Studies of Catecholamine Metabolism in Schizophrenia/Psychosis-II

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Acutely psychotic schizophrenic patients were maintained on debrisoquin (DBQ) throughout 5 weeks of treatment with haloperidol. Treatment with haloperidol caused initial increases in urinary homovanillic acid (HVA) output that returned toward baseline by the 5th week. During haloperidol treatment, plasma levels of HVA tended to decrease, concurrent with increased renal clearance of HVA. Plasma 3-methoxy-4-hydroxyphenylglycol (MHPG) levels and urinary MHPG output both decreased over the course of treatment. The differences in HVA and MHPG metabolism suggest differential effects of treatment on dopamine and norepinephrine systems. Neuroleptic treatment also abolished the marked morning decreases in plasma HVA concentrations (reported in part I). ***[Neuropsychopharmacology 8:111–116, 1993]***

KEY WORDS: *Schizophrenia; Psychosis; Dopamine; Norepinephrine; HVA; MHPG; Renal clearance; Neuroleptic actions*

In the first of these two papers (Maas et al. 1992), the background for the interest in brain dopamine (DA) and norepinephrine (NE) systems in schizophrenia and psychosis was given and the hypothesis that changes in both DA and NE central nervous system (CNS) systems are associated with schizophrenia/psychosis was developed. Further, information and references regarding advantages and problems with using debrisoquin (DBQ) to obtain a clearer signal as to brain DA and possibly NE system function by using plasma and urinary measures of their metabolites, homovanillic acid (HVA) and 3-methoxy-4-hydroxyphenylglycol (MHPG), were noted. The data in the preceding paper focused on information obtained from schizophrenic/psychotic patients prior to the administration of neuroleptic drugs. In this paper we present data on HVA and MHPG in plasma and urine while a subset of the patients described in the preceding paper were undergoing a 5-week trial on haloperidol. Only data from patients who were able to complete the entire treatment period are reported here.

METHODS

Subject selection, subject characteristics, analytic chemical methods, materials, and statistical procedures were the same as those described in the previous paper that dealt with pretreatment amine metabolites. In this study, after all of the pretreatment procedures described in the preceding paper, the patients continued receiving 10 mg of DBQ four times daily (40 mg/day) and in addition were treated with 10 mg of haloperidol three times daily. Anticholinergics were given only on an as needed basis. At weekly intervals, for 5 weeks, patients had blood samples drawn at 8:00 A.M. and 10:00 A.M. and 3.5-hour urine specimens collected under super-

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Received January 23, 1992; revised June 18, 1992; accepted July 7, 1992.

Published by Elsevier Science Publishing Co., Inc.
655 Avenue of the Americas, New York, NY 10010

0893-133X/93/$6.00

vision as previously noted. Behavior ratings (types described in previous paper) were also obtained. Because of the relatively high dose of haloperidol, as well as clinical factors associated with nonresponse, some patients did not enter and others did not complete the treatment phase of these studies. At the end of 5 weeks of treatment with haloperidol the patients were again challenged with placebo, apomorphine, or a neuroleptic, using the procedures described in the preceding paper. In this present paper, however, only the data obtained with the placebo will be reported. The other challenge data will be reported elsewhere.

For comparison purposes we used two different baseline days to compare weekly results during 5 weeks of treatment with haloperidol. The first was the baseline data of the patients after 7 days receiving DBQ. The second is the baseline of the control subjects after 7 days receiving DBQ. The particular baseline used for a given comparison is referred to in the text.

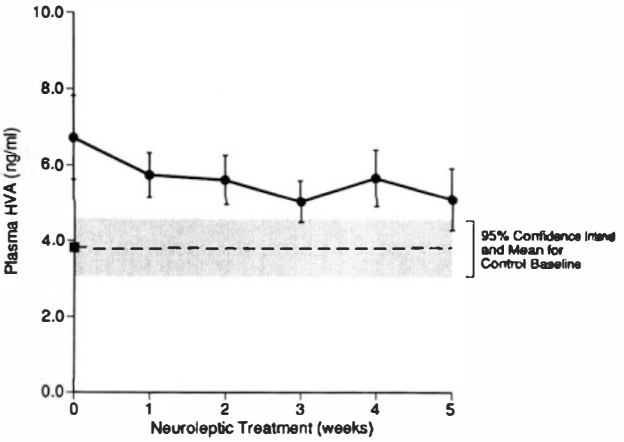

Figure 1. Patient plasma HVA concentrations expressed as nanograms per milliliter ± SEM and control baseline value as mean nanograms per milliliter (- - -) and 95% confidence interval (*shaded area*). -●- Patients ($\bar{x}$ ± SEM) n = 10; ■ Controls ($\bar{x}$ ± 1.96 · SEM) n = 9.

