Psychological Medicine, 1997, **27**, 1223–1225. Printed in the United Kingdom

BRIEF COMMUNICATION

Low superoxide dismutase activity in schizophrenic patients with tardive dyskinesia

K. YAMADA,[1] S. KANBA, S. ANAMIZU, K. OHNISHI, I. ASHIKARI, G. YAGI AND M. ASAI

From the Department of Neuropsychiatry, School of Medicine, Keio University, Tokyo, Japan

ABSTRACT

Background. Tardive dyskinesia (TD) is a therapy-resistant adverse effect of neuroleptics. Although the exact pathophysiology of TD is unknown, oxygen radicals have been speculated to play a role in TD based on several lines of evidence. Superoxide dismutase (SOD) is a key enzyme which scavenges oxygen radicals. The authors investigated the association between erythrocyte SOD activity and TD.

Methods. Erythrocyte SOD activities were measured, blinded as to the presence or absence of TD, in 30 patients with schizophrenia who had been on typical neuroleptics for more than 10 years. TD severity was independently assessed, using the abnormal involuntary movement scale (AIMS), by two raters.

Results. There was a significant decrease in erythrocyte SOD activity in the definite TD group ($N = 10$) as compared with the no TD ($N = 8$) and questionable TD ($N = 12$) groups. Erythrocyte Cu,Zn-SOD activities correlated with AIMS scores.

Conclusions. Patients with TD had low SOD activities as compared to those without TD. As a causal link between SOD activity and TD was not established in this study, larger prospective studies are warranted to determine whether patients with low SOD activity are susceptible to neuroleptic-induced TD.

INTRODUCTION

Tardive dyskinesia (TD) is a therapy-resistant adverse effect of neuroleptics. A number of medications have been tried as therapies for TD, but the results have been mostly disappointing (Jeste *et al.* 1988). Although the exact pathophysiology of TD is unknown, oxygen radicals have been speculated to play a role in TD based on several lines of evidence (Lohr, 1991). For example, it has been reported that free radicals, especially superoxide radicals, are produced via increased dopamine turnover associated with long-term neuroleptic treatment (Stein & Wise, 1971; Graham *et al.* 1978; Matsumoto *et al.* 1983). Lower blood or erythrocyte activities of superoxide dismutase (SOD), a key enzyme which scavenges oxygen radicals, have been found in some neurological disorders, including Parkinson's disease, Wilson's disease and Huntington's disease (Lohr, 1991).

An earlier study (Abdalla *et al.* 1986) found no difference in blood SOD activities between schizophrenic patients receiving, and those not receiving, neuroleptics. However, the relationship between SOD and TD remains to be fully clarified. In this study, we measured erythrocyte Cu,Zn-SOD activity in schizophrenic patients with, and without, definite TD and examined the relationship between SOD activity and TD.

[1] Address for correspondence: Dr Kazuo Yamada, Department of Neuropsychiatry, School of Medicine, Keio University, 35 Shinanomachi, Shinjuku-ku, Tokyo, 160 Japan

METHOD

The subjects were 30 male in-patients who met DSM-IV criteria for schizophrenia. All had been on typical neuroleptics for more than 10 years. We fully explained the study design and aims and obtained written informed consent to participate from each patient. None had any medical or neurological complications. The ages ranged from 26 to 80 years old (mean = 61·4, standard deviation (S.D.) = 11·9), onset age of schizophrenia from 13 to 45 years old (mean = 23·8, S.D. = 8·0), and the duration of schizophrenia from 10 to 54 years (mean = 37·7, S.D. = 11·2). The daily dose of the prescribed neuroleptics was equivalent 32·5 to 2475 mg (mean = 427·8, S.D. = 528·6) of chlorpromazine.

TD was assessed, using the abnormal involuntary movement scale (AIMS), by two experienced psychiatrists blinded to the Cu,Zn-SOD activities. Ten patients (TD group) were judged as having definite TD on the basis of satisfying the diagnostic criteria for TD (Moore *et al*. 1983), and on a severity of movement score of 2 (Mild), or worse, made by both observers. All patients in the TD group had oro-facial dyskinesia and three also had trunk or limb dyskinesia. Eight patients had no TD (NTD group), based on severity of movement scores assessed as 0 (None, normal) by both observers, and the remainder (12 patients) were regarded as having questionable TD (QTD group).

