Clinical Assessment of Norepinephrine Transporter Blockade Through Biochemical and Pharmacological Profiles

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Background—To assess the sensitivity of biochemical, physiological, and pharmacological markers of peripheral norepinephrine (NE) transporter (NET) function, we chronically antagonized NET by a range of doses of duloxetine [(+)-N-methyl-3-(1-naphthalenylxoxy)-2 thiophenepropanamine], which blocks the NE reuptake process.

Methods and Results—Duloxetine was administered in a randomized, placebo-controlled study in 15 healthy volunteers. Plasma from duloxetine-treated subjects (ex vivo effect) dose-dependently decreased radioligand binding to human NET (maximum inhibition was 60%) \( (P=0.02) \). The dose of intravenous tyramine required to raise systolic blood pressure by 30 mm Hg \( (PD_{30}) \) increased dose-dependently with duloxetine and was significant at the end of the 120-mg/d dosage \( (P<0.001) \). The plasma dihydroxyphenylglycol to NE (DHPG/NE) ratio was reduced significantly at 2 weeks of treatment with 80 mg/d duloxetine (11.3 at baseline, 3.4 at 240 mg/d, \( P<0.001 \)). Plasma NE was significantly increased starting at 120 mg/d duloxetine. Urine results (corrected for 24-hour creatinine excretion) showed a dose-dependent change from the baseline urinary excretion for NE, DHPG, and the DHPG/NE ratio. The most sensitive measure, the DHPG/NE ratio, was significant at the 80-mg dose. Urinary NE excretion was significantly raised after 2 weeks of treatment with 80 mg/d duloxetine \( (P<0.001) \), the lowest dose used in the study.

Conclusions—These findings suggest that the degree of NET blockade can be assessed with the plasma or urine DHPG/NE ratio and the pressor effect of tyramine. Also, the DHPG/NE ratio is more sensitive at the lower end of NET inhibition, whereas tyramine exhibits a linear relation, with NET inhibition commencing at a higher dose. \( \textit{Circulation. 2004;109: 3202-3207.} \)

Key Words: norepinephrine ■ blood pressure ■ plasma ■ drugs ■ catecholamines

Recently, there has been a rekindled interest in the norepinephrine (NE) transporter (NET). This has been driven by the elucidation of the structure of the gene product, by the development of improved drugs that use NET blockade as their mechanism of action, and by the discovery of polymorphisms in the human NET, at least one of which has been shown to have functional consequences. These developments have necessitated a reevaluation of our techniques for determining the consequences of NET blockade in chronically treated human subjects.

Several classes of antidepressant drugs exert their effects by modifying 5-HT and/or NE neurotransmission through the alteration of the functioning of presynaptic and postsynaptic components of the pre- and post-NE systems, both in the brain and in the periphery.\(^1\)\(^-\)\(^3\) Duloxetine, a potent dual inhibitor of 5-HT and NE uptake, exhibits linear pharmacokinetics in humans.\(^4\)\(^,\)\(^5\)

The objective of the present study was to assess chronic blockade of NET by a range of doses of duloxetine with biochemical, physiological, and pharmacological markers. These measurements allow us to create a profile by which the degree of NET impairment can be assessed in patients receiving NET antagonists or in whom defective transport is suspected.

Methods

Subjects

Healthy subjects were recruited by advertisement and underwent a comprehensive clinical and physical examination. All subjects gave written informed consent for participation in the study. The Vanderbilt Investigational Review Board approved all investigational procedures.

Subjects were randomly assigned into two groups: a treatment group (n=12; 8 women and 4 men) and a placebo group (n=3; 2 women and 1 man). The subjects have a mean age of 26 years (range, 18 to 39 years), a mean body weight of 72.2 kg (range, 48.0 to 121.5 kg), and a mean height of 170.0 cm (range, 153.0 to 188.0 cm).

Subjects received escalating oral doses of duloxetine (40 mg BID for 2 weeks, level 1), followed by 1 week each of 60, 80, 100, and 120 mg BID (levels 2 through 5). Urine was collected over a period

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of 24 hours on day 13 of level 1 and day 6 of levels 2 through 5. Later that day, subjects were admitted to the General Center for Research Studies (GCRC). Alcohol, tobacco, caffeine-containing drinks, and strenuous exercise were not allowed for 48 hours before admission to the GCRC at each dose level. Subjects were required to continue to abstain from these until discharge from the GCRC.

