PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Feasibility of Aerosol drug delivery to sleeping infants
AUTHORS	Amirav, Israel; Newhouse, Michael; Luder, Anthony; Halamish, Asaf; Omar, Hamza; Gorenberg, Miguel

VERSION 1 - REVIEW

REVIEWER	Khaled Saad Department of Pediatrics, Faculty of medicine, University of Assiut, Assiut
REVIEW RETURNED	14-Oct-2013

GENERAL COMMENTS	This paper describes the feasibility of administering inhaled medications during sleep using the SM. STRONG POINTS: Interesting clinical investigation. English on average of good quality MAJOR CRITICISM: Patients NOT very well characterized, just broad term: Wheezy? we need to know what is the clinical condition of the ten patients in details. Minor points: The manuscript is much too long for its message; it should be reduced by almost 50 %. A picture of the device (The SootherMask™ (SM) could be added to study. Half of the references is old, recent ones should be added. CONCLUSION: The paper can be accepted after revisions.

REVIEWER	Mark Everard Univ Western Australi Australia
REVIEW RETURNED	28-Oct-2013

GENERAL COMMENTS	This is a simple study using a solution based delivery system which permits the use of simple lablelling. The message that drug delivery is achieved when using the soother mask during sleep is reasonable thought the sample size is low. The biggest weaknesses are that it does not attempt to account for all the emitted dose and it is unclear how attenuation was calculated. Hence the accuracy of the figures is uncertain.

	It is also not clear whether infants were placed on the gamma camera or whether the camera was moved above a supine infant and if so was the chest in contact with the infant and was the infant always flat. It is also not clear whether 2 actuation were introduced into the chamber at the start of the minute or whether there were two actuations each followed by 1 minute. I presume the nylon wrap was removed from the infants chest before imaging though this is not stated. The device used was a solution based device with a relatively high FPF and hence is not comparable with a traditional pMDI so the comparison with Tal's study is inappropriate particularly given the uncertainty surrounding attenuation corrections in both studies

REVIEWER	Deborah Bickmann Boehringer Ingelheim Pharma GmbH & Co. KG, Germany
REVIEW RETURNED	06-Nov-2013

GENERAL COMMENTS	In this paper, the Respimat is called a MDI. This is not correct. Respimat belongs to the class of "Soft Mist Inhalers", abbreviated as "SMI" (see pages 7 and 13). In Table 1 it would be interesting to have the age of the individual child in months. If available, also height and body weight would be of interest. In addition, a picture of the mask, maybe connected the VHC/SMI would be nice. Editorial changes with regard to the term SMI (see above) should be done. An update of Table 1 and additional pictures would be desirable. I very much enjoyed reading this interesting article with its exciting results. Seems to be a great opportunity for children and their parents to receive/provide inhaled medications without the typical "struggling and crying" of the young child. I am very much looking forward to your next studies.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name Khaled Saad
Institution and Country Lecturer; Department of Pediatrics, Faculty of medicine, University of Assiut, Assiut 71516, Egypt,
Please state any competing interests or state ‘None declared’: I do not have potential conflict of interest

This paper describes the feasibility of administering inhaled medications during sleep using the SM.

STRONG POINTS:
Interesting clinical investigation.
English on average of good quality

MAJOR CRITICISM:
Patients NOT very well characterized, just broad term: Wheezy? we need to know what is the clinical condition of the ten patients in details.
We thank the reviewer for this comment and have now clarified their clinical condition in the text.

Minor points:
The manuscript is much too long for its message; it should be reduced by almost 50 %.
We thank the reviewer for this comment and have now substaintially reduced it.

A picture of the device (The SootherMask™ (SM) could be added to study.
Done as suggested

Half of the references is old, recent ones should be added.
Done as suggested

CONCLUSION:
The paper can be accepted after revisions.

