SEDATION SOLUTIONS

Case report: Post-operative nausea and vomiting

Introduction

Postoperative nausea and vomiting (PONV) remains a nightmare for the sedation practitioner and anaesthetists. It is most of the time difficult to predict, prevent, and to treat.

A 60-year old woman was referred to me for sedation for facial surgery. She had two previous sedation procedures done by two different sedation practitioners.

After the first sedation she started with severe post discharge nausea and vomiting (PDNV) about 12 hours after the procedure while at home. She was taken to hospital for treatment as all the anti emetic drugs administered failed. This included the use of serotonin antagonists, dexamethasone, and metoclopramide.

After the second sedation she started with PONV within 20 minutes after the procedure when she was still in the surgery. She was treated with serotonin antagonists, and dexamethasone. The question is how does one approach a case like this if she has to have a sedation procedure for the third time.

The obvious answer would be not to administer known drugs that may cause PONV, and to administer drugs that may prevent and treat PONV. The approach to this patient will be discussed under conclusion.

A look at the literature

Many articles are available in literature concerning possible causes and treatment of PONV. Not much has been published on post-discharge nausea and vomiting (PDNV) for ambulatory patients, something that concerns us as sedation practitioners.

As sedation practitioners we need to clarify and understand the following issues that may challenge us

- What is the difference between PONV and post-discharge nausea and vomiting (PDNV)

- Who is at risk for PONV and PDNV after surgery under sedation outside the operating theatre
- Which drugs are available to prevent and treat PONV and PDNV
- Which drugs must we stay away from that we know can increase the incidence of PONV

PONV in the context of sedation would probably mean that the patient has nausea and vomiting while still in the surgery or recovery area after sedation and before discharge home. This is not something we often see but we do need a protocol to prevent and treat this when it happens.

The overall incidence of PONV is quoted in literature as between 25-30%[1] for all operations and patient population groups under general anaesthesia, and can even be as high as 70%. Procedures outside the hospital setting are increasing in popularity and here the incidence can even be higher. Very little information is available regarding nausea and vomiting in sedation practice. A concern for us is the incidence of PDNV as patients may be at home where there may not be any infrastructure to treat PDNV effectively.

Various predictors of PONV are known i.e., previous history of PONV, female gender, non-smokers, use of volatile anaesthetics, use of the opioids, an increased duration of surgery, and some surgical procedures.

Apfel at el[2] defined who is at risk for PDNV after ambulatory surgery. This is an article that all sedation practitioners must take note of as it gives us direction as to the issues that may challenge us doing sedation. He claims that PONV can be predicted with a simplified risk score, also known as the Apfel score[3]. There is however not a risk score available for PDNV.

Apfel[2] studied 2170 adult patients undergoing general anaesthesia for outpatient procedures. He reported an overall incidence of PDNV of 37%; 5% of patients had severe vomiting. PDNV was defined as nausea and vomiting that occurred from discharge of the patient until the end of the second

post-operative day.

Apfel[2] claims that the incidence of PDNV can be predicted after general anaesthesia depending on the number of the following factors, i.e., female gender, age under 50 yrs., a previous history of nausea and vomiting, opioid administration, or nausea in the post-operative recovery area: the patient's risk for PDNV can be predicted as 10%, 20%, 30%, 50%, 60%, or 80%. Zero, one, two, three, four, and five of these factors were associated with a PDNV of 7%, 20%, 28%, 53%, 60%, and 89%, respectively. It is suggested that patients who are nauseous in the recovery area after a procedure have a high risk for developing PDNV.
It looks like that even with a "favourable" patient and in the best hands the risk of PDNV is about 7% after ambulatory surgery under general anaesthesia.
But what about conscious sedation!

It is reported[4] that ondansetron (Zofran®) is equally effective against nausea and vomiting (PONV) but if it is administered during the operation it does not decrease the risk of PDNV. This is probably due to the short plasma half-life of about 3 hours of this drug.

The above information is extremely useful for us as sedation practitioners who provide sedation for cases outside the hospital setting to decide about the possibility of prophylactic anti emetics before patients are discharged. We need to take into consideration the short half-lives of certain drugs and consider the possibility of combining drugs.

