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Clozapine-Associated Myocarditis

A Review of 116 Cases of Suspected Myocarditis Associated with the Use of Clozapine in Australia During 1993–2003

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Abstract

Background: Clozapine is an antipsychotic medication associated with a lower suicide rate compared with other antipsychotic agents. Clozapine is used specifically in patients for whom previous therapy was inadequate or not tolerated, and is the only antipsychotic agent associated with the development of myocarditis.

Objective: To retrospectively review all adverse drug reaction reports voluntarily submitted to the Australian Adverse Drug Reactions Unit mentioning suspected myocarditis in clozapine-treated patients.

Patients and methods: We accessed all electronic database entries and case reports citing suspected myocarditis associated with clozapine therapy from January 1993 through to December 2003, inclusive.

Results: 116 case reports of suspected myocarditis amongst clozapine-treated patients were identified during the specified time frame (incidence between 0.7% and 1.2% of treated patients). Median patient age for these cases was 30 years (SD 11.1 years) compared with 37 years from the Clopine® registry. The condition developed within a median 16 days (mean 19.8 days; SD 17.3 days) of commencing clozapine for the bulk of patients developing myocarditis within 6 months (n = 93, 80.2%). For all cases with known treatment commencement and cessation dates (n = 106), the condition developed within a median 17 days (mean 171.7 days, SD 530.9 days). Over nine-tenths of cases were prescribed clozapine within the dose range of 100 mg/day to 450 mg/day. Sixty patients (51.8%) recovered from their episode when reported or during follow-up reports, whereas 17 patients (14.7%) had not yet recovered: 27 patients (23.3%) had unknown outcome when reported and the remaining 12 patients (10.3%) died.

Conclusion: Clozapine is uncommonly but importantly related to myocarditis, often fatal or near fatal and sometimes in relatively young patients with early onset after treatment initiation. The most striking feature about this condition is

the wide diversity of nonspecific symptoms that occur in afflicted patients. Additional pharmacovigilance, improved reporting systems and further investigation of mechanisms of drug-induced myocarditis and related cardiovascular conditions (such as heart failure) are clearly warranted. A case-control study would be suitable for investigation of baseline predictors.

Background

Schizophrenia is a debilitating condition with considerable medical and economic burden. Clozapine is a last-line antipsychotic medication specifically indicated for patients in whom previous drug therapy has been inadequate or not tolerated. Clozapine has been proven cost effective via epidemiological modelling.[1] A recent meta-analysis concluded that patients treated with clozapine for long term had significantly lower risk of suicidal tendencies and successful suicides compared with other treatments. However, a large variation in design and outcome amongst the studies was noted.[2] A recent study showed superiority of clozapine compared with olanzapine, a similar antipsychotic, with respect to a reduction in suicidal attempts and rescue interventions in high-risk patients.[3]

Clozapine is available in Australia under the Highly Specialised Drug (Section 100) Program. Clozapine is the only antipsychotic agent known to be associated with myocarditis.[4,5] Myocarditis, generally the result of an infective process, has a poor prognosis with manifestations ranging from sub-clinical to fatal – it has been reported that 56% of infective myocarditis patients die within 4.3 years.[6] The prognosis of drug-induced or hypersensitivity myocarditis is unknown, probably owing to the range of agents associated with the condition, but is likely to be similar based on the reported mortality rates as high as 50% for clozapine-associated myocarditis.[5,7,8]

Clozapine is also associated with other adverse effects, most notably neutropenia and agranulocytosis, which is the primary reason for the existence of the Clozapine Monitoring Scheme.[9] All patients receiving clozapine in Australia must be entered into a registry. Three such registries currently exist in Australia (two currently contain Australian data and are operated by Novartis and Mayne Pharma, whereas the other is operated by Synthon Australia but has no Australian data at present).

Heightened pharmacovigilance and reporting systems may explain the increased incidence of reporting of adverse reactions especially myocarditis in clozapine-treated patients in Australia compared with the rest of the world. The worldwide published literature is quite scarce, consisting of only a handful of case reports of clozapine-associated myocarditis or clozapine-associated cardiomyopathy.[5,7,8,10-22]

The aim of this study was to retrospectively review all adverse drug reaction (ADR) reports voluntarily submitted to the Australian Adverse Drug Reactions Unit (ADRU) between January 1993 and December 2003 mentioning suspected myocarditis in clozapine treated patients.

