Paroxetine affects metoprolol pharmacokinetics and pharmacodynamics in healthy volunteers

Objective To investigate the effect of multiple-dose paroxetine intake on the stereoselective pharmacokinetics and the pharmacodynamics of metoprolol.

Methods We conducted an open trial with two sessions in eight healthy male volunteers. Racemic metoprolol (100 mg single oral dose) was administered before and after paroxetine treatment (20 mg/day for 6 days). The (R)- and (S)-metoprolol pharmacokinetics, metoprolol metabolic ratio (MR), exercise heart rate and blood pressure were assessed for 12 (pharmacodynamic data) to 24 (pharmacokinetic data) hours after each metoprolol intake.

Results Paroxetine treatment increased the mean area under the plasma concentration–time curve extrapolated to infinity (AUC) of (R)- and (S)-metoprolol significantly (169 to 1340 ng · h/mL [P < .001] and 279 to 1418 ng · h/mL [P < .001], respectively), with an approximately twofold increase in both maximum plasma concentration and terminal elimination half-life. Furthermore, the (S)/(R) AUC ratio was significantly decreased, from 1.72 to 1.07 (P < .001). The mean metoprolol MR was significantly increased, from 0.17 to 5.69 (P < .05). The AUC of the metoprolol–induced decrease in exercise heart rate versus time curve was increased, with 46% (P < .01) after multiple-dose paroxetine intake, reaching significance from 6 hours after metoprolol intake, illustrating a more sustained β-blockade. Similar results were obtained for the effect on exercise systolic blood pressure. Multiple-dose metoprolol administration combined with paroxetine can lead to an accumulation of the β-blocking (S)-enantiomer of metoprolol, possibly resulting in unacceptable bradycardia, loss of cardioselectivity, or both.

Conclusion Multiple-dose paroxetine intake affects both metoprolol pharmacokinetics and pharmacodynamics and suggests that when paroxetine is added to an ongoing metoprolol therapy, caution is warranted and a reduction of the metoprolol dose may be required to prevent undesired adverse effects. (Clin Pharmacol Ther 2000;67:283-91.)
inhibit CYP2D6 both in vitro and in vivo. A recent study investigated the in vitro inhibitory effect of SSRIs and some of their metabolites on the α-hydroxylation and O-demethylation of metoprolol. Among the compounds studied, paroxetine, fluoxetine, and norfluoxetine were shown to be the most potent, with inhibition constant (K_i) values around 1 µmol/L for both metabolic pathways. Furthermore, there is in vivo evidence that paroxetine and fluoxetine can inhibit metoprolol metabolism, as illustrated by two case reports in which severe bradycardia was described when metoprolol was given together with paroxetine or fluoxetine. Because of their lack of significant cardiovascular effects, the SSRIs are often selected for treatment of depression in patients with heart diseases. Simultaneous administration of a β-blocker such as metoprolol and an SSRI is therefore probable.

This trial in healthy volunteers was conducted to determine whether administration of multiple-dose paroxetine affects the stereoselective pharmacokinetics and the pharmacodynamics of metoprolol in vivo.

METHODS

Subjects

Eight healthy, white, nonsmoking male volunteers (age range, 20 to 29 years) gave written informed consent for participation in the study. All subjects underwent a complete physical examination, including an electrocardiogram, urinalysis, and hematologic, biochemical, and immunologic screening within 2 weeks before study entry. Only extensive metabolizers for CYP2D6, as determined by genotyping, were entered in this study.

Exclusion criteria included any clinically relevant abnormality identified at the physical examination or laboratory screening, the use of any medication within 14 days before the first drug administration, blood donation within 60 days before the start of the study, a history of alcohol or drug abuse, and a documented history of drug allergy.

Study design

The study was an open-label trial with two sessions. The study protocol was approved by the Ethics Committee of the Gent University Medical School.

