



## Clinical course and analysis of ten fatal cases of clozapine-induced myocarditis and comparison with 66 surviving cases

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### ARTICLE INFO

#### Article history:

Received 28 November 2010

Received in revised form 20 January 2011

Accepted 23 January 2011

Available online 12 February 2011

#### Keywords:

Schizophrenia

Clozapine

Myocarditis

Drug hypersensitivity reaction

Fatality

Coronary artery disease

### ABSTRACT

**Background:** Fatal clozapine-induced myocarditis has not been investigated systematically. We describe the clinical course of 10 fatal cases of myocarditis with clozapine and identify factors associated with fatality.

**Methods:** Cases of myocarditis were documented from the patient's medical records and fatal cases also from autopsy reports.

**Results:** The fatal cases of myocarditis occurred 1996–2009 and were diagnosed at autopsy. Before death, three had no symptoms of illness and only three had cardiac-specific diagnostic results. None was investigated by cardiac imaging techniques, and in none was myocarditis suspected before death. Duration of clozapine for the fatal cases was 14–33 days with an outlier at 4.5 months. Only 3 cases had significant coronary artery disease at autopsy.

Comparison of these ten cases with 66 non-fatal cases indicated no significant difference in gender, age, smoking status, dose at onset or concomitant sodium valproate. However, obesity (BMI > 30 kg/m<sup>2</sup>) was significantly more frequent among fatal than non-fatal cases (60% vs 26%;  $p < 0.03$ ) and duration of clozapine was significantly longer for fatal cases (20.8 vs 17.0 days;  $p < 0.006$ ), after exclusion of one outlier. Creatine kinase (CK) > 1000 U/L was also associated with death ( $p = 0.0004$ ).

**Conclusions:** Routine monitoring for myocarditis for the first 4 weeks of clozapine, and discontinuation of clozapine in the presence of evidence consistent with myocarditis may assist to prevent fatalities occurring from early-onset myocarditis. Investigation by cardiac imaging will give a measure of severity and need for intervention. Obesity may increase the risk of mortality and CK > 1000 U/L may indicate life-threatening illness.

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### 1. Introduction

The association between myocarditis and therapeutic use of clozapine has been known with some confidence at least since the regulatory agencies in the United Kingdom (Committee on Safety of Medicines, 1993), Australia (Australian Adverse Drug Reactions Advisory Committee, 1994) and New Zealand (Medsafe Editorial Team, 1995) published alerts on the subject. A subsequent article by Kilian et al. (1999), describing 15 cases of clozapine-related myocarditis occurring in Australia in the first month of therapy, provided supportive evidence for the association, with the incidence of fatality from this cause a thousand-fold increase on the background rate.

Since the publication of the paper by Kilian et al. (1999), the awareness of clozapine-induced myocarditis in Australia has in-

creased dramatically. Consequently, when Haas et al. (2007) reviewed the cases reported to the Australian Therapeutic Goods Administration up to the end of 2003, using numbers of patients registered with the two sponsor companies, they estimated an incidence of 0.7–1.2%. Another Australian estimate of about 2% was based on data from a single regional psychiatric service (Tirupati, 2006). Merrill et al. (2005) in a review article have avoided estimating the incidence of clozapine-induced myocarditis, citing a number of reasons for the risk being substantially underestimated, including low rates of reporting to spontaneous adverse reaction reporting databases, variability in the presentation of myocarditis making diagnosis difficult, and the low likelihood of psychiatric patients seeking medical attention for physical illness. The data presented by Haas et al. (2007) suggest the mortality rate with cases of myocarditis is about 10%.

Kilian et al. (1999) reported five fatal cases and subsequently individual fatal cases have been described by Fineschi et al. (2004) and Annamraju et al. (2007). Fatal cases have also been listed in series based on data collected by a national adverse reaction reporting system (Hagg et al., 2001; La Grenade et al., 2001; Haas et al., 2007;

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Hill and Harrison-Woolrych, 2008), including 18 deaths reported to have occurred in the United States up to 2001 (La Grenade et al., 2001). In addition, Meeker et al. (1992) described a fatal overdose in which myocarditis was diagnosed at autopsy.