Methods

We obtained both the data-entry report (processed by ADRU) and the case report submitted to ADRU for each individual patient identified with suspected myocarditis. Cases were provided to ADRU on a voluntary basis by various members of the healthcare profession, namely prescribing physicians, treating nurses, pharmacists and the manufacturing pharmaceutical companies' postmarketing surveillance departments. An overall summary report of all ADR terms associated with clozapine therapy was also obtained from Australian Adverse Drug Reactions Advisory Committee (ADRAC). Information from both the data-entry report and submitted case report for each case were amalgamated into a singular dataset.

Data obtained via this process included the following: ADRAC identification number, reported date, reporter location, ADRAC computer entry date, age, date of birth, gender, height, weight, ADR

Table I. Data available for analysis according to various patient/adverse drug reaction (ADR) characteristics

Characteristic	Number of cases with known characteristic	Number of cases in which characteristic is unknown
Age	110	6
Date of birth	95	21
Gender	112	4
Height (cm)	8	108
Weight (kg)	14	102
Reporter location	94	22
ADR onset date	111[a]	5
Clozapine start date	104	12
Days on clozapine before ADR	106	10
Clozapine stop date	112	4
Clozapine dosage (mg/day) at date of ADR onset	105	11
Outcome	116	0
Causality (reporter assigned)	116	0

a ADR onset date was only specified as occurring during the year 2001 in one case and during the year 2003 in another case, with the remaining 109 cases reported with specific dates between 1993 and 2003.

onset date, clozapine start date, days on clozapine before the suspected ADR, clozapine date of cessation, clozapine dosage at date of ADR onset, outcome, causality assigned by ADRU, concomitant ADR terms (classified in accordance with the WHO-Adverse Reactions Terminology dictionary), clinical investigations, concomitant medications, treatment of episodes, family/patient history and unique additional notes presented by the reporter.

Results

Table I summarises the available data from the 116 reported patients, of whom 90 (77.6%) were male, 22 were female and in 4 patients gender was unspecified. Both active clozapine registries in Australia reported that approximately two-thirds of all patients with schizophrenia treated with clozapine in the specified time period were male (table II). The reported date of onset of suspected myocarditis for 82 of the patients (70.7%) was between January 2000 and December 2003.

Age of Patient at Onset of Suspected Myocarditis

Age distribution of the 110 patients with a reported age is shown in figure 1. The median age of patients with suspected myocarditis was 30 years (SD 11.1 years, range of 45 years, interquartile range 14 years [25–39 years], minimum 16 years, maximum 61 years, mode 27 years). This compares with the median age of 37 years of patients treated with the Clopine® brand of clozapine (Mayne Pharma) [Tymensen K, personal communication].

Number of Days on Clozapine before Onset of Suspected Myocarditis

The distribution of the number of days that a patient was on clozapine before developing suspected myocarditis, where that information was available, is shown in figure 2. These data have been stratified according to length of onset for all cases in table III. In addition, the ten cases citing concomitant cardiomyopathy have also been stratified according to the length of onset, with short-term development of suspected myocarditis defined as <1 month following initiation of clozapine therapy.

Clozapine Dosage at the Date of Onset and Overall Outcome

Ninety-seven out of 105 cases (92.4%) with a reported dosage at the ADR onset date had utilised doses between 100 mg/day and 450 mg/day.

Of all cases reported, 60 patients (51.8%) recovered from their episode at the time of reporting or

Table II. Australian registry data

Variable	Clozaril® registry (Novartis)[a]	Clopine® registry (Mayne Pharma)[b]	Our study data (ADRU)
Number of patients exposed[c]	13 553	3522	Minimum: 10 031 Maximum: 17 075[d]
Males (number)	UK[e]	2372	90
Males (%)	66	67.3	77.6
Age (years)			
mean	UK[e]	38[f]	NA[g]
median	UK[e]	37[h]	30

a Jerram A, personal communication.

b Tymensen K, personal communication.

c Number of patients exposed as at 31/12/2003.

d These numbers represent the estimated incidence in Australia up to 2003, using the two extreme scenarios: (i) duplicated patients in both clozapine registries (13 553 − 3522 = 10 031); (ii) no duplicated patient in either clozapine registry (13 553 + 3552 = 17 075).

e Unknown (cannot be ascertained from the Clozaril® registry database).

f 37 years of age for males and 42 years of age for females.

g NA (inappropriate since age is heavily skewed to the right).

h 35 years of age for males and 40 years of age for females.

