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Dose-Response Relationships and Plasma Concentrations of Digitalis Glycosides in Man

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Summary. An inter-individual, randomized, double-blind study of digitoxin (Dt) and β-acetyl digoxin (D) was performed in 120 healthy male volunteers. Groups of 10 persons each received orally D 0, 0.1, 0.2, 0.3, 0.4, 0.5 or 0.6 mg and Dt 0.04, 0.08, 0.12, or 0.16 mg daily for 7 days; Loading doses were given for the first three days. Plasma levels were measured with an ^{86}Rb-erythrocyte assay 24 h after the last dose. ECG, carotid artery pulse and phonocardiogram were recorded prior to (b) and 24 h after (a) the last dose. QTc, amplitude of T-waves in V2 to V6, electromechanical systole (QS_2c) and left ventricular ejection time (LVETc) were measured. The differences between a and b (Δ-values) reflect glycoside-induced changes in heart function. The plasma glycoside concentrations depended on dose and ranged from 0 to 2.4 ng/ml for D and from 0 to 42 ng/ml for Dt. QTc, QS_2c, and LVETc were significantly shortened by the glycosides and typical parallel, sigmoid, log dose-response curves were obtained for the Δ-values. Dt was 3.8-times as potent as D in diminishing these parameters. The maximal effect of the two glycosides was almost identical at the highest doses: Δ-QTc = -45 ms, Δ-QS_2c = -25 ms, Δ-LVETc = -12.5 ms. The latter two parameters showed a plateau of maximum efficacy. Both glycosides caused significant flattening of T-waves, Dt being 7.2-times as potent as D. Significant relationships between plasma concentration and cardiac effects were observed ($p < 0.001$) – Δ-QTc (D: $r=0.7$; Dt: $r=0.77$), Δ-QS_2c (D: $r=0.7$; Dt: $r=0.75$), and Δ-LVETc (D: $r=0.46$; Dt: $r=0.43$); D correlated less well than Dt with the flattening of T ($r=0.46$; $r=0.76$, respectively). The most important conclusions were that: Dt was about 4-times as potent as D in influencing cardiac performance; the effects of D and Dt on systolic time intervals reached a plateau at "therapeutic" doses; Dt induced more pronounced flattening of the T-wave than D; and plasma glycoside levels within the "therapeutic" range corresponded to observed effects on the heart.

Key words: Digitoxin, β-acetyldigoxin, plasma levels, cardiac performance, dose-effect relationship, 86-Rb-erythrocyte assay, systolic time intervals.

Determination of digitalis plasma level is a commonly used method of monitoring glycoside therapy. For the diagnosis of glycoside intoxication, the value of this method appears well established [17]. However, there are few data about the relationship between therapeutic plasma levels of digitalis and glycoside effects. The first attempts to correlate glycoside concentration and therapeutic effect were made from the reduction in heart rate during atrial fibrillation [23]. Studies correlating plasma concentration with cardiac effects using systolic time intervals (STI) have given conflicting results [8, 16, 26].

There is a further problem about the dose-response relationship of digitalis glycosides. In contrast to many other drugs, the dose-response relationships of digitalis glycosides in man have only been established for single doses in a relatively narrow dose range [1, 20, 28]. Ideally, however, dose-response curves should be based on the effects attained under equilibrium conditions and should cover the range of therapeutic doses [10].

In order to elucidate these problems of the clinical pharmacology of digitalis glycosides, it was the aim of the present study (a) to correlate plasma levels of digitoxin (Dt) and the β-acetyl derivative of digoxin (D) with their cardiac effects, and (b) to establish the dose-response relationships of these glycosides

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for their effects on cardiac performance following chronic administration.

Methods

Volunteers

The study was carried out in 120 healthy male volunteers, aged 19 to 35 years (average 26 years), weighing 55 to 102 kg (average 76 kg). Persons with a weight exceeding ± 10 per cent of BROCA's index [15] were excluded from the study. Written, informed consent was obtained from each volunteer.

Values of cardiac variables were determined prior to and following a 7-day period of drug administration, the measurements always being made at the same time of day.

Drug Administration Period

Every participant received D or Dt daily for 7 days. The treatments were performed as an inter-individual, controlled randomized double-blind study. Each volunteer took part in only one treatment period.

Groups of 10 volunteers each received the following daily maintenance doses of D: placebo, 0.1, 0.2, 0.3, 0.4, 0.5 or 0.6 mg; and the daily doses of Dt were: placebo, 0.04, 0.08, 0.12 or 0.16 mg.

The following loading scheme was used:

Day	1	2	3	4 7		
D	3-	2-	1-	1-	1-	multiple of
Dt	6-	6-	3-	1-	1-	maintenance dose

Thus for D there was a 2-day, and for Dt a 3-day loading period. During days 1 to 3 the doses were divided into equal parts and were given at 8 a. m. and 6 p. m. From days 4 to 6 the doses were administered at 8 a. m., and the last dose on day 7 was given exactly 24 h before the various records were made.

The digoxin preparation used was a β-acetyl derivative (0.1 mg tablets − Novodigal mite®). It is completely desacetylated after absorption [24] and shows a high absolute biovailability of ~ 80 per cent compared to an intravenous standard [11]: Tablets of Dt 0.12 mg (for the loading period) and 0.04 mg were used. D, Dt and placebo tablets were kindly provided by Dr. N. Heinz, Beiersdorf AG, Hamburg, Western-Germany. The various tablets had identical galenical composition and showed the same rapid dissolution rate − > 90% solution within 1 min under standardized conditions [18]. Daily ingestion of the tablets was supervised.

Recordings and Measurements

All measurements were done blind. Recordings of STI (QS_2 and LVET) and ECG (RR, PQ and QT-intervals) were made under steady state conditions (24° C; between 6:30 and 8:30 a. m.; in the fasting state).

