Chapter 3

MHPG and heart rate as correlates of nonresponse to drug therapy in Panic Disorder patients.
a preliminary report

Bernhard R. Slaap, M.A.
Irene M. van Vliet, M.D.
Herman G.M. Westenberg, Ph.D.
Johan A. Den Boer, M.D. Ph.D.

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Abstract

Little is known about biological predictors of treatment response in panic disorder (PD). In the present study heart rate, blood pressure, plasma cortisol and plasma MHPG were investigated at baseline in a sample of 44 PD patients as possible predictors for nonresponse to treatment. We used a strict definition of nonresponse to find patients who did not respond at all after 12 weeks of treatment with brofaromine or fluvoxamine. Patients were considered nonresponders when they fulfilled two criteria: they did not show a 50% reduction of agoraphobic avoidance and they still experienced panic attacks at endpoint. The variables that differed significantly between the groups were used to predict nonresponse to drug therapy. Using this strict definition of nonresponse 15 patients (32.6%) were considered nonresponders. These patients were characterised by a higher plasma MHPG concentration and a higher heart rate at baseline. These variables were subsequently used to predict nonresponse.
**Introduction**

In panic disorder (PD) there is a growing interest in the prediction of response to treatment, as witnessed by the increasing number of studies concerning this topic. Factors which have been identified as being predictive of nonresponse to treatment in PD are: severity of illness (Noyes, Jr. et al 1984; Rosenberg et al 1991; Scheibe et al 1992; Basoglu et al 1994; Woodman et al 1994), intensity of phobic avoidance (Rosenberg et al 1991; Basoglu et al 1994; Woodman et al 1994), duration of illness (Noyes, Jr. et al 1984; Basoglu et al 1994), presence and severity of depressive symptoms (Rosenberg et al 1991; Basoglu et al 1994; Woodman et al 1994) and comorbidity (Mavissakalian and Hamann 1987; Reich 1988; Black et al 1994).

Little is known about biological predictors of treatment response in PD. This is in contrast to depression, where an impressive amount of research has been conducted on biological predictors of antidepressant treatment outcome (Joyce and Paykel 1989; Balon 1989).

In depression, studies with imipramine have reasonably consistently shown that low urinary 3-methoxy-4-hydroxyphenylglycol (MHPG) levels are predictive of clinical response (Garvey et al 1990). A similar relationship of low urinary MHPG and treatment response probably also applies to nortriptyline and maprotiline (Joyce and Paykel 1989).

Several studies have highlighted a role for central noradrenergic neuronal systems in the pathogenesis of PD. Challenge studies, using the $\alpha_2$ adrenoceptor antagonist yohimbine, have suggested involvement of this receptor in PD (review Charney et al. (1994)). These studies suggest an enhanced sensitivity of PD patients to the anxiogenic effects of yohimbine, as well as augmented blood pressure and MHPG responses. Studies using the $\alpha_2$ adrenoceptor agonist clonidine revealed a blunted growth hormone response in PD patients (Charney and Heninger 1986; Nutt 1989; Abelson et al 1992; Tancer et al 1993). In some studies with clonidine, an enhanced MHPG response and greater drop in systolic blood pressure was found, although other studies failed to replicate this finding (Uhde et al 1989; Abelson et al 1992).

A diminished function of the peripheral $\beta$ adrenergic receptor system in PD has also been reported recently by several investigators (Nesse et al 1984; Brown et al 1988; Aronson et al 1989). Maddock and co-workers (1993a; 1993b) have investigated pretreatment $\beta$ adrenoceptor density as a possible predictor of response. From their studies there appears to be a relation between a lower $\beta$ adrenoceptor density and a better treatment response. In one study they only found a trend ($p<0.10$) towards a correlation between a reduced $\beta$ adrenoceptor density and treatment response (Maddock et al 1993b). In the other study it was found that pretreatment $\beta$ adrenoceptor density was significantly lower in patients who later responded to treatment with either adinazolam or placebo (Maddock et al 1993a).

In PD only one study reports on the relationship between urinary MHPG levels and treatment response. Garvey et al. (1989) reported a trend ($p<0.08$) for higher pretreatment urinary MHPG levels to be associated with a positive treatment response to alprazolam or diazepam.
In challenge studies using sodium lactate two studies reported a relationship between plasma MHPG levels and panic frequency. Den Boer et al. (1989) found significantly higher baseline plasma MHPG concentrations in patients who panicked during sodium lactate infusion. This result is at variance with findings of Pohl et al. (1987), who found no differences in baseline plasma MHPG level between panickers and non-panickers.

