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Interaction between digoxin and calcium antagonists and antiarrhythmic drugs

The influence of several calcium antagonists and antiarrhythmic drugs on digoxin kinetics and actions were investigated in 36 healthy men during digoxin steady state (0.375 mg/day). The subjects were randomly assigned to three subgroups and each group received placebo (control) and two of the following regimens (doses three times a day) in a randomized sequence for 2 wk each: verapamil (80 mg) and nifedipine (10 mg), verapamil (120 mg) and gallopamil (50 mg), or propafenone (150 mg) and quinidine (250 mg). Plasma digoxin concentration (PDC) rose during the cotreatments in the sequence: gallopamil (+16%) <propafenone (+37%) <nifedipine (+45%) <verapamil (almost independent of dose, +69%) <quinidine (+118%). These increases in PDC correlated closely to decreases in renal digoxin clearances. Renal creatinine clearance was virtually unaffected. The rise of PDC resulted in increased glycoside effects, as measured by the shortening of systolic time intervals and flattening of T wave. There was a linear correlation between PDC and changes in mean corrected electromechanical systole and T wave flattening. We conclude that, in addition to quinidine, other antiarrhythmic drugs and various calcium antagonists interact kinetically with digoxin and that the increasing PDCs are cardioactive.

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Various drugs react kinetically with digoxin to cause elevated digoxin blood levels; among these are the antiarrhythmics quinidine[11, 12, 30] and verapamil,[2, 27, 28, 32] the last belonging to the group of calcium antagonists.[15] The question remains controversial whether the increased digoxin levels from these interactions are cardioactive and whether an increase or a reduction in the digoxin dosage is appropriate.[4, 8, 22, 31, 34] Our aim was to investigate whether other calcium antagonists interact with digoxin, and to acquire further information on the mechanism of these interactions. We also sought to determine whether kinetic digoxin interactions are paralleled by changes in glycoside effects.

Methods

Our subjects were 36 healthy men who were 20 to 33 yr old and weighed 56 to 105 kg. The calcium antagonists used were verapamil, gal-

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lopamil, and nifedipine. Quinidine, propafenone, and placebo were included as controls. Propafenone, a class one antiarrhythmic drug,[33] was selected because it was considered not to influence digoxin levels.[8]

All subjects openly received a basic treatment of 0.125 mg t.i.d. digoxin throughout the complete 6 wk study period. Subjects were then randomly assigned to one of three subgroups. To the basic daily digoxin protocol, during three randomized periods of 2 wk duration, each subject received in randomized sequence each of the treatments assigned to his group: group 1—80 mg verapamil, 10 mg nifedipine, placebo; group 2—120 mg verapamil, 50 mg gallopamil, placebo; group 3—150 mg propafenone, 250 mg quinidine bisulfate (slow time release), placebo.

These oral medications were given, without the subjects' knowledge of their content, with digoxin at 8:00 A.M. and 2:00 and 8:00 P.M. and compliance of drug intake was monitored daily.

The subjects were studied for baseline values before any drugs had been given and at the end of each 2 wk treatment period. Between 7:30 and 9:50 A.M. the fasting subjects reported to the laboratory for study, exactly 12 hr after the dose of the previous evening. Detailed restrictions[1] concerning food, fluid, and activities were strictly observed. During each combined drug period a 24-hr urine specimen was collected (the morning of registration). A 15-min resting period in supine position (head at 15 degrees) preceded the recordings. Immediately after the recordings venous blood was drawn and the plasma stored at −20°.

