Author's response to reviews

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

Authors:
- Rudolf A de Boer (rudolfdeboer@wanadoo.nl)
- Tonnis H van Dijk (t.h.van.dijk@mz.nl)
- Nicole D Holman (n.d.holman@mz.nl)
- Joost P van Melle (j.p.van.melle@thorax.umcg.nl)

Version: 2 Date: 20 June 2005

Author’s response to reviews: see over
Dear Dr. Newmark,

Please find enclosed our revised manuscript entitled “QT interval prolongation after sertraline overdose: case report”, which we submit for publication as a case report in *BMC Emergency Medicine*.

This case report reports that sertraline in overdose may elicit QT prolongation. Since sertraline is among the most prescribed antidepressants in Western society, and because the patients prescribed this drug can be subject to overdose and selfpoisoning, this may be even more important.

We have received the reviewers’ remarks. We have made the changes reviewer 1 suggested.

Reviewer 2 came up with a lot criticism on this report (and case reports in general), stating that the findings are in contradiction with published data of his own group. He also (accidentally?) included his recommendation to you, which is to reject the paper.

We cannot fully comprehend the nature of his criticism – is it not science that we observe (and report!) new findings every day, so that medical practice improves? Naturally, it would be impossible for us to fully conform to his remarks. We have taken at heart the criticism to tone the conclusions down.

We feel that this paper could be of interest for the readers of *BMC Emergency Medicine* given the implications of this case for future clinical practice.

The undersigned authors transfer all copyright ownership of the manuscript “QT interval prolongation after sertraline overdose: a case report” to Biomed Central Ltd. in the event the work is published. We will pay for the article-processing charge in the event the article is accepted. All undersigned authors warrant that the article is original, is not under consideration by another journal, and has not been published previously.

We have no conflict of interest to state. All authors have read and approved submission of the manuscript.

Thank you in advance for reviewing the manuscript,

Dr. Rudolf A. de Boer, MD

Martini Hospital, Department of Internal Medicine, Intensive Care Unit  
P.O. Box 30033, Groningen, The Netherlands, 9700 RM  
Phone: +31505245870 / Fax: +31505245889 / E-mail: rudolfdeboer@wanadoo.nl
Reviewer’s report

Title: QT interval prolongation after sertraline overdose: a case report.
Version: 1 Date: 20 May 2005
Reviewer: Victor Vieweg

We would like to thank this reviewer for his helpful comments. We have made changes according to his commentary as delineated:

Reviewer’s report:

RE: de Boer et al QT interval prolongation after sertraline overdose: a case report

De Boer et al describe a healthy female who took 2250 mg of sertraline, 200 mg of diazepam, and 400 mg of temazepam in a suicide attempt. She was admitted to the Intensive Care Unit. The initial electrocardiogram showed a normal QT interval. The next day, the QTc interval was 525 ms. Subsequently, the QTc interval returned to normal. Echocardiography and exercise electrocardiography were normal. Follow discharge from the hospital, sertraline administration was reinstated. Thereafter, the QTc interval remained normal while she received therapeutic doses of sertraline. The authors point out that sertraline overdose may be associated with QTc interval prolongation.

My comments are as follows.

Suggest opening the Abstract with Selective serotonin reuptake inhibitors (SSRIs) are the most common antidepressants used in first-world countries.

We have changed this.

In the Abstract, I believe tricyclic antidepressants is better than traditional antidepressants.

Change was made.

In the Case Presentation of the Abstract, the authors imply that they continued to administer sertraline despite the patient have just taken 2250 mg. Sertraline was apparently stopped when QTc interval prolongation was discovered.

Obviously, sertraline was immediately withdrawn. After a few weeks, the drug was reinstalled for refractory depressive symptoms. ECG control showed norma QT interval.

Was an electrocardiogram specifically ordered the day following admission or did cardiac monitoring show progressive lengthening of the QT interval prompting the order for a 12-lead electrocardiogram?

In our ICU, daily ECG’s are performed. This revealed the QT interval prolongation.

In the Background, torsades de pointes is the proper spelling.
Thank you, we changed this.

Page 4 of the Case Presentation, use heart rate rather than heart frequency.

We changed this.

Page 5 of Case Presentation, the echocardiogram can simply be reported as normal. RE exercise testing, the authors can simply report that their patient on exercise testing was able to reach 88% of her maximum heart rate and there were no abnormal ST-segment changes. Table 1 and the electrocardiograms can be dropped. The authors have a single point to make. I suggest shortening this paper to 600 words and use the present list of references.

We have made changes accordingly and shortened the report.

When I did a PubMed search using sertraline qt interval prolongation, I found the single article by Sala et al listed at the end of this review.

We have added this reference.

Reviewer’s report

Title: QT interval prolongation after sertraline overdose: a case report.
Version: 1 Date: 22 May 2005
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.

This reviewer questions the validity of this case, since his group and others have not seen QT interval prolongation in large patients groups presenting with sertraline overdosing. We feel that the nature of this case, i.e. a patient who has a documented normal QT interval while on normal dose sertraline, with prolonged QT interval after overdosing, and normalization of the QT interval hereafter, nevertheless suggests an acquired long QT interval due to overdosing sertraline. It may very well be true that this side effect is very rare, so that it has not been detected thus far.

We have toned down the conclusions. By no means we tried to deceive the readers, it is however our genuine concern that overdosing sertraline indeed may have this potentially dangerous side-effect.

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.
We respond to this issue under 2.

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 measure.

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?

We agree this is a limitation and had put forward this topic as a limitation in the first version of the manuscript. Likely, sertraline levels were higher on the first day after ingestion, but again, we have no data on this.

4. The value of a “case report” versus a previously published series of over 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).

We have never intended to put more weight on our presented case than over (any) other reports. This seems a major point for this reviewer. We have toned down the conclusions.
Our view is that SSRIs may cause QT interval prolongation, and that some SSRIs are far more likely to cause this than others. In the case of sertraline it seems a rare event, so rare it has not been picked up in larger series. However, it would a major scientific mistake to state that, since in a series with over a 100 patients with a overdose of sertraline no QT interval prolongation was observed, this phenomenon simply could not occur in sertraline overdose.

Case reports have an important role: to point out (undesired) effects of drugs that are unknown to colleagues thus far. Clearly, a case report is limited by the small number, usually just one. This reviewer unfortunately does not see the cause for a case report in the field of SSRIs and QT interval prolongation.

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.

We do not see the point here. This case report is not about citalopram or a series of patients – it is about a potentially dangerous and therefore important observation that sertraline in a overdose, on rare occasion, may cause QT interval prolongation.

It comes down to the question: does one believe that the report of Isbister and colleagues presents a definite answer to the question: could sertraline cause QT interval prolongation? The reviewer clearly thinks so. We are not convinced, and feel that our observation adds something new to our knowledge on this topic.

We did not recommend to monitor patients in an ICCu or CCu – we used the word “suggest”, that doctors treating such patients may consider this. We have omitted this in the revision.

6. “Our data are in line with the experiences with other SSRIs, 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.

We have discussed this topic before: we believe, that despite the publication of this reviewer that QT interval prolongation was not observed in > 100 cases of sertraline overdose, QT interval prolongation may actually occur in patients with sertraline overdose, although it may be a very rare observation.

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?

No, serum Mg was on the lower limit but still within normal range, so we decided not to supplement.

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.

This was omitted.

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