British Journal of Anaesthesia 1992; **69** (Suppl. 1): 40S–45S

ANAESTHETIC FACTORS CONTRIBUTING TO POSTOPERATIVE NAUSEA AND VOMITING

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This article reviews the anaesthetic contribution to postoperative nausea and vomiting (PONV). It does not discuss the physiology or mechanisms of causation of PONV, the patient and surgical factors contributing to, or the treatment of PONV, which are dealt with elsewhere in this supplement.

Review of the literature on anaesthetic factors contributing to PONV is rendered extremely difficult by lack of standardization of the definition of nausea and vomiting, and frequently by failure to standardize other factors which may contribute to this condition, including patient age, sex, type of operation, duration of anaesthesia, experience of the anaesthetist and postoperative management, including transport and mobilization of the patient. These problems are alluded to or dealt with in greater detail elsewhere in this supplement. The purpose of the present review is to describe briefly only those factors related to anaesthesia and for which there is reasonable evidence implicating them as causes of postoperative nausea and vomiting.

THE ANAESTHETIST

It has been known for many years that the experienced anaesthetist has fewer patients who suffer PONV than the inexperienced [5, 52]. Belville postulated that this may result partly from a tendency for the inexperienced anaesthetist to maintain deeper levels of anaesthesia [4]. More recently, it has been shown that manual ventilation of the lungs using a face mask before tracheal intubation was associated with more nausea and vomiting when it was performed by an inexperienced anaesthetist compared with an experienced one [31]; this effect persisted for up to 6 h after operation. The authors suggested that it may result from inadvertent distension of the stomach with anaesthetic gases. This mechanism would also provide an explanation for the excess PONV observed in obese patients, in whom ventilation of the lungs by face mask may be difficult [45, 61].

(Br. J. Anaesth. 1992; **69** (Suppl. 1): 40S–45S)

KEY WORDS

Anaesthetics, intravenous. Anaesthetics, volatile. Vomiting: nausea.

PREMEDICATION

Opioids

It is commonly observed that premedication with opioids results in an increased incidence of PONV. In 1960, Riding demonstrated that in women undergoing evacuation of retained products of conception, premedication with morphine 10 mg was associated with an incidence of PONV of 66.7% compared with 22.4% in controls. Atropine had significant antiemetic properties; a dose of 0.6 mg was associated with an incidence of PONV of 35.2% when given with morphine; when atropine was given without an opioid, the incidence was 11.5% [49].

Although attempts have been made in the past to compare the rates of PONV after different opioids, results from older studies should be treated with caution because of the less rigid methodology adopted at that time.

In 1957 Burtles and Peckett suggested that premedication with pethidine resulted in less PONV than that associated with morphine [8]. In contrast, Bellville, Bross and Howland [5] suggested the opposite. Furthermore, they demonstrated also that the extent of PONV was related to the dose of pethidine administered; the lowest incidence of emetic symptoms occurring with a dose of 1 mg kg^{-1} [5]. Dundee, Kirwan and Clarke demonstrated that a combination of morphine 10 mg with atropine 0.6 mg resulted in significantly more PONV in the 1–6-h period after operation than pethidine 50 mg with atropine 0.6 mg [19], which is perhaps not surprising in view of the fact that these doses were not equipotent. However, in a study comparing morphine 10 mg and atropine 0.6 mg with pethidine 100 mg and atropine 0.6 mg as premedication, before anaesthesia with propanadid for minor gynaecological surgery, Clarke and Dundee demonstrated that those receiving morphine had a greater degree of PONV in the first 6 h after operation [11]. They also found that morphine 10 mg resulted in the same incidence of PONV as diamorphine 5 mg, although increasing the dose to morphine 15 mg and diamorphine 7.5 mg resulted in a small increase in PONV in the diamorphine group [20]. As may be expected, in a subsequent study, the Belfast group

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also showed that the emetic effects of morphine and papaveretum were similar [39].

In paediatric practice, papaveretum has been shown consistently to be associated with high incidences of PONV [16, 51, 56]. Fentanyl is associated also with a high incidence of PONV in paediatric practice. In a recent study of the use of oral transmucosal fentanyl, the incidence of PONV was found to be 64% compared with 32% in children given placebo; when oral transmucosal fentanyl was administered with droperidol, the incidence was found to be 40% [24].

The use of opioids in a balanced anaesthetic technique as a substitute for volatile agents is associated with increased incidences of PONV. In a large multicentre study, Forrest and colleagues found that the use of fentanyl was associated with incidences of nausea and vomiting of 25.1% and 18.4%, respectively, compared with 18–19% and 11–13% for volatile anaesthetic agents [23].

