Review article

Anesthesia and the gastrointestinal tract

Alexander Ng and Graham Smith

University Department of Anaesthesia, Critical Care and Pain Management, Leicester Royal Infirmary, Leicester LE1 5WW,
United Kingdom

Introduction

In this article, we have briefly reviewed areas relating to the gastrointestinal (GI) tract of interest to the anesthesiologist; they include gastroesophageal reflux and aspiration of gastric contents, postoperative nausea and vomiting (PONV), gastrointestinal ileus, and intestinal anastomotic leakages. These areas represent major causes of morbidity and delay in recovery from anesthesia and surgery. In addition, we have briefly described the use of the GI tract for the purpose of drug administration in the perioperative period.

The subjects of regurgitation and aspiration have recently been reviewed by us in some detail [1]: so these areas are summarized only briefly.

Gastroesophageal reflux and aspiration of gastric contents

Incidence of aspiration and mortality attributable to aspiration

The incidence of aspiration has remained relatively low over the past three decades. Data from several studies have shown that the incidence varies between 0.7 and 10.2 per 10 000 general anesthetics [2–8]. Over this same period, mortality attributable to aspiration during general anesthesia varied between 3.8% [9], 4.5% [3], and 4.6% [2].

In obstetric practice, however, mortality attributable to aspiration has declined over time. The triennial re-

ports of the Confidential Enquiry into Maternal Deaths in the United Kingdom have demonstrated that mortality attributable to aspiration has decreased from 52% to 65% 50 years ago, to 0% to 12% in the last 10 years [10]. Over the same period, there has been an increase in the total number of anesthetics administered, as a result of increasing instrumental rates and deliveries by cesarean section [10]. Therefore, the reduction in the proportion of anesthetic deaths is likely to be have been related not only to general improvements in anesthetic training and skills over time, but, more importantly, to the progressive move away from general anesthesia to epidural and spinal anesthesia.

Anesthetic management of gastroesophageal reflux and aspiration of gastric contents

Anesthetic management of gastroesophageal reflux and aspiration of gastric contents requires the consideration of factors that predispose to aspiration pneumonitis and also methods to minimize regurgitation and aspiration (Table 1).

Factors that predispose to aspiration pneumonitis

Gastric contents. Gastric contents that are considered to increase the risk of aspiration pneumonitis are a pH less than 2.5 and gastric volume of $0.4\,ml\cdot kg^{-1}$ and a composition comprising milk. While there is controversy over the minimum critical gastric volume [11–13] above which the risk of aspiration pneumonitis is increased, there is concordance from animal studies that a very low pH (less than 1) [14], and breast milk or a dairy formula [15], predispose to an increased severity of aspiration pneumonitis compared with less acidic contents or a soya-based milk [16].

Lower esophageal sphincter (LES) tone. Reduction in tone of the lower esophageal sphincter is an important physiological mechanism for reflux of gastric contents.

Table 1. Management of gastroesophageal reflux and aspiration of gastric contents [1]

Factors predisposing to aspiration pneumonitis	Methods to minimize regurgitation and aspiration

Gastric contents
  pH < 2.5
  Volume >0.4 ml·kg^{-1}
  Human breast milk
  Dairy milk
	Control of gastric contents
	  Preoperative starvation
	  Nasogastric tube
	  Prokinetics
	  Reducing gastric acidity: H$_2$ antagonists, PPIs

LES and UES
  Reduced sphincter tone in the lower and upper esophagus
    during anesthesia
	Nasogastric tube with an occluding balloon
	Application of cricoid pressure
	  Correct timing, magnitude and direction

Protective airway reflexes impaired in the perioperative period:
  Apnea with laryngospasm
  Coughing
  Expiration
  Spasmodic panting
	Careful airway management. Devices to be considered are:
	  Tracheal tube
	  Laryngeal mask airway (LMA)
	  Intubating laryngeal mask airway (ILMA)
	  Esophageal-tracheal combitube (ETC)

PPIs, Proton pump inhibitors; LES, lower esophageal sphincter; UES, upper esophageal sphincter

The factor which inhibits regurgitation is the barrier pressure, i.e., the difference between gastric pressure and LES pressure. During anesthesia, it has been shown that LES pressure and also barrier are decreased by induction agents (thiopental), inhalation agents (halothane and enflurane), opioids, and anticholinergic drugs (glycopyrrolate, atropine) [1].

Upper esophageal sphincter (UES) tone. UES tone is also reduced by induction agents (thiopental) [17], sedative agents [17], and muscle relaxants (succinylcholine [18], atracurium, pancuronium, and vecuronium [19–22]).

However, the risk of aspiration depends not only on UES tone but also on coordination between the pharyngeal muscles and the UES during swallowing. It has been possible to study the deleterious effect of partial neuromuscular blockade on aspiration using video manometry. These studies have been conducted in healthy volunteers, and the extent of neuromuscular blockade adjusted according to the train-of-four (TOF) pattern of adductor pollicis during supramaximal stimulation of the ulnar nerve. Significant delay in relaxation of the UES following contraction of the inferior constrictor muscle begins to occur at a TOF of 0.7 with atracurium [21] and 0.60 with vecuronium [20]. In 28%, 17%, 20%, and 13% of volunteers receiving atracurium, pharyngeal muscle dysfunction occurred at a TOF of 0.60, 0.70, 0.80 and ≥0.90, respectively. Of these swallows with pharyngeal dysfunction, 80% were misdirected, with contrast medium reaching the level of the vocal cords [21]. Although pharyngeal muscle dysfunction was demonstrated in patients given atracurium but not vecuronium, misdirected swallows still occurred in 6 of 14 volunteers at various levels of blockade with vecuronium [20]. These studies suggest that, even with clinically adequate neuromuscular transmission, con-

scious patients in the recovery room may still be at risk of aspiration.