Reviewer: 2
Reviewer Name Mark Everard
Institution and Country Univ Western Australi
Australia
Please state any competing interests or state ‘None declared’: None declared

This is a simple study using a solution based delivery system which permits the use of simple lablelling. The message that drug delivery is achieved when using the soother mask during sleep is reasonable thought the sample size is low.

The biggest weaknesses are that it does not attempt to account for all the emitted dose and it is unclear how attenuation was calculated. Hence the accuracy of the figures is uncertain.

We thank the reviewer for this comment and have now clarified how all the emitted dose was accounted for and how attenuation was calculated.

It is also not clear whether infants were placed on the gamma camera or whether the camera was moved above a supine infant and if so was the chest in contact with the infant and was the infant always flat.
The reviewer's comments are in place and we have now clarified it in the methods and in the result sections.

It is also not clear whether 2 actuation were introduced into the chamber at the start of the minute or whether there were two actuations each followed by 1 minute.
There were two actuations each followed by I minute and this is now clarified in the methods.

I presume the nylon wrap was removed from the infants chest before imaging though this is not stated.
The reviewer's presumption is correct and we have now explicitly stated it.

The device used was a solution based device with a relatively high FPF and hence is not comparable with a traditional pMDI so the comparison with Tal's study is inappropriate particularly given the

uncertainty surrounding attenuation corrections in both studies
The reviewer's comment is well appreciated and we have now removed this comparison.

Reviewer: 3
Reviewer Name Deborah Bickmann
Institution and Country Boehringer Ingelheim Pharma GmbH & Co. KG, Germany
Please state any competing interests or state 'None declared': Respimat is an inhalation device that is provided by Boehringer Ingelheim.

In this paper, the Respimat is called a MDI. This is not correct. Respimat belongs to the class of "Soft Mist Inhalers", abbreviated as "SMI" (see pages 7 and 13).
The reviewer is correct and we thank her for this. We have now corrected all references to Respimat as "Soft Mist Inhaler".

In Table 1 it would be interesting to have the age of the individual child in months. If available, also height and body weight would be of interest.

We thank the reviewer for this comment and have now included the age in the Table as well as his/r gender. Unfortunately we do not have available height and weight.

In addition, a picture of the mask, maybe connected the VHC/SMI would be nice.
Done as suggested

Editorial changes with regard to the term SMI (see above) should be done.
Done as suggested

An update of Table 1 and additional pictures would be desirable.
Done as suggested

I very much enjoyed reading this interesting article with its exciting results. Seems to be a great opportunity for children and their parents to receive/provide inhaled medications without the typical "struggling and crying" of the young child. I am very much looking forward to your next studies.

VERSION 2 – REVIEW

REVIEWER	Khaled Saad, MD Department of Pediatrics, Faculty of medicine, University of Assiut, Assiut
REVIEW RETURNED	24-Dec-2013

GENERAL COMMENTS	-The review is well clarified by authors -accept the paper in revised form

REVIEWER	Laura Hamill Emergency Dept Hutt Hospital Lower Hutt Wellington New Zealand
REVIEW RETURNED	29-Jan-2014

GENERAL COMMENTS	A novel study. Well written. May not have a high level of practical implications. Of limited benefit. Good pilot study. It would be good to see a bigger study subsequently. Need to see if infants who don't usually suck a pacifier will take to the device - likely they will. Limitations include that drugs can only be administered during sleep. When a child is most sick and needs the medications most eg. in the emergency setting, they will not be sleeping. However, this is still a good pilot study and well written. Well done.

