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Research Paper

Steady-State Clozapine and Norclozapine Pharmacokinetics in Maori and European Patients

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ABSTRACT

Background: Clozapine is the most effective drug for treatment-resistant schizophrenia, but its use is limited by toxicity. Because ethnicity has been reported to affect clozapine metabolism, we compared its steady state pharmacokinetics in New Zealand Maori and European patients.
Methods: Clozapine and norclozapine steady state bioavailability was assessed over 24 h under fasting and fed conditions in 12 Maori and 16 European patients treated for chronic psychotic illnesses with stable once-daily clozapine doses. Plasma clozapine and norclozapine concentrations were assessed using liquid chromatography with tandem mass spectrometry; pharmacokinetic parameters were calculated using standard non-compartmental methods, and compared using unpaired *t*-tests.
Findings: Mean pharmacokinetic parameters (AUC, C_{max} and C_{min}) for clozapine and norclozapine were virtually identical in Maori and European subjects, under both fed and fasted conditions.
Discussion: Clozapine bioavailability does not vary between Maori and European patients, and thus does not need to be considered in prescribing decisions. Additional studies are needed to identify if there are differences between Maori and European populations for drugs metabolized by other enzyme pathways.

1. Introduction

Compared with other antipsychotic drugs, clozapine is the most effective pharmacotherapy for schizophrenia; its use is generally restricted to treatment-resistant patients because of safety risks, notably agranulocytosis, myocarditis, and severe constipation (Barnes et al., 2011). Surveys have identified similar (Wheeler et al., 2008) or somewhat higher (Dey et al., 2016) rates of clozapine use in Maori compared to Europeans, the two dominant ethnic groups in New Zealand. Ethnicity has been shown to influence clozapine pharmacokinetics in some settings; for example, compared with Caucasians, lower daily clozapine doses are needed to achieve comparable blood levels in Asian (Ng et al., 2005) and Mexican patients (González-Esquivel et al., 2011). There are no published data on the pharmacokinetics of clozapine in Maori, although mean daily clozapine doses were similar in Maori and European patients in a retrospective cross-sectional survey (El-Badri and Mellsop, 2011). Effective treatment of schizophrenia in Maori is of particular importance given its apparently higher prevalence compared with the European population (Kake et al., 2008). This study used data from a bioequivalence trial of two clozapine formulations (Glue et al., 2012) in order to compare the pharmacokinetics of clozapine and its active metabolite norclozapine in Maori and European patients.

2. Materials and Methods

A detailed description of the bioequivalence study, including sample size calculation, is provided elsewhere (Glue et al., 2012). In brief, the study enrolled 30 male and female subjects, aged 18 to 55 years, established on stable doses of clozapine for at least 3 months. Subjects were required to have a body mass index (BMI) between 18 and 35 kg/m^2, and be in good health. Clozapine was prescribed in multiples of 50 mg, taken as a single evening dose. Subjects provided written informed consent prior to participation. The study conformed to standards indicated by the Declaration of Helsinki; approval was provided by the New Zealand Multi-Region Ethics Committee (MEC/10/09/094). The study design involved an 11-day dosing period with one formulation, tablet or suspension, with pharmacokinetic blood sampling under fasting and fed conditions on days 10 and 11, respectively. Study subjects were then switched to the alternate formulation from days 12–22, with repeated pharmacokinetic sampling on days 21 and

Abbreviations: C_{max}, maximum plasma concentration; $AUC_{0-\tau}$, area under the curve from time 0 to the end of the dosing interval; t_{max}, time to C_{max}; C_{min}, minimum plasma concentration.

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22. The order in which formulations were administered was based on a computer-generated random code. The formulations were found to be bioequivalent under fasting and fed conditions (Glue et al., 2012). This report describes the pharmacokinetics of the tablet formulation (Clozaril®, Novartis) in Maori and European participants.

On Days 10 and 21, subjects were admitted to the study clinic at least 10 h prior to drug administration, and were discharged after the final blood draw in the morning of Days 12 and 23. Clozapine was administered after an 8-hour fast on Days 10 and 21, and was dosed under fed conditions on Days 11 and 22 after consumption of a standardized high-fat meal (Food and Drug Administration, 2002). All clozapine doses were administered with 240 mL water. There was no washout period between the two treatment periods. On Days 10, 11, 21 and 22, blood samples were collected at baseline and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 14, 16, 20 and 24 h after dosing. Following centrifugation, plasma samples were stored in polypropylene tubes at 70 °C until assayed using validated liquid chromatography with tandem mass spectrometry methods. Clozapine was assayed using a previously reported method (Glue et al., 2012). The norclozapine assay was similar although a different internal standard (*N*-desmethylmirtazapine) was used.