Protective airway reflexes. Airway reflexes are impaired by premedication with diazepam [23], by advancing age [24], and by incremental doses of fentanyl [25], in addition to progressively increasing depth of anesthesia. Loss of these reflexes during anesthesia increases the risk of aspiration pneumonitis.

Methods to minimize regurgitation and aspiration
Methods to minimize regurgitation and aspiration involve control of gastric contents, application of cricoid pressure, and control of the airway.

Control of gastric contents and application of cricoid pressure. Preoperative starvation is a universal method for controlling gastric contents. Studies on gastric emptying demonstrate that clear fluids, breast milk, nonhuman milk, and solids are emptied at correspondingly slower rates. From these studies involving paracetamol absorption [26–32], electrical impedance tomography [33–35], radiolabelled diet [32,34,36–39] ultrasonography [40–43], aspiration of gastric contents under direct vision with a gastroscope, polyethylene glycol dilution and blind aspiration of gastric contents, it is generally held that the preoperative starvation time should be 2 h for clear fluids, 4 h for breast milk, and 6 h for nonhuman milk and solids [44].

Gastric emptying has been shown to be inhibited by atropine [45] and opioids [46], but facilitated by erythromycin [47], cisapride [48], and metoclopramide [49]. The presence of a nasogastric tube may impair UES and LES tone [50], leading to gastroesophageal reflux [51]. However, there is evidence from two cadaver studies that the efficacy of cricoid pressure is not

diminished by the presence of a nasogastric tube [52–53].

Evidence from clinical trials clearly shows that H_2 antagonists and proton pump inhibitors (PPIs) are two drug groups that may significantly lower gastric acidity [54–56] and, hence, reduce the risk of aspiration pneumonitis. However, there is no available evidence to support their routine use, probably because of the low incidence of aspiration and multiplicity of factors that are linked to this complication.

To minimize the passage of gastric contents through the esophagus, use of a nasogastric tube with an inflatable balloon to occlude the gastric cardia has been effective in a study involving pigs [57]. Application of cricoid pressure, however, is more usual in anesthetic practice, despite the lack of good evidence to demonstrate that it has reduced the incidence of aspiration or mortality. Recent studies have criticized cricoid pressure because of its effect in lowering LES tone [58], possible cricoid occlusion and vocal cord closure at a pressure of 44 N [59], occurrence of retching if applied too early [60], incorrect direction of application causing impaired laryngoscopy [61], variability in perceived force of application [62], and unsustainable force of application over time [63].

Control of the airway. During general anesthesia, an unobstructed airway is of paramount importance; this issue was highlighted by the Australian Incident Monitoring Study [9], in which the difficult airway was considered to predispose to regurgitation, vomiting, and aspiration.

Although tracheal intubation is considered to be the standard method for airway protection during general anesthesia, recent studies have challenged this view. The main issues are: firstly, whether tracheal intubation is effective; and secondly, whether aspiration is a problem if tracheal intubation is avoided. Clinical trials in the intensive care setting [64,65] have clearly demonstrated that high-volume, low-pressure cuffs do not prevent passage of methylene blue between the longitudinal folds. In addition, a case series of patients anesthetized without tracheal intubation in the peripartum period did not show an increased incidence of aspiration [7]. There was one case of mild aspiration among 1870 patients anesthetized for obstetric procedures, except for cesarean sections.

The standard laryngeal mask airway (LMA) has been evaluated extensively in clinical trials. It appears to reduce barrier pressure [66] and, while promoting gastroesophageal reflux of acid to the lower esophageal level, seems to spare the upper esophageal level [67–69]. The ProSeal LMA (PLMA) is a recent modification of the standard LMA [70]. It has an esophageal vent that allows the passage of a nasogastric tube. Although this device allows the stomach to be emptied, it remains to be seen whether it will play an important role in minimizing the risk of aspiration pneumonitis.

The esophageal-tracheal combitube (ETC) is a double-lumen tube with a high-volume, low-pressure tracheoesophageal distal cuff and a proximal pharyngeal balloon. The ETC may protect against the risk of aspiration and has been given a role in the American Society of Anesthiologists (ASA) practice guidelines for the management of the difficult airway [71]. Complications of its use, such as esphageal lacerations, subcutaneous emphysema [72], sore throat, hematoma, and dysphagia, appear to have been related to blind insertions rather than insertions under direct vision [73,74].

Postoperative nausea and vomiting (PONV)

Clinical trials

Evidence on the outcome of different treatments for PONV has been collated in quantitative systematic reviews (meta-analysis) of many double-blind randomized controlled trials (RCTs). Although these systematic reviews represent Level One Evidence, some assessment of the treatment effects of the individual trials must be made before a decision is made on whether the pooled results are valid. Overall, the applications of quantitative systematic reviews, as well as their limitations, have been discussed extensively in a recent article by Choi and Jadad [75].

