Host: Welcome to the ANESTHESIOLOGY journal podcast, an audio interview of study authors and editorialists.

Dr. BobbieJean Sweitzer: Hello. I’m BobbieJean Sweitzer, Professor of Anesthesiology at Northwestern University and an Associate Editor for ANESTHESIOLOGY and you are listening to an ANESTHESIOLOGY podcast designed for physicians and scientists interested in the research that appears in our journal.

Today we are speaking with one of the authors of a publication that appears in the November 2019 issue of the journal. With us is Dr. Maud A. S. Weerink. Dr. Weerink is a lead author of an article titled “Pharmacodynamic Interaction of Remifentanil and Dexmedetomidine on Depth of Sedation and Tolerance of Laryngoscopy.”

She is a resident-in-training in the Department of Anesthesiology at University Medical Center, Groningen, University of Groningen in The Netherlands. She did this research as part of her Ph.D. Welcome, Dr. Weerink.

Dr. Maud A. S. Weerink: Hello.

Dr. BobbieJean Sweitzer: So, what was the primary aim of your study?

Dr. Maud A. S. Weerink: The primary aim of our study was to gain insight in the effects of dexmedetomidine and the combination of dexmedetomidine and remifentanil. We wanted to study and quantify the pharmacokinetic and also the pharmacodynamic interaction between those drugs.

Dr. BobbieJean Sweitzer: Can you give us a little more information about which drugs you administered in the different study groups? How did you actually go about comparing these two?

Dr. Maud A. S. Weerink: Our subjects received preinfusion regimens of stepwise increasing drug concentration and the first day received dexmedetomidine and on a second occasion they received stepwise increasing infusion of remifentanil. And then the same day after allowing remifentanil to wash out, they received the combination of the two.

Dr. BobbieJean Sweitzer: So, interesting. So each patient actually got all three of the different study protocols?

Dr. Maud A. S. Weerink: Yes, indeed. We used the crossover study design, so each patient got all three of the infusions.

Dr. BobbieJean Sweitzer: Thank you. So, was this study done in actual patients or were these healthy volunteers?

Dr. Maud A. S. Weerink: No. For this study we, indeed, recruited 30 healthy volunteers.

Dr. BobbieJean Sweitzer: And will you explain to our listeners a little bit more about the design of this study? I think you mentioned about a crossover design; as we’ve noted, each participant participated twice in both the dexmedetomidine only, remifentanil only, and then in the combination of this. Could you just give us a little bit more details about how you accomplished this study?

Dr. Maud A. S. Weerink: Yes. For this study we, indeed, used the crossover trial design. This means that all volunteers received all three infusion regimens, so as you mentioned as well. And the trial design—which encompasses the different concentration steps, the number of volunteers, and the combination of the given doses—was optimized before the study started using computer simulation. And the goal of these simulations was to maximize the chance of being able to detect an interaction between dexmedetomidine and remifentanil.

And based on these simulations, we decided to go for the crossover design that is described in the paper. And for those of you who wish to dig into it, the result of these simulations are also included in an online supplement to the paper.

Dr. BobbieJean Sweitzer: Excellent. So, this is very interesting, I think, and kind of designs of studies that we can accomplish today that were not possible 50 years ago, right? We didn’t have these simulation techniques and things like that?

Dr. Maud A. S. Weerink: Uh-huh [affirmative].

Dr. BobbieJean Sweitzer: So, now, it sounds like the involvement and commitment of the volunteers was pretty significant. I mean, they were subjecting themselves to these drugs. I think you noted in the paper that you placed arterial lines for sampling. And then, obviously, the potential negative effects, which I want to ask you about a little bit later in this conversation. So, how did you recruit these people and were they compensated for this?

Dr. Maud A. S. Weerink: Yes, yes. Absolutely. For recruiting the volunteers we used the website which advertises medical research and on this website there is a short description of the study with a description of the type of test persons needed, like healthy, smoking, nonsmoking, et cetera.

And then there’s with it an amount of financial compensation which, of course, they got after joining the study. And then if someone was interested in the study, the person could sign up and receive the complete subject information for participation; that’s a document which also has to be approved up front by the Medical Ethical Review Board.

And if volunteers were still willing to volunteer after reading all this information, they visited me for a standard health screening and at that visit I also explained all the study procedures with them in detail and I used pictures of the study setup so they really knew what they were up to and all of that.

Dr. BobbieJean Sweitzer: Was it difficult to get people?

Dr. Maud A. S. Weerink: Not really. There was a lot of people actually interested in the study. We got like 200 people signing up for it immediately and then, well, of course after reading the complete file, some people were not interested anymore; they thought it was too much. But still there was a lot of people that wanted to participate.

Dr. BobbieJean Sweitzer: So, in this trial I think you used a design you described as a hierarchical interaction model. Can you explain what this means and why you chose this?

