# QUINIDINE-DIGOXIN INTERACTION: CARDIAC EFFICACY OF ELEVATED SERUM DIGOXIN CONCENTRATION

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# Quinidine-digoxin interaction: Cardiac efficacy of elevated serum digoxin concentration

*Cardioactivity due to elevated serum digoxin concentration (SDC) after quinidine (Q) and digoxin (D) was evaluated in six healthy subjects by means of measurement of systolic time intervals (STIs). Each subject randomly received basic treatments with 0.2 mg D and placebo ($PL_1$). Randomized coadministrations with Q (1 gm/day), sparteine (SP) (0.8 gm/day), and placebo ($PL_2$) were given for 7-day periods. A steady-state dose of 0.4 mg D was added. Mean SDC increased from 0.48 ng/ml during 0.2 mg D + $PL_2$ to 1.13 ng/ml on 0.2 mg D + Q ($P < 0.05$); it was unchanged by SP. On 0.4 mg D there were further shortenings of STIs compared to those on 0.2 mg D + $PL_2$. Q markedly prolonged STIs; the SP effects were similar but less pronounced. When given with Q or SP, the effect of D was obscured by opposing inotropic properties; consequently, despite increasing SDC, measurable STIs were unchanged. The true glycoside effect was determined by comparing the effects of the pure antiarrhythmic to those of the antiarrhythmic with D. These calculations showed that the glycoside effect of the elevated SDC during Q + D dosing was much the same as the effect of 0.4 mg D.*

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The use of D with Q results in a rise in SDC.[7] Conflicting results have been reported on the dynamic effect and clinical relevance of this elevation.

In two studies that measured STIs it was concluded that the elevated SDC during Q use did not reflect an increased glycoside effect on the heart.[17, 28] In another study we evaluated the effects of a single dose of Q during long-term D and placebo (PL).[4] Under these conditions, when no kinetic interaction was detectable, Q and D maintained direction and intensity of their opposing cardiac effects. This resulted in an almost mathematic subtraction of their negative or positive inotropic effects. This independency of effect is a strong argument in favor of the cardioactivity of the elevated SDC after long-term Q and D. This consideration is supported by clinical reports,[9, 21, 24] as well as by in vitro and animal experiments.[1, 7, 8, 13, 19, 20] In the light of the conflicting reports, further study seemed indicated.

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*Abbreviations used*

| | |
|---|---|
| D: | Digoxin |
| Q: | Quinidine |
| SP: | Sparteine |
| $PL_1$: | Basic placebo treatment |
| $PL_2$: | Coadministration of placebo with basic treatment |
| STI: | Systolic time interval |
| $QS_2$: | Electromechanical systole |
| PEP: | Pre-ejection period |
| LVET: | Left ventricular ejection time |
| QT: | Electrical systole |
| -c values: | Parameters corrected for heart rate for any of the above cardiac parameters (e.g., $QT_c$, LVETc, PEPc) |
| SDC: | Serum D concentration |
| SQC: | Serum Q concentration |
| SSPC: | Serum SP concentration |
| HR: | Heart rate |

## Methods

Our subjects were six healthy men with a mean age of 26.6 yr (SD 3.9), a mean height of 180.5 cm (SD 3.9), and a mean body weight of 79.0 kg (SD 8.1). Complete physical examinations revealed no abnormalities. No drugs other than those being studied were permitted.

***Design.*** Our design included control studies with PL and a noninteracting antiarrhythmic drug, SP. SP does not effect SDC but has dynamic properties resembling those of Q.[4, 26, 33] The first part of the study was of a randomized, crossover, double-blind format and was followed by a nonrandomized study in which the glycoside maintenance dose was doubled.

***Glycoside.*** The methylated lipophilic derivative of D ($\beta$-methyldigoxin), which has a high bioavailability and interacts with Q in the same manner as D, was used.[3, 7, 25] For the crossover phase each subject received $PL_1$ and a daily maintenance dose of 0.2 mg D for a period of 28 days each; the sequence of these basic treatments was randomized. For loading, 0.4 mg D or an equivalent number of $PL_1$ tablets were given on the initial 2 days of the basic treatment period. Thereafter, from days 3 to 28, $PL_1$ or 0.2 mg D were given at 8:00 P.M. The two basic treatment periods were separated by a 3-wk washout phase.

