minute ventilation. In the operating room before induction to general anesthesia. We used the negative confirmation with the sleep study that they did not suffer from this. Patients having surgery for a surgical correction of obstructive sleep apnea. Dr. Anthony G. Doufas: We selected our patient population from among selected and then how the study was conducted. Patients and control subjects you used for the study, first, how they were conducted this study, what your methods were. Walk us through how the be able to detect it in some ways. Ventilation, perhaps respiratory arrests of those intubations—and then you'd decreased more sensitive to remifentanil and have bad things happen—decreased obstructive sleep apnea are more sensitive to remifentanil-induced ventilatory depression. This claim is moderate-to-severe obstructive sleep apnea and controls with no or mild obstructive sleep apnea. The diagnosis of obstructive sleep apnea was based on the recent sleep study. Remifentanil infusions in patients' data were input to a previously published pharmacokinetic-pharmacodynamic model in order to predict effect site concentrations. Subsequently, we used a sigmoid pharmacodynamic model to describe the relationship between the predicted effect site remifentanil concentration and the minute ventilation. Looking at the raw data, we observed that towards the end of this ten-minute long remifentanil infusion, the ventilatory depressant effect of the drug started dissipating with the minute ventilation slowly rising toward the baseline. We assumed that this was the effect of the slowly rising carbon dioxide in the blood of our subjects counteracting the ventilatory depressant effect of the remifentanil and we accounted for that effect of the CO₂, the carbon dioxide, using a previously published indirect response model describing the kinetics of carbon dioxide in subjects receiving remifentanil under non-steady state conditions. Dr. James P. Rathmell: So, it’s important to point out that you didn’t directly measure effect site concentrations of remifentanil. There were no direct measurements and they were estimated based on computations from this pharmacologic model and then you adjusted for this uptick in CO₂ increase in ventilation toward the end. And I assume you adjusted it back down to the rate prior to that rise in minute ventilation. Is that correct? Dr. Anthony G. Doufas: Correct. Dr. James P. Rathmell: So, you measured minute ventilation directly, that was the direct measurement and you did it at baseline and then during this standardized infusion. And then you modeled the minute ventilation as a function of the effect site concentration and estimated carbon dioxide and you used those data as estimates of the degree of respiratory depression... Dr. Anthony G. Doufas: Correct. Dr. James P. Rathmell: …that was produced by the remifentanil. Perfect. Now, how did you assemble the data to answer your question about remifentanil respiratory depression and obstructive sleep apnea? Dr. Anthony G. Doufas: We used a nonlinear mixed effects model— it’s called NONMEM, it’s a pharmacological modeling software— to estimate the basic pharmacodynamic parameters of our model, including the remifentanil concentration in the effect site associated with half-maximal depression of the minute ventilation, or else the Ce₅₀. It’s an indicator of the sensitivity to the particular opioid. Subsequently, we tested certain prespecified variables as covariates on the Ce₅₀. These variables included the study group assignment—obstructive sleep apnea versus controls—body mass index, sex, age, the number of apnea and hypopnea events per hour of sleep and the minimum nocturnal SpO₂ during sleep measured by pulse oximeter during the sleep study. Statistical significance was assessed by standard criteria by a decrease in the objective function of the model as well as an improvement of the model fit of the data. Now, in order to assess how confident was our model on the estimation of the Ce₅₀, we also directly tested our primary hypothesis that obstructive sleep apnea affected remifentanil-induced ventilatory depression by estimating an additional parameter indicating the fractional change in the Ce₅₀ as a result of obstructive sleep apnea diagnosis. The log-likelihood profile of this parameter addresses the confidence in the parameter relative to the overall model and was used to estimate the 99% confidence intervals for the fractional effect of obstructive sleep apnea on the Ce₅₀. Dr. James P. Rathmell: So, in the end you arrive at an estimate of the remifentanil effect site concentration at half-maximal depression of minute ventilation, or the Ce₅₀ for both the control and the sleep apnea groups. What did you discover? Dr. Anthony G. Doufas: First of all, the estimated typical value of the Ce₅₀ for the whole population was 2.20 ng mL⁻¹ with a 95% CI between 2.09 - 2.33 ng·mL⁻¹. The estimated value of the Ce₅₀ for OSA patients was
2.3 ng·mL⁻¹, while the Ce₅₀ for the patients without OSA or with mild OSA was 2.1 ng·mL⁻¹ and that was a statistically nonsignificant difference. Now, the typical value for the effect of OSA on the Ce₅₀ as a fractional parameter was a 7% increase in the Ce₅₀ in OSA patients, meaning a 7% decrease in the remifentanil sensitivity in patients suffering from moderate to severe OSA. The 99% confidence intervals for this estimate ranged from -5% to +21% and includes 0, thus precluding a statistically significant effect. None of the examined covariates on the Ce₅₀ for remifentanil-induced ventilatory depression was found to be significant.

