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Time Course of the Effects of Single Intravenous Doses of Digitoxin and Digoxin in Normal Volunteers

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Summary: We conducted a randomized, placebo-controlled, double-blind, crossover study to evaluate the effects of 0.5 and 1.0 mg of digitoxin and 1.0 mg of digoxin during the first 4 h after intravenous administration to eight normal subjects. We followed electrocardiographic [heart rate (HR), QT interval corrected for HR (QTc), T-wave amplitude], impedance cardiographic (Heather Index, stroke volume, total peripheral resistance), and mechanocardiographic [electromechanical systole corrected for HR (QS_2c)] parameters and arterial blood pressure. Heather Index and total peripheral resistance showed significant increases at some intervals after glycoside administration, but multivariate analysis for the total 4-h course revealed no significant increases. Stroke volume and mean arterial pressure did not change appreciably. The typical glycoside-induced effects (shortening of QTc and QS_2c, decrease of heart rate, flattening of T-wave) were observed with both glycosides, and the effects were significant for the total course in multivariate analysis as well as in comparison to placebo in single measured points. The time course of onset of action differed during the first 60 min. Digitoxin effects were evident during the first 60 min, but the effects of digoxin were more pronounced and significant. Between 60 and 120 min, the effects of both glycosides were no longer different, and the maximal effects of both were reached during this period. These results show that with digitoxin a maximal effect can be achieved earlier than generally assumed. **Key Words:** Cardiac glycosides—Digitoxin—Digoxin—Electrocardiogram—Systolic time intervals.

During the last decade, digoxin has become the cardiac glycoside of choice in most parts of the world and the use of digitoxin has decreased markedly (1). Doherty (2) gives two reasons for this state of affairs: the long duration of action that complicates digitoxin dosage adjustments and can result in prolonged toxicity, and the slow onset of action. The first reason can be questioned on several grounds. Although the half-life of digitoxin is substantially longer (3) than that of digoxin (4–6), it is independent of renal function (7,8). Owing to the incidence of impairment of renal function, digoxin toxicity has been described in approximately 20% of patients (review: 9). In contrast to this, similar studies have de-

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scribed an incidence of toxicity during digitoxin therapy of about 5% (10,11). In cases of life-threatening digitoxin toxicity, the efficacy of hemoperfusion is much greater than during digoxin intoxication (12). Finally, the bioavailability of digitoxin is much less variable than that of digoxin (1,13).

Concerning the more rapid onset of action of digoxin, several factors must be considered. Older studies in atrial fibrillation suggested that after intravenous injection the peak effect of digitoxin is reached after 8–12 h (14,15) and that of digoxin after 2 h (15). In 1970, Shapiro et al. (16) reported that intravenously injected digoxin had a peak effect after 3 h and digitoxin after 4–6 h. We found recently that under controlled conditions β-acetyl digoxin and digitoxin induced inotropic peak effects 2–3 h after oral ingestion (17). Subjects were studied for 10 h, and during this period no further increases were observed. In the light of the above, we decided to compare in a double-blind study the time course of the pharmacodynamics of intravenous digitoxin and digoxin.

METHODS

The study had a randomized, controlled, crossover, double-blind design with a wash-out period of 28 days between the various phases of the study. The following substances were used: digitoxin (Digimerck®) 1.0 mg and 0.5 mg, digoxin 1.0 mg, and placebo. The drugs as well as the placebo (the solvent medium of Digimerck) were made up to a volume of 10 ml with physiological saline. Eight healthy male volunteers participated in the study after written informed consent was obtained. Their mean age was 34.8 ± 5.3 years, the average height was 175.0 ± 5.1 cm, and the average weight was 73.1 ± 6.4 kg. No drug intake except for the test substances was allowed during the study period.

Protocol

From 6 p.m. on the previous night until the completion of each study phase no strenuous exercise, caffeine-containing drinks, alcohol, or nicotine were allowed. At 7 a.m. on each study day the volunteers took a standardized continental breakfast at home. During the course of the study water intake was allowed and a standardized meal was given between 10:45 and 11:45 a.m. Fifteen minutes after this meal, the impedance cardiography electrodes were applied and the volunteers had to lie down their heads at +15° to the horizontal. The first recordings were made 2 h after the mid-day meal. Drugs were administered through an infusion system inserted 40 min before the first registrations. Blood samples were obtained through another infusion system on the opposite arm inserted 25 min before the first recordings. Both systems were kept open by the infusion of physiological saline at a rate of 20 drops/min. Drugs were administered with an automatic pump (Perfusor, Braun-Melsungen, Federal Republic of Germany) over 120 ± 2 s. The end of the infusion period was taken as the 0 point of each study period. Two base-line recordings were made at an interval of 10 min, the last one immediately before start of the infusion. Subsequent recordings were made at 5, 10, 30, 60, 120, 180, and 240 min. Blood samples were obtained immediately after each recording. After the 1st h, volunteers were allowed to sit, but had to lie down 15 min before each further recording.