At the end of the two crossover phases a final posttreatment phase was included. The subjects completing the $PL_1$ phase as the last basic treatment received 0.4 mg D as a loading dose for 2 days, followed by 0.2 mg D daily for 5 days. The subjects who received 0.2 mg D in the second basic treatment phase continued on this dosage for 7 more days, after which the final phase began with all subjects receiving 0.4 mg D at 8:00 P.M. for a week.

***Antiarrhythmics.*** After the first week of either $PL_1$ or D pretreatment, subjects received, in a randomized double-blind fashion, each of the following drugs for 7-day coadministration periods: 500 mg b.i.d. Q bisulfate, slow time release; 400 mg b.i.d. SP sulfate, slow time release; and $PL_2$ tablets, b.i.d. The drugs were taken at 8:00 A.M. and 8:00 P.M.; compliance was monitored daily.

***Protocol.*** From 6:00 P.M. the previous night until all data were recorded for each study day no strenuous exercise, caffeine containing drinks, alcohol, or nicotine were permitted. On the study day fasting subjects reported to the laboratory at between 7:30 and 8:45 A.M. All tracings were done at the end of each treatment phase 12 hr after the last drug doses. After a resting period of 15 min, recordings were made with the subject in a supine position and his head at a 15 degree angle. Immediately after the measurements were taken, 50 ml venous blood was drawn and the serum was frozen at $-20°$.

***Recordings.*** All measurements and recordings were in duplicate and the mean of the two values was used for calculations. ECG lead $CM_5$, phonocardiogram $m_2$, and carotid pulse tracings were recorded simultaneously. Twenty-five complexes at 10 mm/sec were recorded followed immediately by 10 complexes at 100 mm/sec while the subjects held their breath after normal expiration. Recordings were by Cardirex 3T jet recorder (Siemens Elema). Blood pressure was measured by a standard cuff mercury manometer.

***Measurements and calculations.*** All cardiac parameters were analyzed by an independent investigator who was not aware of the drugs used. HR was obtained by measuring the last 20 R-R intervals at 10 mm/sec; mean values of the first five complexes of the 100-mm/sec tracings were used for the STIs as described

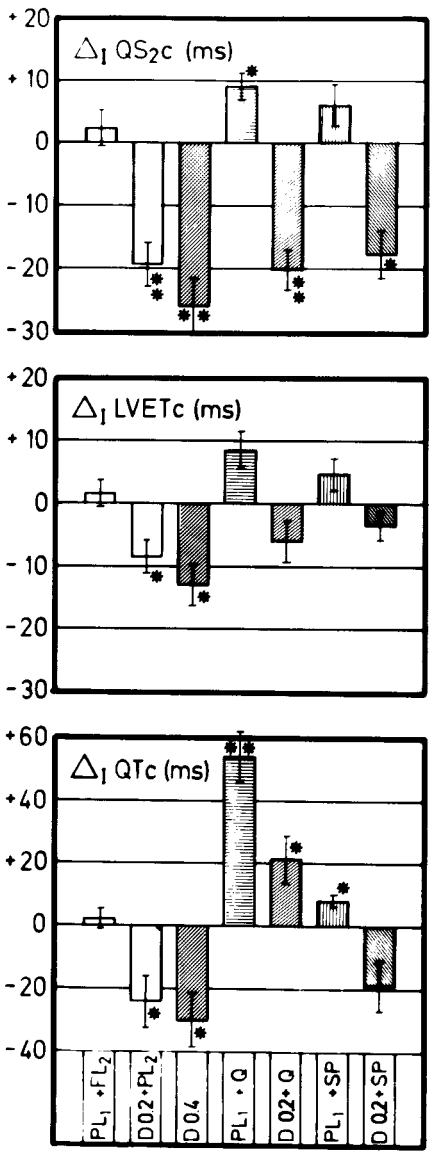


**Fig. 1.** Mean (±SEM, n = 6) ΔI values. All tracings were done 12 hr after the last drug dose. *P < 0.05; **P < 0.01.

elsewhere.[5, 12, 27] Cardiac performance was assessed by measurement of $QS_2$ and LVET. PR, QRS, and QT intervals were recorded by ECG. Corrections for HR of STIs were according to the method of Weissler et al.[31] The differences between the measured and the predicted STIs are -c values. QTc was calculated by Bazett's formula.[2] Brachial artery mean pressure was calculated by Wezler's and Böger's[32] equation.