Statistical Analysis

The change-over time in plasma HVA and MHPG during the placebo challenge day before and after neuroleptic treatment was analyzed using one-way repeated-measures analysis of variance (ANOVA). Repeated-measures ANOVA with two repeated factors, time and day interaction was used to compare the time response on the two placebo days (i.e., before and after neuroleptic treatment). A similar one-way repeated-measures ANOVA was used to compare levels of plasma and urinary metabolites during 5 weeks of neuroleptic treatment. To obtain some measure of whether patient metabolite values during the haloperidol treatment decreased to "normal" levels, we have plotted the patient data (as mean ± SEM) against a 95% confidence interval for the mean of normal subjects, using the baseline of the control subjects after 7 days receiving DBQ.

RESULTS

Longitudinal Changes in Neurotransmitter Metabolites During 5 Weeks of Treatment with Haloperidol

The sequential changes in plasma and urinary HVA and MHPG during 5 weeks of haloperidol treatment are shown in Figures 1 through 4. The patients' weekly values (mean ± SEM) were contrasted with the baseline values from the control group (shown as the controls' mean baseline value with a 95% confidence interval). At baseline the patients' plasma HVA values were significantly higher than the values for the controls. During haloperidol treatment, plasma HVA values declined but did not reach control values (see Fig. 1).

Urinary HVA (Fig. 2) was increased by the 1st and 3rd weeks of treatment, but by the 4th and 5th weeks returned toward the original baseline values.

Values for plasma and urinary MHPG during the course of haloperidol treatment are shown in Figures 3 and 4. During haloperidol treatment, at time zero (no drug) the patient values were significantly higher than those for control subjects but during the 5 weeks of treatment the patient values gradually fell toward the normal range. This was particularly so for the plasma values.

In summary, for urinary HVA values there was an initial increase during haloperidol treatment and then a decrease in values toward normal. Urinary MHPG values simply decreased gradually during the 5 weeks of treatment.

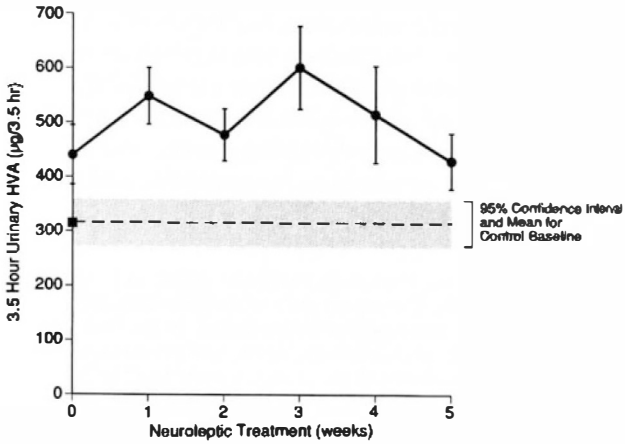

Figure 2. Patient urinary HVA levels as µg/3.5 hr ± SEM and control values as mean µg/3.5 hr (- - -) and 95% confidence interval (*shaded area*). -●- Patients ($\bar{x}$ ± SEM) n = 8; ■ Controls ($\bar{x}$ ± 1.96 · SEM) n = 10.

