EFFECT OF DIGOXIN ON THE SENSITIVITY TO FLICKERING LIGHT

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- 1 The sensitivity to flickering light at various light frequencies (DeLange curve) was determined in 20 controls and 45 patients receiving maintenance doses of digoxin.
- 2 Flicker thresholds (mean percentage of maximal light modulation $\pm$ s.d.; F 30 Hz) were 7.6 ± 1.7 in controls and 9.4 ± 1.7 in patients with optimal plasma digoxin levels (0.5–1.9 ng/ml), but they rose to 15.5 ± 1.9 at subtoxic levels (2.0–3.0 ng/ml), and to 21.8 ± 2.6 at toxic levels (above 3.0 ng/ml).
- 3 Flicker sensitivity was inversely correlated with plasma digoxin levels and returned to baseline values when the administration of digoxin was interrupted.
- 4 The DeLange curve seems to be a valuable tool to measure the toxic effects of digitalis on the visual system.

Introduction

Various symptoms such as fatigue, drowsiness, confusion and visual disturbances, including colour vision defects, belong to the clinical picture of digitalis intoxication. Those effects on the central nervous system seem to be less common than cardiac arrhythmias or gastrointestinal effects; they have been reported in 5 to 15% of intoxicated patients and they occur mainly after severe overdosage, but they may have been underestimated (Lely & Van Enter, 1972; Storstein *et al.*, 1977). The central effects of digitalis glycosides were investigated in a small number of subjects by means of flicker fusion tests, but these studies gave conflicting results (Gibson *et al.*, 1965; Robertson *et al.*, 1966; Towbin *et al.*, 1967). Recently, Rietbrock & Alken (1980), and Aronson & Ford (1980) showed that colour vision defects can be detected frequently in patients receiving digoxin if appropriate methods are used; in these patients the extent of the visual disturbances was correlated with plasma drug levels.

The purpose of the present study was to determine the sensitivity to flickering light in controls and in patients with various plasma digoxin levels. A more sensitive method than the usual flicker fusion test was used, in order to study the flicker sensitivity to a broad range of light frequencies (DeLange, 1957; Kelly, 1972).

Methods

Selection of the patients

Sixty-five patients (40 males and 25 females) were selected among patients hospitalised in the Department of Medicine. Forty-five of them were taking digoxin for congestive heart failure due to ischaemic heart disease (31 subjects), idiopathic cardiomyopathy (12), or valvular lesions (2). Twenty controls were selected among patients not taking digoxin; 10 had ischaemic heart disease and the others had pulmonary embolism, thrombophlebitis, liver cirrhosis, pyelonephritis, gout, oesophagitis, enteritis or viral infection. Patients suffering from severe retinal lesions, glaucoma, epilepsy, organic brain syndrome, acute heart failure, or receiving depressants of the CNS such as barbiturates, morphine and phenothiazines, or chloroquine, and those not willing to collaborate, were excluded. The protocol of the study was approved by the ethical committee of the Department.

Treatment groups

Controls (group A; $n = 20$) had not received any cardiac glycoside for at least 1 month. The other subjects had received maintenance doses of digoxin for several months (40 subjects), or a loading dose

followed by maintenance doses for 5–10 days (five subjects). They were divided into three treatment groups according to steady state plasma levels of digoxin: 0.5–1.9 ng/ml (0.6–2.4 nmol/l) in group B ($n = 14$), 2.0–3.0 ng/ml (2.6–3.8 nmol/l) in group C ($n = 14$), and above 3.0 ng/ml (3.8 nmol/l) in group D ($n = 17$). Patients of group A and B were matched with those of group C and D in order to have comparable groups with regard to age. Mean ages $\pm$ s.d. were 66.9 ± 6.3 years in group A, 66.7 ± 10.5 in group B, 72.6 ± 8.6 in group C, and 70.8 ± 10.3 in group D. Maintenance doses of digoxin were 0.28 ± 0.11 mg per day orally in group B, 0.23 ± 0.03 in group C and 0.25 ± 0.08 in group D. Serum creatinine levels were in the normal range in group A ($87 \pm 4 \mu\text{mol/l}$) and B (98 ± 22), but they were increased in group C (128 ± 79) and D (153 ± 45); the high plasma levels of digoxin measured in patients of group C and D appeared to be due to decreased renal excretion of the drug. Quinidine was administered to 3 patients of group B, 4 of group C and 10 of group D, β -adrenoceptor blocking agents to 3 of group A and 2 of group B, and low doses of benzodiazepines to 10 of group A, 10 of group B, 12 of group C and 11 of group D.