Standard ECG leads V_2 to V_6 were recorded and the mean T wave amplitude (T_{V2-6}) calculated.[5] Cardiac performance was assessed by systolic time intervals (STIs)[35, 36] and submitted to blind analysis. ECG lead CM_5, phonocardiogram (m_2), and carotid pulse tracings were recorded simultaneously with a Cardirex 3T jet recorder (Siemens Elema). Measurements were made from five consecutive heart beats[13] at a paper speed of 100 mm/sec and the results were averaged. Parameters selected for evaluation were electromechanical systole (QS_2), left ventricular ejection time (LVET), and electrical systole (QT) (methodology as described elsewhere).[5, 13] Heart rate was calculated from 20 R-R intervals at 10 mm/sec preceding the STI registration. The heart rate corrected (e.g., LVETc) values are the differences between measured and predicted STI.[35, 36] Heart rate–corrected QT resulted in QTc.[5]

A ^{125}J digoxin radioimmunoassay (Diagnostic Prod) was used for determination of plasma (PDC) and urine digoxin concentrations; interference by either drug had been excluded. Verapamil and gallopamil plasma concentrations were analyzed by gas chromatography; quinidine and propafenone plasma concentrations were measured by HPLC. No analysis method was available for nifedipine plasma concentrations. Serum and urine creatinine concentrations were measured using Test Combination Creatinin. Twenty-four–hour renal digoxin (RDC) and renal creatinine (RCC) clearances were determined at the end of each treatment period.

Using the SAS GLM-procedure, data were analyzed by the method of Grizzle[17, 18]; pairwise comparisons were also made using linear contrasts ($\alpha = 0.05$, two-sided testing). No period effects were detected.

Results

The means of the time points and parameters are specified in Table I. There were only minor changes in PR interval and blood pressure during the experiment. Heart rate fell after digoxin and this effect was intensified by administration of verapamil ($P < 0.05$), but not by the other drugs (Table I). Plasma concentrations of the antiarrhythmic/calcium antagonistic drugs are listed in Table II. Fig. 1 shows PDC during the various experimental periods.

Digoxin alone.* At the end of the 2-wk periods on digoxin alone, PDC for the three subgroups averaged 0.55 ng/ml and RDC totaled 204 ml min^{-1} 1.73 m^{-2}. Compared to baseline, QTc, QS_2c, and LVETc were distinctly shortened ($P < 0.01$) and T wave was flattened ($P < 0.001$).

Verapamil-digoxin. Verapamil increased PDC by about 70% ($P < 0.0001$) over that after digoxin alone. The higher verapamil dose in-

*For brevity, digoxin 0.375 mg/day with placebo will be referred to as digoxin alone.

Table I. *Physiologic responses to digoxin and various cotreatments (mean ± SD)*

Variable	Group 1 (n = 12)				Group 2 (n = 12)			
	B	*PL*	*V 80*	*N*	*B*	*PL*	*V 120*	*G*
Heart rate (min^{-1})	65 ±9	59 ±8*	53 ±8*†	57 ±10*	60 ±7	55 ±9*	50 ±5*†	54 ±9*
BP syst. (mm Hg)	114 ±7	115 ±9	115 ±8	111 ±7	118 ±11	115 ±9	120 ±10	120 ±12
BP diast. (mm Hg)	76 ±8	72 ±6	74 ±6	74 ±5	76 ±7	68 ±6*	69 ±7*	72 ±6†
PR (msec)	178 ±21	186 ±24*	183 ±24	189 ±28*	178 ±21	183 ±20	180 ±18	178 ±21
QTc (msec)	393 ±16	363 ±17*	359 ±17*	361 ±18*	390 ±17	362 ±14*	360 ±19*	357 ±16*†
$T_{V\ 2-6}$ (mV)	0.662 ±0.139	0.482 ±0.115*	0.454 ±0.136*	0.511 ±0.098*	0.563 ±0.128	0.407 ±0.132*	0.337 ±0.114*†	0.398 ±0.179*
LVETc (msec)	−0 ±11	−11 ±10*	−17 ±13*†	−15 ±13*	−4 ±12	−11 ±12*	−15 ±13*	−15 ±9*
QS_2c (msec)	−13 ±14	−30 ±14*	−41 ±15*†	−36 ±14*†	−20 ±16	−35 ±15*	−46 ±19*†	−42 ±14*†
PDC (ng ml^{-1})	0	0.505 ±0.162	0.894 ±0.295†	0.734 ±0.228†	0	0.583 ±0.257	0.940 ±0.308†	0.674 ±0.312
RDC (ml min^{-1} 1.73 m^{-2})	—	218 ±90	148 ±42†	154 ±41†	—	202 ±101	140 ±63†	221 ±146
RCC (ml min^{-1} 1.73 m^{-2})	—	108 ±20	112 ±22	121 ±6†	—	112 ±13	107 ±21	113 ±24

