Beta-Adrenergic Blockade in the Treatment of Exercise-Induced Paroxysmal Ventricular Tachycardia


Paroxysmal ventricular tachycardia of the type provoked by exertion or excitement is a rare condition well described by Wilson et al. in 1932. The circumstances under which paroxysms occur suggest that sympathetic stimuli are important in producing the arrhythmia. Responses to sympathetic stimuli have been classified by Ahlquist as either α-adrenergic or β-adrenergic. Chronotropic and cardiac arrhythmic effects are in the latter group and blockade of β-adrenergic responses is a rational approach to therapy.

The β-adrenergic blocking drug pronethalol (or nethalide) is effective in the treatment of some cardiac arrhythmias, particularly those induced by digitalis. This report describes the use of pronethalol in the treatment of a patient with exercise-induced paroxysmal ventricular tachycardia.

Case Report

A 34-year-old electrician complaining of palpitation on exertion was admitted to hospital on May 25, 1964. Nine years earlier he had first noticed a rapid heart action that came on suddenly while he was cutting wood. This episode passed off spontaneously after 2 days but he was unable to return to work for 2 months because minor exertion produced palpitation. He gradually improved although until 1962 episodes of palpitation lasting for several minutes occurred at about weekly intervals. During 1962 their frequency increased and he was given quinidine 0.2 Gm. three times daily. This produced some improvement initially but over the 6 months preceding admission, his symptoms became progressively more severe. Excitement or minor exertion brought on a rapid irregular heart action associated with retrosternal tightness at the onset, breathlessness, and faintness, and he was unable to work.

He had had acute nephritis in childhood. For 3 years he had occasional episodes of acute gouty arthritis from which his father also suffered. Physical examination was normal. His weight was 148 lb. and height 6'1". The heart was in regular rhythm and the blood pressure was 150/80 mm. Hg. There were no gouty tophi.

At rest the electrocardiogram showed very occasional isolated ventricular ectopic beats but was otherwise normal. After exercise there were runs of ventricular tachycardia of 6 to 20 consecutive beats separated by one or two beats of sinus or atrial origin (fig. 1). The proportion of ventricular to sinus beats gradually returned to normal with rest until regular sinus rhythm was restored after several minutes (fig. 1). The chest x-ray was normal, showing no cardiac enlargement. Renal function was slightly impaired; the urine contained 30 mg. per cent albumin but no abnormal cells, the blood urea was 58 mg. per 100 ml., and intravenous pyelography showed some delay in excretion. Serum uric acid was 10.3 mg. per 100 ml. (normal < 6 mg. per 100 ml.). Serum cholesterol, serum electrolytes, blood glucose, tests of liver function, I uptake, and basal metabolic rate were normal. Serologic tests for syphilis were negative.

Observations and Treatment of the Cardiac Arrhythmia

After quinidine was stopped for 1 week, exercise invariably provoked the arrhythmia. Over 7 days, 12 periods of exercise (Master's steps at 40 steps per minute) were given and each resulted in ventricular tachycardia in 1 to 6 minutes (mean 2.4 min.). When exercise was stopped, regular sinus rhythm returned between 1 and 12 minutes later (mean 3.9 min.). The arrhythmia was quite constant in pattern (fig. 1).

When pronethalol (100 mg. intravenously over 10 min.) was given prior to exercise, the arrhythmia was totally inhibited. On two occasions, 10

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*Kindly supplied as Alderlin by Imperial Chemical Industries, Limited; chemically 2-isopropylamino-1 (2-naphthyl)-ethanol hydrochloride.
minutes and 15 minutes of stepping, the last followed by running up and down seven flights of stairs, failed to provoke it (fig. 2).

Oral pronethalol, 100 mg, three times daily, was then commenced. Over the subsequent week nine periods of exercise were undertaken. In three of these, stepping for 15 minutes failed to produce an arrhythmia. In six, the arrhythmia appeared after 5 to 12 minutes of exercise. One episode lasted for 4 minutes but the others were greatly attenuated, consisting only of pairs of ventricular and sinus beats and lasting less than a minute. Very occasional ventricular ectopic beats could still be seen at rest. Side effects of pronethalol noted at first were nausea, blurred vision, tinnitus, vertigo, and insomnia. Minimal vertigo with sudden head movements has persisted over 5 months. The patient still feels a lack of need for sleep but the other side effects disappeared after 2 weeks.

