Rapid clozapine dose titration and concomitant sodium valproate increase the risk of myocarditis with clozapine: a case-control study

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Abstract

Background: Despite the implementation of cardiac monitoring guidelines, clozapine-induced myocarditis continues to cause deaths in Australia, and the risk is a barrier to prescription of this effective drug for the treatment of schizophrenia. This study was designed to identify clinical and phenotypic risk factors for clozapine-induced myocarditis.

Method: Possible cases of clozapine related myocarditis occurring between June 1993 and November 2009 and a comparative group of controls taking clozapine for at least 45 days without cardiac disease were documented from the patients' medical records.

Results: 105 cases, with time to onset 10-33 days, and 296 controls were included in the study. In multivariate analysis, the risk of myocarditis increased 26% for each additional 250mg of clozapine administered in the first nine days of clozapine titration (odds ratio 1.26; 95% confidence interval 1.02-1.55; p=0.03) and concomitant sodium valproate more than doubled the risk (2.59; 1.51-4.42; 0.001). Further, each successive decade in age was associated with a 31% increase in risk (1.31; 1.07-1.60; 0.009).

Nevertheless, 33 cases received less than 920mg of clozapine during the first nine days of dose titration, did not take sodium valproate and were aged less than 40 years; and nine control patients received sodium valproate and more than 920mg of clozapine in the first nine days without developing myocarditis.

Conclusions: Clozapine should be initiated by slow dose titration and sodium valproate is best avoided, if clinically feasible, during this period. All patients commencing clozapine should be monitored for myocarditis up to Day 28.

Key words: clozapine; myocarditititis; case-control study; risk factors; schizophrenia; drug hypersensitivity reaction

1. Introduction

Clozapine is a second generation antipsychotic with activity at dopaminic (D_1, D_4), muscarinic, serotoninergic and histaminic receptors. Even now, 40 years after its development, it is unsurpassed with respect to efficacy and safety, including prevention of suicide, in the treatment of schizophrenia (Leucht, et al. 2009; Tiihonen, et al. 2009). Nevertheless, it causes two potentially life-threatening adverse reactions, agranulocytosis and myocarditis. The risk of agranulocytosis is reduced by routine blood monitoring, but no mechanism has been successful in reducing the risk of myocarditis. In Australia, where cardiac monitoring guidelines were disseminated in December 1999 by Novartis Australia Limited, deaths from myocarditis have continued to occur (Ronaldson, et al. 2011a).

Myocarditis, inflammation of the heart muscle, is a hypersensitivity reaction which typically occurs in the third week of clozapine therapy and can be fatal (Kilian, et al. 1999; Merrill, et al. 2005; Ronaldson, et al. 2011b). Because the signs and symptoms of myocarditis are non-specific, its incidence is difficult to assess unless a suitable monitoring program is assiduously followed. In the Australian context, at least four estimates have been made. The first was in 1999 by Kilian et al. who calculated a rate of 0.2%, using cases reported to the national spontaneous reporting program. This study was the first publication to provide a strong indication that myocarditis was causally related to clozapine use. The second estimate, by Haas et al. (2007), used the same source of cases with an extended time range of 1993-2003. A rate of 0.7-1.2% was determined. From 2000-2003, monitoring guidelines for myocarditis were being used across Australia, and there was a considerable degree of awareness of the possibility of this occurrence. It can be presumed that the percentage case ascertainment was higher in the later period than before December 1999. The two other estimates by Reinders et al (2004) and Tirupati (2006) are from single health services at which rates were 8.5% and 3%, respectively. Estimates from other jurisdictions have been based on spontaneous reporting, only, and in the absence of monitoring guidelines: 0.015% from the United States (La Grenade et al. 2001); 0.05% from Sweden (Hägg et al. 2001); 0.03% from Germany and Switzerland (Degner et al. 2000).