Blood samples were drawn for ex vivo NET activity assay at 6 AM. The subjects then underwent pharmacodynamic testing, including a posture study with plasma catecholamine measurement and tyramine testing.

### Ex Vivo Binding

Ex vivo binding of [3H]-nisoxetine to the NE transporters was evaluated as previously described by Bymaster et al.\(^6\) All assays were performed in triplicate. Nonspecific binding was determined by including 10 \(\mu\)M/L desipramine. The data are reported as the percentage of specific binding in the presence of control plasma.

### Tyramine Test

Tests were performed in the morning after a 12-hour fast. The test subjects rested for 30 minutes to permit stabilization of the blood pressure. Increasing bolus doses of tyramine were injected over a period of 10 seconds by a 3-way stopcock, and the transient increase in blood pressure was recorded. The dosage was increased until the PD\(_{30}\) was reached. Blood pressure and heart rate were recorded continuously until the effect had subsided.

### Posture Study

The study was conducted after overnight fast early in the morning. A baseline blood sample for catecholamine determination was drawn. The subject then stood at the bedside as motionless as possible for 10 minutes. Heart rate and brachial blood pressure were recorded at baseline and every several minutes thereafter. Blood was obtained from the contralateral arm for catecholamine determination.

### Catecholamine Analysis

Concentrations of plasma and 24-hour urine catecholamines and their metabolites were measured by batch alumina extraction followed by high-performance liquid chromatography for separation with electrochemical detection and quantification, in a method modified from Holmes et al.\(^7\)

### Statistics

Data are expressed as mean±SD or 95% CI. Mean change from baseline was obtained by repeated-measures ANOVA, using a mixed-effects linear model within duloxetine doses treated as an intrindividual effect. A probability value of <0.05 was considered significant. Graphical presentations of plasma catecholamine results are depicted by box plots. The box plot presents median values as horizontal lines and mean values as plus signs within each box. The 25th and 75th quartiles are represented by the bottom and top of each box. An asterisk below or above the box represents a possible outlier value. Statistical software SAS version 8.02 was used for statistical analyses and graphics.

### Results

#### Ex Vivo Binding Studies

Plasma samples from duloxetine-treated subjects dose-dependently inhibited ex vivo radioligand binding to the human norepinephrine transporter (Table 1). The changes became significant after 2 weeks of treatment with 80 mg/d duloxetine (\(P<0.02\)), with 13% inhibition (87% of control). Maximum inhibition achieved with the highest dose of duloxetine used in this study (240 mg/d) was 42% (58% of control). Thus, plasma from duloxetine-treated subjects dose-dependently decreased binding to human norepinephrine transporters.

#### Tyramine Test

The results of the tyramine test showed that the estimated PD\(_{30}\)s increased dose-dependently during treatment with increasing doses of duloxetine (Figure 1). A large degree of variability among subjects was observed (data not shown). The mean changes became significant at the end of the third treatment week (120 mg/d) (\(P=0.01\)). Tyramine sensitivity with 6 repeated testings at 1- to 2-week intervals between tyramine tests in the placebo group (PD\(_{30}\) 4.33 to 5.00 mg) showed no significant changes.

#### Posture Study

Mean supine and standing heart rate increased dose-dependently from 67 bpm at baseline to a maximum of 71 bpm (supine) and from 91 to 104 bpm (standing). Table 2 presents the summary statistics of the supine and upright heart rates for duloxetine-treated subjects. Supine heart rate increased steadily as the duloxetine dose increased. The main changes became significant at the end of the fourth treatment week (160 mg/d) (\(P=0.048\)). Furthermore, the change in upright heart rate across duloxetine treatment doses became significant from the baseline, starting from the end of the third treatment week (120 mg/d) (\(P=0.03\)). The statistical analyses clearly showed a significant effect of increasing doses of duloxetine in increasing standing heart rate from the baseline measurements. The analysis showed no significant increases in the placebo group across the 5 study levels (level 1

### Table 1. Inhibition of NET Binding ([3H]Nisoxetine Binding) by Plasma Samples (25 \(\mu\)L) From Duloxetine-Treated Subjects (% Control Binding)

<table>
<thead>
<tr>
<th>Duloxetine Dose</th>
<th>Mean</th>
<th>95% CI</th>
<th>(%) Control Binding</th>
<th>(P) Relative to Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo and duloxetine</td>
<td>102.8</td>
<td>99.7, 106.0</td>
<td>0.0005</td>
<td></td>
</tr>
<tr>
<td>80 mg</td>
<td>82</td>
<td>74.6, 90.0</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>120 mg</td>
<td>73.6</td>
<td>67.2, 80.7</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>160 mg</td>
<td>66.1</td>
<td>60.3, 72.5</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>200 mg</td>
<td>59.4</td>
<td>54, 65.3</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>240 mg</td>
<td>53.3</td>
<td>48.2, 59.0</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

All values after treatment are the averages from 12 subjects and represent percentages of control plasma binding.