ADRU = Adverse Drug Reporting Unit; **NA** = not applicable; **UK** = unknown.

during follow-up reports. One of these patients had possible sequelae, which included sinus tachycardia, frequent atrial ectopic beats, nonspecific ST-T wave changes and findings consistent with cardiac failure (enlarged left ventricle, global systolic dysfunction and bilateral pleural effusions), which developed a couple of days after cessation of clozapine.

There were also 17 patients (14.7%) that had not yet recovered at the time of reporting, in which the duration between diagnosis and last follow-up (considered to be the reporting date) was skewed at a median of 15 days (mean 27 days; SD 25 days). Twenty-seven patients (23.3%) had an unknown outcome at the time of reporting, whereas the remaining 12 patients (10.3%) had a fatal outcome. Ten of the fatal cases were definitively classified as cardiac-related deaths, predominantly via autopsy – one other case was described as death by ischaemic heart disease (hypercholesterolaemia and hypertension) with signs of myocardial inflammation consistent with a drug reaction, whereas no other cause for myocarditis was identified in the remaining one case.

Concomitant Adverse Drug Reaction Terms, Clinical Investigations and Concomitant Medications Cited by Reporters

The most commonly reported concomitant ADR terms, clinical investigations and concomitant medications are detailed in table IV, table V and table VI. As would be expected, a majority of the items described by reporters were cardiac ADR terms, cardiac/vascular investigations and psychoactive medications. It is pertinent to note that a wide variety of nonspecific symptoms (such as leukocytosis, dyspnoea and fever) have been described by reporters as concomitant ADR terms, additionally indicating the complexity of this condition.

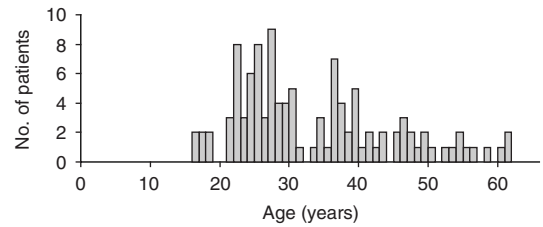

Fig. 1. Patient age at onset of suspected clozapine-induced myocarditis.

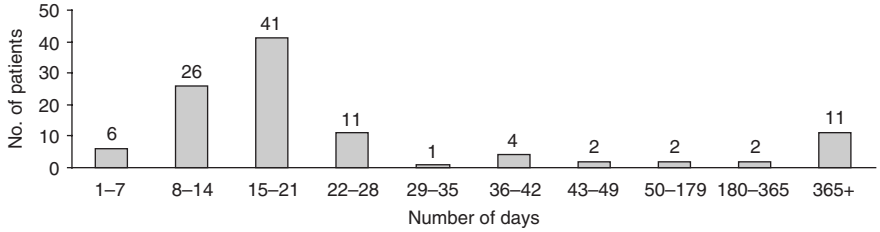

Fig. 2. Number of days on clozapine before onset of suspected clozapine-induced myocarditis amongst reported patients.

Study Limitations

As a result of its retrospective nature this study is bound to have some limitations. In the first instance, the collected data rely completely upon the tenacity of the reporter to include as much information as possible, especially in relation to the presenting symptoms and the time-course progression of the condition. It is also important to note that these case reports also include mere suspicions of myocarditis which, in the ideal world, would be confirmed definitively via a 'gold-standard' technique such as endomyocardial biopsy or, at the very least, by clinical investigations recommended by organisations such as the Royal College of Pathologists of Australasia (RCPA).