Following the method of Blumberger [6], STI was obtained from simultaneous high speed recordings (100 mm/s) of ECG lead A [22], a carotid pulse trace [7] and a phonocardiogram (> 140Hz). Twenty consecutive heart cycles were averaged to obtain STI. Variables measured were: QS_2 (electromechanical systole), LVET (left ventricular ejection time), RRI (R-R interval) from which the heart rate (HR) was calculated, PQ-duration and QT. The amplitude of the T-wave was measured in 5 consecutive beats in leads V_2 to V_6 of the standard ECG and averaged as follows:

$$\overline{T_{V2-V6}} = \sum_{N=5} T_{V2} + \sum_{n=5} T_{V3} \ldots + \sum_{n=5} T_{V6} / 25$$

QT_c was calculated according to Bazett [3]. Correction of STI was done according to Weissler et al. [29]. The difference between predicted and calculated STI was defined as QS_2c and LVETc. The effects of treatment were defined as Δ-values, i. e. the difference between the value before and after treatment.

Immediately following the second measurement (a) of STI and ECG, plasma concentrations of glycoside were measured using a modified ^{86}Rb-erythrocyte assay [4, 5, 19].

Calculations and Statistical Analysis

As a first step the groups of volunteers were tested for homogeneity using the absolute values of QTc and $\overline{T_{V2-6}}$. Prior to treatment, the groups were found to be equal at the 5% level, but after treatment they were inhomogeneous.

As a prerequisite for analysis of variance, the variance within the different groups was shown to be equal by means of Bartlett's test [27] performed on all absolute and Δ-values.

The analysis of variance was performed both on absolute and Δ-values. Differences were considered to be significant when $p < 5\%$. Several tests, especially when Δ-values were used, exhibited a significance of less then 0.1%. After performance of the analysis of variance, the means of the groups (with

exception of HR and PQ) were compared with each other using Duncan's test [27] at a 5% level of significance. When various data were correlated with plasma concentrations, the slope of the regression line was shown to differ significantly from zero. For descriptive purposes the mean and standard error of the mean (SEM) have been used. Logarithmic dose-response curves of the mean effects were analysed for half-maximal effect using graphic logit regression.

Results

The measurements of STI, ECG and plasma glycoside concentrations are shown in Table 1.

Glycoside Plasma Concentrations

With D 0.1 mg the average plasma level was 0.37 ng/ml, and with D 0.6 mg it was 1.25 ng/ml. The administration of Dt 0.04 mg daily led to a mean plasma level of 9.3 ng/ml, and 0.16 mg to one of 33.5 ng/ml.

Correlation between Plasma Glycoside Concentration and Cardiac Effects

Correlation coefficients and equations are shown in Table 2 and the interdependence of plasma levels and Δ QTc and Δ QS_2c are illustrated in Figs. 1 and 2. There was significant shortening of the parameters with increasing plasma concentration of each glycoside. In Figure 3 the correlation between plasma level and Δ T is shown. In principle there seemed to be no difference between the two glycosides, as T flattened with increasing plasma concentration. However, whereas for Dt the degree of correlation was the same as for STI and QTc, the correlation for D was much poorer than those for changes in cardiac performance. The absolute slopes of the correlations of the two glycosides could not be compared since the plasma concentrations had different ranges, although a relative comparison was possible. For this purpose Δ QS_2c was assumed to be the most suitable variable to represent the glycoside effect on cardiac performance. For D and Dt, respectively, the slopes of the correlations between plasma levels and Δ QS_2c were set to 1.0 as the reference slopes. The relative slopes for the other parameters were calculated by dividing their absolute slopes by the absolute slope of Δ QS_2c. For D the following slopes were obtained: Δ LVETc = 0.7, Δ QTc = 1.7, Δ $\overline{T_{V2\text{-}6}}$ = 6.0 × 10^{-3}; and for Dt the corresponding values were: Δ LVETc = 0.6, Δ QTc = 1.3, Δ $\overline{T_{V2\text{-}6}}$ = 11.3 × 10^{-3}. The ratios of the relative slope D/Dt were: Δ QS_2c = 1.0, Δ LVETc = 1.2, Δ QTc = 1.3, and Δ $\overline{T_{V2\text{-}6}}$ = 0.5.

Dose Effect-Relationships

Systolic Time Intervals. The shortening of QS_2c by the two glycosides was parallel (Fig. 4). The highest doses of the glycosides shortened this parameter by an average of ~ 25 ms. From the digitoxin curve it could be inferred that maximum efficacy had almost been reached. The values for half maximum effect (100% = maximum Dt-effect) were 0.2 mg daily for D and 0.052 mg daily for Dt. Thus, Dt was 3.8-times as potent as D in shortening QS_2c.

Shortening of LVETc revealed a plateau of maximum efficacy (-12.5 ms) for both glycosides. The half maximum effect occurred at 0.22 mg daily for D and 0.06 mg daily for Dt, i.e. Dt was 3.8-times as potent as D in shortening LVETc.

Electrocardiographic Parameters

Compared to the placebo, both glycosides showed only minor and insignificant effects on heart rate and PQ-interval (cf. Table 1). The dose dependent shortening of QTc is shown in Figure 5. Parallelism of the curves for D and Dt is apparent. The highest doses of the two glycosides induced almost identical shortening of QTc. A shortening of 24 ms (i.e. 50 per cent of maximum effect of D) was produced by D 0.3 mg daily and by Dt 0.077 mg daily. From these values it was calculated that Dt was 3.9-times as potent as D in shortening QTc.

Dt caused a statistically significant dose-related flattening of T (Fig. 5). The curve was similar to that of QTc. The maximum effect at the highest dose of D was only 65% of the greatest Dt effect. The dose necessary to cause flattening of the T-wave by 0.17 mV (i.e. 50 per cent of the maximum effect of Dt) was 0.51 mg daily of D and 0.07 mg daily of Dt, i.e. Dt was 7.2-times as potent as D in flattening T at this degree of effect.

