 (15.4%)	2/35 (5.7%)	6/61 (9.8%)

[1] $P < 0.02$ *vs* men on enalapril
[2] $P < 0.025$ *vs* total nifedipine
[3] $P < 0.05$ *vs* total nifedipine
[4] $P < 0.05$ *vs* men on nifedipine

Yeo, W. W. & Ramsay, L. E. (1990). *J. Human Hypertension*, **4**, 517–520.

Reproducibility of immediate change in cardiac output with standing assessed by electrical bioimpedance cardiography

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Standing up produces a transient age-dependent tachycardia exceeding that produced by passive tilting (Dambrink & Wieling, 1987). Cardiac output usually falls in changing from the supine to the standing or tilted position but the acute changes during the first minute have not been studied extensively because of lack of suitable methodology. Transthoracic electrical bioimpedance cardiography (TEB) provides a means of monitoring beat to beat changes in stroke volume during physiological manoeuvres (Smith *et al.*, 1987) and has already been used to study the sustained effects of passive tilting (de Mey & Enterling, 1987).

An automated impedance cardiograph (BoMed, NCCOM3-R6) was used to compute stroke volume and HR on line. TEB (averaging every 12 heart beats) and BP recordings (1 min intervals) were made on six fasting healthy male volunteers for 5 min supine after an initial 5 min supine rest and for 5 min standing. This was repeated immediately and the whole procedure repeated the next morning. TEB recordings were made for beat to beat values and the HR, stroke index (SI) and cardiac index (CI) compared within subjects by coefficient of variation (CV) for the four episodes of standing from 10 heart beats prior to standing to 60 beats after standing. Mean values from the 10th min supine and the fifth min standing were also compared.

Within subject CVs of mean CI values (mean supine 5.3% [range 1.9–11.8]; standing 5.0% [3.4–6.5]) were similar to mean HR values (mean CV supine 6.2% [1.5–15.0]; standing 4.0% [1.4–6.7]. Within subject variation for beat to beat CI over standing was greater (mean CV 9.8% [6.5–12]) but this was again similar to HR variation (mean CV 9.1% [7.9–11.3]). The pattern of response in SI and CI differed between subjects but all showed elevations above supine levels of CI during the first min of standing which appeared mainly due to a greater proportional increase in HR than decrease in SI but in some subjects changes in SI did not exactly mirror changes in HR. Mean values (with s.d.) for one subject are shown in Figure 1.

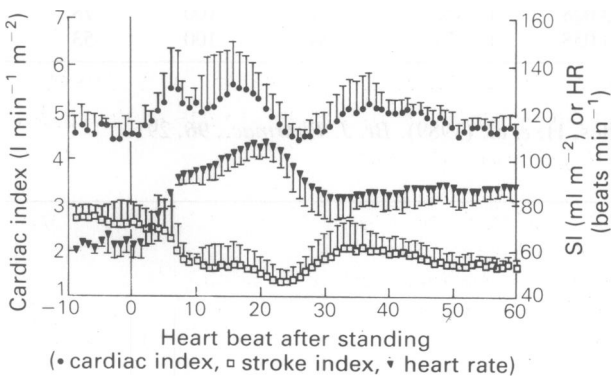

Figure 1 Heart beat after standing (● cardiac index, □ stroke index, ▼ heart rate).

Elevations in CI after standing showed similar reproducibility to HR changes with TEB. If this finding can be confirmed it may provide an additional means of studying the effects of drugs on autonomic reflexes.

Dambrink, J. H. A. & Wieling, W. (1987). *Clin. Sci.*, **72**, 335.
de Mey, C. & Enterling, D. (1987). *Am. J. Noninvas. Cardiol.*, **1**, 188.
Smith, S. A. *et al.* (1987). *Clin. Sci.*, **72**, 423.

Effect of a prostaglandin DP-receptor partial agonist (192C86) on platelet aggregation and the cardiovascular system in healthy volunteers

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Prostaglandin (PG) D_2, PGI_2 and PGE all inhibit platelet aggregation, but their use in anti-thrombotic therapy is limited by vasodilatation. Since PGD (DP)-receptors on platelets and vascular smooth muscle are similar (Giles *et al.*, 1989), selective inhibition of platelet aggregation by a DP-receptor agonist could only be achieved if receptor density is higher on platelets. To determine whether such differential receptor density exists, we have examined the acute effects on platelet aggregation and the cardiovascular system of a highly selective DP-receptor partial agonist 192C86 [(±)-5-(3-carboxypropylthio)-1-(2-cyclohexyl-2-hydroxyethylideneamino)-3-ethyl-hexahydrocyclopenta-(d)imidazol-2(1H)-one] in healthy volunteers.

Using an open, dose-escalating study design, four healthy male volunteers received constant rate intravenous infusions of 192C86 for up to 60 min. *Ex vivo* platelet aggregation to ADP (2–5 μM) and collagen (0.1–1.0 μg ml^{-1}) in platelet-rich plasma (PRP) (Payton dual-channel aggregometer) and whole blood (WB) (Ultra-Flo 100 Platelet Counter) was studied at baseline, at 15, 30 and 60 min of each infusion and at 180 min post-infusion. Heart rate (HR), systolic (SBP) and diastolic (DBP) blood pressure were measured at frequent intervals. Adverse experiences were monitored by checklist. Facial flushing was assessed by the volunteer using a visual analogue scale, by an observer using a three-point scale and by full face colour photographs. Blood was taken for assay of plasma 192C86 concentration by r.i.a.

192C86 inhibited platelet aggregation to ADP and collagen both in PRP and WB in a dose-dependent manner. However, this was always accompanied by a decrease in DBP, increase in HR and facial flushing.

The highest rate infusion was poorly tolerated and was stopped after 20 min due to symptomatic hypotension on standing. Principal reported adverse experiences were related to symptoms of vasodilatation (facial flushing, nasal stuffiness and headache) and their severity was dose-related. Plasma concentrations of 192C86 were at or below the limits of sensitivity of the r.i.a. (0.5 ng ml^{-1}).

The dose-response relationships for inhibition of platelet aggregation and vasodilatation by 192C86 were not separable. There was no evidence of a difference in receptor density which could be exploited to obtain selective inhibition of platelet aggregation by DP-receptor partial agonists.

Table 1 Mean ± s.e. mean results

Infusion rate (μg kg^{-1} *min)*	n	*Maximum % inhibition of aggregation*				*Maximum change in HR (beats* min^{-1}*) and supine BP (mm Hg)*			*Maximum scores of flushing*	
		ADP		*Collagen*					*Observer*	*Volunteer*
		PRP	*WB*	*PRP*	*WB*	*HR*	*DBP*	*SBP*	*(0–3)*	*(0–100)*
0.007	4	20 (±11)	23 (±6)	57 (±17)	19 (±9)	+8 (±4)	−12 (±3)	−5 (±4)	1.75 (±0.25)	18.4 (±4.4)
0.014	4	36 (±18)	38 (±6)	73 (±17)	49 (±14)	+14 ±5)	−11 (±2)	+11 (±4)	2.5 (±0.29)	28.0 (±3.7)
0.028	1	55	47	100	78	+28	−11	+17	3	26.5
0.058	1	71	34	100	53	+28	−16	−17	2	26.5

Giles, H. *et al.* (1989). *Br. J. Pharmac.*, **96**, 291.

Adequacy of twice daily dosing with potassium chloride and spironolactone in thiazide-treated hypertensive patients

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Thiazide-induced hypokalaemia is common, usually mild, and probably harmless to most patients. It predisposes to arrhythmia in those taking digoxin and drugs prolonging the QT interval, and these patients need effective prophylaxis. Spironolactone 50 mg proved more effective than potassium chloride 64 mmol daily in correcting hypokalaemia (Ramsay *et al.*, 1980), but plasma K was measured only at a single time point. Plasma K may vary markedly during a dose interval (Toner & Ramsay, 1985), and predispose to arrhythmias because of changes in the ratio extra- : intra-cellular K. We examined the plasma K concentration-time profile within dose intervals during treatment with potassium chloride and spironolactone.

Eighteen hypertensive patients (age 36–71 years) taking bendrofluazide 5 mg daily were randomised to potassium chloride 32 mmol twice daily, spironolactone 25 mg twice daily, or placebo twice daily, each given 12 hourly. Plasma K concentration-time profiles and 24 h urinary K were measured before and after 4–6 weeks of treatment. When compared with placebo, potassium chloride and spironolactone increased the peak and 12 h AUC for plasma K (Table 1). The 12 h AUC for plasma K was 35% larger with spironolactone than potassium chloride (NS). Potassium chloride increased urine K significantly, and had bioavailability of 96%. With both active drugs peak plasma K occurred 2–3 h after dosing and efficacy tended to wane at 12 h. However variability within dose intervals was not increased markedly. 12 h dosing is probably satisfactory for potassium chloride and spironolactone at these doses.

Table 1 Mean (s.e. mean) changes from baseline values for three treatments

	Placebo	*KCl 64 mmol*	*Spiro 50 mg*
Plasma K			
Pre-dose (mmol l^{-1})	0.26 (0.22)	0.48 (0.15)	0.53 (0.25)
Peak (mmol l^{-1})	0.48 (0.14)	0.99 (0.09)**	1.18 (0.17)#
12 h (mmol l^{-1})	0.15 (0.10)	0.16 (0.19)	0.49 (0.09)
12 h AUC (mmol l^{-1} min)	57 (79)	321 (79)*	463 (94)**
Urine K (mmol 24 h^{-1})	−7 (5.9)	+31 (1.7)##	−2 (4.4)

* $P < 0.1$, ** $P < 0.05$, # $P < 0.02$ *vs* placebo.
$P = 0.002$ *vs* placebo and spironolactone.

Ramsay, L. E. *et al.* (1980). *Clin. Pharmac. Ther.*, **27**, 533.
Toner, J. M. & Ramsay, L. E. (1985). *Br. J. clin. Pharmac.*, **19**, 489.

Frusemide disposition in patients on continuous ambulatory peritoneal dialysis (CAPD)

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CAPD is extensively used in the treatment of end stage renal failure and drugs may be eliminated across the peritoneal membrane during the procedure. The disposition of frusemide has been investigated in patients with chronic renal failure with conflicting results (Bowles Ponto, 1990) and studies have therefore been performed in patients on CAPD to provide a model for the non renal clearance of frusemide and to assess the extent of its peritoneal elimination. Eight CAPD patients (creatinine clearance < 5 ml min^{-1}) had renal failure due to polycystic kidneys (2), pyelonephritis (1), nephrocalcinosis (1) and chronic glomerulonephritis (4). The mean age was 67 years (58–73), mean weight 62 kg (48–74) and mean duration of CAPD 43 months (7 months–10 years). Four 2 l exchanges were performed each day via an indwelling Tenckhoff catheter with standard peritoneal solutions containing 1.36% or 2.27% glucose. The fasting patients took two 40 mg frusemide (Lasix) tablets. Venous blood was sampled for 8 h and all urine and dialysate collected for 24 h. The study was repeated a week later with 80 mg of frusemide infused intravenously over 1 h. Frusemide was assayed by h.p.l.c. The 'SIPHAR' pharmacokinetic programme was used to fit plasma concentration-time data to a one compartment model with extended least squares weighting. Clearance was calculated as dose/AUC and V_{ss} as clearance × MRT.

Oral frusemide was absorbed slowly after a lag of 12 to 90 min. The mean C_{max} was 3.2 ± 1.4 mg l^{-1} and t_{max} varied from 60 to 240 min. Bioavailability was from 56–100%. The mean plasma $t_{½}$ was 232 ± 76 min after oral and 162 ± 50 min after intravenous dosing. The total clearance was 60 ± 18 ml min^{-1}. Six patients produced small quantities of urine but less than 1% of the dose was

excreted in 24 h and less than 1% was eliminated via the peritoneal membrane over the same time period. The results suggest that the oral absorption of frusemide in CAPD patients is delayed and the bioavailability variable. The renal clearance is negligible. Peritoneal clearance does not contribute significantly to non renal clearance perhaps because frusemide is highly bound to plasma proteins.

Table 1 Results (expressed as mean ± s.d.)

	Lag time (min)	C_{max} *(mg l^{-1})*	t_{max} *(min)*	*Bioavailability (%)*	$t_{½}$ *(min)*	*MRT (min)*	*Clearance (ml min^{-1})*	V_{ss} *(l)*
Oral	32 ± 28	3.2 ± 1.4	142 ± 58	80.5 ± 15.4	232 ± 76	415 ± 110	–	–
i.v.	–	–	–	–	162 ± 50	257 ± 62	60 ± 18	15 ± 4.4

Bowles Ponto, L. L. & Schoenwald, R. D. (1990). *Clin. Pharmacokin.*, **18**, 381.

