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 two authors of publications that appear in the January 2019 issue of the journal. With us is Dr. Ashraf S. Habib. Dr. Habib is a lead author of an article titled “Amisulpride for the Rescue Treatment of Postoperative Nausea or Vomiting in Patients Failing Prophylaxis: A Randomized, Placebo-controlled Phase III Trial.” He is a Professor in the Department of Anesthesiology, Duke University Medical Center in Durham, North Carolina. Welcome, Dr. Habib.

Dr. Ashraf Habib: Hello, Dr. Sweitzer. Thank you for having me.

Dr. BobbieJean Sweitzer: And joining Dr. Habib is Dr. Jai Darvall who wrote an accompanying editorial “Pounds of Prevention but Only Ounces of Cure—The Need for More Research on the Treatment of Postoperative Nausea and Vomiting.” Dr. Darvall is from the Department of Anesthesia and Pain Medicine, Royal Melbourne Hospital, Royal Melbourne Hospital Clinical School and the Centre for Integrated Critical Care Medicine, all in Melbourne, Australia. Welcome, Dr. Darvall.

Dr. Jai Darvall: Thanks for having me, Dr. Sweitzer.

Dr. BobbieJean Sweitzer: So, first we’ll start with you, Dr. Habib. Can you tell us what your primary goal or aim of this study was?

Dr. Ashraf Habib: The primary goal of this study was to assess the efficacy and safety of intravenous Amisulpride for the treatment of postoperative nausea and vomiting in patients who have already received prophylaxis but still developed postoperative nausea and vomiting. And the prophylaxis had to be with agents that work on either receptors other than those that Amisulpride works on.

Dr. BobbieJean Sweitzer: So, I’m not sure how many of our listeners are familiar with Amisulpride. Can you tell us a little bit more about this drug? Maybe the mechanisms of action, how it is administered, how fast does it work?

Dr. Ashraf Habib: Amisulpride is actually an atypical antipsychotic that has been used internationally for more than 30 years. It’s a substituted benzamide working as an antagonist at the dopaminergic receptors: the D2 and D3 receptors. When the order of formulation is used for the antipsychotic effect in doses of 50 to 1200 mg per day, much lower doses in the order of 5 mg to 10 mg of an intravenous formulation are used for the management of postoperative nausea and vomiting. It has a rapid onset of action with the time to maximum plasma concentration being under two minutes.

Dr. BobbieJean Sweitzer: And it’s given as just an IV bolus push or…

Dr. Ashraf Habib: That’s correct.

Dr. BobbieJean Sweitzer: Is this drug available in the United States?

Dr. Ashraf Habib: Not yet. It’s currently undergoing FDA review but might become available sometime in 2019.

Dr. BobbieJean Sweitzer: Dr. Darvall, how many people will fail optimal postoperative nausea and vomiting prophylaxis?

Dr. Jai Darvall: Well, it remains a problem: prophylaxis is, unfortunately, not perfect even with multiple drugs. Probably the best evidence in efficacy of prophylaxis comes from, it’s a little old now, but the 2004 [The] New England Journal of Medicine paper by probably the doyen of postoperative nausea and vomiting, Apfel.

So, (sounds like: I did the impact paper) which you may remember was the factorial study looking at a number of different drugs and the combination thereof in reducing the risk of postoperative nausea and vomiting. And there was a relative risk reduction of about 25% for each additional antiemetic prophylactic drug used which is good but not perfect, obviously.

So, what that means in practice is that really, as the authors state in that landmark paper, that the best that can be expected even with total intravenous anesthesia in combination with three different class of antiemetic prophylactic drugs is probably a 70% relative risk reduction.

So, what that means is that there will still be a proportion of patients, depending on risk profile, that will, despite best efforts, experience recurrence or failed prophylactic nausea and vomiting.

Dr. BobbieJean Sweitzer: So, it sounds like there was a need for this kind of study and for a drug that we can use?

Dr. Jai Darvall: The other, I guess, problem is that efficacy under trial conditions doesn’t always translate to real-world effectiveness and that’s very evident in the case of prophylaxis for nausea and vomiting.