Flicker sensitivity tests

The flicker sensitivity was determined by means of a standard visual stimulator which has been described elsewhere (Vo Van Toi & Grounauer, 1978) and is commercially available ('Papillomètre', Metabo SA, CH 1066 Epalinges). It generates a sinusoidal signal which is directed to one eye through a 40° field eye piece assuring a Maxwellian view, the other eye being occluded. The modulation depth M and the flicker frequency F can be varied independently. The luminance of the stimulus L was about 30 cd/m^2 ; and only natural pupils and white light were used. The modulation M , which is defined as a ratio of the amplitude A over the average luminance L_m of the stimulus, was expressed in percent ($M = 100\%$ if $A/L_m = 1$), and the frequency in Hertz. The stimulator was handled by the investigator who made stepwise changes of M or F until the subject could detect a flickering light and pushed a knob indicating the threshold value. Neither the investigator, nor the subject, was aware of the reading before the threshold was reached. The subject was sitting in bed or at a table, and was investigated in the ward under daylight conditions. The critical flicker frequency (CFF) was determined as in the usual flicker fusion test; M was constant (100%) and F was decreased until the threshold was reached; the higher the CFF, the higher the flicker sensitivity. Then the critical flicker modulations (CFM) were determined; F was constant and M was increased from very low values (steady light) until the threshold was reached; the lower the CFM, the higher the flicker sensitivity. CFM were determined successively

for values of F of 30, 20, 15, 10 and 5 Hz. Each threshold was measured three times and mean values were plotted on log/log graphs; these curves represent the limits above which the subject does not see the flicker (DeLange curve; Figure 1). In 55 patients these determinations were repeated in the same conditions, either one or two days later (group A, B and C), or several times until plasma digoxin levels were in the normal range (group D).

Other methods

Plasma digoxin concentrations were determined by radioimmunoassay in duplicate (^{125}I -digoxin and antibodies supplied by Pharmacia, Uppsala, Sweden). Digoxin was administered as a single daily dose around 08.00 h, and blood samples were drawn immediately before the drug was taken. In patients in which digoxin was withdrawn, blood samples were also taken at 08.00 h. All these determinations were done on the same day as flicker tests. Electrocardiograms were recorded also on the same day, and were classified according to the criteria of Beller *et al.* (1971) as 'not suggestive of digitalis toxicity', or showing 'definite signs of digitalis toxicity'. The investigator used a checklist and a scoring system (absent, moderate, severe) to record gastrointestinal, nervous and visual side effects possibly related to digitalis toxicity. Since values of CFM and CFF have been shown to be log-normally distributed (Kelly, 1972), the results obtained in the four groups of patients were compared by a two-way analysis of variance and by t -tests in which log values were used; levels of significance above 0.05 were indicated by N.S. The 95% confidence limits of CFM in controls (group A) were calculated by the formula $\text{s.d.} \times 1.96$. Chi-square tests were used to compare the proportion of patients showing signs of toxicity in each group.

Results

Critical flicker frequency (CFF)

The CFF measured at maximal light modulation in controls (group A) was slightly higher than that of patients with optimal plasma levels of digoxin (group B); means $\pm$ s.d. were 58.4 ± 1.2 and 48.8 ± 1.2 Hz, respectively ($P < 0.05$). However, the differences between CFF of group B and CFF of group C with subtoxic drug levels (51.9 ± 1.2) or group D with toxic levels (44.1 ± 1.3) were not significant. There was no obvious relationship between plasma levels of digoxin and CFF (Figure 2).

Figure 1 Diagram of a critical flicker modulation curve. Flicker thresholds were determined for various light frequencies by increasing the amplitude, i.e. the modulation, from very low values ('steady light'; up on the ordinate) to a critical value at which the subject could detect a 'flicker' (down on the ordinate). The lower the value, the higher the flicker sensitivity.

Critical flicker modulation (CFM)

The critical flicker modulation curves showed peaks indicating maximal flicker sensitivity around 15–20 Hz (Figure 2). Flicker thresholds at a light frequency of 30 Hz rose progressively from group A to group D; mean values $\pm$ s.d. were $7.6 \pm 1.7\%$ in group A, $9.4 \pm 1.7\%$ in group B, $15.5 \pm 1.9\%$ in group C, and $21.8 \pm 2.6\%$ in group D. The analysis of variance gave a F ratio of 8.76 (df 3, 62; $P < 0.01$); significant differences were found between group A and C, A and D, and B and D ($P < 0.05$ or 0.01), but not between A and B, B and C, and C and D. These results indicate that flicker sensitivity was not reduced at optimal digoxin levels, but decreased at toxic levels; values of subjects with subtoxic levels were intermediate and not significantly different from those found at optimal or toxic levels. Flicker thresholds measured at a lower fre-

quency (20 Hz) in group A, B, C and D, were $4.0 \pm 1.6\%$, $5.0 \pm 1.9\%$, $9.5 \pm 1.8\%$ and $9.2 \pm 2.3\%$, respectively (F ratio = 7.71, $P < 0.01$; significant differences between A and C, A and D, B and C, and B and D, but not between A and B, and C and D). These values did not have exactly the same trend as those measured at 30 Hz, since those of subjects with subtoxic drug levels (group C) were significantly different from those of subjects with optimal levels and equivalent to those of subjects with toxic levels. The same trend was observed at a frequency of 15 Hz, but at lower frequencies (5–10 Hz) the differences between groups were smaller and a drug effect could not be demonstrated.

