ANTINUCLEAR ANTIBODIES IN PATIENTS ON ACEBUTOLOL

The development of the β -adrenergic receptor blocking drugs has been a major advance in the therapy of cardiac arrhythmias and hypertension. Because of their relatively low incidence of side effects, these drugs are used extensively in the treatment of large numbers of patients. One of the early β -adrenoceptor blocking drugs, practolol, was withdrawn because of the development in some patients of the oculomucocutaneous syndrome. In many of these cases antinuclear antibodies (ANA) were detected (Levy & David, 1978). This finding suggested that the appearance of ANA might herald similar reactions in patients treated with other β -adrenoceptor blockers, or the finding of an increased ANA incidence associated with therapy with particular drugs of this group could indicate their potential for provoking practolol-like or lupus syndromes. Until recently the available data indicated that treatment with β -adrenoceptor blocking drugs other than practolol did not lead to an increased frequency of ANA. In a previous report (Wilson, Bullock, Sutherland, Main & O'Brien, 1978) involving 767 hypertensive patients, we could find no evidence of an association between therapy with β -adrenoceptor blocking drugs and increased ANA incidence, although the frequency of ANA in the small group of patients on acebutolol was greater than that in the group treated with other β -adrenoceptor blockers. Since then, more patients on acebutolol have been examined and the results clearly demonstrate an increased ANA incidence in these patients compared with patients on other forms of therapy.

All patients attending the Auckland Hospital Hypertension Clinic over a 30-month period were tested for the presence of ANA in their sera and careful drug histories were recorded. Sera and drug histories were also obtained from patients attending other hypertension clinics in New Zealand. ANA were detected by indirect immunofluorescence as described previously (Wilson *et al.*, 1978) using cryostat cut sections of a composite block of tissue from human thyroid, ox adrenal, pig stomach and salivary gland. When present, ANA always reacted with nuclei of all tissues. Titres of 1:8 or more were considered significant.

Of the 58 hypertensive patients whose treatments included acebutolol, 7 (20.0%) of 35 males and 10 (43.5%) of 23 females had serum ANA with a titre of 1:8 or greater (29.3% of 58 patients). In contrast, of the 1281 hypertensive patients whose therapies did not include acebutolol, only 68 (10.2%) of 667 males

and 97 (15.8%) of 614 females were ANA positive (12.9% of 1281 patients). The influence of various combinations of drugs on ANA incidence is shown in Table 1. Of particular note is the data concerning patients on treatments which exclude methyldopa (the drug most frequently associated with increased ANA incidence). Within this subgroup 28.3% of the 46 patients on acebutolol were ANA positive compared with only 7.7% of the 854 patients on other hypotensive medication.

In patients who were tested for ANA only once, or patients who were already ANA positive on their first visit to the Hypertension Clinic, it is not possible to relate the presence of auto-antibodies to their therapy. However, 25 of the patients on acebutolol who were tested sequentially were ANA negative either before commencing treatment with acebutolol or at their first visit while on this drug. Eight of these patients (six F) developed ANA during the course of this study (32%). In three of these patients acebutolol was the only hypotensive medication, and only one of the eight was taking methyldopa. Titres of ANA in the positive sera from acebutolol-treated patients were 1:8, four patients; 1:16, ten patients; 1:32, two patients; and 1:64, one patient. Each of these positive sera was screened for antibodies against double-stranded DNA but none were detected.

An examination of the age distribution of patients on acebutolol and patients on other hypotensive therapy (Figure 1a) revealed that only in those over 60 years was there a significant increase in ANA associated with acebutolol treatment ($P < 0.005$). However, when patients taking methyldopa were excluded from this analysis (Figure 1b), a significantly increased ANA incidence ($P < 0.02$) also became evident in younger acebutolol-treated patients (40–59 years). Thus the increased frequency of ANA in patients on acebutolol could not be attributed to concurrent methyldopa therapy because exclusion of patients taking methyldopa from the analyses resulted in a significant increase (rather than decrease) in the association between acebutolol and ANA.

Our data strongly suggest that treatment with acebutolol is associated with an increased incidence of ANA. Cody, Calabrese, Clough, Tarazi & Bravo (1979) have also reported the appearance of ANA in patients during acebutolol therapy. In their study eight of the nine patients who were ANA negative before beginning treatment with acebutolol became positive by the 20th week of therapy. In addition, LE cells were found in some of these patients. ANA titres

Table 1 The influence of various drug combinations on the incidence of ANA in patients

Drug combination	Not on acebutolol			On acebutolol		
	Males %	Females %	Total patients %	Males %	Females %	Total patients %
On other β -adrenoceptor blockers	10.5 (458)	16.4 (391)	13.2 (849)	16.7 (6)	70.0 (10)	50.0 (16)
Not on other β -adrenoceptor blockers	9.6 (209)	14.8 (223)	12.3 (432)	20.7 (29)	23.1 (13)	21.4 (42)
On methyldopa	19.7 (228)	27.1 (199)	23.2 (427)	25.0 (4)	37.5 (8)	33.3 (12)
Not on methyldopa	5.2 (439)	10.4 (415)	7.7 (854)	19.4 (31)	46.7 (15)	28.3 (46)
Not on other β -adrenoceptor blockers, not on methyldopa	5.8 (137)	9.1 (154)	7.6 (291)	18.5 (27)	27.3 (11)	21.1 (38)

