

Ocular, systemic and antinuclear antibody changes with acebutolol

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SUMMARY. A group of 29 hypertensive patients were studied for side effects of acebutolol. An antinuclear antibody titre of $\geq 1/64$ developed in 23 per cent of patients during a 12-month course of treatment. Full ophthalmic examination before and after the treatment period showed a statistically significant increase in tear secretion at one year. One patient had a slight worsening of her psoriasis. No patients developed any symptoms or signs of oculomucocutaneous syndrome (OMCS) or systemic lupus erythematosus (SLE).

Introduction

AN association between the use of practolol and the development of oculomucocutaneous syndrome (OMCS)¹ and systemic lupus erythematosus (SLE)² has been suggested. So far as we know there is no definite link between any other beta blocker and OMCS,³ although an atypical example was reported with oxprenolol in a woman who developed psoriasis and keratoconjunctivitis sicca.⁴ Antinuclear antibody (ANA) was found in 30 per cent of 20 female patients on practolol,⁵ and up to 64 per cent of patients on practolol who developed subconjunctival fibrosis showed a positive rise in ANA. Subsequent work has thrown doubt on the relationship of drug-induced lupus syndrome and OMCS, although the former condition is now thought to have a benign course compared with the fatal outcome in OMCS.⁶ Monitoring patients for ANA is thus only useful for detecting drug-induced lupus. Wright¹ found that 100 per cent of 27 patients developing OMCS had ANA. Wilson⁷ has named many cardiovascular drugs which produce a significant rise in ANA, including acebutolol, a cardioselective beta-adrenergic receptor blocking drug possessing both intrinsic sympathomimetic activity and membrane stabilizing activity. In a small series of patients taking acebutolol 88 per cent (eight out of nine patients) developed positive ANA on high dosage of the drug whereas in a larger series the incidence was 32 per cent (eight out of

25 patients).⁸ Moreover, there has been one possible case of systemic lupus erythematosus connected with a large dosage of acebutolol (1,600 mg).⁹

We carried out a prospective study of the side effects of acebutolol on a group of hypertensive patients, measuring the serum titre of ANA and any ocular changes to investigate a possible correlation between the two.

Methods

Twenty-nine patients with mild hypertension—24 women and five men (average age 59.7 years, range 43.0–69.5 years)—were studied. These were the only new patients with mild hypertension who presented during the recruitment period in a practice with a female to male ratio of 2:1 in the over 50-year-olds.

All patients had a phase 5 sitting diastolic pressure measurement of at least 100 mmHg on three separate visits before treatment and were then treated in general practice for 12 months with acebutolol taken once daily.

Of the 29 patients, 24 had never received drug treatment for high blood pressure, five had received treatment for hypertension in the past but none in the previous 12 months. Twelve of the patients smoked cigarettes. Three patients were on concomitant longterm therapy: one patient was using cimetidine, one was using lactulose, and one was using intermittent prednisolone for rheumatoid arthritis. No other type of hypotensive drug was used during the study.

The following tests were carried out.

Ocular tests. Full ophthalmological examination included measurement of visual acuity for both near and distance sight, slit-lamp examination of precorneal and marginal tear film, biomicroscopic examination of conjunctiva for papillary changes, Schirmer's augmented test¹⁰ prior to Rose Bengal dye test, corneal staining with Rose Bengal and fluorescein dyes, visual screening using the Friedman field analyser.

Other tests. Measurements were made of the levels of haemoglobin, white cell count, platelets, urea, electrolytes, creatinine, alkaline phosphatase, transaminases, and bilirubin. An electrocardiogram (ECG) and a chest radiograph were also obtained.

Antinuclear antibody (ANA) test. The methods used to measure ANA and DNA binding have been described before.¹¹ DNA binding was determined in all patients who developed an ANA titre of at least 1/64.

The laboratory tests were performed 'blind' by being included in the routine test requests sent to the hospital, and the laboratory observers were unaware of the clinical trial being

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conducted. Previous experience of dealing with this laboratory for other investigations has shown that reproducibility can be assured. The laboratory tests were performed before admission to the study and at one year.

After admission to the study, patients were seen at two weeks, four weeks and then every four weeks for a period of 12 months. During these visits, blood pressure was measured by the same observer in the same room, at the same time of day (where possible) and in the same arm (non-dominant), with the patient lying down for 10 minutes and then standing. The dose of acebutolol was titrated until diastolic pressure measurement was 95 mmHg or less in all patients.

Compliance

Out of a possible 15 visits, 21 of the patients attended 15 times, six attended 14 times, one attended 12 times and one attended only 10 times. Blood acebutolol concentrations were measured before treatment and from four to seven times during the 12 months of treatment in each patient. One patient who attended only 10 times had no detectable acebutolol level in plasma on all four occasions and was excluded from the analysis.

