The control of postoperative nausea and vomiting (PONV) remains a difficult task. The optimal strategy to prevent PONV or to treat established symptoms is far from being obvious. Systematic reviews suggest that prophylaxis does not work very well, that there is a finite risk of adverse drug reactions with most antiemetic interventions, and that treatment may be more cost-effective than prophylaxis (1). Also, some interventions do not seem to work at all, and others are qualitatively or quantitatively very poorly documented.

The intention of this second part of a series of two papers on rational strategies to control PONV symptoms was twofold. First, to provide clinically applicable recommendations on optimal prevention and treatment of PONV, based on data which represent the highest level of evidence currently available on efficacy and harm of antiemetic interventions. For this purpose, data from systematic reviews of relevant and valid randomised controlled trials only were considered (1). This does not exclude the possibility that clinicians may modify or adapt these recommendations by using valid data from individual studies on antiemetics which have not yet been reviewed systematically, and by taking into account their personal clinical experience. The second aim was to define an agenda for future PONV research. Systematic reviews are powerful tools to identify what we do not know (i.e. lack of evidence), and what we know with such confidence that further research is not required. Thus, they are valuable sources of information to guide clinical research. Here, “lack of evidence” does not mean that the intervention is not efficacious, but it indicates that there are not enough valid data (i.e. not enough randomised controlled trials) to draw conclusions on the same level of evidence as if there was a systematic review of randomised trials.

Recommendations for prevention and treatment of PONV

There are three strategies towards an optimal control of PONV symptoms: 1. Keep the baseline risk low; 2. Wait and see, and, if necessary, treat; 3. Try to prevent PONV in exceptional cases only; but then do it effectively.

Strategy 1: Keep the baseline risk low

There are several strategies which, on an intuitive basis, may help to keep the baseline risk of PONV low, for instance, premedication with sedative drugs (benzodiazepines or anti-histamines), or avoidance of intra- and postoperative opioids. There is, however, strong evidence from systematic reviews of randomised trials that three interventions may help to keep the baseline risk of PONV low. First, consider a propofol anaesthetic (2, 3). This may work to some extent. However, you have to use propofol both for induction
and maintenance (2). You also have to take into account that at best 1 in 5 patients may profit, that high-risk patients only will profit form this intervention, and that the beneficial effect on PONV is likely to be of short duration after surgery (2). Thus, the day-case patient may be discharged, and may then start to vomit in the car, or at home. Finally, there is an increased risk of bradycardia in susceptible patients (typically in children undergoing squint repair due to the oculocardiac reflex (4)). The most effective method to prevent pain on injection with propofol is with a Bier’s block (i.e. a rubber tourniquet at the forearm for 30 s) with intravenous lidocaine 0.5 mg/kg (5).

Second, consider omitting nitrous oxide (6–8). The beneficial effect on vomiting is about as good as when using a propofol anaesthetic (9). There is, however, no effect on nausea, and there is an increased risk of intraoperative awareness (6). There is a lack of evidence to support the widely held view that the combination of using propofol and omitting nitrous oxide (i.e. a propofol TIVA) is especially beneficial.

Third, consider omitting antagonism of neuromuscular blockade at the end of surgery (10). This may make a difference if large doses of an anticholinesterase drug (for instance, neostigmine >2.5 mg) were to be used. There is, however, an increased risk of prolonged muscle paralysis in the postoperative period (10). Thus, long-acting neuromuscular blocking agents should be avoided, and neuromuscular function should be monitored.

Strategy 2: Wait and see, and, if necessary, treat
Clinicians tend to extrapolate efficacy data arising from trials on prophylaxis to the therapy of established symptoms. The example of ondansetron shows clearly that this approach may be flawed. Ondansetron is the only antiemetic which has been tested in several therapeutic PONV trials; these have been reviewed systematically (11). Thus, for treatment of established PONV symptoms, recommendations have to be based on ondansetron data. For all other antiemetic interventions, there is a lack of valid data on their therapeutic efficacy in the PONV setting or they are not established symptoms. The example of ondansetron shows clearly that this approach may be flawed. Ondansetron is the only antiemetic which has been tested in several therapeutic PONV trials; these have been reviewed systematically (11). Thus, for treatment of established PONV symptoms, recommendations have to be based on ondansetron data. For all other antiemetic interventions, there is a lack of valid data on their therapeutic efficacy in the PONV setting or they are very sparse only. No conclusions on their relative efficacy and optimal doses are then possible.

