Author's response to reviews

Title: Substantially increased sildenafil bioavailability after sublingual administration in children with congenital heart disease: two case reports

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Author's response to reviews: see over
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Author’s response to reviews. Please find our corrections highlighted in yellow:

3. Please change the description of the patient’s gender to male?
The gender ‘male’ was included in the Abstract and Cases.

Reviewer comments: Dick Tibboel

These are 2 interesting cases of the conversion of Sildenafil to a sublingual application in 2 very complicated cases, one even with a diagnosis of ACD. The case report is justified based on the transfer from enteral to sublingual but it is very difficult to identify the individual contribution of Sildenafil in the success of therapy as both patients received more than 15 different drugs for a variety of reasons. At least a significant difference of the C-average was determined in both patients.

We are aware of the fact, that we emphasize in our report the increase of plasma concentrations by switching the routes of administration because this is our main message. We are bit secretive in the evaluation of the clinical assessment based on n=2. However, by implication, we claim, that the plasma concentrations after oral administration have no pharmacodynamic effect, based on the current available literature.

Apart from the case description I feel it is important to make a note of the recent FDA-warning for the use of Sildenafil as published in the American Journal of Respiratory and Critical Care Medicine, 2013 and the comment from the working group on PH in the USA.

Thank you for this advice; it helped us to improve our manuscript. We added following phrases to the section “discussion”:

Barst et al showed in children (n=235, 1-17 years), suffering from PAH, a dose dependent (low-, medium-, and high dose, 10-80 mg) hemodynamic effect of oral sildenafil compared to placebo over a time period of 16 weeks. The results of the open-labelled extension study exhibit that children, receiving high doses of sildenafil over 3 to 7 years, had a higher mortality rate then medium and low doses of sildenafil (14% and 9% versus 20%) (Barst et. al, 2012). As a consequence the FDA enunciated a strong label warning for the use of sildenafil in children (FDA, Drug Safety communication). This and the findings of the underlying data are actively discussed by Abmann and colleagues who point out that (1) most children died, had an idiopathic PAH which comes along with a higher mortality risk anyway, (2) children < 20 kg body weight do not have an increased risk with high doses, (2) 40% died had a higher baseline pulmonary artery pressure (functional class III and IV), and (3) had higher baseline N-terminal pro-brain natriuretic peptide values. Despite these facts and the approval of sildenafil by the EMA the authors conclude that low doses of sildenafil are safe and that further studies are warranted to validate safety and efficacy of sildenafil in children (Abman et al. 2012).
Reviewer comments: Ruth Heying

Carls et al describe an increased bioavailability after sublingual administration of sildenafil in 2 patients. They conclude to choose for sublingual administration in patients with poor enteral availability.

Comments:

1/ Case 1 and 2: Please comment on the interaction of the different medications which are used. Do the other medications have any interference with sildenafil?

Case 1: the cursive phrases were added to the following sentence:
Concurrently the child was also maintained on ambrisentan, midazolam, chloral hydrate, clonidine, teicoplanin, ceftazidime, levetiracetam, nystatin, ethacrynic acid, furosemide, spironolactone, metalozone, acetaminophen, levomethadone, colecalciferol, sodium fluoride, levothyroxine, acetylcysteine, salbutamol, omeprazole and phenobarbital, a strong enzyme inducer which could possible lower sildenafil concentrations.

Case 2: Concurrently, the child was also maintained on milrinone, dobutamine, metildigoxin, epinephrine, clonidine, neostigmine, furosemide, lisinopril, metamizole, acetaminophen, levomethadone, simethicone, omeprazole, caspofungin, ceftazidime, and erythromycin, fluconazole two strong enzyme inhibitors, which could possible increase sildenafil concentrations.

In the section “discussion” we addressed this issue also:
However, both children were maintained on enzyme inducing agents (phenobarbital or metamizole [15]) probably partly explaining the differences in MR observed between sublingual and enteral administration.

2/ Case2: The cardiac diagnosis should be stated in a more systematic way. Does this child have a univentricular physiology?

The cardiac diagnosis was restated:
2.5 years after a hybrid approach (stenting of the ductus arteriosus and bilateral pulmonary artery banding at the age of 6 weeks) a child (male, Turkish), diagnosed with atrial and ventricular septum defects, hypoplasia of the left ventricle, aortic isthmus stenosis, mitral valve insufficiency, and persistent left superior vena cava (body weight 11 kg), underwent a Glenn procedure combined with a Damus-Staye-Stansel anastomosis to enlarge the systemic outflow tract which resulted in functional univentricular heart.

3/ Discussion: Congenital heart disease with pulmonary vascular diseases does not really go “usually” along with PHT. This sentence is too much simplifying. Please rewrite.

The sentence was rewritten:
Congenital heart diseases, combined with pulmonary vascular diseases are frequently accompanied with a large circulating blood volume, flooding the lungs through shunts and causing severe PH [1].

4/ Discussion middle part: Please explain phase I metabolic capacity.

For explanation we added following information (cursive):
These findings suggest extensive enteral or hepatic first-pass metabolism which is unexpected in infants with generally not yet fully developed phase I metabolic capacity, which largely addresses the cytochrome P450 enzyme family, e.g. the isoenzyme CYP3A4 [14].
5/ Conclusion: Please comment on a general recommendation of sublingual administration. Why do you not suggest this for a broader indication, not only for patients with poor enteral availability?

A statement for sublingual administration was provided:
And moreover, sublingual administration can be generally useful in the administration of medication, in particular with a low oral bioavailability and/or a high first-pass metabolism, also challenged by dysphagia, i.e. in neonates and geriatric patients.

6/ Figures Case 2: sublingual administration: Please verify the use of solid and open symbols. Can it be that the metabolite is lower than the sildenafil?? Is there a mistake concerning change of symbols?? That does not fit with the other curves.

In the second case, after sublingual administration, the metabolite is lower than the mother compound which reflects bypassing of the first-pass metabolism and is the intended outcome of the switch, beside the overall increased plasma concentration. This effect is not that optimal and strong in case 1 but also tending towards it, mirrored by the increased metabolic ratio.

Minor comment:
Page 2, abstract conclusion: ….suggesting that not only the absorption……: change typing mistake
In this case we mean by “net”, the sum accounting for absorption. To make it more clear we rephrased the sentence:
Concurrently the metabolic ratio increased, suggesting that not only the overall absorption was enhanced, but also first-pass metabolism was partially bypassed.

Quality of written English: the manuscript was revised concerning the English language and was partly corrected.