

REVIEW**5-HT₃-Receptor-Associated Mechanisms of PONV A Risk Factor Targeted Approach to Anti-emetic Therapy**

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Postoperative nausea and vomiting (PONV) has been the focus of countless clinical trials leading to the identification of risk factors¹ and publication of international guidelines.² Unlike many other causes of nausea and vomiting however, PONV is multi-factorial. Many neurotransmitters are involved and no single drug is effective in all cases. Philosophy has thus shifted from single agent to combination therapy but there is inadequate data from large clinical trials about optimum drug combinations. One novel approach would be to consider that different clinical risk factors for PONV¹ may be associated with different physiological mechanisms for vomiting and may be amenable to therapy with specific drugs. Since the 1980s, more data pertaining to 5-HT₃ receptor antagonists has been generated than for any other drug class. In this article, the extent of what is known of the role of 5-HT₃ receptors in vomiting from pre-clinical data is discussed and an attempt made to apply these pre-clinical concepts to different clinical situations in which the exact mechanisms of vomiting may differ.

The physiology and pharmacology of nausea and vomiting

Vomiting results when a central pattern generator (CPG), previously referred to as the 'vomiting centre', is activated by converging stimuli which may broadly be divided into:

- 1) the area postrema / nucleus tractus solitarius complex (AP-NTS)
- 2) Vagal afferents from the periphery with their cell bodies in the nodose ganglia and terminating in the AP-NTS
- 3) the vestibular nuclei and
- 4) higher cerebral inputs which probably modulate the signals from the other three

Post-operative vomiting is assumed to arise when mechanical and pharmacological factors in the peri-operative environment activate one or more of these converging routes.³ There is no discrete 'Vomiting centre' in the reticular formation as originally described by Borison and Wang⁴ but the term is sometimes used synonymously

with the CPG to describe the network of nuclei, (including respiratory pattern generators), which coordinate vomiting itself. Nausea is a subjective experience and is difficult to model in animals⁵⁻⁸ but higher cerebral systems presumably play an even more important role, the inferior frontal gyrus being one area implicated in human imaging studies.⁹ With regards PONV these mechanisms arbitrarily lend themselves to division into those which are associated with 5-HT₃ receptor activation and those which are not. The other mechanisms include opioids and the vestibular apparatus. Clearly all mechanisms may be involved in any given clinical situation but 5-HT₃ receptors may play a greater or lesser role in some.

The role of 5-HT₃ receptors in nausea and vomiting

The 5-HT₃ receptor is the only ligand-gated ion channel in a receptor family of at least 14.^{10,11} They are found on vagal terminals in the mucosa-submucosa junction of the GI tract¹² while the NTS and AP contain the highest levels in the human brainstem.¹³

Much of what is believed about the role of 5-HT₃ receptors in PONV has been extrapolated from their role in chemotherapy-induced nausea and vomiting. 5-HT₃ antagonists injected directly into the AP of cats and ferrets inhibited cisplatin-induced emesis¹⁴ which led to the assumption that brainstem 5-HT₃ receptors performed an analogous role to dopamine and opioid receptors in mediating emetic responses to circulating toxins.¹⁵ Cisplatin however does not directly interact with any known receptor in the AP-NTS and causes emesis only after a significant delay when injected intravenously suggesting a slower process originating elsewhere.¹⁶ Moreover, 5-HT₃ antagonists do not inhibit the emesis induced directly by the potent dopamine receptor agonist apomorphine¹⁷ or motion and despite apparently having limited clinical efficacy, do not usually inhibit morphine or loperamide induced emesis in animal studies either.^{17,18} The exact role of

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brainstem 5-HT₃ receptors is further brought into question by their existence in species, such as the rat, which have no vomiting reflex.¹⁹

Electrical stimulation of the abdominal vagus induces retching and vomiting in animals^{20,21} and activates the AP and NTS in 2-deoxyglucose imaging studies.²⁰ Vagotomy demonstrates that the vagus nerves are pivotal in radiation and chemotherapy-induced emesis and furthermore, the potential of chemotherapeutic agents to induce emesis is directly related to their ability to release 5-HT (increased excretion of its metabolite, 5-HIAA). There is now overwhelming evidence that the 5-HT is released in the G.I. tract activating 5-HT₃ receptors on vagal afferents^{16,17} terminating in the NTS where 5-HT₃ receptors are also located presynaptically (5-HT₃ binding sites in the NTS as well as the AP diminish after supranodose vagotomy).^{22,23} The role of brainstem 5-HT₃ receptors in modulating these vagal inputs is relatively minor but important in certain situations. Depletion (by fenfluramine) of central 5-HT markedly reduced the emetic response to apomorphine²⁴ but depletion (with parachlorophenylalanine) did not inhibit opioid-induced emesis in the ferret²⁵ suggesting interaction between 5-HT and dopamine mediated emesis centrally but not between 5-HT and opioids. Vagal signals terminating in the NTS induce neuronal plasticity subsequently lowering the threshold for vomiting induced through further stimulation of the AP-NTS.²⁰