In response to the article by Kilian et al. (1999), Devarajan et al. (2000) proposed three potential risk factors for myocarditis in the Australian context: genetic factors influencing metabolism; clinical management involving rapid dose titration; and environmental factors leading to high ozone in the breathed atmosphere and consequential cholinergic dysfunction. Apart from our publications which have characterised clozapine-induced myocarditis (Ronaldson, et al. 2010), proposed monitoring guidelines (Ronaldson, et al. 2011b) and compared fatal cases with non-fatal (Ronaldson, et al. 2011a), no systematic studies have been conducted of this important adverse reaction, one which is a barrier to many persons with schizophrenia benefiting from the most effective treatment available for this debilitating disease.

From medical records, we have documented cases of clozapine-induced myocarditis and matched controls, from the start of clozapine initiation. We have analyzed factors related to clinical management (for example, rate of dose titration, concomitant medication) and phenotypic characteristics (for example, age, body mass index, BMI) which may predispose to the development of myocarditis in individuals commencing clozapine.

2. Methods

2.1 Ethics

The 3 institutes and 13 of the health services from which the approval of the Human Research Ethics Committee was obtained have been listed elsewhere, along with the 2 organisations with which access agreements were signed (Ronaldson, et al. 2011b). In addition, ethics and governance approval was obtained for Sydney South West Area Health Service (Concord and Western Zones), New South Wales and for The Albert Road Clinic, Melbourne, Victoria. The 16 health services included in this study were in Victoria, New South Wales and Queensland, Australia. All ethics committees gave permission to access medical records without patient consent, and also to contact patients, their case manager or carer to seek missing data.

2.2 Documentation of cases and controls

The methodology has been described elsewhere (Ronaldson, et al. 2010). Briefly, suspected cases of myocarditis were documented from the patients' medical records and data for each patient were reviewed by the study steering group which included a cardiologist (AJT) for compliance with the case definition involving histological evidence or a combination of clinical and diagnostic criteria, and onset within 45 days of clozapine initiation (Figure 1)(Ronaldson, et al. 2010). Up to four controls were matched to each case by mental health service and by approximate clozapine start date. Controls were also documented from medical records and were required to have taken clozapine for at least 45 days with documented evidence sufficient to exclude myocarditis (at least one of: no tachycardia with frequent checks, no rise in troponin with at least three determinations during the first four weeks of clozapine, normal echocardiogram after at least 45 days of clozapine therapy without interruption) or to have taken clozapine for at least 6 months continuously without manifest cardiac disease. No case or control had previously developed clozapine-induced myocarditis. Patients commenced clozapine between June 1993 and November 2009, inclusive, and almost all were hospital inpatients during initiation.

Data collected for cases and controls included date of birth, sex, ethnicity, height, weight, clozapine start date, dose of clozapine administered each day, other medication administered each day, previous use of clozapine, psychiatric diagnosis, duration of psychiatric illness, other diseases, smoking status, recent alcohol abuse and illicit drug use, and diagnosis of asthma. If data on ethnicity, smoking status, diagnosis of asthma and height were not available in the medical record, efforts were taken to obtain this information from the patient, case manager or carer. Most individuals commenced clozapine as inpatients. Clozapine dose, and dose of other medication, was recorded for this study on the basis of administration having been recorded by signature in the medication chart.

2.3 Data preparation

In Australia, clozapine is introduced by slow dose titration, usually starting with 12.5mg on Day 1, 25mg on Day 2, 25 or 50mg on Day 3 and ongoing up to a dose achieving a suitable therapeutic response and without tolerability problems (Supplementary Table 1). For some individuals, documentation of doses of clozapine was missing (5 cases and 17 controls had at least 1 dose missing on Days 1-9). In such instances the doses were imputed, using doses considered most likely given recorded doses before and after the missing doses and dose-titration protocols.

2.4 Rate of clozapine dose titration as a parameter

Cumulative dose of clozapine was used as a surrogate for rate of dose titration as a potential risk factor for myocarditis. The first 9 days was the longest period which allowed cumulative dose to be calculated for all cases. Cumulative dose for Days 1-9 was stratified post hoc into four dose

categories (0-499mg; 500-619mg; 620-920mg; >920mg). The central two categories include expected cumulative doses from following one of the two dosing protocols (612.5mg and 812.5mg, respectively) (Supplementary Table 1).