Trials that have had event rates of 20% to 60% for early PONV (0 to 6 h) and 40% to 80% for late PONV (0 to 48 h) have been included in some systematic reviews, excluding studies with extreme values that were not deemed to reflect the overall clinical situation. Treatment effect in many of these reviews has been quantified in terms of relative benefit, relative risk, or odds ratio and also as absolute risk reduction. The relative benefit, relative risk, or odds ratio allows a relative comparison of the outcome of one treatment over another, but does not take into account the magnitude of the problem. However, the absolute risk reduction does take into account the importance of the treatment effect, providing the clinician with more information from which to decide whether the treatment is worth administering. The reciprocal of the absolute risk reduction gives the term "number needed to treat" (NNT). The NNT is the number of patients who have to be treated to obtain one additional favorable outcome [76]. More efficacious treatments have a low NNT, while less useful treatments have a high NNT. All treatments have adverse effects, and in a similar way to the above consideration of benefits, "number needed to harm" (NNH) can be obtained from the reciprocal of absolute risk increase.

Factors that influence the occurrence of PONV

PONV is more common in females and in patients with a previous history of PONV or motion sickness. It appears to be associated with strabismus surgery, adenotonsillectomy, orchidopexy, and prolonged surgery. Other factors predisposing to its occurrence are the use of etomidate, opioids, and pancuronium, and the use of atropine and neostigmine [77]. Propofol, on the other hand, has the opposite effect, and in a systematic review of 84 RCTs involving 6069 patients, its effect on early and late PONV was assessed [78]. When used for maintenance instead of inhalation agents, propofol had an NNT (95% confidence interval [CI]) of 4.9 (3.7 to 7.1), and 7.1 (3.4 to ∞) for early and late PONV, respectively, suggesting that any antiemetic advantage is short lived. Propofol used solely for induction did not confer an advantage over other intravenous agents. In a reassessment [79] of a systematic review of RCTs in which use of nitrous oxide was assessed [80], it was shown that omission of nitrous oxide had beneficial effects on early (NNT 4.8 (3.6 to 7.3)) and late vomiting (NNT 5.6 (3.9 to 10)), but not early (NNT 9.1 (4.1 to ∞)) or late nausea (NNT ∞ (80)).

Methods to prevent and treat PONV

A management plan for the prevention of PONV has been summarized in Table 2. Techniques to minimize PONV may be classified into two categories, pharmacological agents and nonpharmacological methods. Studies on readily available pharmacological agents have compared the use of single agents versus placebo; combination of agents versus single agents; and administration of an antiemetic with an opioid via a patient-controlled analgesic device. In addition, data have been available concerning the possible antiemetic effect of 80% inspired oxygen compared with 30% [81]. In this RCT, oxygen was given intraoperatively and for the first 2 h postoperative in patients undergoing colorectal surgery, and it has been found that the higher oxygen concentration had an antiemetic effect.

Neurokinin (NK)-1 receptor antagonists

NK-1 antagonists are thought to act by blocking the effect of substance P on NK-1 receptors [82]. For the prevention of PONV, evidence from a double-blind RCT of females listed for abdominal hysterectomy demonstrated that 100 mg or 200 mg of oral CP122721, administered 60 to 90 min preoperatively, was more effective than placebo for prevention of PONV within 8 h and 72 h into the postoperative period [83]. Within the first 8 h, the higher dose of this NK-1 antagonist was more effective than the lower dose (the incidences of PONV being 10% and 33%, respectively). This benefit was not demonstrable within 72 h. It is possible that further clinical studies may reveal a role for NK-1 antagonists in patients at high risk of PONV.

5HT$_3$ antagonists

Although several 5HT$_3$ antagonists have been evaluated, ondansetron has been studied most extensively. The efficacy of ondansetron has been assessed for both

Table 2. Management of PONV

Plan	Example
Identify the patient at risk	Female sex
	Nonsmoker
	Positive history of PONV
	Positive history of motion sickness
	Duration of anesthesia >60 min
Use an antiemetic anesthetic technique	Use propofol
	Minimize use of emetogenic agents e.g., opioids, etomidate
Consider specific antiemetic treatments	Individual pharmacological agents
	NK1 antagonists
	5HT$_3$ antagonists
	Dexamethasone
	Droperidol
	Cyclizine
	Combination agents
	5HT$_3$ antagonists with cyclizine
	5HT$_3$ antagonist with dexamethasone
	5HT$_3$ antagonist with NK1 antagonist
	Physical therapy
	Acupuncture

PONV, Postoperative nausea and vomiting; NK1, Neurokinin

the prophylaxis and treatment of PONV. In a meta-analysis of 53 placebo-controlled RCTs involving 7177 patients, 24 different ondansetron regimens were evaluated [84] for the prevention of PONV. Although a broad range of NNTs were obtained, ondansetron showed treatment benefit (NNT 5 to 6) at 8 mg i.v. and 16 mg orally, for prevention of early and late PONV. In addition, there was a significant increased risk of elevated liver enzymes (NNH of 31) and headache (NNH of 36).