Discussion

The present study involved comparison of plasma-levels of glycosides with certain pharmacodynamic parameters. For noninvasive measurement of glycoside effect STI were used. They reflected drug induced change in cardiac performance. Certain electrocardiographic parameters (amplitude of T-wave, PQ-interval and QTc) were added to indicate change in the electrophysiological properties of the heart.

Correlations between Plasma Glycoside Concentration and Cardiac Effects

In the present inter-individual study on D and Dt, relatively high correlations were found between

Table 1. Measurements before (b) and after (a) treatment with digitalis. Each group shows data from 10 volunteers; the entire series contains 120 males. On the left the various doses of the glycosides are shown. HR = heart rate; PQ = PQ-interval; T_{V2-6} = mean amplitude of the T-waves in the standard ECG leads V2 to V6; QTc = QT − interval corrected for heart rate (according to Bazett (3)); QS_2 = electromechanical systole; LVET = left ventricular ejection time; plasma glycoside concentrations were measured using an ^{86}Rb-erythrocyte assay

	No.	HR (min^{-1})	PQ (ms)	$\overline{T}_{V2-6}$ (mV)	QTc (ms)	QS_2 (ms)	LVET (ms)	Plasma Glycoside (ng/ml)
β-Acetyl - Digoxin Plazebo	1b	59.5	15o.5	o.354	4o1.2	4o8.5	3o8.2	
	a	67.5	155.7	o.256	41o.1	4o2.3	294.3	0
	2b	62.7	196.1	1.132	385.5	4o4.2	291.6	
	a	53.2	171.5	1.o91	359.7	419.o	3o5.o	0
	3b	82.5	15o.6	o.8o6	417.7	363.7	279.5	
	a	1o2.3	144.8	o.727	419.6	318.7	247.o	0
	4b	6o.4	163.1	o.862	4o2.9	416.3	297.o	
	a	64.5	156.4	o.736	397.1	4o8.1	3oo.8	0
	5b	53.8	171.4	o.817	4o6.6	446.7	316.o	
	a	61.2	164.2	o.629	418.8	447.8	319.6	0
	6b	48.8	148.3	o.647	443.5	478.2	349.9	
	a	46.2	15o.6	o.714	428.2	497.4	36o.7	o.18
	7b	58.o	152.3	1.184	393.4	4o9.o	298.5	
	a	63.o	145.o	1.147	426.8	4o5.2	293.o	0
	8b	67.1	165.7	o.286	429.5	398.3	3o1.6	
	a	71.o	152.6	o.373	422.2	386.5	287.5	0
	9b	6o.2	156.7	o.478	382.7	431.9	31o.1	
	a	58.o	157.2	o.493	376.1	436.5	314.6	0
	1ob	58.7	143.5	o.929	425.2	42o.2	319.6	
	a	45.9	16o.6	1.o52	415.6	446.2	33o.5	o.25
β-Acetyl - Digoxin o.1 mg	1b	53.9	181.o	o.646	368.6	423.2	315.5	
	a	52.5	171.8	o.562	369.o	431.4	319.9	o.3
	2b	6o.2	16o.o	o.458	392.1	436.8	295.6	
	a	63.3	168.8	o.455	39o.8	426.2	298.o	o.1
	3b	55.6	179.o	o.675	4oo.1	431.1	319.7	
	a	52.5	186.5	o.6o7	411.5	436.3	329.9	o.49
	4b	63.9	175.7	o.54o	4oo.5	384.7	293.o	
	a	58.1	191.2	o.644	389.5	417.3	311.o	o.22
	5b	81.3	152.8	o.356	344.4	398.2	285.2	
	a	67.6	153.2	o.27o	359.6	4o8.6	312.1	o.5o
	6b	6o.5	132.5	o.812	435.9	445.9	318.6	
	a	58.3	131.6	o.642	412.5	435.8	323.3	o.85
	7b	48.o	159.5	o.811	373.6	442.4	334.7	
	a	46.8	166.o	o.721	352.2	435.3	316.3	o.38
	8b	71.6	156.9	o.56o	4o9.6	415.o	3oo.5	
	a	57.1	155.9	o.685	393.4	45o.4	314.o	o.31
	9b	67.o	147.5	o.558	417.2	369.2	283.o	
	a	69.8	15o.8	o.478	433.1	371.o	287.8	o.27
	1ob	59.4	189.o	o.62o	411.7	423.2	3o3.2	
	a	49.2	196.9	o.49o	39o.9	443.7	317.5	o.26
β-Acetyl - Digoxin o.2 mg	1b	73.5	125.4	o.77o	435.3	386.1	285.6	
	a	67.6	126.7	o.521	423.2	386.7	294.5	o.43
	2b	68.4	136.9	o.9o2	422.2	4o7.o	288.2	
	a	62.3	14o.2	o.745	427.6	4o6.6	3o6.9	o.57
	3b	54.7	192.2	o.629	422.2	442.4	332.7	
