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The Long-Term Effect of Verapamil on Plasma Digoxin Concentration and Renal Digoxin Clearance in Healthy Subjects

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Summary. Single-dose investigations in healthy subjects have demonstrated substantial impairment of renal and extrarenal clearance of digoxin during co-administration of verapamil. A longitudinal study has been performed to assess the changes in digoxin disposition during long-term verapamil therapy. After one week of verapamil 240 mg/d mean plasma digoxin had risen from 0.21 ± 0.01 ng/ml (SE) to 0.34 ± 0.01 ng/ml ($p < 0.01$), and renal digoxin clearance had fallen from 197.57 ± 17.37 ml/min to 128.20 ± 10.33 ml/min ($p < 0.001$). These changes gradually subsided, and after six weeks, renal digoxin clearance had normalized and plasma digoxin had declined to 0.27 ± 0.02 ng/ml (NS). The 24-h urinary recovery of digoxin increased from $46.46 \pm 3.23\%$ before to $69.78 \pm 3.69\%$ ($p < 0.001$) after six weeks of verapamil co-administration, and this elevation persisted throughout the study. The verapamil-induced suppression of renal digoxin elimination disappears over a few weeks of drug exposure, whereas the inhibition of the extrarenal clearance of digoxin seems to persist.

Key words: digoxin, verapamil; digoxin-verapamil interaction, kinetics, plasma level, renal clearance, extra-renal clearance

The pharmacokinetics of digoxin is subject to clinically important interactions with drugs commonly co-administered, such as quinidine (Hager et al. 1979; Pedersen et al. 1980) and spironolactone (Waldorff et al. 1978). Recently, single-dose studies in healthy subjects have revealed inhibition of both renal and extrarenal elimination of digoxin in the presence of verapamil (Pedersen et al. 1981). The mechanism underlying the renal interaction appears to be suppression of active tubular secretion of digoxin. However, results from animal (Ochs et al. 1978) and human studies (Ford et al. 1979) suggest that repeated exposure to digoxin may cause changes in both the elimination and the tissue binding of the drug. The intervention of similar adaptive mechanisms to counteract the effects of interacting drugs is possible.

The present investigation was undertaken in order to assess the time course of the verapamil-induced changes in digoxin kinetics in a longitudinal study, to compare these findings with results from single-dose studies, and to elucidate the possible development of adaptive changes in digoxin pharmacokinetics during long-term co-administration of verapamil.

Materials and Methods

Subjects

The study comprised seven healthy subjects, one female and six males, aged 26–53 years, who gave informed consent to participation. All had on previous occasions undergone single-dose experiments. General physical examinations, electrocardiograms and base-line biochemical tests, including plasma electrolyte and creatinine concentrations, were normal. Except for drugs administered as specified in the protocol, no medications were taken during the study.

Protocol

The study design is shown in Table 1. Initially, all subjects were digitalized by an oral loading dose of 1 mg/48 h, followed by an oral maintenance dose of 62.5 micrograms b.i.d. After two weeks on this maintenance dose, digoxin steady state has been achieved,

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Table 1. Plasma digoxin concentrations and renal digoxin clearance before and during co-administration of verapamil