Referring to table I, the non-reporting of certain simple characteristics, such as age, gender, reporter location, ADR onset date, clozapine start date and clozapine dosage, definitely impacts upon the integrity of our dataset. This may lead to potential underestimation of the extent of concomitant ADR terms, details of clinical investigations and the number of concomitant medications. It is also important to note that ADR reporting throughout this time period was, and currently remains, completely voluntary, potentially leading to further underestimation of the extent of the problem.

In addition, in a number of reports certain dates of importance had been recorded in an imprecise fashion or not at all requiring estimation for analysis. Unfortunately, this limitation prevents the precise calculation of exposure to clozapine in person-time units (and thus also prevents calculation of incidence in person-time units), a convention commonly accepted in epidemiological studies.

Discussion

The majority of suspected myocarditis reports in this study were reported between January 2000 and December 2003. This could be explained by increased awareness of the problem following the publication of the paper by Kilian et al.[5] in November 1999.

The median age of patients with suspected myocarditis was 30 years amongst 110 cases in which age was a known characteristic. Myocarditis is a

Table III. Interval between commencement of clozapine and onset of suspected myocarditis

Time to onset (days)	All cases (n = 106)[a]	Bulk of cases with onset <6 months (n = 93)	Concomitant cardiomyopathy (n = 10)	Concomitant cardiomyopathy, with short-term development of myocarditis (n = 4)
Median	17	16	330	14.5
Mean	171.7 (SD 530.9)	19.8 (SD 17.3)	711.3 (SD 1065.8)	15.25 (SD 2.63)
Range	1–3285	1–120	13–3287[b]	13–19
Interquartile range	13.5–24	12.5–21	15–730	13.5–17
Mode	15	15	Nil (data too sparse)	Nil

a Data unavailable for 10 of the 116 cases reported.

b Four cases were reported as cardiomyopathy <3 weeks after commencing clozapine therapy.

Table IV. Most common concomitant adverse drug reaction (ADR) terms cited by researchers

ADR	Frequency (%)
Cardiac	311 (37.9)
ECG/echocardiography abnormality	66
tachycardia	46
troponin increased	36
CK increased	31
Vascular/blood	164 (20)
leukocytosis	28
neutrophilia	26
eosinophilia	25
Sensory/CNS	122 (14.9)
chest pain	32
Respiratory	59 (7.2)
dyspnoea	27
Hepatic/renal/enzymatic	27 (3.3)
Other	138 (16.8)
fever	49
influenza-like symptoms	22

CK = creatine kinase.

relatively uncommon condition, especially drug-induced, and is even less expected in physically healthy young people.[5] Based on the statistics gathered in this study, the incidence of myocarditis amongst patients utilising clozapine therapy in Australia is between 0.7% and 1.2% of clozapine-treated patients, a much higher rate than quoted figures from the rest of the world (between 0.015% and 0.188%).[5,7,8,14,23] Obviously, it is quite concerning that this is the case, particularly amongst young patients treated with clozapine.

Although suspected myocarditis tends to appear at any time during treatment with clozapine, a particular 'danger-period' appears to exist during the first 4 weeks following initiation of clozapine therapy (84 cases in this investigation developed myocarditis within this time frame in a similar manner to other studies[5,7,8]).

Approximately three-quarters of the cases with a reported dosage at the ADR onset date were prescribed clozapine within the dosage range of 200 mg/day to 450 mg/day when myocarditis was suspected, and this figure increased to over nine out of ten cases within the dosage range of 100 mg/day to 450 mg/day. Since a majority of patients are treated with a dosage of clozapine below 450 mg/day in accordance with the product information, it appears that dosage itself may not be a factor complicating this issue. However, it remains unclear as to whether rapid dose escalation to these prescribed dosages is a potential risk factor for the development of myocarditis.

A high proportion of outcome in these reported cases was unknown or 'not yet recovered' at the time of reporting (38% combined), which was usually at least 2 weeks after the adverse reaction. In addition, 10.3% of cases had fatal outcome. Considering that these circumstances occurred in a short time frame following the introduction of clozapine, and that recovery from the condition was not always spontaneous, further investigation into the mechanisms of drug-induced myocarditis and other drug-induced cardiovascular conditions (such as heart failure) is clearly warranted.