So, despite well-promulgated guidelines and, I think, probably certainly in the Australasian community, good knowledgebase about the best drugs to use and when to use them. We know from the evidence that this doesn’t translate well into optimal prophylaxis for our patients.

Compliance with guidelines probably sits at best around 30% to 50% if you look at the literature. So, there’s definitely a role for improving our prophylaxis of patients as well. What this means is that there will always be a role for good rescue medication.

Dr. BobbieJean Sweitzer: Yes. It does seem like we still struggle with this issue.

Dr. Jai Darvall: Did you evaluate just one dose of Amisulpride? And what drug or drugs did you use as a comparison or did you compare Amisulpride against?

Dr. Ashraf Habib: So, I actually evaluated two doses of Amisulpride in the study: a 5-mg dose and a 10-mg dose. The 5-mg dose was the one that was shown in prior study to be the optimal dose for prophylaxis and we hypothesized that a higher dose might be needed for treatment in those patients who have received prior prophylaxis and failed; therefore, we decided to include the two doses of Amisulpride: the 5-mg dose and the 10-mg dose.

And with regards to the comparison, this was actually a placebo-controlled trial. So, Amisulpride was compared to placebo, not to an active drug in this study.

Dr. BobbieJean Sweitzer: Were patients randomized and blinded?

Dr. Ashraf Habib: Correct. So, patients who have received prior prophylaxis and who developed PONV in the PACU were randomized to receive the 5-mg dose, the 10-mg dose or a placebo. And then there was a 30-minute evaluation for postoperative nausea and vomiting.

Initially during this time if the patients need any—requested any further treatment, they could have further treatment, but usually it was discouraged to have treatment prior to 30 minutes to allow the study drug to have its effect, but the patients could still request rescue treatment during this time. Or if the provider deemed it was necessary to provide further treatment during this time, it was done so.

And interestingly this was in the protocol, but where eventually no patients received extra doses during this 30-minute time period.

Dr. BobbieJean Sweitzer: And was this a single-center study? And how many patients did you enroll?

Dr. Ashraf Habib: No, this was actually a multicenter study that enrolled over 700 patients and it was conducted in 23 centers in the United States, in Canada as well as in Europe.

Dr. BobbieJean Sweitzer: Quite a broad swath of patients. Can you tell us a little more about the population that were enrolled, what type of surgeries they had, that sort of thing?

Dr. Ashraf Habib: So, the study enrolled adult patients who were undergoing a wide range of surgeries, either open or laparoscopic elective surgery that was expected to last at least one hour. Those patients had to receive...
a general anesthesia with inhaled agents and they were deemed to be at moderate or high risk for experiencing postoperative nausea and vomiting. They should have received prophylaxis for postoperative nausea and vomiting using antiemetics from classes other than the dopaminergic antagonist which is – I am even surprised is a dopaminergic antagonist.

Dr. BobbieJean Sweitzer: So, Dr. Darvall, Dr. Habib mentioned about patients had to be at moderate to high risk for nausea and vomiting. Can you review for us the typical risk factors for postop nausea and vomiting and how a patient would be determined moderate to high risk?

Dr. Jai Darvall: Sure. So, anesthesiologists would be well aware and familiar with the Apfel scoring system which is a really neat bedside four-point scale looking at the factors that add about a 20% raise on risk to a patient’s risk of nausea and vomiting; so, that’s being a female gender, a nonsmoker, a past history of motion sickness or, indeed, postoperative nausea and vomiting and the use of postoperative opioids.

This is a really neat bedside tool to help determine a risk profile with patients with two or more risk factors considered at moderate or high risk.

More recently the same group, Apfel’s group, has conducted and updated meta-analysis looking at, indeed, these factors and they’re probably not all as equal as each other; so, female gender is probably the strongest patient-specific predictor with an increase in the odds ratio is probably about 2.5 times compared to male patients. A history of postoperative nausea and vomiting would be next and then a history of nonsmoking status.

