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Influence of Verapamil on the Inotropism and Pharmacokinetics of Digoxin

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Summary. Verapamil has been demonstrated to inhibit the elimination of digoxin and to increase its steady state plasma level by 60–80%. Animal studies suggest that verapamil abolishes the intropic action of other drugs such as ouabain and dopamine. The clinical consequences of this drug interaction were investigated by examining the inotropic activity of single doses of digoxin (assessed from systolic time intervals), with and without coadministration of verapamil. Verapamil decreased total-body clearance of digoxin from 4.68 ± 0.41 to 3.29 ± 0.26 ml/min/kg ($p < 0.001$) and increased the plasma half-life of the drug from 33.50 ± 2.38 to 41.31 ± 2.27 h ($p < 0.01$). Verapamil had no influence on the base-line values of the systolic time intervals. Both in the absence and presence of verapamil, digoxin caused significant shortening of the total electromechanical systole and the left ventricular ejection time. However, compared to control conditions, the decay of these changes was slower in the presence of verapamil, in parallel with the prolongation of the plasma half-life of digoxin. A linear relationship was established between reductions in the systolic time intervals and the computer-derived concentration of digoxin in the deep compartment. These regression lines, which represent the concentration-effect relationships of the inotropism of digoxin, were not affected by verapamil. Thus, verapamil per se had no measurable effect either on base-line contractile function of the heart or on digoxin-induced inotropism. The elevated plasma digoxin concentration induced by verapamil appears cardioactive in terms of inotropism.

Key words: verapamil, digoxin; drug interaction, digoxin pharmacokinetics, inotropic effect, systolic time intervals

In a previous single-dose study in healthy subjects, it was shown that the calcium-antagonist, verapamil, reduced the total-body clearance of digoxin by 35% due to impairment of both its renal and extrarenal elimination [1]. As anticipated, therefore, coadministration of verapamil is associated with an approximately 60% increase in the steady state plasma digoxin concentration in cardiac patients [2] and in healthy subjects [3]. Since the effect of verapamil on digoxin kinetics is very similar to the digoxin-quinidine interaction, identical questions may be raised about the clinical consequences of the elevated plasma digoxin level. Experiments in vitro and animal studies have suggested that quinidine may displace digitalis glycosides from myocardial binding sites [4, 5, 6], which will tend to counteract the effect of an elevation in plasma digoxin. Clinical studies have indicated that quinidine reduces the inotropism of digoxin [7, 8], but the observations have been disputed [9].

A negative inotropic effect of verapamil has been demonstrated on animal myocardium in vitro [10, 11, 12], but several studies have shown that therapeutic doses of verapamil have no measurable negative inotropic effect in man [13, 14, 15]. In conscious dogs, verapamil caused inhibition of the inotropic effect both of ouabain and dopamine, which might be due to a blockade of calcium influx [16]. Virtually no information appears to exist about the influence of verapamil on digoxin-induced inotropism in man, but it would be desirable in defining the clinical importance of this drug interaction.

The aim of the present study was to evaluate the influence in vivo of verapamil on digoxin-induced changes in left ventricular contractile function, as assessed by measurement of systolic time intervals, and to correlate these findings with kinetic parameters obtained at the same time.

Materials and Methods

Subjects

The study comprised eight healthy male volunteers, aged 21–32 years. None was taking any medicine and none had any disease as judged by the history, general physical examination and E.C.G. Base-line biochemical tests were normal. Written informed consent was obtained from each subject before the study.

Protocol

The study was designed as a repeated single-dose investigation, performed in the same subjects with a wash-out interval of 2 weeks. In control trials, each subject received digoxin 1 mg administered as an intravenous bolus into an antecubital vein. Venous blood samples were taken from the opposite arm through an inwelling catheter, or by separate venepuncture, at 0, 10, 20, 40 min and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 24, 36, 48, 54, 72, 80 and 132 h after the injection. Blood samples were processed within 1 h and plasma samples were kept at −21 °C until assayed.

