Prolongation of the QT interval by ketanserin

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Summary: In hypertensive patients single doses of ketanserin 40 mg prolonged the corrected QT interval (QT_c) for at least 8 hours, with a maximal increase of 35 ms ($P < 0.001$, $n = 6$) after 2 hours. During chronic dosing (20 and 40 mg b.d.) the QT_c was further prolonged, by 46 and 45 ms respectively. QT_c prolongation after treatment with a mean dose of 73 mg/day for 7 weeks ($n = 26$) was significantly related to body weight ($r = -0.58$, $P < 0.01$), and to the dose of ketanserin corrected for body weight ($r = 0.63$, $P < 0.01$), but not to plasma concentrations of ketanserin, ketanserinol, potassium or calcium. High doses of ketanserin (mean dose 167 mg/day, $n = 9$) increased the QT_c by 40 ms ($P < 0.001$), with prolongation of up to 80 ms in individual patients. Treatment with ketanserin at doses proposed for clinical use (40–80 mg/day) may carry a risk of ventricular arrhythmias.

Introduction

Ketanserin is a selective antagonist of serotonin (5-hydroxytryptamine, 5-HT) at 5-HT₂ receptors which is currently being evaluated for the treatment of hypertension,^{1,2} intermittent claudication^{3,4} and Raynaud's phenomenon.⁵ It prolongs the corrected QT interval on the electrocardiogram (ECG) of healthy subjects.⁶ Drug-induced QT prolongation may predispose to serious ventricular arrhythmias, particularly the polymorphous form of ventricular tachycardia known as torsade de pointes.⁷ We have examined the influence of ketanserin on the QT interval of 81 patients with hypertension or intermittent claudication who participated in three studies. Our aims were to confirm that ketanserin prolonged the QT interval; to examine the time-course of the phenomenon after single doses and during chronic treatment; to determine whether the effect was dose-dependent; and to explore the relation of QT prolongation to plasma drug concentration and other variables such as body weight.

Materials and methods

All patients gave written informed consent to the studies which were approved by the hospital ethics

committee. The protocols are described in the results section for clarity of presentation. No patient was taking any drug which causes pronounced prolongation of the QT interval, and drug therapy other than ketanserin or placebo was held constant throughout all three studies. Patients with important hepatic or renal dysfunction were excluded.

In each patient the QT interval was measured from a single lead (usually lead II), recorded at a paper speed of 50 mm/s, as the time from the first deflection of the QRS complex to the point where a tangent drawn along the descending limb of the T wave crossed the isoelectric line. U waves were excluded. All measurements were made by a single observer who was unaware of the treatment taken or sequence of traces, to avoid bias. The QT interval was corrected for heart rate using Bazett's correction.⁸ Because of controversy over the most appropriate method of correcting the QT interval for heart rate⁹ a further method of analysis was used in Study 2, the largest of the three studies. The relations between the uncorrected QT interval and the R–R interval were compared in ketanserin and placebo-treated patients by linear regression. The slopes of the regression lines were constrained to be parallel¹⁰ and the intercepts for ketanserin and placebo treatment were compared. A significant difference between the intercepts in this analysis indicates a difference in QT interval which is independent of heart rate and any correction factor.

Blood was taken for assay of plasma concentrations of ketanserin and its major metabolite ketanserinol, at the time of each QT interval

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measurement. Samples were stored at -20°C prior to assay by high performance liquid chromatography with fluorescence detection. R 46594 (Janssen Pharmaceutica, Beerse) was used as an internal standard. The limit of detection of the assay was 1 ng/ml and the coefficients of variation were 5.0% (ketanserin) and 2.7% (ketanserinol) at a concentration of 200 ng/ml. Serum potassium and calcium concentrations were measured before treatment and at the final assessment. Serum calcium values were corrected for serum albumin concentration.

Histograms and normal probability plots suggested that the data were normally distributed. Values for plasma ketanserin and ketanserinol concentrations were log-transformed before analysis. The statistical methods used were paired *t*-tests, analysis of variance and multiple linear regression.

Results

Study 1

Protocol Six patients with essential hypertension (3 men, 3 women; mean age 59.8 years) were given a single oral dose of 40 mg ketanserin and changes in the QT_c interval were assessed over the next 8 hours. The patients were then treated with ketanserin 20 mg b.d. for 4 weeks, and changes in the QT_c interval were examined for 4 hours following the morning dose. They were subsequently treated with ketanserin 40 mg b.d. for 4 weeks and the same procedure was repeated.