![Figure 1. Mean tyramine dose required to increase systolic blood pressure by 30 mm Hg (PD\(_{30}\)) across duloxetine doses.](http://circ.ahajournals.org/)

**\(P=0.001\); **\(P<0.0001\).
TABLE 2. Change in Heart Rate With NET Blockade

<table>
<thead>
<tr>
<th>Treatment and Dose, mg</th>
<th>% Change From Baseline</th>
<th>P Value of Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (bpm): baseline 67 supine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duloxetine 80</td>
<td>0.9</td>
<td>0.5926</td>
</tr>
<tr>
<td>Duloxetine 120</td>
<td>2.0</td>
<td>0.1974</td>
</tr>
<tr>
<td>Duloxetine 160</td>
<td>3.0</td>
<td>0.0488</td>
</tr>
<tr>
<td>Duloxetine 200</td>
<td>4.0</td>
<td>0.0150</td>
</tr>
<tr>
<td>Duloxetine 240</td>
<td>5.1</td>
<td>0.0075</td>
</tr>
<tr>
<td>Heart rate (bpm): baseline 91 upright</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duloxetine 80</td>
<td>6.8</td>
<td>0.0958</td>
</tr>
<tr>
<td>Duloxetine 120</td>
<td>8.7</td>
<td>0.0314</td>
</tr>
<tr>
<td>Duloxetine 160</td>
<td>10.6</td>
<td>0.0110</td>
</tr>
<tr>
<td>Duloxetine 200</td>
<td>12.5</td>
<td>0.0042</td>
</tr>
<tr>
<td>Duloxetine 240</td>
<td>14.4</td>
<td>0.0017</td>
</tr>
</tbody>
</table>

through level 5). None of the above changes in heart rate, however, was clearly associated with any adverse events.

Plasma Catecholamine Measurements

The inhibition of NET by duloxetine is shown by the analysis of plasma catecholamines and their metabolites. Dihydroxyphenylglycol (DHPG), the major intraneuronal metabolite of NE, is produced through oxidation of NE by monoamine oxidase. NE, which leaks from vesicles or is taken up by the NET, is converted to DHPG, which can diffuse out of the nerve terminal into the plasma.

The venous plasma catecholamine data in the supine and upright positions for subjects randomly assigned to escalating doses of duloxetine treatment are presented in Table 3. NET inhibition by duloxetine caused a steady increase in the levels of NE across the treatment doses both in the supine and upright positions. The upright levels were significantly greater than the supine values across the treatment doses. Furthermore, the changes of both supine and upright NE were significant from predose measurements starting at 120 mg/d duloxetine (P=0.001; P=0.009, respectively). Placebo treatment did not cause any significant changes of these variables (data not shown). DHPG concentration was highest at baseline and decreased modestly in both supine and upright positions across the treatment doses. The levels in the upright position were higher than those of the supine position. Furthermore, the DHPG/NE ratio was highest at baseline and decreased steadily with increasing duloxetine dose. The upright DHPG/NE ratio changed significantly after 2 weeks of treatment with 80 mg/d duloxetine (P<0.001).

Other catecholamines, including epinephrine, dopamine, dihydroxyphenylalanine (DOPA), and dihydroxyphenylacetic acid (DOPAC), did not show any specific pattern to the different degrees of NET blockade. Placebo treatment did not cause any significant changes of these variables. Table 3 summarizes the statistical analysis of the plasma catecholamines for duloxetine-treated subjects. Figure 2 shows the effect of duloxetine doses on increasing mean heart rate, increasing the mean plasma NE, and decreasing the ratio of DHPG to NE after 10 minutes in the supine position. Figure 3 shows the corresponding relation between the mean heart rate, the mean NE level, and the ratio of DHPG to NE with increasing doses of duloxetine in an upright position (also see Figure 4).