There are, of course, some other more minor predictors which add risk and that might include the usage of nitrous oxide, operation type is still debated: gynecological surgery, cholecystectomy, laparoscopic surgery seeming to be of increased risk as well. Whether this is just because female gender patients tend to have these operations more commonly it’s not known.

The contribution of intraoperative opioids is probably weaker than first thought, but certainly adds some risk.

So, yes, there’s a wide range of risk factors that contribute, but it’s useful to be able to calculate that risk score preoperatively to identify those moderate- to high-risk patients.

Dr. BobbieJean Sweitzer: So, you mentioned nitrous oxide. I still hear this debated quite a bit. Is it like if you use nitrous oxide for more than a certain amount of time, any exposure to nitrous oxide? How important is that risk factor?

Dr. Jai Darvall: It’s a good question, Dr. Sweitzer. It’s probably not well teased out, that duration question in particular because of significant heterogeneity in individual studies.

Again that updated meta-analysis in the British Journal of Anaesthesia in 2012 by Apfel’s group looked at this question. It does contribute, probably does have a duration with dose response effect, but it is a weak predictor. I think the odds ratio there was calculated at 1.45, so not nearly the risk imparted by being senile or having a past history; but it would be considered a minor predictor of postoperative nausea and vomiting.

Dr. BobbieJean Sweitzer: Dr. Habib, were these the kinds of risk factors that you used to stratify your patients and select them?

Dr. Ashraf Habib: Yes. So, we selected patients who were deemed to be at moderate or high risk for experiencing postoperative nausea and vomiting according to the Apfel risk score according to these four risk factors that Dr. Darvall just mentioned: female gender, history of PONV or motion sickness, nonsmokers and use of postoperative opioids.

So, 51% of patients we included in the study had four risk factors, meaning that they had about 80% risk for developing PONV according to the Apfel score. And 43% of those patients had three risk factors meaning that they were considered to have about 60% risk for developing postoperative nausea and vomiting according to the Apfel score.

Dr. BobbieJean Sweitzer: And what were the typical prophylactic drugs that the study patients received and what percentage of them got one versus two or even three drugs?

Dr. Ashraf Habib: So, the most commonly used antiemetics in the study were ondansetron and dexamethasone which is similar to current practice. A few patients received granisetron, scopolamine or other antiemetics and in general 50% of patients in the study received one agent, 42% received two agents and 7% received three or more prophylactic antiemetics.

Dr. BobbieJean Sweitzer: So, Dr. Darvall, can you tell us what we already know regarding which drugs are effective for treatment versus prevention of PONV?

Dr. Jai Darvall: Sure. So, similar classes of drugs are useful for both and that’s the first thing to say, I guess, and that’s useful for us as anesthesiologists: we don’t have to think too carefully about it.

For prophylaxis, the typical classes of drugs that would be used would be the 5HT-3 receptor antagonists such as the setrons. According to steroids, dexamethasone, antidopaminergic drugs such as Aminopridure, but more longstanding use drugs would be droperidol, haloperidol, antihistamines, anticholinergics with some weak evidence for other classes of drugs: gabapentinoids, alpha-2 antagonists, that sort of thing.

The classes of drugs seem to be equal in efficacy; so, again, going back to that impact [The] New England Journal of Medicine paper in 2004 that the doses and drugs used there, ondansetron 4 mg, droperidol 1.25 mg, dexamethasone 4 mg for prophylaxis were equally effective, as mentioned before, reducing the risk of PONV by about 25%. A similar effect is seen with propofol as a total intravenous anesthetic technique.

For treatment, the first thing to say, I guess, is that an antiemetic from a different pharmacological class should be used from – that’s failed for prophylaxis. So, that’s been well-shown in the literature.

In terms of the 5HT-3 antagonists, doses are smaller. So, ondansetron perhaps only 1 mg versus 4 to 8 for prophylaxis. And again, the other classes of drugs are equally effective for PONV; so, dexamethasone, droperidol, promethazine. The antiemetic effect with low doses of propofol is certainly seen but is probably brief when used as a rescue treatment.