Results The changes in QT_c and mean plasma drug concentrations after a single 40 mg dose of ketanserin are shown in Figure 1. The QT_c averaged 401 ms before dosing, increased by 26 ms ($P < 0.01$) after 1 hour, reached a maximum increase of 35 ms ($P < 0.001$) at 2 hours, and remained significantly prolonged after 4 and 8 hours. Plasma concentrations of ketanserin and ketanserinol peaked after 1 and 2 hours respectively and paralleled the increased in QT_c interval (Figure 1). The findings at steady-state after four weeks of treatment are shown in Figure 2. During treatment with ketanserin 20 mg b.d. the QT_c was increased by 19 ms (not significant) before the morning dose, and lengthened to a maximum increase of 46 ms ($P < 0.01$) four hours after dosing. After four weeks' treatment with ketanserin 40 mg b.d. QT_c prolongation before dosing was 24 ms (not significant), increasing further to 45 ms ($P < 0.01$) at 4 hours. Change in QT_c interval was weakly but significantly correlated with plasma ketanserin

concentration ($P = 0.48$, 95% CI 0.21, 0.75) and plasma ketanserinol concentration ($P = 0.54$, 95% CI 0.27, 0.81).

Comment Single doses of ketanserin increased the QT_c interval substantially and the effect was more pronounced during chronic dosing. At steady-state the degree of lengthening varied markedly during the dose interval, with a two fold difference in QT_c

Figure 1 (a) Changes in QT_c interval (ms) after a single 40 mg dose of ketanserin (●). (b) Plasma concentrations of ketanserin (○) and ketanserinol (Δ) after a single 40 mg dose of ketanserin. Mean and s.e.m. data ($n = 6$). * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

Figure 2 Changes in QT_c interval (ms) from pre-treatment values at steady-state during treatment with ketanserin 20 mg b.d. (●) and 40 mg b.d. (○). Mean and s.e.m. data ($n=6$). * $P<0.05$; ** $P<0.01$; *** $P<0.001$.

interval prolongation between pre-dose and 4-hour values. Changes in QT_c interval were not clearly dose-dependent in this study, perhaps because of the small sample-size. They were only weakly correlated with plasma concentrations of ketanserin or ketanserinol, but followed a similar time-course to plasma drug and metabolite concentrations.

Study 2

Protocol Fifty-four hypertensive patients (33 men,

21 women, mean age 50.4 years) were randomly allocated to treatment with ketanserin ($n=26$) at a mean daily dose of 73 mg or to matching placebo ($n=28$), each for 7 weeks. The QT_c interval, plasma drug concentrations, serum potassium and serum calcium were measured at entry and at the final visit, 14 hours after dosing. The observations therefore correspond to the pre-dose 'trough' measurements in Study 1.

Results The mean QT_c interval was similar in the two treatment groups at entry (ketanserin 420, s.d. 23 ms; placebo 410, s.d. 27 ms). Compared to placebo, ketanserin increased the QT_c interval by 14 ms (95% CI +4, +24 ms, $P<0.01$). The patients had been stratified into three sub-groups according to existing treatment (no treatment, bendroflumazide 5 mg/day, or atenolol 100 mg/day), and QT_c interval prolongation was not significantly different whether ketanserin was used as monotherapy or added to a diuretic or β -blocker (mean increases 13.6 ms, 9.1 ms and 20.3 ms respectively). In all ketanserin-treated patients ($n=26$) the change in QT_c interval was negatively correlated with body weight ($r=-0.58$, $P<0.01$, Figure 3). QT_c interval prolongation was observed particularly in women, who weighed less than men. After adjustment for weight, sex and age ketanserin still prolonged the QT_c interval significantly compared to placebo, by a mean of 15 ms (95% CI +5, +25 ms, $P<0.01$). The increase in QT_c interval was significantly related to the dose of ketanserin when corrected for body weight ($r=0.63$, $P<0.01$, Figure 4). There was no significant relation between plasma drug or metabolite concentrations and QT_c prolongation. Serum potassium and calcium concentrations did not alter during the study and were not related to changes in the QT_c interval.

The relation of uncorrected QT interval to R-R interval was examined by linear regression to ensure that the findings described above were independent of Bazett's correction (see Methods). There was a significant difference of 22 ms ($P<0.02$) between the intercepts for ketanserin and placebo (Figure 5), indicating that ketanserin prolonged the QT interval by 22 ms independent of heart rate.

Electrocardiograms with QT_c prolongation frequently showed T wave flattening, and in some cases the T wave was bifid, independent of the U wave (Figure 6). There was no change in QRS duration and thus QT interval prolongation resulted from lengthening of the JT segment.