To date there has been no review specifically of fatal cases. In this paper we describe the clinical course of ten fatal cases, compare key characteristics with those of surviving cases, and seek to identify factors which may serve as clues to the prevention of myocarditis-related fatality in patients starting clozapine.

## 2. Methods

Fatal and non-fatal cases of clozapine-related myocarditis were identified from reports submitted to the Therapeutic Goods Administration, the Australian drug regulatory authority, between January 1993 and December 2009; details of other cases were communicated to the authors by staff of the health services for which ethics committee approval had been obtained (see 2.1); and fatal cases alone were identified from cases in the National Coroners' Information Service database.

Documentation of each case included the date of birth, sex, clozapine start and end dates, dose of clozapine taken each day, baseline pathology results and results obtained during the course of clozapine treatment and until death or resolution of symptoms for surviving cases, signs and symptoms recorded in the progress notes and details described in the autopsy report. Documentation for each case was reviewed by the study steering group for compliance with the case definition for clozapine-related myocarditis (Ronaldson et al., 2010).

### 2.1. Ethics committee approvals

Approval for the study was obtained from the Human Research Ethics Committees of the following institutions and health services: Monash University, Austin Health, Barwon Health, Bayside Health, Bendigo Health, Department of Human Services, Department of Justice, Eastern Health, Mercy Health, North West Mental Health, Peninsula Health, St Vincent's Health, Southern Health (all from Victoria); Northern Sydney Central Coast Health, Sydney South West Area Health Service (Royal Prince Alfred Hospital and Concord Hospital Zones) (from New South Wales); and Prince Charles Hospital (from Queensland). The approvals covered access to medical records without patient consent. In addition, an Access Agreement was signed with the Victorian Institute of Forensic Medicine for access to the National Coroners' Information System database and a Deed of Confidentiality and Conflict of Interest with the Therapeutic Goods Administration for access to original case reports.

### 2.2. Statistical methods

Statistical analysis was conducted using STATA/IC version 10. Risk ratios as for a cohort study were calculated for categorical variables, with *p*-values based on the Chi-squared test. The 2-tailed Students *t*-test was used to investigate the difference in means for continuous variables.

## 3. Results

Myocarditis was diagnosed at autopsy in each of the 10 fatal cases by the presence of mixed inflammatory infiltrates in cardiac histology. All except one case had hyperinflated and/or congested lungs, and four showed cardiac enlargement.

The age and sex distribution of the fatal cases is indicated in Table 1. Table 2 presents further characteristics of the same cases and Table 3 the clinical and diagnostic details. The ten cases occurred between 1996 and 2009. Six patients had a body mass index (BMI) of more than 30 kg/m<sup>2</sup> and seven (of nine; data missing for one) were smokers.

**Table 1**

Characteristics of the 10 fatal and 66 non-fatal cases of clozapine-induced myocarditis.

	Fatal cases	Non-fatal cases	<i>p</i> -value
Gender (% F)	40	26	0.34
Mean age (range) years	40 (27–61)	38 (21–73)	0.77
Smokers (%) <sup>a</sup>	78	77	0.96
Body mass index (BMI) > 30 kg/m <sup>2</sup> (%) <sup>a</sup>	60	26	0.025
Mean duration of clozapine (range) days	20.8 (14–33)	17.0 (10–26)	0.0057
	Outlier at 136 days		
Mean dose at onset (range) mg	315 (50–750)	246 (50–800)	0.12
Concomitant sodium valproate (%)	40	36	0.82

<sup>a</sup> Data on smoking status available for 9 fatal and 61 non-fatal cases and on BMI for all 10 fatal and 53 non-fatal cases.