2.5 Statistical analysis

Analyses were conducted using Stata (StataCorp, Stata Statistical Software, Release 10, College Station, TX). Odds ratios were calculated using logistic regression analysis. Since neither of the matching factors was expected to be strongly related to myocarditis, the a priori intention was to conduct an unmatched analysis.

Multivariate analysis for each variable adjusted for sex, age (continuous variable), sodium valproate use, previous clozapine exposure and cumulative dose over Days 1-9 (continuous variable). Area under the receiver operating characteristic curve (AUC) was used to summarise the predictive ability of the model that contained the five variables used for adjustment in multivariate analyses.

In sensitivity analyses, other strategies for dose imputation were investigated (described in Supplementary material), as was the effect of using only those cases with at least one control, or at least 3 controls.

3. Results

Of 149 possible cases documented, 105 met the case definition, and 296 out of 331 patients complied with the criteria for controls. Seventy-four cases had 3 or 4 controls each, 12 had 1 or 2 controls each and 19 had no matching controls. Of 401 included patients, 383 (96%) started clozapine during 2000-2009; the remainder commenced during 1993-1999. The cases developed myocarditis after receiving clozapine for 10-33 days (mean ± standard deviation, SD, 17 ± 4 days). Nine of the cases died of myocarditis. Cases were slightly older (mean age 38 years; range 17-74; SD 13 years) than the controls (mean 35 years; range 15-74; SD 11 years). Similarly, cases had a greater BMI (mean 29 kg/m^2; range 17-46; SD 7 kg/m^2) than controls (mean 27 kg/m^2; range 16-61; SD 7 kg/m^2).

In univariate analysis, the risk of myocarditis increased with age (Table 1) and BMI (Table 2). Multivariate analysis found that the risk for those aged greater than or equal to 50 years was more than twice that for those aged 20-29 years (p=0.03), or alternatively that the risk increased by 31% for each 10-year interval (p=0.009) (Table 1). The increase in risk with increasing BMI was attenuated in the multivariate analysis (Table 2). After adjustment by multivariate analysis, there was little evidence that ethnicity, smoking, recent alcohol abuse or illicit drug use, a diagnosis of asthma or psychiatric diagnosis changed the risk of myocarditis.

A longer duration of psychiatric illness appeared, from univariate analysis, to increase the risk of myocarditis, but controlling for age and other factors eliminated this association. As would be expected, previous use of clozapine was a strongly protective factor (adjusted odds ratio, OR, 0.19; 95% confidence interval, CI, 0.06-0.66; p=0.008).

Sodium valproate significantly increased the risk of myocarditis with an adjusted odds ratio of 2.59 (95% CI 1.51-4.42; p=0.001), but apparently without a dose relationship (Table 3). This relationship remained significant after Bonferroni correction for conducting analyses for each of 12 concomitant medications giving a significance threshold of p=0.004 (0.05/12). Repeating the fully adjusted analyses for sodium valproate exposure using those cases with at least one control and those cases

with 3-4 controls yielded odds ratios of 2.51 (95% CI 1.41-4.44) and 2.42 (95% CI 1.31-4.46), respectively (Supplementary Table 2), where the second analysis gave a result on the borderline of significance (p=0.005) with the correction for multiple analyses. Other concomitant medications, first and second generation antipsychotics, the mood stabilizer lithium carbonate and the anti-cholinergic, benztropine, did not change the risk of clozapine-induced myocarditis (Table 2).

3.1 Clozapine dose titration

Cumulative clozapine dose over Days 1-9 demonstrated increasing risk with increasing dose such that doses above 920mg had more than twice the risk of myocarditis of doses less than 500mg (adjusted OR 2.31; 95% CI 0.98-5.48; p=0.06), although the result was of borderline significance (Table 4). Investigating dose as a continuous variable indicated that each additional 250mg of clozapine over Days 1-9 increased the risk of myocarditis by 26% (adjusted OR 1.26; 95% CI 1.02-1.55; p=0.03). Restricting the analysis of the effect of each additional 250mg of clozapine over Days 1-9 to only those cases with 3-4 controls yielded an unadjusted odds ratio of 1.24 (95% CI 1.01-1.52; p=0.04) and results without dose imputation and using alternative dose imputation strategies were broadly in agreement (Supplementary Table 3).