	a	61.9	196.3	o.5oo	416.4	413.7	318.7	o.24
	4b	61.6	189.5	o.478	4o5.7	453.2	31o.3	
	a	69.4	198.7	o.381	422.7	424.1	3oo.8	o.58
	5b	68.5	179.6	1.285	393.2	4oo.1	295.9	
	a	67.5	191.6	o.983	384.5	395.3	291.6	o.75
	6b	71.1	15o.2	o.467	431.9	43o.4	3o8.8	
	a	69.2	15o.1	o.285	4o7.4	422.1	3o8.o	o.75
	7b	78.6	178.7	o.616	43o.6	41o.6	296.6	
	a	69.o	194.2	o.367	4o6.9	411.4	3o5.3	o.5o
	8b	63.5	144.2	o.767	4o2.o	426.9	313.3	
	a	65.3	145.3	o.666	378.7	4o6.3	3o1.9	o.4o
	9b	64.8	151.9	o.73o	43o.o	447.5	318.2	
	a	63.6	153.8	o.57o	4o8.2	445.8	321.6	o.37
	1ob	55.6	161.6	o.518	375.7	428.3	323.7	
	a	52.9	155.8	o.477	37o.4	428.6	318.3	o.44
β-Acetyl - Digoxin o.3 mg	1b	56.o	132.8	o.973	418.6	428.7	3o4.6	
	a	52.2	137.3	o.989	4o6.1	426.9	3o1.6	o.56
	2b	59.1	167.o	o.658	397.4	454.o	329.7	
	a	6o.o	159.2	o.586	393.9	438.3	324.3	o.97
	3b	55.9	191.1	o.566	42o.5	467.3	334.3	
	a	59.6	183.4	o.388	4o5.o	432.9	299.8	1.14
	4b	54.o	189.8	o.653	412.8	437.8	316.4	
	a	63.4	218.7	o.459	412.1	427.o	319.8	1.15
	5b	68.4	122.9	o.642	42o.9	4o1.6	297.4	
	a	59.5	12o.3	o.422	38o.7	386.o	291.o	1.o7
	6b	64.1	172.8	o.543	423.8	425.5	3o1.1	
	a	62.8	144.7	o.399	396.1	41o.9	282.8	o.92
	7b	63.1	144.5	o.686	417.2	421.8	299.4	
	a	6o.4	181.8	o.525	391.o	411.4	293.8	1.1o
	8b	6o.1	113.1	o.564	397.4	422.7	3o9.8	
	a	55.2	116.9	o.425	356.6	414.9	3o1.7	o.92
	9b	8o.6	149.7	o.459	424.9	376.8	285.3	
	a	66.8	155.o	o.375	391.9	393.6	296.8	o.71
	1ob	66.3	164.8	o.822	4o3.2	425.5	319.6	
	a	56.9	184.3	o.698	357.3	432.5	322.4	o.67
β-Acetyl - Digoxin o.4 mg	1b	65.3	94.o	o.761	4o7.7	397.3	297.6	
	a	59.2	94.2	o.598	374.3	39o.2	296.6	o.95
	2b	63.1	16o.7	o.692	427.3	436.4	33o.4	
	a	5o.1	164.7	o.6o4	377.5	438.8	328.9	o.72
	3b	6o.4	172.8	o.555	428.5	436.o	3o6.4	
	a	45.9	177.1	o.3o8	368.4	431.3	311.2	1.o4
	4b	68.4	164.9	o.672	415.9	4o2.7	298.8	
	a	55.7	177.o	o.537	387.9	413.2	3o6.8	1.19
	5b	58.3	173.2	o.753	422.5	429.2	3o4.3	
	a	53.o	199.7	o.682	4o6.8	43o.1	315.3	o.8o
	6b	53.7	128.7	o.88o	419.4	435.9	336.9	
	a	54.7	131.1	o.556	399.4	416.9	326.1	1.1o
	7b	52.4	1o5.2	o.854	374.7	424.9	323.o	
	a	54.9	111.7	o.688	348.o	4o5.6	3o9.7	1.13
	8b	87.8	162.4	o.488	414.6	373.4	266.4	
	a	87.4	149.6	o.33o	387.4	355.7	255.9	o.94
	9b	7o.o	18o.o	o.398	395.6	413.1	291.2	
	a	68.o	187.2	o.296	369.2	398.7	282.5	1.o9
	1ob	86.3	2o3.o	o.638	428.9	399.8	298.1	
	a	72.8	199.8	o.619	394.o	416.4	297.4	o.55
β-Acetyl - Digoxin o.5 mg	1b	78.3	18o.9	o.455	425.4	386.3	279.8	
	a	53.3	19o.7	o.334	356.o	412.7	3o9.1	1.6o
	2b	57.9	183.4	o.916	38o.5	421.6	3o8.o	
	a	52.o	187.2	o.533	364.2	42o.7	313.2	o.82
	3b	56.1	144.5	o.791	4o7.2	442.7	331.9	
	a	57.4	155.4	o.436	356.5	436.8	333.9	1.41
	4b	68.o	192.o	o.689	4o4.7	4o5.5	289.3	
	a	63.3	215.7	o.555	378.1	397.1	278.o	1.o8
	5b	54.o	148.3	o.923	387.3	418.1	315.2	
	a	65.o	15o.o	o.65o	364.5	4o2.1	3o4.1	o.82
	6b	52.5	149.4	o.663	365.3	431.9	3o4.8	
	a	51.7	152.4	o.6o1	347.2	4o6.o	299.9	1.oo
	7b	68.9	149.4	o.258	421.9	412.9	3o7.o	
	a	55.o	162.o	o.24o	369.5	42o.2	3o2.o	o.9c
	8b	58.o	155.9	o.412	412.6	437.9	319.4	
	a	59.9	181.8	o.523	376.6	399.1	289.4	1.56
	9b	62.4	153.1	o.842	423.9	424.5	318.9	
	a	57.o	154.o	o.637	379.4	411.4	313.4	1.43
	1ob	62.8	153.4	o.746	4o2.5	431.8	315.8	
	a	64.7	153.1	o.486	394.4	411.7	3o4.7	1.14