Erythrocyte Cu,Zn-SOD activity was measured by the nitrite method (Oyanagui, 1984). Briefly, hydroxylamine or its O-sulfonic acid, xanthine oxidase, hypoxanthine, EDTA, and the sample were incubated with or without KCN at pH 8·2, 37 °C, for 30 min. Diazo dye-forming reagent was added and the absorption was measured at 550 nm.

Data were analysed with analysis of variance (ANOVAs). *Post-hoc* analysis was performed with Fisher's protected least significant difference (PLSD). A P value of less than 0·05 was considered statistically significant.

RESULTS

There were no differences among the three groups in mean age, mean onset age of schizophrenia, mean duration of schizophrenia, or the mean daily dose of the prescribed neuroleptics (see Table 1). As to erythrocyte Cu,Zn-SOD activities, there was a significant decrease (F = 5·818, df = 2, 27, P = 0·0079) in the TD group (mean = 1188·2 U/1E10 erythrocyte, S.D. = 139·5) as compared with the NTD group (mean = 1402·1 U/1E10 erythrocyte, S.D. = 195·5) and the QTD group (mean = 1332·5 U/1E10 erythrocyte, S.D. = 79·7) (see Table 1). The erythrocyte Cu,Zn-SOD activities correlated with the AIMS scores (r = −0·45, P = 0·013).

DISCUSSION

Our results indicate that patients with TD have lower erythrocyte Cu,Zn-SOD activities than those with questionable or no TD, and there was a significant correlation between TD severity and erythrocyte Cu,Zn-SOD activities. For this study, we selected only patients who had been on neuroleptics for at least 10 years. AIMS were

Table 1. *Clinical characteristics and SOD activities of the three groups*

	TD group (N = 10)		QTD group (N = 12)		NTD group (N = 8)		Analysis	
Variable	Mean	S.D.	Mean	S.D.	Mean	S.D.	F(df = 2, 27)	P
Age (years)	64·0	9·3	64·2	11·0	54·1	14·3	2·219	0·13
Onset age (years)	25·4	8·7	24·0	7·6	21·4	8·1	0·557	0·58
Duration of illness (years)	38·6	10·1	40·3	8·7	32·8	15·3	1·151	0·33
Neuroleptics (CP equiv.)	458·3	547·2	461·5	682·5	339·3	169·3	0·144	0·87
Total AIMS score	5·75	2·03	1·33	0·75	0	0	53·6	0·0001
SOD (U)	1188·2	139·5	1332·5	79·7	1402·1	195·5	5·818	0·0079

Note: TD definite tardive dyskinesia, QTD questionable tardive dyskinesia, NTD no tardive dyskinesia, CP equiv. equivalent dose of chlorpromazine (mg/day).

There were significant differences in SOD activities between the TD and NTD groups (P < 0·005) and between the TD and QTD groups (P < 0·05) by *post-hoc* analysis with Fisher's PLSD.

https://doi.org/10.1017/S0033291797005114 Published online by Cambridge University Press

then evaluated independently by two psychiatrists in order to identify those with definite TD.

Previous hypotheses have included the concept that free radicals, especially superoxide radicals, produced via increased dopamine turnover associated with long-term neuroleptic treatment (Stein & Wise, 1971; Graham *et al*. 1978; Matsumoto *et al*. 1983), induced destabilization and protein oxidation in the central nervous system (Halliwell, 1989). In addition, it has been reported that lipid peroxidation was increased in cerebrospinal fluid from patients taking phenothiazines (Pall, 1987) and that free radical activity was higher in patients with TD than in those without TD (Lohr *et al*. 1990). The possible involvement of oxygen radicals in the pathophysiology of TD was discussed in a review article (Lohr, 1991). Along with the aforementioned reports, several lines of evidence have been presented indicating that vitamin E may be effective even for advanced TD (Lohr *et al*. 1987; Elkashef *et al*. 1990; Egan *et al*, 1992; Dabiri *et al*. 1994). Thus, chronic exposure to superoxide radicals produced by neuroleptics may increase the risk of TD, while SOD and free radical scavengers like vitamin E may play a preventive role. Our investigation involved a small sample size and was cross-sectional. Larger, prospective studies are warranted to determine whether measurement of Cu,Zn-SOD activity may allow prediction of susceptibility to TD, in patients requiring long-term neuroleptic treatment, and whether coadministration of superoxide scavengers with neuroleptics for those with low Cu,Zn-SOD activity may be an effective method of reducing the risk of TD.