The issue of whether ondansetron is effective in preventing PONV in high-risk patients has been addressed. In a meta-analysis of RCTs, ondansetron 4 mg and 8 mg i.v. showed increased effectiveness for prevention of PONV in patients with motion sickness compared with patients without this history [85]. The pooled odds ratios (95% CI) were 2.07 (1.69–2.52) and 2.19 (1.5–3.19) for the two respective doses. In another meta-analysis comparing patients with and without a previous history of PONV, there was no significant difference in the effectiveness of ondansetron for vomiting within the first 24 h postoperatively, at 4 mg i.v. [86]. There was a trend to effectiveness at 8 mg i.v., but this effect was not statistically significant.

Ondansetron has been compared against other individual antiemetic drugs in addition to placebo. In a meta-analysis [87] of 23 RCTs with 3863 patients comparing ondansetron with droperidol, and 19 RCTs of 2502 patients comparing ondansetron with metoclopramide, the pooled odds ratio (95% CI) for prevention of vomiting were 0.70 (0.52 to 0.94) and 0.43 (0.31 to 0.61), respectively. The corresponding odds ratios (95% CI) for prevention of nausea were 0.99 (0.66 to 1.47) and 0.70 (0.45 to 1.10), demonstrating that ondansetron was significantly more effective than either droperidol or metoclopramide in preventing vomiting, but not nausea. Doses of all drugs varied: ondansetron 4 to 8 mg, and $0.10\,\mathrm{mg\cdot kg^{-1}}$ to $0.15\,\mathrm{mg\cdot kg^{-1}}$; droperidol 0.625 mg to 2.5 mg, and $20\,\mu\mathrm{g\cdot kg^{-1}}$ to $75\,\mu\mathrm{g\cdot kg^{-1}}$; metoclopramide 10 mg, and $0.25\,\mathrm{mg\cdot kg^{-1}}$ to $0.5\,\mathrm{mg\cdot kg^{-1}}$. This mixed effectiveness of ondansetron over droperidol contrasts with another quantitative systematic review, in which data in adults from 20 RCTs showed that the odds ratio (95% CI) was 0.56 (0.41 to 0.76) and NNT (95% CI) was 12 (7.32) in favor of ondansetron over droperidol. Data on doses used were not available for assessment [88].

The role of ondansetron lies not only in the prevention of PONV but also in the treatment of established PONV. In a quantitative systematic review [89] of seven RCTs, it was shown that intravenous ondansetron was effective compared with placebo for the treatment of established early and late PONV. For the treatment of early PONV, the NNT values (95% CI) were 3.8 (2.6 to 6.6), 3.2 (2.3 to 5.2), and 3.1 (2.4 to 4.5) with 1, 4, and 8 mg of ondansetron, respectively. The respective NNT values at the corresponding doses for the treatment of established late PONV were 4.8 (3.5 to 7.9), 3.9 (3.0 to 5.7), and 4.1 (3.1 to 6.2). Thus, at doses used clinically there is no additional benefit in using higher doses of ondansetron for the treatment of established PONV. These results contrast with the situation in which ondansetron was used for the prophylaxis of PONV, when increased effectiveness was demonstrated at higher doses.

Dexamethasone

Dexamethasone, in doses of 8 mg to 10 mg, and 1 to $1.5\,\mathrm{mg\cdot kg^{-1}}$, has been evaluated in a quantitative systematic review [90]. Results from 15 placebo-controlled trials show that dexamethasone was effective for the prevention of early and late PONV. The NNT values (95% CI) for the prevention of early and late vomiting were 7.1 (4.5 to 18) and 3.8 (2.9 to 5.0), respectively, in data from children and adults. Data for nausea were available in adults but not children. The NNT values for early and late nausea were 5.0 (−21 to 2.2) and 4.3 (2.3 to 26). Analysis of other trials in this review showed that antiemetics, such as ondansetron 4 mg i.v., granisetron 3 mg i.v., and perphenazine $70\,\mu\mathrm{g\cdot kg^{-1}}$ were more effective than dexamethasone for the prevention of PONV.

Other issues with dexamethasone concern the dose and timing of administration. In a double-blind placebo-controlled RCT of females undergoing thyroidectomy it was found that the minimum effective dose for the prevention of PONV was dexamethasone 5 mg i.v., given at induction of anesthesia [91]. Furthermore, in an RCT of 120 females undergoing hysterectomy, 10 mg of dexamethasone, given after induction anesthesia, significantly reduced the incidence of PONV within the first 2 h postoperatively, compared with administration at the end of the procedure, and rescue antiemetic consumption was significantly reduced [92].

Droperidol

Droperidol is a butyrophenone that may cause dose-dependent sedation and drowsiness. Therefore, the main issue with its use concerns the minimum dose required to prevent PONV. In a systematic review [93], it was shown that 0.5 mg to 0.75 mg of droperidol was sufficient to prevent early nausea and that at least 1 mg to 1.25 mg was required for late nausea, in adults. For early vomiting, at least 1 mg to 1.25 mg i.v. of droperidol was required, compared with a lower dose of 0.5 mg to 0.75 mg i.v. for late vomiting, in adults. In children, there was a dose-dependent effect for early and late vomiting, and the relative risk was clearly in favor of droperidol compared with placebo, at doses of $50\,\mu\mathrm{g\cdot kg^{-1}}$ to $75\,\mu\mathrm{g\cdot kg^{-1}}$ compared with $10\,\mu\mathrm{g\cdot kg^{-1}}$ to $20\,\mu\mathrm{g\cdot kg^{-1}}$.