ß-Acetyl - Digoxin o.6 mg

No.	HR (min^{-1})	PQ (ms)	$\overline{T}_{V2-6}$ (mV)	QTc (ms)	QS_2 (ms)	LVET (ms)	Plasma Glycoside (ng/ml)
1b	72.3	192.o	o.711	422.2	414.1	3o8.7	
a	64.2	2o7.3	o.451	381.7	413.9	3o6.7	o.86
2b	66.2	14o.2	o.467	419.7	418.o	291.2	
a	55.8	141.5	o.335	369.8	4o2.6	291.6	1.54
3b	69.5	14o.6	o.593	394.7	387.6	291.2	
a	66.8	151.8	o.32o	359.7	385.3	292.8	o.93
4b	62.o	162.5	o.829	4o7.4	422.3	314.4	
a	58.6	167.2	o.662	389.8	421.4	314.4	o.76
5b	7o.4	161.1	o.377	428.o	42o.3	314.4	
a	63.5	176.o	o.188	373.3	4o8.4	3o5.3	o.96
6b	71.6	151.2	o.583	417.9	4o2.2	3o1.6	
a	69.1	162.8	o.4o4	358.8	384.o	292.9	1.41
7b	62.9	214.2	o.921	399.3	417.4	313.3	
a	74.o	21o.5	o.515	364.8	388.4	286.5	1.14
8b	55.9	166.6	o.473	421.3	444.3	325.2	
a	51.1	173.4	o.459	393.2	433.1	318.7	o.95
9b	51.6	165.7	o.821	43o.3	451.4	325.9	
a	48.2	181.6	o.4o2	371.8	425.4	315.1	1.51
1ob	57.3	132.2	o.862	416.1	45o.o	325.8	
a	42.1	134.8	o.646	346.9	451.8	336.9	2.43

Digitoxin Plazebo

No.	HR (min^{-1})	PQ (ms)	$\overline{T}_{V2-6}$ (mV)	QTc (ms)	QS_2 (ms)	LVET (ms)	Plasma Glycoside (ng/ml)
1b	62.7	174.o	1.ooo	429.o	414.1	31o.o	
a	57.9	176.3	1.o9o	413.7	433.5	314.9	o
2b	82.3	13o.o	o.67o	433.9	414.5	286.7	
a	71.3	129.1	o.715	436.7	424.2	289.5	o
3b	64.6	157.4	o.681	399.8	4o7.6	295.o	
a	64.3	152.2	o.696	4o2.5	412.4	3o5.o	o
4b	53.7	159.4	o.6o9	4o9.8	428.2	312.6	
a	54.1	15o.9	o.61o	4o9.o	43o.2	315.7	o
5b	54.8	154.6	1.o62	388.6	4o6.9	299.2	
a	46.3	159.4	1.o52	379.1	423.6	3o8.5	3.5o
6b	73.5	188.o	o.337	392.4	4o1.2	264.4	
a	74.9	185.8	o.262	392.3	399.7	262.7	o
7b	6o.o	13o.3	o.617	385.o	412.7	292.9	
a	67.1	126.6	o.641	399.5	4o7.9	3o3.7	o
8b	59.2	151.8	o.642	4o9.7	426.4	318.1	
a	67.3	155.8	o.632	4o6.6	4o7.8	294.3	o
9b	63.8	175.1	o.451	369.o	4o2.9	3o6.5	
a	65.4	18o.5	o.579	362.8	413.o	3o3.2	o
1ob	57.4	158.4	o.496	4o8.2	416.4	3o7.o	
a	59.1	161.7	o.461	398.5	419.7	3oo.9	o

Digitoxin o.4 mg

1b	56.4	148.4	o.588	4o3.o	446.6	338.9	
a	55.9	153.6	o.499	396.7	432.6	334.5	8.8o
2b	63.6	182.3	o.546	413.1	4o6.4	3o6.1	
a	54.2	187.8	o.6o6	4oo.5	428.4	316.1	1o.8o
3b	74.1	148.1	o.758	436.2	422.5	3o3.1	
a	59.6	154.o	o.556	4o8.8	417.2	3o1.2	1o.2o
4b	57.5	18o.4	o.757	394.4	393.7	3o4.7	
a	5o.6	198.8	o.74o	376.2	418.2	318.3	7.7o
5b	63.2	144.9	o.761	4o3.8	412.3	295.4	
a	64.4	146.3	o.52o	399.6	397.o	291.9	15.oo
6b	66.8	149.1	o.86o	379.5	4o6.7	292.5	
a	57.3	147.6	o.787	36o.5	414.2	3o5.6	8.2o
7b	56.1	145.9	1.5o8	416.o	435.9	3o9.3	
a	55.2	178.8	1.387	395.o	431.7	3o7.3	2.8o
8b	57.6	193.1	o.782	387.7	418.4	299.9	
a	7o.1	2o5.5	o.7o1	412.7	388.8	294.9	1o.9o
9b	71.2	132.1	o.7o9	442.4	398.3	3oo.9	
a	65.1	131.9	o.752	424.7	4o9.3	3o9.7	7.oo
1ob	59.7	177.1	o.952	395.5	415.3	3o1.6	
a	6o.9	187.7	o.757	372.9	4o2.5	289.4	11.5o

Digitoxin o.8 mg

1b	51.1	15o.3	1.o12	426.5	456.8	335.8	
a	44.7	151.2	o.758	383.4	453.3	337.8	23.5o
2b	58.4	127.1	o.676	389.2	428.3	313.9	
a	56.8	141.5	o.441	36o.5	413.3	3o8.9	23.2o
3b	65.4	159.o	o.266	423.1	4o8.1	297.5	
a	64.o	159.8	o.24o	4o4.4	4o3.2	294.8	17.7o
4b	67.6	129.7	o.785	388.1	431.o	3o1.4	
a	64.5	134.o	o.559	354.6	4o5.2	284.9	24.7o
5b	74.5	178.9	o.673	397.4	369.3	294.o	
a	66.9	197.7	o.522	393.o	369.8	288.6	2o.3o
6b	64.2	142.7	o.528	416.3	419.1	298.1	
a	69.6	153.1	o.219	391,6	4o6.3	293.5	21.9o
7b	6o.3	18o.9	1.o5o	41o.4	429.1	311.2	
a	53.7	172.6	o.869	382.8	426.4	325.2	14.2o
8b	5o.2	12o.5	o.8o1	4o4.6	444.5	339.2	
a	44.2	12o.4	o.594	387.9	457.7	348.5	16.9o
9b	62.4	165.8	o.634	387.6	4o1.5	298.4	
a	48.2	182.8	o.543	341.6	415.8	3o9.5	26.3o
1ob	58.o	163.8	o.889	42o.3	439.o	312.9	
a	57.4	171.5	o.664	4o4.3	423.o	3o1.o	24.1o