Drug treatments. On day 1 of the first session, all subjects received a single oral dose of 100 mg metoprolol conventional tablet formulation (Lopresor, Novartis Pharmaceuticals, Barcelona, Spain) at the trial location between 8 and 9 AM after overnight fasting. During the outpatient phase, from day 2 to day 7, the subjects were instructed to take 20 mg paroxetine (Seroxat, SmithKline Beecham, Mayenne, France) divided over two oral doses of 10 mg, with a 12-hour interval between doses, to obtain steady state at the end of this period. In a second session, on day 8, the subjects received again a single oral dose of 100 mg metoprolol conventional tablet formulation together with 10 mg paroxetine at the trial location between 8 and 9 AM after overnight fasting. All medications were taken together with 150 mL water. On days 1 and 8, the subjects remained at the clinical research unit until 12 hours after drug administration and received standardized meals 4 and 10 hours after drug intake; they were allowed to drink water ad libitum from 2 hours after metoprolol intake and could resume their normal diet from 12 hours after metoprolol dosing. Drugs (other than the study medication) and alcohol were not allowed to be taken during the course of the trial.

Blood sampling. On days 1 and 8, venous blood was drawn from an antecubital vein, with an indwelling catheter or by venous puncture (sampling after 24 hours after intake), just before and at 1/2, 1, 1 1/2, 2, 3, 4, 6, 8, 10, 12, and 24 hours after metoprolol intake. Blood samples were collected in heparinized polyethylene tubes and centrifuged for 10 minutes at 2500 rpm within 1 hour after collection. After centrifugation, the plasma was separated and frozen at −20°C until analyzed.

Urine collection. On days 1 and 8 the subjects voided just before metoprolol intake, and 20 mL urine was stored in a polyethylene container at −20°C until assayed. All urine was then collected up to 24 hours after metoprolol intake; after recording the volume and thorough mixing, an aliquot of 20 mL urine was retained in a polyethylene container and stored at −20°C until assayed.

Pharmacodynamic measurements. Heart rate and blood pressure were measured while subjects were in a sitting position on a bicycle ergometer immediately before and after a standardized exercise test (1/2, 1, 1 1/2, 2, 3, 4, 6, 8, 10, 12, and 80% of the maximum oxygen consumption determined in a maximal ergometer test within 2 weeks before the start of the study). This submaximal stress test was performed before and at 1, 2, 3, 4, 6, 8, 10, and 12 hours after metoprolol administration on days 1 and 8. Heart rate was determined by counting heart beats from the radial artery pulse for 1/2 minute. Blood pressure was determined with use of a mercury sphygmomanometer; phase I and IV Korotkoff sounds were used for the determination of systolic and diastolic blood pressure measurements, respectively.

Subject compliance. Subject compliance with paroxetine treatment during the outpatient phase (days 2 to 7) was evaluated by means of electronic drug exposure
monitors (eDEM; Aardex Ltd, Zug, Switzerland), pill counts, interviews with the subjects, and measurement of paroxetine trough plasma concentrations on day 8.

Adverse experiences. All adverse experiences reported during the trial were recorded.

Analytical methods

HPLC of metoprolol enantiomers in plasma. The metoprolol enantiomers in plasma were quantified with a modified HPLC method according to Vermeulen et al. The HPLC system consisted of a Gilson 307 pump and a Gilson 234 automatic injector (Gilson, Middleton, Wis) with a 100-μL loop (Rheodyne, Cotati, Calif), a programmable fluorescence detector (Kontron, Zürich, Switzerland) and an HP 3395 integrator (Hewlett-Packard, Palo Alto, Calif). A LiChrosorb 100 diol column (150 × 3.0 mm internal diameter, 5 μm) with a LiChrosorb 100 diol guard column (5 × 3.0 mm internal diameter, 5 μm) (Knauer, Berlin, Germany) was used to separate the enantiomers and the internal standard (tert-butylpropranolol) at room temperature. The mobile phase consisted of a mixture of dichloromethane and methanol (99.5:0.5 vol/vol) with addition of 50 μL/L triethylamine and 764 mg/L Z-glycyl-L-proline. The flow rate was 1.0 mL/min. The excitation and emission wavelengths were set at 280 and 320 nm, respectively.

