Clinica Chimica Acta, 169 (1987) 329–332
Elsevier

CCA 04007

Short communication

Decrease of serum malondialdehyde in patients treated with chlorpromazine

A. Bindoli [a], M.P. Rigobello [b], L. Cavallini [b], A. Dalla Libera [c] and L. Galzigna [b]

[a] *Centro Studio Fisiologia Mitocondriale CNR,* [b] *Istituto di Chimica Biologica, Padova and* [c] *Dipartimento di Psichiatria, Ospedale Psichiatrico S. Felice, Vicenza (Italy)*

(Received 20 October 1986; revision received 17 July 1987; accepted after revision 11 August 1987)

Key words: Chlorpromazine; Serum malondialdehyde

Summary

Malondialdehyde determination in serum from schizophrenic patients before and after treatment with chlorpromazine showed that, after treatment, patients had significantly lower values than before. The antioxidant properties of chlorpromazine can be related to its effect on the level of serum lipid peroxides and possibly to its neuroleptic action.

Introduction

Lipid peroxides, normally present in serum in rather small amounts, significantly increase as a consequence of stress conditions such as burn injury [1], liver disease [2], heart disease [3] and cerebrovascular disorders [4].

The increased lipid peroxide concentrations may be secondarily responsible for deleterious effects in intact organs or tissues and particularly at the blood vessel level since lipid peroxides can concur to the early stages of atherosclerosis [5].

It is also known that phenothiazines act as potent antioxidants in vitro [6] and some experiments showed that chronic administration of chlorpromazine (CPZ) decreases the concentration of malondialdehyde (MDA) normally found in rat brain [7].

In the present paper we report MDA concentrations in serum of a group of psychiatric patients before and after the administration of CPZ.

Correspondence to: Alberto Bindoli, Istituto di Chimica Biologica, Via F. Marzolo 3, 35131 Padova, Italy.

Materials and methods

The patients were 23 clinically diagnosed male schizophrenics aged 30–66 yr; they were given 80 mg of CPZ three times per day (at 7 a.m., 2 p.m. and 9 p.m.) for 3 wk. Blood was collected by venepuncture 1 h before and 1 h after the first and the last dose of CPZ, left to coagulate at 25 °C for 4–6 h and then centrifuged at $1500 \times g$ for 10 min. Sera were then collected and stored frozen at −20 °C.

MDA was determined in serum by adapting the 2-thiobarbituric acid method described by Yagi [1]. Briefly: 100 µl of serum were treated with 3.9 ml of 50 mmol/l H_2SO_4 and 0.5 ml of 34.29 mmol/l phosphotungstic acid, vigorously mixed and then centrifuged for 10 min at $1\,500 \times g$. Supernatant was discarded, the pellet was treated again in the same way and then resuspended to a final volume of 4 ml in a mixture of 2.5 g/l Nonidet P-40 (from Sigma Chemical Co., St. Louis, MO, USA), 0.36 mmol/l butylated hydroxytoluene, 8.4 mmol/l thiobarbituric acid and 480.4 mmol/l acetic acid. The reaction mixture was heated at 95 °C for 60 min, cooled and centrifuged at $7\,700 \times g$ for 10 min. The content of MDA of the clear supernatant was measured spectrophotometrically at 532 nm after subtracting the values measured at 580 nm by using an ϵ_M value of 156 000.

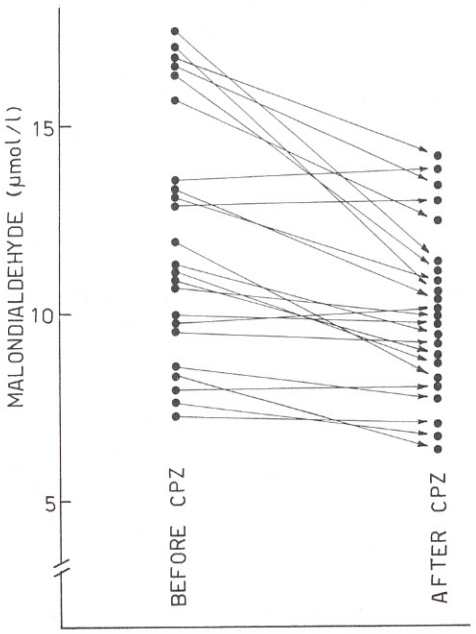

Fig. 1. Serum malondialdehyde concentration before and after administration of 80 mg of chlorpromazine (CPZ) 3× day for 3 wk.

Results and discussion

As shown in Fig. 1, serum MDA decreased in all patients after taking CPZ for three weeks. Before CPZ treatment the mean ± SD concentration of serum MDA was 12.03 ± 3.20 μmol/l, while after the administration it was 10.06 ± 2.14 μmol/l of serum ($p < 0.001$ by the Wilcoxon test [8]). Control values were measured in sera obtained from 5 unmedicated healthy volunteers aged 25–35 yr under the same conditions used for the patients' sera and the MDA concentration was not substantially different from that found in the schizophrenic patients before the treatment with CPZ. We observed that the number of freezings and thawings and the duration of the storage at −20 °C tend to increase the amounts of MDA determined. In any case the sera obtained before and after chlorpromazine treatment were stored frozen for the same time so that the MDA increase due to storage artifact should be comparatively similar.