Subject	Digoxin 62.5 μg at 8 a.m. and 8 p.m.						Digoxin 0.125 mg at 8 a.m. and 8 p.m.					
	Control	Verapamil 80 mg at 8 a.m., 2 p.m. and 8 p.m.								Verapamil 120 mg at 8 a.m. 2 p.m. and 8 p.m.		Control
		1 week	2 weeks	3 weeks	4 weeks	5 weeks	6 weeks	8 weeks	9weeks	10 weeks	11 weeks	13 weeks
Plasma digoxin concentration [ng × ml^{-1}]												
1	0.25	0.35	0.30	0.33	0.23	0.36	0.20	0.76	0.60	0.57	0.58	0.56
2	0.24	0.31	0.33	0.33	0.25	0.28	0.29	0.58	0.45	0.59	0.61	0.49
3	0.18	0.34	0.31	0.36	0.27	0.21	0.24	0.60	0.57	0.54	0.51	0.51
4	0.21	0.40	0.30	0.34	0.35	0.22	0.27	0.65	0.75	0.65	0.62	0.40
5	0.24	0.40	0.38	0.26	0.36	0.27	0.25	0.42	0.41			0.34
6	0.18	0.30	0.24	0.41	0.39	0.28	0.38	0.49	0.56	0.56	0.75	0.44
7	0.18	0.29	0.22	0.31	0.30	0.28	0.21	0.45	0.52	0.66	0.69	0.40
Mean ±	0.21	0.34[a]	0.30[b]	0.33[b]	0.31[c]	0.27[b]	0.27	0.56[b]	0.55	0.59[c]	0.63[c]	0.45
SEM	0.01	0.01	0.02	0.01	0.02	0.02	0.02	0.04	0.04	0.02	0.03	0.03
Renal digoxin clearance [ml × min^{-1}]												
1	113.51	115.36	116.41	98.48	114.48	112.53	139.53	117.68	156.25	132.10	128.21	110.69
2	240.06	168.41	191.54	151.98	234.05	208.70	194.16	226.59	187.22	223.56	220.04	216.31
3	239.81	129.00	156.14	181.65	192.72	233.73	253.99	214.50	225.93	215.95	232.12	184.52
4	175.67	86.81	156.83	125.12	175.82	155.06	110.62	154.16	173.61	181.11	222.70	195.49
5	229.04	143.91	129.63	153.36	152.21	218.52	315.11	238.12	261.59			229.91
6	176.09	146.41	148.26	121.13	148.84	158.03	161.11	188.11	142.69	186.09	140.23	185.43
7	208.79	107.51	187.96	166.13	205.62	161.62	249.52	249.98	211.57	214.65	193.05	225.56
Mean ±	197.57	128.20[a]	155.25[c]	142.53[a]	174.82	190.85	203.43	198.46	194.12	192.24	189.39	192.56
SEM	17.37	10.33	10.45	10.92	15.10	18.79	27.44	18.13	15.72	13.92	18.28	15.29

[a] Significantly different from control ($p < 0.001$)
[b] Significantly different from control ($p < 0.01$)
[c] Significantly different from control ($p < 0.05$)

as determined by three measurements of plasma digoxin concentration, and the 24-h urinary digoxin excretion.

On Day 1, oral administration of verapamil 80 mg t.i.d. was commenced. Plasma digoxin concentration and 24-h urinary digoxin excretion were measured on Days 2, 3, 4, 5, 6, 7, 8, 9, 10, and after 2, 3, 4, 5, 6 weeks. The dose of digoxin was then doubled and, after equilibration, plasma digoxin and 24-h urinary digoxin excretion were measured once weekly for further four weeks. In the latter two weeks, the dose of verapamil was increased to 120 mg t.i.d., except in Subject V, who remained on 80 mg t.i.d. Finally, verapamil was withdrawn and control values of plasma digoxin concentration and 24-h urinary digoxin excretion were determined after re-equilibration.

Throughout the study, digoxin and verapamil were always administered at 8 a.m., 8 p.m., and at 8 a.m., 2 p.m. and 8 p.m., respectively. Voided urine was collected from 8 p.m. to 8 p.m and blood samples were taken at 8 a.m. Both during initial digitalization and following dose adjustment or withdrawal of drugs, all subjects were allowed to equilibrate for one fortnight. In each case, the presence of the steady state for digoxin was confirmed by making three measurements of plasma digoxin and 24-h urinary digoxin excretion.

Data Analyses

Renal clearances of digoxin and creatinine were calculated from the corresponding plasma concentrations and 24-h urinary excretions. When calculating urinary digoxin excretion, total excretion of creatinine was used as a correcting factor to minimize any effect of incomplete collection of urine.

The significance of differences between the various pharmacokinetic parameters of digoxin was evaluated by one-way analysis of variance and Student's t-test for paired observations.

Analytical Methods

Plasma and urinary concentrations of digoxin were determined in duplicate by radioimmunoassay, using a commercial ^{125}I kit. The plasma analyses had a total coefficient of variation of 7.8–9.2% (1.0–0.51 ng/ml),

