Profound hypotension after the first dose of ketanserin

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Summary: Two patients developed profound hypotension approximately one hour after taking an initial oral dose of ketanserin 40 mg. The reaction appeared similar to that reported with prazosin, and may have been due to the α_1 -adrenoceptor antagonist action of ketanserin. Both patients were taking regular β -blocker therapy, which may exacerbate such a reaction.

Introduction

Ketanserin is a selective antagonist at 5-hydroxytryptamine 2 (S_2) receptors which also has α_1 -adrenoceptor antagonist activity. In hypertensive patients it lowers blood pressure with no significant orthostatic effect.¹ The relative roles of S_2 and α_1 -adrenoceptor antagonism in its antihypertensive action in man are uncertain.^{2,3} Alpha₁-adrenoceptor antagonists such as prazosin occasionally cause a first dose reaction,⁴ due to an unpredictably large fall in standing blood pressure. This phenomenon was not observed in one study of 21 hypertensive patients who were given doses of 20 or 40 mg ketanserin.⁵ However, marked symptomatic hypotension has been reported after a 10 mg intravenous injection of ketanserin⁶ and after 60 mg oral dosage.⁷ We report severe hypotensive reactions in two patients following treatment with a first dose of ketanserin 40 mg. Both patients had consented in writing to participate in formal studies which had been approved by the hospital ethics committee.

Case reports

Case 1

A 65 year old woman with a 14 year history of hypertension, but no evidence of ischaemic heart disease, had been treated with atenolol 100 mg and bendrofluazide 5 mg daily, and had taken these drugs

on the day of the reaction. During a study investigating the pharmacokinetics of ketanserin in hypertensive patients she was given ketanserin 40 mg orally after an overnight fast, and was observed supine in the laboratory. Blood pressure and heart rate were measured by a Dinamap 845 semi-automated recorder. Before taking ketanserin her blood pressure was 154/96 mm Hg and heart rate 66/minute. After 50 minutes she became pale, nauseated and faint. Although she remained supine she lost consciousness briefly, but recovered before any action was required. Blood pressure had fallen to 74/50 mm Hg and she had a bradycardia of 43/minute (Figure 1). Electrocardiographic monitoring showed no arrhythmia and

Figure 1 Effect of 40 mg single dose of ketanserin on blood pressure and heart-rate (Case 1). ●—●, systolic blood pressure; ■—■, diastolic blood pressure; ○.....○, heart-rate.

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serial 12-lead electrocardiograms showed no abnormality. Twenty minutes after the syncopal episode her blood pressure had risen to 120/68 mm Hg and she felt better. However, nausea and drowsiness persisted for 6 hours, after which she recovered completely.

Case 2

A normotensive 62 year old man had a 15 month history of chronic stable angina, but no evidence of previous myocardial infarction. His usual treatment was atenolol 100 mg daily and isosorbide dinitrate 5 mg b.d., and he had taken both drugs on the morning of the reaction. He continued to experience angina despite this treatment, and entered a study designed to examine the anti-anginal effect of ketanserin when added to beta-blocker therapy.⁸ He received 40 mg ketanserin orally after an overnight fast. Prior to this his standing blood pressure was 118/84 mm Hg and heart rate 70/minute. After 50 minutes he complained of dizziness and was noted to be pale. Standing blood pressure had fallen to 60/0 mm Hg and his heart rate was 43/minute. After resting in the supine position for 20 minutes his blood pressure had recovered to 114/70 mm Hg. He became drowsy and slept for 2 hours, and then felt completely well. Electrocardiographic monitoring and 12-lead electrocardiograms showed no arrhythmias or acute ischaemia.

Discussion

The reactions to the first dose of ketanserin experienced by these two patients were very similar as regards time of onset (50 minutes), the occurrence of profound hypotension and bradycardia, and the presence of persistent drowsiness. The onset of the reaction coincided with the time that the plasma ketanserin concentration usually reaches its peak.⁹ We have observed a

similar reaction in a third patient after a first dose of 40 mg ketanserin, but blood pressure was not measured during the episode.

These reactions appear very similar to those reported after the first dose of prazosin and may be related to the α_1 -antagonist activity of ketanserin. Prazosin reactions are usually preceded by a slowing of the heart rate, and the ability to maintain a reflex tachycardia may be important in preventing syncope.¹⁰ The patients we describe were both taking atenolol and it is known that concomitant administration of a β -adrenoceptor antagonist reduces this reflex response.¹¹ Prazosin reactions are generally more severe in patients pre-treated with a β -blocker.¹²

Hosie & Gould⁵ did not observe any first dose reaction in 21 patients given an initial dose of 40 mg ketanserin. However, the 95% confidence limit for an observed incidence of 0/21 is 14%,¹³ so this problem could be quite common despite the negative finding. It also should be noted that their patients were given ketanserin alone. Other workers have observed severe hypotension following intravenous ketanserin 10 mg⁷ and in two of 10 patients given a 60 mg oral dose.⁷ We have not observed this reaction in 51 patients who started ketanserin at a dose of 20 mg. This does not exclude the possibility of initial reactions to this dose. The true incidence could be as high as 6%, which is the 95% confidence limit for an observation of 0/51.¹³ We suggest that initial doses of ketanserin higher than 20 mg should be avoided, and that the suitability of a 20 mg starting dose should be examined in a large population of patients, particularly those treated with a β -blocker.

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