### 3.1. Clinical details of fatal cases

The time from commencement of clozapine to death was 14–34 (mean 21.4) days with an outlier at 136 days (4.5 months). One patient had discontinued clozapine at the time of death (Case 1). Another had missed a dose 3 days before death, and then had a reduction in dose from 100 to 50 mg/day (Case 7). The others were continuing clozapine without interruption.

Six patients were showing clinical signs of illness at the time of death. Two of the cases, perhaps three, were apparently well, including Case 3 who reported that he was “feeling great” on the day before he died overnight in his sleep. Cases 4, 5 and 6 were thought to have upper respiratory tract infections, Case 7 was investigated for neuroleptic malignant syndrome and Case 1 had mild fever and renal impairment (creatinine 250 μmol/L). Case 10, which occurred after 4.5 months, had been admitted non-specifically unwell both physically and mentally 10 days before death. It is unclear whether this illness was related to myocarditis, but the post mortem indicated acute and chronic myocardial inflammation.

Only four patients had cardiac-specific investigations (Table 3), but none had echocardiography or other direct investigation of cardiac function.

Case 9 is notable for having died of myocarditis following re-initiation of clozapine, having used clozapine previously without any indication of an adverse effect, although documentation was insufficient to confidently exclude a missed episode of myocarditis during the initial exposure.

The plasma clozapine concentrations (0.1–2.7 mg/L) among the fatal cases reflect the prescribed clozapine dose of each individual. In no case was alcohol or any illicit drug found in the post mortem blood.

A key feature of these cases is that myocarditis was not suspected in any of these patients prior to death.

### 3.2. Coronary artery disease

Autopsy indicated that five of the fatal cases were free of coronary artery disease, two had minimal atheroma and three had significant disease with stenosis greater than or equal to 50% (Table 3). Those with BMI greater than 30 kg/m<sup>2</sup> were equally divided between those with significant atherosclerosis and those free of disease. The autopsy report for Case 4, who had the most severe atherosclerotic narrowing, recorded that ischaemic heart disease and hypertension had contributed to the death as independent causes. Case 9 was found to have thromboemboli occluding both pulmonary arteries and myocarditis was a secondary cause. In no other case was pre-existing cardiovascular disease considered to have contributed to the deaths.

### 3.3. Comparison of fatal and non-fatal cases

Table 1 compares characteristics of the fatal cases and the non-fatal cases. There was no significant difference between fatal and non-

**Table 2**  
Characteristics of the 10 fatal cases of myocarditis.

Case no.	Body mass index (kg/m <sup>2</sup> )	Last clozapine daily dose (mg)	Duration of clozapine (days)	No. days to death	Other medications	Clozapine concentration at autopsy (mg/L)
1	27.2	300	15	17	Diazepam	0.47
2	35.0	200	15	15	None	0.9
3	19.1	300	18	18–19	Benztropine	0.4
4	44.3	100	21	21	Lactulose Benztropine Lithium carbonate Clonazepam	0.4
5	45.8	500	24	24	Amlodipine Haloperidol	2.5
6	34.2	200	14	14	Glibenclamide Metformin Sodium valproate	1.6
7	32.7	50	18	19	Venlafaxine Olanzapine Risperidone Sodium valproate	0.1
8	32.5	750	33	34	Venlafaxine Salbutamol Propranolol Diazepam	2.7
9	27.0	300	29	30	Temazepam Escitalopram Quetiapine Sodium valproate	0.4 (ante-mortem)
10	26.2	450	136	136	Sertraline Sodium valproate Atenolol Thyroxine	1.1

fatal cases for gender, age, proportion of smokers, dose at onset or proportion taking sodium valproate. However, the risk ratio for death with BMI above 30 kg/m<sup>2</sup> was 3.5 (95% CI 1.1–10.9;  $p < 0.03$ ) and duration of clozapine was significantly longer ( $p < 0.006$ ) for the fatal cases compared with those that were non-fatal, even after removal of the outlier.

