Author's response to reviews

Title: Fatal accidental methanol ingestion

Authors:

Jelle L Epker (j.epker@erasusmc.nl)
Jan Bakker (jan.bakker@erasusmc.nl)

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Author's response to reviews: see over
Dear Madam, Sir,

After we were able to comply with the ethical/consent issue raised by the editor, four reviewers were assigned to our case report “Accidental methanol ingestion”.
Of course we have done our utmost to give adequate and balanced answers to all four reviewers. We think their efforts and different points of view were most helpful to improve the quality and level of interest of this report and we therefore hope that BMC Emergency Medicine itself will eventually benefit from the final version.
The questions of and the answers to the four reviewers are listed below in their original order. Our answers are already highlighted in red to make the distinction between the original questions and our answers more clear. Whenever a question or remark led to a change in text, then this is indicated in the answer or reply. We hope that the reviewers will acknowledge that we took advantage of their helpful suggestions and advices. We especially like to thank BMC Emergency Medicine for their efforts to have our work thoroughly reviewed. With kind regards,

Jelle Epker

Reviewer: 1
Reviewer’s report:
This is an interesting case report of a young man who ultimately died from a methanol overdose, despite good medical treatment. While reports of methanol poisoning are far from unusual, this report may be of some interest to some and a reminder of the key symptoms of the initial presentation of methanol poisoning. The following observations/comments are offered (all could be classified as "minor", except where noted).

1. More information should be included in the Abstract, such as the measured methanol concentration (4.4 g/l) and the initial anion gap and osmolar gap. The authors should bear in mind that the Abstract is often all that the reader may see in order to judge whether they need to obtain a copy of the full paper.
   First we’d like to thank the reviewer for his thorough review and very helpful comments.
   We do agree with the reviewer that some of the interesting information was indeed missing in the abstract, the suggested changes have of course been made.

2. Near the end of the Case Report section, the authors refer to a “document with a negative toxicology screen for alcohol and drugs”. While this is mildly interesting - especially given that the drug screen included methanol (one assumes this was some type of certification that the person was drug and alcohol-free at the time of hiring by the shipping company?) - it is largely irrelevant as the testing was presumably performed long before the ship left its original port. This reviewer questions whether it is necessary to include a
The figure the reviewer mentions, does indeed not offer a scientific contribution to this report, but it is a peculiar and interesting accent in the story told. The cruel irony of the situation is part of the human tragedy that took place, therefore it was well considered added to the report and we hope that since its indicated as a discretionary revision, the figure may remain part of this case report.

3. Immediately before reference to the drug screen document, the authors refer to a high osmolar gap of "77" mOsmol/Kg. However, the calculations further down that page show a value of 73 mOsmol/Kg. Is the figure of "77" incorrect?

The 77 mentioned in the text was incorrect, the number has been changed to 73.

4. In the Discussion, it is stated that the first roughly estimated maximum methanol concentration was 2.5 g/Kg (presumably in serum?). Later, they refer to a laboratory measured value of 4.4 g/L. It is acknowledged that one value was estimated based on an Osmolar gap and the other measured directly, but the discrepancy does seem to be remarkably large. It would be useful to the reader if the authors could discuss possible reasons for the difference.

This difference was a surprise and a question for us also; the most reasonable explanation is that the osmol measurement was taken from a diluted blood sample. A lot of measurements are automatically done on arrival on the Emergency Department. I know that serum osmolarity is not one of the standard tests. Sometimes it is requested separately as one of the colleague’s suspects alcohol/glycol intoxication. Potentially the osmol sample was taken from an IV tube running with resuscitation fluid or a flushed artery line. Unfortunately only one measurement was done, so it’s impossible to compare with other samples from this patient. Another possibility is that the osmolality measurement in itself is less accurate than the methanol measurement, but even then the discrepancy is remarkably large. A new part addressing this issue is added to the discussion.

5. Can the authors state how the 4.4 g/l methanol was measured? Was it by gas chromatography or another method?

It was measured by gas chromatography, a text change to explain this was made.

6. In the Conclusions, the authors state that “methanol intoxication alone is no contraindication for organ donation”. While this may be true in most circumstances, it does not appear to be based on anything the authors have presented in their report. (Discretionary)

As the reviewers correctly suggests, the conclusion is indeed not based on our own findings, so this conclusion has been removed from the conclusion sections.

Reviewer: 2
Reviewer's report:
I am interested in the article of severe methanol intoxication. However, I have some questions.
1) Why was the toxicology screening for methanol negative? Could you give me the explanation?

