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ORIGINAL INVESTIGATION

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Catatonia: short-term response to lorazepam and dopaminergic metabolism

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Abstract Therapeutic response to lorazepam and dopaminergic metabolism were investigated in 18 neuroleptically naive acute catatonic patients. They were diagnosed as catatonic according to criteria by Lohr and Rosebush and treated exclusively with lorazepam (2–4 mg) during the first 24 h. Dopaminergic metabolism (plasma HVA, plasma MHPG), anxiety (HAM-A) and parkinsonic/dyskinetic movements (SEPS, AIMS) were measured under standard conditions before initial treatment with lorazepam (day 0) and 24 h after initial treatment (day 1). On day 0 responders to lorazepam treatment (complete remission of catatonic syndrome after 24 h according to Rosebush and Lohr) showed significantly higher ($P = 0.004$) plasma HVA (130.4 ± 51.2 pmol/ml; means ± SD) than non-responders (no remission of catatonic syndrome after 24 h; 73.2 ± 40.5 pmol/ml; means ± SD). On day 1 plasma HVA did not differ any more significantly between both groups Clinically, responders showed significantly higher HAM-A ($P = 0.025$) and AIMS ($P = 0.022$) scores as well as significantly lower SEPS ($P = 0.049$) scores than non-responders on day 0. Hence catatonic short-term responders and non-responders to lorazepam can be distinguished with regard to plasma HVA, anxiety and dyskinetic/parkinsonic movements.

Key words Catatonic syndrome · Lorazepam · Plasma, HVA · Anxiety · Movements

Introduction

Kahlbaum introduced the term catatonia by describing a specific disease entity with motor abnormalities like akinesia, posturing, catalepsy, rigidity, negativism, grimacing, waxy flexibility and verbigerations (Kahlbaum 1874). In contrast to Kahlbaum, Kraepelin (1905) and Bleuler (1911) primarily referred to catatonia as a subtype of schizophrenia. Nowadays catatonia is rather considered as a non-specific syndrome which may be associated with either organic or non-organic (e.g. psychiatric) diseases (Gelenberg 1976; Cummings 1985; Editorial 1986; Taylor 1990; Fink et al. 1993). Lorazepam is generally regarded as a standard treatment in catatonia (Salam et al. 1987; Wetzel and Benkert 1988; Menza 1991; Fink et al. 1993). About, 70–80% of all catatonic patients respond dramatically to lorazepam, given orally or intravenously (Rosebush et al. 1990; Ungvari et al. 1994). Catatonic responders to lorazepam showed rather hypokinetic movements (Rosebush et al. 1990) and reported retrospectively often about intense anxiety during the catatonic state (Rosebush et al. 1991; Northoff et al. 1995). Dopaminergic metabolism in catatonia has so far been investigated only by Gjessing and Northoff et al.: urinary and plasma homovanillic acid (HVA) was increased in acute catatonic patients (Gjessing 1974; Northoff et al. 1994). Investigations of plasma HVA in catatonic responders and non-responders to lorazepam are not known. Schizophrenic patients with a good response to neuroleptics show slightly increased plasma HVA, whereas it is slightly decreased in schizophrenic non-responders (Chang et al. 1990; Baker et al. 1991; Davidson et al. 1991).

The present study was conducted to determine the relation between dopaminergic metabolism (plasma HVA), anxiety (HAM-A) and associated dyskinetic/parkinsonic movements (AIMS/SEPS) in catatonic responders and non-responders to lorazepam. In order to distinguish between central and peripheral sources of plasma HVA we measured plasma 3-hydroxy-4-methoxy phenyl glycol (MHPG) as an index of peripheral dopaminergic and noradrenergic activity (Amin et al. 1992). Eighteen neuroleptically

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naive acute catatonic patients, diagnosed according to criteria by Lohr (1987) and Rosebush and Wisniewski et al. (1990), were investigated before (day 0) and after (day 1) initial treatment with lorazepam. Similiar to the relation between plasma HVA and neuroleptic response in schizophrenia, catatonic responders to lorazepam were expected to show increased levels of plasma HVA. Catatonic non-responders were expected to show rather low levels of plasma HVA.

