Practolol-induced autoantibodies and their relation to oculo-cutaneous complications

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Summary

Tissue auto-antibodies were investigated in fifty-one patients (twenty-five female, twenty-six male) receiving practolol for ischaemic heart disease or dysrhythmias and compared with those found in 204 patients (fifty-eight female, 146 male) with ischaemic heart disease who did not receive practolol.

Antinuclear factor (ANF) was found in 24% female and 16% male patients receiving practolol, but only in 5% of female and 4% of male patients who were not taking practolol. Thyroid cytoplasmic antibody (TCA) was detected in 16% female and 20% of male patients receiving practolol, compared to 10% of females and 6% of males in the control group. The incidence of ANF and TCA was significantly higher ($P < 0.05$) in patients receiving practolol compared to the control group. The occurrence of gastric parietal cell antibody (PCA) and smooth muscle antibody (SMA) was not associated with practolol therapy (odds ratio of 2.4 and 1.9 respectively).

The incidence of skin and eye complications was found to be 10% and the female to male ratio of this complication was 4 : 1. The correlation between auto-antibody production and oculo-cutaneous complications could not be established in such a small group but three of the five patients with the complications were found to have PCA, although PCA was found not to be associated with practolol therapy. Four of the five patients with the complications did not have circulating ANF.

Introduction

Practolol is a useful β -blocking drug (Jewitt, Mercer and Shillingford, 1969; Jewitt, Burgess and Shillingford, 1970; Jachuck and Husaini, 1971; Jachuck, 1973) but the adverse effect of this drug (Wiseman, 1971; Rowland and Stevenson, 1972; Raftery and Denman, 1973; Felix, Ive and Dahl,

1974; Wright, 1975; Amos, Brigden and McKerron, 1975; Farr, Wingate and Shaw, 1975) warrants caution in its long-term use. Three cases of possibly practolol-induced lupus erythematosus were described by Raftery and Denman (1973) and since then Raftery (1974) has described an incidence of 11% of circulating antinuclear factor (ANF) in seventy-one patients receiving practolol for an average period of 6 months. Ocular complications and psoriasiform cutaneous lesions have also been described with oxprenolol (Lyll, 1975; Cumberbatch, 1974; Holt and Waddington, 1975).

Antibodies binding to epithelial tissue were demonstrated in twenty-seven patients with adverse effects probably induced by practolol (Amos *et al.*, 1975) and ANF was present in all (Wright, 1975). Felix *et al.* (1974) described twenty-one patients suffering from practolol-induced rashes but only five had positive ANF.

The incidence of circulating autoantibodies in fifty-one patients receiving practolol therapy for ischaemic heart disease (IHD) or dysrhythmia has been reported. These results were compared with the incidence of circulating autoantibodies found in patients of similar age group, with IHD, not receiving practolol, who had their autoantibodies assessed as part of another study by the same workers (J.S. and T.B.) in the same laboratory and using the same technique. The significance of circulating autoantibodies, when screening patients for oculo-cutaneous complications following the use of β -blocking drugs, is now reported.

Methods and patients

Fifty-one patients (twenty-five female, twenty-six male) receiving practolol for ischaemic heart disease or dysrhythmia were included in the study. Their ages ranged between 32 and 72 years and all had

received practolol for 1–4 years. A group of 204 patients (fifty-eight female, 146 male) suffering from ischaemic heart disease, but not receiving practolol, were also studied.

Coon's indirect immunofluorescent technique, with composite cryostat 7- μ m sections of human thyroid, mouse liver, kidney and stomach, was used to detect thyroid cytoplasmic antibodies (TCA), gastric parietal cell antibodies (PCA), smooth muscle antibody (SMA) and ANF. Serum from each patient was titrated by doubling the dilution, starting at 1/20. The antibody tests for both groups were done by the same workers (J.S. and T.B.) who had not been informed of the diagnosis. The diagnosis was known to one of the authors (S.J.) who had no access to the results of the antibody tests until the end of the study.

Results

The incidence in the patients of ANF, TCA, PCA, and SMA, is given in Table 1.

TABLE 1.