Plasma digoxin levels and CFM

Plasma digoxin concentrations and flicker thresholds

Figure 2 Flicker thresholds (mean $\pm$ s.e. mean) in controls (●) and in patients with plasma levels of digoxin of 0.5–1.9 ng/ml (○), 2.0–3.0 ng/ml (Δ) or > 3.0 ng/ml (□).

(CFM; F 30 Hz) of all patients taking maintenance doses of digoxin were plotted on a log/log graph (Figure 3). These values were significantly correlated; the higher the plasma level of the drug, the higher the threshold, i.e. the lower the flicker sensitivity. However, CFM values showed quite large individual variations around the regression line.

Changes in CFM during follow-up

Flicker sensitivity showed negligible day to day variations in controls; this indicates the absence of a learning phenomenon which could have interfered with repeated measurements in the same subject (Table 1). Under optimal and stable plasma digoxin levels (group B), flicker sensitivity was also stable. In some patients with subtoxic drug levels (group C) the administration of the drug was continued at the same or a slightly lower dosage and in others it was interrupted; flicker sensitivity tended to increase in patients in which digoxin was withdrawn, but this

change was not significant. Digoxin was interrupted in all patients with toxic drug levels (group D), and this was followed by a significant increase of flicker sensitivity up to values found in controls. Changes in flicker sensitivity were particularly impressive in six patients of this group which could be investigated several times during one or two weeks (Figure 4). Patients a, b and c showed a rapid drop of plasma digoxin associated with a rapid increase of flicker sensitivity. In patients d, e and f, on the other hand, the plasma elimination rate of the drug was slower, and the flicker sensitivity reached normal values (upper 95% confidence limits of CFM at 30 Hz in controls i.e. 20.4%) only 4 to 6 days following interruption of digoxin.

Flicker sensitivity and other signs of digitalis toxicity

Flicker sensitivity was decreased (CFM at 30 Hz above 20.4%) in one third of the subjects with subtoxic digoxin levels, and in one half of those with toxic

Figure 3 Correlation between plasma levels of digoxin and critical flicker modulation in patients receiving maintenance doses of the drug.

Table 1 Variations of flicker sensitivity in controls (group A), and in patients with optimal (group B), subtoxic (group C) and toxic (group D) plasma levels of digoxin.

	Group A	Group B	Group C		Group D
Administration of digoxin	none	unchanged	not interrupted ¹	interrupted	interrupted
<i>n</i>	18	10	9	3	15
Mean plasma digoxin level (ng/ml) ²					
first determination ³	—	1.15	2.27	2.53	4.26
last determination ⁴	—	1.09	1.68	1.57	1.56
s.d. of changes	—	± 0.25	± 0.47	± 0.40	± 0.92
<i>p</i> ⁵	—	NS	< 0.01	NS	< 0.01
Mean critical flicker modulation (%) ⁶					
first determination ³	7.1	9.9	14.1	13.6	19.3
last determination ⁴	7.2	9.4	12.7	9.5	7.4
s.d. of changes	± 1.7	± 1.7	± 1.2	± 1.2	± 1.7
<i>p</i> ⁵	NS	NS	NS	NS	< 0.01

¹ Daily doses slightly reduced in three, unchanged in six patients.

² Factor of conversion in international units: 1.28

³ At the time of the selection.

⁴ One or two days later (group A, B, C), 2–14 days later (group D).

⁵ Paired *t*-test.

⁶ Light frequency: 30 Hz.

Figure 4 Plasma digoxin levels and critical flicker modulation during and after administration of digoxin in six severely intoxicated subjects. The drug was interrupted on day 0. Upper limits of optimal plasma levels of digoxin and lower limits of flicker sensitivity in controls are indicated by horizontal dashed lines.

levels (Table 2). Flicker abnormalities were detected in 14 subjects and ECG changes indicating 'definite digitalis toxicity' in 12 subjects. However, these signs of toxicity were not always associated; eight subjects had flicker and ECG changes together, six had flicker changes alone, four had ECG changes alone, and twenty seven had neither flicker nor ECG changes. Visual symptoms tended to be more frequent in subjects with high digoxin levels, but this difference was not significant. Other nervous symptoms and gastrointestinal disturbances were reported by many

patients, but they were not related with the severity of the intoxication.