Oral administration of verapamil chloride (Isoptin®, Knoll 120 mg three times daily was initiated on Day 7 and was continued unchanged throughout the study. After 7 days of verapamil pretreatment, all investigations were repeated using the same dose of digoxin and similar blood sampling.

Systolic Time Intervals

Systolic time intervals (STI) were calculated from simultaneous recordings of ECG, phonocardiogram and carotid pulse tracing, obtained after at least 10 min at rest, using a 6-channel Mingograph 82 (Siemens Elema). Blood pressure was measured with an ordinary cuff mercury manometer. Total electromechanical systole (QS_2) was measured from the beginning of the QRS complex to the start of the high frequency vibrations of the second heart sound. Left ventricular ejection time (LVET) was measured on the carotid pulse tracing from the beginning of the upstroke to the nadir of the dicrotic notch. Pre-ejection period (PEP = QS_2-LVET) and the PEP/LVET ratio were also calculated.

Base-line STI values were recorded just before digoxin administration and again after 15 and 45 min and 1, 2, 3, 4, 6, 8, 24, 36, 54, 80 and 132 hours. Blood for digoxin assay was obtained by venepuncture at the same times. In both trials, digoxin was administered at 8 a.m., and the same time schedules and technique for STI measurements were used.

All STI data were based on mean values from five consecutive cardiac cycles. Prior to the study, the relationship between STI and heart rate was evaluated in a matched control group ($n=18$). A linear correlation was found between LVET and QS_2 versus heart rate, which was used to correct the STI values to heart rate of 60/min. The heart rate-corrected values are denoted QS_2-I60 and LVET-I60. PEP appeared to be independent of heart rate at rates below 100/min. Control measurements of STI in each subject were made at least two weeks after the investigation. The diurnal variation in these data was used for individual correction of the serial STI values obtained in the trials. Measurements of STI were performed by a blinded observer.

Analytical Methods

Plasma digoxin concentration was determined in duplicate by radioimmunoassay, using an [^{125}I]-kit (Diagnostic Corporation, USA). The characteristics of this method have previously been described [1].

Analysis of Pharmacokinetic Data

Individual plasma digoxin concentration versus time data were fitted to a biexponential function by means of iterative, weighted, non-linear, least-squares regression analysis using the computer program, Nonlin, as described in elsewhere [1]. The computer-derived function, which represents an open two-compartment model, was then used to calculate total body clearance, volumes of distribution, biological half-life and the derived time course of the apparent concentration of drug in the deep compartment [17, 18].

Statistical Analysis

The differences between various pharmacokinetic parameters of digoxin were evaluated by Student's *t*-test for paired observations. Serial measurements of STI were tested by two-way analysis of variance. The correlation between changes in STI and digoxin concentration in the deep compartment were evaluated by linear regression analysis.

Results

Pharmacokinetics

No untoward reactions attributable to digoxin or verapamil were observed. The kinetic parameters obtained are summarized in Table 1. In the presence of

Table 1. Pharmacokinetic parameters of digoxin in the absence (CON) and presence (VER) of verapamil

Subject No.	Total body clearance [ml·min^{-1}·kg^{-1}]		V_P [l·kg^{-1}]		V_C [l·kg^{-1}]		Biological half-life [h]	
	CON	VER	CON	VER	CON	VER	CON	VER
1	4.12	2.70	8.75	9.09	0.91	0.88	33.66	49.68
2	4.91	3.81	8.29	7.30	1.22	1.47	30.21	32.46
3	2.87	2.20	5.94	6.68	1.33	0.84	34.89	43.83
4	5.55	3.37	8.94	9.38	0.59	0.72	27.79	40.76
5	6.24	4.31	9.81	10.65	1.76	1.32	27.62	37.08
6	5.62	3.75	11.84	9.98	0.79	0.68	36.78	41.62
7	3.37	2.54	10.75	8.85	0.95	0.84	47.93	50.00
8	4.76	3.66	8.37	7.82	0.84	0.98	29.12	35.07
Mean	4.68	3.29[a]	9.08	8.72	1.05	0.97	33.50	41.31[b]
±SEM	0.41	0.26	0.63	0.48	0.13	0.09	2.38	2.27