A number of medications have been implicated as the cause of cardiovascular complications such as myocarditis and heart failure, e.g. antibacterials

Table V. Most common clinical investigations cited by researchers

Clinical investigation	Frequency (%)
Vascular/blood	229 (41.6)
WBC	61
neutrophils	57
eosinophils	39
Cardiac	213 (38.7)
ECG/echocardiography	76
troponin	54
CK	48
Radiological	29 (5.3)[a]
chest x-ray	23
Hepatic/renal/enzymatic	24 (4.4)
Other	55 (10)
histology	14[b]
toxicology	12
rechallenge	9[c]

a Non-cardiac specific radiological investigations.

b Endomyocardial biopsy specified in two cases, myocardial biopsy specified in one other case and 'heart biopsy' specified in another case.

c Seven specific rechallenges (dates recorded or approximated for all cases), plus two cases of non-medically initiated exposures in July 2002.

CK = creatine kinase; **WBC** = white blood cell count.

Table VI. Most common concomitant medications cited by researchers

Concomitant medication	Frequency [n (%)]
Psychoactive	135 (63.4)
benzodiazepines	25[a]
sodium valproate	21
antidepressants	15[b]
Gastrointestinal	18 (8.5)
ranitidine	6[c]
Cardiac	16 (7.5)
β-adrenoceptor antagonists	4
Respiratory	10 (4.7)
Antibacterial	7 (3.3)
cephalosporins	2
amoxicillin	1
sulfamethoxazole	1
trimethoprim	1
Other	27 (12.7)
paracetamol (acetaminophen)	4
metformin	3
thyroxine (levothyroxine sodium)	3

a Diazepam (n = 14), temazepam (n = 4), clonazepam (n = 3), alprazolam (n = 1), midazolam (n = 1), oxazepam (n = 1), unspecified (n = 1).

b Sertraline (n = 5), amitriptyline (n = 2), venlafaxine (n = 2), citalopram (n = 1), dothiepin (n = 1 – may have been ceased before ADR), fluvoxamine (n = 1), mirtazapine (n = 1), moclobemide (n = 1), paroxetine (n = 1).

c In one case, the patient was treated with ranitidine during both initial exposure to clozapine and during rechallenge with clozapine.

n = number of reports.

(sulfonamides and β-lactams), lithium, cisapride, thyroxine (levothyroxine sodium) and certain antidepressant agents. Several of these agents are listed amongst the concomitant medications cited in these reports. The possibility that these concomitant agents may contribute to the development of myocarditis should be considered, either in their own right or as part of a drug-drug interaction. It was interesting to note that ranitidine, a gastrointestinal medication, was cited in six cases as a concomitant medication (in one case, ranitidine was utilised during both the initial therapy and rechallenge of clozapine therapy). Further investigation into this possible interaction is warranted considering that a report of ranitidine-associated myocarditis exists in the medical literature.[24]

The most striking feature about myocarditis is the wide diversity of nonspecific symptoms that occur in afflicted patients. In order to overcome the deficiency relating to the diagnosis and reporting of myocarditis, a concise case definition needs to be developed which considers the range of clinical manifestations of myocarditis. Merrill et al.[14] state that initial suspicion of myocarditis associated with clozapine therapy is often low as a result of the fact that the condition is uncommon and symptoms are usually nonspecific. The real possibility of diagnostic misclassification of myocarditis with conditions of a similar nature cannot be ignored, both nationally and internationally, potentially leading to major underestimates of the severity and extent of this problem.

A combination of the signs and symptoms as well as laboratory (and diagnostic) confirmation is mandatory for the development of a case definition for myocarditis, which currently appears to be a broad set of guidelines overlapping considerably with other common cardiac conditions such as cardiomyopathy and heart failure. Investigation of the most reliable clinical indicators of myocarditis and, which markers are the most useful, effective and cost-efficient is also important.