BP = blood pressure; B = baseline registrations before start of treatments; PL = placebo (t.i.d.); V 80 = 80 mg t.i.d. verapamil; N = 10 mg t.i.d. nifedipine; V 120 = 120 mg t.i.d. verapamil; G = 50 mg t.i.d. gallopamil; Q = 250 mg t.i.d. quinidine; P = 150 mg t.i.d. propafenone.

*P < 0.05 compared to baseline values of the respective treatment group.

†P < 0.05 compared to digoxin plus placebo of the respective treatment group.

duced no further increase in PDC. RDC fell to 68% ($P < 0.05$) and RCC was not affected. Compared to digoxin alone, with verapamil 80/120 mg there were the following changes in effects: $QS_2c = -11.5/-10.2$ msec ($P < 0.001/0.01$); LVETc = −6.3/−4.2 msec ($P < 0.05/P > 0.05$); $T_{V2-6} = -0.028/-0.070$ mV ($P > 0.05/P < 0.05$).

Nifedipine-digoxin. With nifedipine there was a mean PDC increase of about +45% ($P < 0.001$). PDC were lower during nifedipine ($P < 0.05$) than during verapamil. Nifedipine diminished RDC to 71% of the level with digoxin alone ($P < 0.05$), but slightly increased RCC (+13%, $P < 0.05$). QS_2c was further shortened by −5.8 msec ($P < 0.05$) compared to after digoxin alone.

Gallopamil-digoxin. Concomitant gallopamil resulted in a PDC rise of only +16% ($P > 0.05$). RDC and RCC were not affected. For the cardiologic parameters QTc fell −5.0 msec ($P < 0.05$) and QS_2c fell −7.0 msec ($P < 0.05$) below that after digoxin alone.

Propafenone-digoxin. Propafenone and digoxin led to a 37% increase in PDC ($P < 0.01$), but these values were lower ($P < 0.001$) than those after quinidine. Propafenone induced a borderline fall in RDC ($P = 0.053$), to 83%, while RCC fell to 87% ($P > 0.05$). Propafenone intensified T wave flattening (−0.069 mV, $P < 0.001$), but the other parameters did not differ from those after digoxin alone.

Quinidine-digoxin. Quinidine induced an +118% increase in PDC ($P < 0.0001$), but RDC and RCC decreased to 58% ($P < 0.0001$) and 84% ($P < 0.05$). Compared to digoxin alone there was a further T wave flattening (−0.142mV, $P < 0.0001$), and a shortening of QS_2c (−9.2 msec, $P < 0.01$) and LVETc (−6.9 msec, $P = 0.055$). Note that these glycoside effects were intensified during quinidine, whereas the digoxin-induced QTc

Group 3 (n = 12)			
B	PL	Q	P
66	60	62	61
±7	±6*	±4	±7*
118	120	118	120
±10	±7	±9	±6
78	75	74	73
±9	±6	±6	±5
191	202	213	214
±29	±33*	±53*	±37*
396	365	377	360
±24	±22*	±17*†	±17*
0.624	0.477	0.335	0.408
±0.173	±0.140*	±0.104*†	±0.143*†
−6	−15	−21	−17
±9	±14*	±11*†	±13*
−12	−27	−36	−27
±17	±19*	±17*†	±14*
0	0.568	1.240	0.776
	±0.196	±0.373†	±0.197†
—	191	110	158
	±75	±40†	±58
—	128	108	111
	±25	±27†	±21

shortening was attenuated by +11.8 msec ($P < 0.01$).

Renal digoxin clearance and plasma digoxin. Fig. 2 illustrates the correlation ($r = 0.90$) for the inverse relationship of mean RDC and mean PDC for the various groups.