Drugs

No anti emetic drug is universally effective in the prevention or treatment of PONV. Most of the drugs used for PONV have short half-lives and are of limited value in the prevention of PDNV. It is yet unclear whether drugs with long-halve lives i.e., neurokinin – 1 receptor antagonists i.e., aprepitant (Emend®) may offer value in the prevention of PDNV. There is however no reason why they cannot be tried in PDNV.

Not all clinicians agree on the prevention and treatment of PONV. Guidelines from the Society for Ambulatory Anaesthesia (SAMBA)[5] suggest that no prophylactic medications should be given if a patient is at low risk for PONV. One or two anti emetics should be considered in adults with a moderate risk,

two or more anti emetics (preferably different classes of drugs) for high risk patients.

Various anti emetic drugs are available for the prevention and treatment of PONV. The three major anti emetic drug classes are dopamine-2 receptor antagonists i.e., droperidol, serotonin-3 receptor ($5HT_3$) antagonists such as ondansetron and dolasetron, and corticosteroids such as dexamethasone. Each is believed to reduce the relative risk of nausea and vomiting by 25%[7].

The antihistamines, metoclopramide, and the neurokinin-receptor antagonists are also used for PONV. Promethazine, a neuroleptic medication belonging to the phenothiazine family, has been used as an anti emetic in pregnancy. It is a potent antihistamine that act as an antagonist at both serotonergic and dopaminergic receptors[8]. Promethazine is considered a weak antipsychotic, but dyskinesia has been reported. It is not the drug of first choice nowadays for the prevention and treatment of PONV.

There are some concerns about some anti- emetic drugs causing QTc prolongation. Concerns about this possibility prompted the Food and Drug Administration (FDA) to issue a black box warning for droperidol in 2001[9]. The FDA's report about ondansetron causing prolongation of the QTc seems to be based on large doses of ondansetron, as used for chemotherapy.

The $5\text{-}HT_3$-receptor antagonists ondansetron (Zofran®) and granisetron (Kytril®) are commonly used to prevent and treat PONV.

Ondansetron is a popular anti emetic drug for prevention and treatment of PONV that can be administered by mouth 8mg, 1-2 hours before treatment; alternatively intramuscular or a slow intravenous injection 4mg before the start of the procedure or for treatment of PONV.

Granisetron (Kytril®) for PONV is given by intravenous administration (diluted to 5cc and administered over 30 seconds). It can be used for prevention of PONV in the same dose intravenously; maximum of 2mg in one day.

There is however a lot of interest in newer serotonin antagonists that have longer half-lives. They may be of special interest for sedation practitioners for the control of PDNV where patients go home soon after the operation and cannot be treated with intravenous injections at home.

Ramosetron[6] is a new 5-HT_3-receptor antagonist that has a higher affinity and more prolonged activity than ondansetron. The elimination half-life of ramosetron is 9 hours compared to that of ondansetron that is 3 hours. This leads us to expect that ramosetron would have an advantage over ondansetron as far as effectiveness is concerned for late PONV or even PDNV.
Mihara et al[6] showed in their meta-analysis of 1372 patients that 0.3mg of ramosetron is safe and effective for preventing both early and late PONV. Their study suggests that ramosetron has statistically significant differences in preventing early and late PONV compared with ondansetron.

The question is, is ramosetron superior to ondansetron for the prevention of PONV. Park et al[10] compared ramosetron with ondansetron for prevention of PONV in children who received fentanyl, an opioid, for analgesia during general anaesthesia. They found significantly less PONV during the first 24 hours after surgery and concluded that ramosetron is more effective than ondansetron in preventing PONV in children.

Two anti-emetic drugs that are also used for prophylaxis of PONV are droperidol(Inapsin®) and metoclopramide.
Merker et al[11] did a systematic literature research for randomized controlled trials comparing the two drugs. A total of 41 trials with a total number of 3491 patients were included. A total number of 1797 patients were treated with droperidol (0.25 – 5 mg) and 1694 with metoclopramide (5 – 50 mg).
In the early period (0 – 6 hours) the risk for PONV was 35% higher than after prophylaxis with droperidol. In the next 24 hours the risk for PONV after metoclopramide was increased by 20%.

