

# Metabolic differences between Asian and Caucasian patients on clozapine treatment

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**Objective** To establish if there are ethnic differences in the various metabolic disturbances that are common with clozapine treatment.

**Method** Forty subjects (20 Asians and 20 Caucasians) with a diagnosis of schizophrenia were recruited for the study. Clozapine blood levels as well as fasting blood glucose, lipid levels, and liver function tests were established. Other clinical parameters such as blood pressure and Body Mass Index (BMI) were recorded for each patient.

**Results** The mean clozapine dose was significantly higher in the Caucasian subjects ( $432.5 \pm 194.7$  mg) as compared to the Asian subjects ( $175.6 \pm 106.9$  mg) ( $p < 0.001$ ) while the mean weight-corrected dose for Asian patients was lower ( $3.0 \pm 1.9$  and  $5.0 \pm 2.1$  mg/kg, respectively,  $p = 0.005$ ). There were, however, no ethnic differences in the mean plasma clozapine concentration ( $415.3 \pm 185.8$  ng/ml in Caucasians and  $417.1 \pm 290.8$  ng/ml in Asians). BMI were significantly higher in Caucasians, as were the number of subjects with hypertension; levels of hepatic enzymes were higher in the Asian group.

**Conclusions** Not only are there pharmacokinetic differences between Asian and Caucasian patients receiving clozapine, but there may also be differential emergence of certain metabolic abnormalities like hypertension and weight gain in these two ethnic groups. However, the effects of life style including diet and exercise cannot be excluded. Copyright © 2007 John Wiley & Sons, Ltd.

KEY WORDS — clozapine; schizophrenia; treatment resistance; ethnicity; body mass index; hypertension

## INTRODUCTION

While antipsychotic medications remain the mainstay of treatment in schizophrenia, these drugs are not effective for all patients nor are they free of side effects. With conventional or first generation antipsychotics (FGAs) as many as 25–30% of patients derive little, if any, benefit (Kane, 1996). This subpopulation of patients also known as ‘refractory’, ‘treatment-resistant’, and ‘non-responder’, has responded well to treatment with clozapine (Kane *et al.*, 1988).

Clozapine is a dibenzodiazepene with unique preclinical and clinical properties. It is unique in its relatively higher affinity for D1 than D2 dopamine receptors, its affinity for 5-HT<sub>2A</sub> serotonergic receptors and its strong affinity for D4 dopaminergic receptors. It has a markedly less propensity to cause certain side effects that are common with the FGAs like the extrapyramidal symptoms (EPS), tardive dyskinesia, (Casey, 1989) and neuroleptic malignant syndrome (Fitton and Heel, 1990). However, it does have other side effects including agranulocytosis, sedation, seizures, weight gain, hypertriglyceridemia and diabetes (Popli *et al.*, 1997).

Clozapine is mainly metabolised by cytochrome P4501A2 (CYP1A2) (Jerling *et al.*, 1994). With caffeine as the substrate, CYP1A2 activities have been reported to be highly variable and are affected by individual ethnicity (Grant *et al.*, 1983) and dosage

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used (Kalow and Tang, 1991). Studies have suggested pharmacokinetic and pharmacodynamic differences between the Asian and Caucasian populations receiving clozapine. Asians generally have a higher plasma concentration than Caucasians given the same weight-adjusted dose (Chong *et al.*, 1997). A study of 17 Korean–American and 17 Caucasians matched for age, gender and diagnoses found that the Asians showed greater improvement than Caucasians despite lower mean doses of clozapine. However, the Koreans are more likely to experience adverse effects even at a lower dose-corrected clozapine concentration (Matsuda *et al.*, 1996).

In our earlier study (Ng *et al.*, 2005) in which we compared Australian Caucasian patients with Singaporean Asian patients with schizophrenia, we have shown that despite a significantly lower mean clozapine dose than the Caucasian, plasma clozapine levels were similar—even after controlling from gender, body mass index (BMI), cigarette, alcohol and caffeine use. This paper further describes the findings of this study with the specific aims of comparing the differential rates of metabolic abnormalities and types of side effects between the Asian and Caucasian patients.