Materials and methods

Subjects

Eighteen neuroleptically naive and psychotropically naive acute catatonic patients (nine women, nine men; age: 32.4 ± 9.6; means ± SD) participated in the study. All patients were admitted for the first time to a psychiatric hospital and were selected from all incoming patients into the psychiatric university clinic of Frankfurt. Sampling time was from March 1991 to February 1994. Patients with concomittant Parkinson's disease or other neurological movement disorders were excluded. Catatonic patients with abnormal dyskinetic movements were not primarily excluded because such movements may occur in catatonia as well (Lohr and Wisniewski 1987). All investigations were performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Catatonic syndrome was diagnosed according to criteria by Lohr and Wisniewski (1987; at least 3 from 11 symptoms) and Rosebush et al. (1990; at least 4 from 12 the symptoms). All patients had to fulfil the criterias of a catatonic syndrome developped by both authors above mentioned. Clinical evaluation was executed by two independent psychiatrists (G.N.; J.W.) with special experience in catatonia. Patients on whom they disagreed with regard to diagnosis of catatonic syndrome were excluded.

Co-morbid diagnosis were made according to DSM III R (APA 1987) by two independent psychiatrists with a structured clinical interview at discharge.

Anxiety and movements

Anxiety was rated with HAM-A (Hamilton 1959). Dyskinetic and parkinsonic movements were evaluated by AIMS (Guy 1976) and SEPS (Simpson and Angus 1970). General psychopathology was measured by GAS (Endicott et al. 1976). All psychopathological ratings were done by G.N. and J.W., who had both completed special rating trainings. Assessment of the interrater and intrarater reliabilities for the different scales revealed average intraclass correlation coefficients between 0.90 and 0.95.

Response to lorazepam

All catatonic patients received lorazepam 2–4x 1–2,5 mg (means: 4.8 mg) either orally ($n = 5$; all responders) or intravenously ($n = 13$; seven responders, six non-responders) in the first 24 h. According to clinical response to lorazepam in the first 24 h, judged by the criteria of Lohr and Rosebush, we distinguished between short-term responders and short-term non-responders. Evaluation of catatonic syndrome as well as measurements of plasma HVA/MHPG and psychopathology (HAM-A, AIMS/SEPS) were done on day 0 before initial treatment with lorazepam and on day 1, 24 h after initial treatment with lorazepam.

Plasma HVA

Influencing factors (Davidson et al. 1987; Amin et al. 1992) like circadian rhythm (collection of blood samples at 8.20–8.30 a.m. in all patients) and renal function (exclusion of patients with abnormal renal function) were controlled. Due to different admission times it was not possible to collect blood at 8.00–9.00 a.m.in two patients ($n = 2$; one responder and one non-responder; no significant difference between these two patients and the other ones with regard to plasma HVA). Due to lack of control of catatonic patients before admission, we were neither able to account for diet and physical activity nor for seasonal variations (Amin et al. 1992), because patients were admitted throughout the whole year. Patients who drank excessive amounts of alcohol (more than one bottle of beer or one or two glasses of wine) or took drugs (heroin, cocaine, etc.) in the days before/on admission were excluded.

One blood sample was obtained from an antecubital vein on day 0 (before initial medication with lorazepam) and day 1 (24 h after admission). Blood samples were drawn in heparinized tubes, plasma was prepared by means of a refrigerated centrifuge and stored at −60°C until measurement of HVA and MHPG.

In order to determine the origin of plasma HVA, either central or peripheral, we measured plasma MHPG (Amin et al. 1992): plasma HVA is considered to be a metabolite of peripheral as well as of central dopamine. Plasma MHPG is regarded as an index of solely peripheral dopaminergic and noradrenergic activity. Thus possible increases of plasma HVA might be localized in their source, either central or peripheral, measuring plasma MHPG in addition.

Plasma homovanillic acid (HVA) concentrations were biochemically determined by using high pressure liquid chromatographic (HPLC) methods as described by Seiler and Hiemke (Seiler and Hiemke 1993) and 3-hydroxy-4-methoxy phenylglycol (MHPG) in accordance with a method described by Sarre et al. (1992). Inter- and intra-assay coefficients of variation of both procedures were lower than 5%.

Data analysis

All results were expressed in means and standard deviations. Deviations from normal distributions were calculated by use of Kolmogoroff-Smirnov of fit goodness test. Statistical significance was computed with the chi-spuare test and the t-test for random samples. All computations were executed with the SPSS-X statistics software system.