[a] Significantly different from control ($p<0.001$)
[b] Significantly different from control ($p<0.01$)
V_P: Apparent volume of deep compartment
V_C: Apparent volume of central compartment

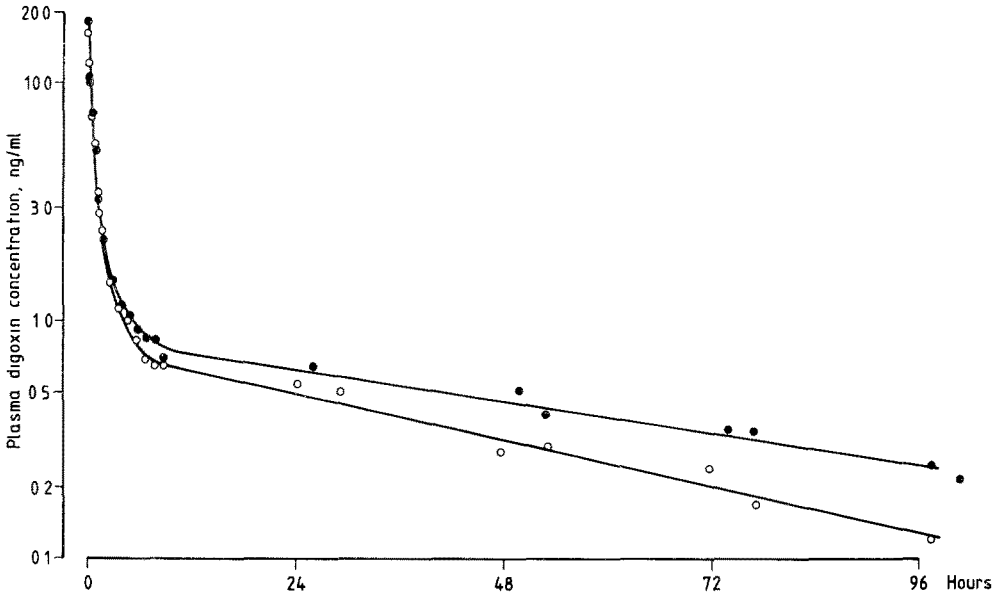

Fig. 1. Semilogarithmic plots of plasma digoxin concentration versus time after intravenous administration of digoxin 1 mg before (○) and during (●) verapamil coadministration (Subject 1)

verapamil, the mean total body clearance of digoxin decreased from 4.68 ± 0.41 to 3.29 ± 0.26 ml·min^{-1}·kg^{-1} ($p<0.001$), whereas its peripheral and central distribution volumes were unaltered. In accordance with the impairment of elimination, the average biological half-life of digoxin increased from 33.5 ± 2.4 h to 41.3 ± 2.3 h ($p<0.01$). The decay of plasma digoxin in a typical subject is presented in Fig. 1.

Pharmacodynamics

The two parameters of principal interest, QS_2-I60 and LVET-I60, were substantially reduced in all subjects after bolus administration of digoxin, whereas no consistent change in PEP or PEP/LVET was observed. The time course of the relative changes in QS_2-I60 and LVET-I60 are shown in Fig. 2. During control investigations both parameters showed a rapid decrease shortly after digoxin administration, with the maximum effect being reached within 4 h. The changes then slowly subsided in parallel with the decay of the body content of digoxin. The reductions in STI were not correlated with plasma digoxin concentration (representing the central compartment), as shown by the striking discrepancies between drug concentration (Fig. 1) and effect (Fig. 2) during the distribution phase in the initial 4–6 h after drug ad-