POSTER COMMUNICATIONS

The lack of interaction between temafloxacin and oral contraceptive steroids

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Oral contraceptive steroids (OCS) are the most effective form of contraception in regular use. However, in long term use it has been reported that their efficacy may be impaired by concomitant use of broad spectrum antibiotics since such antibiotics might interrupt the enterohepatic recirculation of ethinyloestradiol. The Committee on Safety of Medicine has recorded 63 reports of contraceptive failure over a 17 year period in women taking antibiotics with their OCS (Back *et al.*, 1988). However controlled studies have not shown any systematic evidence of interaction between broad spectrum antibiotics and OCS. Temafloxacin is a new quinolone antibiotic that has a broad spectrum of activity against both gram positive and gram negative aerobic bacteria. We have therefore studied the interaction between temafloxacin and OCS.

Twelve women aged 22–32 years who were in good health and were taking long term OCS were recruited into the study. All were taking OCS preparations containing 30 μg ethinyloestradiol (EE_2) and levonorgestrel (Ng) (150 μg, $n = 11$) and 250 μg ($n = 1$), and had been taking them for a minimum of 6 months. Blood samples (10 ml) were taken 10–12 h after dosing on days 5, 6, 7 and 8 of the cycle of contraceptive use in a control cycle and in the following cycle during which they took temafloxacin 600 mg twice daily for 7 days starting on day 1 of the contraceptive cycle. Plasma samples were stored at −20° C until assayed for EE_2, Ng, FSH and LH. Blood samples were also taken on 19, 20 and 21 of each cycle for measurement of plasma progesterone concentrations. All assays were performed using radioimmunoassay. The women gave informed consent to the study which was approved by the local Ethics Committee.

There were no significant changes in any of the parameters measured. In the control cycle the mean EE_2 concentration (± s.d.) was 61.4 ± 21.1 pg ml^{-1} while in the temafloxacin cycle the value was 68.5 ± 26.6 pg ml^{-1} ($P > 0.1$). The mean levonorgestrel concentration was 2.07 ± 0.78 ng ml^{-1} in the control cycle and 1.89 ± 0.77 ng ml^{-1} in the temafloxacin cycle ($P > 0.1$) while the FSH results were 2.90 ± 1.17 and 3.05 ± 1.33 miu ml^{-1} respectively. There were no significant changes in LH levels. The mean progesterone concentration on days 19, 20 and 21 of the control cycle was 0.53 ± 0.2 ng ml^{-1} and 0.60 ± 0.24 ng ml^{-1} in the temafloxacin cycle ($P > 0.1$) indicating that no woman had ovulated in the temafloxacin cycle. Plasma concentrations of temafloxacin on days 5 and 7 were 8.2 ± 1.6 μg ml^{-1} and 8.6 ± 1.3 μg ml^{-1} respectively indicating good compliance with temafloxacin therapy. We conclude that there is no evidence of a systematic interaction between temafloxacin and OCS.

Back, D. J. *et al.* (1988). *Br. J. clin. Pharmac.*, **25**, 527.

The lack of interaction between clarithromycin and oral contraceptive steroids

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Oral contraceptive steroids (OCS) are the most effective form of contraception in regular use. However, in long term use it has been reported that their efficacy may be impaired by concomitant use of broad spectrum antibiotics. The Committee on Safety of Medicines has recorded 63 reports of contraceptive failure over a 17 year period in women taking broad spectrum antibiotics with their OCS (Back *et al.*, 1988). However controlled trials with antibiotics such as ampicillin have failed to show any evidence of a systematic interaction between such antibiotics and OCS. Clarithromycin is a new synthetic macrolide antibiotic that has a broad spectrum of activity against both gram positive and gram negative organisms and we have therefore studied the interaction between clarithromycin and OCS.

Ten women aged 19–30 years who were in good general health and were taking long term OCS were recruited into the study. All were taking contraceptive preparations containing 30 μg ethinyloestradiol (EE_2) while the progestagen varied between desogestrel (Dg) 150 μg ($n = 5$) and levonorgestrel (Ng) 250 μg ($n = 5$). All had been taking the same OCS preparation for at least 6 months and the OCS preparation did not change during the study. Blood samples (10 ml) were taken 10–12 h after dosing with the OCS preparation on days 5, 6, 7 and 8 of the contraceptive cycle in both a control cycle and in the following cycle during which each woman took clarithromycin 250 mg twice daily for 7 days starting on day 1 of the contraceptive cycle. Plasma samples were stored at −20° C until assayed for EE_2, Ng or Dg, FSH and LH. Blood samples were also taken on days 19, 20 and 21 of each contraceptive cycle for measurement of progesterone concentrations. All assays were performed using radioimmunoassay. The women all gave written informed consent to the study which was approved by the local ethics committee and under Section II(ii) of the Control of Clinical Trials Act (Ireland) 1987.

All 10 women completed the trial satisfactorily and there were no significant changes in any of the parameters measured. In the control cycle the mean EE_2 concentration (± s.d.) was 59.4 ± 29.8 pg ml^{-1} while in the clarithromycin cycle the mean EE_2 value was 63.3 ± 22.3 pg ml^{-1} ($P > 0.1$). The plasma progesterone concentrations did not rise significantly thus indicating no ovulation took place in the clarithromycin cycle. The mean progesterone concentration was 0.47 ± 0.19 ng ml^{-1} in the control cycle and 0.48 ± 0.26 ng ml^{-1} in the clarithromycin cycle ($P > 0.1$). The mean F.S.H. concentration in the control cycle was 2.7 ± 1.2 miu ml^{-1} and in the test cycle was 1.5 ± 0.67 miu ml^{-1} ($P > 0.05$) and there were no significant changes in plasma LH concentrations. We conclude that there is no evidence of a systematic interaction between clarithromycin and OCS.

Back, D. J. *et al.* (1988). *Br. J. clin. Pharmac.*, **25**, 527.

Effect of cimetidine and rifampicin on the metabolism of the specific bradycardic agent, alinidine

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Studies with alinidine (*n*-allyl clonidine) have indicated some metabolism to clonidine, in both patients and healthy volunteers (Harron & Shanks, 1985). The present study investigated the effects of an enzyme inhibitor, cimetidine, and an enzyme inducer, rifampicin, on the metabolism of alinidine to clonidine.

Twelve healthy volunteers (age: 23.9 ± 2.4 years; weight: 69.8 ± 9.6 kg) received alinidine, orally 60 mg depot, twice daily for two periods of 17 days (phase 1 and phase 2). From day 4–17, subjects received 14 days concurrent treatment with cimetidine (200 mg three times daily, 400 mg at night), and rifampicin (600 mg daily as a single dose), in a blind and randomised crossover comparison. A 20 day wash-out period (placebo) of the enzyme inducer and inhibitor followed (18 days included the washout of alinidine). Alinidine was then continued (day 37) for a further 17 days (phase 2) with the alternative treatment, cimetidine or rifampicin. Single oral doses of antipyrine were administered before the commencement of the study, at the end of phase 1, placebo, and phase 2; plasma samples for determination of pharmacokinetic parameters were obtained at 0, 2, 4, 6, 8, 12, and 24 h. Plasma samples for the determination of alinidine and clonidine concentrations were taken at 0, 2, 4, 6, 8, and 12 h, following drug administration on days 3, 17, 37, and 52. C_{max}, T_{max}, AUC, half-lives ($t_{½}$), and oral clearance were calculated, and comparisons made between controls, rifampicin, and cimetidine (Table 1) using ANOVA and Student's *t*-tests.

The mean results (Table 1) indicate that the enzyme inhibitor, cimetidine, had little effect on either alinidine, clonidine, or antipyrine plasma levels. In contrast, the enzyme inducer, rifampicin, decreased antipyrine ($P <$ 0.05) and increased the metabolically-formed clonidine

($P < 0.05$) plasma levels; no effect was noted on alinidine plasma levels.

In conclusion, the formation of clonidine, from alinidine, is increased in the presence of the enzyme inducer, rifampicin.

Table 1

	Antipyrine					*Alinidine*				*Clonidine*		
	C_{max} ($\mu g ml^{-1}$)	t_{max} (h)	$t_{½}$ (h)	$AUC(\infty)$ ($\mu g ml^{-1} h$)	CL ($l h^{-1}$)	C_{max} ($\mu g ml^{-1}$)	t_{max} (h)	$AUC(0–12)$ ($ng ml^{-1} h$)	CL ($l h^{-1}$)	C_{max} ($ng ml^{-1}$)	t_{max} (h)	$AUC(0–12)$ ($ng ml^{-1} h$)
Control	9.89 ±1.38	2.58 ±0.93	12.56 ±3.35	185.4 ±59.0	2.97 ±0.93	143.7 ±47.4	4.00 ±1.30	1206 ±325	53.16 ±13.98	1.41 ±0.47	8.54 ±2.81	15.29 ±5.33
Cimetidine	10.20 ±1.95	2.33 ±9.78	13.84 ±3.71	219.3 ±65.8	2.51 ±0.89	166.9 ±37.3	4.44 ±0.88	1328 ±219	46.21 ±6.92	2.01 ±0.52	7.58 ±3.23	22.19 ±5.79
Rifampicin	8.11 ±0.87	2.00 ±0.00	5.47* ±1.25	72.59* ±19.22	7.40* ±2.18	150.2 ±53.8	5.11 ±1.05	1289 ±442	50.26 ±12.13	4.99* ±1.82	7.67 ±2.39	52.49* ±19.8

* $P < 0.05$

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The excretion of ampicillin in breast milk and its effect on the suckling infant

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A recent survey of drugs administered in the puerperium, carried out in the three major Belfast maternity units indicated that 10.5% of mothers were prescribed ampicillin post delivery. The available published literature has failed to include strict infant monitoring protocols for side-effects to milk excreted ampicillin (e.g. Matheson *et al.*, 1988). The aims of the present study were twofold: to measure the steady-state serum and milk concentrations of ampicillin in mothers receiving ampicillin therapy and to examine whether maternal ampicillin therapy leads to adverse effects in the suckling infants.

Ten breast feeding mothers who were prescribed ampicillin alone post delivery were recruited into the trial which was approved by the University Ethics Committee. Paired milk and blood samples were taken from the mothers at 2, 4 and 6 h post-dosing on treatment days 3 and 4 of ampicillin therapy (500 mg four times daily). Milk and serum samples were assayed for ampicillin content using a sensitive, selective h.p.l.c. technique (Terada & Sakabe, 1985). A further group of breast feeding mothers ($n = 21$), who were receiving ampicillin alone, monitored their infants using a specially designed record sheet, for signs of possible ampicillin induced side-effects including furring of the tongue, spots in the mouth, feeding difficulties, changes in stool frequency and consistency, napkin rash and skin rash, for a period of 15 days post delivery. A scoring chart (Weaver *et al.*, 1988) was used by the mothers to describe stool consistency. A control group of mothers ($n = 45$; no antibiotic therapy) also monitored their infants as did a third group ($n = 14$) who were prescribed Augmentin®. Participating mothers were instructed on how to complete the monitoring sheet by a clinical pharmacist and were assisted (while remaining in hospital) when required, by the paediatric house doctors. These doctors were blinded as to the medication being received by the mothers. Weight change from birth to discharge and the development of jaundice were also recorded.

Serum ampicillin concentrations ranged from 0.56–5.42 $\mu g\ ml^{-1}$ while milk concentrations ranged from 0.015–1.67 $\mu g\ ml^{-1}$. The mean value (± s.e. mean) for the M/S (milk/serum) ratio for ampicillin was 0.23 ± 0.05 (range 0.02 to 0.525). Using the highest ampicillin concentration found in milk, the maximum dose of ampicillin which would be received by the infant is only 0.84 mg. Chi square analysis indicated that there were not significant differences ($P > 0.05$) from control values in any of the monitored parameters in both the ampicillin and Augmentin® infant groups. There were also no significant differences ($P > 0.05$) in the three groups concerning the mean infant birth weights, discharge weights or age when discharged from the maternity units.

Results of both the kinetic and infant monitoring studies indicate that ampicillin is a safe drug for use during breast feeding. Allergic sensitisation is, however, possible. The preliminary data on Augmentin® also suggest that it too is safe during breast feeding.