And, of course, there is emerging interest and evidence for alternative treatments for rescue treatment of nausea and vomiting as well.

Dr. BobbieJean Sweitzer: Such as?

Dr. Jai Darvall: So, there’s some evidence for isopropyl alcohol inhalation, so that’s an emerging area. Anesthesiologists will be familiar with acupunc-ture and acupuncture which has a fairly robust evidence base now, although it hasn’t been taken up widely. I think in part because of the need for training and knowledgebase around its uses is not great.

Our clinical trials network in Australian and New Zealand is studying chewing gum as a rescue treatment for nausea and vomiting which has been shown to be of some early benefit in a pilot randomized controlled trial and we are currently conducting a large multicenter, multinational randomized controlled trial looking at chewing gum versus ondansetron as a rescue treatment for established nausea and vomiting after surgery.

Dr. BobbieJean Sweitzer: So, interesting stuff and maybe soon we’re going to find out whether Aminopridure is also an emerging treatment. But before we get to the results of this study, I want to ask Dr. Habib another question.

So, I was struck by the fact that in spite of these patients being sort of moderate to high risk for nausea and vomiting, 50% of them received only one prophylactic drug and I thought it was sort of recommended that for each risk factor one should give a drug.

Was this a real-world kind of case where you just allowed the anesthesiologist to do their own prophylaxis and then you guys were just coming in with the rescue evaluation? Or did you try to encourage or were they given guidelines around prophylaxis?

Dr. Ashraf Habib: So, in the study, the prophylaxis really was left at the discretion of the anesthesiologist at each participating center. The only guidance for this trial was that prophylactic agents to be used should be from a different pharmacological class than antidopaminergic drugs.

And as we discussed earlier on, the study really was a multicenter, multinational study where numerous centers in different countries had participated and maybe the practice really varies in these different centers as far as prophylaxis.

And I agree with your comments, currently it is – I mean, there are two approaches that are recommended for PONV prophylaxis: either a risk- stratified approach where you personalize prophylaxis based on the number of risk factors that the patients have; and, an easy recipe for this is giving one agent for each risk factor. Or a second approach is using universal...
multimodal approach where you use a combination of antiemetics to all patients irrespective of risk factors.

And this has to do somehow with the full compliance of providers with guidelines that we discussed earlier on in this podcast.

Dr. BobbieJean Sweitzer: Yes, I’m still very puzzled by why the best evidence doesn’t somehow get translated to clinical practice.

So, the moment we’ve been waiting for: tell us what you found from your study.

Dr. Ashraf Habib: So, what we found from our study, we found that the 10-mg dose of Amisulpride was superior to placebo at treating established PONV in those patients who have failed prophylaxis whereas the 5-mg dose was not superior to placebo.

So, the 5-mg dose was the one that was actually shown to be the optimal dose for prophylaxis. But interestingly in this treatment study the 10-mg dose was the only dose that was found to be effective.

Dr. BobbieJean Sweitzer: So, I guess that was very wise of you to appreciate that maybe you were going to need a larger dose and study that.

Dr. Ashraf Habib: I mean, I think this was discussed at the study design stage and I guess at the end we were happy that we decided to include both doses of 5 mg and the 10-mg dose since the 5-mg dose actually did not show to be effective.

Dr. BobbieJean Sweitzer: Dr. Darvall, I recall that almost 50% of the patients in this study who received a placebo had a complete response at two hours. Do you think this was because the PONV just resolved on its own over time or that placebo is pretty darn good?

Dr. Jai Darvall: That’s a good question, Dr. Sweitzer. We know that there’s a strong placebo effect for many medications in trials. But, no, no, no, certainly Amisulpride works. I suppose one thing to say about nausea and vomiting is that it does resolve over time. And so, regardless of a placebo effect or even just not treating nausea or vomiting, a proportion will get better.