Recordings

The following curves were recorded: (a) Standard ECG leads V_1 to V_6 at 25 mm/s. (b) Simultaneous recordings of ECG lead CM_5, phonocardiogram (m_2) recorded from the third left intercostal space and a thoracic impedance curve (Minnesota Impedance Cardiograph, model 400). Twenty-five complexes at 10 mm/s were obtained, and immediately following this, 10 complexes at 100 mm/s while subjects held their breath after a normal expiration. All recordings were made on a Cardirex 3T (Siemens-Elema). Blood pressure (BP) was measured with an ordinary cuffed mercury manometer.

Calculations

The Δ-values represent the differences of the respective values at the different times following application and the mean of the two registrations before drug application.

Systolic Time Intervals

Heart rate (HR) was obtained by measuring RR intervals in 20 complexes obtained at 10 mm/s; the first five complexes of the 100 mm/s registration were used for obtaining systolic time intervals (18). HR correction for the total electromechanical systole (QS_2) was done using standard methods (17,19–24) and resulted in QS_2c.

Electrocardiogram

The mean T-wave amplitude in leads V_{2-6} (T_{V2-6}) was obtained as previously described (19). QT-time was corrected for heart rate and resulted in QTc (25).

Impedance Cardiogram

Stroke volume (SV), cardiac output, and Heather Index were obtained by standard means (26–31). Hematocrit determinations were done to determine the electrical resistance of the blood (32). Total peripheral resistance (TPR) was calculated assuming brachial artery mean pressure (BAPm): BAPm = BP diastolic + (BP systolic − BP diastolic) × 0.43 (33) and right atrial mean pressure 3 mm Hg.

Statistics

Statistical evaluation of the effects of the various treatments was made for the following variables: HR, QTc, T_{V2-6}, QS_2c, SV, Heather Index, BAPm, and TPR. The time course of these variables was analyzed by multivariate methods considering the values obtained at the successive measurement times (5–240 min) after drug application as multivariate response vectors. The influence of the treatments and the treatment periods on the response vectors were analyzed by a multivariate analysis of covariance using the changes of the measurements during the observation period (Δ-values) as response and the mean of the two basic values before application as covariate. Measurements at different treatment periods were considered as statistically independent, but the dependence of measurements observed from the same volunteer at different times within the same treatment

period was included in the multivariate model. By using the mean initial value as covariate, a possible influence of the individuals in the corresponding treatment period can be adjusted. The global hypothesis of "no influence" of the treatments to the adjusted changes of the response variables was tested using Wilks Λ-statistic [assuming multivariate normal distribution of the response vectors and homogeneous covariance matrices (34)]. For a detailed analysis, the adjusted differences between the changes in the treatment groups and placebo group were estimated for each measurement time and compared with its standard error (SE). Ratios higher than 2 were considered as "significant" treatment effects corresponding to a case-wise error probability of $\alpha < 5\%$ of the t test.

Serum Glycoside Concentrations

Serum glycoside concentrations were measured using specific ^{125}J digitoxin and ^{125}J digoxin radioimmunoassay systems (Diagnostic Prod. Corp., Los Angeles, Calif.).

RESULTS

In Table 1, the mean and the SEM (n = 8) for the initial values (arithmetic mean of the two basic registrations) are presented. The reproducibility of the methods is shown by the nearly identical values obtained on the four occasions. The time course of the mean differences of the values to the initial values is shown in Figs. 1–3. As the results with 0.5 mg of digitoxin were in most instances approximately 50% of those seen with 1.0 mg of digitoxin and as the curves had a parallel course, the 0.5 mg results are not included in the figures for the sake of clarity. For the overall treatment effects, the following significance probabilities could be achieved using the multivariate analysis of covariance: HR: p = 2.6%; QTc: p = 0.6%; T_{V2-6}: p < 0.1%; QS_2c: p = 8.9%; SV: p = 62.8%; Heather Index: p = 28.7%; BAPm: p = 88.3%; TPR: p = 47.3%.