Allosteric modulation of 5-HT₃ receptors by anaesthetic agents

It has recently become apparent that ligand-gated ion channels can be modulated by alcohols and anaesthetic agents acting allosterically i.e. at sites separate from the agonist recognition site. An example is the modulation of GABA_A receptor function by benzodiazepines, barbiturates and zopiclone which all act on different non-agonist sites. Although general anaesthetic agents do not interact with the 5-HT binding site of the 5-HT₃ receptor at clinically relevant concentrations,²⁶ several intravenous and inhalational agents can modulate the 5-HT₃ receptor allosterically. While some appear to facilitate 5-HT₃ receptor mediated signalling, others are capable of inhibiting it.²⁷ A potentiating effect on 5-HT₃ receptor function has been demonstrated with isoflurane, halothane²⁸, ethyl ether, several alcohols and several halogenated alcohols.^{27,29} Halothane and isoflurane potentiate 5-HT₃ receptor mediated depolarisation in concentrations at or lower than their MACs and furthermore the effects of ethanol and halothane are additive suggesting that, as with the GABA_A receptor, there are different modulatory sites on the 5-HT₃ receptor.²⁸ Agents inhibiting 5-HT₃ receptor function include

thiopentone, methohexitone and propofol³⁰ while findings with ketamine have been conflicting.³⁰⁻³² In outside-out patch clamped N1E-115 mouse neuroblastoma cells, propofol inhibited 5-HT₃ receptor mediated inward currents at an IC₅₀ approximating to a tissue concentration of 2.5 µg/ml. Suppression of 5-HT₃ receptor function exhibited slow kinetics, requiring prolonged exposure to propofol and displaying prolonged inhibition after propofol washout.³³

Clinical importance of 5-HT₃ receptors in PONV

It is postulated that vagal afferents from the GI tract play a significant role in the generation of PONV.³⁴ 5-HT₃ receptors in abdominal and pelvic viscera may be stimulated during (and following) some surgical procedures. Distension of abdominal viscera and gastro-duodenal stasis resulting in bile entering the stomach would stimulate vagal afferents in the mucosa³ as would direct handling of gut or pelvic structures. Vagal afferents from the heart and pharynx may be involved in other circumstances,³⁴ and 5-HT₃ receptors in the spinal trigeminal tract may contribute to the high incidence of PONV following head and neck surgery.³⁵ Gastric distension secondary to bag-mask ventilation may be another cause of 5-HT₃ receptor activation and could theoretically occur during anaesthesia for any surgery to some extent.

It is not easy to find trials demonstrating that 5-HT₃ antagonists have a relatively greater efficacy when used in the management of the above types of surgery. The evidence is weak because trials have not been designed to investigate this but more importantly, what evidence there is does not refute the concept. Certain types of surgery have frequently been found to be associated with a higher risk of PONV than others for example gynaecology, head and neck, strabismus and middle ear surgery.³⁶⁻⁴¹ In their five-way factorial RCT, Apfel and colleagues did not find that type of surgery affected the relative efficacy of a 5-HT₃ antagonist and anti-histamine however they only considered strabismus surgery and ENT.⁴² A systematic review and meta-analysis comparing droperidol with ondansetron found equal efficacy across a broad range of surgery.⁴³ The authors reported that surgical subgroup analysis did not affect the overall outcome however on closer examination, all the trials where ondansetron showed greater efficacy involved either gynaecology or ENT patients while those showing superiority of droperidol or equal efficacy included strabismus and major orthopaedic cases. A systematic review and meta-analysis of post-discharge vomiting following gynaecology surgery found that ondansetron was effective but cyclizine was not.⁴⁴ Metoclopramide at standard dose has frequently been found to have limited efficacy overall⁴³ however at significantly higher dose it has 5-HT₃

receptor blocking properties and has been shown to be equal in efficacy to ondansetron following gynaecology surgery.⁴⁵ Against this may be the finding that higher dose metoclopramide was not as effective as ondansetron following tonsillectomy in children.⁴⁶ The meta-analysis of Domino et al however, showed that ondansetron is generally more effective than droperidol when children were analysed as a subgroup.⁴³ Indeed, a systematic review of paediatric tonsillectomy cases provided good evidence for the anti-emetic efficacy of 5-HT₃ antagonists and standard dose metoclopramide but insufficient evidence for the efficacy of either anti-histamines or droperidol.⁴⁷ The mechanism of chemotherapy-induced emesis involves peripheral 5-HT release and the most emetic agents can be shown to increase levels of the 5-HT metabolite 5-HIAA.¹⁷ A study of patients undergoing ENT surgery has found that PONV is also associated with significant increases in plasma 5-HIAA.⁴⁸ It remains to be seen if PONV is also associated with 5-HIAA release during abdominal surgery.