Two types of comparisons of the effects were made. For the first, the values at the end of the 1 wk with $PL_1$ pretreatment were used as baseline. The difference between the values obtained during this baseline and the various treatments were calculated individually and are expressed as ΔI (Fig. 1). The individual differences in the STIs between the basic treatments of 0.2 mg D and $PL_1$ for respective coadministration periods (e.g., 0.2 D + Q vs $PL_1$ + Q) are indicated as ΔII values and reveal the true glycoside effect in the presence of the other drugs. Mean ΔII values are shown in Fig. 2.

***Serum concentration measurements.*** A highly specific $^{125}J$ digoxin radioimmunoassay (Diagnostic Prod., Los Angeles) was used for SDC determination. Interference of the test by either Q or SP was excluded. The gas chromatography of SP serum concentrations were determined according to the method of Dengler et al.[6] Q serum concentrations were measured by high-pressure liquid chromatography.

***Statistics.*** The influences of treatment with $PL_1$ or D, coadministration of Q, SP, or $PL_2$, and posttreatment with 0.4 mg D on all parameters were analyzed by paired comparisons (paired t tests with Scheffé's correction for multiple comparisons) between measurements after the combined treatment periods and after pretreatment. It was assumed that order of crossover did not influence these comparisons.

## Results

Mean values of the physiologic parameters and drug concentrations are detailed in Table I. This table presents the crude mean values, whereas the Figs. 1 and 2 present the mean ΔI and ΔII values.

SDC during the various combined-drug dosing periods with 0.2 mg D basic treatment and during posttreatment with 0.4 mg D are shown in Fig. 3. During Q treatment mean SDC rose by 135%; SP did not change the SDC. After the 0.4-mg D dose, mean SDC was higher than during Q + D. Mean SDC values after 0.2 mg D + Q and 0.4 mg D treatments are two and three times the 0.2 mg D + $PL_2$ treatment values (P < 0.05). Mean SQC and SSPCs were nearly identical during both $PL_1$ and D treatment phases and were in the lower therapeutic

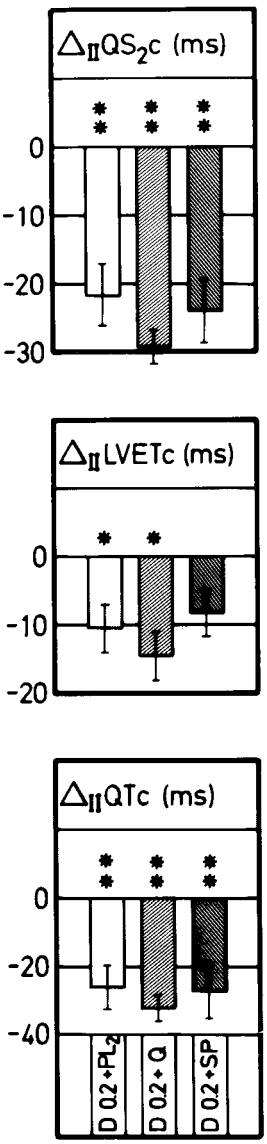


**Fig. 2.** Mean (±SEM, n = 6) ΔII values during the various treatment phases. *P < 0.05; **P < 0.01.

range[6, 23] 12 hr after the last dose. There were minor changes in PR interval, QRS duration, HR, and mean arterial blood pressure during the various treatment periods (Table I).

***Effects on STI and QTc***

*Digitalis effects.* Glycoside resulted in the expected dose-dependent shortening of $QS_2c$, LVETc, and QTc. In comparison with baseline, 0.2 D + $PL_2$ induced shortening of $QS_2c$ (−19 msec, P < 0.01), LVETc (−9 msec, P < 0.05),

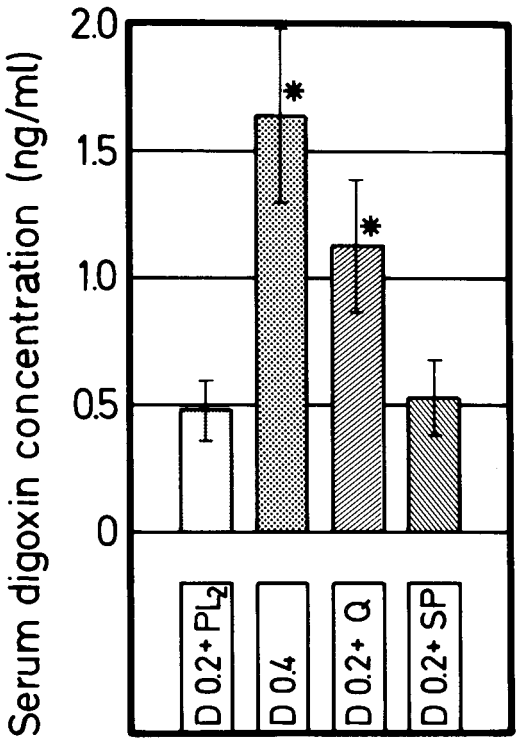


**Fig. 3.** Steady-state SDCs 12 hr after last dose. Values are mean ± SEM (n = 6). P < 0.05 compared to 0.2 D + $PL_2$.

and QTc (−24 msec, P < 0.05). On 0.4 mg D glycoside effects were −26 msec for $QS_2c$ (P < 0.01), −13 msec for LVETc (P < 0.05), and −31 msec for QTc (P < 0.05).