Plasma digoxin and cardiac effects. The mean changes (Fig. 3) in QS_2c and T wave (Fig. 4) correlated with mean PDC ($r = 0.87$ and 0.95).

Discussion

An increase in serum digoxin concentration has been reported after verapamil,[2, 27, 28, 32] as reported for quinidine.[11, 12, 30] Our findings confirmed these results and demonstrated that a daily verapamil dose above 240 mg does not lead to a further PDC increase. Nifedipine induced a rise in PDC, although to a lesser degree than verapamil, whereas gallopamil, a verapamil derivative, did not increase PDC significantly. Since all doses were of therapeutic effectiveness one can assume that it was not the calcium antagonistic effect itself, but that different mechanisms are responsible for the interaction with digoxin. Propafenone also induced a small interaction with digoxin, in contrast to previous reports in cardiac patients.[8]

Table II. *Plasma concentrations of antiarrhythmic or calcium antagonistic drugs 12 hr after last dose (mean ± SD)*

Treatment period		Serum concentration (ng/ml)
Verapamil	80 mg	33.2 ± 21.1
Verapamil	120 mg	57.7 ± 41.5
Nifedipine	10 mg	Not available
Gallopamil	50 mg	1.0 ± 1.4
Propafenone	150 mg	96.2 ± 100.7
Quinidine	250 mg	1042.0 ± 300.0

The kinetic mechanisms by which the various drugs increase PDC are not completely understood. Interference of the drugs with the digoxin assay have been excluded by us and others.[8, 34,*] A drug-induced decrease of digoxin distribution volume results only in a transient PDC rise.[16] Quinidine-induced changes in digoxin bioavailability have also been ruled out as a possible cause.[20] Reduction of renal or extrarenal digoxin clearances remain as the mechanisms responsible for the quinidine-digoxin interaction.[8, 10, 19, 24] Our results support the view that all interacting drugs reduced RDC. PDC and RDC were closely related and the correlation analysis ($r^2 = 0.808$) revealed that 80% of the mean PDC variation can be attributed to changes in the mean RDC. Glomerular filtration, as measured by RCC, was influenced by two of the drugs; nifedipine increased it by 13% and quinidine decreased it by 16% (Table I). Despite their opposing effects on RCC, however, both drugs reduced RDC. Probably, as reported for the quinidine-digoxin interaction,[10, 24] extrarenal digoxin clearance is also influenced by the interacting drugs.

The dynamic effectiveness of the elevated digoxin blood levels resulting from kinetic interactions is controversial. So far experimental work has concentrated on the quinidine-digoxin interaction. Studies in vitro and in dogs[9, 25, 26, 29] suggest an increase in glycoside effects after

*Belz GG, et al: Unpublished data.

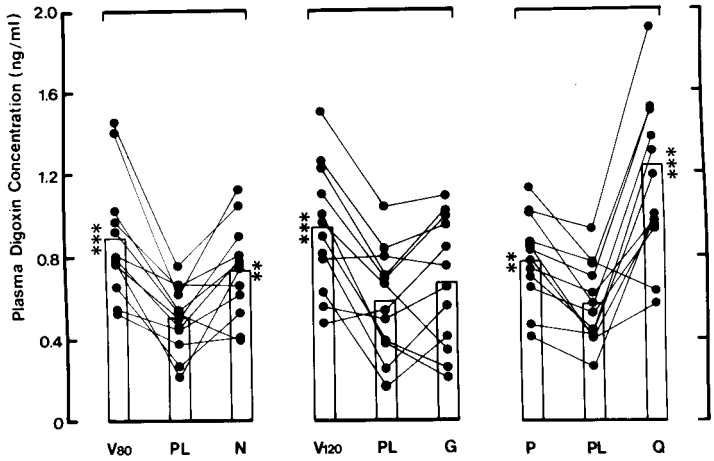

Fig. 1. Individual and mean *(bars)* PDCs for each treatment group. Statistical analysis of variance indicates difference from the placebo phase for the respective treatment groups as follows: $^{**}P < 0.01$; $^{***}P < 0.001$. See Table I for abbreviations.