The significant treatment effects are mainly due to differences in the measurement curves after administration of placebo or 0.5 mg digitoxin on the one hand

TABLE 1. *Initial values of the four treatment phases*

Variable	Placebo		DT 0.5 mg		DT 1.0 mg		D 1.0 mg	
HR (min^{-1})	58.1	(2.6)	58.8	(2.8)	58.0	(2.6)	59.9	(3.3)
T_{V2-6} (mV)	0.527	(0.050)	0.547	(0.036)	0.569	(0.060)	0.516	(0.042)
QTc (ms)	386	(6)	387	(8)	393	(7)	387	(5)
QS_2c (ms)	−21	(4)	−24	(6)	−23	(5)	−20	(4)
SV (ml)	132.6	(7.8)	132.6	(7.5)	127.5	(14.3)	123.9	(9.1)
Heather Index ($\Omega \cdot s^{-2}$)	11.5	(0.8)	11.7	(0.7)	11.7	(0.8)	11.7	(0.9)
BAPm (mm Hg)	97.8	(2.0)	99.8	(2.7)	97.7	(1.6)	98.5	(1.8)
TPR ($dyn \cdot s \cdot cm^{-5}$)	1018	(69)	1029	(74)	1119	(107)	1105	(126)

Mean values of the initial values (arithmetic mean of the two basic registrations at an interval of 10 min) before the four drug administrations. The numbers in parentheses represent the SEM values (n = 8). *Abbreviations:* HR, heart rate; T_{V2-6}, mean amplitude of the T-waves in leads V_2 to V_6, QTc, QT interval corrected for heart rate; QS_2c, electromechanical systole corrected for heart rate; SV, stroke volume; BAPm, brachial artery mean pressure; TPR, total peripheral resistance; DT 0.5/DT 1.0 mg, treatments with 0.5 mg/1.0 mg digitoxin; D 1.0, treatment with 1.0 mg digoxin.

and 1.0 mg digitoxin or digoxin on the other hand. Significant differences after administration of 1.0 mg digitoxin or digoxin could not be observed.

A detailed analysis of the changes at single registration times and for the different drug treatments compared with placebo administration supported by the results of the analysis of variance for the total course of effects (see above) shows the following results:

1. ECG parameters (HR, QTc, T_{V2-6}) (Fig. 1): As expected, both digoxin and digitoxin decreased T-wave amplitude and HR and shortened QTc. As Fig. 1 indicates, the effects during the first 60 min appeared more rapidly after digoxin than after digitoxin. Between 60 and 120 min both glycosides reached fairly constant and equivalent maximal values.

The final effects achieved by both these drugs in 1.0 mg doses differed significantly from the corresponding placebo values, but showed no significant differences from each other. However, there is a slight trend towards more flattening of the T-wave with digitoxin compared to digoxin. The total treatment effects are significant for all of the ECG parameters ($\alpha < 0.05$).

2. Parameters of the cardiac contractile performance (QS_2c, SV, Heather Index) (Fig. 2): the total treatment effects were significant for QS_2c at 10% level. However, the analysis of the changes at single registration times showed that with digoxin 1.0 mg, significant effects at a 5% level (compared to placebo) were achieved continually after 10 min, whereas with digitoxin 1.0 mg, the effect be-