Dr. James P. Rathmell: So, what do you conclude from the study? Does having obstructive sleep apnea influence a patient’s sensitivity to the ventilatory depressant effects of remifentanil?

Dr. Anthony G. Doufas: Under the circumstances of the present experiment, there’s no difference in the sensitivity to remifentanil-induced ventilatory depression between patients with moderate-to-severe OSA and controls.

Dr. James P. Rathmell: So, what do you think the take-home message is for practicing anesthesiologists? Can you generalize your findings to other opioids?

Dr. Anthony G. Doufas: As long as it pertains to awake patients with OSA, this patient population does not seem to be more vulnerable to the ventilatory depressant effect of remifentanil compared to normal subjects or those who suffer from mild OSA conditions. This is by no means a definite answer to the question of opioid-induced ventilatory depression in patients suffering from OSA. The main reason is that OSA is a highly heterogenous disorder with both anatomical and functional causes that may differentially affect ventilatory responses to opioids. Before we experiment more, I would urge caution about generalizing these results to other opioids, different dosing schemes or, more importantly, to states of decreased wakefulness; as, for example, the immediate postoperative period when patients with OSA, obstructive sleep apnea, might be more vulnerable to the upper airway obstruction and de facto ventilatory depression than others.

Dr. James P. Rathmell: Absolutely. So, that’s really the important part to emphasize: this doesn’t indicate that all opioids are safe for patients with obstructive sleep apnea, not by a long shot.

Dr. Anthony G. Doufas: So, Dr. Henthorn, I want to turn to your editorial view now; it’s titled “Where’s the Beef?: How Much Can We Skimp on Pharmacokinetic-Pharmacodynamic Data?” and you coauthored this with Dr. Olofsen. You warn readers, and I quote here, “We should be very cautious drawing conclusions in the language of pharmacokinetic-pharmacodynamics when there are no drug concentration data.” Tell us how pharmacokinetic-pharmacodynamic drug studies are typically conducted and how this study differed.

Dr. Thomas K. Henthorn: Let’s start with what anesthesiologists are most familiar with and that’s MAC determinations in which we simply relate a drug concentration under steady-state conditions with a response. When we move into the realm of pharmacokinetic-pharmacodynamic studies, these are not at steady state as Dr. Doufas’s title implies. And so, to fully understand the drug concentration response relationship, we combine the drug-concentration time profile with the drug-effect time profile. Thus, we need both drug concentration data from blood samples as well as measurements of drug effect during its onset, at its peak and then as it dissipates. In this study, all we have is a drug dose to relate to respiratory depression measurements which are changing over time. Therefore, the author simulated the remifentanil concentration versus time profiles that would result from the infusion that they gave their patients following mean literature values for remifentanil pharmacokinetics. Remifentanil was never actually measured in the blood.

In addition, the respiratory depression that was measured was only during the onset of drug effect due to the need to get the surgery started. Usually the offset of drug is measured as well.

Dr. James P. Rathmell: Some significant limitations. Now, you listed a series of concerns that you really talk through elegantly using the language of pharmacokinetic-pharmacodynamic models. But I want you to try and explain your primary concerns and simplify them a bit so that the average anesthesiologist can understand how they might impact the study findings.

Dr. Thomas K. Henthorn: So, the main concern is that in a simple-dose response study, such as this one, investigators can’t separate differences between groups that are pharmacokinetic in origin versus those that are pharmacodynamic in origin.

That is, do sleep apnea patients maybe clear remifentanil differently than normals do? Or do they have more respiratory depression at the exact same blood level? Knowing which is which might affect how you would approach an individual patient.