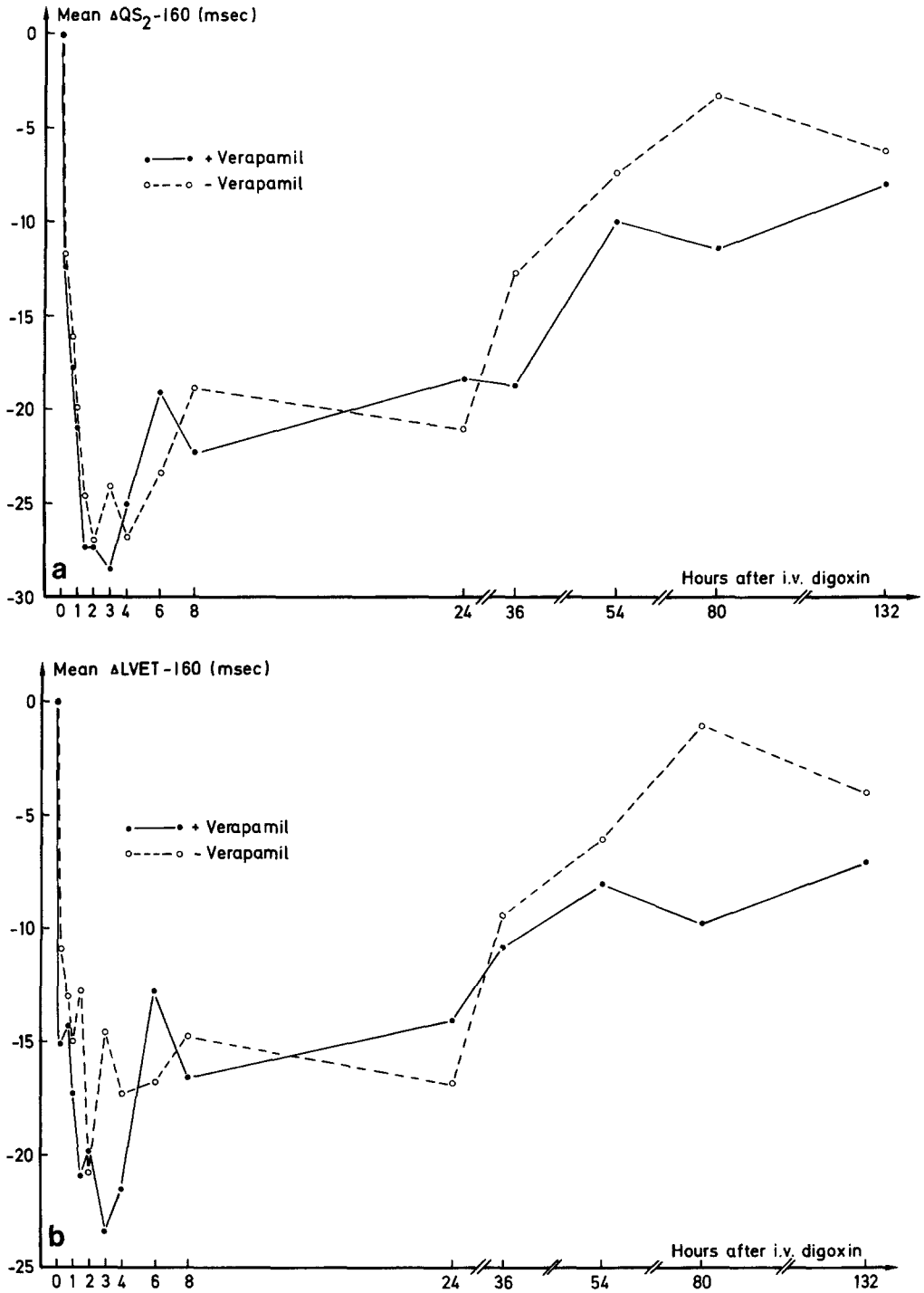

Fig. 2. Time course of the mean changes in ΔQS_2-I60 and ΔLVET-I60 after intravenous digoxin administration in the absence (○) and presence (●) of verapamil

ministration. In the post-distributive phase, changes in STI and plasma digoxin roughly occurred in parallel.

The mean change in LVET-I60 is compared to the computed mean concentration of digoxin in the deep compartment in Fig. 3. It appears that the two parameters showed strictly parallel changes both during the distribution and the elimination phases of digoxin. QS_2-I60 behaved similarly.