Dr. Maud A. S. Weerink: Yes. The hierarchical interaction model is a way of modeling a response surface. So, graphically a (sounds like: single-drop) concentration effect that’s just a plot as a simple curve, usually it’s (sound like: wide L)-shaped; whereas an interaction model is describing two drug concentrations and for every combination of those two drugs there is an effect. So, this does not result in a line, but in a surface, a so-called response surface.

And in the literature there are various equations describing such a response surface and the hierarchical interaction model is one of those. In this model, one of the drugs does not exert an effect, but when this drug is combined with the other drug, it alters the effect of the other drug.

And this model is often used when modeling opioids hypnotic interaction as an opioid on its own does not result in sedation, but combined with an hypnotic, it results in deeper sedation.

And it’s clearly described and explained earlier by Bouillon and Shafer in a paper which they published in 2004—also in ANESTHESIOLOGY—and in this paper they used the hierarchical interactional model to describe the interaction between propofol and remifentanil.

Dr. BobbieJean Sweitzer: So, how were the infusions managed and what dosages did you administer into the different study groups?
Dr. Maud A. S. Weerink: We used target-controlled infusion or PCI pumps and those pumps are like part of standard clinical practice in The Netherlands and these pumps are programmed for the PK/PD model.

So, instead of an infusion rate, an anesthesiologist can target the concentration that he or she wishes to achieve and then can enter the patient’s age, gender, weight and length and then this model in the pump calculates the amount of drug needed as an initial bolus and then also continues to calculate the infusion rate of the drug needed to keep concentration at the targeted level.

So, in our trial we used stepwise increasing concentration targets up to 8 ng/ml for dexmedetomidine and up to 7 ng/ml for remifentanil. And then in the combination phase, dexmedetomidine was set to a fixed concentration of 2 ng/ml whereas remifentanil on top of this was increased up to 4 ng/ml.

Dr. BobbieJean Sweitzer: And you had chosen those targets based on your simulation that you had done ahead of time?

Dr. Maud A. S. Weerink: Yes, exactly. We used the simulation also to see what targets we should use and when we should sample.

Dr. BobbieJean Sweitzer: So, our audience, presumably being primarily anesthesiologists, are likely very familiar with remifentanil and dexmedetomidine. But can you briefly define for us the properties of the different drugs that you were most interested in for this study?

Dr. Maud A. S. Weerink: For dexmedetomidine I think it’s generally known that it results in arousable sedated states whereas higher concentrations they are described to result in a deep unarousable sedation and dexmedetomidine is not a potent analgesic.

And then remifentanil, on the other hand, is a fast-acting and potent analgesic and it’s known to induce the synergistic interaction when combined with other hypnotics like propofol.

And we were interested in this combination, as with those two drugs we have on one hand the hypnotic effects of dexmedetomidine which might be synergistically enhanced by remifentanil and also the potent analgesia of remifentanil on the other hand.

And we wanted to find out whereas this combination would result in deep unarousable sedation which might even be useful for clinical practice in the operating room.

Dr. BobbieJean Sweitzer: And how did you measure the effects of the drugs?

Dr. Maud A. S. Weerink: Well, at every infusion step we assessed the depth of sedation using a so-called MOAA/S score and in addition we measured the continuous EEG derivative called the Patient State Index. Then, when a patient appeared deeply sedated based on the preceding MOAA/S score, a laryngoscopy was performed.

Dr. BobbieJean Sweitzer: So, can you tell us a little bit more about this Patient State Index you used?

Dr. Maud A. S. Weerink: Yes, sure. The Patient State Index uses frontal EEG electrodes and it’s connected to a Masimo Root monitor running SedLine software and this software then calculates the PSI which is a EEG-derived index to monitor the depth of sedation. And this PSI ranges from 100 to 0 with an index of 100 representing awake state and 0 denoting no detectable brain activity.

Dr. BobbieJean Sweitzer: Is this typically something that’s just used for research purposes or is this a clinical monitor that people use in The Netherlands?

Dr. Maud A. S. Weerink: Well, I think in The Netherlands most anesthesiologists use the BIS monitor, but this is like – the similar monitor is the BIS monitor but it is called – from a different company and both with PSI.

Dr. BobbieJean Sweitzer: Got it. Yes, we typically use the BIS monitor in The States as well. And what about that MOAA/S score? I think that stands for Modified Observer’s Assessment of Alertness and Sedation score?

Dr. Maud A. S. Weerink: The MOAA/S score was used to quantify the level of sedation and it consists of several successive stimuli and the first one is calling the name of the subject in normal tone and then a bit louder; and then the subject was shaken by the shoulder while shouting a name; and, finally, a trapezoid squeeze.

And the MOAA/S score ranges from 5 to 0 and at 5 the subject readily responds when his or her name was called whereas at 0 the subject did not respond to a trapezoid squeeze.