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Plasma concentrations and response to halofantrine in Thai patients with acute uncomplicated falciparum malaria

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Halofantrine (Hf) has generally been shown to be highly effective against multi-drug resistant strains of *Plasmodium falciparum* in Thailand (Boudreau *et al.*, 1988) although some recent clinical trials have suggested differences in efficacy of oral Hf which may possibly be due to pharmacokinetic factors. In this study our aim was to monitor plasma concentrations during the treatment of a group of Thai patients with acute uncomplicated falciparum malaria, to relate these to the clinical outcome and compare the results obtained with those available from studies in healthy volunteers. Twelve patients, aged 15–60 years were recruited, each gave written informed consent and the study was approved by the Ethics Committee of the Faculty of Tropical Medicine, Mahidol University, Bangkok. Patients received Hf-HCl (500 mg orally) at 6 h intervals for three doses. Parasite counts were performed twice daily until negative then once daily until day 42. Ten patients showed a sensitive response with fever and parasite clearance times of 50 ± 29 and 78 ± 20 h respectively. Two patients had an RII response. Whole blood samples were removed at regular intervals for 14 days. Plasma was obtained, frozen (−20° C) prior to analysis by h.p.l.c. (Milton *et al.*, 1988). Peak concentrations of Hf in responders, observed after the first, second and third doses were 762 ± 458 (mean ± s.d.), 912 ± 489 and 1147 ± 437 $\mu g\ l^{-1}$ respectively). This final value was lower than that obtained in healthy Caucasians (Broom, 1989). Mean maximum concentrations of desbutyl halofantrine (Hfm; $n = 8$) were 397 ± 160 $\mu g\ l^{-1}$ achieved at 55 ± 26 h. The apparent terminal half life of Hf was 4.7 ± 1.3 days. A similar value was obtained from the metabolite profile (4.9 ± 1.6 days). One patient, diagnosed RII, showed peak concentrations of Hf (and Hfm) two orders of magnitude lower. Although this patient vomited 6 times during treatment, this could not entirely explain the RII response as a second RII patient who also vomited showed concentrations of Hf and Hfm within the range of the sensitive responders. We suggest that the large intersubject variability in plasma Hf concentrations may relate in part to its poor and inconsistent bioavailability and that this, rather than true resistance might be responsible for some of treatment failures.

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The effect of fluorination on the metabolic activation of oestrogens to potential carcinogens *in vivo*

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It has been suggested that oxidative metabolism plays an important role in the carcinogenicity of steroid oestrogens. The principal biotransformation considered to be involved in oestrogen carcinogenesis is the formation of C-2 hydroxylated (catechol) metabolites which can be oxidized to chemically reactive species. Substitution of fluorine into C-2 of oestradiol (E_2) reduces the carcinogenicity of E_2 while not affecting its hormonal activity (Liehr, 1983). The present study investigated the influence of fluorination on catecholoestrogen formation *in vivo*.

2-Fluoro[6,7-^{3}H]-oestradiol ([^{3}H]2-FE_2) was synthesised by fluorination and reduction of [^{3}H]-oestrone (Page *et al.*, 1990), and purified by h.p.l.c. It was administered i.v. to anaesthetized male and female rats with biliary cannulae ($n = 4$; 72.5 $\mu g\ kg^{-1}$). Bile was collected for 6 h. Major organs were excised for measurement of residual radiolabelled material.

Four glucuronide metabolites were rapidly and extensively eliminated in bile by males (77% of the dose over 6 h). Females excreted one major and two minor glucuronides. Neither unchanged 2-FE_2 nor E_2 was detected in bile. Hepatic residues represented 0.9% of the dose, whilst < 0.1% per organ(s) was found in kidneys, heart, lung, spleen and brain.

Enzymic hydrolysis liberated three deconjugated metabolites from male and female bile. 2-Fluoroestrone (2-FE_1), identified by co-chromatography, was the major metabolite in both sexes, and the minor metabolites appeared to be D-ring oxidation products. They were isolated from the bile of male rats given a large dose (870 $\mu g\ kg^{-1}$) of [^{3}H]2F-E_2, and characterised by mass spectrometry. The major metabolite yielded the spectrum of 2-FE_1 (m/z 288, $M^{+\cdot}$; m/z 231, M-57), and the two minor metabolites gave spectra with putative $M^{+\cdot}$ (m/z 304) and fragments (m/z 231 & 232) indicative of D-ring oxygenation.

In conclusion, these studies have shown that C-2 fluorination blocks C-2 hydroxylation but not 3-*o*-glucuronylation. This provides a metabolic rationale for the reduced carcinogenicity of 2-FE_3 (Liehr, 1983).

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Inhibition of dapsone-induced methaemoglobinaemia during chronic dapsone administration in the rat

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Dapsone (DDS) undergoes *N*-acetylation to monoacetyl DDS (MADDS) as well as *N*-hydroxylation to a hydroxylamine which is responsible for the toxicity (i.e. methaemoglobinaemia; Met Hb) of the drug. Studies with a single dose of dapsone in man have indicated that Met Hb formation may be greatly reduced by the prior administration of cimetidine (Coleman *et al.*, 1990). Since DDS is always given chronically, we have investigated the ability of cimetidine to inhibit Met Hb formation caused by repeated administration of DDS. DDS was given (i.p.) to four groups ($n = 6$ per group) male Wistar rats (330–360 g). Group I received 10 mg kg^{-1} DDS at 1, 24, 48 and 72 h. Group II received 10 mg kg^{-1} DDS at 1, 8, 24, 32, 48, 56, 72 and 80 h. Group III rats received DDS as for group I, except cimetidine (50 mg kg^{-1}) was administered 1 h prior to DDS. Group IV rats received the same DDS dosage as group II, except cimetidine (50 mg kg^{-1}) was given 1 h prior to each DDS dose. Blood samples were obtained at 0, 1, 8, 9, 24, 25, 32, 33, 48, 49, 56, 57, 72, 73, 80 and 81 h. Met Hb was measured spectrophotometrically and DDS and MADDS concentrations by h.p.l.c.

Twice daily DDS administration (group II) resulted in a significantly greater ($P < 0.05$) Met Hb AUC, DDS AUC and MADDS AUC compared with a single daily DDS dose (group I). The administration of cimetidine prior to once daily DDS (group III) resulted in a significant fall ($P < 0.05$) in Met Hb and an increase in both the DDS and MADDS AUCs in comparison with a single dose of DDS daily (group I). Administration of cimetidine prior to DDS twice daily (group IV) resulted in no significant change in Met Hb or MADDS levels, but in a marked increase in the AUC of DDS compared with control ($P < 0.05$; group II). Hence although cimetidine inhibited DDS-mediated Met Hb formation during once daily DDS administration, inhibition did not occur during twice daily DDS administration.

Table 1

Group	*Met Hb% (h^{-1})*	*[DDS] ($\mu g\,ml^{-1}\,h$)*	*[MADDS] ($\mu g\,ml^{-1}\,h$)*
I	584 ± 115	113 ± 22.9	10.8 ± 4.6
II	757 ± 135	140 ± 17.5	48.2 ± 18.3
III	302 ± 179	151 ± 22.2	33.6 ± 5.8
IV	790 ± 114	303 ± 53.2	76.3 ± 31.1

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The use of the apparent fragment constant f′ to predict the buccal absorption and hence the renal excretion of basic drugs

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Beckett & Triggs (1967) demonstrated a direct relationship between buccal absorption (BA) pH curves and renal tubular absorption changes with pH. They devised an *in vivo* model based on the shape of the BA curve to predict the renal excretion of drugs.

Blackett & Turner (1989) described the relationship between the apparent partition coefficient as defined by f′ (f′ = f/1 + antilog [pH-pka]) and BA. The use of the f′ would appear to be an appropriate *in vitro* index for BA as it takes into account the fundamental influence of lipid solubility (f), pH and the drug's pKa. On this basis it is suggested that the *in vivo* model put forward by Beckett & Triggs (1967) may be replaced by an *in vitro* model. The new model arranges the classification of Beckett & Triggs into a more logical sequence, but uses f′ as it changes with pH to model the mechanism of BA and therefore the relationship of BA to renal excretion.

The urinary excretion of many basic drugs is dependent on the pH of the urine and the innate lipophilicity of the drug such that drugs in class D when fully ionised (ie acidic pH) still have a sufficient lipophilic nature to be reabsorbed in the kidney tubules. Drugs in class A even at alkaline pH values are only poorly reabsorbed because of the low innate lipophilicity. Thus the more negative the f′ the less lipophilic is the drug such that only when f′ approaches 0 and greater is there a rise to 10% or more BA.

The proposed classification based on changing f′ with pH may be used to determine the order of partitioning into biological membranes of a variety of drugs at differing pH values. Using this information it would be possible to predict the excretion profiles of these drugs in man under normal and controlled pH conditions.

Table 1

Drug	New class	pH 5.0 f'	pH 5.0 %BA	pH 6.0 f'	pH 6.0 %BA	pH 7.5 f'	pH 7.5 %BA	pH 9.0 f'	pH 9.0 %BA
Norephedrine	A	−3.69	2.4	−2.69	3.0	−2.05	7.5	0.16	12.5
Atenolol		−4.41	0.0	−3.41	0.0	−2.01	8.7	−0.50	0.0
Amphetamine	B	−2.92	0.0	−1.92	0.0	−0.42	17.5	1.03	67.0
Mephentermine		−3.30	2.0	−2.30	3.3	0.10	17.0	0.68	66.2
Pethidine	C	−1.76	0.0	−0.75	3.0	0.72	15.0	1.78	66.0
Nicotine		−1.26	3.3	−0.26	10.0	1.10	19.0	1.61	28.2
Dimethyl-amphetamine		−2.16	0.0	−1.16	0.0	0.33	13.5	1.77	68.6
Benzphetamine	D	2.74	6.7	3.66	12.0	4.30	47.3	4.35	81.0
Methadone		0.91	9.5	1.90	16.6	3.34	40.0	4.10	71.0
Fenfluramine		−0.26	14.5	0.74	22.0	2.23	45.0	3.49	84.0
New classification		A		B		C		D	
Range of f' over pH 5–7.5		< −3 to −2,		−2 to 0,		−2 to 1,		−0 to > 2	
Beckett's classification		2		1		4		3	

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Influence of sodium, cephradine and glycyl proline on the buccal absorption of captopril

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In a previous study we showed that the buccal absorption of captopril did not obey the normal pH partition hypothesis (Al-Furaih *et al.*, 1988), indicating that mechanisms other than passive diffusion were involved in the absorption of captopril across the buccal mucosa. Similar data have also been reported by Hu & Amidon (1988) using the *in situ* rat intestine; they showed that the dipeptide glycyl proline, cephradine and the lack of sodium in the perfusate led to inhibition of captopril absorption from the rat intestine. Since captopril is chemically similar to glycyl proline, Hu & Amidon (1988) suggested that the absorption of captopril in the rat was, at least in part, via a peptide carrier system. The aim of the present study was to determine if a similar carrier system was present in the buccal cavity of man by examining if glycyl proline, cephradine or a lack of sodium influenced the buccal absorption of captopril in healthy volunteer subjects.

Six healthy male volunteers (age range 25–34 years) took part in the present investigation. The study was carried out in a randomised single blind cross-over fashion and was approved by the University Ethics Committee. The buccal partitioning method, first described by Beckett & Triggs (1967) was used. This method involves circulating a buffered drug solution in the mouth for 5 min after which the drug remaining unabsorbed is measured. The present study involved the use of a sodium free buffer (potassium hydrogen phosphate/potassium hydroxide, pH 7), and buffered solutions (McIlvaine's citrate phosphate buffer, pH 7) of cephradine (0.5 mM) and glycyl proline (15 mM), each containing 2 mg captopril 20 ml^{-1}. Control absorption data were obtained by examining the buccal absorption of captopril alone using the latter buffer. After circulating the solutions (20 ml) in the mouth for 5 min, the unabsorbed captopril was quantified in each case using reverse phase h.p.l.c. with u.v. detection. A minimum wash-out period of 24 h was allowed between treatments. In a final experiment the influence of glycyl proline (15 mM) on the rate of captopril (2 mg 20 ml^{-1}) absorption was examined using the same procedure as before, however, this time 200 μl aliquots of the solution were removed from the mouth at 1 min intervals over the 5 min absorption period.

The amount of captopril absorbed under the control conditions was 35.7 ± 5.8%. Absorption under test conditions was as follows (mean ± s.e. mean): sodium free buffer (30.7 ± 5.8%); cephradine (38.25 ± 3.2%); glycyl proline (35.4 ± 2.2%). Analysis of variance indicated that the amount of captopril absorbed did not differ significantly ($P > 0.05$) from control values under these test conditions. The rate of captopril absorption in the absence of glycyl proline was 100.4 ± 13.7 μg min^{-1} while in its presence the rate was 120.7 ± 15.7 μg min^{-1}. These rates were not significantly different ($P > 0.05$; paired *t*-test).

Collectively the data indicate that, under the present experimental conditions, captopril absorption from the buccal cavity in man was unaffected by glycyl proline, cephradine or a lack of sodium. Further work is underway using other transport inhibitors in an attempt to characterise the mechanisms involved in the buccal absorption of captopril.