Pharmacokinetic parameters, calculated using standard non-compartmental methods, included maximum plasma concentration (C_{max}), area under the plasma concentration–time curve from time 0 to the end of the dosing interval ($AUC_{0-\tau}$), time to C_{max} (t_{max}), and minimum concentration (C_{min}). Because patients were taking different daily doses of clozapine, all clozapine and norclozapine plasma concentrations and pharmacokinetic data were normalised to a dose of 100 mg.

Table 1
Demographic, prescription and smoking data.

Participant	Ethnicity	Gender	Age (years)	BMI (kg/m^2)	Clozapine mg/day	Tobacco cigarettes/day	Concomitant medications
1	Maori	Male	42	24	400	20	Amitriptyline 25 mg twice daily
2	Maori	Male	46	32.5	100	20	Lamivudine 100 mg daily Pantoprazole 40 mg daily
3	Maori	Male	42	42	400	0[a]	Omeprazole 20 mg daily Metformin 850 mg daily Diclofenac 75 mg PRN
4	Maori	Male	28	38	350	16	Omeprazole 20 mg daily Sodium valproate 1.6 g daily
5	Maori	Male	30	31.4	450	15	Amisulpride 400 mg twice daily
6	Maori	Male	28	33.9	700	10	Venlafaxine 150 mg daily
7	Maori	Male	57	29.7	700	24	Lithium carbonate 1.5 g daily
8	Maori	Female	46	37	400	5	Quetiapine 50 mg daily Fluoxetine 20 mg
9	Maori	Male	27	33.4	400	0[a]	Nil
10	Maori	Male	48	29.8	400	0[a]	Risperidone 0.5 tab daily Benztropine 2 mg daily
11	Maori	Female	33	30.8	100	0[a]	Quetiapine 50 mg twice daily Loperamide 2 mg (if required) Propanolol 40 mg twice daily
12	Maori	Male	25	24	600	13	Nil
13	European	Male	42	22.8	400	0[a]	Citalopram 40 mg daily Simvastatin 10 mg daily Clonazepam 0.5 mg daily
14	European	Male	40	24.2	700	20	Clonazepam 2 mg daily Simvastatin 20 mg daily
15	European	Male	29	24	500	0[a]	Lithium carbonate 2.5 g daily Simvastatin 40 mg daily
16	European	Male	56	28	300	5	Omeprazole 20 mg daily Calcium carbonate 1.25 g daily
17	European	Male	41	29.7	400	8	Nil
18	European	Female	45	37.8	650	0[a]	Haloperidol 50 mg i.m. monthly Haloperidol 5 mg nocte PRN Cilazapril1.25 mg daily Pantoprazole 40 mg daily
19	European	Female	48	22.1	200	0[a]	Levonorgestrel 20 mcg daily
20	European	Male	48	37	600	20	Chlopromazine 100 mg daily Clonazepam 2 mg daily Levothyroxine 0.05 mg daily Sodium valproate 1.8 g daily Lithium carbonate 1.2 g daily
21	European	Male	29	28	350	0[a]	Nil
22	European	Male	40	35.4	600	0[a]	Sodium valproate 600 mg Nocte Amisulpiride 300 mg nocte Citalopram 40 mg daily
23	European	Male	38	32.8	100	0[a]	Omeprazole 20 mg daily
24	European	Male	29	27.7	350	0[a]	Omeprazole 40 mg daily Sodium valproate 1.4 g daily Simvastatin 20 mg daily
25	European	Male	26	32.4	400	0[a]	Nil
26	European	Female	39	32.5	350	0[a]	Metoprolol 95 mg daily Omeprazole 20 mg daily Atorvastatin 30 mg daily
27	European	Male	34	34.7	500	10	Amisulpride 600 mg twice daily Lithium carbonate 1.2 g daily
28	European	Male	24	32.2	500	5	Fluoxetine 40 mg daily

[a] Non-smoker or abstinent for least six months.

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