## METHODS

Forty subjects (20 Asians and 20 Caucasians) were recruited for the study. The Australian patients were of Anglo-Saxon lineage except for one who was born in Greece; and all were residents of Australia. The Asian patients (13 Chinese, 4 Indians and 3 Malays) were all born, and lived in Singapore. All patients had a Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition (DSM-IV) (American Psychiatric Association, 1994) diagnosis of schizophrenia and met the research criteria for treatment resistance (Lehman *et al.*, 2004). The Asian patients were recruited from the Institute of Mental Health of

Singapore, while the Australian patients were those attending the St Vincent's Community Mental Health Clinic or treated by private psychiatrists in Melbourne. All patients had been on clozapine treatment for at least 6 months and maintained on a stable dose for at least the last 2 months. The sociodemographic and clinical characteristics of the two groups are shown in Table 1. Approval was given by the respective ethics committees and written informed consent was obtained from all the patients. Details of the methodology are described in our earlier report (Ng *et al.*, 2005). In brief, the patients were stable clinically as assessed by their psychiatrists. Those with alcohol or substance dependence according to DSM-IV criteria or were given depot antipsychotic medication within the preceding 6 months were not included in the study. None of the patients had been any documented history of diabetes or hypertension.

Clinical parameters including blood pressure (measured in both sitting and standing positions and the average was taken as the final reading) and the BMI were determined. Blood samples were taken for plasma clozapine and its metabolites. Fasting blood samples were collected for lipid profiles, blood sugar and liver function test. The type and dosages of all concomitant medications were recorded. Dietary factors, including use of alcohol, nicotine, caffeine and traditional herbal medicine, were also documented. We defined heavy smokers as those who smoked at least 10 sticks of cigarettes daily, and heavy caffeine users as those who consumed at least four cups of coffee daily.

## Statistical analysis

Descriptive summary statistics were obtained for demographic, efficacy and side-effect measures for both groups. Statistical procedures used included independent samples *t*-tests, Fisher's exact test and Pearson's correlation as appropriate. Multiple linear

Table 1. Sociodemographic and clinical characteristics of the two ethnic groups

Variables	Caucasians ( <i>n</i> = 20)	Asians ( <i>n</i> = 20)
Age (years)	40.2 ± 8.6	36.3 ± 13.4
Gender	4/16	18/2**
Weight (kgs)	89.8 ± 18.6	59.3 ± 11.3**
Heavy smoking (>10 cigarettes/day) Yes/No	12/8	1/19**
Heavy caffeine use (>4cups/day) Yes/No	8/12	0/20**
Duration of Illness (years)	16.5 ± 7.1	11.9 ± 5.2*
CGI Severity	3.15 ± 0.49	3.4 ± 0.68
PANSS Total Score	49.85 ± 10.55	60.3 ± 16.08*

\**p* < 0.05; \*\**p* < 0.005.

regression was performed with smoking, nicotine & alcohol use, gender, age, ethnicity, daily dose of Clozapine, Clozapine plasma level and total cholesterol to determine the significant predictors for BMI. Using the same variables except total cholesterol and including BMI as a predictor, multiple linear regression was performed to determine significant predictors of liver enzymes, triglycerides, total cholesterol and blood glucose levels. Statistical significance was set at  $p < 0.05$ .

## RESULTS

The 40 patients had a mean age of 38.2 years (SD = 11.3) (range 22–74 years). There was no significant difference in age between the two ethnic groups but there were more males ( $n = 16$ ) in Caucasian group than the Asians ( $n = 2$ ), and the duration of illness was also significantly longer in the Caucasians ( $16.5 \pm 7.1$  vs.  $11.8 \pm 5.1$  years,  $p = 0.02$ ).

The mean clozapine dose was significantly higher in the Caucasian population ( $432.5 \pm 194.7$  mg) as compared to the Asian population ( $175.6 \pm 106.9$  mg) ( $p < 0.001$ ). Clozapine doses were recalculated as dose/weight ratios; the mean weight-corrected dose for Asian patients remained significantly lower than Caucasian patients ( $3.0 \pm 1.9$  and  $5.0 \pm 2.1$  mg/kg, respectively,  $p = 0.005$ ). There were no ethnic differences in the mean plasma clozapine concentration ( $415.3 \pm 185.8$  ng/ml and  $417.1 \pm 290.8$  ng/ml, respectively in Caucasians and Asians).