Urine Catecholamines

Urine was collected for 24 hours at the end of each dosing level. The results, corrected for 24-hour creatinine excretion, showed a dose-dependent change from the predose urinary excretion for NE, DHPG, and DHPG/NE ratio.

Urinary excretion of NE increased significantly for all duloxetine doses when compared with the baseline value. The change was significant after 2 weeks of treatment with 80 mg/d duloxetine (P=0.03). Other catecholamines, including epinephrine, dopamine, DOPA, and DOPAC, did not show any specific pattern to the different degrees of NET blockade. DHPG concentration was highest at baseline and decreased modestly across the treatment doses. DHPG/NE ratio was highest at baseline and decreased significantly from the baseline urinary excretion for all duloxetine doses (P<0.0001). This was similar to the changes observed in plasma.

Table 4 summarizes the statistical analysis of the mean change in urinary NE, DHPG, and the ratio of DHPG to NE relative to the mean baseline urinary excretion.
Assessment of the level of NET blockade in human subjects has historically been dependent on tyramine sensitivity. With improved understanding of catechol metabolism and of NET function, ancillary approaches have become possible. Unfortunately, most studies addressing this have been short-term studies, whereas more long-term studies could provide information of greater relevance to genetic impairment of NET function and could be of greater practical value in the way drugs in this class are administered clinically.

In this study, we assessed a range of degrees of chronic NET blockade by determining the relative sensitivity of various methods for calibrating NET blockade. The principal new finding in these studies is that alterations in plasma and urinary catechols are more sensitive to NET blockade than tyramine sensitivity, as used in chronic human studies.

The level 1 dose (80 mg/d) was given for 2 weeks because previous studies showed no tyramine shift when duloxetine (60 mg/d) was taken for 14 days by normal healthy volunteers. The authors speculated that the lack of response to tyramine pressor effect might be due to several not-yet-understood factors, including the concomitant serotonergic drug action, duration of treatment before challenge, and potential physiological differences between normal and depressed subjects.

The ability of duloxetine to block NE transporters in a dose-dependent fashion was confirmed with the ex vivo assay in which subjects’ plasma samples were directly applied to membranes from cells transfected with human NET. These results are similar to in vitro and in vivo studies that showed that systemic administration of duloxetine resulted in penetration into the brain and inhibition of NET.

Administration of tyramine demonstrated the functional effect of impaired NE reuptake. The administration of duloxetine resulted in a linear dose-dependent increase in the amount of tyramine required to cause an increase of 30 mm Hg systolic blood pressure (PD$_{30}$) from 120 mg/d.

Our results showed that duloxetine at 80 mg/d for 14 days inhibited NET by 13%, whereas 5-HT transporter was inhibited by 65% (data not shown). Tyramine is biotransformed into dopamine by cytochrome P450 2D6 (CYP2D6). CYP2D6 exhibits variable and heterogeneous expression in individuals. 5-HT transporter inhibitors might have an effect to reduce plasma NE in contrast to...
NET blockers. It appears that the response to tyramine challenge in subjects taking low-dose duloxetine could be the result of a combined 5-HT/NET effect, especially the serotonergic inhibition, tyramine pressor effect, and the vasodilatory aspect of dopamine. The cardiovascular effect of NET inhibition showed a graded dose-response increase in heart rate, both in supine and upright positions. The orthostatic tachycardia effect was prominent early, even before the tyramine pressor effect. This supports the concept that the heart is particularly dependent on reuptake of NE for its inactivation and is consistent with reports of an increase in heart rate with standing after systemic administration of desipramine, sibutramine, and reboxetine.

Analysis of catecholamine levels revealed a dose-dependent increase in plasma NE levels both in supine and upright positions, consistent with a loss of NE clearance. Because plasma NE levels are dependent not only on clearance of NE but also on NE release, plasma NE alone is not a good marker of sympathetic activity. Because plasma DHPG reflects concentrations of an intraneuronally derived metabolite of NE, comparison of the ratio of plasma DHPG to plasma NE can provide an index of neuronal reuptake but must be interpreted cautiously, as the peripheral DHPG reduction depends on both reduced sympathetic nerve activity and impaired synaptic NE reuptake. The significant decline of the DHPG/NE ratio across the treatment doses indicates that the doses of duloxetine used in this study were effective in inhibiting NE reuptake, and the ratio provides, despite its limitations, a sensitive measure of combined central and peripheral NET inhibition. The 24-hour urine catecholamine levels mirrored the plasma levels because most plasma metabolites of NE (including DHPG) are converted to vanillylmandelic acid in the liver. The magnitude of the DHPG/NE change in urine was therefore of particular interest. This provides an alternative method of catecholamine measurement in cases or situations in which blood sampling might not be optimal. Chalon et al reported a similar decrease in urinary catecholamine metabolites but no significant change in the levels of NE. This might be due to the use of 80- and 120-mg/d doses in their study.