5-HT₃ receptor stimulation may be potentiated in the presence of inhaled volatile anaesthetics. Apfel and colleagues determined that volatile anaesthetics were a more important cause of early PONV than any other factor although this situation changes within 2 hours as volatile agents are eliminated.⁴² The particular volatile agent itself seems to make no difference to the incidence of PONV^{42,49} however dose-effect relationships have been apparent in studies where volatile usage was strictly controlled.⁵⁰ Several teams have observed that 5-HT₃ antagonists are considerably more efficacious for symptomatic treatment than for prophylaxis and furthermore, ondansetron at least, is more effective when administered later rather than sooner intra-operatively.⁵¹⁻⁵³ This may suggest that 5-HT₃ receptor activation becomes more important as surgery progresses and that the effects of early gastric distension are less marked in comparison to the consequences of surgical stimuli.

The negative allosteric 5-HT₃ receptor modulating properties of propofol predict that this agent has the potential to reduce PONV. Intravenous maintenance of anaesthesia is certainly associated with less PONV⁵⁴ but whether propofol demonstrates anti-emetic properties *per se* or simply spares the use of volatile agents has been debated for some time. The IMPACT trial, a five intervention analysis of 4086 patients has suggested that the majority of benefit from a total intravenous anaesthetic with propofol in terms of PONV reduction is secondary to a volatile anaesthetic sparing effect.⁵

Dexamethasone and 5-HT₃ receptors

In the nineties it was noticed that dexamethasone, given to

reduce pain and swelling after oral and maxillofacial surgery, also reduced the incidence of PONV.⁵⁶ Its usefulness in the treatment of delayed chemotherapy-induced vomiting had been known for some time.^{17,57} Dexamethasone is now frequently used in the management of PONV in its own right. A systematic review and meta-analysis found it to be better than placebo as a single agent but the data were insufficient to state whether it was equal in efficacy to other drugs.⁵⁸ The same systematic review found that the combination of dexamethasone with a 5-HT₃ antagonist was significantly beneficial whereas the data were insufficient to identify benefits of combining dexamethasone with other classes of drug.⁵⁸ There has however been a more recent study reporting the beneficial combination of dexamethasone with a dopamine antagonist.⁵⁹ Again, the meta-analysis was too limited to identify types of surgery for which dexamethasone may have relatively increased efficacy⁵⁸ however it is clear that it has greater efficacy for late PONV than early PONV.^{58,60} The mechanism of action of dexamethasone is only just beginning to be unravelled. There are moderate numbers of glucocorticoid receptors in the NTS⁶¹ and anti-emesis has been demonstrated in the cat when dexamethasone was injected bilaterally into the NTS but not the AP.⁶² The mechanism may involve prostanoids or cytokines.⁶³ Prostanoids are emetic in animal studies⁶⁴⁻⁶⁶ and both the NTS and vagal afferents have been implicated.⁶⁷ Cyclooxygenase inhibitors inhibit vomiting induced by chemotherapy⁶⁷ but not resiniferatoxin⁶⁸ suggesting an action not quite as far downstream in the emetic pathway as NK₁ receptors. Dexamethasone may alter regional levels of neurotransmitters⁶⁹ or their precursors⁷⁰ but there is also evidence for an interaction with 5-HT₃ receptors. In the house musk shrew, loss of emetic sensitivity to 5-HT₃ receptor agonists in one particular colony was associated with loss of the anti-emetic effect of dexamethasone against cisplatin-induced emesis⁷¹ and more recent *in-vitro* work has demonstrated that dexamethasone can attenuate 5-HT₃ receptor ion flux directly.⁷²

Non 5-HT₃ mechanisms of PONV

The AP is a highly vascularised nucleus on the floor of the fourth ventricle, structurally outside the blood-brain barrier.¹³ Stimulation of dopamine D₂, mu, kappa and delta opioid and alpha₂ receptors in the AP result in vomiting⁷³ and AP lesioning abolishes the emetic response to both apomorphine⁷⁴ and opioids in animal studies.²⁵ In further support of its role as a chemoreceptor trigger zone (CTZ), single AP neurones may be stimulated *in-vitro* by multiple neurotransmitters and chemicals.¹⁵ Whether dopamine receptors are actually on AP neurones or on neurones of

the NTS branching into the AP is not known since AP lesioning often damages both structures.³ Nevertheless the AP at least acts as a window into the NTS, probably bilaterally.⁶² It may be argued that the NTS, is not just involved in the CPG⁷⁵ but is the closest thing to a 'vomiting centre' so far identified. The proximity of dopaminergic and opioid receptors in the AP may be the reason dopamine antagonists have efficacy against opioid-induced nausea and vomiting.

