Reviewer’s report

Title: QT interval prolongation after sertraline overdose: a case report.

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Reviewer: Geoffrey K Isbister

Reviewer’s report:

General

The authors present a case report of a patient that develops QT prolongation a day after the ingestion of an overdose of sertraline and two benzodiazepines. The patient has no other major clinical effects. The authors conclude that the QT prolongation is associated with sertraline overdose and recommend that all sertraline overdoses be monitored (telemetry).

I have significant concerns about the case and discussion as presented. The authors essentially present a single ECG a day after a sertraline overdose - although there is a reasonable possibility that the QT prolongation is associated with sertraline overdose - the authors place far too much emphasis on this - they do not provide drug concentrations at the time of the QT prolongation, there is no evidence that QT prolongation in sertraline overdose is clinical significant (no reports of Torsades de Pointes in the literature, compared to say citalopram), the method of QT measurement is questionable. To recommend that overdoses of one of the most common SSRIs all get monitored based on this one case report is inappropriate. Further, we have published a series of 103 sertraline overdoses demonstrating that it is unlikely to cause QT prolongation.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. Method of QT measurement. The authors are referred to the appropriate literature on QT measurement and the problems with QT measurement and HR correction (see below). This is a complex area, however although it is poorly understood in clinical toxicology we must make reference to the extensive and ever increasing pharmacology literature on the subject. To measure QT in a single lead (V2) as the authors has done is not a very robust measure – usually a number of leads are measured and the median taken (this is due to QT dispersion). Doing this I would suggest the QT is about 520 msec in the second ECG.

   • Malik M, Farbom P, Batchvarov V, Hnatkova K, Camm AJ. Relation between QT and RR intervals is highly individual among healthy subjects: implications for heart rate correction of the QT interval. Heart 2002; 87(3):220-228

2. HR correction is not a simple process, and the use of QTc based on Bazett is problematic, particularly in clinical toxicology where tachycardia is common. This has been discussed previously (see below). Although looking at therapeutic use of drugs, Fossa et al have shown another way to view QT and RR relationships. In the case presented, the absolute QT is most likely the most useful
3. No information on the drug concentration and relationship to QT prolongation. Although it can be hypothesized from the case that the sertraline concentration increased after the only concentration taken, there is no way to be sure of this. There is no published PK data on sertraline overdose. In addition it is reasonable to suggest that the peak QT effect is probably delayed compared to the peak in drug concentration – but by how much? The authors provide no drug concentration at the time of the QT prolongation, or better, serial drug concentrations and serial QT measures to examine this. This is important because a “marked” delay in the QT effect may mean that it is due to a metabolite, rather than the parent drug. This all leaves the reader with more questions – is it really sertraline that caused the QT effects?

4. The value of a “case report” versus a previously published series of over a 100 cases by our group. The authors appear to place the same weight on their case of a possible association between sertraline, and QT prolongation and our series of 103 cases where one patient had a QT of 500 (one patient each with QT of 460, 450, 440 and the remainder were 420 or less – data not available from our initial publication but provided here). This is the problem with “case reports” – they are hypothesis generating, not hypothesis testing research. So a more appropriate view is that they report a patient with moderate QT prolongation possibly associated with sertraline overdose following a series where 1/103 cases had a QT of 500 (not more). The best they can suggest is that it would be worth prospectively evaluating the relationship between serial sertraline concentrations and serial QT measures – the cannot make recommendations for clinical management (see next point).

5. Conclusions: the authors conclusions are completely unjustified (see point 4). They recommend that all patients with sertraline overdose be monitored based on a single case. We only suggested that citalopram overdose should be monitored based on our study of over 300 SSRI cases, and where citalopram had an odds 5 times that of sertraline for developing QT>440 – so how can these authors recommend all these patients get monitored. Citalopram has been reported twice in the literature to cause Torsades de Pointes, but sertraline has never been reported to cause this. It would be different if the authors were reporting a case of Torsades, but they are merely reporting an intermediate predictor based on other drug QT prolongation. The conclusions should be completely revised – the comment on post-marketing surveillance is fine; and a comment along the lines of point 4 – further research should be done – but no clinical advice can be stated.

6. “Our data are in line with the experiences with other SSRI, pointing to a possible class effect of these agents.” This is simply not correct and a misinterpretation of the literature. Our study Isbister et al 2004 J Tox Clin Tox presents a large series of SSRI overdoses and demonstrates there is differential toxicity within the SSRI class, with citalopram overdose being far more likely to be associated with QT prolongation. This statement must be deleted and the authors properly discuss this – ie. although they report a moderate prolongation of QT with sertraline, is this clinically important based on the previous research and the problems with the association in this case.

7. Limitations: the authors need to discuss the previous points as limitations. The second limitation they discuss is important, however, the first is inappropriate. Rechallenge is usually more appropriate in the context of therapeutic drug use – to rechallenge an overdose is not the appropriate way to test the hypothesis. If they reproduced the effects in this patient – it would still not demonstrate that it was a drug effect – what needs to be done is a population study of sertraline overdose – to look at a toxic drug effect.
Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1. Electrolyte abnormalities: the authors state this was unlikely based on results taken on admission. The Mg was 0.7 (lower limit of normal) on admission – what was it at the time of the ECG that showed QT prolongation – did the patient receive Mg supplementation?
2. Second last paragraph of the discussion: delete; this bare little relation to the subject, is experimental work on other SSRIs – the SSRIs are similar because of their action on serotonin reuptake – there is no reason that if one SSRI effects HERG channels, the others will. So to discuss the effect of fluvoxamine and fluoxetine (again both not shown to cause clinical QT prolongation in overdose by us) on HERG channels is irrelevant; there is a lot of literature on various antidepressants causing effects on various ion channels – but it would only be relevant to discuss sertraline.

Discretionary Revisions (which the author can choose to ignore)

What next?: Reject because too small an advance to publish

Level of interest: An article of limited interest

Quality of written English: Needs some language corrections before being published

Statistical review: No

Declaration of competing interests:

I declare that I have no compete interests