Aprepitant and Fosaprepitant Drug Interactions: A Systematic Review

Priya Patel[1,2], J. Steven Leeder[3,4], Micheline Piquette-Miller[1], L. Lee Dupuis[1,2,5]

[1]Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Ontario, Canada, [2]Department of Pharmacy, The Hospital for Sick Children, Toronto, Ontario, Canada, [3]Division of Clinical Pharmacology, Toxicology & Therapeutic Innovation, Department of Pediatrics, Children's Mercy-Kansas City, Kansas City, MO, USA, [4]School of Medicine, University of Missouri-Kansas City, Kansas City, MO, USA, [5]Child Health Evaluative Sciences, Research Institute, The Hospital for Sick Children, Toronto, Ontario, Canada

OBJECTIVES

- To conduct a systematic review of the literature to determine if the administration of aprepitant or fosaprepitant results in:
  1. A clinically significant change in the pharmacokinetic (PK) disposition of a concomitant medication (i.e. a victim drug)
  2. A clinically significant adverse event (AE) as a result of giving another medication concomitantly

BACKGROUND

- Aprepitant is recommended by clinical practice guidelines for the prevention of chemotherapy-induced nausea and vomiting
- Aprepitant and fosaprepitant are moderate and weak CYP3A4 inhibitors, respectively. Aprepitant is also a weak CYP2C9 inducer.
- There is no systematic literature review describing interactions between aprepitant or fosaprepitant and other drugs.

METHODS

INFORMATION SOURCES:

- Databases Searched (from inception to September 11, 2016): Ovid MEDLINE(R) + Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Embase Classic + Embase, Cochrane Central Register of Controlled Trials and Web of Science Core Collection
- Grey literature search conducted September 17, 2016

STUDY SELECTION:

- Abstract screening and full text screening completed independently by two reviewers

INCLUSION CRITERIA

- Articles reporting primary data (no date restriction) or conference abstracts (published in 2013 or more recently)
- Human studies
- Evaluates PK disposition of a drug in the presence and absence of aprepitant/fosaprepitant or evaluates/reports AE potentially attributed to an aprepitant/fosaprepitant drug interaction

EXCLUSION CRITERIA

- Duplicate or abstract version of a fully published study
- Not retrievable

DATA COLLECTION

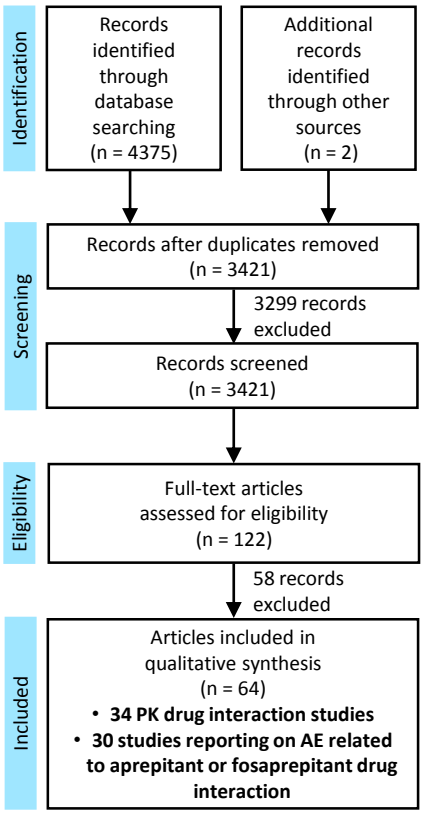
- Data extracted by one investigator and checked for accuracy by a second reviewer
- Risk of bias assessment completed for fully published studies independently by two reviewers using modified Downs and Black quality assessment tool

