

Nine Fatal Cases of Clozapine-Induced Myocarditis compared with 66 Surviving Cases

Ronaldson KJ¹, Taylor AJ², Topliss DJ³, Fitzgerald PB⁴, McNeil JJ¹

¹Department of Epidemiology & Preventive Medicine, Monash University; ²The Heart Centre, Alfred Hospital; ³Department of Endocrinology & Diabetes, Alfred Hospital; ⁴ Monash Alfred Psychiatric Research Centre, Alfred Hospital and Monash University, Melbourne, Victoria, Australia

Context

Clozapine is an exceptionally effective treatment for schizophrenia, but its use is limited by its side effects, including myocarditis.

In Australia, despite a widespread practice of monitoring for myocarditis fatal cases still occur.

Clozapine-induced myocarditis :

- ❖ Drug hypersensitivity reaction
- ❖ Incidence about 2%
- ❖ About 10% of cases are fatal
- ❖ Typically occurs in the third week of clozapine therapy
- ❖ No systematic analysis of fatal cases

Aim

To analyse the characteristics of 9 fatal cases of clozapine-induced myocarditis and compare these with those of 66 non-fatal cases.

Methods

Data collection:

- ❖ Documented from patient's medical record, and autopsy report for fatal cases.

Diagnosis of cases

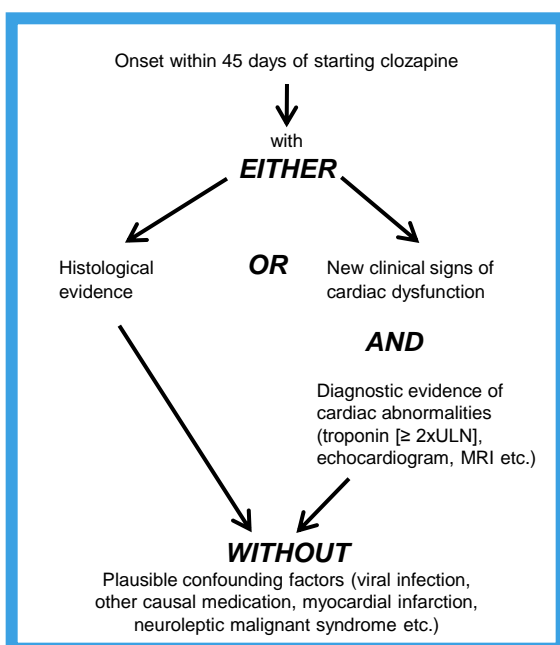
Nine fatal cases:

- ❖ Mixed inflammatory infiltrates on cardiac histology

66 surviving cases:

- ❖ Diagnosed according to the clinical criteria and diagnostic evidence as specified in the case definition

Case definition



Characteristics of 9 fatal and 66 non-fatal cases

	Fatal	Non-fatal	P-value
% Male	67%	74%	0.63
Mean age (range) years	37 (27-61)	38 (21-73)	0.92
Smokers	87.5%	77%	0.5
BMI > 30 kg/m ²	67%	26%	0.02
Mean clozapine duration (range) days	20.8 (14-33)	17.0 (10-26)	0.006
Mean last daily clozapine dose (range) mg	300 (50-750)	246 (50-800)	0.25
Concomitant valproate	33%	36%	0.85

Critical observation

Myocarditis was not suspected prior to death in any fatal case

Key observations (continued)

Clinical features:

- ❖ 6 fatal cases were ill with non-specific symptoms prior to death; 3 had 'flu-like illness'
- ❖ In only 1 fatal case had clozapine been discontinued.
- ❖ 3 fatal cases were asymptomatic; one fatal case had no tachycardia and reported 'feeling great' the day before he died overnight

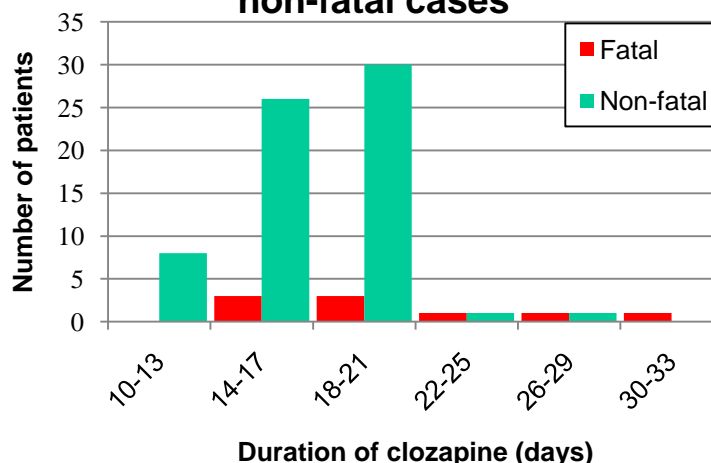
Diagnostic parameters:

- ❖ Only 3 had cardiac-specific investigations (troponin or CK MB) prior to death
- ❖ These were elevated but not alarming
- ❖ No action was taken in response to results

Non fatal cases

- ❖ C-reactive protein (CRP) is typically raised before troponin
- ❖ 3 asymptomatic non-fatal cases identified by routine monitoring
- ❖ Echocardiography confirms the presence of myocarditis in those 10% of cases without raised troponin

Duration of clozapine for fatal and non-fatal cases



Key observations

Deaths occurred 1996-2006

Death was associated with:

- ❖ BMI > 30 kg/m²
- ❖ Longer duration of clozapine

No difference between fatal and non-fatal cases for:

- ❖ Age
- ❖ Gender
- ❖ Smoking status
- ❖ Last daily clozapine dose
- ❖ Concomitant medication

Drug concentrations

- ❖ Clozapine concentrations at autopsy were 0.1-2.7 mg/L and were consistent with the patient's daily clozapine dose
- ❖ Clozapine concentrations not suggestive of clozapine toxicity or overdose as cause of death
- ❖ Alcohol and illicit drugs not detected at autopsy

Preventing death from myocarditis

- ❖ Death from myocarditis may occur suddenly and without symptoms of illness
- ❖ There is no known monitoring approach that guarantees to prevent all fatalities

Nevertheless we recommend:

- ❖ Monitor CRP and troponin weekly for 4 weeks after clozapine initiation
- ❖ Withdraw clozapine if CRP > 100mg/L or troponin $\geq 2 \times \text{ULN}$ (upper limit of normal)
- ❖ Conduct cardiac imaging to assess need for drug therapy or supportive measures

Conclusions

- ❖ The longer mean duration of clozapine for the fatal cases suggests that earlier clozapine withdrawal may have prevented death
- ❖ Obesity may predispose to fatality if myocarditis develops
- ❖ Deaths may be prevented if troponin and CRP are checked on Days 7, 14, 21 and 28.