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Plasma metronidazole concentrations after vaginal pessary administration

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Metronidazole is an antimicrobial agent with applications including gynaecological and anaerobic infections. There are considerable data about absorption of the drug after oral administration, but there are little data about its absorption after vaginal administration. The purpose of this study was to determine the pharmacokinetics of metronidazole after repeated vaginal dosing with metronidazole pessaries.

Metronidazole (Flagyl) 500 mg pessaries were administered vaginally every 12 h for 5 days to 13 healthy women (ages 18–35 years) starting on day 10 of their menstrual cycle. Subjects were examined to ensure the absence of gynaecological disease and abstained from sex and alcohol for the duration of the study. Blood samples (10 ml) were taken on day 1, from the antecubital vein before (0) and at 2, 4, 6, 8 and 12 h after placement of the first pessary in the vagina. On day 5 before insertion of the last pessary, blood was taken at 08.00 h precisely, then further sampling as on day 1, with additional samples at 14 and 24 h. Plasma metronidazole concentrations were determined using a specific and sensitive high performance liquid chromatography assay. The peak plasma concentration was 1.22 ± 0.16 $\mu g\ ml^{-1}$ (mean ± s.e. mean) on day 1 and 1.92 ± 0.23 $\mu g\ ml^{-1}$ on day 5 ($P < 0.05$, Student's paired t-test). The median time to peak concentration was 6.0 (range 4–12) on day 1 and 4.0 (range 0–12) on day 5 ($P < 0.05$, Student's paired t-test). On day 1 the AUC(0,12) was 8.6 ± 1.0 $\mu g\ ml^{-1}$ h (mean ± s.e. mean) and on day 5 (steady state) 19.4 ± 2.3 $\mu g\ ml^{-1}$ ($P < 0.01$, Student's paired t-test).

The concentration of metronidazole achieved in the plasma after vaginal administration was above the minimum inhibitory concentration (MIC) for anaerobic *Streptococci* and *Clostridium tetani.*

Antifungal drug sensitivity of *Candida albicans* from HIV positive patients

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Oral *Candida albicans* is a common pathogen in HIV positive patients. Around 28% of the isolates recovered in this study exhibited detectable variation in colony morphology at primary isolation and some of these gave rise to derivatives that showed high frequency alteration of colony morphology. Forty-two clinical isolates of *Candida albicans* and their derivatives from 14 HIV positive patients were tested against a range of polyene and imidazole antifungals using agar plate dilution method (Shadomy *et al.*, 1985). The primary multiple phenotype strains and the majority (80%) of their derivatives were sensitive to ketoconazole, minimum inhibitory concentration (MIC) 8–24 $\mu g\ ml^{-1}$ and amphotericin, MIC 2–4 $\mu g\ ml^{-1}$ while the remaining derivatives were markedly less sensitive to ketoconazole, MIC 128 $\mu g\ ml^{-1}$. Cross-resistance to miconazole occurred, but was less marked; sensitive strains, MIC 3.9 $\mu g\ ml^{-1}$; resistant strains 7.8 $\mu g\ ml^{-1}$. It was notable that none of the apparently resistant derivatives had been exposed to antifungal drugs before sensitivity testing. In order to simulate this type of exposure, two sensitive isolates were cultured repeatedly on agar plates containing sub-inhibitory concentrations of ketoconazole. When retested they were found to show increased tolerance to the drug. The hyphal elongation assessment method (Marichal *et al.*, 1985) confirmed the differential sensitivity of the isolates and derivatives shown by the agar plate dilution method. In sensitive strains hyphal elongation was halted at $1–9 \times 10^{-8}$ M ketoconazole and in resistant strains at $1 \times 10^{-6}–1 \times 10^{-4}$ M ketoconazole. Miconazole and itraconazole also showed a comparable degree of resistance with this method.

Candida albicans possesses the ability to generate substantial numbers of morphologically distinct phenotypes, some of which are predisposed to resistance to antifungal drugs *in vitro*. If this occurs *in vivo* it could contribute to treatment failure and relapse of candidiasis in HIV positive patients (De Wit *et al.*, 1989; Mandal, 1989).

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Changes in plasma 5-HT levels during cisplatin treatment in man

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The importance of 5-hydroxytryptamine (5-HT) in the emetic response to chemotherapeutic agents such as cisplatin, has been highlighted by the ability of the 5-HT_3 receptor antagonists to abolish chemotherapy-induced emesis in animals (Costall *et al.*, 1986) and man (Cunningham *et al.*, 1987). Here we investigate the possibility of increased plasma 5-HT levels in patients receiving cisplatin.

Ten male patients (20–39 years) were intravenously administered cisplatin (20 mg m^{-2}) and a standard antiemetic regime of lorazepam (2 mg), metoclopramide (10 mg) and dexamethasone (8 mg) at time = 0. Additional antiemetic support was given on patient request. Blood sampling was effected immediately before (time zero) and at 2, 4, 6, 8, 16 and 24 h after drug treatment by removing 5 ml of blood prior to collection of 2.7 ml into a 2.7 ml monovette vial containing EDTA (Sarstedt). Samples were centrifuged at 15000 *g* for 3 min. 5-HT was extracted (Artigas *et al.*, 1985) from 200 µl of resulting plasma and assayed using h.p.l.c.-e.c.d. (Barnes *et al.*, 1988).

During the first 8 h post-chemotherapy 4/10 patients exhibited marked increases (500–1000%) in plasma 5-HT levels above initial control values (386 ± 104 pg ml^{-1}). In the remaining patients there were no significant elevations in plasma 5-HT (Figure 1). These findings and the recent report by Cubeddu *et al.* (1990) that large increases in urinary 5-HIAA levels are associated with chemotherapy induced emesis, may indicate that emesis in some patients could be related to increased plasma levels of 5-HT. The possibility that higher doses of cisplatin may evoke more consistant changes in plasma 5-HT remains to be investigated.

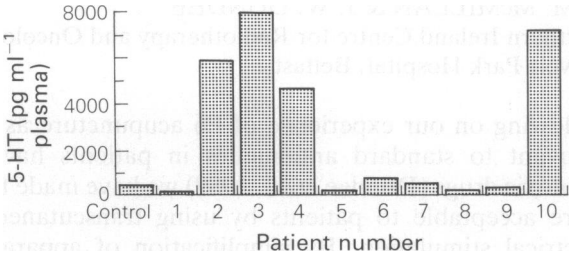

Figure 1 Maximum plasma 5-HT levels during 24 h post-chemotherapy (n = 10).

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Tolerability of intravenous dosing of ondansetron 16 mg

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Ondansetron is a 5-HT_3 receptor antagonist used for treatment of nausea and vomiting associated with chemotherapy. Studies are currently exploring the effects of ondansetron in anaesthetic related nausea and vomiting. This study was designed to investigate the effects of ondansetron on the cardiovascular and respiratory systems, and on factors affecting blood coagulation to predict possible interactions with co-administered anaesthetic drugs, and to investigate potential interference with haemostasis.

Six healthy male subjects (mean age 34 years, range 27–40 years) participated in a double-blind two way crossover study. Ondansetron 16 mg (twice the anticipated therapeutic dose) or placebo was infused i.v. over 5 min. Cardiac output (BoMed Impedance Cardiograph) and ECG (Kontron Arrythmia Cardule) were monitored continuously for 15 min before dosing and for 60 min after dose. Blood pressure (Narco Scientific automated blood pressure recorder) and 12 lead ECGs were examined at regular intervals before, and for 60 min after dosing. A CO_2 rebreathing experiment to determine respiratory CO_2 sensitivity (Read, 1967) was conducted before, and at 20 and 40 min after dosing. Haematological parameters, platelet count and function (ADP and U-46619 (thromboxane agonist) induced platelet aggregation in whole blood *ex vivo*), fibrinogen, fibrinogen degradation products, prothrombin time ratio, activated partial thromboplastin time, von Willebrand factor antigen and multimer pattern and plasma cholinesterase were measured prior to dose, at 15 and 60 min after dosing, and at 24 and 48 h after dose.

Results were as follows (all values ondansetron-placebo (95% C.I.)). Mean difference in cardiac output (post infusional average) (l min^{-1}) between treatments was − 0.12 (−0.64, 0.41) P = 0.58. Mean heart rate (beats min^{-1}) difference was −2.97 (−6.72, 0.79) P = 0.09. Mean systolic blood pressure (mm Hg.m) AUC difference was −106.7 (−897.9, 684.5), P = 0.72. Mean diastolic blood pressure AUC difference was 2.5 (−642.4, 647.4) P = 0.99. Mean CO_2 regression line shift for 20 min post, *vs* pre-infusion was −0.127 kPa l^{-1} min^{-1}

(−1.222, 0.968) $P = 0.76$ and at 40 min was 0.105 (−0.249, 0.458) $P = 0.46$. There was no significant difference for any ECG or haematological parameter. Ondansetron was well tolerated with the only reported unwanted effect being mild tingling at the infusion site during the infusion in one of the volunteers. This would suggest that ondansetron is likely to be well tolerated as an agent for treatment of postoperative nausea and vomiting. Lack of effect on the cardiovascular and respiratory systems reduces the likelihood that there might be potentiation of the depressant effects of anaesthetic agents. In addition, ondansetron is unlikely to increase the incidence of perioperative bleeding or thrombosis.

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Problems of self-administration of P6 (Neiguan) antiemesis

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Following on our experience of P6 acupuncture as an adjuvant to standard antiemetics in patients having cytotoxic drugs (Dundee *et al.*, 1989) we have made this more acceptable to patients by using transcutaneous electrical stimulation. By simplification of apparatus and electrodes we have made self-administration (5 min every 2 h) a feasible option. The following problems were encountered in the first 30 patients.

Mental clouding Drug induced drowsiness, including the soporific effects of morphine and the amnesic action of lorazepam make it difficult for patients to understand and recall a simple set of instructions. Some metabolic disturbances have a similar effect.

Physical While best results are obtained from the stimulation of the dominant side (Dundee *et al.*, 1988) some patients have had difficulty in operating the machine with the non-dominant hand. The presence of an intravenous infusion also caused problems. Debilitated patients and those with active vomiting also had difficulties.

Apparatus Using the commercially available Minitens, patients have confused frequency and current settings, used incorrect output sockets (in dual output machines), had difficulty in adjusting current level, and allowed batteries to become exhausted. The latter is contributed to by patients administering a significantly higher ($P < 0.05$) current than physicians to elicit Qi, a sensation which give them confidence that 'something is happening'.

Table 1

	Physician administered (n = *104*)	*Self-administered* (n = *137*)
Mean ± s.d. current E-2mA	7.6 ± 1.6	11.6 ± 1.9

Dundee, J. W. *et al.* (1988). *Br. J. clin. Pharmac.*, **25**, 679.

Dundee, J. W. *et al.* (1989). *J. Roy. Soc. Med.*, **82**, 268.

Blood cyclosporin absorption profiles and renal function in heart transplant recipients

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Cyclosporin (cyclosporin A, Sandimmun) is a potent immunosuppressive agent which, in excess, has serious adverse effects on renal function. Measurement of pre-dose cyclosporin concentrations is widely used in an effort to optimise therapy by avoiding the high concentrations associated with toxicity (Holt *et al.*, 1986). However, the pharmacokinetics of cyclosporin vary widely between patients, especially with respect to oral absorption. Thus, reliance on pre-dose measurements could be misleading, since wide fluctuations in cyclosporin concentrations may occur between doses. One group has shown that, in renal transplant patients, high peak cyclosporin concentrations were associated with subsequent renal dysfunction (Phillips *et al.*, 1988).

To identify patients with rapid absorption and high peak cyclosporin concentrations we performed 12 h pharmacokinetic profiles in 17 patients (16M/1F) with a median (range) age of 51.5 (36–60) years, who had undergone heart transplantation 10–347 (median 18) days prior to study. All patients received standard immunosuppression with steroids, azathioprine and cyclosporin. Changes in renal function were evaluated using serum creatinine estimations, commencing on the 10th post-operative day, which were correlated with time using Spearman rank correlation. Follow-up was for 37–419 (median 133) days. Blood samples were obtained prior to and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 and 12 h following an oral dose of cyclosporin (mean ± s.d., 4.7 ± 1.2 mg kg^{-1}). Whole blood cyclosporin concentrations were measured by a radioimmunoassay specific for

the parent compound (Sandimmun-Kit, Sandoz, Basle).