Verapamil had no influence on base-line STI values. The mean LVET-I60 was 303.8 ± 3.5 msec during the control period and 305.0 ± 5.4 ms (NS) during

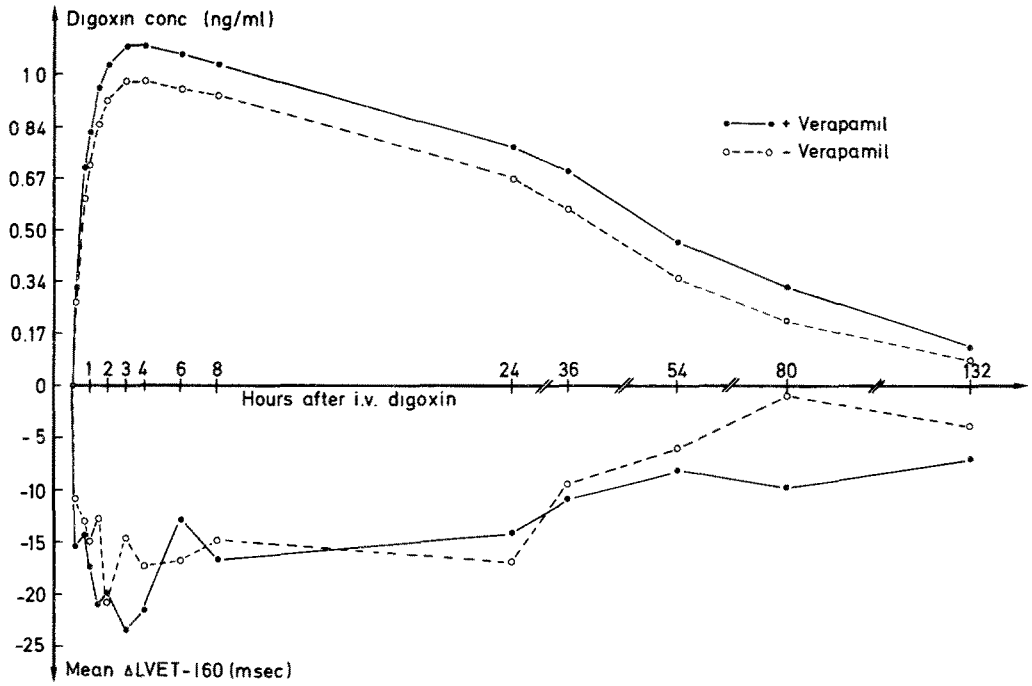

Fig. 3. Time course of the estimated mean digoxin concentration in the deep compartment and corresponding mean changes in ΔLVET-160 in the absence (○) and presence (●) of verapamil

verapamil coadministration. The corresponding values for QS_2-I60 were 409.5 ± 5.9 ms and 412.1 ± 5.9 ms (NS), respectively. These results indicate that verapamil per se had no measurable effect on left ventricular contractility in vivo.

The impact of the impaired elimination of digoxin induced by verapamil mainly appeared as a substantial elevation of the terminal drug concentration (Figs. 1 and 3). While plasma and tissue digoxin concentration after 48 h was increased by more than 40% during verapamil coadministration, the relative change in drug concentration in the early phase of the trials was minimal. Corresponding to these findings, the early changes and the maximum reduction in STI were almost identical in the absence and presence of verapamil (Fig. 2). In Table 2, two-way analysis of variance of the overall changes in STI is presented. Both parameters showed significant alterations with and without verapamil coadministration, but no overall difference was detectable between the control and verapamil trials. However, in parallel with the changing kinetics, the inotropism of digoxin decayed more slowly during verapamil coadministration than in control studies. Semilogarithmic plots of the mean change in STI (obtained in the post-distributive phase) versus time were linear both in the absence and presence of verapamil ($r > 0.88$; $p < 0.001$). In control studies, the mean half-lives of the changes in LVET-I60 and QS_2-I60 derived from these regression lines were 40.9 hours and 47.8 h, respectively. The corresponding values in the presence of verapamil were 84.9 h and 74.2 h. Thus, even though the half-lives of the drug effects were somewhat longer than their biological half-lives, they showed a similar prolongation when verapamil was present.