The physical and metabolic indices associated with clozapine treatment are shown in Table 2. An independent sample *t*-test comparing BMI showed a significant difference between the two groups ( $p < 0.001$ ) with lower values in Asian (range 16.9–30.6) compared to Caucasian patients (range 18.2–36.2). Ethnicity ( $p = 0.02$ ) and age ( $p = 0.01$ ) remained significant predictors upon performing

multiple linear regression, with BMI as the dependent variable.

A significant group difference was also noted in the mean systolic and diastolic blood pressure ( $p < 0.001$ ). When the indices were categorised into normotensive and hypertensive (defined as a systole of  $>140$  mmHg and diastole of  $>90$  mmHg) groups, significantly more Caucasian patients (35%) had hypertension while none of the Asian patients were hypertensive ( $\chi^2 = 8.11$ ,  $p = 0.004$ ). Systolic and diastolic blood pressures were correlated with BMI ( $r = 0.76$ ,  $p < 0.001$ ). Eighty-five per cent of the Caucasians had an abnormal BMI  $>25$ , while only 40% of the Asians had a BMI  $>25$ . ( $\chi^2 = 8.6$ ,  $p = 0.003$ ) (WHO, 1995). There were no significant differences in the fasting glucose and lipids levels between the two groups. On performing a multiple linear regression, female gender ( $p = 0.004$ ), BMI ( $p = 0.006$ ) and ethnicity ( $p = 0.04$ ) were found to be significant predictors of triglyceride levels. Clozapine dose ( $p = 0.02$ ), age ( $p = 0.001$ ), BMI ( $p = 0.006$ ) and ethnicity ( $p = 0.01$ ) remained significant predictors of total cholesterol levels, while BMI ( $p = 0.03$ ) and age ( $p = 0.007$ ) were significant predictors of LDL cholesterol. Female gender ( $p = 0.02$ ) and age ( $p = 0.04$ ) were found to be significant predictors of glucose levels. However a binary logistic regression revealed no significant predictors of hypertension.

Prevalence of metabolic syndrome in our sample was assessed using the National Cholesterol Education Program's definition of metabolic syndrome (Expert panel on detection, evaluation and treatment of high blood cholesterol in adults, 2001). The fasting glucose cutoff level was updated to reflect the American Diabetes Association's new cutoff point of 100 mg/dl (American Diabetes Association, 2004). Only three (7.5%) patients in our sample met criteria for metabolic syndrome. Of those meeting the criteria

Table 2. Metabolic indices during clozapine treatment between ethnic groups

	Caucasians			Asians		
	Mean	SD	No. of abnormal cases	Mean	SD	No. of abnormal cases
Triglycerides (mmol/L)	2.01	0.86	4 (50%)	1.94	1.13	7 (37%)
Cholesterol total (mmol/L)	5.33	0.92	2 (22%)	5.53	1.03	8 (42%)
Cholesterol HDL (mmol/L)	1.15	0.36	0 (0%)	1.37	0.38	1 (5%)
Cholesterol LDL (mmol/L)	3.21	0.93	1 (11%)	3.28	0.98	6 (32%)
BP systolic/diastolic	123/79*	12/7	7 (35%)*	114/65	5/7	0 (0%)
Blood glucose (mmol/L)	5.67	1.05	5 (28%)	5.53	1.05	5 (26%)
Body mass index	28.86*	4.43	8 (40%)	23.38	3.81	3 (16%)

\* $p < 0.01$ .

Table 3. Liver function indices of the two ethnic groups

Liver function indices	Caucasians		Asians	
	Mean	SD	Mean	SD
Bilirubin (total) (umol/L)	7.8	2.7	7.3	3.6
Alkaline phosphatase (U/L)	93.2	27.3	83.1	19.0
Alanine aminotransferase (U/L)	24.8*	11.4	34.4	14.7
Aspartate aminotransferase (U/L)	19.2*	2.7	23.4	6.5

\* $p < 0.05$ .

two were females and one was a male. One was of Caucasian and two were of Asian origin.

Levels of alanine (ALT) and aspartate amino transferases (AST) were significantly higher in the Asian population. However, only two Asians and one Caucasian patient had higher than normal values. When the liver enzymes were correlated with clozapine doses, a significant negative correlation was found only with serum aspartate aminotransferase levels ( $r = 0.56$ ,  $p = 0.002$ ). No correlation was found with between serum clozapine levels and liver enzymes. On performing a multiple regression, female gender, being of Caucasian ethnicity and BMI, were significant predictors of alanine aminotransferase levels ( $p = 0.02$ ,  $p = 0.001$  and  $p = 0.003$ , respectively), while female gender and clozapine dose were significant predictors of aspartate aminotransferase levels ( $p = 0.04$ ; Table 3).

