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Plasma homovanillic acid and treatment response in a large group of schizophrenic patients*

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Plasma levels of homovanillic acid (pHVA), a metabolite of dopamine, were measured in ninety-five Chinese schizophrenic patients free of neuroleptics for at least four weeks. These patients were treated with classical antipsychotics for six weeks. Pretreatment pHVA was positively correlated with the subsequent clinical response ($r=0.408$, $p<0.0001$). Good responders (BPRS improvement $\geqslant 50\%$, $n=47$) had higher pretreatment pHVA levels than poor responders (BPRS improvement $<50\%$, $n=48$) (15.7 ± 8.4 ng/ml versus 9.9 ± 3.7 ng/ml, $p<0.0001$). A higher than 15 ng/ml pretreatment pHVA level was associated with a more consistent clinical response to the subsequent treatment. Using a pHVA level of 12 ng/ml as a demarcation point, 72% of patients (34 of 47) who had pHVA $\geqslant 12$ responded whereas 65% (31 of 48) who had <12 did not respond (chi-square $=13.02$, $p<0.0001$). These results suggest that higher pretreatment pHVA levels may predict a better clinical response to antipsychotics. Based upon the pHVA findings, two hypothetical subtypes of schizophrenia are proposed.

Key words: Plasma homovanillic acid; Neuroleptic response; Subtype; (Schizophrenia)

INTRODUCTION

The dopamine (DA) hypothesis of schizophrenia which proposes that enhanced central dopaminergic activity is causally related to this mental disorder has been one of the most important and enduring concepts in biological psychiatry in the last two decades. The measurement of the DA metabolite homovanillic acid (HVA) in body fluids has been one of the most widely used strategies for studying aspects of DA function in neuropsychiatric disorders. This approach has been based, in part, on the possibility that metabolite production reflects neurotransmitter release and turnover in the brain. Even though no more than 25% of plasma HVA (pHVA) appears to be of central origin according to current estimates (Amin et al., 1992), plasma may still be the most useful body fluid for HVA measurement as a correlate of clinical state. Based on both lines of reasoning, pHVA studies in psychiatric patients have been conducted in a number of research centers (Bowers et al., 1984; Pickar et al., 1984; Davis et al., 1985; Chang et al., 1988; Davila et al., 1988).

Several reports of pHVA concentrations in schizophrenic patients have produced interesting, yet inconsistent, results. Pickar et al. (1984) found that pHVA levels in schizophrenic patients are significantly higher than those in normal control volunteers, whereas Davidson and Davis (1988) reported the reverse. In addition, significant positive correla-

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tions between baseline pHVA levels and symptom severity have been reported by Pickar et al. (1984) and Davis et al. (1985) but not by others (Bowers et al., 1984; Chang et al., 1990; Javaid et al., 1990; Mazure et al., 1991). Differences in patient population and study design methods could potentially account for the different findings. In contrast, a more consistent finding is that pretreatment pHVA levels are associated with clinical outcome in psychiatric patients (Bowers, 1991; Bowers et al., 1984, 1987; Chang et al., 1990; Davidson et al., 1991; Mazure et al., 1991) although not all studies agree (Javaid et al., 1990). We have previously reported that pretreatment levels of pHVA in a group of schizophrenic patients ($n=22$) who had a relatively favorable clinical response to a fixed-dose (20 mg/day) haloperidol treatment are significantly higher than those in poor responders ($n=11$) (Chang et al., 1990). Moreover, a time-dependent decrement in pHVA in good responders but not in poor responders was found in our previous studies (Chang et al., 1988, 1990). Based upon these findings, we have suggested that two biologically distinct subtypes can be differentiated among schizophrenic patients. In the present study we replicate and extend our initial observations to a new and larger group of patients who were treated with a variable dose of haloperidol or flupenthixol ($n=62$). Combined with the 33 subjects on fixed-dose haloperidol, this study provides data in a total of 95 schizophrenic patients.

METHODS

Subjects were ninety-five physically healthy Chinese patients (59 men aged 19–52 and 36 women aged 18–51) who were admitted to the psychiatric wards of Taipei City Psychiatric Center, National Taiwan University Medical Center and Military 818 Psychiatric Center from April 1985 to March 1990. All patients met DSM-III criteria for schizophrenic disorder (American Psychiatric Association, 1980), gave informed consent to participate in the study, and had not received oral antipsychotics for at least 4 weeks and depot antipsychotics for at least 3 months prior to study entrance. The patients were kept on a low-monoamine and caffeine-restricted diet throughout the study. One to three blood samples were obtained from the subjects after an overnight fast between 06.30 and 07.00 h on the successive 3 days before treatment. All patients then received a 6-week course of antipsychotic drugs. The drug trials involved three groups of patients: a previously reported fixed-dose haloperidol (20 mg/day) (Haldol, Janssen Pharmaceutica, Beerse, Belgium) group ($n=33$) (Chang et al., 1990), a variable-dose haloperidol group ($n=43$), and a variable-dose flupenthixol (Fluanxol, A/S Lundbeck, Copenhagen, Denmark) group ($n=19$). The dosages of the variable-dose groups were titrated on a clinical basis in the first two weeks and kept at the same levels during the subsequent 4 weeks. The dose ranges were 10 to 30 mg/day for haloperidol and 6 to 24 mg/day for flupenthixol, respectively. Anticholinergics and benzodiazepines were permitted during the six-week protocol.