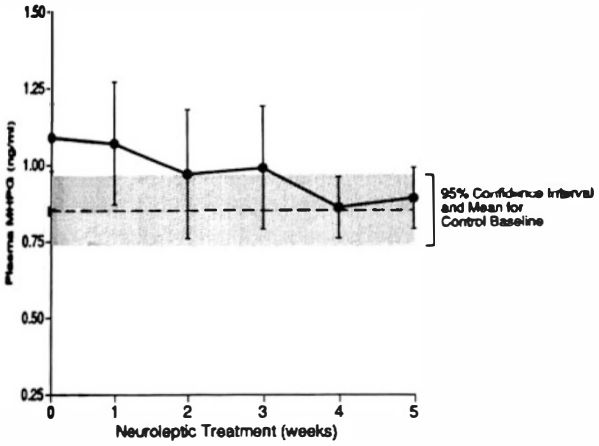

Figure 3. Patient plasma MHPG concentrations expressed as mean nanograms per milliliter ± SEM and control values as nanograms per milliliter (- - -) and 95% confidence interval (*shaded area*). -●- Patients ($\bar{x}$ ± SEM) n = 7; ■ Controls ($\bar{x}$ ± 1.96 · SEM) n = 9.

The effects of neuroleptic treatment on renal clearance of HVA during the 5-week treatment period were calculated. An overall ANOVA with repeated measures was significant ($p = 0.044$). For the individual contrasts paired *t*-tests were used (Table 1). The 5 weeks of neuroleptic treatment were associated with a significant increase in the renal clearance of plasma HVA from the patients' own baseline levels at weeks 1, 3, and 4. This increase in renal clearance of HVA would be expected to increase urinary HVA values and to decrease plasma HVA concentrations, and it is thus of interest that plasma HVA tended to fall during haloperidol treatment and urinary HVA initially increased. However, renal clearance was not significantly different from baseline during the 5th week of treatment but plasma HVA concentration tended toward being lower than the patients' (but not the controls') baseline. These findings are consistent with an initial increase and then a decline in DA synthesis and with an increase in renal clearance associated with haloperidol administration. For reasons noted in the preceding paper, calculations for renal clearance of MHPG are not meaningful.

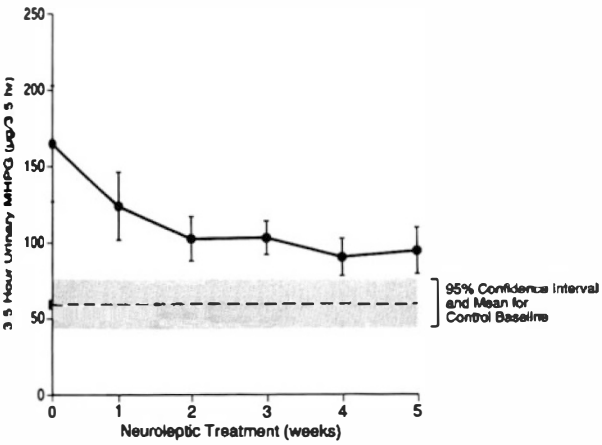

Figure 4. Patient urinary MHPG as mean μg/3.5 hr ± SEM and control baseline values as mean μg/3.5 hr (- - -) and 95% confidence interval (*shaded area*). -●- Patients ($\bar{x}$ ± SEM) n = 7; ■ Controls ($\bar{x}$ ± 1.96 · SEM) n = 10.

Table 1. Comparisons Across Time of Urinary HVA Clearance by Patients

Baseline	328 ± 110	
Week 1	461 ± 122	$p < 0.01$
Week 2	442 ± 188	$p = 0.19$
Week 3	579 ± 242	$p < 0.01$
Week 4	458 ± 158	$p = 0.04$
Week 5	443 ± 202	$p = 0.15$

Values are expressed as milliliters per minute ± SD. The number of subjects was eight. The *p*-values are for the comparison of each time point with baseline by paired *t*-tests. The overall repeated-measures ANOVA was significant ($df_1 = 5$; $F = 2.56$, $p = 0.04$, $n = 8$).

Results with the Placebo Pharmacologic Challenge Repeated after 5 weeks of Haloperidol Treatment

As noted earlier, challenge tests with placebo, apomorphine, and haloperidol were given to patients who had ceased treatment with neuroleptics and again after 5 weeks of receiving haloperidol. Only the placebo data are presented here. After haloperidol treatment the previously noted strong time effect for plasma HVA was no longer seen (Table 2). The time curve for plasma HVA after 5 weeks of haloperidol treatment is somewhat flattened out. Overall, plasma HVA levels did not differ significantly between the two challenge days. In addition, values (not shown) for plasma MHPG were compared between the first and second challenges. Plasma MHPG values were lower during challenge 2 than during challenge 1 ($p = 0.01$), but were still higher than controls.