First of all we’d like to thank the reviewer for his thorough review of our case report and the valuable suggestions made.

The toxicology screening was done only a few weeks before the patient arrived in our hospital. The screening was part of a test program for his certification to be able to be hired to sail on international ships. To our surprise he was apparently even tested for the (ab)use of methanol, a liquid that is considered a drink nowhere in the world. As a cruel coincidence this paper was the first thing that was handed over to us on the day he accidentally intoxicated himself with methanol! Just because of this peculiar coincidence that made the human tragedy even sadder, we added this figure well considered to this case report.

2) Why not include the good paper about visual disturbance due to methanol intoxication of Fujita M, et al.
We’d like to thank the reviewer for this very useful suggestion; the new reference is of course added to the text.

3) How about the head CT scans on ER arrival if you have it?
The reviewers asks an interesting question, retrospectively we also wondered why no scan was made in the ER, but when the patient arrived in the ICU we focused on the hemodynamic and metabolic derangements. Unfortunately no CT scan was made on arrival, so we can’t use the results in the discussion or show the pictures for comparison.

Minor Points
3 of HCO3-, down.
Indeed, this is corrected
Osmol gap is 73 instead of 77 in the context.
77 in the text is wrong is corrected to 73
Use point (comma) instead of period for the number.
The relevant changes have been made, all numbers are now correctly noted.
You should choose which gram/L or g/L.
Indeed, changes have been made to g/L
In the figure 2, concentration gram/L instead of mgram/L
Error in text figure 2, changed to g/L

Reviewer: 3
Reviewer's report:
You describe a late presenting patient with severe methanol poisoning who subsequently died despite aggressive management.

MAJOR COMPULSORY REVISIONS
1. The patient was treated with CVVH-DF. It would be useful to have some kinetic information about the clearance of methanol calculated on the basis of what you observed. That would significantly strengthen this report.

First of all we’d like to thank the reviewer for his thorough review and his valuable questions and advices!

We certainly do agree with the reviewer that information about the clearance of CVVH-DF in this case would make the report even more interesting. Unfortunately no samples of the dialysate were taken during the period the patient stayed with us. If we had had these samples we certainly would have presented them. Without the methanol concentrations in the different dialysate samples no real, true clearance can be calculated like Kan et al all did. Nevertheless some information about the potential or estimated clearance of methanol with CVVH-DF should have been mentioned indeed, therefore the text has been changed and a very relevant reference concerning this subject is added. Based on our observations we can conclude that the methanol halve time (T\(_{1/2}\)) was about 3.5 hours and that the kinetics follow first order elimination kinetics (Ln[methanol] versus time is straight line, graph not shown). This apparently relatively short halve time can be explained by the aggressive fluid resuscitation that took place in the first hours (Almost 10 liters filling, that must have given a direct dilution of the methanol concentration in contrast with an increased clearance), the preserved kidney function of the patient (urine production of 7 liters the first 24 hours) and another important factor maybe also the much larger filter surface area: we used a 1.9 m\(^2\) filter in contrast with the 0.6 m\(^2\) described by Kan et al all.

We hope that with this new information the relevance of this report improved!
2. There are some inconsistencies regarding your reporting of the patient’s initial methanol level. In the Case Report you say it is 4.4 g/L yet your figure describes it as approximately 4.4 mg/L. I assume the figure should be g/L. In your figure legend you may want to describe it as g/L instead of using the symbols you have now.

The 4 mgram/L in the figure is wrong as the reviewer correctly suggests, it has been changed to 4.4 g/L. The figure legend is changed as well.

Comments to Author(s)
Case: 3. What happened to this patient’s colleague who was drinking with him?
In total there were 3 intoxicated sailors, the first was presented in our hospital, he was the one with the most severe methanol intoxication. One (the one who was talked to) survived with full recovery after a few days in a second hospital, the third one who also had a high level of methanol died after 3 weeks in a third hospital with the clinical picture of multiple organ
failure and irreversible brain damage.

DISCRETIONARY REVISION
4. Did anybody do a funduscopic examination on this patient? And if so, what were the results?
No funduscopic examination was performed in the emergency room, in the ICU when the neurologic picture deteriorated, there was evidently papillary edema, but no specific signs of methanol induced retinal/optic nerve damage were to be seen (anymore). No text change concerning this topic has been made.

MINOR ESSENTIAL REVISION
5. When you describe the patient as having “signs of severe neurological damage, potentially even brain death” could you provide some more detail regarding the neurological examination?
Like the reviewer correctly suggests the loss of brainstem reflexes as explained in the discussion are now also mentioned in the case description itself, to clarify the situation.

