Intravenous amisulpride: A safer and possibly effective anti-emetic for postoperative nausea and vomiting

Sir,

Postoperative nausea and vomiting (PONV) is a common phenomenon after receiving an anaesthetic for surgery. Currently, the prevalence of PONV has been estimated to be 30-40% even after two or three prophylactic antiemetic medications and in patients with all four of the Apfel risk factors for PONV.[1] The most common factors predisposing to PONV are the female gender, history of PONV and/or motion sickness, non-smokers, younger age group patients, volatile anaesthetic with or without nitrous oxide, opioids use. PONV not only adds significant postoperative discomfort and dissatisfaction but also increases the length of hospital stay and overall cost of treatment. Presently the commonly used medications for PONV prophylaxis are dexamethasone, 5 HT_3-antagonists (ondansetron, ramosetron, palanosetron), anti-histaminic, neurokinin-1 receptor antagonist aprepitant, scopolamine, and metoclopramide.[2,3]

Amisulpride is a potent and selective dopaminergic D2 and D3 receptor antagonist which was available for clinical use as an atypical antipsychotic since 1970. It became popular due to the lesser incidence of extrapyramidal effects with recommended doses (50-1200 mg) at that time. Recently the United States Food and Drug Administration (US-FDA) has approved intravenous (IV) amisulpride for managing PONV. The D2 receptor is notorious for manifesting PONV even in surgical patients. Therefore, it was hypothesised that drugs with D2 receptor antagonist properties can be used as prophylaxis and for treating PONV. Droperidol was developed with this knowledge and was used successfully till it was issued a black-box warning in 2001 due to reports of prolonged QTc and life-threatening arrhythmias like torsade de pointes.[4]

QTc prolongation mediated by dopaminergic antagonists is because of binding to the potassium ion channel human ether-à-go-go-related gene (hERG). Antiemetics like droperidol, haloperidol, and prochlorperazine have a high affinity to hERG channel and thus the higher propensity of developing arrhythmias. Amisulpride has an edge over other agents in this regard because its affinity to hERG channel is less than 100 times weaker. The effect of IV amisulpride on QTc was demonstrated in a study by Täubel *et al*.[5] Authors compared a 5 mg single dose with a 40 mg IV amisulpride in 40 healthy subjects. They concluded that there is dose-dependent QTc prolongation (with 40 mg dose). However, the recommended dose is 5-10 mg IV which is considered safe. The use of IV amisulpride has not demonstrated any serious drug interactions yet and is devoid of enzyme induction or inhibition of cytochrome liver enzymes. All antipsychotics including amisulpride have a propensity of QTc prolongation therefore caution should be exercised.

The initial IV preparation of amisulpride was known by the name APD421. As early as 2013,

Table 1: Published Papers Which Investigated Efficacy and Safety of Intravenous Amisulpride

Authors/ Year	Type of Study	Number of Patients	Key Findings
Kranke *et al*./2013[5]	Randomised, double-blind, placebo-controlled, multicentre trial	215	APD421 is safe and effective at reducing PONV in moderate/high-risk adult surgical patients.
Gan *et al*./2017[1]	Two Concurrent, Randomised, Double-blind, Placebo-controlled Trials	626	Amisulpride was safe and superior to placebo in reducing the incidence of PONV in adult inpatients at moderate to high risk of PONV.
Täubel *et al*./2017[3]	Randomised, double-blind, placebo and positive-controlled, four-way crossover study	40	The proposed therapeutic dose (5-10 mg) for management of PONV does not lead to a prolongation of QTc.
Habib *et al*./2019[2]	A Randomised, placebo-controlled Phase III Trial	702	A single 10-mg dose of intravenous amisulpride was safe And effective than placebo at treating established PONV in patients failing PONV prophylaxis.
Candiotti *et al*./2019[6]	Randomised, double-blind, placebo-controlled study	560	IV amisulpride at 5 and 10 mg was safe and efficacious in the treatment of established PONV in surgical patients undergoing general anaesthesia with no prior PONV prophylaxis

PONV-Postoperative nausea and vomiting

Kranke *et al*. conducted a randomised, double-blind, placebo-controlled, multicentric trial by recruiting 215 adult surgical patients with more than 2 Apfel risk factors for PONV undergoing surgery and expected to last more than 1 hour with standardised inhalational anaesthesia.[6] The authors concluded that when administered before surgery, amisulpride i.e., APD421 is safe and effective at reducing PONV in moderate/high-risk adult surgical patients. Several studies followed thereafter and established the safety and efficacy of IV amisulpride [Table 1]. It has been shown in pharmacokinetic studies that after the initial IV dose of 5-10 mg, there are therapeutic levels for at least 24 hours with a terminal half-life of 4-6 hours and a complete clearance from the system in approximately 96 hours.

Amisulpride is presently marketed as BARHEMSYS by Acacia Pharma, United States. US-FDA has approved its use for preventing PONV, either alone or in combination with another antiemetic and also for treating PONV in patients who have received antiemetic prophylaxis with an agent of a different class or those who have not received prophylaxis.[7] It should be used with caution in patients with rhythm disturbances, electrolyte abnormalities (low potassium/magnesium levels), and with other drugs causing QTc prolongation. Future studies could focus on the efficacy of amisulpride in patients undergoing specific surgeries with a high propensity for PONV.

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Conflicts of interest
There are no conflicts of interest.

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