Reviewer's report

Title: Remifentanil is more effective than sufentanil in suppressing hemodynamic and metabolic stress responses to intense surgical stimuli

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Reviewer: Christoph Wiese

Reviewer's report:

Dear authors,

thank you for giving me the opportunity to read this well done and interesting investigation.

In this prospective, randomized, double-blind study the authors fairly conclusively showed that remifentanil was more effective than sufentanil in reducing the hemodynamic and metabolic stress response to sternotomy and sternal spread. They quantified the stress response with changes in blood pressure and cardiac output. They measured sympathetic nervous system activation by changes in skin conductance, whole-body oxygen consumption and Surgical Pleth Index.

They hypothesized from their data that remifentanil might have a site of action other than mu-opioid receptors. There are no outcome data but that was not the aim of the study. The interesting thing is that remifentanil seems to act differently than a simple mu-opioid agonist. If this is the case, remifentanil might be of great interest to cardiac anesthetists.

General comments

Researchers are still trying to find a "stress-free" anesthesia that reduces the hemodynamic, metabolic and endocrine stress responses. Sternotomy with sternal spread is a standard benchmark stressor because it is very intense. Even extremely high doses of morphine, fentanyl, alfentanil or sufentanil do not reduce the response to sternotomy in most patients.

It is a common clinical observation that remifentanil can reduce blood pressure increases during surgery better than sufentanil. However, it has not been systematically studied if this was because the dose of remifentanil relative to the maximum possible effect was greater than the corresponding sufentanil dose, or if remifentanil is really more effective, perhaps because of different mode of action.

In this interesting and well designed study the authors avoided the question of equipotent doses by giving all patients a sufentanil dose that gave plasma concentrations that were far higher than necessary to achieve the maximum effect. That means that an additional dose of sufentanil would not have increased the effect. This is in line with results in the literature.

They showed that adding remifentanil was able to reduce the response to
sternotomy and sternal spread. They concluded that because the mu-opioid receptors were occupied by sufentanil (it has a higher affinity than remifentanil), that remifentanil might have had its action on other sites, such as the delta-receptors.

Specific comments.

Patients and methods
1. How long before induction of anesthesia was the premedication given?
2. How was the skin prepared and were special electrodes used to measure skin conductance? 3. Was skin resistance or conductance measured directly, or was the change measured?
4. What was the temperature of the injectate used for thermodilution cardiac output?
5. Was the remifentanil infusion started at the same time as the second sufentanil bolus injection or later?
6. I would have liked to see catecholamine measurements, but these would have been meaningless because exogenous catecholamines were being given to the patients.

Whole-body oxygen consumption is related to sympathetic nervous system activity.
7. Cortisol measurements might have been useful, but cortisol concentrations react with some delay and the patients were put on extracorporeal circulation right after the end of the hemodynamic and metabolic measurements. The ECC would have greatly confounded the cortisol data and made interpretation almost impossible.

Results
1. I would like to see a table with the demographic data of the patient population.
2. I believe that the postoperative NRS scores should be described as median and range.
3. Who decided when the patient should be given oxycodone postoperatively?

In summary, the findings of this working group will be of interest to many readers in the field. Personally, I found the subject to be of great interest. Therefore, I strongly recommend the paper for publication in “BMC Anesthesiology” after all revisions which I have stated are corrected..

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.