The numbers in brackets indicate the total number of patients in the group

Figure 1 The age distribution of patients on acebutolol (▨) or on other hypotensive medication (□) expressed as a percentage of the total patients in each group. ■ represents the patients with positive ANA. (a). All hypertensive patients (58 on acebutolol, 1281 not on acebutolol). (b). Hypertensive patients not on methyldopa (46 on acebutolol, 854 not on acebutolol).

in their patients tended to be higher than in our study, reaching 1 : 160 in three patients. In neither their study nor our own were antibodies against DNA detected, nor clinical evidence of lupus-like syndrome observed. In contrast, De Soyza, Murphy, Kane & Laddu (1979), studying nine males with coronary artery disease treated with acebutolol for at least 8 months could not detect ANA, and Tse & Tsui (1978) reported no change in ANA in a group of 48 patients with essential hypertension treated with acebutolol for up to 40 weeks.

The conflict between our observations and those of De Soyza *et al.* (1979) and Tse & Tsui (1978) could be explained in a number of ways. We have found that the association between ANA and acebutolol increases with the age of the patients and is also more evident in females than in males. The patients studied by De Soyza *et al.* (1979), were all males but no information about their ages was reported. In the study by Tse & Tsui (1978) the ages of the patients ranged from 34–64 years (mean age 47) but the sexes of the patients were not included. In addition, the technical details of the ANA assay can produce major differences in the detection of ANA. The dilution of serum and the conjugate used for the screening may vary widely from one laboratory to another, and, as described by Cody *et al.* (1979), differences in the substrate used for ANA detection can have a profound effect on the sensitivity of the technique.

In our study, ANA positivity was not assessed on the basis of reactivity with a single substrate but all positive sera were found to react with four different tissue substrates. More importantly, almost one-third (32%) of the patients who were negative at the

beginning of the study developed ANA while on acebutolol. Irrespective of the clinical significance of this observation, it is clear that ANA will appear in some patients during therapy with acebutolol. The presence of ANA does not necessarily indicate clinical disease, but the close association between drugs which induce ANA and the drug-induced lupus syndrome suggests that patients showing rising ANA titres while on acebutolol treatment should be carefully monitored clinically to prove or disprove the drug's disease provoking potential.

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SOME FURTHER EVIDENCE FOR PARTIAL AGONIST ACTIVITY OF LABETALOL

Labetalol is a combined α - and β -adrenoceptor antagonist (Brittain & Levy, 1976). It possesses little or no partial agonist activity at β_1 -adrenoceptors (Katano, Takeda, Nakagawa, Hashimoto, Nakazawa, Tsukada, Otorii & Imai, 1978). Labetalol does, however, appear to have distinct partial agonist activity at β_2 -adrenoceptors in rat isolated uterus (Carey & Whalley, 1979). This present communication reports the effect of intravenously administered labetalol on blood glucose in man which may provide a further demonstration of partial agonist activity at β_2 -adrenoceptors.

Six healthy male volunteers were studied on four occasions, each separated by a minimum of 7 days. After an overnight fast, a forearm vein was cannulated and the subject rested supine for 30 min. Blood pressure was monitored at 5 min intervals with

an Elag sphygmomanometer. At time 0, 10 ml blood were withdrawn for baseline estimations. The test drug, diluted to 20 ml, or 20 ml saline, was administered through the cannula. Samples of blood were obtained at 5, 10, 15, 30, 45, 60 and 120 min. The drugs studied were labetalol (1 mg/kg), phentolamine (10 mg) and hydralazine (20 mg).

For the purpose of the present communication, only the changes occurring during the first 45 min of observation will be described.

Labetalol and hydralazine both produced a comparable significant reduction in diastolic and systolic blood pressures during the first 15 min following administration of the drug. Phentolamine caused less reduction in blood pressure which was not significantly different from placebo during this period of observation.

Table 1 Mean $\pm$ s.e. mean changes in plasma glucose expressed as percent of base-line (time 0) concentration

Drug	Time (min)				
	5	10	15	30	45
Placebo	97.3 $\pm$ 1.6	98.7 $\pm$ 1.6	98.7 $\pm$ 1.6	96.8 $\pm$ 3.1	95.5 $\pm$ 1.7
Hydralazine	99.9 $\pm$ 1.3	99.5 $\pm$ 0.8	98.7 $\pm$ 1.5	96.8 $\pm$ 1.2	99.0 $\pm$ 1.2
Phentolamine	100.1 $\pm$ 0.9	100.0 $\pm$ 1.0	99.5 $\pm$ 0.9	98.1 $\pm$ 0.9	99.2 $\pm$ 1.1
Labetalol	106.1 $\pm$ 1.7	110.9 $\pm$ 3.4*	106. $\pm$ 1.9*	104.4 $\pm$ 2.0	99.4 $\pm$ 1.2

*Significantly different ($P < 0.05$) from placebo, hydralazine and phentolamine.