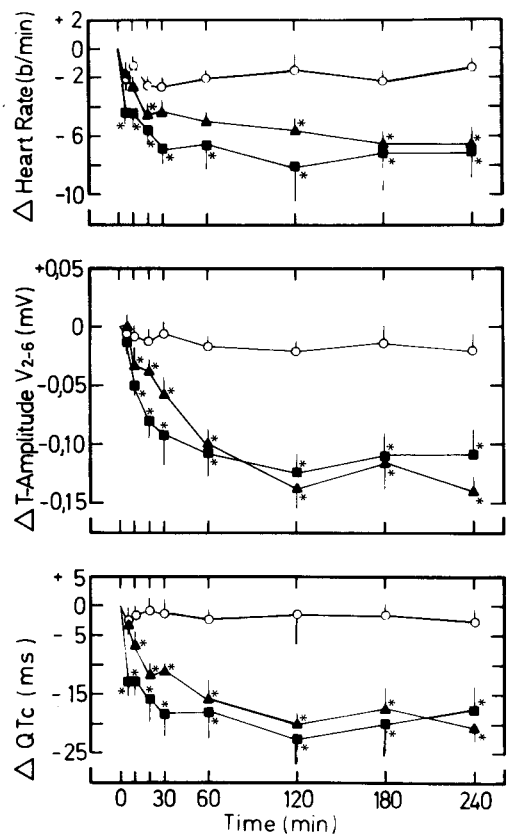

FIG. 1. Changes of electrocardiographic parameters following intravenous application of 1.0 mg doses of digoxin (■) or digitoxin (▲) and of placebo (○). Application during the first 2 min before time point 0. Mean values (±SEM) of eight volunteers in postabsorptive state. *Abbreviations:* QTc, QT duration corrected for heart rate. *The adjusted difference to the placebo value exceeds 2 SE ($\alpha < 0.05$).

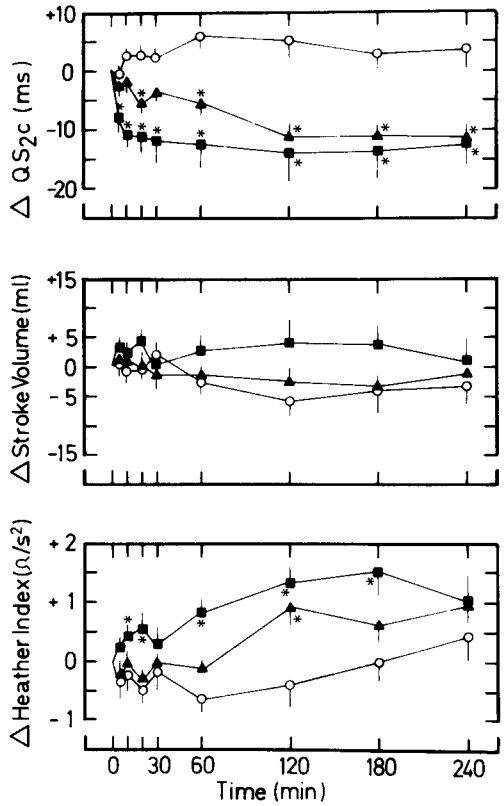

FIG. 2. Changes of parameters of cardiac performance following intravenous application of 1.0 mg doses of digoxin (■) or digitoxin (▲) and of placebo (○). Application during the first 2 min before time point 0. Mean values (±SEM) of eight volunteers in postabsorptive state. *Abbreviations:* QS_2c, electromechanical systole corrected for heart rate. *The adjusted difference to the placebo value exceeds 2 SE ($\alpha < 0.05$).

came significant only after 60 min. After 120 min the differences between digoxin and digitoxin were minimal. The SV showed insignificant and minor changes during the experiment. In general, the Heather Index increased slightly (total course not significant) under glycoside treatment (digitoxin 1.0 mg < digoxin 1.0 mg); however, there were individual points different from the placebo values significant at the 5% level.

3. Vascular parameters (BAPm, TPR) (Fig. 3): These showed no significant overall treatment effects. The mean arterial blood pressure differed only minimally between the various treatment groups. The total peripheral resistance showed a greater increase after digitoxin and less pronounced and apparently only shortlasting effects for digoxin. There were individual significant points for both digoxin and digitoxin during the registration time.

4. The serum glycoside concentrations obtained during the study are shown in Table 2. The serum values after 1.0 mg doses of digitoxin were slightly less than twice those after the 0.5 mg doses. An analysis of correlation between cardiac effects and serum glycoside concentration revealed no dependency during the 4 h of observation.

DISCUSSION

The typical effects on ECG, HR, and systolic time intervals were visible within 10 min after intravenous injection of 1.0 mg doses of digoxin and digitoxin. In full

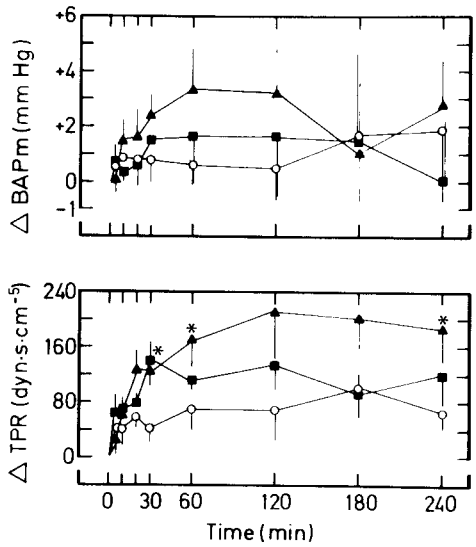

FIG. 3. Changes of brachial artery mean pressure (BAPm) and total peripheral resistance (TPR) following intravenous application of 1.0 mg doses of digoxin (■) or digitoxin (▲) and of placebo (○). Application during the first 2 min before time point 0. Mean values (±SEM) of eight volunteers in postabsorptive state. *Adjusted difference to the placebo value exceeds 2 SE ($\alpha < 0.05$).