Results

Response to lorazepam

Twelve patients showed a dramatic short-term response to lorazepam within the first 24 h so that they were classified as responders whereas six patients were non-responders. With regard to age and sex, there were no significant differences (Chi-Quadrat) between responders (age: 31.2 ± 10.3; sex: five women, seven men) and non-responders (age: 33.6 ± 8.9; sex: four women, two men).

Responders and non-responders showed the following catatonic symptoms (as percentage) according to Rosebush on day 0 and 1: immobility (responders on day 0/1: 61/4, non-responders on day 0 and 1: 69/32), staring (72/2, 67/44), mutism (75/1, 76/52), rigidity (24/6, 20/20), autism (54/2, 65/40), posturing (62/3,

Table 1 Plasma HVA, anxiety and movements in catatonic responders and non-responders

	Day	Responder mean (±SD)	Non-responder mean (±SD)	*t*-test (*P*)
Plasma HVA (picomol/ml)	0	130.4 (51.2)	72.2 (40.5)	0.004
	1	119.4 (46.6)	118.9 (49.8)	n.s.
Plasma MHPG (picomol/ml)	0	15.9 (10.5)	16.8 (12.0)	n.s.
	1	15.6 (10.1)	15.2 (10.1)	n.s.
GAS	0	11.2 (5.1)	11.3 (6.2)	n.s.
	1	26.6 (5.9)	15.2 (5.8)	0.013
HAM-A	0	28.2 (6.3)	17.5 (8.2)	0.025
	1	14.7 (5.9)	15.2 (6.1)	n.s.
AIMS	0	14.3 (15.2)	6.3 (11.3)	0.022
	1	3.9 (9.5)	4.0 (8.2)	n.s.
SEPS	0	11.6 (4.8)	18.8 (5.9)	0.049
	1	10.2 (4.6)	12.4 (5.1)	n.s.

61/50), grimacing (36/4, 27/26), negativism (29/7, 33/30), waxy flexibility (44/4, 46/32), echolalia/echopraxia (22/5, 28/20), stereotypies (29/7, 35/30), verbigerations (27/5, 25/18). Catatonic symptoms did not differ significantly between responders and non-responders on day 0 so that with regard to catatonic syndrome they could not be distinguished. On day 1 non-responders showed significantly more catatonic symptoms than responders.

According to Lohr and Wisniewski (1987), we classified six patients as excited catatonia and 12 as retarded catatonia. The response to lorazepam did not differ significantly between patients with excited and retarded catatonia (chi-square).

Responders and non-responders showed the following co-morbid diagnosis according to DSM III R:

Catatonic schizophrenia (295.2): 4 responders/0 non-responder.

Paranoid schizophrenia (295.3): 1 responder/0 non-responder.

Residual schizophrenia (295.6): 1 responder/4 non-responders.

Major depression (296.3): 2 responders/1 non-responder.

Bipolar mania (296.4): 1 responder/0 non-responder.

Brief reactive psychosis (298.8): 1 responder/0 non-responder.

Dysthymia (300.4): 1 responder/0 non-responder.

Organic catatonia: 1 responder (AIDS encephalopathy)/1 non-responder (Morbus Hodgkin).

Significant relationships (chi-square) were found between responders and non-residual schizophrenia as well as between non-responders and residual schizophrenia ($P < 0.05$).

Anxiety and movements

Table 1 shows scores for the different rating scales in responders and non-responders on day 0 and 1. On day 0 responders showed significantly more anxiety (HAM-A) and dyskinesias (AIMS) as well as significantly fewer parkinsonic symptoms (SEPS) than non-responders. On day 1 no significant differences could be found between responders and non-responders (see Table 1). Significant correlations were not found between plasma HVA/MHPG and anxiety scores (HAM-A) or between plasma HVA/MHPG and AIMS/SEPS on days 0 and 1. Moreover, no significant correlations were obtained between HAM-A scores and AIMS/SEPS.

Plasma HVA and MHPG

On day 0 responders showed a significantly higher plasma HVA than non-responders. There were no significant differences on day 1 anymore (see Table 1). Only responders showed a significant difference of plasma HVA between days 0 and 1. Plasma HVA did not differ significantly between patients with excited and retarded catatonia on day 0 and 1 ($P < 0.005$).