Digitoxin o.12 mg

1b	58.8	129.2	o.825	4o9.2	4o9.8	3o5.4	
a	53.2	137.7	o.743	381.o	421.8	3o5.2	15.7o
2b	57.7	161.6	o.937	4o5.7	417.o	3o2.5	
a	5o.1	178.o	o.576	366.2	4o5.9	3o6.4	27.3o
3b	61.2	97.4	o.578	4o6.o	411.1	3oo.6	
a	46.7	117.o	o.416	363.8	4o6.o	3oo.o	27.8o
4b	68.5	153.4	o.817	425.3	441.6	3o4.o	
a	67.7	153.4	o.6o6	389.3	412.4	29o.1	27.6o
5b	79.3	161.5	o.536	4o1.o	392.9	283.7	
a	72.3	184.5	o.454	37o.1	364.1	268.3	23.1o
6b	58.o	157.1	o.762	389.3	424.9	312.5	
a	57.9	169.5	o.591	355.3	4o3.3	3o3.7	26.9o
7b	6o.1	2o5.4	o.6o7	393.1	438.7	3o5.7	
a	66.o	214.5	o.458	372.8	399.5	289.1	23.7o
8b	67.7	182.9	o.686	4o6.3	4o8.1	3o7.8	
a	8o.2	176.8	o.198	386.8	359.1	268.6	18.9o
9b	64.9	145.4	o.833	388.9	4o8.3	31o.o	
a	65.7	16o.7	o.5o4	38o.1	394.2	3o4.8	14.8o
1ob	49.6	145.1	1.2oo	411.o	433.4	327.7	
a	55.o	155.3	o.788	397.3	4o6.4	312.4	2o.6o

Digitoxin o.16 mg

1b	71.6	134.9	1.oo4	411.5	377.6	27o.2	
a	6o.2	224.3	o.416	37o.5	388.7	293.o	33.2o
2b	91.8	139.3	o.315	443.7	367.5	273.8	
a	88.o	133.2	o.142	398.3	346.8	259.o	28.1o
3b	51.1	193.9	o.672	386.9	415.5	31o.8	
a	46.o	218.2	o.332	341.1	399.9	299.1	32.5o
4b	63.o	196.1	1.128	42o.3	439.3	316.o	
a	52.7	22o.3	o.8o2	37o.1	435.8	321.3	31.6o
5b	62.o	192.5	o.963	395.3	4o9.o	283.4	
a	53.4	18o.9	o.459	356.4	398.7	281.5	36.3o
6b	44.9	122.3	o.855	373.o	462.9	326.1	
a	46.2	132.8	o.613	34o.8	448.1	322.1	26.1o
7b	7o.4	152.6	o.583	427.o	423.4	312.9	
a	71.8	162.7	o.3o1	387.o	4oo.9	3o2.3	32.8o
8b	79.7	121.6	o.559	436.3	398.5	293.6	
a	58.1	139.2	o.374	369.o	4o2.7	3o6.3	34.2o
9b	58.6	188.9	1.o48	395.o	427.2	299.8	
a	54.3	182.9	o.552	364.4	4o5.5	3o1.5	38.5o
1ob	66.9	157.o	o.7o1	397.1	415.5	291.2	
a	6o.o	172.5	o.396	365.8	4o5.5	3oo.9	41.9o

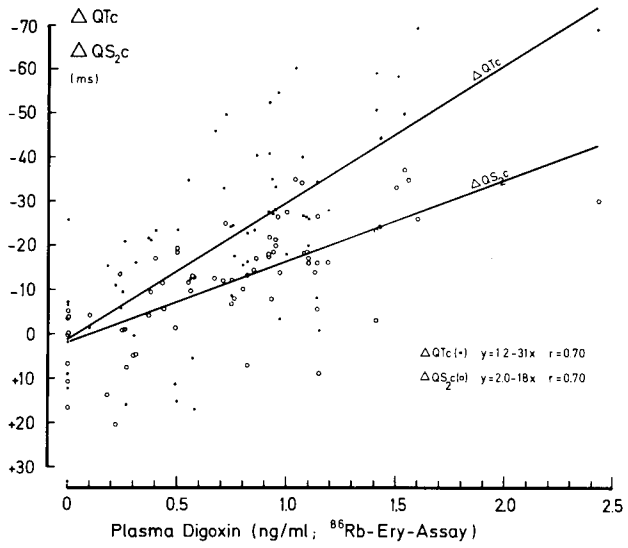

Fig. 1. Correlation between individual plasma digoxin level and changes in QTc and QS_2c. Abscissa: plasma glycoside concentration 24 h after the last dose. Ordinate: differences of QTc and QS_2c before and after treatment (Δ-values).
The slopes were significantly ($p < 0.001$) different from zero

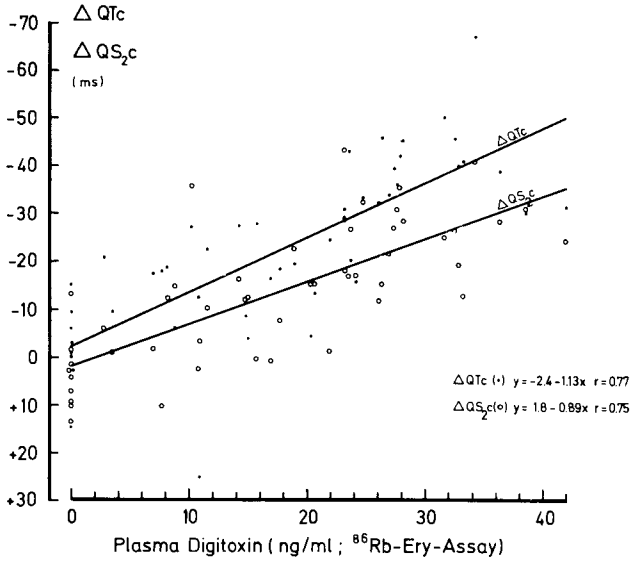

Fig. 2. Correlation between individual plasma digitoxin level and changes in QTc and QS_2c. Plot as in Figure 1.
The slopes differ significantly from zero ($p < 0.0001$)

