Author's response to reviews

Title: The Breast Feeding Mother and Xenon Anaesthesia: Four Case Reports
Breast Feeding and Xenon Anaesthesia

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Author's response to reviews: see over
We the authors would like to thank you for the opportunity to send a revision of our manuscript “The Breast Feeding Mother and Xenon Anaesthesia: Four Case Reports”

General information:
The sections competing interests and authors contribution are now included in the manuscript. The investigation was of course approved by the IRB and informed consent was obtained. This is now included in the manuscript.
Regarding the bmc_article template we had great problems, spending hours trying to get the text into the template but without success. We were using the MiKTeX 2.8 version but did not succeed. Due to this reason we submit the manuscript as a word.doc.

We have added most of the reviewer’s comments into the manuscript (see the response to reviewer below) and all changes are made in italics.

Response to the reviewers

Reviewer: Jan-Hinrich Baumert
First of all we would like to thank you for your comments and have prepared the following answers:

1. Abstract, p2, line 5: it is not appropriate to use a mean when there are only four observations. Please report single data.

The maximum and minimum time form end of anaesthesia to extubation are now reported.

2. Introduction, p3, line 6: Please reference the recommendation to interrupt breast feeding after anaesthesia.

The following sentence was inserted into the manuscript: Traces of anaesthetics have little or no effect on older infants, but may cause problems in neonates or pre-term babies predisposed to apnoea [1]. In such cases, breast feeding must be suspended for 12-24 hours. A general recommendation is an interruption of breast feeding for 24 h following anaesthesia but without clear evidence to the author’s knowledge.

3. Methods, p 4, case 2: Midazolam premedication can be a more important problem for breast feeding than propofol. Please discuss why this was done in this case – and obviously not in the other patients.

None of the four patients were getting midazolam premedication but one was scheduled to get midazolam premedication but did not get it. The following sentence was inserted into the manuscript: the patient was planed to get midazolam 7.5 mg as premedication but did not receive this drug.

4. Methods, p 5, line 1: It is problematic to base a statement that a method is validated on unpublished results. I would suggest to omit this part of the sentence.

The method is validated and the data are now accepted for publication and will be printed soon. The reference is inserted into the list of references.

5. Methods, p 5, lines 5,6: Please reference the pharmacokinetic models mentioned here. They’re not common knowledge.

Both models mentioned here are now referenced in the list of references.
6. Methods, p 5, line 11: Please report the actual settings of the ventilator.
*Ventilator settings are now reported.*

*The meaning of the EEG-stadium E0 / E1 are now explained and the corresponding paper is inserted into the list of references.*

8. Results, p 7, line 10: Please report the exact times after completion of anaesthesia, when breast feeding was resumed.
*The exact times are now reported in the manuscript.*

9. Discussion, p 8, 1st paragraph: The last sentence is not clear. Please explain further or omit, as it is not essential to this report.
*The sentence was removed.*

10. Discussion, p 8, last paragraph: There is some contradiction here. In the first sentence you state that, “… the milk concentration is rarely greater than 1-2% of the original dose.” Dose and concentration are different things, so this is not clear. In the following sentences you mention that propofol can be concentrated in milk as compared to plasma. Please revise to make this understandable.
*We agree with the reviewer that dose and concentration are tow different things. To make this part of the discussion more understandable this part is rewritten into:*  
The breast milk *accumulation in 24 hours* of most drugs is rarely greater than 1-2% of the original dose[16]. Drugs with high lipid solubility like propofol are found at higher concentrations in breast milk than in plasma *dependent on the time and amount of milk production during propofol administration.*

11. Discussion, p 9, last paragraph: Why do xenon's physicochemical properties explain its anesthetic effect? I would suggest to omit this because it is not relevant to this report.
*The things mentioned in this part of the discussion are the basics of the theory of inhalation anaesthesia. Perhaps it is not relevant to this report but relevant to understand the effect of inhalation anaesthesia.*

12. Discussion, p 10, 2nd paragraph: This is redundant, please omit.
*The sentence was removed.*

13. Conclusion, p 11, 1st paragraph: The first two sentences do not fit into a conclusion and may better be moved to the introduction.
*We have moved the tow sentences into the introduction as recommended by the reviewer.*

14. Reference List: There are several spelling errors and incomplete references. Please revise carefully. Moreover, it is not clear why the two largest clinical studies on xenon so far are not mentioned.
*The study of Rossaint et al. is now mentioned. The reference list is build with the software “Reference Manager”.*

Discretionary revisions:
1. Abstract, p 2: The last sentence is redundant and could be omitted
The sentence was removed.