The more recently introduced synthetic opioids are equally as culpable as the older agents in causing PONV. Large doses of sufentanil were found to be associated with increased PONV after outpatient gynaecological surgery [62], and alfentanil was found to be associated with a similar incidence of postoperative emesis as that induced by fentanyl [60].

Anticholinergic agents

The antiemetic properties of the old anticholinergic agents have been utilized traditionally as i.m. premedication. Clarke, Dundee and Love observed more than 25 years ago that hyoscine 0.4 mg was more effective than atropine 0.6 mg [12]. The antiemetic properties of the anticholinergic agent result from a central rather than a peripheral mode of action, as demonstrated by the fact that glycopyrronium, when used as an alternative to hyoscine, was associated with no antiemetic properties [43]; more recently, in a double-blind comparison of glycopyrronium and atropine in 100 patients, it was found that the former agent was associated with a two-fold higher incidence of PONV than that in the atropine group [53]. These results are consistent with the inability of the highly polarized glycopyrronium molecule to cross the blood–brain barrier.

Benzodiazepines

Although benzodiazepines are used in the management of chemotherapy-induced emesis, where it is thought they may possess antiemetic actions [1], there is no evidence to suggest that their use as premedication for anaesthesia is associated with antiemetic effects. Whilst Kamath and colleagues found that premedication with temazepam 10 mg or 20 mg was associated with a 22% incidence of PONV, compared with 36% in those who had received placebo, in a study of 182 women undergoing dilatation and curettage, variations in postoperative movement may have accounted for this difference [34]. In a large database of 3483 patients who had experienced nausea after general anaesthesia, Forrest, Beattie and Goldsmith found that the use of diazepam as premedication was not a risk factor [22], and similarly in children, Karlsson, Larsson and Nilsson observed no difference in the incidence of PONV between children premedicated with diazepam and those who received no premedication, although this was not a controlled study [35]. To date, there has been no well controlled prospective study which has examined the effect of benzodiazepine premedication on PONV.

ANAESTHETIC AGENTS

I.v. induction agents

It is well known that the i.v. induction agents are associated with differing degrees of PONV [10]. Thiopentone, used with nitrous oxide for minor gynaecological surgery, was found to be associated with a 12% incidence of PONV [55], whilst in a review in 1984, Clarke indicated that methohexitone, propanidid and etomidate were associated with significantly higher rates of PONV [10]. Although it is frequently assumed that ketamine causes postoperative emesis [59], there are no well controlled data to support this contention.

There is currently great interest in the lower incidences of PONV associated with propofol compared with thiopentone when used for i.v. induction of anaesthesia followed by inhalation agents [7, 18, 41]. The use of propofol by infusion for maintenance of anaesthesia was found, in a group at a high risk for PONV (children undergoing day-case strabismus surgery), to be associated with a lower incidence of PONV than in a group which received propofol for induction followed by maintenance of anaesthesia with inhalation agents [58].

Because of the low incidence of PONV associated with propofol anaesthesia, it has been postulated that this drug possesses antiemetic properties [41], but this has not been demonstrated conclusively [58].

Inhalation anaesthetic agents

Nitrous oxide. Cursory examination of the literature would suggest that the effect of nitrous oxide on the incidence of emesis is controversial. Unfortunately, many studies in this area are open to criticisms of inadequate size of populations, non-standardized populations, lack of standardization of definition of emesis, invalid statistical assumptions, etc. Nonetheless, it is generally believed that nitrous oxide is associated with PONV, the possible mechanisms including actions on central opioid receptors, gut distension and pressure on the middle ear [42, 45].

There have been several studies on the effect of nitrous oxide on PONV in patients undergoing gynaecological laparoscopy. In a prospective, randomized study of 87 women, Lonie and Harper [40] found an incidence of emesis of 49% when nitrous oxide was used, but only 17% when it was omitted. In a similar study in 80 patients, Sengupta and Plantevin [54] found an incidence of vomiting of 33% in the group which received nitrous oxide, but only 12.9% in the control group. Whilst there was no significant difference between the two groups, a power analysis had not been performed and it is

likely that the number of patients examined was too small to provide a statistically significant result. When a study of 185 women undergoing laparoscopic sterilization was performed, Felts, Poler and Spitznagel found that the overall incidence of nausea in the nitrous oxide–enflurane group was 29.2%, and 9.3% in a group receiving air–enflurane; there was a highly significant difference in these incidences [21]. However, Hovorka, Kortilla and Erkola found no difference between those receiving nitrous oxide or those receiving air in a study of 150 women undergoing gynaecological laparoscopy [29].

