Documented Sustained Response of Intravenous Amisulpride for Rescue Treatment of Postoperative Nausea and Vomiting: Results from a Phase III Trial

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Background

Postoperative Nausea and Vomiting (PONV)

- Estimated incidence of PONV is approximately 30% in the general surgical population and as high as 80% in high-risk cohorts[1]
- Associated with significantly longer PACU length of stay, unanticipated hospital admission, and increased health care costs[1]
- Can lead to patient and provider dissatisfaction[1]

Amisulpride

- Selective dopamine D_2 and D_3 receptor (D_2R, D_3R) antagonist[2]
- Only FDA approved antiemetic for PONV rescue treatment
- FDA approved in 2020 for[2]:
  - Prevention of PONV, either alone or in combination with an antiemetic of a different class
  - Treatment of PONV in patients who have received antiemetic prophylaxis with an agent of a different class or have not received prophylaxis
- Demonstrated efficacy for both prophylaxis and treatment of PONV with a comparable safety profile to placebo in clinical trials[3-6]
- High binding affinity and selectivity for both D_2 and D_3Rs (Ki = 1-3 nM)
- Regional preference for D_2/D_3Rs in limbic but not striatal structures, corresponding with observed CNS safety (no sedation) and low occurrence of extrapyramidal symptoms[7-10]
- No other pharmacologically relevant receptor interactions and minimal affinity for other dopamine and non-dopamine receptor subtypes, decreasing off-target receptor adverse events[8]
- Demonstrates linear pharmacokinetics (PK) with peak plasma concentration achieved at the end of the administration period, and mean elimination half-life is approximately 4-5 hours [2,9]

Study Objective

The purpose of this analysis was to evaluate the plasma concentrations of a single dose of IV amisulpride 10 mg for rescue treatment of PONV based on a prespecified PK subset of patients.

Acknowledgements and Disclosures

The authors would like to thank the patients and the staff who participated in these trials. EL and LB are employees of Eagle Pharmaceuticals and hold company stock, and TM is a consultant for Eagle Pharmaceuticals.

Methods

This was a prespecified pharmacokinetic (PK) subset of patients (n = 27 out of 230 patients) from a phase III, randomized, multicenter, double-blind, placebo-controlled, parallel-group study in adult surgical patients with moderate to high risk of PONV who failed antiemetic prophylaxis[4]

Patients

- Adults scheduled to undergo elective ambulatory or inpatient surgical procedures lasting ≥1 hour under general inhalational anesthesia with a qualifying event: PONV episode (emesis [retching or vomiting] or need for antiemetic rescue medication) within 24 hours after surgery
- Patients were randomized to receive a single dose of IV amisulpride 5 mg or 10 mg or placebo after experiencing PONV in the first 24 hours following wound closure

Study Design

- The primary endpoint was complete response (CR), defined as no emetic episodes (vomiting or retching) or administration of antiemetic rescue medication, for 24 hours after study drug administration
- Amisulpride plasma samples were collected at 5 and 30 min, and 2-, 6-, and 24-hours following study drug administration (unless subject already discharged) in a prespecified PK subset of patients

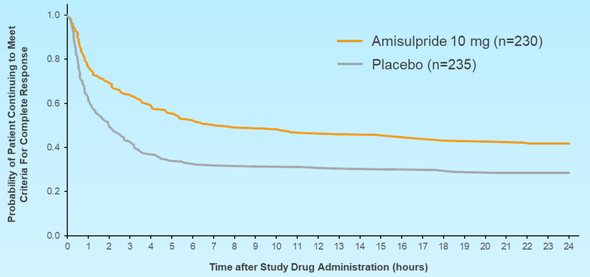
Selected Baseline Characteristics

- N = 702 patients
  - Amisulpride 10 mg (n = 230)
    - PK subset with amisulpride plasma samples collected (n = 27)
  - Placebo (n = 235)
  - Amisulpride 5 mg (n = 237)
    - 5 mg dose not significantly superior to placebo; therefore, only data on 10 mg dose (approved dose for rescue treatment) are presented

	Amisulpride 10 mg n = 230	Placebo n = 235
	Number (%) of Patients	
Female	208 (90.4)	212 (90.2)
Number of PONV Risk Factors:		
3	108 (47.0)	105 (44.7)
4	111 (48.3)	121 (51.5)
PONV Prophylaxis:		
1 antiemetic	121 (52.6)	120 (51.1)
2 antiemetics	91 (39.6)	96 (40.9)
≥3 antiemetics	18 (7.8)	12 (5.1)

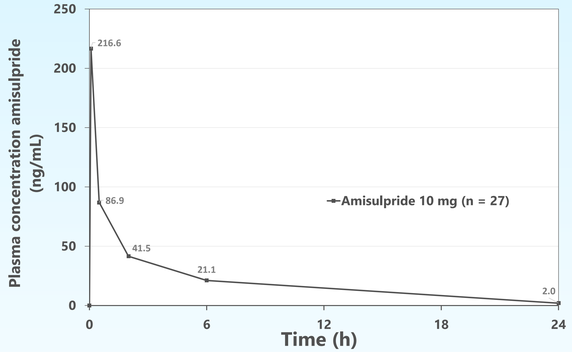
Results

Figure 1. Kaplan Meier Curve of Complete Response



- CR was significantly greater in patients receiving IV amisulpride 10 mg (41.7%) compared to placebo (28.5%) 13.2% difference (95% CI, 4.6 to 21.8; odds ratio, 1.80; P = 0.006)
- Amisulpride demonstrated an immediate separation of the Kaplan Meier curves and was maintained over 24 hours

Figure 2. Plot of Amisulpride Mean Plasma Concentration vs Time



- The mean plasma concentration of amisulpride at 24 hours was 2 ng/mL
- Based on the molecular weight of amisulpride (369.48 g/mol) and the mean plasma concentration of amisulpride at 24 hours, this converts to 5.42 nM, which exceeds the Ki at the D_2/D_3Rs (1-3 nM)
- Supratherapeutic amisulpride plasma levels were maintained for at least 24 hours after a single dose of IV amisulpride 10 mg

Discussion

- Supratherapeutic plasma concentrations were maintained for at least 24 hours, exceeding the binding affinity for amisulpride at D_2/D_3Rs (1-3 nM), thus allowing amisulpride to bind to D_2/D_3Rs
- Since the dopaminergic neurons of the area postrema, believed to be critical to the nausea and vomiting response, lie outside of the blood brain barrier, plasma levels are an appropriate indicator of concentrations at the relevant receptors
- Pharmacodynamically, significantly more patients exhibited a sustained antiemetic effect, as measured by CR, at 24 hours for PONV rescue after a single dose of amisulpride 10 mg IV compared to placebo
- Amisulpride also displayed a rapid onset of action, displayed in the immediate separation of Kaplan Meier curves and continued for at least 24 hours after the study drug was administered

Conclusion

- In the PK subset of patients, a single dose of IV amisulpride 10 mg exhibited supratherapeutic amisulpride plasma concentration levels at 24 hours for PONV rescue
- There is potential antiemetic effect of amisulpride 10 mg beyond 24 hours demonstrated by the continued complete response rate as well as the sustained supratherapeutic amisulpride plasma concentration levels
- This allows perianesthesia nurses to understand the pharmacokinetics and pharmacodynamics of amisulpride when used for the rescue treatment of PONV
- Further investigation is warranted to determine further details of the durable antiemetic effect of amisulpride

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