2. Methods, p 4, 1st par.: “Cases” cannot agree to something, please change into “patients”.
Cases are changed into patients.

3. Methods, p 5, line 10: Is it really the membrane which is monitored? Transmission might be a better expression.
We have changed it into transmission as recommended by the reviewer.

4. Discussion, p 8, last line: The last sentence is a little unclear, I would suggest something like “…protein binding as is the case with remifentanil…”.
The sentence was changed as recommended by the reviewer.

5. Discussion, p 11, last sentence: This sentence is somewhat puzzling. I suggest something like: “Taking also into account the low oral bioavailability, babies will be exposed to a negligible quantity of propofol during breast feeding.”
The sentence was rewritten as recommended by the reviewer.

6. Conclusion, p 12, 1st sentence: There is absolutely no evidence that xenon could be harmful when ingested orally. My suggestion would be to omit this part and simply put: “…xenon can be detected in milk.”
The sentence was rewritten as recommended by the reviewer.

7. Table 4: I am not sure if this information is important to this report. Please consider omitting it.
Table was removed.

8. Figure 1: This figure contains some interesting information However, it is not easily read and does not add to the content of this report. As it might in fact puzzle the reader, please consider omitting it as well.
In our opinion the figure contains some important information and we have decided to leave the figure.

Reviewer: Cheston Berlin
Thank you for your comments and first of all we have to apologize for our neglect of duty to mention the informed consent and IRB approval.

The major issue with this paper is the absence of evidence of informed consent. Xenon is not approved in the USA and the authors state in the introduction "Once xenon has been granted marketing approval in Europe..." which implies that is has not been approved in any European country. Even if it is an approved drug, there must be IRB (institutional research board)approval to take sample of maternal blood and milk. The paper should not be published without evidence of IRB approval.
Xenon is approved in 14 European countries.
We are very sorry about our omission to mention the informed consent and the IRB approval.
The following sentences are inserted into the manuscript.
Written informed consent was obtained one day before anaesthesia. The investigation was approved by the institutional research board and the ethic committee of the hospital. The investigation was performed in compliance with German regulatory requirements as well as the internationally valid applicable guidelines.

Other comments:
1. Abstract, l 9. "was limited" - concentrations should be given; limited is too general a word.
   The concentration is given now.

2. Abstract, l 10. insert after "xenon gas" "at any time"
   “At any time” was inserted as recommended by the reviewer.

   Concentration is given now.

Introduction:
1. In the UDSA the "normal" recommendation is that breast feeding may be resumed after inhalation anaesthesia as soon as the mother is conscious. The authors are correct in stating that there is a paucity of evidence of informed consent. Xenon is not approved in the USA and the authors state in the introduction "Once xenon has been granted marketing approval in Europe..." which implies that it has not been approved in any European country. Even if it is an approved drug, there must be IRB (institutional research board)approval to take sample of maternal blood and milk. The paper should not be published without evidence of IRB approval.
   of evidence for this, and this paper does provide some evidence, although admittedly the number of patients is very small.

Patients and Methods.
1. Lack of evidence of informed consent as noted above.
   There was now lack of informed consent as noted above. As mentioned above we are very sorry about our omission.

2. Page 5 lines 5 and 6 - references to the methods of Schnider and Minto should be given. The non anesthesiologist will be unfamiliar with these methods.
   References to both models are now given.

3. Line 7. Where is the "effect concentration" measured? Maternal plasma?
   The “effect concentration” is not measured! The “effect concentration” in the brain is calculated according to the model of Schnider.

4. Line 10. How is "monitoring of the neuromuscular membrane" performed?
   We have changed “monitoring of the neuromuscular membrane” it into transmission as recommended by reviewer 1. We used the TOF and TOF-ratio for monitoring of the neuromuscular transmission.