In addition, all three of the fatal cases for which results were available had very high creatine kinase (CK) results ( $> 1000$  U/L). In contrast, only 3 of 65 surviving cases had a CK value of more than 1000 U/L ( $p = 0.0004$ ; Fisher's exact test), and only 12 had results exceeding twice the upper limit of normal.

#### 4. Discussion

Compared with surviving cases, there is nothing remarkable about the fatal cases in age, sex, smoking status, last clozapine daily dose and concomitant medication. Sodium valproate was included in the analysis because it was the only medication other than clozapine taken by more than two fatal cases. The apparent association of a BMI of more than 30 kg/m<sup>2</sup> with a greater likelihood of death may be a random occurrence, but it is biologically plausible that cardiac compromise in the setting of obesity reduces the prospect of recovery. The significantly longer mean duration of clozapine use for fatal cases

**Table 3**  
Clinical and diagnostic features of the 10 fatal cases of myocarditis.

Case no.	Pro-dromal illness	Heart rate (bpm)	Other clinical observations	Cardiac specific parameters	Other parameters	Other diagnoses at autopsy	Coronary artery disease
1	Yes	119	Mild fever – 37.6 °C RR 48 bpm	NA	CK 2900 U/L WBC $12.8 \times 10^9/L$	NMS excluded	Mild atheroma (<30% luminal narrowing)
2	NA	NA		NA			Free of disease
3	No	90	Afebrile, 'feeling great'	NA	WBC $6.9 \times 10^9/L$	Asthma	Free of disease
4	Yes	NA	Flu-like illness	NA	WBC $11.7 \times 10^9/L$	Pneumonia and PE excluded	75% stenosis of left anterior descending coronary artery
5	Yes	126	Fever – 39.1 °C nasal congestion RR 40/min	NA	WBC $15.3 \times 10^9/L$	Diabetic Ketoacidosis; PE excluded	Free of disease
6	Yes	128	Fever – 39.1 °C	CK MB 39 (ULN 25) U/L – 7 h pre-death	CK 1328 U/L WBC $4.3 \times 10^9/L$	NMS, PE and serotonin syndrome excluded	50% stenosis of left anterior descending coronary artery
7	Yes	130	Fever – 38.5 °C RR 24/min Chest pain	Troponin I 0.47 (ULN 0.15) µg/L – 3 days pre-death		PE excluded; Asthma	60% focal stenosis of left anterior descending coronary artery
8	No	98		Troponin I 0.05 (ULN 0.08) µg/L – on cardiac arrest	WBC $21.5 \times 10^9/L$ CRP 15.9 mg/L		Free of disease
9	Yes	136	Collapse, seizure	Troponin T 0.2 (ULN 0.03) µg/L – 1 day pre-death	CK 1730 U/L	PE	Minimal atheroma
10	No	118	Collapse, seizure Afebrile	NA	FBE normal – on day of death		Free of disease

Abbreviations: bpm, beats per minute; CK, creatine kinase; CK MB, creatine kinase muscle and brain; CRP, C-reactive protein; FBE, full blood examination; NA, not available; NMS, neuroleptic malignant syndrome; PE, pulmonary embolism; RR respiration rate; WBC, white blood cells; ULN, upper limit of normal.

may be an indication that fatality followed delayed recognition of illness and delayed withdrawal of clozapine.

With regard to plasma clozapine, Taylor et al. (2009) have reported a range of plasma levels for patients currently taking clozapine of 0.0–2.61 (mean 0.34; 114 patients) mg/L. In a study by Flanagan et al. (2005), post mortem clozapine blood concentrations following seven cases of fatal self-poisoning were 3.7–12 mg/L in individuals who had been poorly compliant or who had used clozapine prescribed for another person. These literature comparisons suggest that there is no reason to believe that clozapine toxicity was a factor in the ten fatalities caused by myocarditis.

The high CK results for three cases are notable, in comparison with data for the non-fatal cases and in view of the absence of data for the other fatal cases. Lee et al. (2006) found that higher CK values (mean for 11 cases  $1708 \pm 1217$  U/L) were associated with fulminant myocarditis compared with milder non-fulminant disease.