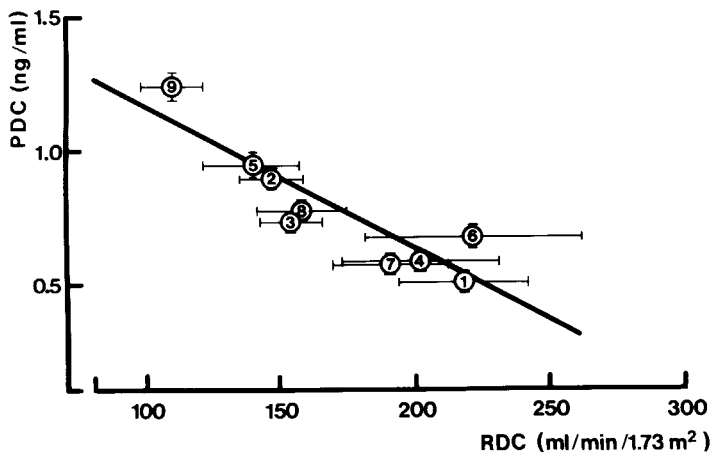

Fig. 2. RDC and PDC (mean ± SEM, N = 12 each). Symbols for drugs given three times a day with digoxin: ①, ④, and ⑦ = placebo; ② = 80 mg verapamil; ③ = 10 mg nifedipine; ⑤ = 120 mg verapamil; ⑥ = 50 mg gallopamil; ⑧ = 150 mg propafenone; ⑨ = 250 mg quinidine.

this interaction. We have shown that, after single doses of quinidine in digitalized subjects, each of the two drugs maintains its opposing inotropic properties on STI. This leads to a vectorial subtraction of effects.[1] In a study with repetitive dosing, we found that, provided the antagonistic effects of digoxin and quinidine were taken into account,[4] there was a marked increase in glycoside influence after circulating digoxin levels had risen. In our present study, even without consideration of the opposite inotropic effects, distinctly increased inotropism accompanied the increased digoxin level.

Thus, the doubts about cardioactivity of the high PDC resulting from this interaction[22, 34] can be refuted on the basis of several independent controlled studies. Extending these considerations further, from our investigation with other drugs it is obvious that there is an overall direct correlation between cardiac responses and rising PDC (Figs. 3 and 4). Consequently, nearly independent of the drug inducing the in-

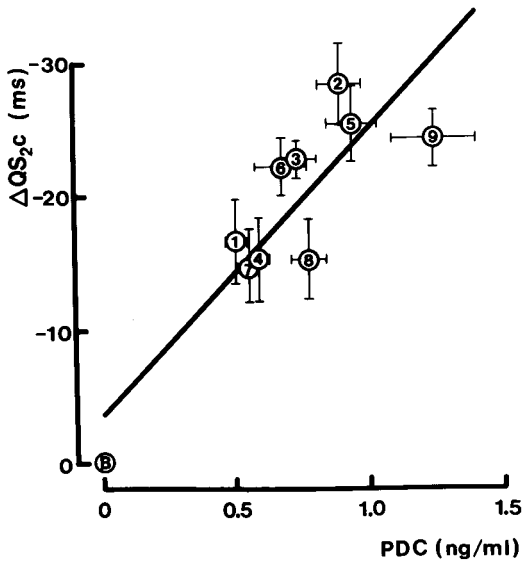

Fig. 3. Correlation between PDC and changes in QS_2c (Δ). Mean ± SEM. ○ = baseline measurement. For other symbols see Fig. 2 legend.