	Practolol				No practolol			
	Female (25)		Male (26)		Female (58)		Male (146)	
	No.	%	No.	%	No.	%	No.	%
ANF	6	24	4	16	3	5	6	4
TCA	4	16	5	20	6	10	9	6
PCA	3	12	4	16	6	10	6	4
SMA	1	4	2	8	2	3	5	3

The ANF was found to be positive in ten patients (six female, four male); incidence of ANF was also high in the females in the series reported by Raftery and Denman (1973), Felix *et al.* (1974) and Wright (1975). In nine patients with a positive test, the titre remained unchanged despite continuing the drug. In one patient, the ANF titre became progressively higher and the patient developed an allergic skin rash as well as bilateral blepharo-conjunctivitis; no LE cells were seen in the blood, and no other antibodies were detected in this patient. Discontinuation of practolol resulted in the disappearance of the oculo-cutaneous complications and the test for ANF was negative 11 months later.

The TCA was detected in nine patients receiving practolol and the titre became progressively higher in three patients, only one of whom developed a skin rash; this subsided after stopping practolol, and no ANF or LE cells were detected.

The PCA was found in seven patients receiving practolol and three of them developed oculo-cutaneous complications. No circulating ANF or LE cells were detected in these patients.

The SMA was positive in three patients receiving practolol but it was not present in any of the five patients with ocular or cutaneous complications.

Eye and skin complications and their relationship to the circulating antibodies are shown in Table 2.

Discussion

The systemic complications of practolol therapy occur with its long-term use and these complications are associated with immunological disturbances (Leading Article, 1975). Felix *et al.* (1974) noted the appearance of ANF in one patient 4 months after commencing the drug and Raftery noted its appearance in four patients 6 months after starting the drug (Raftery, 1974).

The incidence of ANF was said to be higher in male patients with ischaemic heart disease (Mathews *et al.*, 1973). In this study, the incidence of ANF in patients receiving practolol was 24% in female patients compared to 16% in male patients receiving practolol, and 5% and 4% in females and males, respectively, not receiving the drug. All five patients with positive ANF in the studies by Felix *et al.* (1974) were female and two of the three patients with DLE described by Raftery and Denman (1973) were female. The sex distribution was not reported by Raftery (1974) in his review of seventy-one patients receiving practolol. The incidence of positive test for ANF was 60% in females compared to 40% in males in Wright's series of twenty-seven patients with oculo-cutaneous lesions following practolol. The overall odds ratio in this study (Armitage, 1971) was 4.9 (95% confidence limits 1.8 and 13.2), suggesting an association between antibody production and the drug therapy ($P < 0.05$).

The prevalence of certain autoantibodies in the blood is higher in the female population while TCA is particularly high in female patients with ischaemic heart disease (Bastenie *et al.*, 1972; Mathews *et al.*,

TABLE 2

Case no.	Complication	Sex	ANF	TCA	PCA	SMA
6	Grittiness in the eye	M	—	—	+	—
14	Bilateral conjunctivitis	F	—	—	+	—
15	Skin rash	F	—	+	—	—
19	Itchy skin rash	F	—	—	+	—
24	Bilateral blepharo-conjunctivitis and allergic skin rash	F	1/20 1/80	— —	— —	— —

1973). In this study, the overall odds ratio of TCA was 2.6 (95% confidence limits 1.1 and 6.3), and hence the high incidence of TCA in the patients receiving practolol suggests significant association ($P < 0.05$) between the drug therapy and the antibody production.

The overall odds ratio for gastric PCA was 2.4 (95% confidence limits 0.9 and 6.4) and for SMA was 1.9 (95% confidence limits 0.5 and 7.6). Since 1 lies inside the confidence interval for the odds ratio, PCA and SMA production are not associated with practolol therapy (Armitage, 1971).

Eye and skin complications were found in 10% of patients taking practolol. Three of the five patients with the complications were found to have PCA but it has already been shown that PCA induction is not associated with practolol therapy. The mechanism might be similar to antibody binding to epithelial tissue, described by Amos *et al.* (1975). Although ANF production is induced by the drug, a progressive rise in the titre associated with oculo-cutaneous complications was seen in only one patient, and conversely the complications may occur without positive ANF, unlike the report of Wright (1975). Antibodies binding to epithelial tissue have been reported in patients with adverse effects probably due to practolol (Amos *et al.*, 1975), but such antibodies were not searched for in the present study.

It is confirmed that practolol, as do some anti-anginal and anti-dysrhythmic drugs, induces ANF production, and a higher incidence of ANF is also reported from females receiving practolol. Drug-induced TCA has not been reported before but a statistically significant increase in TCA ($P < 0.05$) was found in the patients receiving practolol compared to the control group. Skin and eye complications were also found more commonly in women. It is suggested that the test for circulating autoantibodies (ANF, TCA, PCA and SMA) is not useful for predicting the occurrence of oculo-cutaneous complications in patients receiving β -blocking drugs.

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