To 1.0 mL plasma, 100 μL internal standard (tert-butylpropranolol; 75 ng/mL in water) and 100 μL of 2N sodium hydroxide was added in a glass tube; the metoprolol enantiomers were extracted with 5 mL dichloromethane. After extraction and evaporation of the organic phase, the sample was reconstituted in 150 μL mobile phase, and 100 μL was injected onto the column. Calibration curves for the metoprolol enantiomers were constructed over the range from 5 to 70 ng/mL and were linear over this range. Plasma samples with an anticipated plasma concentration–time data, the following pharmacokinetic data. Based on the individual plasma concentration–time data, the following pharma-
cokinetic parameters of (R)- and (S)-metoprolol were determined with noncompartmental modeling by means of WinNonlin (version 1.5, Scientific Consulting, Inc, Apex, NC): maximum plasma concentration (C<sub>max</sub>), time to reach C<sub>max</sub> (t<sub>max</sub>), terminal elimination half-life (t<sub>1/2</sub>), and AUC. All data points above the quantification limit of (R)- and (S)-metoprolol were included for the calculation of the pharmacokinetic parameters. The t<sub>1/2</sub> was calculated as ln2/λ<sub>z</sub>, in which λ<sub>z</sub> is the terminal log-linear slope determined by least-squares regression analysis. The AUC was calculated by use of the log-linear trapezoidal rule with extrapolation from the last predicted concentration (based on the linear regression performed to estimate λ<sub>z</sub>) to infinity.

For urinary data, the metoprolol metabolic ratio (MR) of the subjects before and after multiple-dose paroxetine intake was calculated as follows: the amount of metoprolol/amount of α-hydroxymetoprolol excreted in the urine over 24 hours after metoprolol intake. Subjects were designated phenotypic poor metabolizers if their metoprolol MR >10.5.14

**Pharmacodynamic data.** For every subject, the effect (E) of metoprolol on the exercise-induced heart rate at each measuring point before and after paroxetine treatment was calculated as the percentage change from baseline (before metoprolol intake) in 4-minute exercise-induced heart rate (EHR)15:

\[
E(\%) = \frac{EHR_0 - EHR}{EHR_0} \times 100
\]

in which EHR<sub>0</sub> is the 4-minute exercise heart rate for a given subject at time 0 hour (baseline), and EHR is the 4-minute exercise heart rate at each measuring point for that subject.

Similarly, the effect of metoprolol on the systolic blood pressure after exercise at each measuring point with and without paroxetine coadministration was calculated as the percentage change from baseline (before metoprolol intake) in systolic blood pressure after a 4-minute exercise.

The area under the effect–time curve (AUEC) for both the exercise-induced heart rate and systolic blood pressure from 0 to 12 hours after each metoprolol intake was calculated for every subject according to the linear trapezoidal method.

**Statistical analysis.** All results are reported as mean values ± SD. The changes in pharmacokinetic parameters, metoprolol MR values, and AUEC values were tested by the Student t test for paired samples. A two-way ANOVA for repeated measurements was used to compare the effect–time curves before and after paroxetine treatment; a significant P value in the ANOVA was followed by pairwise comparisons (Student t test for paired samples) of the different measuring points. A P value less than .05 was considered to be statistically significant.

**RESULTS**

All subjects were compliant with paroxetine treatment during the outpatient phase as judged by the interview with the subjects, the pill counts, and the output of the electronic drug exposure monitors. The paroxetine steady-state trough plasma concentrations on day 8 ranged from 1.6 ng/mL to 17.3 ng/mL and were within the range of previously reported trough concentrations after multiple-dose administration of 20 mg/day paroxetine.16

**Safety and tolerability**

All subjects completed the study, and the side effects reported were mild to moderate. Five volunteers reported side effects during part of the period of multiple-dose paroxetine intake: (1) increased stool frequency, (2) decreased appetite, (3) sleepiness, (4) fatigue, and (5) diarrhea, sleepiness, and dizziness. These side effects are reported in the package insert of Seroxat. For both experimental sessions with metopro-
Table I. Mean ± SD pharmacokinetic parameters of (R)- and (S)-metoprolol in eight healthy subjects after a single oral dose of 100 mg metoprolol before and after paroxetine treatment (20 mg/day for 6 days)