Metoclopramide

Metoclopramide is an antagonist at central dopaminergic receptors, central and peripheral $5HT_3$ receptors, and peripheral $5HT_4$ receptors. In a systematic review of 66 randomized placebo-controlled trials involving 6266 patients, no antiemetic effect was detected within 6h postoperatively and at 48h [94]. In adults, doses varied from 5mg to 35mg via i.v., i.m., oral and intranasal routes. In children, the doses were $0.1 mg \cdot kg^{-1}$ to $0.5 mg \cdot kg^{-1}$, given i.v. in all but one trial. Adverse reactions, such as extrapyramidal symptoms, sedation, drowsiness, dizziness, vertigo, and headache were uncommon, even at higher doses of metoclopramide.

Combination antiemetic therapy

Combination antiemetic therapy or "balanced antiemesis" [95] is another technique that some investigators have been studying for the prevention of PONV. Combinations of a $5HT_3$ receptor antagonist (ondansetron 4mg; granisetron 3mg, or $20 \mu g \cdot kg^{-1}$ to $40 \mu g \cdot kg^{-1}$) with either dexamethasone 8mg [90] or cyclizine 50mg i.v. [96] have been shown to exhibit increased effectiveness compared with the individual $5HT_3$ antagonist. Pueyo et al. [97] compared a combination of intravenous ondansetron 4mg and droperidol 3.75mg with ondansetron 4mg, and found increased effectiveness, although Bugedo et al. [98] found no advantages in a combination of ondansetron 4mg and droperidol 2.5mg compared with ondansetron 4mg. In a meta-analysis of RCTs, combinations of droperidol and a 5HT3 antagonist did not have any significant advantages compared with individual agents [99].

Combination antiemetic therapy for PONV involving the administration of 200mg of the oral NK-1 antagonist, CP1222721, and 4mg i.v. of ondansetron has been compared with the individual drugs in a double-blind RCT [83]. There was a significant improvement in the median emesis-free time for 75% of patients in the combination group compared with the findings in the patients receiving CP1222721 or ondansetron separately. While there was no significant difference in nausea scores between the three groups within 8 and 24h. The incidence of emesis within 24h was significantly less with the combination compared with ondansetron but not with CP1222721. Another NK-1 antagonist has been assessed recently in patients receiving chemotherapy. The addition of the NK-1 antagonist, L754030, 300 to 400mg, to granisetron $10 \mu g \cdot kg^{-1}$ i.v. and dexamethasone 20mg orally was found to produce significant antiemetic benefits [100].

In summary, it appears that combination therapy involving the addition of some agents, such as dexamethasone, cyclizine, or an NK1 antagonist, to a $5HT_3$ antagonist provides additional prophylaxis against PONV compared with the individual $5HT_3$ antagonist.

Prophylactic antiemetics during PCA opioids

The effectiveness of administering an antiemetic to an opioid via a PCA device has been assessed in a quantitative systematic review of 14 eligible RCTs of 1117 patients [101]. Morphine was used in all but one RCT. Of the various antiemetic agents, such as hyoscine, propofol, metoclopramide, clonidine, promethazine, droperidol, ondansetron, and tropisetron, the most frequently used were the latter three drugs. Although droperidol, with an NNT (95% CI) of 2.8 (2.1 to 3.9), was effective for the prevention of PONV, no dose-response effect could be identified. Ondansetron and tropisetron were administered in various doses, and both drugs were found to be effective for the prevention of PONV. Their respective NNTs (95% CI) were 2.9 (2.1 to 4.7) and 4.7 (3.0 to 11).

Acupuncture

The effect of the stimulation of the P6 acupuncture point on PONV was assessed in a meta-analysis of 19 RCTs involving 1679 patients undergoing tonsillectomy, laparoscopy, cesarean section, and gynecological and general surgery [102]. The acupuncture varied in terms of the type used, and its method, timing, and duration of administration. Manual acupuncture, electroacupuncture, transcutaneous electrical stimulation, and acupressure to P6 were given preoperatively, intraoperatively, and postoperatively, depending on the trial. In addition, the duration of treatment varied from 5min to 7 days. It was found that this nonpharmacological technique had significant benefit compared with no treatment or sham treatment in adults for preventing nausea and vomiting, within 6h. For early nausea, therefore, the relative risk (RR) (95% CI) was 0.34 (0.20 to 0.58) with an NNT (95% CI) of 4 (3 to 6). For early vomiting, the RR was 0.47 (0.34–0.64) and the NNT was 5 (4–8). There was no treatment benefit for late vomiting (0–48h) in adults, or for early and late vomiting in children. In seven trials within this meta-analysis, stimulation of P6 and antiemetics (metoclopramide, cyclizine, droperidol) were compared, and it was found that there was no significant difference between these techniques in the prevention of early and late vomiting in adults.