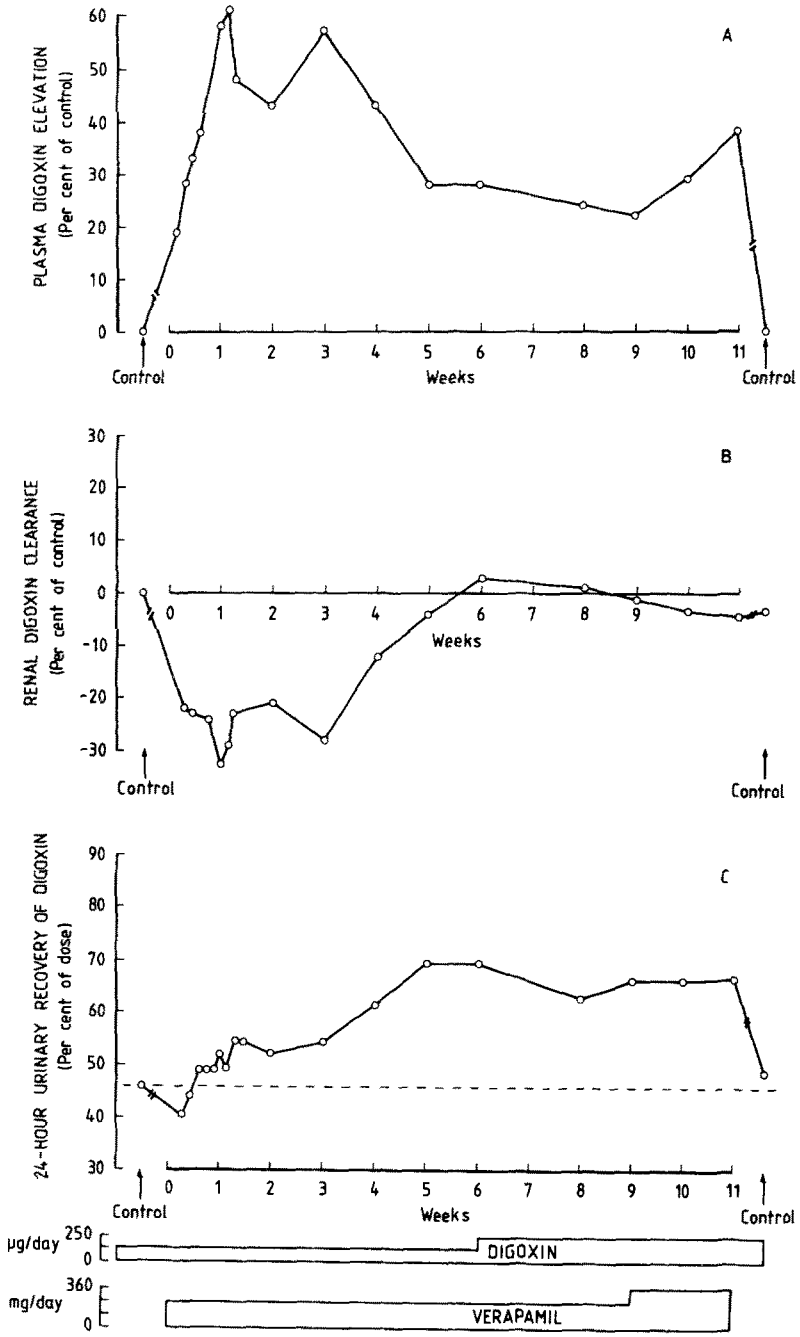

Fig. 1. Time course of the mean changes in plasma digoxin concentration (**A**), renal digoxin clearance (**B**) and 24-h urinary recovery of digoxin (**C**) during verapamil coadministration. (Standard errors have been omitted for clarity, but are available on request from the authors)

and the serial variations, based on duplicates, were 5.61% (1.41 ng/ml), 6.30% (0.85 ng/ml) and 7.15% (0.31 ng/ml).

Urinary digoxin was analyzed after 1:100 dilution with human serum. This method had a total coefficient of variation of 4.72–5.68% (141.6–48.2 ng/ml), and a serial variation based on duplicates of 4.49% (73.30 ng/ml), 4.33% (49.32 ng/ml), 7.15% (28.05 ng/ml) and 7.71% (9.17 ng/ml). The recovery was 95.5% ± 12.1 (SD).

All analyses were done with the same batch in order to minimize analytical variation. The assay showed no cross-reaction with verapamil.

Results

The initiation of verapamil administration was accompanied by slight dizziness, flushing and palpitations in several subjects. These complaints disap-

peared within a few days, and in the remaining part of the study no side-effects attributable either to verapamil or digoxin were observed. Clearance of creatinine, calculated once weekly throughout the study, showed no consistent change either in the absence or presence of verapamil.

In all subjects, the concomitant administration of verapamil was associated with an elevation of the steady state plasma digoxin concentration (Table 1). The time course of the changes is outlined in Fig. 1a. The rise in plasma digoxin, which was detectable even on the second day of verapamil administration, mainly took place within the first five days. However, in subsequent weeks, the mean plasma digoxin concentration gradually declined from about 60% to about 30% above control values, in spite of the unchanged doses of digoxin and verapamil.