Pharmacodynamic measures demonstrated a certain degree of plateau with continued administration of duloxetine. This raises the question of modulating elements for the function of NE and 5-HT terminals. Long-term administration of antidepressant drugs that are selective NE reuptake inhibitors, or of monoamine oxidase inhibitors, have been shown to desensitize the α2-adrenergic heteroreceptors, the function of which is to limit the release of 5-HT from serotonergic terminals. Similarly, a desensitization of NET after a 14-day treatment with the tricyclic drug desipramine has been suggested on the basis of in vivo electrophysiological results obtained in the rat hippocampus. Whether α2-adrenergic autoreceptors, which negatively control the release of NE, desensitize after long-term antidepressant

### Table 4. Change in Urine Catecholamines After NET Blockade

<table>
<thead>
<tr>
<th>Baseline Mean (μg/g creatinine over 24-h collection)</th>
<th>N</th>
<th>Dose Baseline, mg</th>
<th>Change From Baseline</th>
<th>P Value of Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>NE</td>
<td></td>
<td>80</td>
<td>8.97</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>120</td>
<td>11.89</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>160</td>
<td>14.80</td>
<td>0.0009</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>200</td>
<td>17.71</td>
<td>0.0002</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>240</td>
<td>20.62</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DHPG (μg/g creatinine over 24-h collection period)</td>
<td></td>
<td>80</td>
<td>-10.02</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>120</td>
<td>-9.69</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>160</td>
<td>-9.35</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>200</td>
<td>-9.01</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>240</td>
<td>-8.67</td>
<td>0.10</td>
</tr>
<tr>
<td>Ratio DHPG to NE over 24-h collection period</td>
<td></td>
<td>80</td>
<td>-1.04</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>120</td>
<td>-1.08</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>160</td>
<td>-1.13</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>200</td>
<td>-1.17</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>240</td>
<td>-1.22</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
treatment with NE reuptake blockers or monoamine oxidase inhibitors still remains unclear. Therefore, several elements modulating the function of 5-HT and NE terminals can be altered after long-term administration of various types of antidepressant drugs. It could be argued that the measures applied only reflect peripheral changes of the NET. However, recent findings with risperidone suggest that the changes of the DHPG/NE ratio may reflect changes in the brain.22 Moreover, the reduction in plasma DHPG by NET blockade probably reflects both reduced central sympathetic outflow (yielding less peripheral NE synthesis) as well as peripheral NET blockade. Other studies have shown that neuronal NET turnover in suprabulbar subcortical regions of the brain is increased and positively correlated with the level of whole-body NE spillover in human congestive heart failure.23

The limitation of this study lies in the fact that the agent used, duloxetine, is a dual 5-HT/NE reuptake inhibitor. The 5-HT component might have contributed to the increased NE levels. However, recent findings with short-term administration of the 5-HT transport blocker sertraline in healthy human subjects suggested, if anything, a reduction in plasma NE rather than an increase.12 Sertraline treatment also resulted in a modest reduction in both supine and standing heart rates. Finally, the results obtained from this study are similar to those seen in human NET dysfunction and in a recent acute study with the selective NET antagonist reboxetine.15,24

Although these results provide insight into the assessment of peripheral effects of NET blockade and hence are relevant for the study of NET alternations in heart failure and genetic disorders affecting NET function, the results may not predict an antidepressant effect because the relation of this effect to NET is not fully understood.

In summary, the present study demonstrates the early sensitivity of the DHPG/NE ratio in documenting the NET inhibition effect, a response that occurred even sooner than a demonstrable shift in the tyramine dose-response curve. The lowest dose that shows a significant change in the DHPG/NE ratio has not been determined for duloxetine. There might be even further distinction from the tyramine pressor test, inasmuch as the latter does not become significant until 120 mg/d is reached. With the combination of pharmacological testing with tyramine, orthostatic heart rate, and postural catechol studies, one can reasonably assess small degrees of NET functional impairment such as might be encountered during drug therapy or in patients with NET polymorphisms or mutations.

Acknowledgments

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