Clinical pharmacology of moclobemide during chronic administration of high doses to healthy subjects

Abstract The objectives of this study were to assess the tolerability, safety, pharmacodynamics and pharmacokinetics of high-dose moclobemide in healthy subjects. Two sequential groups of six male and six female subjects (eight on active treatment, four on placebo) received for 8 days moclobemide 450 mg b.i.d. and 600 mg b.i.d., respectively. Intravenous tyramine pressor tests were conducted at baseline, at the beginning of treatment and at steady state. Oral tyramine pressor tests with 50, 100 and 150 mg tyramine were conducted under steady-state conditions. Pharmacokinetic parameters of moclobemide and two of its metabolites in plasma and urine were determined after the first and last dose of moclobemide. The incidence and intensity of adverse events was dose-dependent. The most frequently reported adverse events were insomnia, headache, dizziness and dry mouth. The IV tyramine pressor sensitivity during both moclobemide dosing regimens was enhanced 3 to 4-fold. Intake of tyramine 50 mg did not result in systolic blood pressure increases greater than 30 mmHg. With regard to blood pressure increases, tyramine 100 mg is still compatible with moclobemide 450 mg b.i.d. but not with 600 mg b.i.d. The clearance of moclobemide decreased by about 60% on multiple dosing, but no differences were found between both dosing regimens. The urinary excretion of the N-oxide metabolite doubled during multiple dosing. In conclusion, the maximum tolerated dose of moclobemide in healthy subjects is 600 mg b.i.d. provided the tyramine content in a meal is not higher than 50 mg.

Key words Moclobemide • High dose • Tolerability • Pharmacodynamics • Pharmacokinetics

Introduction

Moclobemide is a reversible and selective inhibitor of monoamine oxidase (MAO) A and was found to be effective in the treatment of depression (Silverstone 1993; Fulton and Benfield 1996). In addition to being effective in depressive disorders, studies have shown moclobemide to be effective in anxiety disorders (Versiani et al. 1992, 1997; Nutt and Montgomery 1996). In contrast to the classical MAO inhibitors such as phenelzine and tranylcypromine, which irreversibly inhibit both MAO-A and MAO-B, moclobemide has a low propensity to induce drug–drug and drug–food interactions (Amrein et al. 1992, 1997; Dingemanse 1993; Livingston and Livingston 1996). The adverse event profile of moclobemide differs from that of irreversible MAO inhibitors, tricyclic antidepressants and also selective serotonin reuptake inhibitors (Chen and Ruch 1993; Chen and Ruch 1993; Fulton and Benfield 1996). Only dizziness, nausea and insomnia/sleep disturbance were slightly but significantly more frequently reported with moclobemide than with placebo. The drug is as well tolerated in elderly as in young patients after either short- or long-term treatment (Moll et al. 1994; Roth et al. 1996; Amrein et al. 1997). Moclobemide potentiates the effects of orally administered tyramine only approximately 3- to 4-fold, which is not considered clinically significant (Korn et al. 1988). Dietary
restrictions are therefore not necessary during moclobemide therapy.

Moclobemide is rapidly and completely absorbed after oral administration (Mayersohn and Guentert 1995). The clearance decreases with dose and time, with a constant value reached after about 1 week of multiple administration (Schoerlin et al. 1987). However, even after multiple dosing, the elimination half-life is short (about 3 h).

The recommended initial dosage of moclobemide is 300–450 mg/day, given in two to three divided doses. The recommended therapeutic dose range is 300–600 mg/day. However, it was deemed necessary to investigate tolerability, pharmacodynamics and pharmacokinetics of moclobemide also at higher dose levels for the following reasons. First, in cases of therapy resistant depression, sometimes high dose monotherapy treatment with an antidepressant is tried before combination treatment with two antidepressants is initiated. This is appropriate in view of the interaction liability of many antidepressant drug classes. Also, in case of social phobia, high doses of moclobemide seem to elicit better efficacy (Nutt and Montgomery 1996; Versiani et al. 1996). Secondly, the pharmacokinetics of moclobemide were shown to be dose-dependent over the therapeutic dose regimen, although this was not clearly reflected in the potentiation of tyramine sensitivity. It is therefore of particular interest to obtain knowledge on the interaction between tyramine and moclobemide administered at high doses. Thirdly, information on the tolerability and safety of high-dose moclobemide would be of use in the treatment of overdose.