3.2 Predictive power of the model

Despite the observations that sodium valproate increased the risk of myocarditis, and that high cumulative doses of clozapine in the first nine days were also associated with elevated risk, nine individuals received sodium valproate and more than 920mg of clozapine during Days 1-9 of the dose titration and did not develop myocarditis. In addition, 33 cases received less than 920mg of clozapine during the first nine days of dose titration, did not take sodium valproate and were aged less than 40 years, meaning according to this analysis their risk of myocarditis was low. Evaluation of the logistic regression model, using the variables employed for multivariate adjustment, as a predictive tool for development of myocarditis during commencement of clozapine, yielded an AUC of 0.71 (95% CI 0.65-0.76) (For ROC curve see Supplementary Figure 1).

4. Discussion

This analysis found that higher cumulative doses of clozapine during Days 1-9 are associated with an increased risk of clozapine-induced myocarditis, and that sodium valproate increases the risk approximately two and a half-fold. Increasing age also conferred a greater risk of myocarditis, with a 31% increase for each decade. Despite these identified associations, a substantial proportion of cases developed myocarditis following a standard rate of clozapine dose titration and without taking sodium valproate, and some controls had combinations of identified risk factors without manifestation of myocarditis.

4.1 Cumulative clozapine dose

Following the clozapine dose titration protocols used in Australia, a person would be given 612.5mg or 812.5mg in the first nine days (Supplementary Table 1). The existence of these protocols has meant that the range of doses used in the early period of clozapine therapy is limited, reducing our ability to explore fully the effect of the rate of dose titration. Nevertheless, our analyses have indicated that doses lower than 500mg in the first nine days may be associated with a reduced risk of myocarditis and that doses higher than 920mg in the same period may increase the risk relative to the protocol-derived doses.

4.2 Sodium valproate

The only concomitant medication showing a significant association, increasing the risk of myocarditis in people commencing clozapine, was sodium valproate. Sodium valproate has been associated with an increased risk of another hypersensitivity reaction, by pharmacokinetic interaction with the anti-epileptic drug, lamotrigine (GlaxoSmithKline Australia Pty Ltd. 2011). The risk is controlled by introducing lamotrigine more slowly in patients taking sodium valproate (GlaxoSmithKline Australia Pty Ltd. 2011). The Australian product information for Epilim (sodium valproate) advises that sodium valproate may potentiate clozapine and vice versa, due to competitive protein binding, but there is no warning about an effect on the rate of metabolism (Sanofi-Aventis Australia Pty Ltd. 2011). Diaz et al. (2008), including data from 37 patients, of whom 10 were smokers, found that sodium valproate increased plasma clozapine in non-smokers and decreased it in smokers. However, Couchman et al. (2010), using data from individuals monitored through a national monitoring service, found no difference in mean or 90% confidence intervals for plasma clozapine and norclozapine concentrations using data on 1184 patients taking clozapine and sodium valproate and no other medication compared with 24,000 taking clozapine alone. None of these observations leads to a satisfactory explanation for the effect of sodium valproate co-administration on the risk of clozapine-induced myocarditis.

4.3 Increasing age

With regard to the association of myocarditis with increasing age, associations of this nature have been observed for other drug hypersensitivity reactions: severe cutaneous reactions with allopurinol (Hung, et al. 2005) and cholestatic hepatitis with flucloxacillin (Fairley, et al. 1993).

4.4 Smoking

Smoking increases the rate of metabolism of clozapine by acting on the CYP 1A2 enzyme and may reduce the plasma concentration of clozapine by as much as 50% (Haslemo, et al. 2006).[18] The effect is sufficiently potent to induce clozapine toxicity when a person taking clozapine stops smoking suddenly (Brownlowe and Sola, 2008). Assuming that plasma concentration (or bioavailability) of clozapine during clozapine initiation is a factor in the development of myocarditis, as suggested by the association with rate of dose titration, it was considered that a non-smoker with the same rate of dose titration as a smoker may be more likely to develop myocarditis. However, these data revealed no significant difference in risk between smokers and non-smokers.

