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Is rolapitant effective in reducing the incidence of chemotherapy-induced nausea and vomiting (CINV) in patients receiving emetogenic chemotherapy?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

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ABSTRACT

Objective: The objective of this selective EBM review is to determine whether or not rolapitant is safe and effective in reducing the incidence of chemotherapy induced nausea and vomiting (CINV) in patients receiving emetogenic chemotherapy.

Study Design: This review is based on three randomized controlled trials (RCTs) all published in 2015. The studies compared the safety and efficacy of rolapitant in decreasing the incidence of CINV.

Data Sources: All articles used were published in English, in peer-reviewed journals, and found using PubMed and the Cochrane Review database.

Outcomes Measured: All included studies measured the safety and efficacy of rolapitant on CINV. Specifically, studies evaluated incidence of emesis, use of rescue medications, and clinically significant nausea based on patient reporting in a study diary and answers to a study-specific questionnaire.

Results: Rapoport et al.¹ found statistical significance ($p = 0.032$) in the effectiveness of rolapitant in reducing CINV in the overall phase. Rapoport et al.² also found statistical significance of this ($p = 0.0013$) as well as Schwartzberg et al.³ ($p = 0.0012$). In the two studies conducted by Rapoport et al. it was found that rolapitant achieved statistical significance in achieving a CR in the acute, delayed, and overall phases. In Schwartzberg et al.³ rolapitant did not achieve a significant response in the acute phase but it did in the delayed phase. Overall rolapitant was well tolerated and any mild side effects were presumed to be a result of the underlying malignancy or the chemotherapy.

Conclusions: Results of all 3 studies included indicate that prophylactic 180mg rolapitant is effective in reducing the incidence of CINV in patients receiving either moderately or highly emetogenic chemotherapy. Since all three studies used concomitant 5-HT₃ receptor antagonists, further studies are warranted to prove the benefit of rolapitant as monotherapy. The question of the effectiveness of rolapitant as compared to others in its same class (NK-1 receptor antagonists) remains as well.

Keywords: Rolapitant, chemotherapy.

INTRODUCTION

Some patients may have risk factors that predispose them to the development of cancers but in reality, cancer can occur at any time and in any patient. It is well known that patients with a variety of different types of cancer will, at some point, be faced with the decision to undergo treatment with chemotherapy. Chemotherapy in itself carries negative stigma. This is probably because it is associated with cancer but can also be attributed to the many side effects that it can cause. Of the many side effects two of the most feared by patients are nausea and vomiting.⁴ CINV is predicted to occur in up to 90% of patients receiving highly emetogenic chemotherapy.⁵ When patients experience these symptoms they may seek treatment via family practice or possibly the emergency room if they develop significant complications such as dehydration.⁵ The point here is that this condition can be seen in many different settings and therefore becomes relevant to medical professionals in a variety of different practices.

It is also relevant because it places a significant economical burden on healthcare. Different types of cancer affect countless patients each year and so, there is no shortage of patients receiving chemotherapy. In a study conducted by Burke, T. in 2011, it was found that more than one in eight patients had a follow-up hospital visit associated with CINV after receiving emetogenic chemotherapy. In this study the average cost of said follow up visit was \$5,300.⁵ Although the exact number of hospital visits related to CINV is unknown, the study showed that 13.8% of patients receiving emetogenic chemotherapy experienced one or more CINV-associated hospital visit.⁵

CINV remains prevalent due to its poorly understood mechanism. Some research exists and the most widely accepted theory is that chemotherapeutic drugs cause nausea and vomiting by activating neurotransmitter receptors in the small intestine; which stimulate the brainstem to

induce vomiting.⁷ Two receptors known to be involved in this pathway are the 5-HT receptor and NK-1 receptor.⁷ For this reason they are a major target of pharmacotherapy. 5-HT₃ receptor antagonists such as granisetron and ondansetron have been valuable in treatment.⁶ NK-1 receptor antagonists such as aprepitant and fosaprepitant have been formulated more recently and have shown to provide more CINV prevention in the overall phase than 5-HT₃ receptor antagonists.⁶ Glucocorticoids, namely dexamethasone, have been evaluated and are used alone or in conjunction with 5-HT or NK-1 receptor antagonists.⁶ Over the past decade or so there have been advances in the medications used to treat CINV but it still remains prevalent even with the most recent therapeutic options.⁶ This is why rolapitant is being proposed as a new medication used to treat CINV. It is a NK-1 receptor antagonist with a much longer plasma half-life than either aprepitant or fosaprepitant.⁶ The hope is that this medication will be more effective in achieving complete control of CINV in patients who are being treated with highly or moderately emetogenic chemotherapy.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not rolapitant is safe and effective in reducing the incidence of chemotherapy induced nausea and vomiting (CINV) in patients receiving emetogenic chemotherapy.

