Preliminary study of the efficacy of xamoterol in bradycardia-tachycardia syndrome

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Following 4 weeks on placebo, eighteen patients with bradycardia-tachycardia syndrome (BTS) were treated with 100 mg xamoterol twice daily for 2–4 weeks. Ambulatory 24 h Holter electrocardiogram recordings showed that xamoterol decreased maximum heart rate from 140 ± 5.1 to 107 ± 6 beats min⁻¹ (P < 0.001) during exercise, increased minimum heart rate from 43 ± 1.7 to 51 ± 2.4 beats min⁻¹ (P < 0.005) at night and shortened maximum duration of sinus arrest from 3438 ± 484 to 1767 ± 202 ms (P < 0.005) in BTS. Symptomatically, patients reported that palpitations were improved and syncopal attacks disappeared. Although the study has the limitation of an open design, effects of treatment were objectively evaluated using Holter monitoring by investigators who reviewed the recordings in a blinded manner. The findings suggest that xamoterol may be useful in the treatment of BTS. Further studies are needed to evaluate fully its therapeutic potential in this condition.

Keywords bradycardia-tachycardia syndrome β-adrenoceptor partial agonist

Introduction

The pathophysiology of bradycardia-tachycardia syndrome (BTS) has not yet been fully elucidated. Syncopal attacks and dizziness, or occasional seizures, are associated with decreased cerebral blood flow due to bradycardia, while palpitations and chest pain associated with ischaemic changes may develop during episodes of tachycardia. In particular, syncopal attacks are frequent in BTS and require treatment. Drug therapy is usually ineffective. One of the therapeutic strategies for BTS is the use of antiarrhythmic drugs to prevent tachycardia after the implantation of a pacemaker to control bradycardia or sinus arrest [1]. An ideal drug therapy for the disease should prevent episodes of bradycardia and tachycardia without the necessity of implanting a pacemaker.

Xamoterol is a β₁-adrenoceptor partial agonist. Animal experiments showed that the drug modified the response of the heart to the prevailing sympathetic activity. It provides a modest degree of positive inotropic support both at rest and exercise, but as a consequence of its occupancy of the β-adrenoceptor, prevented the excessive stimulatory effects of catecholamines which could cause excessive tachycardia [2]. The drug has positive inotropic and chronotropic actions at rest, while the tachycardia during maximum exercise is attenuated [3].

The present study was conducted to evaluate the efficacy of xamoterol [4] in patients with BTS.

Methods

Eighteen out-patients (nine male, nine female, aged 37–78 years) with BTS gave their informed consent to take part in the study, which was approved by the hospital Ethics Committee. Some of the patients had associated mild or moderate heart failure (using New York Heart Association definitions: NYHA Class II, n = 7; NYHA Class III, n = 5) while the remainder had no symptoms of heart failure. Regarding the underlying cardiac pathology, six patients had ischaemic heart disease, four had valvular disease, two were hypertensive, one had an idiopathic cardiomyopathy while the remaining five patients had no obvious pathology. Fourteen patients were in sinus rhythm and four patients...
had atrial fibrillation. BTS was diagnosed by subjective symptoms and confirmed by a 24 h Holter ambulatory electrocardiogram. The electrocardiographic criteria were persistent sinus bradycardia with 50 beats min\(^{-1}\) or less, sinoatrial block, or sinus arrest together with paroxysmal supraventricular tachycardia (100 beats min\(^{-1}\) or more) or paroxysmal atrial fibrillation. Nine patients also underwent an overdrive suppression test. Drug therapy had been used unsuccessfully in 11 patients before entry to the study.

After a 4 week single-blind placebo run-in period, xamoterol (100 mg twice daily) was given for 2-4 weeks. Ambulatory 24 h Holter electrocardiograms were recorded and assessed by observers who were blinded to the treatment status of the patients. Changes in subjective symptoms were ascertained by questioning the patients. Data are expressed as the mean ± s.d. and statistically analysed by paired \(t\)-tests (\(P < 0.05\) regarded as significant).