*Effects of the antiarrhythmics.* In contrast to digitalis, the antiarrhythmics induced lengthening of $QS_2c$, LVETc, and QTc. $PL_1$ + Q resulted in prolongation of $QS_2c$ (+9 msec, P < 0.05) and QTc (+54 msec, P < 0.01), while LVETc was only moderately affected (+7 msec, P > 0.05). $PL_1$ + SP resulted in a less pronounced prolongation of STI than did Q. After SP, QTc changed substantially (+8 msec, P < 0.05).

*Effects of combined treatment.* Treatment with 0.2 D + Q resulted in $QS_2c$ and LVETc values similar to those after 0.2 D + $PL_2$. These values, which are almost equal despite the more than doubled SDC, result from the counteracting dynamic effects of digitalis and Q on STI. QTc is prolonged after $PL_1$ + Q, but there is only moderate lengthening with 0.2

**Table I.** *Physiologic response to various treatments (mean ± SD; n = 6)*

| Parameter | Basic treatment $PL_1$ | | | | Basic treatment 0.2 mg D | | | | Posttreatment (0.4 mg D) |
|---|---|---|---|---|---|---|---|---|---|
| | 1-wk pretreatment | $PL_2$ | 1 gm Q | 0.8 gm SP | 1-wk pretreatment | $PL_2$ | 1.0 gm Q | 0.8 gm SP | |
| SDC (ng/ml) | 0 | 0 | 0 | 0 | 0.69 ±0.28 | 0.48 ±0.30 | 1.13 ±0.65 | 0.53 ±0.37 | 1.64 ±0.83 |
| SQC (μg/ml) | — | — | 1.81 ±0.58 | — | — | — | 1.84 ±0.67 | — | — |
| SSPC (μg/ml) | — | — | — | 0.29 ±0.28 | — | — | — | 0.35 ±0.38 | — |
| HR ($min^{-1}$) | 65 ±6 | 68 ±11 | 69 ±8 | 64 ±6 | 60 ±4 | 64 ±8 | 60 ±4 | 58 ±4 | 61 ±6 |
| BAP m (mm Hg) | 95 ±9 | 96 ±10 | 95 ±6 | 95 ±8 | 94 ±14 | 91 ±16 | 99 ±12 | 99 ±15 | 92 ±4 |
| PR interval (msec) | 165 ±23 | 166 ±23 | 169 ±20 | 168 ±25 | 167 ±18 | 170 ±20 | 176 ±23 | 172 ±19 | 168 ±19 |
| QRS duration (msec) | 92 ±4 | 95 ±5 | 97 ±5 | 96 ±6 | 93 ±4 | 91 ±4 | 96 ±4 | 95 ±1 | 89 ±5 |
| QTc (msec) | 389 ±21 | 391 ±19 | 443 ±30 | 397 ±21 | 369 ±18 | 365 ±22 | 411 ±25 | 370 ±18 | 358 ±22 |
| $QS_2c$ (msec) | −5 ±16 | −2 ±11 | 4 ±13 | 1 ±12 | −21 ±12 | −24 ±19 | −25 ±10 | −23 ±14 | −31 ±7 |
| LVETc (msec) | −1 ±11 | 1 ±12 | 7 ±8 | 4 ±9 | −6 ±11 | −10 ±14 | −7 ±5 | −5 ±12 | −14 ±6 |

Arrows indicate $P < 0.05$ by Scheffé adjustment for multiple comparisons.

BAPm = brachial artery mean pressure.

D + Q, due to the glycoside effect. The opposing dynamic effects are further demonstrated after the kinetically noninteracting SP with 0.2 D. After 0.2 D + $PL_2$ the glycoside-induced shortening of the parameters is always less than after 0.2 D + SP.