With ondansetron, treatment was shown to be effective (11, 12) and cheap (13). A dose as low as 1 mg was shown to be efficacious in the treatment of established PONV symptoms; higher doses (i.e. 4 mg or 8 mg) were not shown to be more effective (11). Thus, 1/4 to 1/8 of the recommended prophylactic dose is effective in the treatment of established symptoms. Since there is no evidence of any difference in efficacy and harm of different 5-HT3 receptor antagonists, ondansetron data may be extrapolated to other setrons (granisetron, dolasetron, tropisetron). Therefore, for the treatment of established PONV symptoms, use a “small” dose (i.e. less than the recommended prophylactic dose) of the cheapest 5-HT3 receptor antagonist you can find in your hospital pharmacy. Since treatment is effective and cheap (and fewer patients will be exposed to adverse drug reactions), consider treatment of PONV (rather than prophylaxis) for the majority of patients.

Contrary to prophylaxis, there is also also a lack of data on the efficacy of treatment combinations of drugs (for instance, a 5-HT3 receptor antagonist plus dexamethasone or droperidol) for the treatment of established PONV symptoms. And there is a lack of data on the efficacy of therapeutic antiemetic interventions in children with established PONV.

Strategy 3: Try to prevent PONV in exceptional cases only; but then do it effectively
Consider prophylaxis for the exceptional high-risk patient (“Help me doctor; I am sick after each anaesthetic!”), and for the patient who must not vomit (for instance, the patient with wired jaws). Strategies for prophylaxis are based on three rationales. First, keep the risk low (see above) (2, 3, 6–8, 10). Second, give a combination of drugs (“balanced antiemesis”) (14) rather than a single antiemetic. Third, since there is no such thing as “pre-emptive antiemesis”, give this drug combination shortly before extubation rather than at induction (15); the pharmacological effect will last longer in the postoperative period.

Drug combinations make sense only when different molecules with different pharmacological actions are combined. For instance, ondansetron (16) as other 5-HT3 receptor antagonists (17) shows less anti-nausea and more anti-vomiting efficacy, and there is an increased risk of headache (16). With the dopamine receptor antagonist droperidol, there is more anti-nausea and less anti-vomiting efficacy, and there is protection against headache (15). A combination of these two molecules is, therefore, a logical choice. Another combination which can be recommended is dexamethasone plus a 5-HT3 receptor antagonist (14). For both options, choose an effective dose of the cheapest 5-HT3 receptor antagonist which can be found in the hospital pharmacy and add droperidol or dexamethasone. Optimal doses of these combinations have yet to be identified. However, there is no rationale to give dexamethasone doses which exceed 10 mg iv (0.5 mg/kg in children), or droperidol doses higher than 1 mg iv (50 μg/kg in children). The potential ad-
ditional benefit of combining more than two molecules is unknown.

A special case: opioid-induced nausea and vomiting

Patients using a patient-controlled analgesia (PCA) device with an opioid are often at particularly high risk of nausea and vomiting. These patients may refuse to continue to profit from such a pump due to opioid-induced emesis. A systematic review suggests that the concomitant use of a low dose of droperidol with morphine is an effective means to prevent nausea and vomiting. In adults, no more than 2.5 mg of droperidol should be added to morphine 100 mg (18). There were no relevant paediatric data analysed in this systematic review; we may assume, however, that this regimen is also valid for children.

Interventions which do not work should not be used

Metoclopramide (19), 5-HT₃ receptor antagonists in a PCA pump with morphine (18), propofol for induction (2), and ginger root (20) cannot be regarded as worthwhile prophylaxis; these interventions should not be used. Since no prophylactic antiemetics work very well in the surgical setting (9), there is a strong argument not to use them on their own (i.e. as a mono-therapy) but to combine them whenever prophylaxis is deemed to be useful (i.e. balanced antiemesis).

Research agenda

A standardised methodology in PONV trials would facilitate the interpretation of the results of individual trials, and would enable indirect comparisons of interventions which were tested in independent trials. The meta-analytical combining of homogeneous data would be much easier. Cumulative meta-analyses would make early identification of efficacy and harm possible.

What endpoints are needed?

In a PONV trial, the main interest must focus on the impact of the intervention which is thought to be antiemetic on the incidence of PONV. An antiemetic which does not decrease the incidence of nausea and vomiting, but does, for instance, improve patient satisfaction, is a mood enhancing drug, but not an antiemetic. Of course, a truly antiemetic intervention is expected to have an impact on patient satisfaction.

Nausea is the subjective sensation of a desire to vomit. Retching is an expulsive movement of the stomach muscles when no stomach contents are expelled; it is usually considered as vomiting. Vomiting is a complex reflex from the central autonomic and motor system which leads to a forceful expulsion of gastrointestinal contents through the mouth. Thus, nausea and vomiting are biologically different phenomena (nausea is not “a little vomiting”); they should be reported and analysed separately. An antiemetic may have more anti-nausea and less anti-vomiting efficacy (for instance, droperidol (15)), or more anti-vomiting and less anti-nausea efficacy (for instance, ondansetron (16)).