#### 4.1. Coronary artery disease and fatal myocarditis

Since the study was retrospective, it was not possible for us to reliably document pre-existing cardiovascular disease and risk factors for such disease, such as hypertension, diabetes and hyperlipidaemia, to compare these characteristics in fatal and non-fatal cases. However, we were able to ascertain that only 50% of the fatal cases had some degree of atherosclerosis, and for only one of these was ischaemic heart disease considered to have contributed to the death. Conley et al. (2005) reviewed a cohort of 134 individuals with schizophrenia who died aged  $48.6 \pm 14.8$  years and whose families had donated brain tissue to the Maryland Brain Collection in the US state of Maryland. Sixty eight percent had died of natural causes, including 45.7% who died of cardiovascular disease. The frequency of atherosclerosis among these individuals, determined at autopsy, was 44%, and is similar to that observed among these cases of fatal clozapine-induced myocarditis. It is apparent that coronary artery disease was not a major factor in the death from myocarditis of these cases.

#### 4.2. Prevention of fatalities

The question arises, would any of these ten deaths have been preventable if more had been understood about clozapine-induced myocarditis at the time of presentation? Since myocarditis was not suspected in any of these cases, it may be that more care with monitoring for this outcome during the first 4 weeks after commencement of clozapine and/or taking appropriate steps in response to clinical and diagnostic indicators that myocarditis may have been present would have prevented some of these deaths. The longer duration of clozapine exposure for the nine fatal cases occurring in the first 5 weeks of clozapine compared with the non-fatal would support the view that stopping clozapine earlier may have prevented death.

Even those who do not develop obvious clinical signs and symptoms of illness may be identified if routine monitoring is followed. Although prevention of serious illness and fatality with monitoring is unlikely to be as reliable as for symptomatic cases, three of the non-fatal cases were asymptomatic and for these myocarditis was detected using routine monitoring. The case who had previously taken clozapine without any indication of the development of myocarditis illustrates the importance of monitoring reintroduction of clozapine with just as much care as would be taken for first use.

There remains, however, the possibility that in these patients there were factors such as severity of the inflammatory assault on the myocardium and host factors governing the response of the heart to this assault that may have meant that the patient would have succumbed despite a prompt response to rises in cardiac enzymes or left ventricular impairment measured by echocardiography. In the absence of documentation of such parameters and/or suitable response to these results, this possibility remains speculative. In one

published case, clozapine was withdrawn when the 64-year-old woman developed tachycardia, fever and hypoxia (Annamraju et al., 2007). She nevertheless died 4 days later of sudden cardiorespiratory arrest. Fulminant myocarditis was diagnosed at autopsy. Likewise one of the patients among the present ten had stopped taking clozapine 2 days prior to death.

Since the fatal case occurring after 4.5 months of clozapine is the only case among 76 with onset later than clozapine day 33, late developing cases appear to be very rare. Hence, it is difficult to conceive of a cost-effective monitoring scheme for a death occurring so late after clozapine commencement. However, it is possible that the chronic myocardial inflammation found at autopsy originated during the first 4 weeks of clozapine and the monitoring employed was inadequate to effect identification.

#### 4.3. Case ascertainment

In the month following the publication of the article by Kilian et al. in November 1999, Novartis Australia circulated a cardiac monitoring protocol in Australia. These guidelines have been followed in varying degrees across Australia since that date. Six of the ten cases described here occurred in the context of use of these guidelines and consequent awareness among clinicians and pathologists of the possibility of death from myocarditis in patients recently initiated on clozapine. Hence, there may be an enhanced likelihood of fatal myocarditis in persons taking clozapine at the time of death being identified at autopsy in Australia, compared with other countries.

