Digoxin Does Not Accelerate Progression of Diabetic Retinopathy

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OBJECTIVE — To test the hypothesis that digoxin, an inhibitor of Na^+-K^+-ATPase activity, accelerates the progression of diabetic retinopathy.

RESEARCH DESIGN AND METHODS — We compared the incidence and risk of retinopathy in 120 digoxin-taking vs. 867 non-digoxin-taking diabetic participants in the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) and in 117 digoxin-taking vs. 1,883 non-digoxin-taking diabetic subjects in the Early Treatment Diabetic Retinopathy Study (ETDRS). In both studies, retinopathy was detected by grading stereoscopic color photographs using the modified Airlie House classification scheme, and a two-step difference in baseline retinopathy grade was considered significant.

RESULTS — After controlling for other risk factors, we found no statistically significant association with either 4-year incidence of retinopathy (WESDR) or progression of retinopathy (WESDR and ETDRS) in patients taking digoxin at baseline compared with those not taking digoxin.

CONCLUSIONS — These data suggest that digoxin therapy does not adversely affect the course of diabetic retinopathy.

Patients and animals with diabetes have reduced vascular and neural Na^+-K^+-ATPase activity (1,2), which may be related to the pathogenesis of vascular complications, including retinopathy (3,4). Patients with diabetic retinopathy may have concurrent congestive heart failure or cardiac arrhythmias that require treatment with digoxin. Digoxin improves myocardial contractility and slows cardiac electrical conduction by binding to and inhibiting the catalytic site of Na^+-K^+-ATPase. It is thus possible that digoxin treatment might further reduce already depressed Na^+-K^+-ATPase activity in patients with diabetes. We hypothesized, therefore, that reduction of Na^+-K^+-ATPase activity by both diabetes and digoxin might accelerate progression of diabetic retinopathy. Therefore, we used data from the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) and the Early Treatment Diabetic Retinopathy Study (ETDRS) to determine if digoxin had an adverse effect on the course of diabetic retinopathy in digoxin-treated subjects versus non-treated subjects.

RESEARCH DESIGN AND METHODS

— Both the WESDR and the ETDRS are longitudinal cohort studies of people with diabetes that can provide progression rates of diabetic retinopathy in those taking or not taking digoxin. The details of their study designs have been previously published (5–7). The WESDR is a long-term natural history study of 2,990 diabetic people in an 11-county area in southern Wisconsin, in whom diabetes was diagnosed in 1,210 at <30 years of age and in 1,780 at ≥30 years of age. The ETDRS is a clinical trial of aspirin use and photocoagulation in 3,711 patients with mild nonproliferative to early proliferative diabetic retinopathy (PDR), of whom 1,444 were classified as having type I diabetes and 2,267 were classified as having type II diabetes (2,000 without proliferative retinopathy at baseline). Because very few of the younger-onset group of the WESDR (10 subjects) or patients with type I diabetes in the ETDRS (10 subjects) reported digoxin use at baseline, all analyses in this report are limited to the older-onset group in the WESDR and patients with type II diabetes in the ETDRS. Analyses are limited to the eyes assigned to deferral of photocoagu-

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WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy; ETDRS, Early Treatment Diabetic Retinopathy Study; PDR, proliferative diabetic retinopathy; CI, confidence interval; OR, odds ratio.

Table 1—*Baseline characteristics of the WESDR and ETDRS patients*

	WESDR patients and digoxin use			ETDRS patients and digoxin use		
	Yes	No	*P* value	Yes	No	*P* value
n	120	867		117	1,883	
Sex						
M	41	46	0.32	49	53	0.40
F	59	54		51	47	
Insulin use at QV						
Yes	52	49	0.43	85	73	0.005
No	48	51		15	27	
Baseline retinopathy						
None-to-mild NPDR	86	82	0.50	20	21	0.37
Moderate NPDR	3	7		26	32	
Moderately severe NPDR	3	3		36	31	
Severe NPDR	3	2		19	16	
Age (years)	71 ± 9	64 ± 11	<0.001	60 ± 6	56 ± 8	<0.001
Systolic BP (mmHg)	150 ± 25	145 ± 23	0.07	148 ± 24	145 ± 22	0.16
Diastolic BP (mmHg)	75 ± 11	80 ± 12	<0.001	83 ± 11	84 ± 10	0.14
Duration of diabetes (years)	11 ± 8	11 ± 8	0.90	15 ± 7	13 ± 7	0.01
Glycosylated hemoglobin	12 ± 3	11 ± 2	<0.05	9 ± 2	9 ± 2	0.95

Data are % or means ± SD. NPDR, nonproliferative diabetic retinopathy; QV, baseline examination; BP, blood pressure. Glycosylated hemoglobin (%) for WESDR and HbA_{1c} for ETDRS.

lation in the ETDRS. Aspirin use had no effect on the progression of retinopathy in the ETDRS, and analyses are not adjusted for aspirin use.

At the baseline examination in both the WESDR and the ETDRS, data were collected concerning the use of digoxin as well as a number of possible covariables. Analyses for both studies divided patients into those who reported that they were taking digoxin at the baseline examination and those who did not report digoxin use.

Both studies used a modification of the Airlie House retinopathy grading scheme (8). Progression of retinopathy, adjusting for possible known confounders, was defined as the outcome variable for this study. Progression of retinopathy included the development of any retinopathy for people without retinopathy at baseline (WESDR), a two-step change in the modified Airlie House classification scheme (for patients in the WESDR [9] and eyes randomly assigned to deferral of photocoagulation in the ETDRS [8,10]), and the development of proliferative retinopathy in people (WESDR) or eyes (ETDRS) not having it at baseline. Progression was not evaluated for subjects in WESDR or ETDRS who had proliferative retinopathy at the baseline (11).