Comment Ketanserin treatment prolonged the QT_c interval significantly, by a mean of 14 ms when measured 14 hours after dosing. This pre-dose

Figure 3 Relation of change in QT_c interval after ketanserin treatment and body weight ($n=26$). $\Delta QT_c = 0.066 - 0.0007 \text{ weight}$; $r = -0.58$, $P < 0.01$.

Figure 4 Relation of QT_c interval and dose of ketanserin ($n=26$). $\Delta QT_c = 0.0607 \text{ dose} - 0.017$; $r = 0.63$, $P < 0.01$.

Figure 5 Relation of uncorrected QT and R-R intervals after parallel constraint during treatment with ketanserin ($n=26$) and placebo ($n=28$). Ketanserin: $\bullet$ —; $QT = 0.262 + 0.165 \text{ R-R}$. Placebo: + ----; $QT = 0.240 + 0.165 \text{ R-R}$. Difference between intercepts = 0.22 ms. $P < 0.02$.

increase is likely to be doubled 4 hours after dosing, as shown in Study 1. QT_c prolongation was related to body weight, and the regression equation predicts substantial prolongation (30 ms or more) in those weighing 50–60 kg, but no increase in those weighing 90–100 kg. Lengthening of the QT_c interval with ketanserin was dose-dependent. A dose of 1.6 mg/kg/day increased the QT_c interval by an average of 30 ms 14 hours after dosing, whereas a dose of 0.6 mg/kg/day caused no change. Increases in the QT_c were unrelated to concentrations of ketanserin, ketanserinol, potassium or calcium in blood.

Study 3

Protocol Twenty-one patients with intermittent claudication (14 men, 7 women, mean age 59.8 years) were randomly allocated to ketanserin, mean dose 167 mg/day or placebo, each given for 3 months. The QT_c interval was measured 2–4 hours after dosing.

Results The two treatment groups were well-matched at entry as regards QT_c interval (ketanserin 412, s.d. 39 ms; placebo, 408, s.d. 42 ms). The mean increase in QT_c interval with ketanserin, compared to placebo was 40 ms (95% CI +7, +73 ms, $P < 0.001$). The largest individual increase observed was 80 ms.

Comment These data confirm marked prolongation of the QT_c interval with high doses of ketanserin. They also show that the effect is persistent for at least three months.

Discussion

These studies confirm a previous report⁶ that ketanserin prolongs the QT_c interval. Substantial QT_c prolongation was observed after a single oral dose of 40 mg, and it became more marked during chronic dosing with 20 mg or 40 mg ketanserin twice daily. Prolongation of the QT_c varied markedly during the dose interval, with maximum increases four hours after dosing which were approximately double those observed at the end of a dose interval. Prolongation of the QT_c interval was related to the dose of ketanserin corrected for body weight. It was not related, or at most weakly related, to plasma concentrations of ketanserin or its metabolite ketanserinol, a finding that contrasts with observations made during treatment with amiodarone¹¹ and sotalol.¹² Lengthening of the QT_c interval was associated with T wave flattening

Figure 6 Electrocardiograms taken before and during treatment with ketanserin, showing prolongation of the QT interval. Note that this is independent of the U wave.

and changes in T wave morphology similar to those reported with amiodarone.¹¹ Ketanserin-induced prolongation of the QT_c was observed when the drug was prescribed as monotherapy, and when it was added to thiazide diuretic or β -blocker therapy. It was not related to serum potassium or calcium concentrations. Extreme QT_c prolongation, up to 80 ms, was observed at high doses of ketanserin.

Drugs which prolong the QT interval substantially may predispose patients to serious cardiac arrhythmias, particularly the form of ventricular tachycardia known as torsade de pointes.⁷ Ketanserin may be introduced for the treatment of hypertension in the near future, and the dose proposed is 40–80 mg/day. The results presented here suggest that a dose of 80 mg/day would prolong the QT_c interval by an average of 30 ms in a patient weighing 50 kg when it is measured 14 hours after dosing. In such a patient the expected increase four hours after dosing would be around 60 ms. We have not observed arrhythmias during ketanserin treatment, but as far as we are aware all drugs which prolong the QT

interval to this extent have been associated with serious arrhythmias. Four cases of ventricular arrhythmias during treatment with ketanserin have already been reported.^{13,14} If ketanserin does become available for use in hypertension it will be prescribed to patients with a high prevalence of heart disease, and it may be prescribed with other drugs which prolong the QT interval. The risk of arrhythmias needs to be quantitated in a large population of patients before it comes into general use. Meanwhile, patients treated with ketanserin should have their QT interval monitored regularly, and should not be treated with other drugs known to prolong the QT interval.

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