Scoring systems

In making a decision on whether to provide therapy to prevent the occurrence of PONV, assessment of factors that predict its occurrence is required. An ideal scoring system would be highly discriminative for all types of patients undergoing all forms of surgery, in any hospital,

and be easy to apply. Some scoring systems have identified predictive factors by logistic regression analysis, and, to use such forms of evaluation, the physician must take into account the different weighting of each factor [103]. However, a simplified scoring, based on four risk factors of equal weighting, has been evaluated in orthopedic, ophthalmic, otolaryngological, and general surgical patients. These factors comprised: female sex, history of motion sickness or PONV, nonsmoking, and use of intraoperative opioids. The ability of this scoring system to discriminate between patients who would and would not have PONV has been quantified by the area under the receiver operator curve, a plot of the true-positive rate against the false-positive rate. For a variety of operations, it was found that, in the presence of none, one, two, three, and four risk factors, the incidence of PONV was 10%, 21%, 39%, 61%, and 79% respectively [104]. In making a decision on whether to administer medication for the prevention of PONV, the use of such a simple scoring system would be helpful to the anesthesiologist.

Postoperative gastrointestinal motility

Ileus is a common problem occurring after major surgery and is caused by lack of motility of the left side of the colon. Its occurrence can delay the absorption of enteral nutrition and drugs, in addition to causing abdominal distension, patient discomfort, and prolonged hospital stay. Factors that have been shown to inhibit gastrointestinal motility include sympathetic reflexes and also μ receptor agonists, nitric oxide, substance P, vasoactive intestinal peptide, calcitonin gene-related peptide, and corticotrophin-releasing factor [105]. There is experimental evidence in rats that κ opioid receptor agonists reverse the inhibition of gastrointestinal transit, in a dose-dependent fashion [106]. However, the administration of metoclopramide, cisapride, [107] and erythromycin [108] has not been found to be effective for the treatment of postoperative ileus.

Inhalation agents [77] and opioids [109] used in the intraoperative period for abdominal surgery cause a reduction in gastrointestinal motility. In addition, the type of analgesia employed in the postoperative period is a critical factor that affects the return of normal gastrointestinal motility. In current anesthetic practice, the main options available for providing postoperative analgesia for major abdominal surgery are systemic opioids and epidural analgesia. In a review of 16 studies, of which 10 were RCTs, it has been clearly demonstrated that return of gastrointestinal motility occurred earlier in patients who had epidural analgesia compared with findings in those who had systemic opioids [110]. In these studies, a variety of end points were used, such as time to first bowel sounds, time to first passing of flatus or feces, transit time of radio-opaque markers, and barium transit time. In addition, in three RCTs, it was found that return of gastrointestinal motility was delayed in patients receiving thoracic epidural morphine compared with findings in those receiving thoracic epidural bupivacaine for postoperative analgesia [110]. It is believed that the effectiveness of thoracic epidurals occurs because of blockade of inhibitory thoracolumbar sympathetic efferents, allowing unopposed parasympathetic activity via craniosacral efferents. In addition, there is blockade of nociceptive afferent neural impulses, decreased levels of endogenous circulating catecholamines, and a reduction in the administration of opioids. Despite some lack of evidence for efficacy in postoperative ileus [111], it is currently believed that epidural analgesia should be used as part of a multimodal care pathway of early nutrition, early mobilization [112], and minimally invasive surgery that facilitates postoperative recovery and minimizes morbidity and duration of hospital stay [113]. In addition there is clinical evidence that postoperative ileus following colorectal resection may be minimized by laparoscopic techniques compared with conventional surgery [114].

Effect of postoperative analgesia on anastomotic leakage following colorectal surgery

The etiology of anastomotic leakage following colorectal surgery includes patient factors, such as anemia and comorbidity; surgical factors, such as bowel preparation and operative expertise; and factors related to anesthesia and pain management. For anesthesiologists, the key clinical question is whether there is a relationship between postoperative analgesia and the development of anastomotic leakage. In this section, issues concerning the administration of systemic morphine vs systemic pethidine, in addition to epidural analgesia vs systemic opioid analgesia are examined.

Systemic morphine vs systemic pethidine analgesia

There has been controversy on whether or not the type of opioid used for postoperative analgesia affects the incidence of anastomotic dehiscence. Early studies [115,116], in which morphine and pethidine were administered by the i.m. route on demand, suggested that the incidence of anastomotic dehiscence was more common in patients who received morphine compared with those who received pethidine. Intravenous or intramuscular morphine has been shown to double the frequency of colonic contractions [117] and to increase intraluminal pressure, especially in diverticular disease [118]. Pethidine, on the other hand, is associated with

decreased colonic intraluminal pressure [118], and so there seems to be some theoretical grounds supporting these clinical findings. However, in a recent trial in which equianalgesic doses of PCA morphine or PCA pethidine by the i.v. route were compared, it was found that there was no significant difference in the incidence of anastomotic breakdown [119]. This finding may be explained on the basis that, in the earlier studies, the use of i.m. morphine would have been associated with higher peak plasma concentrations of the drug than those occurring with the i.v. PCA method of administration, and, consequently, with this PCA method, there may be a reduced tendency to the formation of contraction rings.

Epidural analgesia vs systemic opioid analgesia

It has been speculated previously that epidural analgesia would be likely to increase the risk of anastomotic leakage following colorectal surgery, because of increased intestinal motility and intraluminal pressure, in addition to possible reduced anastomotic blood supply. This issue has been examined in a review of RCTs from 1966 to 2000, available on Medline [120]. In 11 RCTs of this review, epidural local anesthetic, with and without opioids, was compared with systemic opioids. Although the incidence of anastomotic leakage was 16/255 for epidurals compared with 9/252 for systemic opioids, there was no statistically significant difference. In addition, data from 3 RCTs of this review comparing pure epidural opioid with epidural local anesthetic with and without an opioid did not demonstrate a significantly increased risk of anastomotic leakage with the type of drugs administered.