4.5 Potential for bias

Matching by service at which clozapine was commenced and by approximate date of commencement was used to control for any prescribing bias associated with differences in practice between services and over time. We expected to control for differences through time and location in the characteristics of patients selected for prescription for clozapine, but this strategy proved also to be a mechanism for controlling for bias associated with medication used concomitantly and for rate of dose titration, and more effectively so where there were four controls for each case. Although this study did not succeed in including four controls for all cases, we were able to repeat analyses using only those cases with at least one control or with 3 or 4 controls, and we conclude that our findings are robust in the face of this possible source of bias.

In order to explore the potential for bias attributable to missing dose data, we used differing dose imputation strategies. The observation that higher rates of dose titration were associated with a

greater risk of myocarditis was stable in these investigations. Hence, it is unlikely that had the missing doses been available, the results of our analysis would have differed in any sizable way, or that an unaccounted for prescribing bias is responsible for the observed increasing risk with increasing cumulative clozapine dose.

4.6 Genetic factors

Predisposing genetic polymorphisms have been identified for several drug hypersensitivity reactions (Ronaldson and McNeil, 2009): hypersensitivity to abacavir (Mallal, et al. 2008); Stevens Johnson syndrome with carbamazepine (Chung, et al. 2004); severe skin reactions with allopurinol (Hung, et al. 2005); and cholestatic hepatitis with flucloxacillin (Daly, et al. 2009). In each instance the genetic polymorphism was in the HLA-B region. In view of the limited predictive power of the model of five factors related to clinical management and phenotypic characteristics, identified in this study, a genetic mutation may account for a substantial proportion of the risk, especially for those who develop myocarditis in the absence of known risk factors. This possibility is worth investigating.

4.7 Conclusion

This is the first study to investigate risk factors for myocarditis associated with initiation of clozapine. Although we did not investigate the metabolic and environmental suggestions of Devarajan et al. (2000), this study has addressed and confirmed their suggestion that rapid dose titration is a factor increasing the risk of clozapine-induced myocarditis. In addition, we have found that concomitant use of sodium valproate and increasing age add to the risk. Nevertheless, many cases developed without an excessive rate of dose titration or exposure to sodium valproate, and many were young people. Conversely, some patients tolerated a very rapid rate of clozapine dose titration and sodium valproate exposure without experiencing myocarditis.

As a consequence of the results of the current study, we recommend that during clozapine initiation, no patient exceeds the doses recommended in the two dose-titration protocols, and that sodium valproate is best avoided during clozapine commencement. For patients taking sodium valproate, consideration should be given to discontinuation before initiation of clozapine, if this is clinically feasible. Until it is possible to conduct genetic screening for myocarditis predisposition, all patients commencing clozapine should receive active monitoring for myocarditis up to Day 28, even if they are initiated on a very low dose regimen or have previously taken clozapine without developing myocarditis (Ronaldson et al. 2011a).

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Figure legend

Figure 1: The case definition for clozapine-induced myocarditis. Abbreviations: MRI, magnetic resonance imaging; ULN, upper limit of normal.

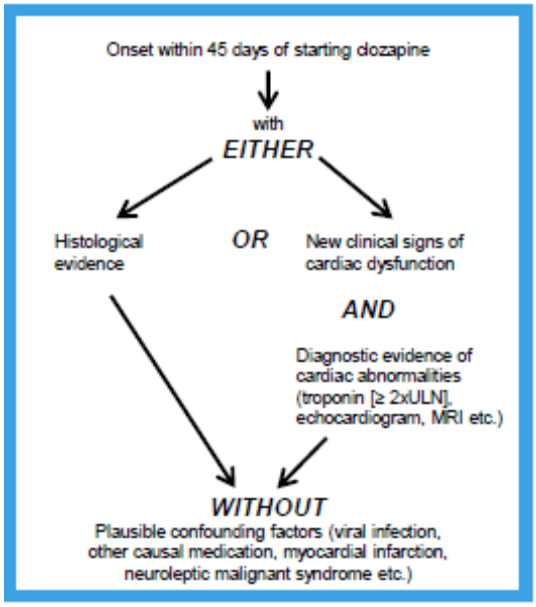

Table 1. Crude (univariate) and adjusted (multivariate) odds ratios for the associations of sex, age and previous clozapine with clozapine-induced myocarditis.