χ^2 and Student's *t* tests were used to compare the baseline characteristics of the digoxin-treated and non-digoxin-treated groups. To assess the risk of occurrence and progression of retinopathy for patients who used digoxin, while adjusting for other risk factors, a multivariable logistic regression analysis was used for the WESDR data. For the ETDRS data, time to progression could be used as an endpoint, and a Cox proportional hazards model, adjusted for other risk factors, was used to assess the risk of progression of retinopathy for patients who used digoxin.

RESULTS — The baseline characteristics of the WESDR and ETDRS subjects are shown in Table 1. In both studies, those taking digoxin were significantly more likely to be older ($P < 0.001$) than those not taking digoxin. In the WESDR, those taking digoxin were significantly more likely to have lower diastolic blood pressure and higher glycosylated hemoglobin levels.

Table 2 shows the proportion of patients, both digoxin users and nonusers, who had progression of retinopathy in both studies (based on ~4 years follow-up in the WESDR and at the 4-year annual follow-up visit in the ETDRS); and Table 3 shows the multivariate analysis of digoxin use and retinopathy. There were no statistically significant differences in rates for any of the types of retinopathy progression studied.

As seen in Table 3, regression analyses (logistic regression for the WESDR and Cox regression for the ETDRS) were adjusted for potential confounders (age, duration of diabetes, glycosylated hemoglobin, and baseline retinopathy, as appropriate). The history of digoxin use was not statistically significantly associated with the incidence or progression of diabetic retinopathy in either study for any of the retinopathy progressions studied. The confidence inter-

Table 2—*Proportion of patients with progression of retinopathy*

	WESDR patients and digoxin use			ETDRS patients and digoxin use		
	Yes	No	*P* value	Yes	No	*P* value
n	120	867		117	1,883	
Incident retinopathy	24 of 64 (38)	159 of 411 (39)	0.86	—	—	—
Any two-step progression	31 of 110 (28)	231 of 796 (29)	0.86	56 of 117 (48)	1,069 of 1,883 (57)	0.059
Progression to PDR	6 of 110 (5)	36 of 796 (5)	0.66	50 of 117 (43)	867 of 1,883 (46)	0.49

Data are *n* (%).

vals (CIs) suggest that as much as a halving or doubling of risk from digoxin use is very unlikely. Because Table 1 shows significantly lower diastolic blood pressures and higher systolic blood pressures in digoxin users in the WESDR, we also examined the effects of systolic and diastolic blood pressures in the multivariate models. Inclusion of these factors had no significant impact on the odds ratios (ORs) (data not shown).

In considering the possibility that some patients might have begun or discontinued digoxin use during the course of the study, we found that 81% of the incidence group and 82% of the progression group in the WESDR who were taking digoxin at baseline were still taking it at follow-up. Baseline digoxin use had no effect on progression of retinopathy in the ETDRS subjects, so we believe the likelihood of an effect during follow-up is very small.

Finally, we examined the possible effect of aspirin in the ETDRS subjects. Aspirin was not associated with progression to proliferative retinopathy (P = 0.91) or with a two-step change (P = 0.74).

CONCLUSIONS— This study examined the hypothesis that digoxin, a commonly used medication in patients with diabetes, might accelerate diabetic retinopathy because, like diabetes, it also reduces Na^+-K^+-ATPase activity. In terms of understanding the mechanism of diabetic retinopathy, these data neither prove nor disprove that alterations in Na^+-K^+-ATPase activity are involved in the pathogenesis of diabetic retinopathy. However, the data strongly suggest that inhibition of Na^+-K^+-ATPase activity by digoxin in typical clinical situations did not initiate or cause progression of existing retinopathy.

Although digoxin levels were not specifically monitored as part of the WESDR or ETDRS, they are monitored frequently as part of routine clinical practice to maintain therapeutic concentrations of 0.5–2.0 ng/ml (12). It is probable that most patients in these studies who were taking digoxin had appropriate therapeutic levels. Therapeutic digoxin levels typically reduce myocardial Na^+-K^+-ATPase activity by 20–30% (13). However, it is not known to what extent therapeutic plasma digoxin concentrations affect retinal endothelial cells or pericytes, and it is possible that digoxin does not substantially reduce retinal vascular Na^+-K^+-ATPase activity. However, the high-affinity isoforms of the catalytic α subunit of Na^+-K^+-ATPase are probably present in cultured bovine retinal endothelial cells and pericytes (14). Intravitreal injection of ouabain, an inhibitor of Na^+-K^+-ATPase structurally similar to digoxin, inhibits Na^+-K^+-ATPase activity by 20% at 10^{-9} mol/l concentration, equivalent to a serum digoxin concentration of 1 ng/ml (15). Therefore, therapeutic concentrations of digoxin are likely to reduce retinal or retinal vascular Na^+-K^+-ATPase activity. Nevertheless, these data suggest that the combination of diabetes and digoxin does not cause a clinically important additive inhibition of retinal Na^+-K^+-ATPase activity. From a clinical standpoint, these data suggest that digoxin can probably be used in patients with diabetic retinopathy without risk of retinopathy progression or visual deterioration.

Table 3—*Multivariable analysis of digoxin and retinopathy*

	WESDR		ETDRS	
	OR	95% CI	OR	99% CI
Incidence of retinopathy	0.94	0.49, 1.80	—	—
Two-step progression	0.96	0.56, 1.62	1.20	0.78, 1.82
Progression to PDR	1.18	0.32, 4.32	1.02	0.77, 1.84

Incidence of retinopathy is adjusted for glycosylated hemoglobin and age. Two-step progression and progression to PDR are adjusted for baseline retinopathy, glycosylated hemoglobin, age, and duration of diabetes, as appropriate.

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