Dr. BobbieJean Sweitzer: So, it sounds similar to what we do when we were trying to wake a patient up in the operating room. [Laughter]

{Crosstalk}

Dr. Maud A. S. Weerink: I don’t remember the exact amount of milliliters, but it was somewhere around 200 ml divided by two study dates, so it wasn’t…”

{Crosstalk}

Dr. BobbieJean Sweitzer: It sounds like giving a unit of blood. So, you actually performed laryngoscopy in these volunteers. Was that at each step, like after just remifentanilyl, after just – or was that with the remifentanilyl and dexmedetomidine combined when you did the laryngoscopy piece?

Dr. Maud A. S. Weerink: Yes. Well, we did it not after every infusion step; we only did the laryngoscopy when the MOAA/S score was low enough. So, when a subject was deeply sedated when it was due to ethical reasons; obviously it’s not possible to do a laryngoscopy also in awake volunteers.

And then while it was not me doing the laryngoscopy, there was three anesthesiologists participating in this study and then the attending anesthesiologist was performed the MOAA/S score and the laryngoscopy.

Dr. BobbieJean Sweitzer: Got it. I wondered about that at first. So, how did you define—what I believe you term in the paper—tolerance to laryngoscopy of one of your endpoints?

Dr. Maud A. S. Weerink: Yes. We said that a subject was tolerant to laryngoscopy when the anesthesiologist was able to perform a normal direct laryngoscopy and if he would perform it before intubation.

So, visualizing the sounds like vocal cord without the response of a subject. Then all other occasions. So, if a subject responded to laryngoscopy or a subject responded already to a preceding stimulus like shaking and shouting, then yes, of course due to the ethical reasons, no laryngoscopy was performed as this was a score that’s not tolerant to laryngoscopy.
Dr. BobbieJean Sweitzer: And you measured things like coughing, a movement or vocalization? Or what was sort of non—did they not tolerate the laryngoscopy; how would you define that?

Dr. Maud A. S. Weerink: Yes, that was when a subject was moving or waking up, opening eyes. Those responses were defined as non-tolerant.

Dr. BobbieJean Sweitzer: So, in your paper you discuss and define, I think, the various ways that these drugs behave when combined. Can you define for us what you mean by the term synergistic, additive or intra-additive effects?

Dr. Maud A. S. Weerink: Yes. Well, to simplify, the drugs which have a linear concentration effect relationship. And additive interaction is when the effect for a combination of two drugs is equal to the sum of the individual drug effect. And then synergism is when the combination results in a larger-than-expected effect. And intra-additive is like antagonism is when the effects or the combination is less than what you expect from the individual drug effects.

Dr. BobbieJean Sweitzer: Excellent. So, in anesthetic practices I think we frequently combine various drugs, as you know. Can you recap for us what we already know about dexmedetomidine when it’s combined with typical anesthetic drugs other than perhaps remifentanil?

Dr. Maud A. S. Weerink: Yes. In previous interaction studies, dexmedetomidine has been added to several anesthetic regimens in the operating room and it has shown to reduce the requirements of isoflurane, sevoflurane, propofol, thiopental and fentanyl. And studies investigating the sedative and analgesic properties of dexmedetomidine found that those resulting in mild-to-deep sedation lacked significant analgesic effects.

Dr. BobbieJean Sweitzer: So, did you have set criteria for discontinuing these infusions or aborting the trial for patients?

Dr. Maud A. S. Weerink: Yes, we had a list of stopping criteria which, first of all, after reaching tolerance of laryngoscopy or after completion of all the infusion steps, drug infusion was stopped and a recovery period began.

And in addition, we defined some safety limits and stopping criteria and those were mainly based on hemodynamics; they are described in more details also in our paper.

Dr. BobbieJean Sweitzer: So, what did you find with this study?

Dr. Maud A. S. Weerink: We found that low plasma concentrations of dexmedetomidine are required to induce a sedative effect; however, although the subjects they became sedated and they appeared to be deeply asleep and the PSI values, so corresponding to base studies, they were as low as 20; whereas the majority of the subjects remained arousable when stimulated by calling their name, by shaking the patient or shouting the name or by trapezius squeeze, even when we were reaching supraclinal concentrations of dexmedetomidine and even when we do administer remifentanil.

Dr. BobbieJean Sweitzer: So, I think you also found some effects of age. Can you tell us about that?

Dr. Maud A. S. Weerink: Yes. We found that sensitivity to dexmedetomidine increases with advancing age. So, all the volunteers required lower concentrations of dexmedetomidine compared to younger volunteers.

And within the clinical recommended dose range, concentrations up to about 2.5 ng/ml can be achieved. And at this concentration of 2.5 ng/ml, there was 83% of the 65-year-old subjects unresponsive to calling their name whereas this probability for 20-year-old volunteers at the same concentration is only 36%.