	Cases		Controls		Univariate analyses			Multivariate analyses*		
Parameter	N	%	N	%	OR	95% CI	P-value	OR	95% CI	P-value
	n=105		n=296							
Sex (Male)	74	70	217	73	0.87	0.53-1.42	0.58	0.99	0.59-1.68	0.98
Age (years)										
0-19	1	1	12	4	0.28	0.03-2.22	0.23	0.35	0.04-2.83	0.33
20-29	33	31	110	37	1.00			1.00		
30-39	32	30	95	32	1.12	0.64-1.96	0.68	0.98	0.55-1.77	0.96
40-49	20	19	51	17	1.31	0.68-2.50	0.42	1.19	0.60-2.35	0.61
≥50	19	18	28	10	2.26	1.12-4.56	0.02	2.28	1.08-4.82	0.03
Continuous per 10-years					1.32	1.10-1.59	0.003	1.31	1.07-1.60	0.009
Previous clozapine use	3	3	38	13	0.20	0.06-0.66	0.008	0.19	0.06-0.66	0.008

*Sex, age, sodium valproate, previous clozapine use, and cumulative clozapine dose Days 1-9 were included in the multivariate analysis. For multivariate analysis of age as a stratified variable, the continuous variable was replaced by the stratified variable.

Abbreviations: CI, confidence interval; N, number; OR, odds ratio.

Table 2. Crude (univariate) and adjusted (multivariate) odds ratios for the associations of clinical management factors and phenotypic characteristics with clozapine-induced myocarditis.

	Cases		Controls		Univariate analyses			Multivariate analyses*		
Parameter	N	%	N	%	OR	95% CI	P-value	OR	95% CI	P-value
	n=105		n=296							
Body mass index (BMI)										
0-19.99 kg/m^2	5	6	21	10	0.86	0.28-2.56	0.77	0.87	0.27-2.78	0.82
20-24.99 kg/m^2	18	21	64	29	1.00			1.00		
25-29.99 kg/m^2	31	36	79	36	1.40	0.72-2.72	0.33	1.36	0.68-2.71	0.39
30-34.99 kg/m^2	16	19	33	15	1.72	0.78-3.81	0.18	1.51	0.66-3.48	0.33
≥ 35 kg/m^2	16	19	25	11	2.28	1.01-5.15	0.05	1.99	0.83-4.77	0.12
BMI per 5 kg/m^2	86	82	222	75	1.22	1.02-1.47	0.03	1.18	0.97-1.44	0.09
Other characteristics#										
Other ethnicity vs Caucasian	9/102	9	49/270	18	0.44	0.21-0.92	0.03	0.63	0.29-1.40	0.26
Smoking	74/102	73	223/284	79	0.72	0.43-1.21	0.21	0.71	0.40-1.25	0.23
Alcohol abuse	21/93	23	64/246	26	0.83	0.47-1.46	0.52	0.96	0.52-1.77	0.89
Illicit drug use	23/97	24	80/263	30	0.71	0.42-1.22	0.21	0.84	0.46-1.54	0.58
Asthma	22/55	40	42/121	35	1.24	0.64-2.39	0.52	1.36	0.66-2.81	0.41
Schizophrenia vs Schizoaffective disorder	86/104	83	261/293	89	0.59	0.31-1.10	0.09	0.75	0.38-1.47	0.40
Duration of psychiatric illness#										
0-5 years	22/102	21	84/285	30	1.00			1.00		
>5-10 years	23	23	80	28	1.10	0.57-2.12	0.78	0.85	0.42-1.70	0.65
>10 years	57	56	121	43	1.80	1.02-3.17	0.04	1.03	0.50-2.11	0.93
Other medication										
Amisulpride	10	10	25	8	1.14	0.53-2.46	0.74	0.96	0.42-2.20	0.92†
Aripiprazole	8	8	13	4	1.80	0.72-4.46	0.21	2.52	0.95-6.67	0.06†
Benztropine	21	20	49	17	1.26	0.71-2.22	0.43	1.18	0.64-2.16	0.60†
Chlorpromazine	5	5	16	5	0.88	0.31-2.45	0.80	1.05	0.36-3.04	0.93†
Flupenthixol	5	5	13	4	1.09	0.38-3.13	0.88	0.96	0.32-2.84	0.94†
Haloperidol	7	7	16	5	1.25	0.50-3.13	0.63	0.95	0.34-2.62	0.91†
Lithium	7	7	17	6	1.17	0.47-2.91	0.73	1.45	0.56-3.74	0.44†
Olanzapine	25	24	79	27	0.86	0.51-1.44	0.56	0.83	0.48-1.44	0.51†
Quetiapine	16	15	49	17	0.91	0.49-1.67	0.75	0.88	0.46-1.67	0.69†
Risperidone	24	23	69	23	0.97	0.57-1.65	0.93	0.92	0.52-1.63	0.78†
Zuclopenthixol	6	6	33	11	0.48	0.19-1.19	0.11	0.46	0.18-1.18	0.11†