*ΔII values.* The true glycoside effect can be calculated by the difference between values after the basic $PL_1$ treatment phase and those after digitalis (i.e., $PL_1$ + Q vs 0.2 D + Q, etc.). Fig. 2 illustrates the glycoside effect after the kinetically noninteracting SP; the values for 0.2 D + SP are almost the same as those for 0.2 D + $PL_2$. The respective ΔII values after Q + D are always greater; they exceed those obtained by doubling the glycoside dose (Table II). Thus, the increase in SDC during D + Q is paralleled by increased glycoside effect.

## Discussion

Although Gold et al.[15] observed increased susceptibility to cardiac glycosides in dogs pretreated with Q in 1932, the kinetic interaction between Q and D was not generally recognized before 1978.[10, 11, 22] Reduction of D clearance and of distribution volume are responsible for this interaction.[7, 16]

We observed dynamic and kinetic drug interactions. Using the STIs for assessment of effects we noted a shortening after D, whereas Q and SP induced prolongation; these effects have been documented.[4, 5, 14, 30] Concomitant Q increased SDC, whereas SP did not exert this kind of kinetic interaction. Paralleling the SDC increase after 0.2 D + Q, the true D effects, i.e., the effects after elimination of the Q-induced shift of the original base of D ef-

**Table II.** *ΔII values (mean ± SEM) during various treatments (n = 6)*

| *Treatment phase* | *$QS_2c$ (msec)* | *LVETc (msec)* | *QTc (msec)* | *SDC (ng/ml)* |
|---|---|---|---|---|
| Δ II after 0.2 D + $Pl_2$ | −21.9 ± 4.7 | −10.3 ± 3.5 | −26.3 ± 6.5 | 0.48 ± 0.12 |
| Δ II after 0.2 D + SP | −24.0 ± 4.7 | − 8.2 ± 3.3 | −27.5 ± 8.0 | 0.53 ± 0.15 |
| Δ II after 0.2 D + Q | −29.3 ± 2.5 | −14.4 ± 3.6 | −32.6 ± 3.8 | 1.13 ± 0.27 |
| Δ I after 0.4 D* | −26.2 ± 4.6 | −13.1 ± 3.3 | −30.8 ± 8.7 | 1.64 ± 0.34 |

*Presented for comparison.

fects, also rose (Fig. 2). These increased effects of 0.2 mg D after Q were especially evident when compared with those of D + SP, which did not influence SDC. The true glycoside effects during 0.2 D + Q were in the same range as those during 0.4 mg D. Considering the increase of D effects induced by increasing SDC due to higher D doses or to drug interaction, the slope of the dose effect curve must be taken into account; for $QS_2c$, a ceiling effect is reached at −25 msec and for LVETc, at −12.5 msec.[5] Since the observed values approach this ceiling (Fig. 1), it is evident that there is only a moderate increase in glycoside effect from the distinctly higher SDC after 0.4 mg of D or the combination of 0.2 D + Q. The increased D effects during D + Q dosing give strong support to the assumption that the elevated SDC after Q is cardiac effective.

Differences in design may, in part, account for the difference between our results and those reported in the literature. Hirsh et al.[17] measured the effect of Q alone in fewer than half of the subjects who began the experiment. Steiness et al.[28] added a single dose of D to a basic treatment with quinidine. As recently demonstrated by Williams and Mathew,[34] the sequence of drug application in this drug interaction may be of crucial importance.

Our data were obtained from studies in healthy subjects and should be cautiously applied to the clinical situation. It has been established, however, that STIs in patients with cardiac disease are affected in a similar way by cardiac glycosides as those in healthy subjects.[29]

Almost all antiarrhythmics have negative inotropic properties that diminish the inotropic glycoside effects. This is not the case in long-term use of Q and D since, as we have shown, the simultaneously increasing SDC overrides the negative Q effect. From the viewpoint of cardiac performance this would not indicate a need for reduction of D dose when Q is also given. These considerations are only valid for those aspects of cardiac function influenced in opposing directions by Q and D, however. In areas of cardiac function in which Q and D do not counteract each other, augmentation of the glycoside effect, corresponding to increasing SDC, has to be expected. This argument is supported by the observation of patients with marked prolongation of atrioventricular nodal conduction during Q + D dosing.[9, 21] Thus, since most cases of documented Q syncope were precipitated by premature ventricular beats,[18] concern that elevated SDC during combined drug therapy may induce arrhythmias, which may in turn facilitate the onset of syncope, may be justified. Careful monitoring (by determination of SDC and appropriate adjustment of D dose) of patients receiving both drugs is recommended.

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