After a week on oral pronethalol the patient was discharged from hospital taking 100 mg. four times daily. He returned to work as an electrical fitter and over the next 5 months was able to do heavy work and exercise. During this time he had three episodes of tachycardia, each lasting about 6 minutes. One occurred while he was showering and the other two were apparently unrelated to exertion. Exercise for 15 minutes throughout this period did not bring on an arrhythmia.

It was considered that there may have been a spontaneous or induced remission over the 5 months of treatment so that on November 6, 1964, pronethalol was stopped. He was well until November 19, when he had two episodes lasting several minutes. Next day paroxysms occurred repeatedly when he attempted to work and later in the day it was found that ventricular tachycardia could be produced by 1 minute of exercise. Another approach to therapy, the depletion of myocardial catecholamines by reserpine, was then tried. After 2 weeks on reserpine 0.25 mg, three times daily he was still inconvenienced.
by paroxysms of tachycardia, although they were less than when he was without therapy. He also had several episodes of distressing bradycardia, the nature of which was not documented. He was tired and breathless with moderate exertion, so that on December 6 reserpine was stopped. Pronethalol was recommenced with good effect. Because of the carcinogenic effect of high pronethalol dosage in mice the feasibility of long-term therapy is uncertain and it is proposed to replace pronethalol by the recently developed similar drug, propanalol, which is free from this effect.

Discussion

Patients without evidence of structural heart disease make up only 10 per cent of cases of ventricular tachycardia and, in some of these, episodes may be related to exercise, emotion, or smoking.

Subjects having very frequent paroxysms regularly induced by exertion or excitement are much less commonly seen. Wilson et al. described three patients and reviewed 10 or more others less well documented. Cases have also been included in group reports or in single case reports.

Our patient conforms closely to Wilson's description. There is no evidence of organic heart disease and the patients are often young. Moderate exertion almost invariably produces an attack consisting of a rapid succession of short bursts rather than long attacks, although the latter, lasting for hours or days, may occur. During rest after exercise, the bursts decrease in length and frequency and normal sinus rhythm gradually returns, usually with ventricular ectopic beats having a configuration similar to those during paroxysms. Because of the relation of the arrhythmia to exertion the patient may be considerably incapacitated. Examination at rest may give no indication of the nature of the condition and it is easily overlooked. The prognosis and response to treatment are variable. The disorder may last for many years; both complete remission and sudden death have been recorded.

Treatment with quinidine is not entirely satisfactory. In the cases of Wilson et al., attacks became less frequent, but could still be induced by exertion and one of their patients died suddenly after discharge from hospital. The patient reported by Dimond and Hayes did not benefit.

Wilson et al. postulated that the condition described here is due to unusual sensitivity of the heart to sympathetic stimulation. The known increased sympathetic system activity during exercise, the ability of sympathomimetic drugs to produce ventricular arrhythmias, and the increased rhythmicity of potential ventricular pacemakers with ad-
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renergic stimulation of the heart support this concept. In these subjects ventricular ectopic beats are usually present at rest, although they may be infrequent. Since the focus is the same, it seems likely that adrenergic stimulation of the ventricular focus is responsible for the onset of ventricular tachycardia.

The effectiveness of pronethalol in the case described and in reversing digitalis arrhythmias in which adrenergic stimuli appear to be involved suggests that the antiarrhythmic action of pronethalol is closely related to the property of \( \beta \)-adrenergic blockade. The mechanism has been further elucidated by the finding that pronethalol reduces the depletion of intracellular potassium produced by a cardiac glycoside in dogs. This is consistent with a reduction of permeability of the myocardial cell membrane to cation fluxes, analogous to the membrane effect of quinidine. Quinidine has some \( \beta \)-blocking activity and both pronethalol and quinidine have local anesthetic action. These common properties are also shared by other antiarrhythmic drugs to varying extent. When adrenergic stimuli play a large part in producing an arrhythmia, as in the case described here, the most effective antiarrhythmic drug would be expected to be one having a strong \( \beta \)-adrenergic blocking action.

Summary

The \( \beta \)-adrenergic blocking drug pronethalol was effective in the treatment of a patient with exercise-induced paroxysmal ventricular tachycardia. Adrenergic stimuli are considered important in initiating this arrhythmia. The mode of action of pronethalol is briefly discussed in relation to other antiarrhythmic agents.

References

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