A perfect example of potential misclassification is the condition of cardiomyopathy which is typically a chronic disorder, clinically distinct from myocarditis, which is generally considered acute on presentation. Inclusion of cardiomyopathy as an ADR term occurred in ten cases in our dataset, with four cases occurring <3 weeks after the commencement of clozapine therapy (whereas a few other cases occurred years afterwards). Interestingly, 90 cases of cardiomyopathy (including mentions of congestive and hypertrophic cardiomyopathy) amongst clozapine-treated patients were reported to ADRAC between January 1993 and December 2003 (Hill R, personal communication). Because of potential misclassification, further studies may need to include all of these submitted reports to elucidate the overall cardiovascular risk profile for clozapine, rather than primarily using myocarditis as a search criterion. The same can be said for cardiac failure

(35 ADRAC reports between January 1993 and December 2003), left ventricular failure (12 reports), right ventricular failure (two reports), cardiomegaly (26 reports), abnormal ECGs (73 reports), cardiac disorders (41 reports) and many more search criteria (Hill R, personal communication).

Eosinophilia (125 cases) and leukocytosis (113 cases), associated with clozapine use, were also reported between January 1993 and December 2003 (Hill R, personal communication). It may also be possible that cases of asymptomatic eosinophilic myocarditis are not currently being diagnosed or recognised amongst clozapine patients.

There is also considerable overlap between numerous other conditions with respect to the symptoms of myocarditis, and of cardiovascular conditions in general. A condition of considerable importance is neuroleptic malignant syndrome (NMS),[25] which was reported as a concomitant ADR term in five cases in this study – one diagnosis was confirmed while the others were either suspected or doubted by the treating physician. It was difficult to determine whether the symptomatology expressed by these patients was more indicative of myocarditis or NMS. Patients diagnosed with NMS may or may not experience muscle rigidity or elevated cardiac enzymes (such as creatine kinase [CK]), especially amongst clozapine-treated patients,[26,27] which may confuse diagnosis and lead to further misclassification. Of interest, there have been 57 ADRAC reports between January 1993 and December 2003 involving clozapine-associated NMS (Hill R, personal communication).

Twenty-seven reporters also cited dyspnoea as a concomitant ADR term amongst the clozapine-treated patients in this study, which could of course be a respiratory condition or a symptom of cardiovascular conditions such as myocarditis or heart failure. The use of cardio-selective biomarkers in investigations, such as troponin, and promising results of recent studies involving brain natriuretic peptide[28] and magnetic resonance imaging,[29] could help elucidate whether symptoms experienced by a patient are of a cardiac nature or not.

Because of the complexity of clinical situations related to myocarditis and a potential for such inaccuracies in diagnosis existing, clinicians need to be aware of a 'Dear Healthcare Professional' newsletter, boxed warnings in product information and Clinical Guidelines from both Novartis and Mayne Pharma recommending extensive monitoring at the beginning of therapy[30,31] and heightened vigilance towards a range of signs and symptoms that may indicate clozapine-related myocarditis or cardiomyopathy.[20]

In addition, the RCPA has published guidelines, albeit not concise with respect to definitive values, for the laboratory detection and diagnosis of myocarditis: full blood cell count, differential white blood cell count, blood film, C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR); CK and CKMB; cardiac troponin I and cardiac troponin T are more sensitive and specific. If diagnosis is uncertain or if confirmation is required: myocardial biopsy including viral and bacterial culture.[32] Within the 116 patients in our dataset, white blood cell counts were reported as performed in 61 cases, neutrophils in 57 cases, eosinophils in 39 cases, CRP in 20 cases, ESR in 13 cases, CK (and its variations) in 48 cases, troponin in 54 cases, and endomyocardial biopsy in two cases (another case specified as 'myocardial biopsy' and another case specified as 'heart biopsy').

A number of 'borderline' laboratory test values were reported amongst the patients in our dataset. These results were subsequently not counted as positive test results, although within each individual case it is evident that a rise in the test value of the characteristic did occur. 'Borderline' results occurred amongst tests for troponin (11 cases), neutrophilia (six cases), leukocytosis (five cases), eosinophilia (four cases), and lymphocytosis (one case). Inconsistencies between laboratory test 'reference ranges' may need to be addressed and standardised across hospitals,[33,34] and a case definition may aide in this possibility becoming a reality.