Table 2. Comparison of Diurnal Change in Plasma HVA Levels Before (Challenge 1) and After 5 Weeks of Haloperidol Treatment (Challenge 2)

Time (min)	Placebo Challenge 1 (n = 15)	Placebo Challenge 2 (n = 5)
0	4.88 ± 1.22	4.18 ± 2.01
20	4.56 ± 1.13	4.12 ± 1.80
60	4.34 ± 1.05	3.96 ± 1.55
90	4.25 ± 0.94	3.88 ± 1.71
120	4.07 ± 0.85	3.88 ± 1.70
180	4.08 ± 0.82	4.00 ± 1.52

The strong time effect seen before haloperidol (reported in paper I) was not seen after 5 weeks of haloperidol treatment, although challenge 1 did not differ from challenge 2 when an ANOVA with repeated measures was done. Values for plasma HVA are expressed as nanograms per milliliter, mean ± SD.

Correlations between behavioral ratings and biochemical changes during treatment with haloperidol were not done because of the small number of patients completing the 5-week haloperidol treatment.

DISCUSSION

The time course of plasma HVA and MHPG levels after institution of neuroleptic treatment has been characterized by a number of investigators. With regard to plasma HVA, these reports are somewhat inconsistent regarding the effects during the first days of neuroleptic treatment, but the finding of a downward trend over weeks of treatment as reported here is quite uniform (Pickar et al. 1984, 1986; Doran et al. 1985, 1990; Chang et al. 1988, 1990; Davila et al. 1988; Farde et al. 1988; Alfredsson and Wiesel 1989; Bowers et al. 1989; Davidson et al. 1991). Another effect of chronic neuroleptic treatment, as noted here, which has also been reported by others is the normal diurnal variation of plasma HVA levels seen in unmedicated patients and control subjects. A number of investigators have reported that plasma HVA levels decreased during the late morning hours from about 8:00 A.M. to noon (Contreras et al. 1988; Davidson et al. 1988; Sack et al. 1988; Davila et al. 1989; Doran et al. 1990). Also consistent with this report, others have found that chronic neuroleptic treatment tends to lessen or abolish this diurnal decline in plasma HVA levels (Davila et al. 1989; Doran et al. 1990). These findings could be interpreted as reflecting decreased DA turnover. Our observations with regard to urinary output of HVA, however, do not support this interpretation. Urinary HVA output tended to increase during the first few weeks of haloperidol treatment and, even after 5 weeks, had not decreased. Increased urine HVA output after haloperidol treatment has been previously reported by us (Contreras et al. 1987, 1988). The apparent discrepancy between plasma HVA levels and urinary HVA output might be explained by the demonstrated increased clearance of HVA from plasma (Table 1). Thus, our data are at least in part consistent with the interpretation that two changes occurred during the haloperidol treatment period. First, DA turnover initially increases, as reflected in increased urinary HVA output (this study and Contreras et al. 1987, 1988), and in an increase in cerebrospinal fluid (CSF) HVA (Bowers 1974; Gerlach et al. 1975; van Praag and Korf 1975; Bjerkenstedt et al. 1979; Beckmann et al. 1983; Doran et al. 1989), but tolerance to this effect develops, as reflected in normalization of urine HVA output (this study) and in CSF HVA (Rimon et al. 1971; Gerlach et al. 1974; Bowers and Heninger 1981; Post and Goodwin 1975). Second, during the treatment phase, renal clearance of HVA increases. Effects of dopaminergic and DA-blocking agents on renal HVA clearance and on renal plasma flow have been noted by others (Yeh et al. 1969; Israel et al. 1986; Potter et al. 1989), but this evidence suggests that neuroleptic agents acutely reduce renal plasma flow, which should decrease HVA clearance. Therefore, it is not clear if the changes in HVA clearance are due to haloperidol or to other factors.

The observations with regard to plasma MHPG levels and urinary MHPG output were more straightforward. During the course of haloperidol treatment plasma levels and urinary output decreased over 5 weeks. These decreases presumably reflected decreased CNS NE turnover. In earlier work, Joseph et al. (1976) found that favorable clinical outcome was associated with a reduction in urinary MHPG during neuroleptic treatment. Alfredsson and Wiesel (1989) found that plasma MHPG decreased significantly each week after starting sulpiride. In all these studies other major metabolites of NE were not measured, and the possibility exists that there was shunting of metabolism away from MHPG toward these other metabolites.