Alternative routes of drug administration

Gastrointestinal dysfunction impairs reliable drug absorption via the oral route, and in the immediate postoperative period after major surgery, it is mandatory to avoid oral administration of opioids for postoperative pain relief until it is clear that bowel motility has returned to normal. Otherwise, multiple doses which are not absorbed may be dumped suddenly into the upper GI tract when motility returns, leading to acute toxicity [121]. The presence of intestinal obstruction, abdominal pain, and PONV are common situations in which other methods of drug administration become necessary. In many instances, intravenous access is the standard alternative route. However, in specific situations, such as minor procedures or situations in which intravenous access can prolong hospital stay, other routes of drug administration would be highly desirable. In anesthetic practice, the administration of analgesics and sedative agents by intranasal, oral mucosal, transdermal, and rectal routes has been evaluated.

Intranasal route

The nasal mucosa has a rich blood supply, allowing rapid absorption of some drugs. For example, under optimal conditions, the administration of midazolam via the nasal mucosa may lead to rapid and almost complete absorption. In a study of 14 adult patients with neither rhinitis nor nasal obstruction, time (SD) to peak arterial concentration of midazolam was 14 (2) min after the administration of midazolam $0.15\,\text{mg}\cdot\text{kg}^{-1}$ by nasal spray. Bioavailability (SD) was 83 (15) % with minimal hydroxymidazolam concentrations, indicating minimal first-pass metabolism from the swallowed drug [122]. However, despite these favorable pharmacokinetics, in a study of 44 children given intranasal midazolam $0.2\,\text{mg}\cdot\text{kg}^{-1}$, Griffith et al. [123] did not recommend this route for premedication because of the unpleasant taste, and the complaints of stinging and crying.

The irritant effects observed with midazolam do not seem to occur with intranasal opioids [124]. In a recent study of patients with cancer pain it was found that intranasal fentanyl 20 μg, administered by spray, was tolerable and provided additional analgesia within 10 min [125]. In healthy volunteers [126], intranasal fentanyl 54 μg produced a maximum concentration within 5 min and a bioavailability of 71%. Although the nose is not the standard route for the administration of analgesics, there are plans to introduce a patient-controlled intranasal device [127].

Intranasal oxycodone has also been investigated recently in volunteers. It was found that with alternate sprays of 0.1 ml to each nostril, to a maximum dose of $0.1\,\text{mg}\cdot\text{kg}^{-1}$, the values for mean time (95% CI) to peak concentration and bioavailability (95% CI) were 25(20–240) min and 0.46 (0.25–0.67), respectively. Although oxycodone was absorbed rapidly, there were large interindividual differences, suggesting that careful titration would be required to avoid adverse effects [128].

Oral mucosal route

Within the oral cavity, the sublingual and buccal mucosa are the main sites for drug absorption. Both sites are nonkeratinized, but the buccal mucosa is thicker, relatively immobile, and less permeable than the sublingual mucosa. The sublingual mucosa is relatively mobile and is constantly washed by saliva. Thus, the sublingual route would be appropriate for rapid but infrequent drug delivery, whereas the buccal route is better suited for sustained drug delivery [129].

Of the analgesic drugs administered via the buccal route, fentanyl has been studied in greatest detail. Oral

transmucosal fentanyl has been advocated as a useful non-invasive method of providing analgesia for children undergoing painful procedures. In a clinical trial of 48 children receiving a lollipop of fentanyl 15 to $20\,\mu g \cdot kg^{-1}$, Schechter et al. [130] found that pain scores were significantly less during bone marrow aspiration or lumbar puncture performed 30 min after the lollipop was given. In another trial, in which oral transmucosal fentanyl 10 to $15\,\mu g \cdot kg^{-1}$ was given to children aged 2 to 10 years, there was no evidence of improved cooperation at induction of anesthesia compared with the placebo group. Although patients receiving fentanyl were more sedated than those in the placebo group, there was no vomiting or desaturation in the preoperative period. From pharmacokinetic measurements, the bioavailability was 0.33 [131].

The effects of fentanyl administered via the oral transmucosal route have also been evaluated in healthy adult volunteers. With $800\,\mu g$ of fentanyl consumed over 15 min, the median time (95% CI) to maximum concentration was approximately 24 (20 to 71) min, and the bioavailability (SE) was estimated to be 40 (11)% [132]. In addition, after three doses, at 6-h intervals, there was no evidence of significant changes in pharmacokinetics, suggesting that alterations in drug prescribing are not required when multiple doses of transmucosal fentanyl are used [132]. Dose-proportional pharmacokinetics are observed with oral transmucosal fentanyl, i.e., with increases in dose administered, there are proportional increases in maximum concentration, area under the concentration time curve, and adverse effects, such as respiratory depression [133].