There were also cases in which there may (or may not) have been changes in a particular characteristic. For instance, there were six cases that re-

ported 'non-specific changes' in ECG or echocardiographs, which could perhaps translate to possible ST-T wave abnormalities, T-wave inversions or Q-wave abnormalities (as characterised specifically by other ADR reports).

Future Directions

It is of interest to note that the original manufacturer of clozapine in Australia (Sandoz) had instituted a standardised reporting system for suspected cases of myocarditis. This form remains in current use by Novartis (which was formed from a merger of Sandoz and Ceiby Geigy in 1996) and directs investigators to disclose pertinent information such as specific symptomatology, cardiac abnormalities, viral study results, concomitant medications and drug allergy history. Since all clozapine manufacturers maintain registries of treated patients as part of their monitoring for agranulocytosis, it would seem prudent and extremely worthwhile for symptoms of myocarditis to be monitored concurrently by all pharmaceutical companies manufacturing clozapine as part of the registry process. A common case definition of definitive myocarditis would also be exceptionally useful to apply to the registry databases to encourage awareness of the condition in addition to early detection and treatment of patients. Investigations of this nature are very important in regard to elucidating the mechanism of cardiac events, identifying important cardiovascular-related (and possibly other) information. This would also distinguish whether concomitant medication was for therapy of the underlying condition (thus, possibly a causative agent) or for some other reason (perhaps treatment of resulting ADRs or as alternative therapies for clozapine).

Further avenues of investigation would also include whether any specific ethnicities, ages, gender or co-morbidities may increase susceptibility to the development of myocarditis and other cardiovascular conditions. A small study compared Caucasian with Asian subjects and identified a lower clozapine dosage requirement amongst the Asian subjects after adjusting for differences in gender, body mass index and use of cigarettes, alcohol (ethanol) and caffeine.[35]

Investigation into whether the occurrences of all ADRs are reported to a scheme such as ADRAC in the first place is also a worthwhile pursuit. Complacency amongst prescribers or allied health professionals to report perceived 'known' adverse effects would lead to an underestimate of the extent and incidence of the resulting condition, although this is less likely to be the case in ADRs considered clinically serious.[36] Conversely, potential overestimates may also occur when myocarditis is suspected and reported but subsequently discovered to not actually be myocarditis, supporting the need for a more concise case definition.

A case-control or cohort study would be the ideal forum to investigate the problems relating to clozapine and myocarditis (and other cardiac conditions). A clinically monitored trial is warranted to definitively determine whether clozapine, in itself, is indeed a causative agent in this setting, and what risk factors are significant if causation with clozapine is proven. How particular genetic and immune characteristics correlate with the risk of developing the condition is a further avenue of investigation.

A catastrophic recall along the lines of the rofecoxib withdrawal would not be the aim of further investigations; however, there is a dire need to investigate this issue in greater detail to elucidate the mechanisms underlying this devastating illness. Until definitive answers are available, cautious and judicial usage of clozapine therapy and stringent monitoring of symptoms and therapeutics in the hospital situation are highly recommended by several sources including the pharmaceutical companies manufacturing clozapine (especially serial blood tests and ECGs)[20,30,37] to ensure that an appropriate individualised dosage is provided and that patient safety is of utmost importance throughout therapy. However, even though routine monitoring of echocardiographical changes, troponin and cardiac biomarkers would prove useful in a number of cases, this procedure would be exceptionally cumbersome and expensive, indicating the need for further re-

search to identify the most specific investigations to yield preferable clinical outcomes. A potential alternative may also be the consideration of other psychotropic agents during the maintenance phase following on from the acute phase of treatment-resistant schizophrenia, which has necessitated the commencement of clozapine.[38]

Conclusion

Clozapine has been associated with suspected myocarditis in a number of patients in Australia between 1993 and 2003, with an incidence between 0.7% and 1.2% of treated patients. This condition has been fatal or near fatal, in some young people with early onset after treatment initiation. Additional pharmacovigilance, improved reporting systems, consistency in diagnosis of the condition (possibly avoiding misclassification) and further investigation of mechanisms of drug-induced myocarditis and related cardiovascular conditions (such as heart failure) are clearly warranted. A case-control study would be suitable for investigation of baseline predictors.

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