Low blood selenium concentrations in schizophrenic patients on clozapine

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Aims To compare plasma and red-cell selenium concentrations of schizophrenic patients treated with clozapine, with healthy controls and patients with mood disorders.

Methods Plasma and red-cell selenium concentrations were measured in random venous blood samples from four groups: mood disorder ($n = 36$), schizophrenics treated with clozapine ($n = 54$), schizophrenics not treated with clozapine ($n = 41$) and a healthy control group ($n = 56$). Assays were performed by an independent laboratory that was blinded to the patient groups and specializes in estimating trace metal concentrations.

Results Selenium concentrations in plasma and red cells were found to be significantly lower in schizophrenic patients treated with clozapine as compared with all other groups.

Conclusions Selenium is an essential antioxidant. Its deficiency has been implicated in myocarditis and cardiomyopathy. Low selenium concentrations in clozapine-treated patients may be important in the pathogenesis of life threatening cardiac side-effects associated with clozapine. Further clinical studies are being conducted to explore this important clinical observation and its therapeutic implications.

Keywords: cardiomyopathy, clozapine, myocarditis, selenium, schizophrenia

Introduction

Selenium is an essential nutrient that is incorporated into over 30 selenoproteins and in the form of selenocysteine is the only trace element to be incorporated into the genetic code. It plays an important role in antioxidative protection against free radical damage to membranes, lipoproteins and nucleic acids and is a component of glutathione peroxidase [1, 2]. Deficiency of selenium is implicated in several pathological conditions, notably cardiomyopathy and myocarditis [3, 4]. Coxsackie virus infections, which normally do little harm, generate a virulent myocarditis in selenium-deficient mice [5].

Clozapine is an atypical antipsychotic, which can have dramatic beneficial effects in patients who fail to respond to therapy with either standard or novel antipsychotic medications. Unfortunately it also has severe side-effects, notably agranulocytosis, myocarditis and cardiomyopathy, which can cause death and sometimes sudden death in otherwise stable patients [6, 7]. In a small study of clozapine-treated patients, the group that developed agranulocytosis and the group that did not had lower plasma selenium concentrations than normal controls [8]; however, the authors did not measure red-cell selenium concentrations, and no comparisons were made with schizophrenic patients not treated with clozapine or with other psychiatric patients.

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Methods

We have measured plasma and red-cell selenium concentrations in four large groups (Table 1). The study was approved by the Maroondah Hospital Ethics Committee and was conducted according to the principles of the Declaration of Helsinki. All participants provided written informed consent. A single 10-ml venous blood sample was collected into a trace-element tube with EDTA as anticoagulant. Plasma and red-cell selenium concentra-

Table 1 Plasma and red-cell selenium concentrations in the four groups of individuals.

	Healthy controls	*Mood disorder*	*Schizophrenia no clozapine*	*Schizophrenia on clozapine*
n	56	36	41	54
Male/female	20/36	16/20	24/17	33/21
Mean age (years)	43.1	40.6	37.3	36.1
Plasma selenium	1.49 ± 0.30	1.39 ± 0.29	1.47 ± 0.41	1.28 ± 0.33
F		2.34	0.06	12.87
P		0.13	0.81	0.0005
Red-cell selenium	1.80 ± 0.58	1.70 ± 0.40	1.70 ± 0.48	1.47 ± 0.57
F		0.84	0.74	9.10
P		0.36	0.39	0.003

Selenium concentrations are expressed in μmol l^{-1} and are shown as means and standard deviations. ANOVA was used to see whether there were any overall differences between the four groups. This showed significant differences for both plasma ($F = 4.58$, $P < 0.01$) and red cells ($F = 3.89$, $P < 0.01$). ANOVA was then used to compare each of the patient groups and the normal controls. The *F* and *P* values for these comparisons are shown in the table.

tions were measured at Analytical Reference Laboratories in Melbourne, Australia, according to the method of Jacobson & Lockitch [9]. The laboratory staff that performed the selenium measurements was blind to the grouping of these blood samples.

The four groups consisted of healthy hospital staff controls, medicated patients with mood disorders (major depression, bipolar I or bipolar II), schizophrenic patients being treated with antipsychotics other than clozapine, and schizophrenic patients on clozapine. All patients were classified according to DSM-IV criteria. Patients were from the community mental health clinics or living in a supported residential setting and a very few were from an acute inpatient facility. Most of the patients had a case manager allocated, coordinating their clinical care including adequate dietary intake. Full details of the medications received by all patients are available from the author.

Results

Plasma and red-cell selenium concentrations in these three groups of patients and one group of healthy controls are presented in Table 1. Selenium concentrations in the mood disorder patients and in the schizophrenic patients not on clozapine were slightly but not significantly reduced compared with the healthy controls. In contrast, selenium concentrations in both plasma and red cells in the clozapine group were highly significantly below normal and also significantly below those in the other patient groups.

Discussion

Schizophrenic patients on clozapine have low selenium concentrations that may contribute to their susceptibility to serious cardiac complications. Selenium plays a key role in the functioning of the glutathione peroxidase anti-oxidant system [1, 2]. Oxidative stress has been implicated in the pathogenesis of cardiovascular disease including myocarditis [10, 11]. In patients suffering from schizophrenia there is an increased oxidative stress with decreased anti-oxidant defences with abnormalities in the oxidative pathway of catecholamine metabolism [12]. It is plausible that this abnormality is far more severe in treatment nonresponsive schizophrenics. It is this group of patients who are generally treated with clozapine. Therefore, selenium supplementation may be beneficial in this group of patients.

Diminishing selenium status has been reported in various regions of the world, particularly in parts of Europe, the UK, China and New Zealand [2]. The recommended normal selenium intakes have varied between 55 and 75 μg day^{-1} [1, 2]. Supra-nutritional intakes up to 200 μg have been recommended in certain conditions such as cancer [2].

This study cannot distinguish between the possibilities that clozapine causes the low selenium or that the treatment-resistant patients who progress to clozapine are deficient even prior to starting clozapine. It is also unknown whether selenium supplementation will correct the selenium concentrations and reduce the risk of clozapine-induced adverse events. Further studies are in progress to evaluate these possibilities.

Staff at Analytical Reference Laboratories performed the selenium concentrations. Dr David Horrobin (Laxdale Ltd, Scotland) commented on the manuscript. Funding was from the author's (KSV) Neuropsychiatry Research Fund.

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