The role of nitrous oxide as an emetic stimulus during major surgery is more difficult to define. Nitrous oxide was not shown to be associated with excessive emesis in a group of 110 women undergoing elective abdominal hysterectomy [37]. Similarly, in a large randomized study of 780 patients undergoing various procedures, Muir and colleagues found no association between the use of nitrous oxide and subsequent PONV [44].

Ranta, Nuutinen and Laitinen studied the effect of nitrous oxide on PONV after upper abdominal surgery in 50 patients, and found no difference in the incidence of nausea [46]. They suggested that any beneficial effect provided by omission of nitrous oxide demonstrable in minor surgery may be masked by stronger factors provoking nausea after major surgery.

In support of this hypothesis is the recent demonstration in a study from our department that children undergoing myringotomy under nitrous oxide–oxygen–halothane anaesthesia had a significantly higher incidence of postoperative vomiting than a control group of children anaesthetized with oxygen–halothane [Wilson, personal communication].

Volatile anaesthetic agents

The old, long-established anaesthetic agents which are no longer in clinical use, such as ether and cyclopropane, were associated with a very high incidence of postoperative nausea and vomiting [27, 45]. It was suggested that vomiting was more frequent with those anaesthetic agents that increased circulating concentrations of catecholamines (e.g. ether, cyclopropane and trichlorethylene) [33]. Methoxyflurane was suggested as having lower emetic sequelae than halothane [26].

The volatile anaesthetic agents in current use, notably isoflurane, enflurane and halothane, are known to be associated with lower incidences of PONV than balanced anaesthesia using opioid agents. Whilst there may be differences in emetic sequelae caused by each of these three agents, such differences are small. Some of the older studies in relatively small numbers of patients suggested that there were differences between the three agents, for example Tracey, Holland and Unger compared halothane, enflurane and isoflurane in 75 women undergoing minor gynaecological surgery, and although there were no differences in the recovery room, 32% of patients who had received isoflurane had nausea on the first day after operation compared with 8% and 12% for halothane and enflurane, respectively [57]. In a study of 180 patients undergoing abdominal hysterectomy, Hovorka, Kortilla and Erkola [28] found that patients who had received isoflurane had less emetic sequelae (27%) in the first 2 h after operation than those who had received enflurane (45%). In contrast, in the large multicentre study of 17201 patients undertaken by Forrest and colleagues [23], retrospective analysis of data revealed a similar incidence of emetic symptoms for halothane, enflurane and isoflurane (nausea 18.3%, 18.5% and 19.1%; vomiting 12.6%, 11.9% and 11.5%, respectively). In both of these last cited studies, the substitution of fentanyl for any of the volatile agents used resulted in a considerable increase in PONV.

It was suggested in 1963 that halothane may possess antiemetic properties in subanaesthetic concentrations [25] but there are no recent data to confirm this suggestion; none of the data from studies in which anaesthetic concentrations have been used provide confirmatory evidence for this hypothesis.

Neuromuscular blocking agents

Neuromuscular blocking agents *per se* are not thought to have effects on PONV [45], although antagonism of residual neuromuscular block with a mixture of neostigmine and atropine does result in increased emesis, despite the antiemetic action of atropine. This suggests that neostigmine has significant emetic properties [36].

ANAESTHETIC TECHNIQUES

Spinal anaesthesia

It is generally assumed that spinal anaesthesia alone is associated with a lower incidence of PONV than general anaesthesia, as it avoids the emetic effects of opioids and volatile anaesthetic agents. We have been unable to find a prospective comparison between the incidence of PONV after spinal and general anaesthesia using the appropriate methods described by Korttila in this supplement. There is a quoted paper which purports to describe a difference between general, extradural and spinal anaesthesia [48], however those who quote this work frequently fail to indicate a significant difference in opioid administration, making interpretation difficult. The reported incidences of PONV after spinal anaesthesia suggest that the assumption is probably correct, provided that complications associated with spinal anaesthesia, such as hypotension and high block, are avoided.

The reported overall incidence of PONV after spinal anaesthesia in the older literature varies between 13% and 42% [3, 14, 47]. In a recent prospective study of 952 patients undergoing spinal anaesthesia, Carpenter and colleagues [9] reported nausea in 18% and vomiting in 7% of patients. They found that there was a greater incidence of nausea in patients who were given local anaesthesia with phenylephrine or adrenaline than in those given plain local anaesthetic (the risk increased 4.6 and 3.9 times, respectively). Use of procaine was associated with the highest incidence of PONV in comparison

with other local anaesthetic solutions. The following factors were found to be associated with postoperative nausea.

Height of the block. Patients in whom the block height was > T5 had a 3.9-fold increased incidence compared with those with lower blocks.