During follow-up, nine patients showed a deterioration in renal function reflected by a significant rise in serum creatinine with time. In the remaining eight patients renal function improved or remained unchanged with respect to serum creatinine. The peak concentrations of cyclosporin were in the range 519–1491 $\mu g\ l^{-1}$ (median 731). In the nine patients with a decline in renal function the median (range) peak cyclosporin concentration was 989 $\mu g\ l^{-1}$ (660–1491); seven had a peak cyclosporin concentration greater than 750 $\mu g\ l^{-1}$. In contrast, the median peak cyclosporin concentration in the eight patients with no decline in renal function was 648 $\mu g\ l^{-1}$ (519–751), $P < 0.004$ (Wilcoxon Sign Rank); only one had a peak concentration in excess of 750 $\mu g\ l^{-1}$ ($P < 0.03$, Chi-square test). This level of discrimination between the two groups was not achieved by reference to either the area under the time-concentration curve (AUC) or dose normalised AUC ($P > 0.07$ and > 0.05, respectively).

These preliminary data suggest that, in our group of heart transplant recipients, peak concentrations of cyclosporin in excess of 750 $\mu g\ l^{-1}$ are associated with a significant decline in renal function. If confirmed in a larger patient group, modification of the dosage schedule to minimise such high peak concentrations may be of value in avoiding this adverse effect.

Holt, D. W. *et al.* (1986). *Br. med. J.*, **293**, 1057.

Phillips, T. M. *et al.* (1988). *Transplant Proc.*, **20**, 457.

Precision of measurement of renal plasma flow and glomerular filtration rate using single intravenous injection of PAH and inulin in subjects with normal renal function

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The 0–1 h renal clearance (RC) of *p*-aminohippurate (PAH) and 0–2 h total body clearance (TBC) of inulin following single i.v. injections of both compounds have been used to assess renal plasma flow (RPF) and glomerular filtration rate (GFR) respectively (McAuslane *et al.*, 1988). The aim of this study was to evaluate and estimate the repeatability of these measurements in order to select the most appropriate method for use as an outpatient procedure. Intravenous boluses of PAH (10 mg kg^{-1}) and inulin (75 mg kg^{-1} over 5 min) were administered to eight healthy male volunteers (21 ± 1 years 73 ± 3 kg) on two occasions at least 7 days apart. After 1 h semi-supine, subjects emptied their bladders, blood was sampled frequently for 2 h and urine collected from 0–1 and 1–2 h. Subjects received adequate fluid to ensure a satisfactory urinary output. Plasma and urine PAH were measured by h.p.l.c. with ultraviolet detection, and inulin by spectrophotometric analysis. Plasma data were fitted to an open two-compartmental model by computer analysis and the AUC calculated using the trapezoidal rule. TBC and RC were calculated and compared for 0–1 h and 0–2 h. Creatinine clearance (CC) was also measured at 0–1 h and 0–2 h. All results are expressed as ml min^{-1} 1.73 m^{-2}. The calculated values were used to determine the coefficient of variation (C.V.) and repeatability coefficient (R.Cf. British Standards Institution, 1979).

The equivalent values for TBC of PAH and the low variability over 1 or 2 h suggest this method is preferable to RC of PAH over either time period, for estimation of RPF. The lower C.V. and R.Cf. for inulin TBC (0–2 h) suggest this method is best for assessment of GFR, although there is an overestimation when compared with inulin RC or CC. If inulin RC 0–2 h is to be employed then CC 0–2 h should be measured simultaneously because of the lower R.Cf and C.V.

Table 1

	0–1 h (ml min^{-1} 1.73 m^{-2})					*0–2 h (ml min^{-1} 1.73 m^{-2})*				
	PAH		*Inulin*			*PAH*		*Inulin*		
	TBC	RC	TBC	RC	CC	TBC	RC	TBC	RC	CC
Mean	584	361	175	82	122	582	405	152	116	127
Mean difference	12	47	11	12	22	5	39	2	10	2
R.Cf.	70	160	40	38	36	84	186	42	68	12
C.V. (%)	5.9	22.2	11.2	23	13.8	7.1	22.9	14	29	4.6

British Standards Institution (1979). BS 5497, Part 1, London.

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Benzodiazepine prescribing and utilization trends in Ireland

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Concern about the extent and circumstances in which benzodiazepines are prescribed is felt throughout Europe. Comparing data from a previous study (Corrigan, 1980) with more recent data has allowed us to examine the changes that have occurred in benzodiazepine prescribing and utilization between 1977 and 1987. National utilization was estimated from pharmaceutical wholesaler sales figures and expressed in Defined Daily Doses per 1000 persons per day. Data for patients receiving free medical care (GMS) were expressed in a similar way and by subtraction from the national utilization estimate the non-GMS population's utilization of benzodiazepines was calculated. Pharmacy prescription records were used to obtain prescribed daily doses (PDD) and details of the duration of treatment and the sex of the patient. A gradual fall in the utilization of anxiolytic benzodiazepines has occurred since 1985 (from 23.28 DDD/1000 persons/day to 21.52 DDD/1000 persons/day) while in contrast hypnotic benzodiazepine utilization has increased (1985, 19.01; 1987, 19.82 DDD/1000 persons/day). GMS patients' (which include most of the over 65 years old) utilization was much higher (anxiolytics 36.32 DDD/1000 persons/day) compared with the non-GMS population (12.51 DDD/1000 persons/day) in 1987. The differences between the two populations was even more marked for the hypnotic benzodiazepines (GMS, 35.56 *vs* non-GMS, 10.22 DDD/1000 persons/day) in 1987. Examination of the trends showed that the fall in anxiolytic benzodiazepine use was less and the rise in hypnotic benzodiazepine use greater among GMS than among non-GMS patients between 1985 and 1987. However, over the period 1977 to 1987 the quantity prescribed of each of the most frequently prescribed benzodiazepines (DDD/prescription) fell (diazepam 16.4%; lorazepam 14.8%; nitrazepam 8.1%). Estimates of the prescribed daily doses showed that these were lower overall than the DDD values and the high proportion of women using benzodiazepines was especially notable in the GMS population.

We thank the General Medical Services (Payments) Board and Wyeth (Ireland) for their support.

Corrigan, O. I. (1980). *J. Ir. med. Ass.*, **73**, 295.

Non-steroidal anti-inflammatory drugs – which, when and why? A survey amongst Tayside general practitioners

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Non-steroidal anti-inflammatory drugs (NSAIs) are widely used by general practitioners (GPs). There are over 100 NSAIs in both clinical and research use. This probably reflects the large market available but may also reflect its high incidence of side-effects. Additionally, there is concern drawn to their use and misuse. We therefore, conducted a postal questionnaire survey amongst 323 Tayside GPs to elucidate their pattern and choice of usage of this group of drugs and their responses to side-effects when encountered.

The questionnaire was of multiple choice type and consisted of 10 stem items designed to be completed within 10 min. The items addressed the indications for NSAI therapy, factors which may influence the choice of NSAIs and the practitioners' knowledge and experience of drug interactions as well as the side-effect profile of this group of drugs. Additionally, the practitioners' response to the development of gastric side-effects and the use of NSAIs in patients with known peptic disease were assessed.

One hundred and ninety-eight GPs responded. Effectiveness (50%) followed by previous experience of the agent (33%) were the major determining factors of the choice of NSAI therapy. Only 13% of GPs considered incidence of side-effects to be the most important factor. The most widely used NSAI was ibuprofen (54%) followed by naproxen (24%) and diclofenac (12%) and they were most commonly prescribed in patients with an arthropathy (rheumatoid arthritis 93%, osteoarthritis 78% and gouty arthritis 77%). Other musculoskeletal disorders (47%) and dysmenorrhoea (45%) were also common reasons for NSAI therapy. When treating rheumatoid arthritis most GPs (64%) will try another NSAI before seeking specialist advice if the first one fails. Most were aware of the potential side-effects and interactions with other drugs. The most commonly encountered adverse event was peptic disturbance. Forty-five percent of GPs stated this as a frequently experienced side-effect. When this was anticipated or encountered most GPs (56% and 83% respectively) chose to use non-NSAI analgesia rather than to co-prescribe anti-ulcer agents.

A comparison of the effects of promethazine and lorazepam on saccadic eye movements and psychomotor performance

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Saccades, the rapid conjugate movements of the eye, are regulated by a system of pause and burst motoneurones in the paramedian pontine reticular formation, are sensitive to drugs which impair arousal (Griffiths *et al.*, 1984) and may be able to distinguish between drug effects on brainstem and limbic systems. Since we found impairments with chlorpromazine (King *et al.*, 1990) but not haloperidol (King & Bell, 1990), we studied the effect of promethazine (PMZ), a non-neuroleptic, sedative phenothiazine to explore further the possible neurotransmitter mechanisms involved.

Single doses of PMZ (25 and 50 mg) were compared with lorazepam (L) (2.5 mg) and placebo (Pl) in 12 healthy female volunteers by double-blind balanced randomisation. Drug effects were measured using six saccadic parameters with the EOG/microcomputer-based system of Griffiths *et al.* (1984), a battery of conventional psychomotor tests and 16 visual analogue rating scales. Assessments were carried out at baseline, 0.5, 1, 2, 3 and 6 h and the data analysed by Friedman and Wilcoxon non-parametric statistics, comparing differences from baseline with Pl.

Compared with Pl, PMZ produced dose-dependent impairments of saccadic peak velocity which were maximal at 3 h, while L had a greater effect which started at 1 h and persisted for 6 h (Table 1). Similar patterns of effects of both drugs were found on subjective alertness, choice reaction time, digit symbol substitution and a continuous performance test. Saccadic peak acceleration was affected equally by PMZ and L, while PMZ had a greater effect than L on critical flicker fusion threshold. Neither drug altered pupil size.

Thus these impairments of saccades seem to be centrally mediated by a variety of neurotransmitters including GABA, histamine and possibly acetylcholine, but not dopamine (King *et al.*, 1990).

Table 1

	Saccadic peak velocity ($°s^{-1}$) medians (semi-interquartile range)					
	0	*0.5*	*1*	*2*	*3*	*6*
Pl	443.00 (132.50)	456.15 (72.65)	464.50 (63.50)	446.40 (51.75)	478.50 (90.55)	498.20 (72.85)
L (2.5 mg)	488.80 (46.70)	468.80 (95.15)	410.70 (66.15)*	391.90 (85.20)*	366.05 (102.60)**	438.00 (101.25)**
PMZ (25 mg)	472.10 (63.20)	468.65 (91.30)	460.15 (82.35)	400.70 (90.70)	44.8.10 (121.15)*	449.90 (106.70)
PMZ (50 mg)	477.90 (96.65)	466.45 (78.10)	451.65 (129.15)	409.30 (152.95)*	394.65 (130.60)*	445.05 (130.00)**

Change from 0 h different from Pl, * $P < 0.05$; ** $P < 0.01$.

Griffiths, A. N. *et al.* (1984). *Br. J. clin. Pharmac.*, **18**, Suppl. 1, 73S.
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The McCollough effect as a measure of central cholinergic activity in man

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The McCollough effect (ME) is a contingent after-effect in which, following exposure to alternating vertical red-black and horizontal green-black gratings, complementary phantom colours are perceived on presentation of a white-black test grating. Because the effect may be obtained with an interval of several days between adaptation and testing, Shute (1979) suggested that it reflects a hippocampal learning mechanism involved in 'forgetting' spurious associations between colour and orientation. Such a mechanism should be inhibited by GABAergic neurones and stimulated by cholinergic neurones. Since the ME appears to be sensitive to drugs which alter these central transmitters it is a potentially useful tool for investigating (a) drugs with effects on central cholinergic mechanisms and (b) drugs with unexplained retinal effects. The purpose of the present study was to demonstrate that the ME is in fact sensitive to cholinergic and anticholinergic drugs and also to compare its sensitivity with more conventional tests of psychomotor and cognitive function.

Ten healthy male volunteers received single doses of temazepam (T) (20 mg), physostigmine (Phy) (0.75 mg s.c.), hyoscine (Hy) (1.2 mg), flecainide (F) (200 mg) or placebo (Pl) by double-blind latin square randomisation using a double-dummy technique. Psychomotor function including six saccadic eye movement parameters (latency, duration, accuracy and peak velocity, acceleration and deceleration) using the CSGAAS (Griffiths *et al.*, 1984), were assessed at baseline and after 1 h. Two-way analyses of variance showed significant drug effects for T on VARS(A) ($P < 0.001$), CRT(T) ($P < 0.03$),

CRT(M) ($P < 0.03$), CPT(G) ($P < 0.006$), and saccadic velocity ($P < 0.009$), duration ($P < 0.04$), accuracy ($P < 0.04$) and acceleration ($P < 0.03$); Hy on VARS(A) ($P < 0.008$), saccadic velocity ($P < 0.04$), duration ($P < 0.04$) and acceleration ($P < 0.04$) and pupil size ($P < 0.03$); and for Phy on VARS(A) ($P < 0.03$) and VARS(H) ($P < 0.03$). F had no effect on these tests.

