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Effects of Granisetron and Palonosetron on Haemodynamic Changes as Antiemetics

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Abstract

Introduction: The adverse reactions commonly reported for palonosetron were headache and constipation. All other reactions such as diarrhea, dizziness, abdominal pain, fatigue, insomnia occurred at an incidence of <1%. There were no electrocardiographic changes or dose response effects, including QTc prolongation due to palonosetron up to a 2.25 mg iv dose, a 9-fold safety margin. *Methodology:* In post anaesthesia care unit blood pressure and heart rate were recorded every 10 min for 30 min. Episodes of nausea and vomiting experienced by each patient were recorded by direct questioning. The number of patients who suffered nausea/vomiting were noted during the period's 0-4hrs, 4-12hrs, and 12-24hrs in the post operative period and statistical analysis was done accordingly. *Results*: Systolic, Diastolic BP, Heart rate and oxygen saturation showed no statistically significant difference recorded in PACU between the study groups. *Conclusion*: The number of patients who suffered side effects was more in granisetron group.

Keywords: Palonosetron; Granisetron; Blood Pressure.

Introduction

Granisetron is potent and selective 5-HT_3 receptor antagonist with antiemetic activity. It is indicated for the prevention and the treatment of nausea and vomiting associated with cytotoxic chemotherapy, radiotherapy and postoperative vomiting [1].

Granisetron is an anti-nausea and anti-emetic agent. It is highly selective antagonist of 5-hydroxy-tryptamine (5-HT_3) receptors. Granisetron has negligible affinity for other receptor types including 5-HT_1; 5-HT_{1A} 5-HTI_B/c; 5-HT_2; For dopamine-D2 or histamine-H_1; opioid receptors [2].

Granisetron hydrochloride 1.1 mg is approximately equivalent 1mg of Granisetron base. Following intravenous administration of a dose of 40mcg/kg, the average peak plasma concentration is 30.7 mcg/1. Granisetron is extensively distributed in the body (Vol. of distribution-200 litres). Granisetron is rapidly and extensively metabolised in the liver. In elderly subjects after single intravenous doses, pharmacokinetic parameters were within the range found for non-elderly subjects. In patients with severe renal failure, data indicate the pharmacokinetic parameters after a single intravenous dose are generally similar to those in normal subjects. Half life of Granisetron is 3-9 hrs. Granisetron is 65% bound to albumin in plasma. Following oral administration, Granisetron is completely absorbed [3,4].

Average total plasma clearance of Granisetron is 0.3-0.5 $h^{-1}k^{-1}$. Excretion is in both urine (61% of the dose) and feces (34% of the dose). 12% excreted unchanged in urine.

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Granisetron may reduce lower bowel mobility, and therefore patients with signs of subacute intestinal obstruction should be monitored following administration of Granisetron [5].

No special precautions are required for the elderly or renally or hepatically impaired patient.

Adverse Effects

1. Headache is most frequent side effects.
2. Constipation is also frequently reported effects.
3. Hypersensitivity reaction, occasionally severe anaphylaxis have been reported.
4. Allergic reaction including minor skin rashes have also been reported.
5. Low incidence of transient increases in hepatic transaminases (AST, ALT) greater than twice the normal limit has been seen.
6. Any extrapyramidal action of the drug is not reported.

Palonosetron is the latest 5-HT_3 antagonist licensed and the only drug of its class approved for prophylaxis against both acute and delayed chemotherapy-induced nausea and vomiting (CINV). Its unique properties have led to it being described as the first of a "second-generation" of 5-HT_3 antagonists. Far higher receptor affinity and a much longer half-life than other 5-HT_3 antagonists confer a prolonged duration of action. Following successful Phase III clinical trials the FDA approved its use for prevention of PONV in March 2008 [6].

It is widely distributed in the tissues and is moderately bound to plasma proteins (62%), metabolized in liver by CytochromeP450enzymes, predominantly by CYP2D6 and secondarily byCYP3A4and CYP1A2). 40% of the administered dose excreted unchanged. This slow elimination results in half-life approximately 40hrs as all the 5HT_3 antagonists have got very good safety profile, the Palonosetron also has got side effects which are mild and transient. The common adverse effects are headache, constipation, dizziness. Palonosetron slightly increases QTc intervals from1-3cms. It has been safely used in many patients with cardiac impairment.

Drug interactions: As with all the 5HT_3 antagonists Palonosetron also shows very negligible drug interaction. But there was an adverse reaction with apomorphine which caused severe hypotension and altered sensorium. So it should not be used with apomorphine [7,8].

Palonosetron is a 5-HT3 receptor antagonist which has antiemetic activity at both central and GI sites. In comparison to the older 5-HT3 receptor antagonists, it has a higher binding affinity to the 5-HT3 receptors (Table-3), a higher potency, a significantly longer half-life of approximately 40 hours (4 to 10 times longer than that of dolasetron, granisetron and ondansetron) and an excellent safety profile as demonstrated in a number of Phase II–III studies [9,10].

The adverse reactions commonly reported for palonosetron were headache and constipation. All other reactions such as diarrhea, dizziness, abdominal pain, fatigue, insomnia occurred at an incidence of <1%. There were no electrocardiographic changes or dose response effects, including QTc prolongation due to palonosetron up to a 2.25 mg iv dose, a 9-fold safety margin.

Methodology

Patients were randomly divided into two groups of 30 each.