There is evidence that much of the HVA in plasma and urine is from metabolism of DA in noradrenergic neurons (Anden and Grabowska-Anden 1983; Anden et al. 1985; Scheinin et al. 1984; Scheinin 1986; Scheinin and Virtanen 1986; Kopin et al. 1988a,b,c). In our haloperidol-treated patients, urinary HVA and MHPG changed in opposite directions over the first several weeks. Since a decrease in MHPG would normally be associated with a concurrent decrease in HVA (Kopin et al. 1988a), the observed increase in urinary HVA gives a minimal estimate of increased DA metabolism, i.e., if NE turnover were decreased as much as is indicated by the decreases in MHPG, then DA turnover must have been substantially increased in order to produce the moderate initial increases in urinary HVA that were actually present during neuroleptic treatment.

In the work reported in the preceding paper and in earlier work (Contreras et al. 1988), we found a considerable decrease in plasma HVA concentration between the hours of 8:00 A.M. and noon in control subjects and unmedicated schizophrenics. This time course has been noted by others as well (Sack et al. 1988; Davila et al. 1989; Doran et al. 1990). It was of interest to determine if this diurnal rhythm was affected by haloperidol treatment. As noted in Table 2, this morning decrease in plasma HVA levels was abolished by the end of the 5th week of haloperidol treatment. This finding has recently been published by Doran et al. (1990). Its significance with regard to the mechanism of action of haloperidol is unknown.

During the time that the work reported here was being completed, it was reported that very long-term neuroleptic administration may affect hydroxylation of DBQ in mentally retarded persons (Syvalahti et al. 1986). These authors found that the ratio of DBQ to 4-OH DBQ was significantly raised by administration

of a variety of neuroleptic drugs over many months. This report raised the question of whether chronic neuroleptic administration to patients receiving DBQ could raise the effective concentration of DBQ and thereby alter its effects on monoamine metabolism. In our work we used a high-performance liquid chromatography method to assay DBQ and 4-OH DBQ in urine and plasma in patients who were initially treated with DBQ alone and then received both DBQ and haloperidol. We found that in urine, DBQ concentrations did increase significantly while patients were receiving haloperidol. However, there was a trend in the same direction for 4-OH DBQ and we found no significant effects of haloperidol on the DBQ/4-OH DBQ ratio. Our results agree with the possibility raised by Syvalahti et al. (1986) as to DBQ levels being affected by the administration of neuroleptic agents, but also indicate that the ratio of DBQ/4-OH DBQ is not altered. This suggests that the underlying mechanism of the neuroleptic effect is probably not on hydroxylation. Even though DBQ levels may have increased during haloperidol treatment, it seems somewhat unlikely that such an increase would have significantly influenced the results. In earlier work, we found that increasing the dose of DBQ from 40 mg/day (as used here) to 60 mg/day did not further decrease HVA concentrations in plasma or urine (Maas et al. 1985). Moreover, our finding of decreases in plasma HVA during haloperidol treatment are consistent with the reports of others who studied patients not receiving DBQ. In addition, we found an increase in urinary HVA output during haloperidol treatment, which would certainly not be attributable to greater monoamine oxidase inhibition by DBQ. For these reasons, we conclude that the effects of haloperidol on catecholamine metabolite plasma levels and urinary excretion were not attributable to its effect on DBQ levels.

ACKNOWLEDGMENTS

This study was supported by Grant MH40935 and Clinical Research Center Grant MO1-RR01346 from the National Institutes of Health, Bethesda, Maryland; Veterans Administration Medical Research Funds; and the Hugo A. Auler Professorship of Psychiatry. Hoffman-LaRoche Ltd of Vandrenil, Quebec, Canada supplied the DBQ tablets. We thank the following for their active participation and assistance in this research: the staff of Unit 1C of the Audie L. Murphy Memorial Veterans' Hospital; Donna Irish, the project research nurse; and Rochelle Javors, Betsy Cuvelier, and Ray Benavides for technical assistance with the metabolite assays.

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