Clinical evaluation of atenolol in hypertension

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Summary

1. Atenolol (ICI 66.082, Tenormin) is a new β-adrenoreceptor-blocking agent, devoid of intrinsic sympathomimetic and membrane-stabilizing properties. It does not cross the blood–brain barrier.

2. Atenolol given to hypertensive patients in initial open trials reduced arterial blood pressure significantly.

3. A double-blind comparison between atenolol and placebo in forty-five patients with essential hypertension demonstrated that atenolol gave a statistically significant reduction of blood pressure (Δ 28/15 mmHg, P < 0.005).

4. The optimum anti-hypertensive dose of atenolol in patients with mild to moderately severe essential hypertension was 200 mg daily.

5. Atenolol was compared with propranolol in thirty patients with essential hypertension. No statistically significant differences of anti-hypertensive effect were observed between the two drugs.

6. Long-term results (up to 2 years) in 117 hypertensive patients indicate that drug tolerance is good. No serious toxic effects were observed.

7. In four of twelve hypertensive patients with obstructive airways disease atenolol had to be withdrawn owing to deterioration of ventilatory function.

Key words: atenolol, β-adrenoreceptor antagonists, hypertension, obstructive airways disease, propranolol.

Introduction

Propranolol and other first-generation β-adrenoreceptor-blocking agents have been employed clinically for almost a decade. The widespread use of these agents in the treatment of hypertension stems partly from their effectiveness and partly from their comparatively good tolerability (Hansson & Werkö, 1976).

Atenolol, a new β-adrenoreceptor-blocking agent, would in theory seem to offer certain advantages over currently used first-generation agents of this type. We have therefore carried out a clinical evaluation of its usefulness in hypertension.

Methods

Pharmacology of atenolol

The pharmacological effects of atenolol (ICI 66.082, Tenormin), 4-(2-hydroxy-3-isopropylamino-propoy)phenylacetamide, have been investigated by Barrett, Carter, Fitzgerald, Hull & Le Count (1973). In brief, the important properties of this compound are: (a) cardioselectivity; (b) lack of intrinsic sympathomimetic properties; (c) lack of membrane-stabilizing effect; (d) inability to cross the blood–brain barrier.

Clinical trials

All the studies described here are multicentre trials performed at five medical centres in Sweden. (a) In our first clinical trial with atenolol an open design was used. Twenty hospitalized patients with essential hypertension were given atenolol up to 200 mg daily for 1 week.
The initial trial was followed by an open outpatient study comprising forty-three hypertensive patients given atenolol as the sole therapy for 4 weeks.

(c) Atenolol was then compared with placebo in a double-blind trial. Forty-five patients with essential hypertension were randomly allocated to treatment either with placebo or atenolol for three 4 weeks periods after an initial 4 weeks placebo period in both groups. The dose in the atenolol group was 50 mg twice daily, 100 mg twice daily and 200 mg twice daily respectively during each period of active therapy. Standing and recumbent blood pressure and heart rate were measured at the end of each 4 weeks period. Side effects were assessed by using a check list.

(d) Atenolol was compared with propranolol in a study comprising thirty patients with essential hypertensive patients with obstructive airways disease, nine of whom had bronchial asthma, two chronic bronchitis and one emphysema. Subjective as well as objective evaluations of ventilatory function (FEV1,0 and peak expiratory flow) were performed repeatedly during this trial.

Blood pressure

All blood pressures were recorded with mercury manometers attached to 13 cm × 30 cm cuffs. Blood pressure was recorded after 5 min rest recumbent and after 2 min standing.

Results

(a) In the initial in-hospital open trial the average reduction of recumbent blood pressure was 29/17 mmHg (P < 0.0005); standing blood pressure was reduced by 30/20 mmHg (P < 0.0005). Therapy was withdrawn in one patient owing to sinus bradycardia (45 beats/min) (Hansson, Åberg, Jameson, Karlberg & Malmcrona, 1973).

(b) In the open out-patient trial the average recumbent blood pressure fell from 170/105 mmHg to 141/88 mmHg (P < 0.0005) and standing blood pressure was reduced from 172/112 mmHg to 142/92 mmHg (P < 0.0005). Again side effects were few, consisting of sinus bradycardia (one), nausea (one) and fatigue (one) (Hansson, Henningsen, Karlberg, Åberg, Jameson, Malmcrona & Hersvall, 1974).

(c) The double-blind comparison between atenolol and placebo demonstrated statistically significant differences in blood pressure in the two groups. At the end of the trial recumbent blood pressure was 28/18 mmHg lower in the atenolol group (P < 0.0005), whereas the difference in standing blood pressure was 25/20 mmHg (P < 0.0005). Almost the same number of side effects were recorded during placebo periods as during atenolol therapy (59 vs. 61). Side effects did not increase in number as the dosage of atenolol was increased (Hansson, Åberg, Karlberg & Westerlund, 1975).

A within-patient comparison in the atenolol group showed that the optimum anti-hypertensive effect on recumbent blood pressure was obtained with a daily dosage of 200 mg.

(d) In the comparison between atenolol and propranolol no statistically significant differences in anti-hypertensive effect were observed, the average recumbent blood pressure with atenolol being 140/85 mmHg and with propranolol 142/87 mmHg (P > 0.1) (Hansson, Westerlund, Åberg & Karlberg, 1976).

(e) The long-term evaluation of atenolol in 117 hypertensive patients demonstrated that the anti-hypertensive effect was of the same order as in trials (a)–(c). Significant side effects were registered in twenty-six patients, causing withdrawal of atenolol treatment in six. The most common complaints were fatigue (six) and cold extremities (four). No oculocutaneous reactions of the practolol type were experienced (Hansson, Karlberg, Åberg & Westerlund, Jameson & Henningsen, 1976).

(f) Atenolol given to twelve hypertensive patients with obstructive airways disease reduced recumbent blood pressure by 33/20 mmHg (P < 0.0005). In four patients subjective and objective deterioration of the ventilatory function was observed, causing withdrawal of atenolol. These four patients all had bronchial asthma. The remainder tolerated atenolol well for observed periods up to 6 months (N. C. Henningsen, C. Hersvall, S. Jameson, L. Rosenhall & H. Åberg, unpublished observations).

Discussion

When making a clinical evaluation of any new drug
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a number of different approaches are conceivable. We have chosen a step-by-step technique when studying the anti-hypertensive effect of the new cardioselective β-adrenoreceptor-blocking agent atenolol. Thus, after initial open in-hospital and out-patient trials, a double-blind comparison with placebo as well as a comparison with propranolol have been made. Furthermore, in an attempt to evaluate the clinical importance of atenolol's cardioselectivity, twelve hypertensive patients with obstructive airways disease were treated.

These trials have all shown that atenolol has a useful anti-hypertensive effect, which is of about the same order as that of propranolol. Owing to its greater affinity to β₁-adrenoreceptors, atenolol was well tolerated in eight of twelve hypertensive patients with obstructive respiratory disease.

The optimum daily dose of atenolol in mild to moderately severe hypertension was found to be 200 mg. This has been recently confirmed by Petrie, Galloway, Webster, Simpson & Lewis (1975)

In order to evaluate tolerability and possible toxic effects, 117 hypertensive patients were treated with atenolol for up to 2 years in an ongoing long-term study. Side effects were relatively few and mild.

Thus it can be concluded that atenolol offers a useful anti-hypertensive effect combined with good patient tolerance.

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References