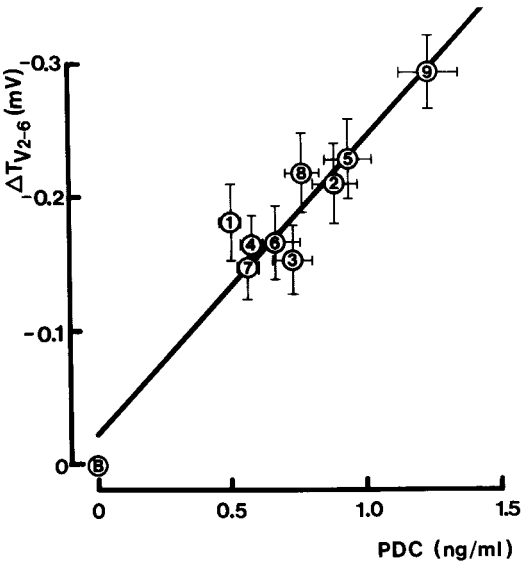

Fig. 4. Correlation between plasma digoxin concentration and changes in T_{V2-6} (Δ). Mean ± SEM. For symbols see Fig. 2 and 3 legends.

teraction, the increasing PDC is followed by intensified glycoside effects. For complete insight into this correlation, the intrinsic properties of each drug must be reviewed without regard to the additional kinetic interaction. Verapamil and nifedipine are reported to decrease peripheral resistance and blood pressure as well as to elicit sympathetic reflexes, thereby increasing heart rate and inotropism.[3, 21] In our study neither heart rate or blood pressure showed such responses; hence this does not support the view that such sympathetic mechanisms are present to any significant degree under these experimental conditions. It is known that the effects of digoxin, quinidine, propafenone, and verapamil flatten T wave and prolong the PR interval[5, 6, 23, 33]; therefore, digoxin added to each of these drugs should result in an synergistic effect. In opposing inotropic actions, digoxin shortens STI,[5, 36] while quinidine, propafenone, and verapamil lengthen it.[1, 7, 14,*] This, during the use of digoxin, antagonistically diminishes their effects.

Our results show that rising PDC, due to the interaction induce an increase in glycoside effect above values of digoxin alone, regardless of whether the parameters are synergistically (T wave) or antagonistically (STI) influenced. This means that the effects of the high digoxin concentrations 12 hr after the last dose distinctly override those of the other drugs. This is to be expected because the calcium antagonists are more rapidly eliminated (N > V)[21] than the glycoside.[23] Our findings with the two verapamil doses further support these considerations; the 120-mg dose slightly increases PDC over that after 80 mg, but the markedly higher plasma verapamil level (Table II) results in an intensified verapamil effect that becomes evident (Figs. 3 and 4) with less shortening of QS_2c and more T wave flattening.

Our data suggest that PDCs increased while RDCs decreased (in ascending sequence) during the use of therapeutic doses of propafenone, nifedipine, verapamil, and quinidine. As shown for quinidine, the increasing PDC is followed by an increase in cardiac response. Since elevated PDC may favor glycoside toxicity, careful monitoring of patients and adjustment of the digoxin dose is essential.

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*Belz GG: Unpublished results.

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Addendum

Since submitting this paper, we performed another interindividual experiment to examine the effects of 80 mg t.i.d. verapamil and 10 mg t.i.d. nifedipine without digoxin. Three groups (each n = 8) of healthy subjects randomly received verapamil, nifedipine, or placebo over a 14-day period. The physiologic responses are shown in Table IA. There were only very small changes (e.g., less than 5 msec for QS_2c, $P > 0.05$) induced by the calcium antagonists. This gives strong support to the assumption that the increased cardiac performance paralleling the increased PDC is due to digoxin.

Table IA. *Changes (mean ± SD) as compared to baseline after placebo (PL), verapamil (V), and nifedipine (Ni)*

	PL	*V*	*Ni*
Heart rate	1	3	0
(min^{-1})	±6	±7	±5
BP syst.	6	6	−1
(mm Hg)	±8	±10	±7
BP diast.	7	−3	−2
(mm Hg)	±4	±5	±7
QTc	−3	10	−1
(ms)	±9	±14	±14
T_{V2-6}	−0.027	−0.068	0.015
(mV)	±0.047	±0.115	±0.070
LVETc	2	−1	−1
(msec)	±8	±13	±9
QS_2c	−2	−4	0
(msec)	±15	±8	±9

BP = blood pressure.