These are significant results for us as sedation practitioners; it would appear from the results that droperidol could be a significantly important drug for us to use for

both PONV and PDNV. This may indicate that droperidol should probably be used in every patient with risk for PONV and PDNV.
The study of Merker[11] et al concluded that droperidol is significantly superior when compared with metoclopramide (in doses below 20 mg) for the prevention of PONV. There was no obvious positive dose response with respect to increasing doses of metoclopramide. There was also a trend towards higher efficacy of droperidol compared to higher doses of metoclopramide (>20 mg). This study shows clearly that droperidol is one of the more effective D (2)-antagonists in our pharmacologic armamentarium to prevent and treat PONV and also PDNV..
For us as sedation practitioners it is clear that metoclopramide alone is not the answer in the prophylaxis and treatment of PONV and PDVN, even if we increase the dose.

As sedation practitioners we are especially interested in anti emetics with long half-lives to prevent the problem of PDNV. The question is do we have them.

Interesting research has been done on the use of a serotonin receptor antagonist palonesetron (Aloxi®)[12]. One of the most significant advances in the pharmacological treatment of chemotherapy-induced nausea and vomiting (CINV) was the emergence of the so-called second generation 5-HT_3 receptor antagonists[12]. They have a significantly longer terminal half-life elimination than the first generation 5-HT_3 receptor antagonists i.e., ondansetron, granisetron, dolasetron and tropisetron[12]. They look like excellent drugs for possible future use to prevent PDNV.

Palonesetron is a second generation 5-HT_3 receptor antagonist with a terminal half-life of elimination of about 40 hours. It is a potent and selective serotonin subtype 3(5-HT_3) receptor antagonist. It is claimed that the drug has little or no affinity for other bio receptors, including other serotonergic receptors (5-HT_1, 5-HT_2 and 5-HT_4). There is no evidence that palonesetron prolongs the QTc interval.

It is also claimed that the efficacy of the 5-HT_3 antagonists is further increased when used in combination with a corticosteroid, such as dexamethasone[13].

Dexamethasone added to a 5-HT_3 receptor antagonist is capable of consistently improving the control of CINV compared with a 5-HT_3 receptor antagonist alone[14]. A dose of 20 mg of dexamethasone is the recommended dose before chemotherapy that may induce nausea and vomiting. In light of this finding the combination of a single-dose 5-HT_3 receptor antagonist plus multiday dexamethasone dosing has become established practice for patients receiving chemotherapy[13].

Celio et al[12] studied 1411 patients who were randomized to receive palonesetron or ondansetron/granisetron intravenously plus dexamethasone dosing. Their study confirmed that the combination of palonesetron and dexamethasone was significantly better in the prevention of CINV than the older generation 5-HT_3 antagonists plus dexamethasone. It is believed that palonesetron in combination with new NK-1 receptor antagonists i.e., netupitant may even offer better results in future to prevent and treat CINV. In a pilot study carried out to prevent CINV no clinically relevant interactions between netupitant and palonosetron were observed.

Conclusion

Now back to our patient mentioned at the beginning of this article that had two previous severe episodes of severe PONV after sedation. It is evident from this article and the previous history that a single drug would not prevent or treat PONV.

So where do we start. I decided to get palonesetron and combine this with droperidol and dexamethasone.

Palonestron is currently approved only for CINV. Each 1 ml of the solution contains 50 mcg palonesetron. Each vial of 5 ml of solution contains 250 mcg palonesetron. As this is an elderly patient I administered 50 mcg slowly intravenously 30 min prior to the procedure. The rest, 200 mcg, was administered slowly in 200 ml saline.

Droperidol 1.25 mg and dexamethasone 8 mg were administered intravenously prior to the operation.

For the sedation technique I used midazolam, propofol, and 5 mg of ketamine before the local anesthesia..
The patient had no episodes of PONV and PDNV.

The issue of PDNV after sedation and anaesthesia has not yet been resolved. What we know is that we need drugs with a longer terminal half-lives, and in combination with other drugs.
I like the idea of using droperidol in this combination as the drug also has sedative actions. It is however not an analgesic drug.

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