There was a significant difference in the smoking and caffeine use—the proportion of heavy smokers and heavy caffeine users was significantly higher in the Caucasian group as compared to the Asians ( $p < 0.005$ ). Use of alcohol was low in both groups with no subjects having more than two standard drinks per day.

## DISCUSSION

Our study found that the mean clozapine dose as well as the mean weight-corrected dose was significantly higher in the Caucasian population as compared to the Asian population. However, there were no significant differences in the mean plasma clozapine levels suggesting that there are significant ethnic differences in the pharmacokinetics of clozapine between these two groups of patients. This could be the result of a reduced CYP1A2 activity, which has been reported in Asians (Shimada *et al.*, 1994). Another possibility is the presence of a functional C → A polymorphism of the CYP1A2 gene which in Caucasians (and only when they are smokers) would confer a highly inducible state (Sachse *et al.*, 1999). Intriguingly,

another polymorphism of the same gene has been reported to result in reduced CYP1A2 activity among Japanese smokers (Nakajima *et al.*, 1999). Hence, the higher rate of smoking in the Caucasian group could have led to a higher CYP1A2 activity, which could have necessitated a higher daily dose of clozapine. Higher activity has been shown in men than in women (Landi *et al.*, 1999), and majority of the Caucasian population were males while majority of the Asian subjects were females, this could be another contributory factor for the higher dose requirement in the Caucasian subjects.

Clozapine treatment appeared to be associated with a high rate of metabolic abnormalities in both groups as 60% of Caucasian and 32% of Asian patients had one or more abnormal metabolic indices. Elevated blood pressure was more frequently observed in the Caucasian group, which was correlated with the higher BMI in this group, however, regression analyses failed to reveal any significant predictor for hypertension. The lower BMI in the Asian group is probably due to the over-representation of females. Female gender, BMI and ethnicity were found to be significant predictors of triglyceride levels, while age, Clozapine dose, BMI and ethnicity were significant predictors of total cholesterol levels. Studies have indicated that there are ethnic differences in the prevalence of dislipidemia (Singh and Deedwania, 2006). The reasons for such disparity appear to be multifactorial and influenced by such factors as lifestyle, diet, culture, genetics and suboptimal healthcare. BMI and gender too have been reported in various studies as independent risk factors for dislipidemia (Reeder *et al.*, 1992; Bautista *et al.*, 2006). The fact that clozapine dose is a significant predictor of total cholesterol levels is important since the effects of clozapine treatment on total cholesterol levels are not very clear, with two studies observing increases in total cholesterol levels from baseline with clozapine (Baymiller *et al.*, 2003; Lindenmayer *et al.*, 2003), while other studies observed no significant changes (Gaulin *et al.*, 1999; Wirshing *et al.*, 2002).

Levels of alanine and aspartate amino transferases were significantly higher in the Asian population. The mean values for ALT are very similar from one population to another, but the degree to which the distribution is skewed varies by gender and ethnicity. Elevated levels of liver enzymes following clozapine therapy has been reported by Gaertner *et al.* (2000) especially ALT in 15% of patients. Our findings suggest that not only are there pharmacokinetic differences between the Asian and Caucasian patients but there may also be differential emergence of certain

metabolic abnormalities in these two ethnic groups although we cannot exclude the influence of environmental factors like level of physical activities, diet and smoking.

This study has some important limitations. It was a cross-sectional study and therefore, we are unable to clarify whether these metabolic differences were present before the initiation of clozapine therapy. We are also unable to determine, the extent BMI changed during the course of clozapine treatment in the two populations and whether there are any ethnic differences in the likelihood of weight gain. The sample size being small, it is difficult to generalise our findings.

However, the study is important because it raises the awareness of clozapine treatment being associated with metabolic abnormalities. Psychiatrist must proactively screen patients on all antipsychotics for potential side effects and medical morbidities (American Psychiatric Association, 2004). Prospective studies on larger sample size are needed to get a complete picture of the impact of clozapine on patients with schizophrenia. Ethnic studies in the metabolic side effects of clozapine are also needed to establish interracial/ethnic pharmacogenetic differences that will help minimise side effects and maximise the impact of maintenance treatment in schizophrenia across different populations.

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