Table 2. Two-way analysis of variance of the changes in QS_2-I60, LVET-I60 and heart rate (HR) in the absence and presence of verapamil

Variable	Verapamil Coadministration	Within individuals	
		F-value	p-value
QS_2-I60	–	7.419	< 0.01
QS_2-I60	+	7.181	< 0.01
LVET-I60	–	5.899	< 0.01
LVET-I60	+	6.144	< 0.01
HR	–	3.705	< 0.01
HR	+	3.634	< 0.01

In order to assess the total inotropic effect of digoxin, the areas under the ΔQS_2-I60 versus time and the ΔLVET-I60 versus time curves were determined according to the trapezoidal rule. Verapamil produced mean increases in these areas of 50% and 33%, respectively. Corresponding to these findings, the mean area under the tissue digoxin concentration-

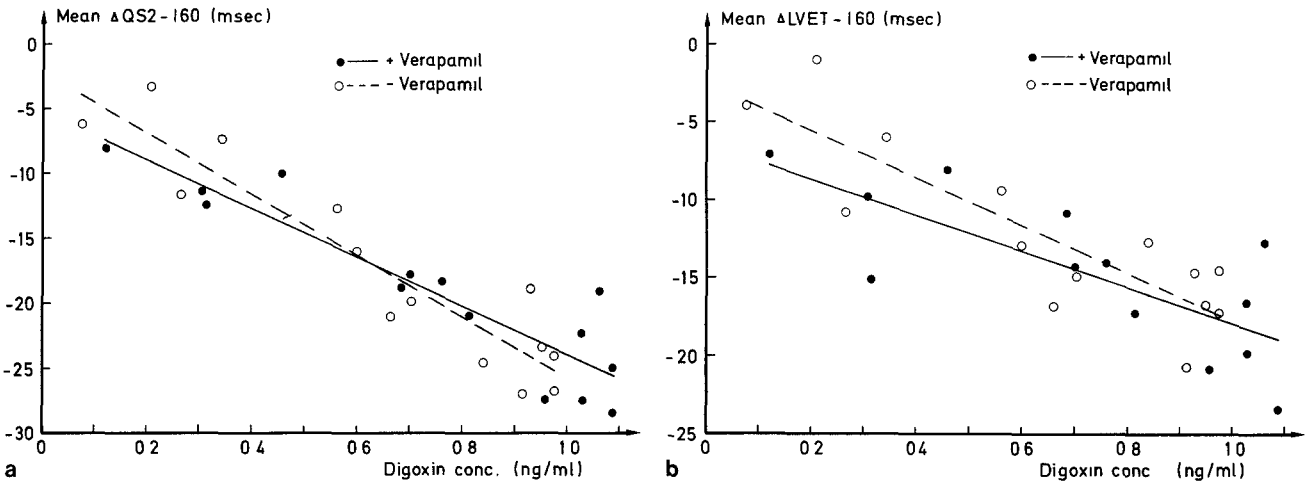

Fig. 4. Relationship between the mean digoxin concentration in the deep compartment and corresponding mean changes in ΔQS_2-I60 and ΔLVET-I60 before (○) and during verapamil coadministration (●). The dotted and black lines represent the best least squares fits in the absence and presence of verapamil, respectively

time curve increased by 41% in the presence of verapamil.

In order to establish concentration-effect relationships for digoxin, the mean changes in STI were plotted against the corresponding mean drug concentration in the deep compartments (Fig. 4). The values appeared to show a strong positive correlation. Linear regression analysis for ΔQS_2-I60 showed: 1) without verapamil: $r=0.93$; $n=14$; $p<0.001$; 2) with verapamil: $r=0.92$; $n=14$; $p<0.001$; and for ΔLVET-I60: 1) without verapamil: $r=0.83$; $n\sim14$; $p<0.001$; and 2) with verapamil: $r=0.86$; $n\sim14$; $p<0.001$. Individual analysis showed that neither the correlation coefficients nor the slopes of the regression lines were significantly influenced by verapamil.

Both systolic and diastolic blood pressure were entirely unaltered throughout the investigations. Heart rate showed a significant decrease 0.5–1 h after the injection of digoxin and then gradually returned to normal. These changes, and those of the base-line heart rate, were identical with and without coadministration of verapamil.