Pretreatment psychotic symptoms were rated using the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) on one of the 3 days before the initial neuroleptic adminstration; ratings were repeated every 2 weeks during treatment. A total score was based on the sum of 16 items using a 0–6 scale. Patients with $\geqslant 50\%$ improvement in the total score by week 6 of treatment were considered as 'good responders'; those with $<50\%$ improvement were 'poor responders'.

One to four steady-state blood samples for plasma drug monitoring were also obtained from most patients ($n=90$).

Venous blood was drawn in heparinized tubes. The plasma samples, separated in a refrigerated centrifuge, were stored in a $-60°C$ freezer until assayed. Plasma free HVA was determined with high performance liquid chromatography using electrochemical detection (HPLC/ECD) (Chang et al., 1983). The sensitivity of this method is 0.5 ng/ml. The intra- and interassay coefficients of variation for this determination are 2.2% and 6.3%, respectively. Plasma concentrations of haloperidol (Korpi et al., 1983; Chang et al., 1989) and flupenthixol (Wu et al., 1978) were measured with HPLC/ECD. The sensitivity is 0.5 ng/ml or less for both assays. The intra- and interassay coefficients of variation are 4% and 12% for haloperidol and 4% and 15% for flupenthixol, respectively.

Statistical analysis was carried out by means of

the Student's t-test, Pearson's product-moment correlation and the chi-square test.

RESULTS

Forty-seven patients were rated as having a good clinical response, and 48 a poor clinical response. As shown in Table 1, the two groups did not differ significantly in terms of age, gender, or pretreatment BPRS rating. However, the pretreatment pHVA in the good responder group was significantly higher than that in the poor responder group (15.7 ± 8.4 ng/ml versus 9.9 ± 3.7 ng/ml, $t = 4.44$, $p < 0.0001$). Moreover, there was a positive correlation between baseline pHVA and clinical improvement after 6 weeks of antipsychotic treatment ($r = 0.408$, $p < 0.0001$) (Fig. 1). Nineteen of twenty-one patients with >15 ng/ml baseline pHVA values were good responders. However, more than one-half of the good responders had baseline pHVA values of <15 ng/ml (26/47). Using a pHVA level of 12 ng/ml as a demarcation point (Mazure et al., 1991), 72% of patients (34/47) who had pHVA $\geqslant 12$ responded whereas 65% (31/48) who had <12 did not respond (Chi-Square = 13.02, df = 1, $p < 0.0001$) (Table 2).

Data on pHVA and clinical response grouped according to fixed-dose and variable-dose schedules are presented in Table 3. Although haloperidol dosages and plasma levels in poor responders were significantly higher than those in good responders (0.48 ± 0.13 mg/kg/day versus 0.32 ± 0.15 mg/kg/day, $t = 2.932$, $p < 0.01$ and 25.9 ± 13.5 ng/ml versus 16.4 ± 10.9 ng/ml, $t = 2.627$, $p < 0.05$) in the variable-dose group, higher baseline pHVA levels in good responders and lower levels in poor responders were found in both fixed and variable dose groups: 17.4 ± 8.8 ng/ml versus 11.4 ng/ml ($p < 0.05$) and 14.0 ± 7.8 ng/ml versus 9.3 ± 3.0 ng/ml ($p < 0.005$).

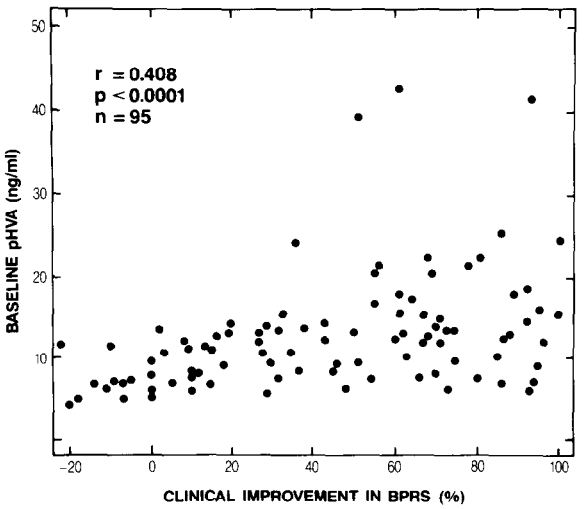

Fig. 1. Correlation between baseline pHVA levels and clinical improvements after 6 weeks of antipsychotic treatment.

