COMT inhibition with nitecapone does not affect the tyramine pressor response

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Nitecapone (OR-462) is a new selective COMT inhibitor with gastroprotective properties. The aim of the present study was to determine whether nitecapone potentiates the haemodynamic effects of a tyramine-induced increase in catecholamine release. The systolic blood pressure response to tyramine was studied in 11 healthy male volunteers (age 20–32 years). Tyramine was given i.v. as rapid bolus injections in increasing doses without drug intake and after oral intake of single doses of 25 mg and 100 mg of nitecapone. The tyramine dose required to increase systolic blood pressure by 30 mm Hg ('pressor dose') was 4.98 mg, 5.04 mg and 4.88 mg after no medication, and with 25 mg and 100 mg of nitecapone, respectively. There were also no differences in the systolic blood pressure response vs time curves between the three regimens. COMT inhibition with nitecapone did not potentiate the haemodynamic responses to tyramine-induced catecholamine release.

Keywords nitecapone COMT inhibition tyramine blood pressure

Introduction

Nitecapone (OR-462) (3-(3,4-dihydroxy-5-nitrobenzylidene)-2,4-pentanedione) is a new, highly potent and selective catechol-*O*-methyltransferase (COMT) inhibitor with gastroprotective properties (Nissinen *et al.*, 1988). Studies in healthy volunteers have shown nitecapone to inhibit effectively COMT activity in erythrocytes and in the gut wall (Gordin *et al.*, 1989; Schultz *et al.*, 1991).

Catecholamines (especially noradrenaline and adrenaline) have marked haemodynamic and metabolic effects. Released catecholamines are eliminated by (1) enzymatic inactivation (deamination by MAO, methylation by COMT and conjugation by phenolsulphotransferase), (2) neuronal and extraneuronal uptake, and (3) by renal clearance (Cooper *et al.*, 1986). The effects of COMT inhibition on catecholamine-mediated responses are largely unknown in man. In theory these responses might be potentiated in conditions where catecholamine release is increased. In a previous study we found that nitecapone did not significantly affect the haemodynamic responses and catecholamine concentrations during exercise, when catecholamine release is increased (Sundberg *et al.*, 1990). The aim of the present study was to determine whether nitecapone increases the pressor response to tyramine which releases noradrenaline from adrenergic nerve endings.

Methods

The study was an open, single-dose, within subject controlled study. The mean age of the 11 healthy male subjects who participated in the study was 25 years (range 20–32).

Before the start of the study the purpose and course of the study were explained both verbally and in writing to the subjects, and they signed a letter of consent. The study followed the guidelines of the Declaration of Helsinki.

A statement of the Ethics Committee of Orion Pharmaceutica was obtained.

The subjects were not allowed to eat tyramine-rich food for 3 days before or during the study, or to take any other medication. The subjects came to the laboratory at about 08.00 h. A cannula was inserted into an antecubital vein and patency of the catheter was assured by a slow constant drop of isotonic saline.

On the first trial day, no nitecapone was given. At 08.30 h, 2 ml isotonic saline was given to the subjects in the supine position as a rapid bolus injection. About 10 min thereafter another rapid bolus injection, containing 0.5 mg tyramine, was given. The following tyramine injection was given when the systolic blood pressure had returned to the basal level ± 5 mm Hg, but not earlier than 10 min after the preceding injection. The

tyramine dose was increased until the systolic blood pressure had increased by 30 mm Hg, whereafter the study was discontinued. The tyramine doses used were 0.5, 1, 2, 3, 4 and 6 mg, all in a solution of 2 ml isotonic saline.

On the second trial day the subjects were given 25 mg and on the third day 100 mg nitecapone orally 30 min before the first bolus injection. In other respects the study design was the same as on the first trial day.

After each tyramine injection blood pressure and heart rate were measured at 1 min intervals. ECG was continuously monitored on an oscilloscope (lead II). Blood pressure and heart rate were measured in the supine position from the non-cannulated hand using an automatic device (Accutracker II, Suntech Medical Instruments, Raleigh, USA).

Linear regression ($y = ax + b$) between the logarithm of the dose and systolic blood pressure was calculated by the least square method (Pace *et al.*, 1988). The tyramine dose required to increase the systolic blood pressure by 30 mm Hg ('pressor dose') was calculated by substituting 30 mm Hg for y (change in blood pressure) and solving for x (logarithm of the dose). The anti-logarithm of x was the estimated 'pressor dose'.

Statistical analysis of the 'pressor dose'-values was made with the univariate repeated measures analysis of variance, where medication was treated as a within subjects factor. A P value < 0.05 was considered statistically significant.

Results

Neither 25 nor 100 mg of nitecapone significantly affected the systolic blood pressure response to tyramine. The tyramine doses required to increase systolic blood pressure by 30 mm Hg were 4.98 mg (s.d. ± 0.95), 5.04 mg ($\pm$

1.33) and 4.88 mg (± 1.01) with no medication, and with 25 mg and 100 mg of nitecapone, respectively. Figure 1 shows the systolic blood pressor responses after 3 and 6 mg of tyramine. The pressor response is almost identical with no medication, and with both doses of nitecapone, after 3 and 6 mg tyramine. The peak pressor response usually coincided with a marked flattening of the T-wave in the ECG, followed by a small decrease in heart rate of about 5–7 beats min^{-1} after the highest doses of tyramine.

Only small changes in the diastolic blood pressure could be seen. The diastolic pressure increased maximally by 5–7 mm Hg and the increases were similar with no medication, and with 25 mg and 100 mg nitecapone.

Discussion

In the present study we evaluated whether COMT inhibition with nitecapone modifies the haemodynamic responses to tyramine-induced increase in catecholamine release. The tyramine pressor response test has been extensively used to evaluate the pressor effect of drugs interfering with catecholamine metabolism (Colombo *et al.*, 1988; Korn *et al.*, 1988; Pickar *et al.*, 1981).

Tyramine is a monoamine that displaces noradrenaline from adrenergic nerve endings, thus mimicking sympathetic stimulation and indirectly causing a rise in systolic blood pressure in a dose-dependent manner (Davey & Farmer, 1963).

If nitecapone potentiates the tyramine-induced pressor response, lower 'pressor doses' should be obtained after administration of nitecapone, i.e., smaller amounts of tyramine are needed to give the same pressor response when nitecapone is present. However, the 'pressor dose' was similar both after 25 and 100 mg nitecapone in comparison with the values without nitecapone.

With regard to other haemodynamic effects of tyramine, there still exists some controversy in the literature about the effects on diastolic blood pressure, some studies reporting no effects (Colombo *et al.*, 1988) and others a slight increase (Korn *et al.*, 1988). We found a slight increase in the present study, the increase in diastolic pressure being 5–7 mm Hg when the corresponding increase in systolic pressure was 30–32 mm Hg. A small decrease in heart rate has more consistently been reported, and the present study is in conformity with this. The flattening of the T-wave in the ECG is most probably a sign of strong sympathetic stimulation, brought about by noradrenaline release from the tyramine injection (Furberg, 1968). We conclude that COMT inhibition with nitecapone does not potentiate the haemodynamic responses to tyramine-induced catecholamine release.

Figure 1 Systolic blood pressure response to 3 and 6 mg of i.v. tyramine after no medication ($\blacktriangle$), 25 mg of nitecapone ($\bullet$), and 100 mg of nitecapone ($\blacksquare$) in 11 healthy male subjects. Mean values are shown.

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