### Results

Mean total heart beats were increased by xamoterol from 97 007 ± 3767 beats day\(^{-1}\) on placebo to 98 169 ± 5409 beats day\(^{-1}\) (NS). During xamoterol, the longest duration of sinus arrest decreased from 3438 ± 484 to 1767 ± 202 ms (\(P < 0.005\), Figure 1), the mean maximum heart rate decreased from 140 ± 5.1 to 107 ± 6 beats min\(^{-1}\) (\(P < 0.001\), Figure 2), the mean minimum heart rate increased from 43 ± 1.7 to 51 ± 2.4 beats min\(^{-1}\) (\(P < 0.005\), Figure 2), and the mean number of premature ventricular contractions decreased from 709 ± 392 to 473 ± 322 beats day\(^{-1}\) (NS). During xamoterol treatment, atrial fibrillation disappeared in two patients, normal sinus rhythm changed to atrial fibrillation in one patient, and first degree AV block appeared in another patient. Abnormal ST-T segments did not appear or worsen in any of the patients during xamoterol treatment.

Systolic blood pressure increased from 126 ± 3.7 mm Hg before treatment with xamoterol to 131 ± 3.1 mm Hg during treatment (\(P < 0.05\)), and diastolic blood pressure from 73 ± 2.0 to 75 ± 2.0 mm Hg (NS).

Palpitations were reported by twelve patients before treatment; during xamoterol treatment, palpitations disappeared in nine of the twelve, but another patient developed palpitations after starting xamoterol not having experienced them previously. In six patients with syncopal attacks before xamoterol, the attacks disappeared in four while the remaining two patients continued to report dizziness although there were no episodes of syncope. Of eight patients who had complained of dizziness before treatment, this disappeared in seven. Of three patients who had experienced anginal pain before treatment, it disappeared in

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**Figure 1** Duration of the longest pauses (s) during treatment with xamoterol and placebo.

**Figure 2** Changes in maximum heart rate (●) and minimum heart rate (○) during treatment with xamoterol and placebo.
two and was improved in one patient. Five patients who had shown improvement in electrocardiographic findings and symptoms continued to be treated with xamoterol after the study, the mean duration of xamoterol therapy being 152 days (range 47–200). The initial benefit from xamoterol was maintained during this long-term administration. No adverse events were observed during the study and no patients reported worsening in their symptoms.

Discussion

Any identifiable and treatable underlying disease which causes BTS should be corrected. These include digitalis intoxication, hyperthyroidism, or valvular diseases which require surgical correction. In the majority of cases, however, the aetiology of BTS is unknown and treatment therefore has to be symptomatic, especially if syncopal attacks occur. Surawicz & Redy [5] reported three possible mechanisms of BTS: 1) tachycardia induced by bradycardia, 2) bradycardia induced by tachycardia, and 3) bradycardia developing independently. In most patients, however, both are present and need to be treated.

An electrophysiological study showed that xamoterol shortened sinoatrial conduction time and atrial-his (A-H) intervals significantly, shortened the effective refractory period and the functional refractory period in the atrioventricular junction, but did not affect sinus rhythm, A-V intervals, nor QT interval [6]. In some patients with sick sinus syndrome, chronic treatment with xamoterol produced improvement in ambulatory 24 h electrocardiogram recordings [7]. This present study has also shown that xamoterol decreased maximum heart rate during exercise, increased minimum heart rate at night, and shortened the maximum duration of sinus arrest. In most patients these objective findings were accompanied by symptomatic improvement; palpitations were improved, and syncopal attacks disappeared. These results confirm that the β1-selective partial agonist xamoterol acts as an antagonist when the sympathetic tone is high (e.g. during exercise) and as an agonist action when the sympathetic tone is low. The data suggest that xamoterol might be useful for patients who predominantly have tachycardia or sinus arrest, and may make it an alternative to pacing in patients with mild forms of BTS. The positive findings from this small study and other studies provide a basis for larger, controlled studies to establish the utility of xamoterol in the management of patients with this disabling condition.

References


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