DISCUSSION

Ninety-five schizophrenic patients were divided into two groups on the basis of their clinical outcome following 6 weeks of antipsychotic treatment. Patients who responded had higher pretreatment pHVA levels than non-responders. A higher than 15 ng/ml pretreatment pHVA level was associated with a more consistent clinical response to

TABLE 1

Data on schizophrenic patients grouped according to clinical response to neuroleptic treatment (mean ± SD)

	Good responders (n = 47)	*Poor responders (n = 48)*	*Difference*
Age (years)	29.6 ± 8.3	30.9 ± 9.1	NS
Sex (M/F)	28/19	31/17	NS
Baseline BPRS	36.5 ± 9.8	36.8 ± 9.8	NS
BPRS improvement (%)	74.4 ± 14.8	14.5 ± 19.4	$p < 0.0001$
Baseline pHVA (ng/ml)	15.7 ± 8.4	9.9 ± 3.7	$p < 0.0001$

BPRS, brief psychiatric rating scale; pHVA, plasma homovanillic acid.

TABLE 2

Comparison of plasma homovanillic acid and clinical response between two studies

Study	*Baseline plasma homovanillic acid*			
	≥ 12 ng/ml		*< 12 ng/ml*	
	Responder	*Nonresponder*	*Responder*	*Nonresponder*
Mazure et al. (1991)	14 (75%)	6 (25%)	5 (29%)	12 (71%)
This study	34 (72%)	13 (28%)	17 (35%)	31 (65%)

TABLE 3

Data on schizophrenic patients grouped according to fixed-dose and variable-dose schedules and clinical response to neuroleptic treatment (mean ± SD)

Variable	*Fixed-dose (n = 33)*		*Variable-dose (n = 62)*	
	Good responders (n = 22)	*Poor responders (n = 11)*	*Good responders (n = 26)*	*Poor responders (n = 36)*
Baseline pHVA (ng/ml)	17.4 ± 8.8	11.4 ± 5.0[a]	14.0 ± 7.8	9.3 ± 3.0[c]
Age (years)	29.4 ± 9.1	29.3 ± 8.7	29.7 ± 7.6	31.4 ± 9.3
Sex (M/F)	14/8	6/5	15/11	24/12
Baseline BPRS	36.4 ± 8.9	43.0 ± 8.3	36.7 ± 10.4	34.9 ± 9.5
Dose (mg/kg/day)				
Haloperidol	0.36 ± 0.06	0.37 ± 0.13	0.32 ± 0.15 ($n = 19$)	0.48 ± 0.13[b] ($n = 26$)
Flupenthixol			0.26 × 0.11 ($n = 8$)	0.29 ± 0.08 ($n = 11$)
Plasma level (ng/ml)				
Haloperidol	18.7 ± 7.0	16.0 ± 6.7	16.4 ± 10.9 ($n = 19$)	25.9 ± 13.5[a] ($n = 26$)
Flupenthixol			3.8 ± 1.7 ($n = 8$)	4.8 ± 1.3 ($n = 6$)
Improvement BPRS (%)	73.2 ± 14.0	25.6 ± 13.9[d]	75.4 ± 15.6	11.2 ± 19.7[d]

Fixed-dose: haloperidol 20 mg/day.
Variable-dose: haloperidol 10–30 mg/day; flupenthixol 6–24 mg/day.
pHVA: plasma homovanillic acid; BPRS: brief psychiatric rating scale.
[a] $p < 0.05$; [b] $p < 0.01$; [c] $p < 0.005$; [d] $p < 0.0001$.

antipsychotic treatment. This is in accord with the findings of several previous investigations (Bowers, 1991; Bowers et al. 1984, 1987; Chang et al., 1990; Davidson et al., 1991; Mazure et al., 1991). Data obtained from a group of 37 psychotic patients including schizophrenics and nonschizophrenics have been recently reported by Mazure et al. (1991). Using a pHVA level of 12 ng/ml as a demarcation point, these investigators found that 75% of patients (14 of 20) who had pHVA ≥ 12 responded whereas two-thirds (12 of 17) who had pHVA < 12 did not respond. Our results are remarkably consistent with these earlier results: 72% of patients (34 of 47) who had higher pHVA levels (≥ 12 ng/ml) responded while 65% of patients (31 of 48) who had lower pHVA levels (< 12 ng/ml) did not (Table 2).