In one study with sodium lactate, significantly higher pre-infusion heart rate and diastolic blood pressure were found in PD patients who panicked during sodium lactate provocation (Liebowitz et al 1985). Yeragani and co-workers (1987a) tried to replicate this finding, but they did not find a significant difference between panickers or non-panickers in resting or pre-infusion heart rates. From this brief review of the literature it is clear, that only a few systematic studies exist on the topic of biological predictors of response in PD. The available data are by and large conflicting.

In the present study we report on heart rate, blood pressure, plasma cortisol and plasma MHPG levels as possible predictors for nonresponse to treatment in PD patients. The aim of the present study was to find biological variables, measured at baseline, which may distinguish responders from nonresponders in a patient sample suffering from PD. The variables that differed significantly between the groups were used to predict nonresponse to drug therapy.

**Materials and methods**

*Design*

For the present study the data of two previously published studies were pooled. In these studies brofaromine, a selective and reversible monoamine oxidase inhibitor (MAOI), was compared with either fluvoxamine, a selective serotonin reuptake inhibitor (SSRI) (van Vliet et al 1996) or placebo (van Vliet et al 1993). Both studies had a double-blind design and lasted 12 weeks. The psychometric scales and the biochemical measurements were similar in both studies. By pooling the data, we obtained a data base of 60 patients. Twenty nine patients were treated with brofaromine, 15 patients were treated with fluvoxamine and 16 patients received placebo. The 44 patients who received drug treatment have been studied in this paper. The patients treated with placebo were excluded from the study because we were interested in predictors of nonresponse to active drug treatment.

The patients who received drug treatment were analysed as one group in this study. Analysis of variance with drug (brofaromine or fluvoxamine) as covariate showed no significant differences between the drug groups. Furthermore, from the study of van Vliet et al. (1996) it appears that there are no significant differences between brofaromine and fluvoxamine on any of the outcome measures.

Nonresponders were defined as patients who still had panic attacks in the last week of treatment and who had a reduction of less then 50% on the Agoraphobia subscore of the Fear Questionnaire (FQ; (Marks and Mathews 1979)). Patients who were free of panic attacks
attacks at endpoint and/or showed an improvement of 50% or more on the Agoraphobia subscore were considered to be responders. The panic frequency was measured by the Utrecht Panic Inventory (UPI), which was completed daily. This is a questionnaire, based on the DSM-III-R definition of a panic attack, measuring the frequency and intensity of panic attacks and the associated symptoms.

Patients

For each study thirty patients were recruited from the outpatient clinic of the department of Biological Psychiatry of the University Hospital in Utrecht. The studies were approved by the Ethics Committee of the Academic Hospital and informed consent was obtained from all patients. Included in the studies were patients suffering from PD with Agoraphobia (59 patients) or without Agoraphobia (1 patient) according to DSM-III-R criteria. Excluded were patients with other anxiety disorders, major affective disorder or psychotic disorder, alcohol abuse, severe sleep disturbance and patients suffering from other medical problems on the basis of a complete medical evaluation. Patients with a score of 15 or more on the Hamilton Depression Scale (HDS; (Hamilton 1967)) were also excluded. During treatment the use of other psychotropic drugs was not allowed except the use of oxazepam to a maximum of 20 mg daily, if required. The sixty patients, 54 females and 6 males, had a mean age (± SD) of 36.6 ± 7.1 years (ranging from 20 to 50) and the mean duration of illness was 9.7 ± 6.2 years (ranging from 0.6 to 32).

In each study patients were randomly allocated to one of the two treatment groups: brofaromine or placebo in one study (van Vliet et al 1993) brofaromine or fluvoxamine in the other (van Vliet et al 1996). The patients in both studies were treated for 12 weeks.

Biochemical measurements

Blood samples were taken prior to the study, at the end of the first week of treatment and during the experimental period at week 2, 4, 8 and 12. The blood was sampled before 10:00 AM. At the same time heart rate, blood pressure and body weight were measured. Heart rate and blood pressure were both measured at the end of the visit with the patient in a supine position, after five minutes acclimatisation. Blood plasma levels of brofaromine or fluvoxamine were monitored to ensure compliance to treatment.

Cortisol

Blood (1 ml) was collected in silicon-coated ice-chilled glass tubes, serum was separated by centrifuging and cortisol was assayed by RIA as described by Thijsen et al. (1980). Cross-reactivity with 21-deoxy-cortisol was 62%; that with corticosterone 11%. Sensitivity of the assay was 0.01 mmol.
3-methoxy-4-hydroxyphenylglycol (MHPG)

MHPG was measured by a liquid chromatographic procedure. Briefly, after extraction with ethylacetate using iso-MHPG as an internal standard, the components were separated on a reverse-phase column and detected with an amperometric detector at 850mV. The sensitivity of the method is about 0.1 ng/ml. The interassay variability was 7% at 7 ng/ml.