But it’s not high. So, we know this from historical studies. It’s hard these days to do placebo-controlled trials in nausea and vomiting, but there was a number of studies conducted in the 1980s and 1990s which there’s a nice systematic reviews of 28 such trials done by Eberhart in BMC Anesthesiology in the early 2000s.

Pulling data from those 28 trials, looking at how good placebo is for established nausea and vomiting, they found a pooled incidence of a recurrence rate of about 70%.

Really, if you don’t treat your patients with nausea or vomiting, only about 30% will get better which, interestingly, it aligns very nicely with the placebo incident rate in Dr. Habib’s study which I think was about 72%.

Certainly there is some effect from placebo or even no treatment with natural resolution and I think all of us that have experienced an episode of vomiting would know that it does make you feel better. But Amisulpride is certainly a lot better than placebo in this study.

Dr. BobbieJean Sweitzer: So, Dr. Habib, does this drug have any common side effects and did you see any problems in the population that you studied?

Dr. Ashraf Habib: We didn’t actually see any problems in our patients as far as side effects; there was no difference in side effects between the Amisulpride group and the placebo group. And this being an anticholinergic drug obviously you worry about extrapyramidal side effects which we did not show – we did not see in this study or in prior PONV studies investigating Amisulpride, there was no increase in sedation or cardiac events.

The only side effect that is known to occur with Amisulpride is actually in serum prolactin as a result of a prolactin release from the interior pituitary; it’s not really clear whether this is of any clinical significance, though.

Dr. BobbieJean Sweitzer: I believe this drug is very similar to droperidol which carries a black box warning regarding a risk of QT prolongation. And I know that’s a very debatable issue, but is this a concern with Amisulpride?

Dr. Ashraf Habib: That’s a good question. Obviously prolongation of the QT interval occurs with D2 antagonists in general because they bind to the HERG potassium channel in the heart.

Droperidol exhibits a high affinity for such channels, but the binding affinity of Amisulpride to those channels actually has been shown to be more than 1,000 folds lower than that of droperidol in (sounds like: in vitro) testing.

And if we look at the PONV studies that investigated Amisulpride, there was no difference between Amisulpride and placebo with regards to QT prolongation; however, Amisulpride does exhibit those related prolongations of the QT interval and there is a nice pharmacokinetic study that involved 40 volunteers that looked at those Amisulpride from 5 mg to 40 mg.

What the study revealed, that antiemetic doses of Amisulpride did not meet the prolongation of the QT interval above the threshold that’s considered to be of concern by that team.

Dr. BobbieJean Sweitzer: That’s an excellent question, Dr. Sweitzer, and I think it’s a real shame that there hasn’t been more study in this area and Dr. Habib and colleagues need to be congratulated for doing what is a hard study to do, particularly considering the economics of scale. I think the latest World Health Organization estimates are that there’s about 300 million surgical procedures conducted around the world annually; that’s a lot of vomiting patients despite best prophylaxis.

So, it does raise the question, why hasn’t there been as much study of rescue treatment? I think the reasons are probably multifactorial: drug companies are likely to look at the economics of scale because prophylaxis is administered to many more patients than true rescue treatment would be; clinical trials for prophylaxis may, indeed, prove more cost effective and lucrative for study; in addition, there’s obviously the need to enroll many more patients for a study into treatment effects.

So, if we look at an incident rate or a failed prophylaxis rate of, say, 30%, then that’s 70% of patients enrolled that won’t ultimately go on to be randomized even though we’re studying a rescue treatment.

I think as well there’s complexity in designing a trial of rescue treatment and that complexity is with regards to the semantics; nausea, do you measure it on an ordinal scale, is it binary? Vomiting, retching, do you look at that? What time points do you look at? So, do we consider any nausea, vomiting or retching in a two-hour period which some studies look at? A 24-hour period?

That makes it quite difficult to standardize rescue treatments or study of rescue treatments whereas failure of prophylaxis is a lot simpler in many ways.