MINOR ESSENTIAL REVISION
Discussion: 6. Please bear in mind that the high anion gap acidosis and a high osmolar gap should also raise the suspicion of ethylene glycol poisoning.
That’s correct indeed, the text has been changed

MINOR ESSENTIAL REVISION
7. Where you say the maximum methanol concentration was estimated to be 2.5 g/kg please indicate that is based on your calculation and not measured level.
With the word “estimated” and the calculation example below, we thought it would be clear that it wasn’t a measured level, but we understand that were not clear enough, so for reasons of clarity we added “calculated with use of serum osmolality” to the relevant text part.

MINOR ESSENTIAL REVISION
8. You say that the recommended threshold for treating methanol poisoning is 0.2 g/L. Various numbers are thrown around but there is certainly no justification for that number, although it is often used. It is important to say that this is by tradition and certainly does not have any empirical support. We do agree with the reviewer that as stated in the discussion the levels of toxicity are very much variable, so a fixed level of 0.2 g/L can be discussed or doubted, a text change has been made, to indicate this uncertainty.

MINOR ESSENTIAL REVISION
9. You tell us in the Discussion that the patient developed diabetes insipidus. Please include this in the case report.
Done!

MINOR ESSENTIAL REVISION
Conclusions/Key Messages: 10. The term “numbers” is a bit colloquial. Perhaps it would be better to say “metabolic improvements do not equal to healing the patient.” We’d like to thank the reviewer for this excellent suggestion, the text has been changed.
MINOR ESSENTIAL REVISION
11. Since organ donation was not an issue with this patient, the last point should be dropped.
We do understand the reviewers point, the statement is deleted.
MINOR ESSENTIAL REVISION
Graph: 12. It would be very helpful to include the time period when CVVH was going on on your graph.
Time indication for CVVH period, as suggested, is added on the graph

Reviewer: 4
Reviewer's report:
Abstract should be rewritten. The patient should be presented in the Abstracts. The conclusion in the abstract should be revised and based on the presented case report
We thank the reviewer for the valuable directions he gave us concerning the abstract and its content. The abstract has been rewritten, clinical information about the patient is added to the abstract and the conclusions are revised.
Background:
The manuscript should begin with short background.
The reviewer correctly suggests that a background session should be added according to the BMC case report template, so this has been done of course!

Case report:
The time between methanol ingestion and admittance to ED should be presented.
The reviewer refers to an important piece of information that is indeed missing in the text. This time period was and is still not clear, probably it was somewhere between 8 and 12 hours before admission, the missing information has been added to the text.
Patient’s weight should be presented.
Done!
The method of methanol measurement should be described.
Done, text has been changed
How rapid was osmolality corrected?
We like to thank the reviewer very much for this valuable question!
Since unfortunately only one osmolality (the first one on the ED) was measured, we are very sorry we can’t reliably answer your question about this issue, we suppose that initially the osmolality will probably have risen because of the initiation of ethanol therapy. After that the osmolality will likely have followed the same line as the lactate and methanol concentrations. But still, we are not sure about this, for the reason mentioned above.

Problems about donor donation in presented patient should be moved from the Discussion in the Case report.
The reviewer suggests that the problem about organ donation should be removed from the discussion. Since organ donation was not an issue with this patient, we do agree with the reviewer that the conclusion about organ
donation can/should be removed from the conclusions section, which in fact we did. The fact that organ donation was considered and mentioned, was because of the brain death protocol. In some countries like the Netherlands intoxications sometimes are considered a contra-indication for donation. To make sure that methanol is not considered a contra-indication by the authors we would very much appreciate it when this particular part may be left unchanged in the discussion.

The paragraph about shopkeeper could be removed or moved in the Case report.
The reviewer suggests that the part concerning the shopkeeper who sold the methanol could be (re)moved. Although the part of the shopkeeper is not of medical relevance it is an elemental part of the peculiar and tragic story we describe, just because these kinds of ethical/judicial matters are also a part of our jobs we thought the story wouldn’t be complete without this particular accent. If the editor agrees that it should be moved, we will of course comply!

Discussion:
The discrepancy between estimated and measured methanol concentration should be discussed.
Indeed, it should be, we added this point the discussion section.
The value of bicarbonate gap in methanol poisoning should be discussed.
The value/use of the Delta gap is added to the discussion, with an essential reference.

Conclusions:
The conclusion should base on presented case report.
Based on the reviewers suggestions we reformulated the conclusions and removed one.