Group 'G' –GRANISETRON group(n = 30)

Group 'P' –PALONOSETRON group (n = 30)

Inclusion Criteria

1. Patients aged20– 50 years
2. Either sex
3. ASA I – II
4. Patients posted for elective laparoscopic surgeries

Exclusion Criteria

1. Patients with previous history of post operative nausea and vomiting
2. History of motion sickness
3. History of gastroeseophageal reflux disease
4. Patient who has taken any antiemetic 24 hours prior to the surgery
5. Obese patients
6. Pregnant females
7. Diabetic patients
8. ASA grade III or above
9. Emergency surgery
10. H/O Drug allergy
11. Full stomach

12. Extremes of age

13. Respiratory disease

14. Difficult airway.

In post anaesthesia care unit blood pressure and heart rate were recorded every 10 min for 30 min. Episodes of nausea and vomiting experienced by each patient were recorded by direct questioning. The number of patients who suffered nausea/vomiting were noted during the period's 0-4hrs, 4-12hrs, and 12-24hrs in the post operative period and statistical analysis was done accordingly.

The side effects like headache, dizziness, hypersensitivity and constipation if any were assessed post operatively for 24 hours.

Results

Most of the patients in both groups belonged to age group 20-30. There was no statistically significant difference in the two groups ($P > 0.05$).

In our study females predominated males in granisetron group (23%) and palonosetron group (17%). But comparable in both groups Systolic, Diastolic BP, Heart rate and oxygen saturation showed no statistically significant difference recorded in PACU between the study groups.

There was no significant difference in CRS and RT between the two groups.

Table 1: Age distribution

Range	Granisetron	Palonosetron
20-30	24 (80%)	20 (66%)
31-40	3 (10%)	5 (17%)
41-50	3 (10%)	5 (17%)
Mean Age ±SD	28.63± 7.62	30.23±9.49

Table 2: Sex distribution

Sex	Granisetron	Palonosetron
Male	7 (23%)	5 (17%)
Female	23 (77%)	25 (83%)

Table 3: Comparision of systolic BP, diastolic BP, HR and SPO_2%

Grade	Granisetron	Palonosetron
Mean Pulse	76.90±1.5	82.73±1.5
Mean SBP	131.46±6.06	131.76±6.23
Mean DBP	79.86±11.25	82.13±8.48
Mean SPO_2%	99.10±0.76	99.17±0.83

Table 4: Clinical recovery score (crs) and recovery time (rt) (mean±sd)

Time Interval	Granisetron
0 hour	5.16
1 Hour	7.03
2 hour	8.33
3 Hour	8.83
4 Hour	10.33
Recovery time (Minutes)	5.67±0.23

Table 5: Comparison of side effects

Side Effects	Granisetron (n =30)	Palonosetron (n =30)
Headache	*6(20%)	*4 (13 %)
Constipation	*4(13%)	*2 (7 %)
Dizzness	*4 (13%)	*2 (7 %)

Occurrence of side effects like headache, constipation and dizziness in granisetrongroup are 6(20%), 4(13%), 4(13%) respectively compared to 4(13%), 2(7%), 2(7%) in palonosetron group. The number of patients who suffered side effects were more in granisetron group.

Discussion

In our study on the clinical recovery score and the recovery time we observed slightly lower clinical recovery score in the Granisetron group compared to Palonosetron and there was not much of significant difference in the recovery time.

Incidence of side effects was significant in our study groups. Incidence of headache was 20% in Granisetron group while it was 12% in Palonosetron group shows statistically significant difference ($P < 0.05$).

Incidence of constipation and dizziness also shows significant difference in Granisetron and Palonosetron groups ($P < 0.05$).

The use of rescue antiemetic in Granisetron group which was about 7(23%) whereas in Palonosetron group about 3(10%) of the patients received rescue antiemetic. Stewart [11] in his study also has same result. Updated guidelines for managing postoperative nausea and vomiting were recently announced at the 2006 Annual Meeting of American Society of Anaesthesiologists in Chicago, Illinois, USA. Evaluating the current medical literature, they recommended the use of antiemetics, with an emphasis on the use of the $5HT_3$ receptor antagonists. The guidelines also suggest a potential benefit of combination prophylaxis. Overall the panel recommended, "Prophylactic therapy with combination, three or more interventions, in patients at high risk for PONV." [12].

So we have studied the effect of Granisetron 2.5 mg i.v. versus palonosetron 75μg i.v, administered to the patients, who had undergone laparoscopic surgery under general anesthesia.

Our study shows no statistically significant difference in the baseline values of hemodynamic variables between the two groups before, during or after giving study drug. Study drugs granisetron and Palonosetron was given the end of the surgery, before extubation. In PACU we have recorded the SBP, DBP and HR over a period of 30min at regular interval. According to our study there was no haemodynamic alteration between these results. Study conducted by Dev [54] also shows the same results. There is no haemodynamic alteration seen in PR, SBP and DBP during study period. Kumar et al [13] in their clinical trial on recovery score and recovery time showed slightly lower clinical recovery scores with metoclopramide group compared to ondansetron which may be attributed to its established unpleasant sedative pharmacological activity. They did not notice any significant difference in the overall incidence of drowsiness or sedation in both the groups.

They further stated that ondansetron doesnot affect patients vigilance, cognition or orientation and concluded that ondansetron (4mg) and metoclopramide (10 mg) do not affect the cognitive aspects following major gynaecological surgery.

Conclusion

Even though there was slightly higher clinical recovery score in the patients who had received intravenous Palonosetron compared to patients who had received intravenous Granisetron, there was no significant difference in the recovery time from anesthesia between the two drugs.

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