Dr. James P. Rathmell: So, extremely important. So, the approach used in the study was really pragmatic: it didn’t require repeated blood sampling to determine actual blood levels. Do you think that lack of blood sampling impacted the conclusions that can be drawn from this study?

Dr. Thomas K. Henthorn: As we covered in the editorial, statistical power is reduced when a measured dependent variable is replaced with an unmeasured intervening variable as conclusions can only be inferred rather than fully estimated.

Without going into great detail, Dr. Olofsen, the editorial’s coauthor, randomly created large datasets from these results and realigned them using several modeling methodologies with all of them returning similar results as those found in the current Doufas study, except for one perhaps minor detail: the authors did not find a relationship with their simulated end-of-infusion remifentanil concentrations and the degree of respiratory depression they actually observed.

When actual individual blood remifentanil concentrations were included in a pharmacokinetic-pharmacodynamic analysis, there was a positive correlation between the remifentanil concentration at the end of infusion and respiratory depression.

To us, this was indicative of the loss of power introduced when drug levels are not measured. Thus, we urge caution when omitting drug concentration measurements in such studies despite the very well-considered analysis and solid conclusions that were provided in Dr. Doufas’s study and by his group.

Dr. James P. Rathmell: So, I think it’s important to emphasize what you’ve said, that in these two groups where we observed similar pharmacodynamic effects or the respiratory depressant effects, that the blood concentrations could have varied dramatically between the two groups.

And that resulted in the observed or the lack of any observed difference because we didn’t measure the actual blood concentration and those two groups may have handled the drug in a different way: one, eliminating the drug more quickly than the other. That’s one reasonable hypothesis for why there was no difference.

Dr. Doufas, I want to give you a chance to respond briefly to the concerns.

Dr. Anthony G. Doufas: Yes. First, I would like to thank Drs. Henthorn and Olofsen for their very insightful editorial and their hard work and taking the time to write this and do the modeling and all. We’re fully aware and recognize many of the issues that Dr. Henthorn discusses and the weaknesses of the study. I agree with his characterization of our experiment as a reduced experiment or economized experiment.

So, correct, we didn’t measure remifentanil in the blood of our patients. Our study was a dose-response experiment rather than a full pharmacokinetic-pharmacodynamic modeling exercise. We theorized that lacking plasma concentrations, effect site concentrations of remifentanil predicted by a previously validated model like Minto’s was our best option.

And we felt confident of our findings, especially in the light that there is no prior evidence or in place any biological theory or hypothesis supporting differences in the kinetics of this specific or other opioid between OSA patients and controls.

Now, having said that, I find the idea of using a kinetic pharmacodynamic approach as this has been raised and explained by Drs. Henthorn and Olofsen in their paper as an approach to bypass the issue of lacking plasma concentrations quite intriguing and might consider it in the future. Yes.

Dr. James P. Rathmell: Well, congratulations, again, on the publication of your work. What comes next for you and your research team?
Dr. Anthony G. Doufas: As I said before, it will be important to examine the same research question in different pathophysiological phenotypes of these OSA conditions, of the obstructive sleep apnea conditions, but most importantly in states of diminished wakefulness. For example, during a recovery from general anesthesia when obstructive sleep apnea patients might be more vulnerable to upper airway obstruction and hypoventilation. And we’re looking forward to future research designs, including this time plasma concentrations of opioids so we can do a full pharmacokinetic-pharmacodynamic model for this very important response.

Dr. James P. Rathmell: Terrific. So, much more work to be done in understanding the true risk of opioids in this population.

I hope today’s discussion will lead many of you listening to read this new article and the accompanying editorial view that will appear in the February 2019 issue of the ANESTHESIOLOGY. You can learn more about obstructive sleep apnea and the effects of remifentanil and respiration as well as the limitations of pharmacokinetic-pharmacodynamic modeling in the absence of measured blood concentrations.

Drs. Doufas and Henthorn, thank you for joining me today and for the terrific explanations about pharmacokinetic-pharmacodynamic modeling.

Dr. Thomas K. Henthorn: It was my pleasure. Thanks so much.

Dr. Anthony G. Doufas: Thank you for the interest to our work. Thank you.

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