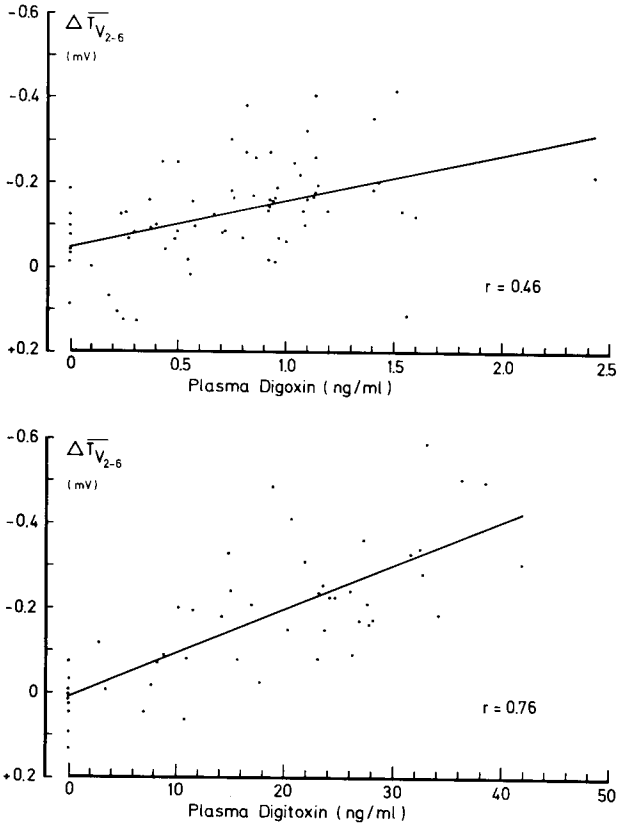

Fig. 3. Correlations between individual plasma glycoside level and changes in the amplitude of the T-waves for digoxin (upper part) and digitoxin (lower part).
Plot as in Figures 1 and 2.
Ordinate: change in the amplitude of T-waves in leads V2 to V6 ($\Delta\overline{T_{V2\text{-}6}}$). The slopes of the two regression lines differ significantly from zero ($p < 0.001$)

Table 2. Correlation coefficients (r) and correlation equations between plasma glycoside concentration (x) and changes in ECG-parameters and STI (y).

	Digoxin		Digitoxin	
	r	equation	r	equation
Δ Heart rate	0.29	$y = -4.41x + 0.15$	0.30	$y = -0.17x - 0.19$
Δ PQ	0.28	$y = +6.18x + 0.06$	0.31	$y = +0.39x + 1.82$
Δ $T_{V2\text{-}6}$	0.46	$y = -0.11x + 0.05$	0.76	$y = -0.01x + 0.01$
Δ QTc	0.70	$y = -30.98x + 1.24$	0.77	$y = -1.13x - 2.39$
Δ QS_2c	0.70	$y = -18.38x + 1.98$	0.75	$y = -0.89x + 1.82$
Δ LVETc	0.50	$y = -10.83x + 1.01$	0.43	$y = -0.37x - 0.79$

plasma level of glycoside and Δ QTc and Δ QS_2c. Dt showed a distinctly higher correlation with flattening of T than did D (Table 2).

It may be concluded from the results of the correlation analysis that there is a statistically close relation between plasma glycoside level and the influence of glycosides on contraction of the heart. The results support the value of plasma glycoside measurement in control of digitalis therapy and not only for the diagnosis of digitalis intoxication.

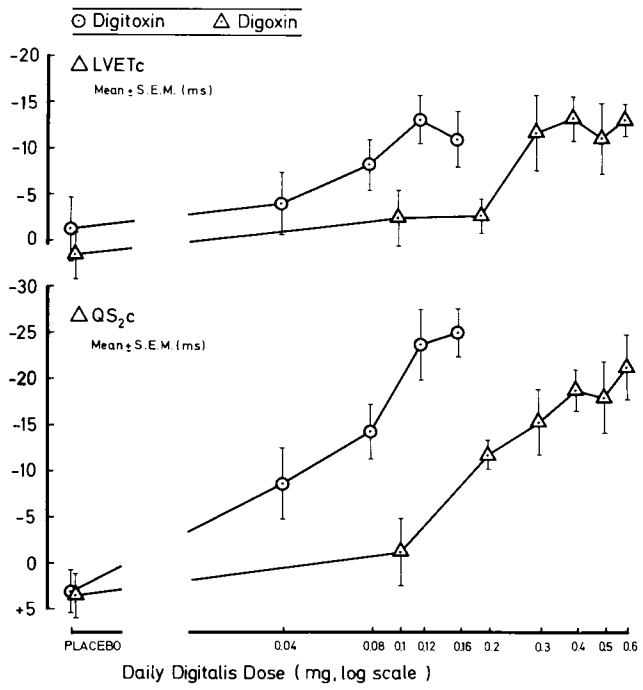

Fig. 4. Digitalis dose versus change in systolic time intervals. Daily oral maintenance doses of the glycosides are given on the abscissa (β-acetyl digoxin = D; digitoxin = Dt). Each point of the log dose-response curves represents the mean of the 10 different individuals (Total no's. for D = 70; for Dt = 50). The differences (Δ-values) of measurements before and after 7 days of treatment (the latter 24 h after the last dose) are shown. LVETc = left ventricular ejection time corrected for heart rate, QS_2c = total electromechanical systole corrected for heart rate. The mean values of the following treatment groups (mg daily maintenance doses) differed significantly at the 5% level in analysis of variance and multiple t-test (27) (0 = placebo).
ΔLVETc − D: 0 versus 0.3 to 0.6; 0.1 versus 0.3 to 0.6
−Dt: 0 versus 0.12 to 0.16
ΔQS_2c − D: 0 versus 0.2 to 0.6; 0.1 versus 0.2 to 0.6
−Dt: 0 versus 0.04 to 0.16; 0.04 versus 0.12 to 0.16; 0.08 versus 0.16