Dr. BobbieJean Sweitzer: And did you have enough people to compare between those two groups or was this the big binary division?

Dr. Maud A. S. Weerink: Well, no. Actually we did some PK/PD modeling on the data and the model can simulate what happens with all age groups, so then you can compare the 65-year-old subjects with the 20-year-old volunteers and can see the relationship.

There are some figures in the paper that will show also the relationship age with the dexmedetomidine concentration.

Dr. BobbieJean Sweitzer: Thank you. Thanks for pointing that out for our listeners. So, can you compare your findings of remifentanil and dexmedetomidine to that of, say, remifentanil and propofol?

Dr. Maud A. S. Weerink: Not really. Remifentanil synergistically reduces the concentration of propofol. It required we reached tolerance of shake-and-shout and tolerance of laryngoscopy and our study’s drug combination behaves in a bit of a different way.

Remifentanil being a potent analgesic did not increase probability of tolerance of shake-and-shout, trapezius squeeze and laryngoscopy. And this seems quite contradictory but it can be explained by the fact that in our study those painful stimuli were only applied eventually after calling the subject by name and shake-and-shout.

So, actually, we first tried to wake our subjects up using our voice or a tactile shake-and-shout and remifentanil simply did not affect arousability of the subject. And if they woke up before even applying a painful stimulus, it was called a nontolerance.

Dr. BobbieJean Sweitzer: Did you observe any adverse effects of these drugs either individually or in combination?

Dr. Maud A. S. Weerink: Yes, of course. We observed the first effects, but not really surprising effects, of either drug individually nor when they were combined. Of course, when administering high concentrations of remifentanil, people developed an opioid breathing pattern and sometimes needed some further stimulation to keep breathing. And one subject developed sporadic rigidity—one receiving remifentanil only—and she required anesthetic induction and intubation.

So, yes, we had some severe side effects but we accounted for them as well in advance. So, we were prepared for events like those.

And for dexmedetomidine we saw clearly the biphasic response in blood pressure with a low concentration leading to hypotension whereas high plasma concentrations resulted in hypertension and bradycardia which is most probably due to the direct intravascular (inaudible) one effect of dexmedetomidine.

And furthermore we saw that administering remifentanil in addition to dexmedetomidine led to an additional 8% or 5% decrease in MAP, but not to an additional decrease in heart rate.

There is a next paper coming out as well describing the hemodynamic effects.

Dr. BobbieJean Sweitzer: Excellent. In ANESTHESIOLOGY?

Dr. Maud A. S. Weerink: Well, I hope so. {Laughter}

{Crosstalk}

Dr. BobbieJean Sweitzer: We hope so too. I think you also saw some significant adverse effects for some extended period of time, actually after these infusions were ended. Can you tell us about that?

Dr. Maud A. S. Weerink: The first effects that we observed were hemodynamic effects and while based on a previous trial performed in our department and the previously developed hemodynamic model describing the effects of dexmedetomidine on heart rate and blood pressure, we knew that it would take several hours for the mean arterial pressure to recover back to baseline.

As such, our protocol already included a long recovery period after the drug infusion was ceased. But at the end of the day when our recovery period ended, not all volunteers were fit for...
discharge. Some volunteers and then especially young volunteers had to stay a few extra hours because they had a strong, significant orthostatic hypotension and vagal reaction when they were getting up.

**Dr. BobbieJean Sweitzer**: Interesting. So, can you, again, summarize the most important results of this study for our listeners?

**Dr. Maud A. S. Weerink**: I think the most important findings are that whereas only low concentrations of dexmedetomidine are required to induce sedation and let the subjects fall asleep, the majority of the subjects remained arousable by calling the subject’s name, by shake-and-shout and by trapezius squeeze, even when reaching supraclinical concentrations of dexmedetomidine and even when adding remifentanil.

So, therefore, although the combination of dexmedetomidine and remifentanil might be useful in conscious sedation or conscious procedures, dexmedetomidine alone cannot be considered suitable to completely replace an intraoperative hypnotic.

And to ensure deep and unarousable sedation as needed for most anesthetic inductions, I think different or additional hypnotics will remain required. And furthermore, we found the relationship with age that the older the subject, the lower the concentration of dexmedetomidine they need.

**Dr. BobbieJean Sweitzer**: Excellent. All very important information for us to have as we continue to learn how to use these drugs and offer our patients different anesthetic options.

**Dr. Maud A. S. Weerink**: Uh-huh [affirmative].

**Dr. BobbieJean Sweitzer**: So, I hope today’s discussion will interest many of our listeners and lead you to read this important article to learn more. Thank you, Dr. Weerink, for discussing your work with us today. I wish you well as you continue your efforts to enhance the practice of anesthesiology and strive to improve the care of our patients.

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