In addition to opioids, the oral mucosal administrations of antiemetics and sedatives has been studied. Buccal prochlorperazine, at a dose of 6 mg, was found to be effective in preventing PONV in patients receiving PCA morphine after abdominal hysterectomy [134]. In a study of buccal midazolam 10 mg in 2 ml for 5 min in adult volunteers, it was found that, although time (± 2 SD) to maximum venous concentration was 48 (28) min, electroencephalography (EEG) effects were evident within 5 min of administration [135]. In a placebo-controlled RCT [136] in children (aged 12 to 129 months) of sublingual midazolam in thick grape syrup, satisfactory sedation was evident in 52% and 64%, 15 min after $0.5\,mg \cdot kg^{-1}$ and $0.75\,mg \cdot kg^{-1}$, respectively.

Transdermal route

In anesthetic practice, the transdermal route has been utilized mainly for the management of chronic pain. This route is particularly helpful for patients with cancer pain or chronic pancreatitis [137], when nausea, vomiting, and dysphagia may preclude oral drug administra-tion. However, owing to its protective barrier functions, and variations in structure and perfusion, the skin does present an obstacle to rapid reliable drug administration. Of all analgesics, fentanyl has been evaluated extensively and may be used to illustrate the pharmacokinetics of the transdermal route.

Transdermal therapeutic systems (TTS) of fentanyl consist of fentanyl dissolved in an enhancer of ethanol and a rate-controlling membrane of ethylene-vinyl acetate. Ethanol extracts lipids in the stratum corneum [138] and, hence, helps to achieve the target drug delivery rate. Variations in skin permeation are minimized by the rate-controlling membrane [139]. The rate of administration is proportional to the surface area of drug exposed to skin, and current patches can deliver fentanyl at rates of 25, 50, 75, and $100\,\mu g \cdot h^{-1}$. The onset time for this route of administration is prolonged, and is reflected in the 17 to 48 h taken to reach maximum plasma concentration [140].

Age has no significant effect on the pharmacokinetics of TTS fentanyl. In a study of a transdermal patch delivering fentanyl at $50\,\mu g \cdot h^{-1}$, for 72 h, it was found that the time to maximum plasma concentrations, elimination half-life, and area under the time concentration curve did not differ significantly between elderly and young adults [141]. In children aged 18 to 60 months, time (SD) to reach maximum concentration was 18 (11) h with a patch designed to release fentanyl at $25\,\mu g \cdot h^{-1}$ for 72 h. As would be expected, maximal fentanyl concentrations were higher in younger children [142].

The use of fentanyl delivered via the TTS is associated with delayed analgesic action, and the TTS is therefore unsuitable for acute pain management. However, it has been possible to enhance transdermal administration by iontophoresis, in which the transport of an ionisable drug is facilitated by an external electric field [143]. A PCA electrotransport therapeutic system (ETS) for fentanyl has been developed, delivering 80 boluses of $40\,\mu g$. Each bolus is administered over 10 min. In a clinical trial of 174 patients, it was found that ETS fentanyl seemed to provide satisfactory analgesia for acute pain after orthopedic and gynecological surgery [144].

Although TTS fentanyl has not been recommended for acute pain, transdermal ketamine has been found recently to be an effective adjuvant after abdominal gynecological surgery, when given at a rate of 25 mg per 24 h, without associated hallucinations or nightmares [145].

Rectal route

Rectal drug administration is particularly useful when the oral route cannot be used. Recently, a new prepara-

tion of 30-mg morphine suppositories, given twice daily for 5 days in patients with cancer, was reported to provide analgesia equivalent to the same oral dose [146]. In comparison with results with the oral morphine, the rectal route was associated with a higher bioavailability of morphine and lower plasma concentrations of morphine-6-glucuronide and morphine-3-glucuronide, indicating reduced first-pass metabolism with rectal administration. Median time (range) to maximum plasma concentrations after the rectal administration of morphine was 4 (0–6) h.

The rectal route has been used extensively by anesthesiologists for the treatment of pain with simple analgesics. In one study, involving children aged 9 weeks to 11 years, $25\,mg\cdot kg^{-1}$ of paracetamol, given rectally at 6-h intervals for 5 days, was shown to be safe, with no evidence of supratherapeutic concentrations [147]. The mean time (SD) to reach maximum concentration in the first dosing interval was 2.37 (1.10) h. In adults, a higher single dose of rectal paracetamol, of $40\,\mu g\cdot kg^{-1}$, did not provide increased analgesia compared with the lower dose of $20\,\mu g\cdot kg^{-1}$, following vaginal or abdominal hysterectomy. Although the maximum plasma concentration of paracetamol was significantly greater with the higher dose of paracetamol, there was no significant difference in the time taken to reach this concentration. The mean times (SD) to reach maximum concentration were 4.2 (1.7) h and 3.6 (1.4) h for the higher and lower paracetamol doses, respectively [148].

Diclofenac suppositories are commonly used in acute and chronic pain management. In healthy male volunteers, it was found that 50 mg of rectal diclofenac exhibited a slightly increased bioavailability compared with that shown with the oral form. In addition, time to maximum plasma concentration for the rectal route was shorter, taking $0.62 \pm 0.06\,h$ compared with $1.58 \pm 0.06\,h$ for the oral route [149].

Conclusion

In the perioperative period, impairment of gastrointestinal function can occur, causing increased morbidity and delayed recovery. Current evidence for the optimal management of gastroesophageal reflux and aspiration of gastric contents, PONV, gastrointestinal ileus, and anastomotic leakage, as well as alternative routes of drug administration, have been discussed. Careful consideration of these factors and the application of appropriate treatments will go a long way to help our patients recover from surgery and anesthesia.

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