<table>
<thead>
<tr>
<th></th>
<th>Before paroxetine</th>
<th>After paroxetine</th>
</tr>
</thead>
<tbody>
<tr>
<td>C\text{max} (ng/mL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(R)-Metoprolol</td>
<td>52 ± 49</td>
<td>134 ± 20**</td>
</tr>
<tr>
<td>(S)-Metoprolol</td>
<td>76 ± 57</td>
<td>149 ± 23**</td>
</tr>
<tr>
<td>t\text{max} (h)</td>
<td></td>
<td></td>
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<tr>
<td>(R)-Metoprolol</td>
<td>1.0 ± 0.3</td>
<td>1.0 ± 0.6</td>
</tr>
<tr>
<td>(S)-Metoprolol</td>
<td>1.0 ± 0.3</td>
<td>0.9 ± 0.4</td>
</tr>
<tr>
<td>Terminal elimination t\text{1/2} (h)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(R)-Metoprolol</td>
<td>2.4 ± 1.1</td>
<td>6.0 ± 2.6***</td>
</tr>
<tr>
<td>(S)-Metoprolol</td>
<td>2.8 ± 1.5</td>
<td>5.9 ± 2.6***</td>
</tr>
<tr>
<td>AUC (ng · h/mL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(R)-Metoprolol</td>
<td>169 ± 155</td>
<td>1340 ± 553***</td>
</tr>
<tr>
<td>(S)-Metoprolol</td>
<td>279 ± 237</td>
<td>1418 ± 574***</td>
</tr>
<tr>
<td>(S)/(R) AUC ratio</td>
<td>1.72 ± 0.27</td>
<td>1.07 ± 0.08***</td>
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C\text{max}, Maximum plasma concentration; t\text{max}, time to reach C\text{max}; t\text{1/2}, half-life; AUC, area under the plasma concentration–time curve extrapolated to infinity.

**P < .01, ***P < .001 versus before paroxetine; differences between the two sessions were tested with the Student t test for paired samples.

Pharmacokinetics

Fig 1 depicts the mean plasma concentration–time curves of (R)- and (S)-metoprolol in the eight healthy subjects after a single oral dose of 100 mg metoprolol before and after multiple-dose paroxetine treatment. Mean plasma concentrations are presented for those sampling points at which metoprolol concentrations were above the lower limit of quantification in at least five volunteers. Before paroxetine treatment, the plasma concentrations of (S)-metoprolol were higher than those of (R)-metoprolol. After multiple-dose paroxetine intake, the plasma concentrations of both metoprolol enantiomers were markedly increased. The effect of paroxetine treatment on the different pharmacokinetic parameters of the metoprolol enantiomers is shown in Table I. Before paroxetine treatment, the average AUC percent extrapolated was 14% and 17%; after paroxetine treatment, the values were 11% and 12% for (R)- and (S)-metoprolol, respectively. Paroxetine, 20 mg/day, resulted in significant eightfold and fivefold increases in mean AUC values of (R)- and (S)-metoprolol, respectively. For (R)- and (S)-metoprolol, both mean C\text{max} and mean t\text{1/2} were significantly increased, with about a factor of two. No significant effect on the t\text{max} was observed. The stereoselectivity in metoprolol pharmacokinetics when metoprolol was given alone was abolished after multiple-dose paroxetine dosing: the (S)/(R) AUC ratio decreased significantly from 1.72 before to 1.07 (P < .001) after paroxetine treatment.

Baseline metoprolol MR of the eight volunteers ranged from 0.06 to 0.51. As shown in Fig 2, multiple-dose paroxetine treatment increased the MR in all eight subjects, with one subject being converted to a phenotypic poor metabolizer. The mean MR was significantly increased, from 0.17 ± 0.15 to 5.69 ± 5.58 (P < .05).