Plasma MHPG, the index of peripheral dopaminergic and noradrenergic metabolic activity, did not differ significantly between responders and non-responders either on day 0 or on day 1. Hence it seems likely that increased plasma HVA in responders on day 0 is derived from central dopaminergic metabolism. Correlations between plasma HVA and MHPG were significant only for non-responders ($P = 0.0001$). Responders did not show significant correlations between plasma HVA and plasma MHPG. This underlines the central origin of increased plasma HVA in responders on day 0. There were no significant correlations between plasma HVA and plasma MHPG in both groups on day 1.

Discussion

High plasma HVA was obtained in neuroleptically-naive patients suffering from paranoid schizophrenia who responded well to neuroleptic treatment (Pickar et al. 1984). In contrast, residual schizophrenic patients showing a bad neuroleptic response had low plasma HVA levels (Davidson and Davis 1988; et al. Davidson 1991; Chang et al. 1990). Hence it is generally agreed that rather than absolute baseline values (Baker et al. 1991), different levels of plasma HVA associated with different responses to neuroleptic treatment may distinguish between paranoid and residual schizophrenia (Chang et al. 1990, Baker et al. 1991; Davidson et al. 1991). Dopaminergic metabolism in catatonia has so far only been investigated by Gjessing (1974) and Northoff et al. (1994): Both authors found an increase in either urinary (Gjessing 1974) or plasma (Northoff et al. 1994) HVA in acute neuroleptically

naive catatonic patients. The relation between catatonic syndrome and response to lorazepam may be similiar to the one between schizophrenia and neuroleptic response: plasma HVA was higher in short-term responders and lower in short-term non-responders. In contrast to Gjessing, we determined plasma MHPG, as a marker of peripheral dopaminergic and noradrenergic metabolic activity, as well. Thus due to the non-significant correlation between plasma HVA and plasma MHPG in both groups, it is likely that increased plasma HVA in responders is of central origin.

Catatonic short-term responders not only showed high plasma HVA but, additionally, high anxiety scores. In the present study there were no significant correlations between anxiety scores and plasma HVA/MHPG. Thus it is unlikely that high plasma HVA in short-term responders may simply be an epiphenomenon of higher anxiety. As shown by Rosebush et al. (1990), we were able to demonstrate a relationship between anxiety and response to lorazepam in catatonic syndrome. This is underlined by investigation of subjective experiences in patients who retrospectivly report predominantly about intense anxieties during the acute catatonic state (Northoff et al. 1995). Nevertheless, the relation between response to lorazepam, anxiety and high plasma HVA remains unclear.

It could be imagined that plasma HVA in catatonic syndrome may be related with dopaminergic metabolism of associated movements: short-term responders showed more dyskinesias whereas short-term non-responders rather exhibited parkinsonic movements. Due to lack of significant correlations between plasma HVA and AIMS/SEPS, it is rather improbable that dopaminergic metabolism may account for associated movements in catatonic syndrome. Similiar to our results in catatonic syndrome, acute schizophrenic patients with neuroleptic response showed dyskinesias whereas residual schizophrenic patients with neuroleptic non-response rather exhibited parkinsonic movements (Mortimer et al. 1990; McKenna et al. 1991). Such an association of schizophrenic type with dyskinetic/parkinsonic movements can be shown in catatonic syndrome as well: short-term responders with increased dyskinsias were either diagnosed as acute schizophrenic or as non-schizophrenic. Short-term non-responders with parkinsonic movements showed, in contrast, a diagnosis of residual schizophrenia.

Considering some methodological shortcomings in our study, interpretation should be made cautiously: we were not able to account for all factors (diet, physical activity, seasonal variation) influencing plasma HVA activity because there was no control of catatonic patients before admission. The number of investigated patients is quite small in the present study because neuroleptically naive catatonic patients are few. Comorbid diagnosis of schizophrenia is overrepresented in our study group ($n = 10$) which may in particular influence results of dopaminergic metabolism. Moreover, there are problems investigating acute catatonic patients because they are often mute. Therefore we did not investigate other psychopathological scales like BPRS etc. However even in the ones we used, evaluation was sometimes difficult due to abnormal catatonic behaviour.

With regard to these methodological constraints conclusions which can be drawn from our study may be limited. Nevertheless, our results indicate that catatonic short-term responders and non-responders may not only differ in their response to lorazepam but also with regard to dopaminergic metabolism, anxiety, associated movements and co-morbid diagnosis. Further investigations may show whether catatonic short-term responders and non-responders to lorazepam may represent two distinct catatonic subtypes.

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