PONV has been associated with movement^{36,38,76} and particularly so when opioids have been administered.³⁷ Although motion sickness is most marked when the eyes and vestibular system send discordant information, neither functioning sight or open eyes are necessary and stimuli such as transferring semi-conscious patients are thought to contribute to PONV. Muscarinic, nicotinic and histaminergic receptors are thought to be involved. Muscarinic receptors are actually found in greater density in the AP, than in the vestibular nuclei, i.e. outside the blood-brain barrier⁷⁷ but clinical evidence suggests that hyoscine and atropine are better anti-emetics than glycopyrrolate^{78,79} and are also more effective in PONV when the vestibular system has been disturbed.⁸⁰ Anticholinergic drugs including glycopyrrolate would otherwise be expected to have similar anti-emetic spectra to dopamine antagonists. Muscarinic receptors within the blood brain barrier must therefore play a greater role in PONV than those located in the AP. Muscarinic receptors are also found in the NTS where reduced post-nodosectomy [3H]-QNB⁸¹ and [3H]-pirenzepine binding indicate that M₁ receptors are located on vagal terminals.¹⁵ Vestibular afferents may similarly terminate in the NTS^{82,83} and interactions between vestibular stimuli and brainstem responses to opiates and toxins are observed³ possibly explaining why drugs which are effective in motion sickness often have efficacy in opioid-induced vomiting.

Ablation of the vestibular system reduces the emetic response to acute nicotine administration in dogs⁸⁴ while chronic exposure to nicotine through smoking is protective against PONV in humans.⁸⁵ Both smokers and nicotine patch wearers suffer less PONV⁸⁶ and smokers are tolerant to the acute emetic effects of nicotine⁸⁷, effects which develop chronically.⁸⁸ Nicotine may induce CYP1A2 and CYP 2E1 which metabolise volatile anaesthetics^{89,90} or receptors may become downregulated with chronic exposure.

Emesis induced by intraventricular injection of histamine is abolished by AP ablation and by H₁ and H₂ receptor antagonists in combination but not by either alone suggesting that both are involved.⁹¹ The NTS is also rich in histaminergic and cholinergic receptors. Of the anti-

histaminergic drugs, well established in the treatment of motion sickness, only cyclizine is regularly used for PONV and is both an H₁ and cholinergic receptor antagonist. Transdermal hyoscine is efficacious in the management of motion sickness while dopamine antagonists are less effective and 5-HT₃ antagonists are not effective at all.³⁷

In trials investigating anti-emetics in middle ear surgery, Khalil et al found promethazine to be more effective than ondansetron.⁹² In another trial, although ondansetron was effective, it was not effective in any patient with a history of motion sickness.⁹³ Transdermal hyoscine had the greatest relative efficacy in middle ear than for other types of surgery in a meta-analysis.⁹⁴ Nitrous oxide may contribute to PONV through middle ear distension (opioid and dopamine receptor interactions are also possible)⁹⁵⁻⁹⁷ and its omission reduces PONV⁹⁸ except when the baseline risk is low.⁹⁹

CONCLUSION

Pre-clinical data predict that different surgical conditions may cause PONV as a result of different neurotransmitters. These differences are potentially one area to exploit in improving the management of this problem. Types of surgery may arbitrarily be considered as either those where 5-HT₃ activation is the prevailing cause of PONV and those where vestibular and opioid causes prevail, a division which may allow a new approach to choosing anti-emetic drugs either as single agents or in combination. Table 1 gives an example of one possible regime which could be based around the degree to which 5-HT₃ receptors are likely to contribute to PONV. These divisions are only intended to predict the most likely pharmacological factors in the aetiology. Since PONV is still multi-factorial, in cases where 1st line treatment fails, 2nd line treatment should then be in the form of an anti-emetic that acts via mechanisms in the opposite division. Clinical data to support these predictions are very limited however evidence to the contrary is even less abundant. Large scale clinical trials allowing variability in single risk factors such as surgical procedure, although very difficult to design, would therefore be justified in the future.

Table 1

An example of an anti-emetic regime based on the division of surgical procedures by their propensity to cause 5-HT₃ receptor activation.

| | 5-HT₃ stimulating surgery | Non 5-HT₃ stimulating surgery |
|--------------------|---|---|
| Prophylaxis | Dexamethasone | Dopamine antagonist |
| 1st line treatment | 5-HT ₃ antagonist | cyclizine |
| 2nd line treatment | cyclizine | 5-HT ₃ antagonist |

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