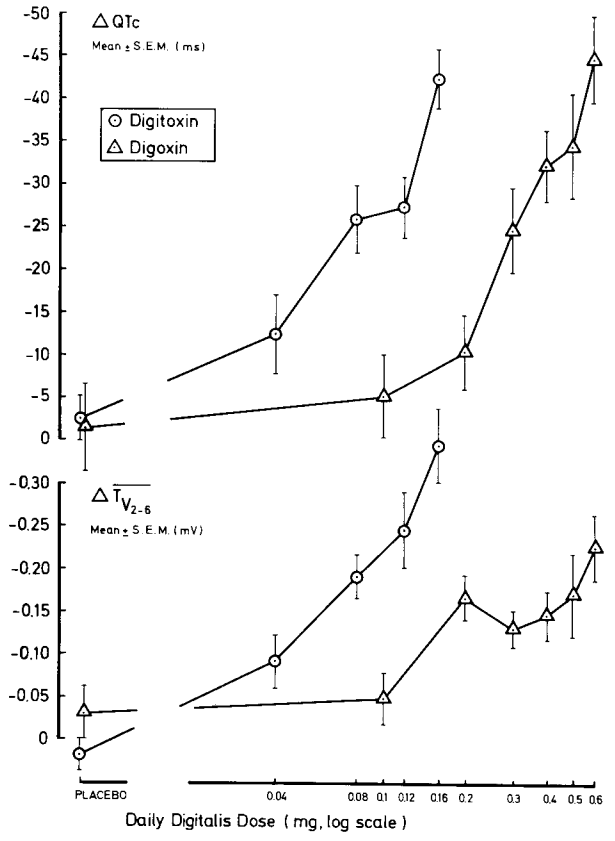

Fig. 5. Digitalis dose versus change in electrocardiographic parameters. Plot as in Figure 4.
QTc = duration of electrical systole corrected for heart rate; $\overline{T_{V2-6}}$ = mean amplitude of the T-waves from leads V2 to V6. The following groups differed statistically significant:
ΔQTc − D: 0 versus 0.2 to 0.6; 0.1 versus 0.2 to 0.6
−Dt: 0 versus 0.04 to 0.16; 0.04 versus 0.12 to 0.16
$\Delta\overline{T_{V2-6}}$ − D: 0 versus 0.2, 0.4 to 0.6
−Dt: 0 versus 0.08 to 0.16; 0.04 versus 0.12 to 0.16; 0.08 versus 0.12 to 0.16; 0.12 versus 0.16

Dose-Effect Relationship

In this study in man sigmoid-shaped, log dose-response curves for glycoside-induced changes in STI and ECG-parameters were demonstrated during maintenance therapy. The doses employed resulted in a plateau of effect (maximum efficacy) for Δ LVETc and Δ QS_2c, whereas for the electrocardiographic parameters (Δ QTc, Δ-amplitude of T-wave) the highest doses still appeared too low to induce maximum efficacy. Higher daily maintenance doses (> 0.6 mg of D, > 0.16 mg of Dt), which would be required to reach this goal, did not appear feasible for ethical reasons.

Generally, it is difficult to state the lowest effective dose and the minimum dose producing maximum efficacy, i.e. to determine the range of dose effect curves. A factor of 3–6 between the lowest effective and the minimal dose producing maximum efficacy was estimated for both glycosides from the curves of Δ LVETc and Δ QS_2c, and this range was in good agreement with the results of Greeff and Schlieper [14]. In a study of dose-effect curves of k-strophanthin on human, guinea pig, and rabbit atrial strips they observed that from onset of action to maximum contractile force the concentration had to be increased by a similar factor (4-fold).

In considering the dose-effect curves of the two glycosides, it should be remembered that the biological half lifes of D and Dt are different [9, 28] and that our measurements were made in a state of equilibrium 24 h after the last dose, when relatively more D would have been eliminated.

Pharmacodynamic Differences between Digoxin and Digitoxin?

It is generally accepted that there are no pharmacodynamic differences between the various cardiac glycosides, although they do differ in respect of their pharmacokinetic properties [12, 13, 21]. In the present study of the mechanical, electromechanical, and electrical phases of ventricular systole, completely analogous behavior of D and Dt was observed. The only striking difference in their influence on ventricular function lay in the relative potency of the two glycosides, which was mainly due to pharmacokinetic differences. However, both from the dose-effect curves and from the degree and the relative slope of plasma level-effect correlations, Dt was seen to cause more pronounced flattening of the T-wave than did D. This observation confirms older findings of Aravanis and Luisada [2]. They observed that the S-T-depression and lowering or inversion of T was much more evident after Dt than after D or other cardiac glycosides.

Assumption of a relatively greater vagomimetic potency of D than of Dt [25] could account for this observation, which has now been confirmed in two independent studies using quite different techniques. However, this hypothesis requires further experimental work.

Conclusions

Since the studies were done in normal man, translation of the results to clinical conditions should be only done with a certain reserve. An almost identical influence of cardiac glycosides on STI in normal subjects and in patients suffering from heart failure was shown, however, by Weissler and Schoenfeld [30].
Three points should be stressed:
1. Changes in cardiac performance induced by digitalis reach a plateau of maximum effect, and a further increase in dose will not result in a further increase in effect.
2. Plasma glycoside levels within the range 0 to 2 ng/ml for D and 0 to 40 ng/ml for Dt agreed well with the glycoside effects on the heart.
3. At an identical level of effect on cardiac systole, Dt had a more pronounced effect on the T-wave than might be expected for D. This may indicate that various cardiac glycosides do exert different actions on the electrophysiological properties of the heart.

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