Subjects were adapted to the ME for 12 min at 1.5 h and tested at 12 min intervals until extinction of the effect. Two factor analyses of variance showed a highly significant interaction between drugs and time ($P < 0.0001$). The initial strength of the ME was decreased by Phy ($P < 0.01$) and increased by Hy ($P < 0.01$) and T ($P < 0.01$), relative to Pl. The duration of the ME was decreased by Phy ($P < 0.01$) and increased by Hy ($P < 0.01$) and T ($P < 0.01$), relative to Pl. The effects of F, an antiarrhythmic known to have peripheral visual side-effects, were not significantly different from Pl.

Thus the ME is capable of detecting cholinergic, anticholinergic and GABAmimetic drug effects in man, in therapeutic doses. Phy was detected by the VARS and ME but none of the psychomotor or saccadic eye movement tests.

Griffiths, A. N. *et al.* (1984). *Br. J. clin. Pharmac.*, **18**, Suppl. 1, 73S.

Shute, C. C. D. (1979). *The McCollough Effect: an indicator of central neurotransmitter activity*. Cambridge: Cambridge University Press.

Abbreviations: CSGAAS: Cardiff System for the Generation and Analysis of Saccades; VARS (A) (H): Visual analogue rating scale (Alert) (Happy); CRT (T) (M): Choice reaction time (Total) (Motor movement); CPT (G): Continuous performance test (G time).

Preanaesthetic medication: a comparison of three doses of oral clonidine with temazepam

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α_2-adrenoceptor agonists have been shown to reduce the requirements for anaesthetic agents, while providing haemodynamic stability during surgery (Bloor, 1980). After ethics committee approval, the effects of three doses of oral clonidine were compared with a standard benzodiazepine premedicant.

The investigation was randomised and double-blind. Healthy women having minor gynaecological surgery under GA were selected and were given one of four oral premedications 90 min prior to induction. Group A received clonidine 0.3 mg, Group B clonidine 0.2 mg, Group C clonidine 0.1 mg and Group D temazepam 20 mg. Anaesthesia was induced with etomidate 0.2 mg kg^{-1}, and maintained with 60% nitrous oxide in oxygen and isoflurane 1%. Blood pressure and heart rate were recorded preoperatively and continuously from arrival in the anaesthetic room to the recovery phase; this included an 8 min period following induction of anaesthesia before surgical stimulation. Anxiety was measured by visual analogue scale (VAS) the evening prior to surgery and immediately before induction. Sedation was assessed using a 3 point scale. The quality of induction was graded according to an established method (Dundee *et al.*, 1962). The occurrence of emetic symptoms was recorded as early (in the first 2 h), or late (from 2 to 24 h).

Results are presented as mean ± s.e. mean for parametric data, and mean ± range for non-parametric data. Kruskall Wallis and Mann Whitney U tests were used to analyse non-parametric data, and ANOVA and *t*-test for parametric data as appropriate. $P < 0.05$ was regarded as significant.

Each premedicant sub group had 20 patients who were comparable in respect of age and weight. Seven patients in group A were noticeably sedated compared with 2 in group C, but this was not significant ($P < 0.1$). Group B had less anxiety than the other three groups, as measured by VAS ($P < 0.001$). Only one patient in group B had an unsatisfactory induction compared with seven in group C ($P < 0.05$) and six in group D ($P < 0.05$). There was no difference in the induction grades between group A and B. The systolic blood pressure was significantly lower throughout the period of measurement in group A as compared with C and D ($P < 0.004$). There were no significant differences between group B and the other groups with respect to blood pressure changes. The changes in heart rate followed a similar trend. No patient in any of the groups required treatment for hypotension or bradycardia in the operative period, although two patients in group A required intravenous fluids to restore blood pressure in the recovery ward (systolic pressure < 80 mm Hg). There was no difference in the incidence or timing of emetic symptoms between the groups.

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Dundee, J. W. *et al.* (1962). *Br. J. Anaesth.*, **34**, 523.

Racial differences in eye sensitivity to drug action

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Although racial differences in eye responses to drugs have been recognized for over half a century (Middleton & Chen, 1927) few carefully conducted quantitative studies with modern techniques have been undertaken. In the present study we have used infra-red photography to compare eye responses of 12 white Caucasians (WC) with those of eight subjects of Middle Eastern and Indian origin (MI) to pilocarpine, cocaine, phenylephrine and tropicamide. Five of the white Caucasians had blue irises, four had green and three had brown irises. All the subjects in the MI group had brown irises. Five of the subjects in WC group and seven of those in MI group were males. The study was carried out in a dimly lit room and each drug was studied at three different concentrations. First photograph of eyes to give basal readings was taken at 36 min after entry into the room. Two drops of an eye lotion were then instilled into the lower conjunctival sac of one eye and the person was asked to keep his/her eyes closed for 5 min. A second photograph was taken at 45 min after instilling pilocarpine, cocaine and phenylephrine and 25 min after tropicamide. Each photograph was taken from a fixed head position which also had a built-in mm scale. The pupillary size was measured with the help of set squares and each reading corrected with reference to photographic reading. Percentage changes in pupillary size were calculated from control readings taken as 100 percent. The results in Table 1 indicate that subjects from MI group are more sensitive to the effect of pilocarpine and cocaine than subjects from the WC group. It appears that the differences in pupillary responses to pilocarpine and cocaine become less marked when the concentrations of the two drugs are increased to 2% and 4% respectively. No significant differences in eye responses of the two groups were found following the instillation of 2.5%, 5.0% and 10% of phenylephrine and 0.25%, 0.5% and 1% tropicamide (results not shown). There were also no significant differences between male and female subjects and between subjects with green and blue eye irises. While these results suggest reduced response of MI to pilocarpine and cocaine, all of the subjects in this group had brown irises. This requires further elucidation.

Table 1 Percent changes in pupillary size following drug instillation (mean ± s.e. mean)

	Reduction in size after pilocarpine			*Increase in size after cocaine*		
	0.5%	*1%*	*2%*	*1%*	*2%*	*4%*
WC ($n = 12$)	49.12 ± 5.10	64.9 ± 2.63	72.58 ± 1.93	17.75 ± 3.61	28.56 ± 3.63	31.26 ± 4.27
MI ($n = 8$)	24.04 ± 4.79	48.97 ± 3.12	58.83 ± 3.31	3.77 ± 3.99	4.16 ± 5.64	11.56 ± 4.47
P value	< 0.01	< 0.01	< 0.05	< 0.05	< 0.01	< 0.05

Middleton, W. S. & Chen, K. K. (1927). *Arch. int. Med.*, **XXV**, 150.

Does tachyphylaxis occur to the non-pulmonary effects of salmeterol?

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Salmeterol (S) is a long acting selective β_2-adrenoceptor agonist for use in the treatment of reversible airways obstruction. As with other inhaled β_2-adrenoceptor agonists it may cause tremor, tachycardia, hypokalaemia and hyperglycaemia at high doses. Tachyphylaxis has not been shown to occur to the pulmonary effects of S in patients (Ullman *et al.*, 1990). This study aimed to investigate the potential for tachyphylaxis to the non-pulmonary effects of S in healthy subjects.

Twelve healthy male subjects aged 23–43 years participated in a double-blind, placebo controlled cross-over study. Subjects received doses of S (as hydroxy-naphthoate salt) by metered-dose inhaler, up to a maximum dose of 400 μg in increments of 50, 50, 100, 100 and 100 μg at 45 min intervals, before and after a 13 day twice daily regime of (a) 100 μg inhaled S or (b) placebo (P). Cumulative dosing with S was stopped when pulse rate increased by more than 20 beats min^{-1}. Subjects tolerated at least 300 μg S before and after each 13 day treatment. Pulse rate (PR), arterial blood pressure (SBP and DBP), physiological tremor (Maconochie *et al.*, 1988), plasma potassium (K), magnesium (Mg), non-esterified fatty acids (NEFA) and blood glucose (Glu) were measured before and during cumulative dose S. There was a minimum interval of 14 days between the two treatments. Eleven subjects completed the study; one subject withdrew due to adverse effects (headache, nausea, tremor).

The linear trend for each measurement against cumulative dose of S was obtained for each subject and each study day. The tremor data was log transformed prior to analysis. The derived responses obtained after 13 days of treatment were subjected to analysis of variance.

Tachyphylaxis occurred to the effect of S on pulse rate, physiological tremor and blood glucose. S produced a dose related fall in plasma potassium but no tachyphylaxis was seen; there was no effect of S on blood pressure, plasma magnesium and NEFA.

Table 1 Measurement of response/100 μg S to S challenge after 13 days treatment with S or P

	*Adjusted mean**		*Difference*			
	P	*S*	*(P–S)*	*95% C.I.*		*P*
PR (beats min^{-1})	+4.5	+2.0	+2.4	(0.8,	4.1)	0.009
SBP (mm Hg)	+0.7	0.0	+0.7	(−1.1,	2.4)	0.401
DBP (mm Hg)	−0.3	−0.9	+0.6	(−0.5,	1.8)	0.239
Tremor (u)	+26.0%	+11.3%	+13.2%	(7.1%,	19.6%)	< 0.001
K (mmol l^{-1})	−0.17	−0.15	−0.02	(−0.08,	0.04)	0.461
Mg (mmol l^{-1})	−0.00	0.00	0.00	(−0.01,	0.01)	0.946
NEFA (mmol l^{-1})	+0.03	+0.03	0.00	(−0.03,	0.03)	0.929
Glu (mmol l^{-1})	+0.29	+0.10	+0.19	(0.04,	0.34)	0.017

* Means are adjusted for the missing subject.

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Pharmacodynamic response to subcutaneous administration of isoprenaline in healthy volunteers

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There is a substantial literature on the pharmacodynamic responses to intravenous and intra-arterial administration of isoprenaline (I) e.g. van Brummelen *et al.* (1981), but little is known about the responses to subcutaneous administration other than in asthmatic patients (Dry *et al.*, 1975, 1976). The aim of the present study was to evaluate the pharmacological effects of ascending doses of (I) after subcutaneous administration delivered via a cannula attached to an infusion pump over a period of 2 min.

Six healthy female volunteers aged 27 to 44 years were studied. Each volunteer received four subcutaneous administrations in total (two on each arm): 400 μl aliquots of saline, 0.05 mg, 0.075 mg and 0.1 mg (I) in physiological saline in that order during one day. At least 1 h of rest was left between administrations. Heart rate (HR), blood pressure (BP) and ECG data were monitored continuously. No change in HR was observed following administration of saline or 0.05 mg (I). After infusion of 0.075 mg (I), increases of 20–30 beats min^{-1} in HR were observed in most subjects 4–20 min later. Administration of 0.1 mg (I) evoked a very marked response. HR was increased by 30–48 beats min^{-1} within 4–8 min after administration in all subjects except one. In one subject, who was 7–17 years older than the rest, (I) had clearly less effect on HR, evoking increases of 11, 16 and 26 beats min^{-1} after 0.05 mg, 0.075 and 0.1 mg respectively. The effects on BP were much less apparent than HR in all volunteers. No effect was observed following administration of saline, 0.05 or 0.075 mg (I), and 0.1 mg evoked a maximal increase of 41 mm Hg (systolic) in one subject, but the increases observed in the other subjects were much less. All the BP changes recorded for the older volunteer showed the smallest changes. No ECG abnormalities were observed other than the expected tachycardia. A localised skin reaction consisting of a central white area surrounded by a dark red ring was observed in all volunteers following administration of all doses of (I), but not saline.

Thus, sub-cutaneous infusions of (I) to six healthy volunteers evoked the positive chronotropic and to a lesser extent inotropic effects associated with β-receptor stimulation, and these data are consistent with an age-related reduction in cardiac and peripheral vascular β-receptor mediated responses previously described by van Brummelen *et al.* (1981). The localised skin reactions were unexpected, but may be due to an α-receptor mediated vasoconstriction surrounded by a reactive hyperaemic response, as has been previously mentioned (Goodman & Gilman, 1975).

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The effect of atrial natriuretic factor on platelet function *ex vivo* in man

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Atrial natriuretic factor (ANF) causes natriuresis, vasorelaxation and the inhibition of the renin-angiotensin-aldosterone system. Radioligand binding studies have now identified ANF binding sites in a variety of tissues including the kidney, vascular smooth muscle, brain and the adrenal. Although binding sites for ANF have been reported on human platelets (Schiffrin *et al.*, 1986), the physiological or functional role of these receptors remains undetermined. Previous *in vitro* platelet aggregation studies have produced contrasting results. Whilst Loeb & Gear (1988) were able to show that pretreatment of human platelets with ANF induced a dose-dependent potentiation of platelet aggregation, De Caterina *et al.* (1985) were unable to demonstrate any significant ANF-mediated effects on human platelet aggregation. We have now examined the effect of intravenously administered ANF on *ex vivo* platelet function in man.