Pharmacodynamics

The predose values for heart rate and blood pressure were not significantly different between days 1 and 8, either during rest or after exercise (eg, heart rate, day 1: 71 ± 9 beats/min during rest, 134 ± 22 beats/min after exercise; day 8: 70 ± 9 beats/min during rest, 139 ± 19 beats/min after exercise).

The mean time course of β\text{1}-blockade by metoprolol, assessed as the percentage of reduction in exercise-
induced heart rate from baseline (predose value) in the eight healthy subjects before and after multiple-dose paroxetine intake is shown in Fig 3. The $\beta_1$-blocking effect of metoprolol was more sustained after paroxetine intake, reaching significance from 6 hours after metoprolol intake. The total $\beta_1$-blocking effect, expressed as the AUEC, significantly increased from 203 ± 75 %·h to 297 ± 74 %·h ($P < .01$). The reduction in exercise systolic blood pressure by metoprolol was more pronounced when metoprolol was taken after multiple-dose paroxetine treatment than alone. The difference was significant at 2 ($P < .05$), 4 ($P < .05$), 8 ($P < .01$), and 10 ($P < .05$) hours after administration. The AUEC of the reduction in exercise systolic blood pressure increased by a factor of two (105 ± 59 %·h to 207 ± 109 %·h; $P < .05$).

DISCUSSION

SSRIs have been shown to exert differential inhibition of CYP-dependent metabolism in vitro and in vivo. To date, many data are available on the effect of SSRIs on the metabolism of other psychotropic drugs. However, the metabolism of several cardiovascular drugs is also dependent on cytochrome P450 activity and thus possibly subject to inhibition by SSRIs. Metoprolol is a cardioselective $\beta$-blocker whose metabolism is highly dependent on CYP2D6 activity. Recently, an in vitro study with human liver microsomes showed that paroxetine and fluoxetine are potent inhibitors of metoprolol $\alpha$-hydroxylation and $O$-demethylation ($K_i = 1 \mu$mol/L for both pathways), two CYP2D6-dependent pathways responsible for the majority of metoprolol metabolism. Although in vitro data and two case reports indicate the potential for a drug-drug interaction between metoprolol and paroxetine (or fluoxetine) in vivo, a formal in vivo study is necessary to assess the extent of an interaction. In this study, we investigated the effect of multiple-dose paroxetine treatment, at the minimum recommended dose (20 mg/day), on the stereoselective pharmacokinetics and on the pharmacodynamics of a single oral dose of 100 mg racemic metoprolol in eight healthy volunteers. In view of the in vitro data available and the case reports published, it was decided to avoid concomitant multiple-dose intake of metoprolol and paroxetine because of possible serious adverse events. Nevertheless, from the results of this metoprolol single-dose study, valuable predictions can be made of what will happen during steady-state conditions. Paroxetine was chosen over fluoxetine on the basis of its much shorter $t_1/2$, allowing steady-state concentrations to be attained within a shorter period of multiple-dose intake.

Paroxetine, 20 mg/day, caused a robust increase in both ($R$)- and ($S$)-metoprolol plasma concentrations, with a significant effect on AUC, $C_{max}$, and $t_1/2$. The respective eightfold and fivefold increases in average AUC values of ($R$)- and ($S$)-metoprolol are comparable with the increases in AUC reported for other CYP2D6 substrates, such as desipramine and perphenazine, when they are combined with 20 mg/day paroxetine.

We evaluated whether the magnitude of this interaction could have been predicted on the basis of in vitro $K_i$ values of paroxetine on $\alpha$-hydroxylation and $O$-demethylation of racemic metoprolol. We used the approach proposed by Ito et al. With that method, an increase in AUC of 1.1-fold is predicted on the basis of free paroxetine plasma concentrations, and a 1.8-fold increase is predicted on the basis of total plasma concentrations. In either case, these predictions greatly underestimate the sixfold increase actually observed in racemic metoprolol AUC. Possible reasons for this discrepancy include errors in the estimation of $K_i$ and of the inhibitor concentration at the enzyme. It has been speculated that the intrahepatic concentrations of SSRIs greatly exceed plasma concentrations. Active uptake could be an explanation for intrahepatic accumulation of lipophilic drugs, such as paroxetine. Inhibition of metoprolol metabolism by paroxetine treatment abolished the stereoselective elimination of
metoprolol in the eight volunteers studied. This finding was consistent with the effect of quinidine, a potent and specific CYP2D6 inhibitor, on the in vitro and in vivo biotransformation of metoprolol.2,24