To increase our understanding of the duration of action of antiemetic interventions, efficacy during different time periods should be reported and analysed. Historically, most PONV trials have reported cumulative incidences of PONV during one or two observation periods; a short period up to about 6 h after surgery, and a long period up to 24 h or 48 h after surgery. Short-term efficacy has an economic impact mainly in day surgery where patients are meant to be discharged within hours after the procedure; they have to be free of PONV to fulfil discharge criteria. Long-term efficacy is a better indicator of the drugs’ antiemetic efficacy and patients’ comfort. It indicates if the patient will remain PONV-free at home (or on the ride home).

The meta-analytical pooling of cumulative incidence data of nausea and vomiting during an arbitrarily defined short (“early”) period (up to 6 h postoperatively) and a long (“late”) period (24 h or 48 h) has been proposed by one group of authors (21), and has subsequently been adopted by others (22–24). Some authors have reported further incidence data during other observation periods (for instance, 2–6 h, 6–12 h etc.). There is, however, no biological basis for an “acute” and a “delayed” efficacy of antiemetic interventions as, for instance, in chemotherapy. Thus, if an additional observation period is reported in a PONV trial, it should be standardised, preferably 6–24 h, to facilitate comparison of studies; it should not replace early and late observation periods.

Other, secondary efficacy endpoints may be reported, for instance, the number of vomiting episodes, the degree of nausea (using a visual analogue scale), the number of patients needing rescue antiemetics, the delay until the first episode of PONV, or the time to discharge from the day-case unit. The interpretation of these endpoints is less obvious; some are prone to bias.

Presence or absence of all adverse events should be reported in dichotomous form (i.e. presence or absence of the adverse event). This is particularly im-
important for rare but potentially major adverse drug reactions, where causation cannot be established with confidence within one single study, because of the limited size of most studies. Meta-analysis of data from several studies may then confirm causation, and enable quantification of the risk. The number of patients needing unplanned hospital admission due to intractable PONV should always be reported.

**What trial design is needed?**

We need randomised, double-blind, placebo-controlled trials of reasonable size in subgroups of patients which represent daily clinical practice. Reporting of trial results should be clear (25). Only in very exceptional situations should data be published more than once; then, a cross-reference to the original report is essential (26).

Randomisation protects against selection bias. Selection bias may lead to overestimation of treatment effect (27). The impact of potential selection bias in PONV trials is unknown. This, however, is no reason to abandon randomisation.

Randomised comparisons of antiemetics with a placebo (A vs placebo) are needed (28). When active comparisons are designed without placebos (A vs B), one of the comparators must be the ultimate gold-standard intervention for the control of PONV. Since this gold-standard is yet unknown, active comparisons should always have an additional placebo group (A vs B vs placebo) (29).

Whenever possible, trial designs should be double-blind, using, for instance, numbered ampoules of identical colour and shape. Lack of blinding may lead to observer bias; observer bias may lead to overestimation of treatment effect (27). The importance of a double-blind design in patients receiving an antiemetic while they are asleep is unknown. However, the impact of observer bias may be particularly important when nonpharmacological antiemetic interventions are used in awake patients (22), or when interventions cannot be properly blinded such as propofol.

Large trials are needed. In small trials, there is a tendency towards an overestimation of treatment effect (11, 24). Also, in small trials, the incidence of PONV in patients receiving a placebo (i.e. the control event rate) has a tendency to show a large variability due to random chance alone; interpretation of treatment efficacy may then become very difficult. Finally, adverse drug reactions are unlikely to be identified in small trials.

Populations studied in PONV trials should represent a reasonable, clinically relevant baseline risk. If nobody vomits without prophylaxis, it is not worthwhile to try to prevent it; even for the most efficacious antiemetic there is then no scope to show efficacy. Worthwhile efficacy of antiemetic prophylaxis in the PONV setting has been arbitrarily defined as a number-needed-to-treat <5 (30) (i.e. 5 patients have to be given the drug for one to profit, who would not have done so had they not received the drug). Thus, the control event rate (i.e. the incidence of PONV in patients receiving a placebo), which to some extent reflects the baseline risk, should be at least 20%, because only then has the antiemetic the scope to achieve a number-needed-to-treat of 5. However, if everybody vomits without prophylaxis, there is a risk of overestimating the efficacy of an antiemetic; any intervention may then show some efficacy. Also, such a high underlying risk would not represent daily clinical practice.

**What further trials are needed?**

The systematic review process is an important tool to unearth what we do not know. Lack of valid data equals lack of evidence. Lack of evidence must lead to a research agenda. Systematic reviews also help to identify what we know with confidence. The continual repetition of very similar PONV trials raises scientific, and thus ethical questions. It has been claimed that each study protocol submitted to a research committee should be accompanied by a systematic review to provide evidence of the necessity of that study (31).