Eight fasting normal male volunteers aged 19 to 22 years were studied on two occasions at least 7 days apart. None had received aspirin nor any other platelet function modifying drugs for at least 10 days prior to the study. On each study day, after resting seated for 80 min, an infusion of either 5% Dextrose (P) or ANF 5 pmol kg^{-1} min^{-1} in P was commenced and continued for 60 min in single-blind randomised fashion. Venous blood was collected into pre-warmed (37 °C) plastic tubes containing 3.2% trisodium citrate solution for the following platelet aggregation studies: (i) spontaneous platelet aggregation (PA); (ii) collagen-induced PA and (iii) ADP-induced PA. Values are expressed as percentage (%) fall in single platelet count. Venous blood was also collected for measurement of plasma aldosterone and ANF levels.

The values are shown as mean ± s.e. mean at times: 0 min (baseline), + 60 min (end of infusion) and at + 90 min (post-infusion). *Spontaneous PA* [%]: 44.9 ± 7.3, 45.3 ± 7.2, 45.6 ± 7.0 (P); 44.9 ± 7.3, 49.5 ± 7.2, 45.6 ± 7.3 (ANF) [NS]; *Collagen-induced PA* [%]: 70.3 ± 7.2, 73.7 ± 7.4, 77.1 ± 6.7 (P); 75.1 ± 7.2, 76.1 ± 8.4, 75.5 ± 9.8 (ANF) [NS]; *ADP-induced PA* [%]: 79.7 ± 5.3, 77.9 ± 3.5, 80.7 ± 3.8 (P); 79.3 ± 4.3, 81.1 ± 3.5, 80.7 ± 3.8 (ANF) [NS]. The plasma ANF and aldosterone levels at times 0 min and + 60 min are as follows: *plasma ANF* (pmol l^{-1}): 6.4 ± 0.7, 6.1 ± 0.5 (P); 7.0 ± 0.7, 67.3 ± 12.7 (ANF) ($P < 0.001$); *plasma aldosterone* (pg ml^{-1}): 153.7 ± 16.8, 155 ± 12.8 (P); 140.3 ± 13.4, 104.0 ± 11.8 (ANF) ($P < 0.01$).

In conclusion, we have shown that a pharmacological dose of ANF does not alter platelet function in man. Platelet hyper-reactivity has recently been associated with a poor prognosis in patients with chronic heart failure as well as following a myocardial infarction. Our results would suggest that the high levels of ANF normally achieved in both conditions are unlikely to be a contributing factor to platelet hyper-reactivity.

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Pharmacodynamics and pharmacokinetics of the novel class III antiarrhythmic drug UK-68,798 in man

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UK-68,798 (N-[4-(2-{2-{4-(methanesulphonamido) phenoxy}-N-methylethylamino}ethyl)phenyl]methanesulphonamide) is a novel selective Class III antiarrhythmic agent (Dalrymple *et al.*, 1989) which has been shown to abolish both ventricular and supraventricular arrhythmias in experimental models (Gwilt *et al.*, 1989; Pfizer, personal communication). The present study evaluated the pharmacodynamics and pharmacokinetics as well as safety and toleration of UK-68,798 after oral (p.o.) and intravenous (i.v.) administration to healthy volunteers.

Nine healthy male subjects (age 23 ± 1 years (mean ± s.e. mean); weight 66.3 ± 2 kg) were administered in random order UK-68,798 0.5 mg p.o. (capsule) and i.v. (infusion over 10–14 min); treatments were separated by at least 7 days. Following p.o. administration serial blood samples for determination of drug content were withdrawn at intervals up to 96 h from an antecubital vein using an indwelling catheter. For i.v. administration UK-68,798 was infused into a vein in the left arm and serial blood samples withdrawn, using an indwelling venous catheter from the right arm. Samples were assayed using a specific radioimmunoassay. 12 lead ECGs were recorded (Marquette) for measurement of RR, PR, QRS and QT_c (a non-invasive index of Class III activity) intervals prior to dosing and serially for 24 h. Maximum QT_c intervals and heart rate were measured from the Holter readings at 2 min intervals before, during and for 20 min after the infusion. BP was measured using a random zero sphygmomanometer.

Safety and toleration were assessed through haemodynamic changes, by open side effect enquiry, by 24 h Holter tape recording and clinical chemistry.

Following i.v. infusion of UK-68,798, the QT_c interval increased ($P < 0.05$) from 401 ± 9 ms to 504 ± 35 ms at the end of the infusion. With p.o. administration the QT_c increased from 396 ± 9ms to 445 ± 9 ms; the time to maximum increase was 2 ± 0.3 h. Significant effects lasted for 3 h following i.v. and 4 h following oral administration. No change occurred in the PR interval and QRS width or HR and BP on either study day; small decreases in supine HR and BP occurred.

Pharmacokinetic analysis of the data indicated plasma elimination half-lives of 7.5 ± 0.4 h (i.v.) and 7.1 ± 0.2 h (p.o.), volume of distribution was 228 ± 17 l and clearance 347 ± 20 ml min^{-1}. Bioavailability was 99 ± 3%. 52 ± 2% of UK-68,798 was excreted unchanged in the urine in the 48 h following dosing. One subject exhibited an excessive prolongation of his QT_c interval which was associated with an asymptomatic run of polymorphic VT. Safety reviews of Holter tapes, side effects, haemodynamic changes and clinical chemistry indicated no other drug related effects in the other volunteers.

In conclusion, UK-68,798 is a selective Class III antiarrhythmic agent which warrants further clinical evaluation.

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A comparison of the incidence and reproducibility of ventricular late potentials (LP) in the time and frequency domain in patients with cardiovascular (CV) disease

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High resolution signal averaging (HR-SA) of the surface ECG has demonstrated LP which are regarded as prognostic indicators for identifying those subjects at risk from a major or fatal arrhythmic event (Vatterott *et al.*, 1988). However, there is controversy with regard to the methods of analysis for detection of LP. The present study compared a number of methods in the time and frequency domain for the detection of LP. HR-SA ECG were recorded (Predictor-Corazonix) from 82 subjects using the orthogonal XYZ lead system; averages of 600 beats or until noise was < 0.3 μV were taken (those > 1 μV were ignored). Two systems for evaluation of LP were investigated. The first system used published parameters for the 25– and 40–250 Hz bandwidths. Five analyses were actually performed using variations of the three parameters: the QRS duration (QRSd), the Root Mean Square of the terminal 40 ms of the QRS (RMS40) and the Low Amplitude Signal duration (LASd) (< 40 μV). For the first 2 analyses A and B (25–250 Hz) LP parameters for A were QRSd > 120 ms, LASd > 35 ms and RMS40 < 25 μV, for B LASd > 40 ms. Methods C, D and E (40–250 Hz); LP parameters for C were QRSd > 110 ms, LASd > 35 ms, RMS40 < 20 μV, D LASd > 40 ms and E QRSd > 120 ms and LASd > 40 ms. At least two of the parameters had to be abnormal for LP definition. Fourier transform (FT) (method F) was performed using a Blackman-Harris window on a 120 ms length starting at the 40 μV level (25–250 Hz) and extending out towards the T wave. The area for 60–120/0–120 Hz was calculated for each lead then meaned (%) (Pierce *et al.*, 1989): a value of > 3% was used for LP detection. The second system of analysis involved setting parameters which were outside the normal distribution (methods G, H and I); G (25–250 Hz) QRSd > 114 ms, RMS40 < 18 μV, LASd > 40 ms, H (40–250 Hz) QRSd > 113 ms, RMS40 < 11.5 μV, LASd > 40 ms. For FT (I), a value of > 3.6% was used. Five groups were studied; Group 1 (G1) Healthy (n = 13), G2 Hypertensive (HP) (n = 10), G3 HP + CV disease (n = 23), G4 = G2 + G3 (n = 33), G5 CV (n = 24) and G6 'Others' (n = 12).

The results (Table 1) indicate the incidence of LP in each group using each method of analysis. A Pearson correlation compared the methods and the subjects with LP for the first system of analysis (methods A to F). This demonstrated a correlation ($P < 0.001$) between methods AB,CD,CE and DE in the time domain but none between time and frequency. The results of the second system of analysis showed no correlation between the groups. The number of subjects detected in the first system as having late potentials by every method (A–F) was four compared with two for methods G–I.

In conclusion the present study confirms a correlation between methods A to E in the time domain for evaluation of LP. However, further studies need to be undertaken with regard to the frequency domain, for example, setting area calculations at different bandwidths.

Table 1

	Groups					
Method	*1*	*2*	*3*	*4*	*5*	*6*
A	2	4	1	5	4	1
B	1	1	1	2	4	1
C	1	3	3	6	6	1
D	1	3	3	6	5	1
E	1	3	3	6	5	1
F	1	4	5	9	4	0
G	1	1	1	2	3	1
H	1	1	2	3	5	1
I	1	1	2	3	3	0

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Vatterott, J. *et al.* (1988). *Mayo Clin. Proc.*, **63**, 931.

HMG Co-A reductase inhibitors and lipoprotein(a) in hypercholesterolaemia

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Recently the level of lipoprotein(a) has been shown to be a major risk factor for coronary heart disease in patients with familial hypercholesterolaemia (Seed *et al.*, 1990). Furthermore it appears to predict the likelihood of restenosis of coronary bypass grafts (Hoff *et al.* 1989). Lipoprotein(a) combines structural elements from low density lipoprotein and the blood clotting plasminogen system. Recent limited studies (Berg & Leren, 1989; Jurgens *et al.*, 1989) have reported contradictory results of the effect of HMG Co-A reductase inhibitors on lipoprotein (a) levels. We therefore measured lipoprotein(a) prior to and during treatment with pravastatin and simvastatin.

Forty-six patients (aged 53 ± 5 years; mean ± s.e. mean) with primary hyperlipidaemia were treated with pravastatin (20–40 mg, $n = 22$) or simvastatin (10–40 mg, $n = 24$) for 12 weeks. None received any other therapy known to influence lipoprotein(a) levels. Lipoprotein (a) levels were determined using an ELISA (Biopool, TintElize) method on plasma samples stored at −20° C. In these patients lipoprotein(a) levels (47 ± 8 mg dl^{-1}) were higher than those of normal control subjects (< 30 mg dl^{-1}). Levels were higher ($P < 0.05$) in patients who had ischaemic heart disease or underwent coronary angioplasty or bypass graft. In a separate group of hyperlipidaemic patients on placebo and whose samples were similarly stored at −20° C there was no change in lipoprotein(a) level or cholesterol. Both drugs reduced cholesterol ($P < 0.01$) but neither had a significant effect on lipoprotein(a).

Despite significant reductions in cholesterol levels with HMG Co-A reductase inhibitors lipoprotein(a) levels were unchanged.

Table 1 Effect of HMG Co-A reductase inhibitors on cholesterol and lipoprotein(a)

	Pre-treatment	*Pravastatin*	*Pre-treatment*	*Simvastatin*
Cholesterol (mmol l^{-1})	8.3 ± 1.2	6.1 ± 0.9*	9.9 ± 1.2	5.9 ± 0.8*
Lipoprotein(a) (mg/dl^{-1})	47 ± 10	45.0 ± 10	48 ± 7	52 ± 10

*$P < 0.01$.

Berg, K. & Leren, T. (1989). *Lancet*, **ii**, 812.
Hoff, H. *et al.* (1988). *Circulation*, **77**, 1238.
Jurgens, G. *et al.* (1989). *Lancet*, **i**, 911.
Seed, M. *et al.* (1990). *New Engl. J. Med.*, **322**, 1494.

Functional muscarinic acetylcholine receptors of the M_2-subtype in adult ventricular cardiomyocytes

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In whole heart tissue which is composed of cardiomyocytes and other cell types, the presence of muscarinic acetylcholine receptors (MAChRs) predominately of the M_2-subtype has been demonstrated. To date MAChRs of the M_2-subtype have not been identified at the cellular level, i.e. on ventricular cardiomyocytes, and this was the aim of the present study.

Ventricular cardiomyocytes were isolated from adult Wistar rats (200–250 g) and resuspended in a modified Tyrode solution containing adenosine deaminase (5 u ml^{-1}). Adenylate cyclase activity was evaluated by determining cellular cAMP accumulation in the presence of the phosphodiesterase inhibitor, Ro 20-1724 (0.5 mM), according to the method of Millar *et al.* (1988). Contractions of cardiomyocytes under electrical field stimulation (pulse: 0.5 ms, 60 V; frequency: 0.5 Hz) were optically recorded as described by Piper *et al.* (1989). Radioligand binding assays were carried out using sarcolemmal membranes isolated from purified ventricular cardiomyocytes.