Dr. BobbieJean Sweitzer: So, Dr. Habib, I think you discussed in your paper and I know you both have mentioned it in this interview that one needs to be sure that they provide a treatment drug from a class that is different than drugs used for prophylaxis. And yet, I seem to see it’s quite common for providers to do repeat doses of particularly 5HT-3 antagonists such as ondansetron.

Do you think this is due to ignorance or a lack of good alternative drugs for a treatment of postop nausea and vomiting?

Dr. Ashraf Habib: This is a very interesting question. I think originally this repeat dosing of ondansetron might have been due to the lack of knowledge about the limited efficacy of this repeat dosing.

But back in, I think, the 1990’s Dr. Kovacs did an excellent study where he showed that repeat dosing of ondansetron is no better than placebo in treating PONV in patients who have previously received ondansetron. So, we have known for a long time that a repeat dosing of ondansetron is not effective and all the guidelines state that.
However, providers like ondansetron mainly because of its favorable side effect and, in particular, lack of sedation. So, I believe currently the practice of repeat dosing of ondansetron is largely due to the lack of antiemetic agents from other classes that are proven to be effective and that have a good side effect profile when used for rescue.

In particular, lack of side effects such as sedation of extrapyramidal side effects are important when choosing an antiemetic for treating PONV in the PACU when you need an effective agent to treat PONV without side effects that might lead to prolongation of PACU stay.

Dr. Bobbie Jean Sweitzer: So, maybe we’re finally going to get that drug if Amisulpride gets approved.

Dr. Habib, do you have a take-home message for our listeners who encounter a patient perhaps today—though it’s getting kind of late unless they’re on call or tomorrow or this week—who is nauseated or vomiting in the PACU after having already received maximum prophylaxis, because after listening to this podcast they’re going to start doing optimal prophylaxis.

But let’s say they’ve already received ondansetron or another 5HT-3 antagonist, like we know is quite common, and dexamethasone intraoperatively for prophylaxis of postop nausea and vomiting. How would you or what would you recommend today, since we don’t have Amisulpride, that they manage that patient?

Dr. Ashraf Habib: So, as we mentioned, we need to use an antiemetic that’s from a different pharmacologic class and that has the rapid onset of action which excludes some agents that are effective for prophylaxis and – but takes some time to exert an antiemetic effect such as scopolamine, for instance.

So, unfortunately, we don’t have a lot of great options currently available, but until an agent such as Amisulpride might become available, which our study suggests it would be a good option, meanwhile in my practice I currently use a low-dose promethazine or metoclopramide or haloperidol for rescue treatment of PONV in the PACU.

Dr. Bobbie Jean Sweitzer: And Dr. Darvall, since you’re in Australia, first off, is Amisulpride available to you? And, secondly, do you have anything to add to Dr. Habib’s formula?

Dr. Jai Darvall: As far as I know, it’s not at this stage available to us in Australasia. So, we keenly await the regulatory approvals that you mention might be coming in the next year or so.

We have a very similar setup, I think. One of the nice things about anesthesiology around the world, particularly with respect to postoperative nausea and vomiting, is that it’s very multinational. I think we have access to all the same drugs, I would use a similar regimen.

Metoclopramide I don’t use as much in my practice; the more recent evidence suggests it’s probably got weaker antiemetic effects than first thought and the doses required are much higher than the 10 mg that certainly I learned growing up. Probably 25 to 50 mg would be the antiemetic dose but, of course, then the side effect profile becomes considerable.

I use a lot of droperidol as a prophylactic drug, try to reserve setrons more for rescue in my practice and dexamethasone is used a lot in Australasia. There are, of course, some concerns about effects on wound infection and other side effects and currently we’re conducting the PADDI Trial looking at that question with intravenous dexamethasone for prophylaxis.

But, yes, I think as Dr. Habib has said, one of the big challenges is to use different classes of drugs for rescue and that’s something that can be hard when you’ve already administered much of your armamentarium as prophylaxis to a high-risk patient.

Dr. Bobbie Jean Sweitzer: I hope today’s discussion will interest many of our listeners and lead you to read this important article to learn more. Thank you, Drs. Habib and Darvall, 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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