The effect of paroxetine treatment on CYP2D6 activity was confirmed by the metoprolol MR, an established in vivo measure of CYP2D6 activity.14 The values of baseline metoprolol MR of the eight subjects fell within the range of metoprolol MR observed previously in white extensive metabolizers.14 Inhibition by paroxetine was apparent because the metoprolol MR of all subjects was increased and because one subject became a phenotypic poor metabolizer. A similar effect of paroxetine has been shown previously with use of dextromethorphan MR as in vivo marker of CYP2D6 activity.25

The marked increase in (S)-metoprolol plasma concentrations after multiple-dose paroxetine administration was associated with a more sustained β-blockade, as shown by the reduction in exercise heart rate and exercise systolic blood pressure. Metoprolol given after paroxetine treatment produced a greater degree of β1-blockade, as estimated by the AUEC of the reduction in exercise heart rate and the AUEC of the reduction in exercise systolic blood pressure. Metoprolol alone did not result in a clinically significant (>10%) reduction in exercise heart rate 12 hours after administration, whereas β1-blockade was well maintained for at least 12 hours after intake of metoprolol after multiple-dose paroxetine intake. The blood pressure–lowering effect was also more sustained for the metoprolol-paroxetine combination than when metoprolol was given alone. The more pronounced β-blocking effect of metoprolol after paroxetine intake did not induce more frequent or severe side effects on day 8. However, the interaction may become clinically important when multiple-dose metoprolol is combined with multiple-dose paroxetine. In monotherapy, multiple-dose metoprolol administration (100 mg/12 h) is expected to result in some accumulation of the β-blocking (S)-enantiomer,26 whereas cotreatment with paroxetine will give a substantial accumulation. Although the therapeutic concentration range of β-blockers such as metoprolol is large, plasma concentrations that are too high may lead to unwanted effects such as unacceptable bradycardia (due to excessive β1-blockade) or loss of cardioselectivity (due to β2-blockade). This loss of cardioselectivity can produce disagreeable leg fatigue after exercise, whereas in patients with chronic obstructive pulmonary diseases, β2-mediated bronchoconstrictor effects could lead to a worsening of asthma.27

Fluoxetine is expected to produce a similar interaction with metoprolol because both fluoxetine and paroxetine are equipotent in inhibiting the metabolism of metoprolol in vitro7 and because multiple-dose intake of 20 mg/day paroxetine or fluoxetine results in comparable increases in AUC of desipramine, another CYP2D6 substrate.19,28 Our finding that paroxetine inhibits metoprolol metabolism suggests that previous clinical observations of severe bradycardia when metoprolol was coadministered with paroxetine (or fluoxetine) were probably the result of this drug interaction.8,9

Little is known about the effect of SSRIs on the metabolism of other β-blockers whose metabolism is CYP dependent. Fluvoxamine coadministration was reported to produce a fivefold increase in propranolol plasma concentrations, with a slight potentiation of the reduction in exercise heart rate and exercise diastolic blood pressure.29,30 This interaction is probably the result of inhibition of propranolol metabolism by fluvoxamine at the level of CYP1A2.31-34

An interaction between paroxetine or fluoxetine and timolol, a β-blocker whose metabolism is dependent on CYP2D6,35 is not unlikely because oral quinidine administration resulted in an increase in timolol plasma concentrations with a greater reduction in exercise heart rate after topical administration of timolol.36

In conclusion, this study shows that multiple-dose paroxetine intake affected both metoprolol pharmacokinetics and pharmacodynamics and suggests that when paroxetine is added to an ongoing metoprolol therapy, caution is warranted and a reduction of the metoprolol dose may be required to prevent undesired side effects.

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