Data analysis

Data were analysed using a commercially available statistical package (SPSS Inc.). To analyse the differences at baseline between responders and nonresponders to drug treatment an ANOVA was performed on the drug group. When the assumption of normality was violated a nonparametric test (Kruskal-Wallis analysis of variance) was applied.

To assess the relationship between the biochemical measures, heart rate and blood pressure Pearson correlation coefficients were calculated. The correlations are reported as significant when the two-tailed p value was less then 5%.

For the prediction of nonresponse to drug therapy a logistic regression analysis was carried out for all significant baseline variables. Subsequently a best fitting model was made with all significant variables using logistic regression with backwards elimination. As criterion for variable selection the likelihood-ratio test was used.

Results

Of the 44 subjects who received drug treatment there was one patient in the fluvoxamine group who did not complete the UPI, therefore this patient was not entered into the statistical analysis.

Of the remaining 43 patients in the drug group, 15 patients (32.6%) were nonresponders. Of the 29 patients in the brofaromine group 11 patients (37.9%) were nonresponders. Of the 14 patients in the fluvoxamine group 4 patients (28.6%) were nonresponders. The difference in response rates was not statistically significant. Based on the assessment of blood plasma levels of brofaromine and fluvoxamine it could be concluded that all patients were compliant to treatment.

Differences at baseline between responders and nonresponders to drug therapy

There were no differences at baseline between responders and nonresponders on sex, age, height, weight or duration of illness (Table 1). Responders had a heart rate at baseline of 72.14 ± 1.53, whereas nonresponders had a heart rate of 79.87 ± 2.90. This difference was statistically significant (F=6.75; df=1,41; p=0.013). There were no differences at baseline between responders and nonresponders in their blood pressure.

Nonresponders are characterized by a higher mean plasma MHPG concentration and a smaller variance (Figure 1). The plasma MHPG concentration (ng/ml ± SEM) of the non-
responders was 3.40 ± 0.12 at baseline; the responders had a concentration of 2.88 ± 0.16. Statistical analysis showed that the difference between the groups was significant (Kruskal-Wallis; p=0.039). Plasma cortisol concentrations did not differ at baseline between responders and nonresponders.

**Correlations**

Baseline plasma cortisol and MHPG concentration were correlated with heart rate and blood pressure. There were no significant correlations between the biochemical measures, heart rate and blood pressure.

**Prediction of nonresponse**

For the prediction of nonresponse to drug therapy we carried out a logistic regression analysis on both significant baseline variables. Baseline plasma MHPG concentration and heart rate each significantly predicted nonresponse (p<0.05). A best fitting model was also calculated by performing a logistic regression analysis with backwards elimination with both significant variables in the initial equation. The elimination process resulted in a prediction based on both variables. With this prediction the overall percentage correctly classified patients was 78.1%. This model fitted quite well ($\chi^2 =15.204; \text{df}=2; p=0.0005$). Of the responders 24 patients (88.9%) were correctly classified. Eight nonresponders (57.1%) were correctly classified.

**Discussion**

The main finding of this study is that nonresponders to drug therapy had a higher plasma MHPG concentration and a higher heart rate at baseline, as compared to responders to antidepressant treatment. There were no differences between responders and nonresponders in plasma cortisol concentration or blood pressure.

Somewhat to our surprise there was no correlation between plasma MHPG concentration and heart rate. Nonresponders differed from responders on both variables, yet there was no correlation between these variables. Apparently, nonresponders can be characterized by either a higher heart rate or a higher plasma MHPG concentration.

It is difficult to explain why PD patients with a higher plasma level of MHPG are likely to be nonresponders to treatment with antidepressants, whereas patients with ‘normal’ MHPG levels are responders. Experiments using the $\alpha_2$-adrenoceptor antagonist yohimbine and the $\alpha_2$ adrenoceptor agonist clonidine led to the hypothesis of noradrenergic involvement in PD (see introduction). The inconsistencies in the literature about this hypothesis could be accounted for by a biological heterogeneity in noradrenergic function in patients suffering from PD. Charney et al (1992) reported that a subgroup of PD patients, who demonstrated abnormal anxiety and MHPG responses to yohimbine, were also the most likely to have
abnormally blunted growth hormone responses to clonidine. These data indicate that it is conceivable that there is a subgroup of PD patients with noradrenergic dysfunction.