*Multivariate analysis included sex, age, sodium valproate, previous clozapine use and cumulative clozapine dose over Days 1-9.

#For these parameters data were incomplete. The denominator for cases and controls indicates the number of individuals for whom the data were available.

†Correcting for multiple analyses (12 concomitant medications, including sodium valproate), the significance threshold is p=0.004 (0.05/12).

Abbreviations: CI, confidence interval; N, number; OR, odds ratio.

Table 3: Crude (univariate) and adjusted (multivariate) odds ratios for the association of sodium valproate with clozapine-induced myocarditis.

	Cases		Controls		Univariate analysis			Multivariate analysis*		
Parameter	N	%	N	%	OR	95% CI	P-value	OR	95% CI	P-value
	n=105		n=296							
Sodium valproate (mg/day)	36	34	46	16	2.84	1.70-4.73	<0.001	2.59	1.51-4.42	0.001†
No valproate	69	66	250	85	1.00			1.00		
200-1000	15	14	19	6	2.86	1.38-5.92	0.005	2.78	1.30-5.95	0.008
1001-1999	15	14	13	4	4.18	1.90-9.20	<0.001	4.11	1.74-9.71	0.001
2000-4000	6	6	14	5	1.55	0.58-4.19	0.39	1.20	0.43-3.39	0.73

* Multivariate analysis included sex, age, previous clozapine use and cumulative clozapine dose over Days 1-9.

Abbreviations: CI, confidence interval; N, number; OR, odds ratio.

†Correcting for multiple analyses, 12 concomitant medications, the significance threshold is p=0.004 (0.05/12).

Table 4. Crude (univariate) and adjusted (multivariate) odds ratios for cumulative clozapine doses over Days 1-9 stratified and unstratified for association with clozapine-induced myocarditis.

	Cases		Controls		Univariate analyses			Multivariate analyses*		
Cumulative clozapine dose Days 1-9 (mg)	N n=105	%	N n=296	%	OR	95% CI	p-value	OR	95% CI	p-value
Stratified analyses										
0-499	12	11	57	19.	1.00			1.00		
500-619	37	35	109	37	1.61	0.78-3.33	0.20	1.62	0.76-3.46	0.22
620-920	35	33	90	30	1.85	0.89-3.85	0.10	1.71	0.80-3.69	0.17
> 920	21	20	40	14	2.49	1.10-5.64	0.03	2.31	0.98-5.48	0.06
Analyses with dose as a continuous variable in increments of 250mg										
Dose					1.25	1.03-1.51	0.02	1.26	1.02-1.55	0.03

*Multivariate analysis used adjustment for sex, age, sodium valproate and previous clozapine use.
Abbreviations: CI, confidence interval; N, number; OR, odds ratio.