A study of Pickar et al. (1984) found that schizophrenic patients who responded to fluphenazine treatment had higher pretreatment pHVA levels than normal subjects. In a study from another center, Davidson and Davis (1988) reported that treatment-resistant patients had lower pHVA levels than controls. Although we did

not have a matched group of normal controls, our results are generally consistent with these combined findings. Taken together, studies support the notion that higher pretreatment pHVA levels in schizophrenic patients are associated with good clinical response to neuroleptics, whereas lower pHVA may be related to poor response.

In other respects, our results differ from those reported by the two just cited research groups. Significant positive correlations between baseline pHVA levels and symptom severity have been reported by Pickar et al. (1984), Davis et al. (1985), and Davidson and Davis (1988). We did not find a significant relationship between pretreatment pHVA and BPRS score (data not shown). In this respect, our findings are more consistent with two other reports (Javaid et al., 1990; Mazure et al., 1991). This discrepancy among studies may be attributable to differences in patient populations and methods of symptom assessment. However, if baseline pHVA is generally correlated to symptom severity, it is hard to understand how mean baseline pHVA level in subgroups of schizophrenic patients who appear equally severely ill prior to treatment can be both higher and lower than in normal controls as reported by Pickar et al. (1984) and Davidson and Davis (1988), respectively.

There is far less discrepancy regarding the correlation between pHVA change and clinical response following antipsychotic treatment reported by a number of groups (Bowers et al., 1984; Pickar et al., 1984, 1986; Davidson et al., 1987, 1991; Chang et al., 1988, 1990; Davila et al., 1988; Mazure et al., 1991). Most investigators find that a time-dependent decrease in concentrations of pHVA is correlated with clinical improvement in response to antipsychotics, while no decrease in pHVA is associated with poor clinical response (Bowers et al., 1984; Pickar et al., 1984, 1986; Chang et al., 1988, 1990; Davila et al., 1988; Davidson et al., 1991; Mazure et al., 1991).

Combined, the various results suggest that a high pretreatment pHVA concentration followed by a relatively large decrease on antipsychotics reflect biochemical processes that play an important role in determining therapeutic response. A possible explanation of the differences in baseline pHVA level and pHVA change during long-term antipsychotic treatment between good and poor responders might be that the syndrome of schizophrenia is biochemically heterogeneous.

On the basis of the differential pretreatment pHVA levels and pHVA changes during chronic administration of antipsychotics as well as the different clinical responses to neuroleptic treatment, we suggest that at least two biologically distinct subtypes can be differentiated among schizophrenic patients: the first would be related to some forms of increased DA activity, and the second one would not. The two subtypes would be in accord with those identified by clinical symptoms (positive and negative), responses to antipsychotic treatment (good and poor), and brain structures determined by computed tomography (without and with brain atrophy) (Crow, 1980, 1985), with the additional characteristics of functional activities in dopaminergic neurons and/or DA synthesizing cells as manifested by pretreatment pHVA levels (high and low), and pHVA changes during long-term antipsychotic treatment (decrease and no decrease). Our results could be interpreted as in accord with the suggestion of Friedhoff (1986, 1988) and Davila (1989) that there may be a DA-dependent restitutive or buffer system for the maintenance of mental stability that reduces dopaminergic activity in the face of mentally destabilizing biological or psychological insults. Patients with evidence of high pretreatment dopaminergic activity (if this produces high pHVA) respond well to neuroleptics correlated with pHVA decrease, because antipsychotic medication is believed to exercise its therapeutic effect by decreasing dopaminergic activity. In contrast, those with low pretreatment DA function (thus low pHVA) have a poor therapeutic response associated with no decrease in dopaminergic activity, as it has already been downregulated by the stabilizing or restitutive system. Our hypothesis also is not inconsistent with the dopamine-serotonin hypothesis as suggested by Meltzer (1989). Treatment-resistent patients who have low baseline pHVA may response to atypical antipsychotics (e.g., clozapine). Measurement of pHVA may be a useful tool for drug choice in the treatment of schizophrenia. Patients with high pHVA can be treated with classical antipsychotics, while those with low pHVA may be need an atypical antipsychotic treatment.

The shortcomings of this study are evident. Data

gathered over a long period of time (5 years) is subject to potential errors. Some investigators have found that seasonal variations in HVA in cerebrospinal fluid and post-mortem brain may exist in humans (Karson et al., 1984; Losonczy et al., 1984). The possibility of a seasonal fluctuation in pHVA levels should be considered (Chang et al., 1993). Moreover, several studies have reported that pHVA and plasma 3-methoxy-4-hydroxyphenyl glycol, a metabolite of norepinephrine, are correlated (Bowers et al., 1984, 1897; Chang et al., 1990). These phenomena suggest the possibility that observed variations in pHVA are contributed by peripheral sources (Amin et al., 1992). For instance, the stress induced by admission might cause an elevation in plasma catecholamine metabolites in some subsets of subjects. Future studies should include efforts to cross these other possible sources of variance in pHVA.

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