This study was supported by a grant from Ohme Keiyu Hospital, Ohme, Tokyo, Japan (Dr N. Otsuka, Director). The authors also thank Jiundou Naika Hospital, Nerima, Tokyo, Japan (Dr S. Itoh, Director) for supporting this project.

REFERENCES

Abdalla, D. S. P., Monteiro, H. P., Oliveira, J. A. C. & Bechara, J. H. (1986). Activities of superoxide dismutase and glutathione peroxidase in schizophrenic and manic-depressive patients. *Clinical Chemistry* **32**, 805–807.

Dabiri, L. M., Pasta, D., Darby, J. K. & Mosbacher, D. (1994). Effectiveness of vitamin E for treatment of long-term tardive dyskinesia. *American Journal of Psychiatry* **151**, 925–926.

Egan, M. F., Hyde, T. M., Albers, G. W., Elkashef, A., Alexander, R. C., Reeve, A., Blum, A., Saenz, R. E. & Wyatt, R. J. (1992). Treatment of tardive dyskinesia with vitamin E. *American Journal of Psychiatry* **149**, 773–777.

Elkashef, A. M., Ruskin, P. E., Bacher, N. & Barrett, D. (1990). Vitamin E in the treatment of tardive dyskinesia. *American Journal of Psychiatry* **147**, 505–506.

Graham, D. G., Tiffany, S. M., Bell, W. R. & Gutknecht, W. F. (1978). Auto-oxidation versus covalent binding of quinones as the mechanism of toxicity of dopamine, 6-hydroxydopamine, and related compounds toward C1300 neuroblastoma cells in vitro. *Molecular Pharmacology* **14**, 644–653.

Halliwell, B. (1989). Oxidants and the central nervous system: some fundamental questions. *Acta Neurologica Scandinavica* **126**, 23–33.

Jeste, D. V., Lohr, J. B., Clark, K. & Wyatt, R. J. (1988). Pharmacological treatments of tardive dyskinesia in the 1980s. *Journal of Clinical Psychopharmacology* **8**, s38–s48.

Lohr, J. B. (1991). Oxygen radicals and neuropsychiatric illness: some speculations. *Archives of General Psychiatry* **48**, 1097–1106.

Lohr, J. B., Cadet, J. L., Lohr, M. A., Jeste, D. V. & Wyatt, R. J. (1987). Alpha-tocopherol in tardive dyskinesia. *Lancet* i, 913–914.

Lohr, J. B., Kuczenski, R., Bracha, H. S., Moir, M. & Jeste, D. V. (1990). Increased indices of free radical activity in the cerebrospinal fluid of patients with tardive dyskinesia. *Biological Psychiatry* **28**, 535–539.

Matsumoto, T., Uchimura, H., Hirano, M., Kim, J,. Yokoo, H., Shimomura, M., Nakahara, T., Inoue, K. & Oomagari, K. (1983). Differential effects of acute and chronic haloperidol on homovanillic acid levels in discrete dopaminergic areas of rat brain. *European Journal of Pharmacology* **89**, 27–33.

Moore, D. C., Glazer, W. M., Bowers, M. B., & Heninger, G. R. (1983). Tardive dyskinesia and plasma homovanillic acid. *Biological Psychiatry* **189**, 1393–1402.

Oyanagui, Y. (1984). Reevaluation of assay methods and establishment of kit for superoxide dismutase activity. *Analytical Biochemistry* **142**, 290–296.

Pall, H. S., Williams, A. C., Blake, D. R. & Lunec, J. (1987). Evidence of enhanced lipid peroxidation in the cerebrospinal fluid of patients taking phenothiazines. *Lancet* ii, 596–599.

Stein, L. & Wise, C. D. (1971). Possible etiology of schizophrenia: progressive damage to the noradrenergic reward system by 6-hydroxydopamine. *Science* **171**, 1032–1036.