agreement with current thought (24), the effects of digoxin were more pronounced than those of digitoxin during the 1st h after injection. These findings differ somewhat from the results of our recent study of glycoside effects after oral ingestion, where no difference in onset of action was found (17). This may be explained on the basis of the more rapid and complete absorption (35,36) of the more lipophilic (37,38) digitoxin. The maximum effect of digoxin is reached within 60–120 min, thereafter a decrease of effects could be observed during the period of study. Despite the slower onset of action during the first 60 min, the maximum effect of digitoxin was also reached between 60 and 120 min, and the effects were maintained throughout the study period. The findings of such a relatively rapid action of digitoxin are in accordance with results following oral administration (17), where maximal effects with digitoxin were seen after 2 h and no further increase observed during the next 8 h. The findings of these controlled studies contrast with conventional thought as perpetuated by current textbooks (e.g., 39,40). An explanation for this misconception could be that the inotropic effects and the effects in atrial fibrillation are dissociated in time. The uncontrolled nature of previous studies could further explain this discrepancy. It is now known that diurnal variation and food intake can produce significant changes in noninvasive

TABLE 2. *Serum glycoside concentrations (ng/ml)*

Treatment	5	10	20	30	60	120	180	240
				(min)				
DT 0.5 Mean	42.9	36.3	30.7	26.1	21.6	16.1	14.8	13.3
SEM	2.9	2.5	2.1	1.6	1.9	1.0	1.2	1.0
DT 1.0 Mean	71.6	61.1	53.2	47.7	37.8	28.5	23.7	21.6
SEM	6.4	4.3	3.2	3.0	1.9	1.2	1.1	1.0
D 1.0 Mean	20.9	15.7	11.7	9.4	5.4	2.5	1.6	1.3
SEM	1.8	1.4	0.7	0.5	0.3	0.2	0.2	0.1

Values 5–240 min following intravenous injection of 0.5 and 1.0 mg of digitoxin (DT) and 1.0 mg of digoxin (D), respectively, in eight volunteers.

measurements of cardiac function (17,41,42). These changes as seen after placebo administration are frequently in the same direction as cardiac glycoside-induced changes (17,41). In this study, done 2 h after the last meal, these changes were much less than in similar studies where food intake occurred during the study (17).

Serum glycoside concentrations (cf. Table 2) were found in the same range as described by others (review: 43), with levels for digitoxin from 3.4- (5 min) to 16.6-fold (240 min) higher levels than after the same 1.0 mg dose of digoxin. The serum concentrations in the distribution phase (up to 4 h) are less significant than under steady-state conditions and they are here documented for reasons of completeness.

Though no statistically significant differences in the global effects of 1.0 mg doses of digitoxin and digoxin were detectable, it is visible from the graphs that 2 h after administration, when both glycosides reached a maximum, several of the effects of digitoxin on cardiac performance were somewhat less pronounced than those seen with digoxin (see Fig. 2). In contrast to this slightly higher inotropic potency of digoxin, digitoxin produced a somewhat more pronounced T-wave flattening than digoxin (see Fig. 1). This observation agrees with previous studies (19,44) in man. The reason may lie in different effects of the two glycosides on the autonomic nervous system. Animal experiments suggest a greater sympathomimetic effect with digitoxin and a greater parasympathomimetic effect with digoxin (45–47). Though only statistically significant for a few of the points, a further indication of a stronger sympathomimetic effect of digitoxin could be the greater increase in total peripheral resistance it produced. Cardiac glycosides can increase the peripheral resistance in healthy man (48–51) by means of a weak direct vasoconstrictor effect or by a central sympathomimetic mechanism (40). At present, the clinical implications of these observations are not clear. The effect of cardiac glycosides on peripheral resistance is probably not noticeable in patients with heart failure owing to preexisting increases in sympathetic tone (49,52). This reflex compensatory mechanism rapidly disappears owing to the effect of glycosides on myocardial contractility. However, the possibility of pharmacodynamic differences between various cardiac glycosides implies that cardiac glycoside therapy might be improved by selection of the preparation most appropriate for the particular clinical problem.

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