Continuation of clozapine following mild myocarditis

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In the course of a study of clozapine and myocarditis, we have documented five individuals who met our case definition of myocarditis but yet continued clozapine without long-term cardiac injury.

The case definition required clinical evidence, together with cardiac specific diagnostic evidence of myocarditis (Ronaldson et al., 2010). Each of the five (four men and one woman, aged 28–52 years) met the criteria, having tachycardia together with troponin I or T more than twice the upper limit of normal (Table 1). Three also had clinical symptoms of illness. Three had echocardiography around the time of the raised troponin and the result was normal for all three, as was follow-up echocardiography in two individuals.

Each of these cases had only mild disease, as measured by troponin concentrations which were between twice and four times the upper limit of normal. However, the degree of the rise in eosinophils for Case 4 and in CRP for Case 5 was suggestive of more severe illness. Two of the cases continued clozapine with no interruption; one had a reduction in dose from 300 to 200 mg/day and two missed 1 or 1.5 days of clozapine and then continued.

Acute clozapine-induced myocarditis, including in cases for whom it is asymptomatic or whose laboratory parameters give no indication of severe illness, can be fatal (Ronaldson et al., 2011a). Nevertheless, in some cases it is clearly safe to continue clozapine. Not only is it safe, but continuation of clozapine might also be highly desirable for the long-term mental health of the individual.

The data available do not permit a demarcation between truly mild cases

Table 1. Cases of continuation of clozapine despite mild myocarditis.

Case no.	Duration of clozapine before myocarditis (days)	Clinical features	Diagnostic features	Transition	Continuation
1	20	HR 116 bpm; sedation	Troponin 0.39 (ULN 0.16) µg/L; eosinophils 1.5 × 10^9/L	Reduction in dose from 300 to 200 mg/day	> 2 years
2	15	HR 117 bpm	Troponin 0.1 (ULN 0.03) µg/L	No interruption in clozapine; dose *increased* from 175 to 200 mg/day	> 6 months Normal echocardiography 3 weeks after myocarditis
3	19	HR 115 bpm; fever (38.9°C), chest pain, cough; dysuria and 'flu-like symptoms	Troponin 0.8 (ULN 0.2) µg/L; CRP 67 (ULN 5) mg/L; normal echocardiography	3 doses omitted 3–4 days prior to troponin peak; otherwise no interruption; 175 mg/day	> 19 days
4	19	HR 112 bpm; diarrhoea	Troponin 0.08 (ULN 0.03) µg/L; CRP 19 (ULN 5) mg/L; eosinophils 3.44 × 10^9/L; normal echocardiography	No interruption in clozapine; 200 mg/day	> 15 months
5	18	HR 127 bpm; dysuria, productive cough, mid-zone crepitations	Troponin 0.14 (ULN 0.06) µg/L, CRP 156 (ULN 8) mg/L; eosinophils 1.1 x 10^9/L; normal echocardiography	Clozapine omitted 1 day and dose reduced from 100 to 75 mg/day	> 4 years Normal echocardiography 4 months after myocarditis

Abbreviations: bpm, beats per minute; CRP, C-reactive protein; HR, heart rate; ULN, upper limit of normal.

and those which are potentially fatal (Ronaldson et al., 2011a). Hence, we recommend extreme caution if a decision is made to continue clozapine despite diagnostic evidence of very mild myocarditis. A cautious approach would include treating the patient in hospital, reducing the clozapine dose and following them with echocardiography, and at least daily troponin and C-reactive protein determinations (Ronaldson et al., 2011b). Further very slow dose titration of clozapine could occur after resolution of all signs, symptoms and diagnostic indications of myocarditis and with appropriate careful monitoring.

References

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