In a previous study we found that PD patients who panicked during infusion of sodium lactate showed a higher mean plasma MHPG at baseline (den Boer et al 1989). It is conceivable that the baseline arousal (or anticipatory anxiety) of PD patients who panic during lactate infusion is higher compared to nonpanickers, which could be reflected by their higher plasma levels of MHPG. It is therefore tentative to speculate that patients with higher plasma MHPG levels constitute a subgroup of PD patients, who are more likely to develop panic attacks. In this context, the higher plasma MHPG level reported in the present study might be viewed as a biological vulnerability factor or trait marker, a finding which is in accordance with our previous lactate study.

A remarkable finding of the present study was that nonresponders had a higher heart rate at baseline. This finding seems comparable with the findings of Slaap et al. (1996), who reported on differences between responders and nonresponders in social phobia. They also found that nonresponders to drug therapy had a higher heart rate at baseline. A possible explanation might be that nonresponders had a disturbed functioning of the autonomic nervous system. There is some evidence to suggest that disturbances in the autonomic nervous system inhere in PD. It has also been reported that PD patients have a higher heart rate (Nesse et al 1984; Liebowitz et al 1985; Roth et al 1986; Bass et al 1989) and higher blood pressure (Yeragani et al 1987b; Yeragani et al 1989; Yeragani et al 1990b).

Another method to establish the functioning of the autonomic nervous system is to analyse the heart rate variability (Akselrod et al 1981; Akselrod et al 1985; Pomeranz et al 1985; van Ravenswaaij-Arts et al 1993). Several studies have shown an altered heart rate variability in PD (Yeragani et al 1990a; Yeragani et al 1993; Middleton et al 1994; Rechlin et al 1994). Klein et al. (1995) found a correlation of illness severity and measures of heart rate variability. In the literature on the prediction of treatment response in PD, illness severity is frequently reported as a predictor of nonresponse (Noyes, Jr. et al 1984; Rosenberg et al 1991; Scheibe et al 1992; Basoglu et al 1994; Woodman et al 1994). Further research is warranted to analyse whether the autonomic nervous system functioning, as measured by the analysis of heart rate variability, is associated with nonresponse to treatment in PD.

In summary, in the present preliminary study we found that patients with PD who had higher plasma levels of MHPG and a higher heart rate at baseline, appeared to be nonresponders to treatment with antidepressants. The apparent dichotomy in treatment response might be accounted for by assuming biological heterogeneity in noradrenergic functioning among patients with PD. A methodological flaw of the present study might be the limited number of patients studied. In future studies we intend to include larger numbers of patients, possibly enabling us to further substantiate the present findings. Another focus of research will be heart rate variability as a possible predictor of nonresponse to treatment in PD.
References


Charney DS, Heninger GR (1986): Abnormal regulation of noradrenergic function in panic disorders. *Arch Gen Psychiatry* 43:1042-1054.


Table 1: Differences between responders and nonresponders.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Responder (mean ± SEM)</th>
<th>Nonresponder (mean ± SEM)</th>
<th>Probability</th>
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</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>37.00 ± 1.34</td>
<td>36.33 ± 1.89</td>
<td>NS</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>170.11 ± 1.25</td>
<td>169.27 ± 1.92</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (kilos)</td>
<td>65.79 ± 2.07</td>
<td>66.2 ± 3.30</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of Illness (years)</td>
<td>8.61 ± 1.24</td>
<td>9.80 ± 1.27</td>
<td>NS</td>
</tr>
<tr>
<td>Heart Rate (BPM)</td>
<td>72.14 ± 1.53</td>
<td>79.87 ± 2.90</td>
<td>F=6.75;df=1,41; p=0.013</td>
</tr>
<tr>
<td>Systolic Blood Pressure (mm Hg)</td>
<td>130.36 ± 1.94</td>
<td>128.33 ± 3.03</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic Blood Pressure (mm Hg)</td>
<td>81.79 ± 1.43</td>
<td>82.67 ± 1.94</td>
<td>NS</td>
</tr>
<tr>
<td>MHPG (ng/ml)</td>
<td>2.88 ± 0.16</td>
<td>3.40 ± 0.12</td>
<td>Kruskal-Wallis; p=0.039</td>
</tr>
<tr>
<td>Cortisol (mol/l)</td>
<td>0.51 ± 0.05</td>
<td>0.57 ± 0.10</td>
<td>NS</td>
</tr>
</tbody>
</table>
**Figure 1**: Histogram of the baseline plasma MHPG concentration (ng/ml) of responders (n = 27) and nonresponders (n = 14).