REVIEWER	Michael D Shields Queen's University Belfast & Royal Belfast Hospital for Sick Children, UK
REVIEW RETURNED	03-Feb-2014

GENERAL COMMENTS	Important and interesting topic. Highly needed and innovative research that is clearly written. 1] I'm not sure from the wording about whether this study had/has received Research Ethics Committee approval separate from approval by the local hospital research committee (or whether this is same as saying Research Ethics approval was granted) 2] The authors noted 1.6% drug delivery to the right lung. I would have liked to see more discussion as to whether this would be an adequate delivered dose to give a clinic response eg to a bronchodilator and also in the longer term to an inhaled corticosteroid. 3] The authors state that not having a control arm is a limitation - I can't see how it is - as I wasn't sure if they meant having normal infants who wouldn't normally be treated as such. I couldn't see how to review the videoclip in this review process - which I'm sure I would have found interesting.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name Khaled Saad

Institution and Country Lecturer; Department of Pediatrics, Faculty of medicine, University of Assiut, Assiut 71516, Egypt,

Please state any competing interests or state ‘None declared’: I do not have potential conflict of interest

This paper describes the feasibility of administering inhaled medications during sleep using the SM.

STRONG POINTS:

Interesting clinical investigation.

English on average of good quality

MAJOR CRITICISM:

Patients NOT very well characterized, just broad term: Wheezy? we need to know what is the clinical condition of the ten patients in details.

We thank the reviewer for this comment and have now clarified their clinical condition in the text.

Minor points:

The manuscript is much too long for its message; it should be reduced by almost 50 %.

We thank the reviewer for this comment and have now substaintially reduced it.

A picture of the device (The SootherMask™ (SM) could be added to study.

Done as suggested

Half of the references is old, recent ones should be added.

Done as suggested

CONCLUSION:

The paper can be accepted after revisions.

Reviewer: 2

Reviewer Name: Mark Everard

Institution and Country Univ Western Australi

Australia

Please state any competing interests or state 'None declared': None declared

This is a simple study using a solution based delivery system which permits the use of simple lablelling. The message that drug delivery is achieved when using the soother mask during sleep is reasonable thought the sample size is low.

The biggest weaknesses are that it does not attempt to account for all the emitted dose and it is unclear how attenuation was calculated. Hence the accuracy of the figures is uncertain.

We thank the reviewer for this comment and have now clarified how all the emitted dose was accounted for and how attenuation was calculated.

It is also not clear whether infants were placed on the gamma camera or whether the camera was moved above a supine infant and if so was the chest in contact with the infant and was the infant always flat.

The reviewer's comments are in place and we have now clarified it in the methods and in the result sections.

It is also not clear whether 2 actuation were introduced into the chamber at the start of the minute or whether there were two actuations each followed by 1 minute.

There were two actuations each followed by I minute and this is now clarified in the methods.

I presume the nylon wrap was removed from the infants chest before imaging though this is not stated.

The reviewer's presumption is correct and we have now explicitly stated it.

The device used was a solution based device with a relatively high FPF and hence is not comparable with a traditional pMDI so the comparison with Tal's study is inappropriate particularly given the uncertainty surrounding attenuation corrections in both studies

The reviewer's comment is well appreciated and we have now removed this comparison.

Reviewer: 3

Reviewer Name Deborah Bickmann

Institution and Country Boehringer Ingelheim Pharma GmbH & Co. KG, Germany

Please state any competing interests or state 'None declared': Respimat is an inhalation device that is provided by Boehringer Ingelheim.

In this paper, the Respimat is called a MDI. This is not correct. Respimat belongs to the class of "Soft Mist Inhalers", abbreviated as "SMI" (see pages 7 and 13).

The reviewer is correct and we thank her for this. We have now corrected all references to Respimat as "Soft Mist Inhaler".

In Table 1 it would be interesting to have the age of the individual child in months. If available, also height and body weight would be of interest.

We thank the reviewer for this comment and have now included the age in the Table as well as his/r gender. Unfortunately we do not have available height and weight.

In addition, a picture of the mask, maybe connected the VHC/SMI would be nice.

Done as suggested

Editorial changes with regard to the term SMI (should be done.

Done as suggested

An update of Table 1 and additional pictures would be desirable.

Done as suggested

I very much enjoyed reading this interesting article with its exciting results. Seems to be a great opportunity for children and their parents to receive/provide inhaled medications without the typical "struggling and crying" of the young child. I am very much looking forward to your next studies.