Statistical analysis

A paired Student's *t* test was applied to the results of the Schirmer's test and the intraocular pressure data. A non-parametric sign test was used for the results of the Rose Bengal and ANA tests. Product moment correlation coefficients were calculated for the correlation between the Schirmer's test and ANA test results.

Results

Eye changes

Tear secretion, as measured by Schirmer's test, was significantly increased following treatment with acebutolol ($0.05 > P > 0.02$) but there were no significant changes in intraocular pressure ($0.5 > P > 0.1$). In one patient (ANA negative) there was a marked fall in tear secretions in both eyes.

Conjunctival examination with Rose Bengal stain showed punctate staining in 12 eyes (seven patients) before treatment and in 19 eyes (10 patients) after treatment. Statistically these changes were not significant ($P > 0.5$).

Corneal fluorescein dye test was negative in all patients, and there were no significant changes in vision during the period of study.

ANA changes

Initially 27 patients had negative or weakly positive values of ANA (22 negative and five weakly positive). Two patients had serum titres above 1/64 before entry to the study, but neither patient had been on hypotensive or cardiovascular drugs in the past.

Of the 26 patients who were initially negative or weakly positive and who complied with therapy, six (all females) had increases in serum titres to at least 1/64 at 12 months, in one case reaching 1/256 (Table 1). None of these six patients had a positive test for DNA antibody. The average age of those developing ANA was similar to that of the study as a whole.

Table 1. Details of six patients who developed raised values of antinuclear antibody (ANA).

Patient (years)	Age	Initial titre	Titre at 6 months	Titre at 12 months	Final dose of acebutolol (mg)
1	67	Negative	WP	1/64	500
2	66	Negative	WP	1/64	800
3	58	Negative	WP	1/64	800
4	52	Negative	1/64	1/256	1,000
5	52	Negative	1/64	1/64	400
6	61	WP	WP	1/64	400

WP = weakly positive.

Overall there was no significant correlation between the average Schirmer's results for the two eyes and the ANA results either before or after treatment ($P > 0.1$). Nor was there any significant correlation between the change in the Schirmer's test result, averaged for the two eyes, and the change in ANA results ($P > 0.1$).

End points and side effects

One patient developed polycythaemia rubra vera after 10 months; she became and remained normotensive after venesection and treatment with radioactive phosphorus. Although she stopped therapy on becoming normotensive, we observed her for the duration of the study and she had the same final investigations as the other patients. One patient developed an inferior myocardial infarction at eight months; after hospital discharge she became hypertensive again, although she was then maintained on a lower dose of acebutolol.

In response to a monthly questionnaire of 39 items answered in the surgery, one patient complained of wheeze, two of cold extremities, two of calf cramps, one of indigestion, one of dry mouth, one of excessive dreaming, and one of a slight worsening of her psoriasis which improved after the drug was stopped.

In response to two questions about ocular problems, which were 'Have you had any other eye symptoms or signs?' and 'Have you had conjunctivitis?', there were no affirmative answers. There were no significant changes in blood indices, biochemistry or urine. There were no ECG changes in any of the patients apart from the woman who had an inferior myocardial infarction. Specifically there were no clinical signs in any of the patients that were suggestive of SLE or OMCS.

Discussion

We found that, with acebutolol, there was an increased incidence of antinuclear antibody (ANA) in patients on no other hypotensive therapy and we also found that a titre of ANA increased with time, confirming the work of Cody and colleagues.¹²

All patients who developed a positive titre of antinuclear antibody were taking 400 mg or more of acebutolol per day. None of the seven patients on less than

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400 mg per day developed a positive titre. This partially confirms the previously reported results, where positive titres occurred only in those patients on a daily dosage greater than 400 mg acebutolol.¹² We found an increase in tear secretion (measured by Schirmer's test) similar to that noted by Shapiro and colleagues;¹³ they suggested that the increase is an irritability mediated reflex leading later perhaps to exhaustion, but there is no evidence to prove this. There were no other significant ocular changes.

We could not demonstrate any correlation between the development of positive titres of ANA and ocular or skin changes. However, the high incidence of positive ANA in patients while taking acebutolol implies that careful observation of such patients for ocular or cutaneous problems should be carried out in the longer term, particularly if the daily dose of the drug is greater than 400 mg.

We would suggest that the ANA measurement could be used in patients on 400 mg or more of acebutolol at one year as a warning guide similar to that suggested recently for hydralazine for detection of drug-induced lupus.⁶

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