The observed elevation in plasma digoxin was paralleled by changes in the renal elimination of the drug, as demonstrated in Table 1 and Fig. 1 b. Verapamil caused an immediate 20%–30% reduction in renal digoxin clearance. After a few weeks, this change had completely disappeared, and in the remaining part of the study renal digoxin clearance did not differ from control values.

In the initial control state, the mean 24-hour urinary recovery of digoxin, calculated from three consecutive measurements, was 46.46% ± 3.23 (SE). Introduction of verapamil caused a shortlived reduction in urinary digoxin excretion, as demonstrated in Fig. 1 c. However, in the succeeding weeks a steady rise was observed, and after normalization of renal digoxin clearance, mean urinary digoxin recovery was 69.78% ± 3.69 (SE; $p < 0.001$). This elevation persisted throughout the study.

Doubling of the digoxin dose was associated with a corresponding increase in plasma digoxin concentration, but had no influence either on renal digoxin clearance or urinary digoxin recovery. The final increase in verapamil dose from 240 mg to 360 mg per day tended to decrease renal digoxin clearance and increase plasma level, but the changes were not significant.

After withdrawal of verapamil, all pharmacokinetic parameters of digoxin normalized within two weeks, with values becoming comparable to the findings in the initial control state.

Discussion

The influence of verapamil on digoxin pharmacokinetics has recently been studied in single-dose investigations (Pedersen et al. 1981). Verapamil consistently decreased total-body clearance of digoxin, with a mean reduction of 35% due to impairment of both renal (20%) and extrarenal elimination (60%). The results from the present investigation, which was performed in the same subjects, are in accordance with these pharmacokinetic changes. The 60% rise in plasma digoxin during the early weeks of verapamil coadministration, which has also been observed by other investigators (Belz et al. 1981; Klein et al. 1980) corresponds in magnitude to the 35% decrease in digoxin total-body clearance.

In the first part of the study, there was a clear discrepancy between the reduction in renal digoxin clearance and the observed rise in plasma digoxin. Furthermore, plasma digoxin remains significantly elevated in spite of the apparent subsidence of renal interaction. Thus, suppression of renal digoxin elimination can only in part have been responsible for the increase in plasma digoxin concentration. It is possible that the substantial increase in urinary digoxin recovery observed after few weeks of verapamil coadministration was caused by an increase in digoxin bioavailability. However, such an interaction appears unlikely considering the passive character of digoxin absorption. In the single-dose studies, a quantitatively similar redistribution in the elimination pathways of digoxin was observed, so we hypothesized that verapamil interfered with digoxin metabolism, leading to a proportionate increase in the urinary excretion of the drug. Thus, both studies seem compatible with regard to the possible mechanism of the interaction.

Complete disappearance of the verapamil-induced suppression of renal digoxin clearance after five to six weeks of drug exposure, which was not observed in shorter studies (Belz et al. 1981; Klein et al. 1980), represents the most inportant finding of the present investigation. The unchanged clearance of creatinine indicates, that the filtration rate of digoxin was not influenced by verapamil. Accordingly, both the initial inhibition of renal digoxin clearance and its reversion to normal seem to involve active tubular secretion of digoxin. In rabbits, similar adaptive increases in digoxin elimination have been demonstrated to occur during repeated administration of the drug (Ochs et al. 1978).

Contrary to these observations, urinary digoxin recovery remained elevated throughout the study, indicating that extrarenal interaction may persist.

The influence of the doses of digoxin and verapamil cannot be assessed appropiately, as changes in renal clearance may have intervened to obscure a possible kinetic response to the changes in dose. However, in agreement with single-dose studies, renal digoxin clearance and urinary digoxin recovery seemed independent of digoxin dose. In longitudinal studies of cardiac patients, Klein et al. (1980) demonstrated a

stepwise elevation of plasma digoxin dependant on the verapamil dose. In our study, only slight elevation of plasma digoxin and inhibition of renal digoxin clearance were observed after increases in the dose of verapamil. It is possible, however, that more pronounced changes might have been achieved during the early weeks of verapamil therapy.

In a clinical context, the significance of the digoxin-verapamil interaction remains obscure. If the pharmacodynamics of digoxin are not influenced by verapamil, a substantial proportion of digitalized patients may temporarily be exposed to toxic plasma levels of digoxin when this drug combination is introduced. During long-term therapy of patients with normal renal function, the plasma digoxin elevation appeared to subside, which may explain the scarcity of adverse reactions reported by clinicians. However, in the presence of renal failure, extrarenal clearance of digoxin will predominate, and in such patients the digoxin-verapamil interaction may prove to be more pronounced.

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