Oxotremorine, a non-selective MAChR agonist, inhibited isoprenaline (10^{-7} M)-stimulated cAMP accumulation in a dose-dependent manner and the IC_{50} was 2×10^{-8} M. The selective M_2-AChR antagonist, AF-DX 116 (10^{-6} M), completely abolished the inhibitory effect of oxotremorine (10^{-7} M). Binding of [^{3}H]-AF-DX 116 at 25° C to sarcolemmal membranes demonstrated the presence of specific binding sites with a mean K_d value of 129 nM ± 36 (s.d.) and a B_{max} of 64 fmol mg^{-1} protein ± 22 (s.d.). Oxotremorine (10^{-7} M) completely abolished the positive contractile response of electrically stimulated cardiomyocytes to isoprenaline (10^{-7} M). This inhibitory effect of oxotremorine could be reversed by AF-DX 116 (10^{-6} M).

These results demonstrate the existence of functional MAChRs of the M_2-subtype in ventricular cardiomyocytes.

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Antihypertensive effect of a fixed combination of felodipine and metoprolol in a new extended release formulation

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The combination of low doses of a calcium antagonist and a β-adrenoceptor blocker has the potential to provide antihypertensive efficacy with good tolerability.

This double-blind, randomised, parallel-group, multicentre study in General Practice compared the antihypertensive effect and tolerability of the dihydropyridine calcium antagonist felodipine (Saltiel *et al.*, 1988) combined with the β-adrenoceptor blocker metoprolol (Sandberg *et al.*, 1988), in a fixed-dose extended-release (ER) combination tablet, with those of higher doses of felodipine and metoprolol alone.

Patients entered the study if seated diastolic blood pressure was 95–110 mm Hg after 4 weeks treatment with felodipine ER 5 mg once in the morning. Patients were randomised ($n = 205$) to receive the fixed combination of felodipine + metoprolol ER (F + M) 5 + 50 mg once in the morning, felodipine ER (F) 10 mg once in the morning or metoprolol controlled release (M) 100 mg once in the morning for a further 4 weeks. Measurements (mean ± s.d.) were made 24 h post-dose. 'Responders' were defined prospectively as having a seated DBP ≤ 90 mm Hg and/or a reduction of 10 mm Hg.

Patients were aged 30–73 (mean 56) years and of either sex (no women of child bearing potential). The baseline characteristics of the three treatment groups were similar.

After 4 weeks, F + M reduced mean seated DBP by 7 mm Hg (from 101 ± 5 to 94 ± 9 mm Hg) compared with reductions of 6 mm Hg on either F or M (from 101 ± 4 to 95 ± 8 and 102 ± 4 to 95 ± 8 mm Hg respectively). There were no statistically significant differences, in the changes, between treatments (one way analysis of variance). Forty-eight percent of the F + M group were responders compared with 45% and 40% respectively for the F and M groups (NS logistic regression). Seated heart rate after F + M treatment was 73 ± 12 beats min^{-1} compared with 78 ± 13 beats min^{-1} on F and 70 ± 9 beats min^{-1} on M. Six patients withdrew due to headache/flushing, leg oedema, tremor or bronchospasm. The total numbers of patients reporting adverse events were 18/66 on F + M, 25/69 on F and 21/67 on M. Most adverse events were classified as mild and included peripheral oedema, headache and flushing. Common adverse events were consistently lower on F + M, e.g. peripheral oedema on F + M = 3/66, F = 9/72, M = 0/67; headache on F + M = 3/66, F = 6/72, M = 4/67.

The fixed combination of felodipine + metoprolol ER 5 + 50 mg had an antihypertensive effect and tolerability as least as good as either felodipine ER 10 mg or metoprolol CR 100 mg.

Saltiel, E. *et al.* (1988). *Drugs*, **36**, 387.

Sandberg, A. *et al.* (1988). *Eur. J. clin. Pharmac.*, **33**, 3.

A comparison of the antihypertensive and metabolic effects of low and conventional cyclopenthiazide during the second year of treatment

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In a previous study we demonstrated that 125 μg cyclopenthiazide was as effective as 500 μg in lowering blood pressure over a 1 year period (Johnston *et al.*, 1990). Serum potassium, urate, and total cholesterol were increased by the 500 μg dose during the first 6 months but were unaltered by the lower dose. At 1 year however the differences in serum potassium and cholesterol between the two doses of cyclopenthiazide were difficult to demonstrate. In this study we examined the effects of a further 1 year's treatment with 125 and 500 μg cyclopenthiazide to see if the adverse biochemical effects observed at high dose were maintained and if the low dose offered any long term advantage.

Forty-eight of the 60 patients who completed the original 1 year study in patients with mild to moderate hypertension continued on the 125 μg dose (20 patients) or 500 μg (28 patients). Patients were visited at home at 3 monthly intervals for a further year. At each visit blood pressure was measured and blood taken for serum potassium, urate, glucose, glycosylated haemoglobin, total cholesterol and apolipoproteins. Criteria for exclusion were a serum potassium less than 3.0 mmol l^{-1} and a blood pressure greater than 100 mm Hg on three consecutive occasions. Statistical analyses were performed using a repeated measures analysis of variance and the significance level chosen was $< 5\%$. Comparisons at different times within groups were carried out using the *t*-statistic, to which appropriate adjustments were made for between-group comparisons of differences from baseline. Results are expressed as mean differences with 95% confidence intervals.

No patients were withdrawn during the second year because of hypokalaemia or an inadequate therapeutic response. During the second year, mean decreases in systolic blood pressure on 500 μg ranged from 12.9 (5.5–20.3) to 20.5 (13.5–27.5) mm Hg and from 4.9 (0.5–9.3) to 12.1 (5.4–18.7) mm Hg on 125 μg; decreases in diastolic blood pressure on 500 μg ranged from 11.7 (8.3–15.3) to 15.9 (12.8–19.0) mm Hg and from 6.8 (1.8–11.9) to 10.0 (5.5–14.2) mm Hg on 125 μg. The effects of 500 μg cyclopenthiazide on diastolic but not systolic blood pressure were significantly greater than with the 125 μg dose ($P < 0.05$). Maximum decreases in serum potassium of 0.36 (−0.08–0.51) mmol l^{-1} and 0.06 (−0.29–0.41) mmol l^{-1} were observed with 500 and 125 μg cyclopenthiazide respectively. The differences between the two doses on serum potassium were statistically significant ($P < 0.05$) but the effect of each dose was less than that observed during the first year. The effects of 500 μg cyclopenthiazide on serum urate observed during the first year were not seen during the second. Decreases in total cholesterol and increases in apolipoprotein A were observed with both doses ($P < 0.05$) and while the mean decreases in cholesterol appeared greater with the low dose, this did not achieve statistical significance ($P = 0.13$).

With the exception of serum potassium, the more favourable biochemical profile of low dose cyclopenthiazide seen during the first year was difficult to demonstrate during the second and blood pressure was not as well controlled as with the higher dose. In the absence of a placebo control, interpretation of the lipid data are difficult and may reflect changes in lifestyle in the patient population.

Johnston, G. D. *et al.* (1990). *Br. J. clin. Pharmac.*, **29**, 586P.

Does placebo lower ambulatory blood pressure measured non-invasively?

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Falls in blood pressure (BP) attributed to a placebo response have been reported in several antihypertensive drug studies (Doyle, 1983). An important observation with ambulatory BP measurement is that patients whose BP is monitored intra-arterially do not show lowering of pressure on placebo (Gould *et al.*, 1981). However, this observation has not been confirmed in any controlled study of the effect of placebo on ambulatory BP monitored using non-invasive techniques to date.

To address this issue, ambulatory BP was measured non-invasively over 24 h in 16 patients with sitting clinic diastolic BP 90 mm Hg or greater at the end of a 4 week run-in period who then entered a randomised cross-over trial, where they were treated with placebo, taken once daily, or no treatment. Twenty-four hour ambulatory BP measurement (Spacelabs 90202) was recorded at entry and at the end of each 4 week treatment period.

In the circumstances of the present study, a placebo effect, i.e. lowering of BP was not apparent on ambulatory BP measurement. We conclude that placebo treatment does not lower blood pressure measured non-invasively in keeping with the findings for intra-arterial monitoring. These findings have important implications for the design of studies evaluating interventions in hypertension.

Table 1 Ambulatory BP (mm Hg). Data are mean ± s.d.

	Entry	*Placebo*	*No treatment*
Systolic	147 ± 13	152 ± 13	147 ± 12
Diastolic	91 ± 8	94 ± 8	92 ± 8

Doyle, A. E. (1983). *Hypertension*, **5** (Suppl. 111), 111-3.

Gould, B. A. *et al.* (1981). *Lancet*, **ii**, 1377.

The effects of nifedipine on the haemodynamics and vasoactive regulation of cyclosporin nephrotoxicity in the normal human kidney

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Cyclosporin (CyA) induced dysfunction in the innervated normal kidney may result from disturbance of the microcirculation but its regulation, reversibility and means of abrogation are poorly defined. In other applications nifedipine may ameliorate CyA toxicity. Eight patients with psoriasis and stable cardiovascular state were treated with low dose CyA (2.5 mg kg^{-1}) for 3 months; after 3 months washout they then received an identical course of CyA with nifedipine S.R. 20 mg twice daily. The effect on GFR, RBF and filtration fraction (FF) was serially assessed using a novel Tc-99m DTPA dynamic technique (Peters *et al.*, 1987) together with the measurement of the vasoactive hormones PRA, aldosterone, angiotensin II (A-II) and atrial natriuretic peptide (ANP).

Table 1

	Time (months) (0)---CyA---(3)---No CyA---(6)---CyA+Nif---(9)			
GFR (ml min^{-1} 1.73 m^{-2})	100 ± 6	85 ± 5[a]	91 ± 5	87 ± 6
RBF (%C.O.)	17.0 ± 1.3	14.4 ± 1.3[a]	15.4 ± 1.4	15.2 ± 1.2
FF (%)	19.9 ± 1.6	21.1 ± 1.9	23.7 ± 2.9	20.7 ± 1.53
PRA (pmol h^{-1} ml^{-1})	4.4 ± 0.8	3.5 ± 1.9	4.0 ± 0.5	3.0 ± 0.4
Aldosterone (pmol l^{-1})	592 ± 57	411 ± 55[a]	440 ± 54	427 ± 47
Mean A-II (pg ml^{-1})	8.7 ± 1.2	11.8 ± 1.7	8.8 ± 1.2	7.5 ± 0.8[b]
ANP (pmol l^{-1})	3.3 ± 0.8	4.2 ± 0.3[c]	2.9 ± 0.3	4.1 ± 0.4[c]

Mean ± s.e. mean, $P = < 0.05$, [a] (0) *vs* (3); [b] (3) *vs* (9); [c] (3) or (9) *vs* (6) month assessments

CyA nephrotoxicity was characterised by reduced GFR, RBF and hypoaldosteronism with a rise in ANP. A-II and FF were closely correlated ($r_P = 0.46$; $P < 0.02$). After nifedipine the fall in A-II did not correlate with RBF whereas during CyA therapy alone RBF and A-II were associated ($r_S = 0.81$; $P < 0.05$).

CyA nephrotoxicity of the intact normal kidney may reflect A–II dependent efferent arteriolar vasoconstriction. These haemodynamic effects were abrogated in individual patients by nifedipine which may potentially be related to the modulation of A-II as well as calcium channel blockade.

Peters, A. M. *et al.* (1987). *Nucl. Med. Commun.*, **8**, 823.

DEMONSTRATION

Computer interactive video model of a cardiovascular case presentation to teach clinical observation, diagnosis and therapy

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A video of the neck of a subject with bradycardia was recorded showing detail of the jugular vein pulsations which assists in diagnosing the cause of the bradycardia.

The program was written in MCAL, an authoring computer language developed at Queen's University, to allow an IBM PS/2 microcomputer to control the video using individual frame code numbers to find the appropriate location on the video recording. High quality still photographs and accurately timed moving sequences can thus be displayed on the computer screen, along with superimposed computer generated text and graphics. The computer program has been written to interact with the student by asking questions and analysing the student's responses (Table 1). The questions require free text replies, which avoids the prompting associated with multiple choice format. If the student does not respond correctly then repeat attempts, spelling reminders and remedial tuition are provided. The video sequences, text and graphics are used to enable the student to learn to recognize the signs, make a diagnosis and decide therapy.

Interactive video has potential for the teaching of clinical pharmacology because the student can make therapeutic decisions and obtain feedback, without exposing a patient to any hazard, and without the need for supervision.

Table 1 Sample questions (answers expected)

What is the heart rate of this patient? (46 beats min^{-1})
Identify the venous wave coincident with the flashing signal. (a or v wave)
What drug is sometimes indicated in patients with bradycardia? (atropine)
How does this drug work? (as a cholinergic antagonist)
What other therapy is sometimes indicated in patients with bradycardia? (artificial pacemaker)
What would you give in this case? (reassurance)