DEFINITIONS

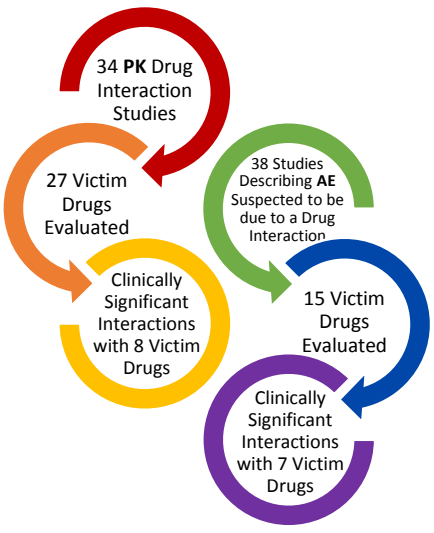
- **Clinically Significant PK Drug Interaction (based on the United States Food and Drug Administration's guidance document for conducting drug interaction studies):**
  - **Geometric Mean Ratio (GMR) of >1.25 or <0.80 for the comparison of a victim drug's maximum concentration (C_{max}) or area under the concentration-time curve (AUC) with aprepitant/fosaprepitant versus without aprepitant/fosaprepitant**
- **Clinically Significant AE Suspected to be a Result of a Drug Interaction:**
  - **AE**: event where a subject experienced discomfort, harm or changes in a laboratory parameter indicative of increased risk for harm
  - **Comparative studies**: statistically significant difference in rate of AE in the presence of aprepitant/fosaprepitant versus absence of aprepitant/fosaprepitant
  - **Case report**: Drug Interaction Probability Scale (DIPS) used to determine probability of interaction with aprepitant/fosaprepitant. DIPS scores ≥5 indicate that a causal relationship between the AE and drug interaction is probable or highly probable.

RESULTS

Figure 1. Study Identification Flow Diagram



RESULTS



Victim Drugs Probably or Highly Probably Associated with Causing a Clinically Significant AE

- Interaction with aprepitant: alcohol, ifosfamide, oxycodone, quetiapine, SSRI/SNRIs and warfarin
- Interaction with fosaprepitant: peripheral IV administration of anthracyclines

Table 1. Summary of Findings Regarding Pharmacokinetic Interactions with Aprepitant/Fosaprepitant

Significance of Interaction	Class of Victim Drug	Drugs Evaluated for PK Interaction with aprepitant	Drugs Evaluated for PK Interaction with fosaprepitant
Clinically significant interaction[a]	Antineoplastic Agent	**bosutinib PO, cabazitaxel IV, cyclophosphamide IV**	none evaluated
	Non antineoplastic Agent	**dexamethasone PO, methylprednisolone IV, midazolam IV and PO, oxycodone PO, tolbutamide PO**	**dexamethasone PO, midazolam PO**
Possibly significant interaction	Antineoplastic Agent	erlotinib (route not reported), ifosfamide IV, pazopanib PO, thiotepa IV	none evaluated
	Non antineoplastic Agent	dexamethasone IV, paroxetine PO, quetiapine PO, tacrolimus IV	none evaluated
Possibly no clinically significant interaction	Antineoplastic Agent	melphalan IV	none evaluated
	Non antineoplastic Agent	alcohol IV, prednisolone PO	none evaluated
No clinically significant interaction[d]	Antineoplastic Agent	dinaciclib IV, docetaxel IV, vinorelbine IV	ifosfamide IV
	Non antineoplastic Agent	digoxin PO, dolasetron PO, granisetron PO, ondansetron IV, palonosetron IV, warfarin PO	none evaluated

[a]met pre-defined definition of clinical significance; [b]significant change in pharmacokinetic parameters observed; GMR of C_{max} or AUC not provided; [c]no significant change in pharmacokinetic parameters observed; GMR of C_{max} or AUC not provided; [d]did not meet pre-defined definition of clinical significance

DISCUSSION & CONCLUSION

- There are clinically significant pharmacokinetic interactions with aprepitant and fosaprepitant
- There is a potential for an adverse event to occur with concomitant use of aprepitant and fosaprepitant and certain victim drugs
- Individuals with reduced capacity to metabolize drugs via CYP3A4 or other pathways may be at higher risk of experiencing clinically significant interactions due to aprepitant/fosaprepitant drug co-administration
- Further investigation of adverse events resulting from aprepitant/fosaprepitant pharmacokinetic drug interactions both in the short term and in the long term is warranted
- Potential for a drug interaction with aprepitant and fosaprepitant should be considered when selecting antiemetic therapy