The objectives of this study were to assess the tolerability, safety, pharmacodynamics (potentiation of cardiovascular effects by IV and oral tyramine) and pharmacokinetics of moclobemide in healthy subjects when given in doses of 450 mg and 600 mg b.i.d. for 1 week.

Materials and methods

Subjects

Twenty-five healthy Caucasian subjects (age range, 19–43 years) participated in this study. One extra subject was recruited because of an early withdrawal from the 600 mg b.i.d. group. The subjects were stratified to obtain a 1:1 male:female ratio for the different treatment groups. Ethics committee (Roche Welwyn Independent Ethics Committee, Welwyn, UK) approval was obtained, and all subjects gave written informed consent before any screening procedures were performed. The study was conducted in full conformity with the principles of the Declaration of Helsinki and its amendments. Volunteers were within ±15% of their ideal body weight and considered to be healthy as assessed by medical history, physical examination, ECG and routine laboratory blood and urine determinations. Tests for drugs of abuse in blood and urine were also performed. No alcohol, concomitant medication and intake of methylxanthine-containing beverages and food was allowed during the study. Females were obliged to practice a reliable method of contraception (oral contraceptives or intrauterine device).

Design

This was a randomized, double-blind, placebo-controlled, multiple-dose study. Twenty-four subjects were recruited sequentially into two groups of 12: the first group was randomized to receive 450 mg moclobemide b.i.d. (eight subjects) or placebo (four subjects); the second group was randomized to receive 600 mg moclobemide b.i.d. (eight subjects) or placebo (four subjects). For evaluation, the two groups of four placebo subjects were pooled. Therefore, there were three groups of eight subjects. The 600 mg b.i.d. group was not commenced until the results obtained from the 450 mg b.i.d. group had been assessed. On days 2–9, subjects received moclobemide/placebo after a standardized breakfast and again after the evening meal. A single dose was given in the morning of days 1 and 10. The greater part of the study was performed on an ambulatory basis. The subjects were only hospitalized on days when pharmacokinetic/pharmacodynamic parameters were to be determined. All drug administrations in the morning were done in the clinic, while administration in the evening was done at home. Each subject received a diary for recording adverse events and times of drug intake.

Assessments

Tolerability and safety

Adverse events were assessed by spontaneous reports, observations and questioning at regular times. The intensity of the adverse events was rated on a 3-point scale (mild, moderate, and severe), and the potential relationship to drug was assessed by the investigator before breaking the code. Semisupine blood pressure and pulse rate were measured just before drug administration on days 1–10 inclusive and at 2, 4, 6, and 12 h after drug administration on days 1 and 10. Clinical laboratory tests were performed just before the morning administration of moclobemide on day 1 and day 6 and at the post-study follow-up.

Pharmacodynamics

Intravenous tyramine potentiation tests (pressor tests) were initially performed as part of the eligibility screening process in order to exclude any subjects with potentially serious ECG changes induced by tyramine. It also served to familiarize eligible subjects with the procedures they would encounter during the study. Tests were performed as part of the pharmacodynamic assessments on study days –1, 1, 2, and 6 at 1 and 4 h after the time scheduled for the morning dose of moclobemide on days 2 and 6. The pressor tests were conducted as described previously (Korn et al. 1988). Prior to the test, a catheter was inserted into an antecubital vein and, after a stabilization period of 30 min, baseline values of systolic (SBP) and diastolic blood pressure (DBP) were measured with automated Spacelab cuff recording devices, and heart rate (HR) was determined electrocardiographically (two-lead recording). On each occasion, syringes containing 1, 2, 3, 4, 6 and 8 mg tyramine were prepared for IV injection. A volume of 1 ml was injected over 30 s. Blood pressure and heart rate were measured at 1-min intervals until any rise in SBP had clearly passed the maximum value. The subsequent higher dose of tyramine was injected only after SBP had returned to baseline, but at intervals of at least 10 min. The objective was to find the dose of tyramine that led to a rise in SBP of 30 mmHg within 2–3 min. Once this threshold dose had been achieved, no further injections were administered. The protocol for the second group of 12 subjects was amended to include an extra incremental step of 1.5 mg tyramine on study days 2 and 6. Phenotolamine was available for IV injection to reverse any excess rise in BP.

Oral tyramine potentiation tests were performed on study days 7, 8, and 9 with doses of 50, 100, and 150 mg tyramine, respec-