Clearly, we need to know more about dose-responsiveness and optimal doses of these drugs, about older antiemetics, drug combinations, efficacy of treatment strategies, and efficacy and harm of antiemetic drugs in children. The optimal dose of an antiemetic is the dose that shows worthwhile efficacy and an acceptable level of adverse effects. For instance, for metoclopramide, no dose-responsiveness has been described, and the optimal dose is still unknown (19). Droperidol is clearly efficacious when given concomitantly with a PCA device with morphine (18). A large variety of different doses of droperidol has been tested in the original PCA trials; the optimal dose, however, is still unknown.

Most of the older antiemetics are poorly documented, (for instance, H₁-antihistamines (diphenydramine, promethazine) or dopamine antagonists (prochlorperazine, chlorpromazine, haloperidol); they have not been discussed here since the necessary randomised trials are lacking. Some of these drugs are used in daily clinical practice. The apparently increased risk of severe adverse effects with older antiemetics has been a popular argument to promote the
use of newer antiemetics such as 5-HT3 receptor antagonists. For droperidol, however, which is clearly antiemetic in commonly used doses, the adverse effect profile does not seem to be a particular problem (15). It may, therefore, be worthwhile to study the relative efficacy and the potential for harm of “old” antiemetics in large trials, and to establish dose-responsive-ness for each of these drugs, both for prevention and treatment of PONV.

Combinations of antiemetics should be studied ("balanced antiemesis"). For the combinations “5-HT3 receptor antagonist plus dexamethasone” and “5-HT3 receptor antagonist plus droperidol”, there is either a biological basis or evidence from systematic review for an additive or even a synergistic antiemetic effect. Minimal effective doses of these combinations need to be established. The combination therapy should be both more efficacious and less toxic compared with the mono-therapy. The efficacy of the combination of several interventions (for instance, a 5-HT3 receptor antagonist plus dexamethasone plus droperidol) is unknown.

There is a striking lack of evidence of the therapeutic efficacy of almost all antiemetic drugs in the surgical setting (with the exception of ondansetron (11)). This may have to do with the fact that therapeutic trials are logistically more difficult to perform than prophylaxis trials. Dose–response relationships for the therapy of established PONV with classic antiemetic drugs (for instance metoclopramide, or droperidol) need to be ascertained. The same applies to the efficacy of drug combinations ("balanced antiemesis") in the treatment of established PONV.

Efficacy and harm of antiemetics are generally poorly documented in children compared with adults. There are almost no data on treatment of established PONV in children. These data are needed.

**What trials should not be done?**

Direct comparisons (A vs B) without an additional placebo group should not be designed (29).

Metoclopramide in the usual doses is not antiemetic (19); it should, therefore, not be used as an “active” comparator for direct comparisons with other antiemetics. Those comparisons will overestimate the efficacy of the tested antiemetic drugs. This does not mean that metoclopramide should not be tested in further trials. Those trials, however, should be designed to establish dose-responsiveness and optimal dose of metoclopramide. Metoclopramide acts on both dopamine and 5-HT3 receptors. Its combination with droperidol or with a setron does not, therefore, make sense.

Yet another comparison of antiemetic A with antiemetic B or a placebo in yet another subgroup of patients undergoing yet another type of surgery with yet another anaesthetic is unlikely to further our understanding on the efficacy of these drugs. Undoubtedly, there are different underlying risks of PONV related to different clinical settings. A trial performed in paediatric strabismus surgery or major gynaecological surgery is likely to show a high control (placebo) event rate. There is, however, no evidence (and no biological basis either) of a selective efficacy of an antiemetic for any specific type of surgery, patient or anaesthesia. Thus, we may assume that if an antiemetic works in one setting with a reasonable baseline risk (and, thus, with a relevant control event rate) it will also work in any other clinical setting with a similar baseline risk rate.

**Conclusions**

All good systematic reviews tell us what we know and, by implication, what we do not know. Systematic reviews of valid randomised controlled trials should be used to establish recommendations for treatment and prevention of PONV symptoms. Cost-effectiveness and benefit–risk ratios suggest strongly that the “wait and see” strategy should be applied to the majority of patients. Systematic reviews may identify interventions which lack worthwhile efficacy; these should not be used. Systematic reviews are valuable tools to define a research agenda for future studies. In the PONV setting, further research is needed to identify more efficacious prophylactic and therapeutic regimens, minimal effective doses of antiemetic drugs, optimal combination strategies (“balanced antiemesis”), and patients who are most likely to profit from an intervention and least likely to suffer from adverse drug reactions.

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