Discussion

The verapamil-induced reduction in the total-body clearance of digoxin observed here, confirms the results of a previous investigation [1], and so emphasizes the consistency of the interaction. Although a daily dose of verapamil of 360 mg was used on this occasion instead of the 240 mg employed previously [1], both studies showed an average reduction of clearance of about 30–35%. Thus, the magnitude of interaction seems virtually dose-independent within the observed range. Since the distribution of digoxin was not influenced by verapamil in the present study, the impairment of the elimination of digoxin produced a corresponding prolongation of the biological half-life of the drug.

Systolic time intervals are a valuable tool for non-invasive assessment of left ventricular contractility. In a number of studies the method has been shown to provide a quantitative measure of the positive inotropism induced by a single-dose or steady-state administration of digitalis glycosides [7, 19, 20, 21, 22]. Both LVET and the QS_2 have proved to be sensitive indicators of this effect of digitalis. The changes in LVET and QS_2 observed in the present control trials were in agreement with the previous results.

The compartemental analysis permitted correlation of the pharmacodynamic effects both to plasma digoxin concentration, which represents the central compartment, and the estimated drug concentration in the deep compartment. The relationships indicated that the myocardial receptor underlying digoxin inotropism is located in the deep compartment. Although drug effects theoretically are proportional to the logarithm of drug concentration [17], the steep initial portion of the concentration-effect curve approximates to linearity. This may explain why a reasonably linear correlation was found between digoxin concentration and the changes in LVET and QS_2.

The present results are in accordance with the single-dose study of Ochs et al. [23], which showed a positive correlation between enhancement of cardiac contractility measured echocardiographically (ejec-

tion fraction, mean rate of circumferential fiber shortening) and plasma digoxin 4–6 h after drug administration.

In the present study, neither QS_2-I60 nor LVET-I60 had returned to their base-line level 132 h after treatment, whereas in no instances digoxin was detectable in plasma after 104 h. A similar discrepancy between the effect of digoxin on the electrocardiogram and the presence of a measurable amount of the drug in plasma has been reported [24]. These observations indicate that digoxin may be retained at the receptor well after its disappearance from plasma.

The present study did not include a placebo trial done to eliminate the influence of possible non-specific cardiovascular changes attributable to the experimental procedure. However, in the study of Ochs et al. [23], placebo trials were not associated with any systematic change in myocardial contractility. Furthermore, such an effect would be most unlikely to influence comparative assessment of digoxin pharmacodynamics with and without coadministration of verapamil, which was the primary aim of the study.

In the presence of verapamil, impairment of digoxin elimination produced a 40% increase in the mean drug concentration in the pharmacodynamically active deep compartment. This kinetic change was associated with a more sustained reduction in STI and corresponding enhancement of the total inotropic effect as determined from the areas under the effect-time curves. Since verapamil itself did not affect myocardial contractility, as judged from baseline STI measurements, the augmentation of inotropism seems to reflect an increased concentration of digoxin at the receptor level. The slopes of the regression lines in Fig. 4 were not significantly influenced by verapamil, which indicates that the concentration-response relationship of digoxin was unaltered. The latter observation represents the principal finding of the present study.

In vitro experiments have shown that calcium antagonists exert a direct negative inotropic effect on the isolated rabbit myocardium [10, 11, 12, 25], and that they may abolish digoxin-induced contractility of human peripheral vessels [26]. These observations seem not to apply to the myocardium in vivo, since the results presented here indicate that digoxin inotropism as such is not measurably influenced by verapamil. The intrinsic negative inotropism of calcium antagonists are probably concealed in vivo by the effects of increased sympathetic tone generated secondary to peripheral vasodilatation [13, 15].

It is concluded that the rise in plasma digoxin, resulting from coadministration of verapamil to healthy subjects appeared to have been cardioactive in terms of inotropism. Further studies are required to show whether these observations also apply to cardiac patients and to evaluate whether this drug combination increases the risk to digoxin toxicity.

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