Ray et al. (2009) recently published an observational study comparing rates of sudden cardiac death occurring in the community in patients taking antipsychotic drugs among Medicaid enrollees in the US state of Tennessee. Although the exposure for clozapine was low, the incident rate ratio was higher for clozapine than for other antipsychotics. It is feasible that at least some of these deaths may have been caused by myocarditis. An early study by Walker et al. (1997) using mortality data for 196 current users of clozapine across the US did not identify myocarditis as a cause of death, but conduction disorders or sudden death and respiratory illness occurred at twice and three times the rate, respectively, in current versus past users. Five deaths were attributed to pneumonia in an analysis conducted in the United Kingdom by Taylor et al. (2009) of causes of death for 21 patients taking clozapine. In this study, cause of death was obtained from case notes or death certificate and the number of deaths investigated by autopsy was not specified. Since patients developing myocarditis frequently have the symptoms of a respiratory tract infection, autopsy findings typically reveal congested and/or hyperinflated lungs, and myocarditis may be missed even if the myocardium is investigated histologically (Feldman and McNamara, 2000), it is possible that some of these fatalities with a diagnosis of pneumonia or respiratory illness may have been missed myocarditis.

#### 4.4. Benefit of clozapine

Despite the risk of death from myocarditis, a recent study including all patients with a diagnosis of schizophrenia in Finland found that clozapine was associated with a significantly lower all-cause mortality than any other antipsychotic medication (Tiihonen et al., 2009). In other studies, protection against mortality had been attributed to a reduction in suicide (Walker et al., 1997; Meltzer et al., 2003), but an implication from the Finnish study is that this may be an incomplete explanation. Further, in a meta-analysis, clozapine rated above other second generation antipsychotics on two out of three measures of efficacy plus overall symptoms and was second only to amisulpride and sertindole for quality of life (Leucht et al., 2009). This evidence of the superior efficacy and safety of clozapine is an incentive to investigate clozapine-induced myocarditis further so that it can be prevented, or at least the consequences minimised.

#### 4.5. Conclusion

This is the first study to examine the clinical features associated with fatal clozapine-related myocarditis, and to compare them with those of surviving cases. The nine early fatal cases illustrate the necessity of routine monitoring for myocarditis in patients commencing clozapine. Monitoring should not be conditional on the presence of clinical symptoms, but it should be intensified in those who develop a physical illness within 4 weeks of commencing clozapine. Those with laboratory results suggestive of myocarditis should have clozapine discontinued, to prevent further injury. Cardiac imaging techniques may assist to assess the seriousness of impairment of systolic function and the need for drug therapy for cardiac failure or supportive measures. High creatine kinase results (>1000 U/L) may be indicative of a high risk of mortality, and obesity may impair the heart's capacity to recover from myocarditis, but these factors warrant further investigation. Death from clozapine-induced myocarditis is independent of coronary artery disease, except in cases where this is severe.

#### Role of funding source

A salary was paid to Dr Ronaldson in 2006 and 2007 from a grant from the Australian National Health and Medical Research Council (NHMRC). Professor Fitzgerald is supported by an NHMRC Practitioner Fellowship. The NHMRC had no input into study design, interpretation of data or decision to publish.

#### Contributors

Professor McNeil conceived of the study of clozapine and myocarditis and has had a supervisory role in the conduct of the project. Dr Ronaldson conducted the data collection and analysis and wrote the paper. Dr Taylor was the adjudicator determining whether each potential case met the case definition. Professor Fitzgerald proposed analysis that could be conducted, using the data collected. All authors contributed to and approved the final shape of the manuscript.

#### Conflict of interest

Professor McNeil has acted as a consultant for Mayne Pharma, one of the sponsors for clozapine in Australia, and for Hospira Australia after the takeover in 2007. Dr Ronaldson, Prof Fitzgerald, Dr Taylor and Prof Topliss have declared no conflicts of interest.

#### Acknowledgement

The authors are grateful for the assistance of Professor J Duflou, Chief Forensic Pathologist, Department of Forensic Medicine, NSW Health & Clinical Professor, University of Sydney for identifying some of the deaths occurring in New South Wales and for supplying autopsy reports.

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