The procedure used for MDA determination avoids both the interference of sialic acid and that of platelet aggregation which could occur during the drawing of the blood and increase MDA formation through the thromboxane synthetase pathway [1]. The inclusion of a detergent, i.e. nonidet P-40 in the assay for the formation of the adduct between MDA and thiobarbituric acid improves the test giving consistently higher and better reproducible values (data not shown).

Our results with chlorpromazine reflect a general antioxidant effect of this drug toward lipid peroxidation; nevertheless, due to its neuroleptic properties, this antioxidant effect should be particularly relevant for the nervous system.

It is perhaps possible to correlate the antioxidant effect of CPZ to its neuroleptic action. In fact, since the blood cerebral flow was reported to increase in schizophrenic patients, together with the utilization of oxygen [9], an excessive production of free radicals could occur with a consequently increased utilization of the physiological antioxidant factors.

According to Mathé et al, the apparently increased metabolism of the schizophrenic brain might be referred to an increased production of prostaglandin E [10]. It has been reported that free radical formation and lipid peroxidation may occur in brain injury and cerebral ischemia [11,12].

Ascorbic acid, a well-established antioxidant [11,13] is actively accumulated in neural tissue where it is present in high concentrations [14]. Even though the therapeutic properties of ascorbic acid in schizophrenia have been criticized [15] it has been shown that ascorbic acid is required in higher amounts by chronic psychiatric patients [16].

The present data are in accord with the reports indicating a CPZ effect in decreasing rat brain MDA formation both in vitro and in vivo [6,7]. In addition blood serum obtained from patients suffering from continuous schizophrenia can alter the functions of mitochondria from rat cerebral cortex in a process prevented by antioxidants [17]. So far the antioxidant properties of CPZ have not been related to the level of serum lipid peroxides or to its neuroleptic action in patients and, from the present results, a rationale for the use of this drug may transpire.

References

1 Yagi K. Assay for serum lipid peroxide level and its clinical significance. In: Yagi K, ed. Lipid peroxides in biology and medicine. New York: Academic Press, 1982;223–242.
2 Suematsu T, Kamada T, Abe H, Kikuchi S, Yagi K. Serum lipoperoxide level in patients suffering from liver diseases. Clin Chim Acta 1977;79:267–270.
3 Dousset JC, Trouilh M, Foglietti MJ. Plasma malonaldehyde levels during myocardial infarction. Clin Chim Acta 1983;129:319–322.
4 Satoh K. Serum lipid peroxide in cerebrovascular disorders determined by a new colorimetric method. Clin Chim Acta 1978;90:37–43.
5 Goto Y. Lipid peroxides as a cause of vascular diseases. In: Yagi K, ed. Lipid peroxides in biology and medicine. New York: Academic Press, 1982;295–303.
6 Slater TF. The inhibitory effects 'in vitro' of phenothiasines and other drups on lipid peroxidation systems in rat liver microsomes and their relationship to liver necrosis produced by carbon tetrachloride. Biochem J 1968;106:155–160.
7 Roy D, Pathak DN, Singh R. Effects of chlorpromazine on the activities of antioxidant enzymes and lipid peroxidation in the various regions of aging rat brain. J Neurochem 1984;42:628–633.
8 Wilcoxon F. Individual comparisons by ranking methods. Biometrics Bull 1945;1:80–83.
9 Sokoloff L. Circulation and energy metabolism in the brain. In: Albers RW, Siegel GJ, Katzman R, Agranoff BW, eds. Basic neurochemistry. Boston: Little Brown and Company, 1972.
10 Mathè AA, Wiesel FA, Sedvall G, Nyback H. Increased content of immunoreactive prostaglandin E in cerebrospinal fluid of patients with schizophrenia. Lancet 1980;1:16–17.
11 Halliwell B, Gutteridge JMC. Oxygen radicals and the nervous system. Trends Nerv Sci 1985;8:22–26.
12 Siesjo Bo K. Cell damage in the brain. J Cereb Blood Flow Metab 1981;1:155–185.
13 Bendich A, Machlin LJ, Scandurra O. The antioxidant role of vitamin C. Adv Free Rad Biol Med 1986;2:419–444.
14 Spector R, Eells J. Deoxynucleotide and vitamin transport into the central nervous system. Fed Proc 1984;43:196–200.
15 Adams RD, Victor M. Principles of neurology, New York: McGraw Hill, 1985;1142–1156.
16 Herjanic M. Ascorbic acid and schizophrenia. In: Hawkins D, Pauling L, eds. Orthomolecular Psychiatry pp. 303–315, San Francisco: Freeman and Company, 1973;303–315.
17 Gulidova GP. Role of peroxides in changes in brain mitochondria energy metabolism following exposure to schizophrenic patients serum. Bull Exp Biol Med 1981;92:42–44.