Discussion

The flicker fusion test is one of the numerous psychometric tests designed to detect acute effects of drugs acting on the central nervous system. Single doses of barbiturates, benzodiazepines, morphine, phenothiazines and tricyclic antidepressants decrease the

Table 2 Flicker sensitivity and other signs of digitalis toxicity

	Group A (controls)		Group B (optimal plasma levels)		Group C (subtoxic plasma levels)		Group D (toxic plasma levels)		Chi-square test (df 3) P
Number of patients studied	20		14		14		17		
Number of patients showing:									
Definite signs of digitalis toxicity on ECG ¹	0		1		3		8		< 0.01
Decreased flicker sensitivity ²	0		1		4		9		< 0.01
Visual symptoms									
moderate	1		3		1		5		NS
severe	0	1	0	3	2	3	1	6	
Nervous and gastrointestinal symptoms									
moderate	15		11		12		10		NS
severe	1	16	2	13	2	14	6	16	

¹ Criteria defined by Beller *et al.* (1971).² Flicker sensitivity below the 95% confidence limits calculated in controls.

sensitivity to flickering light in healthy volunteers (Smith & Misiak, 1976). Flicker sensitivity can be also impaired by β -adrenoceptor blocking agents (Salem & McDevitt, 1981), but flicker fusion tests, as they are usually performed, do not seem to be sensitive enough to detect toxic effects of digitalis glycosides. In the present study, the critical flicker frequency at maximal light modulation (CFF), which is the end point of the usual flicker fusion test, was slightly decreased in patients receiving digoxin, but this effect was not related to plasma levels of the drug. The apparatus used allowed more accurate determinations of flicker sensitivity; the frequency and the amplitude, i.e. the modulation of the stimulus could be varied independently, and critical flicker modulations (CFM) were measured for a broad range of frequencies. CFM for high frequencies (20–30 Hz) increased significantly in patients whose plasma levels of digoxin were above the optimal range. The values measured in patients with optimal drug levels, on the other hand, were roughly identical to those of controls not taking digoxin.

The decreased sensitivity to flickering light demonstrated in the present study appears to be due to a toxic effect of digoxin. This effect may reflect a decreased activity of the cerebral cortex, a mechanism advocated for depressant drugs acting primarily on the central nervous system, or it may be due to disturbances of the receptors located in the retina or to conduction defects along the optic fibres. The method used in the present study does not allow to differentiate central from peripheral effects. The phenomenon was quickly reversible even after long term administration of digoxin. Serial determinations of flicker thresholds after discontinuation of the drug showed that the recovery of the flicker sensitivity

and the plasma elimination of digoxin were closely related.

Flicker sensitivity was correlated with steady state plasma levels of digoxin, but large individual variations of threshold values around the regression line were observed suggesting that other factors may have influenced flicker sensitivity. There was no evidence that short term treatment induced smaller flicker changes than long term treatment; five patients taking digoxin for 5–10 days (digoxin levels: 2.9 ± 1.7 ng/ml) had flicker thresholds (CFM for $F = 30$ Hz) of $10.9 \pm 3.1\%$, which were slightly lower than those of patients on long term treatment with comparable digoxin levels ($15.5 \pm 1.9\%$), but this difference was not significant. The concomitant administration of quinidine could have increased the plasma concentrations of digoxin and its toxic effects (Hager *et al.*, 1979). However this drug did not seem to impair flicker sensitivity; seven patients of group D who received digoxin alone had a mean digoxin level of 4.2 ng/ml and a flicker threshold (CFM for $F = 30$ Hz) of $19.4 \pm 3.4\%$, whereas ten patients of this group who received digoxin and quinidine had values of 4.3 ng/ml and $23.6 \pm 2.1\%$, respectively (NS). The results obtained in patients receiving benzodiazepines or β -adrenoceptor blocking agents also did not differ from those of patients taking digoxin alone. Age (Akos & Akos, 1970) and hypoxaemia (Aisenberg *et al.*, 1974), which are known to decrease flicker sensitivity, might explain these individual variations, since many patients were elderly subjects who still had signs of heart failure while receiving digoxin.

This study was also designed to compare cardiac and non-cardiac toxicity of digoxin. In most surveys on digitalis intoxications, cardiac signs have been reported much more frequently than nervous and

visual symptoms (Beller *et al.*, 1971; Lely & Van Enter, 1972). In the present study, however, flicker abnormalities were detected as often as were electrocardiographic signs indicating definite digitalis toxicity. These results indicate that digitalis glycosides can induce neurotoxic effects which are dose-dependent as are cardiotoxic effects, and they confirm those of previous studies on colour vision disturbances. The relevance of these neurophysiological

tests for the management of digitalis intoxications needs further investigations, but these tests may prove useful when visual or other nervous symptoms are suspected.

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