Resting heart rate. In patients in whom the resting heart rate before induction of local anaesthesia was > 60 beat min^{-1}, the incidence of nausea was increased 2.3-fold compared with those patients with resting heart rates of less than 60 beat min^{-1}. This may reflect preoperative anxiety which has been suggested as a patient factor influencing the incidence of PONV [38].

Hypotension. The incidence of nausea in patients who have developed hypotension was increased 1.7 times compared with those in whom hypotension did not occur.

Local anaesthetic used. The use of procaine and the addition of either phenylephrine or adrenaline were associated with an increased incidence of nausea.

This study confirmed an early observation by Crocker and Vandam who retrospectively analysed the records of spinal anaesthetics administered between 1956 and 1957 [14]. They found that operative emesis was associated with: pain appreciated during surgery; hypotension, as defined by either systolic arterial pressure < 80 mm Hg or a decrease of > 40 mm Hg; a block extending to or above the T4 dermatome; and the concomitant use of intrathecal adrenaline. However, Crocker and Vandam [14] ascribed this factor to the presence of a higher level of block or the type of block produced rather than adrenaline itself.

Both this study and that performed subsequently by Ratra, Badola and Bhargava [47] examined the incidence of intraoperative but not postoperative emesis. Ratra, Badola and Bhargava also found that intraoperative hypotension, as defined by systolic arterial pressure < 80 mm Hg, was associated with an increased incidence of vomiting and retching and that administration of 100% oxygen to patients during spinal anaesthesia ameliorated this problem.

As might be anticipated from the foregoing, it has been observed that prevention of hypotension during spinal anaesthesia by the administration of ephedrine is associated with a reduction in the incidence of intraoperative nausea and vomiting [15].

Regional anaesthesia

Avoidance of general anaesthesia or spinal anaesthesia reduces the incidence of intraoperative and postoperative emesis. In a prospective study of retching and vomiting (but not nausea), Dent, Ramachandra and Stephen found an incidence of emetic sequelae of 11.1% after spinal anaesthesia compared with 4.3% after peripheral regional anaesthesia [17]. Similarly, in a prospective study of both nausea and vomiting over 24 h after surgery, Bonica and colleagues observed an incidence of emesis in 21.1% of patients after spinal anaesthesia but only 8.8% after local block of limbs [6].

INTRAGASTRIC TUBES

There have been several investigations of the effect of passing orogastric and nasogastric tubes during operation on the incidence of PONV. However, the results are conflicting. In some older studies, Dent, Ramachandra and Stephen [17] found no benefit of stomach decompression by means of a gastric tube but her study groups were not matched. In contrast, Smessaert, Schehr and Artusio demonstrated a reduction in PONV after gastric decompression [55] whilst Burtles and Peckett showed a reduction in postoperative vomiting but no decrease in nausea when a nasogastric tube remained *in situ* in the postoperative period [8]. The persistence of nausea was presumably caused by continuous nasopharyngeal stimulation by the presence of the tube.

This early observation that gastric decompression reduced the incidence of postoperative vomiting was confirmed by a more recent study in patients undergoing cholecystectomy [32]. However, in a prospective study designed specifically to investigate this effect of gastric decompression and avoiding persistent nasopharyngeal stimulation by removal of an orogastric tube immediately at the end of surgery, Hovorka, Korttila and Erkola were unable to demonstrate any benefit in 201 women undergoing abdominal hysterectomy [30].

OTHER FACTORS DURING ANAESTHESIA

It has been suggested recently that patients exposed to positive intraoperative suggestions during general anaesthesia may have lower rates of vomiting and nausea after operation compared with those patients exposed to non-suggestive comments played via earphones during anaesthesia [63]. However, this suggestion awaits confirmation in larger studies.

Whilst it has been suggested that the duration of anaesthesia is associated with the incidence of postoperative emesis, this factor cannot be extricated from the duration of surgery and such suggestions can only be speculative [38].

Movement of the patient after operation may provoke nausea and vomiting in patients who have received opioids [13, 44]. Kamath and colleagues found that 66% of patients who identified a cause for postoperative nausea blamed movement [34], and that these patients had a particular susceptibility to motion sickness. They suggest limiting patient movement after operation.

POSTOPERATIVE PAIN

Pain *per se* is associated with nausea and vomiting and relief of pain by optimum administration of opioids results in a reduction in the incidence of nausea, although excessive doses of opioids may provoke opioid-induced emesis. In 1978, Anderson and Krohg [2] found that 90% of patients with

nausea after abdominal surgery also had accompanying pain, and that in 80% of these patients, relief of pain by injection of opioid resulted also in abolition of nausea.

Administration of optimum doses of morphine, administered by patient-controlled analgesia, does not result in greater degrees of emesis than morphine given 4-hourly by i.m. injection [50].

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