METHODS

Three double blind, randomized controlled trials were included in this systematic review. Studies were selected based on patient demographics, interventions used, comparisons made, and the outcomes that were measured. In all three studies patients were included if they were at least 18 years of age and were scheduled to receive a first course of emetogenic chemotherapy. Schwartzberg et al.³ used patients who would be receiving moderately emetogenic chemotherapy

whereas both studies by Rapoport et al.^{1,2} included patients receiving highly emetogenic chemotherapy. In all three studies patients were given either one oral dose of 180mg rolapitant or visually matched placebo 2 hours prior to administration of emetogenic chemotherapy on day 1. Rapoport et al.¹ gave all patients 32mg IV ondansetron and 20mg oral dexamethasone 30 minutes before initiation of chemotherapy on day 1 and 8mg dexamethasone twice daily on days 2-4. Rapoport et al.² gave all patients 10 µg/kg IV granisetron and 20mg oral dexamethasone on day 1, and 8mg oral dexamethasone twice daily on days 2-4. Schwartzberg et al.³ gave all patients 2mg oral granisetron and 20mg oral dexamethasone on day 1 and 2mg oral granisetron on days 2 and 3. The outcome measured in all studies was the percentage of patients achieving a complete response (CR) in the overall phase (0-120h), where CR is defined as no vomiting or use of rescue medication.

I researched PubMed and the Cochrane Database for all articles included in this study. Key words used in my searches included “rolapitant” and “chemotherapy.” Articles needed to meet certain criteria in order to be selected for the study. All articles included were published in peer-reviewed journals in 2015 in English. Articles were included if they demonstrated outcomes beneficial to patients (POEMs) and if they were double blind RCTs with matched placebo. Articles were excluded if the dose of rolapitant was not 180mg. All studies included used statistical analysis on their data including p-values and confidence intervals.

Table 01. Demographics and Characteristics of Included Studies

Study	Type	# of Pts	Age (years)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Rapoport, 2015 (1)	RCT	181	20-77	Patients \geq 18 years scheduled to receive highly emetogenic chemotherapy; Karnofsky performance score of 60 or more	Patients with ongoing vomiting; that had previously received cisplatin or were planning to receive cisplatin; taking other drugs that could interfere with the study (corticosteroids)	14	180mg oral rolapitant vs. visually matched placebo
Rapoport, 2015 (2)	RCT	532	20-90	Patients \geq 18 years old scheduled to receive cisplatin-based chemotherapy; Karnofsky performance score of 60 or more	Patients with ongoing vomiting; current medical condition other than malignant disease that would confound the results of the study or pose risk to the patient; previous use of cisplatin or planning to receive cisplatin	6	180mg oral rolapitant vs. visually matched placebo
Schwartzberg, 2015 (3)	RCT	1,332	22-88	Patients \geq 18 years old scheduled to receive a first course of moderately emetogenic chemotherapy; Karnofsky performance score of 60 or more	Patients with ongoing vomiting; current medical condition other than malignant disease that would confound the results of the study or pose risk to the patient; previous/current use of cisplatin	68	180mg oral rolapitant vs. visually matched placebo

OUTCOMES MEASURED

Outcomes that were significant endpoints to all studies include incidence of emesis, use of rescue medications, and clinically significant nausea. All 3 of the included studies measured their outcomes in the same manner. All events of nausea, emesis, or use of rescue medications were recorded in each patient's study diary for the first 120 hours of cycle 1. Nausea was measured on a 100-mm horizontal 10-point visual analog scale (VAS) with clinically significant nausea being defined as >25mm. The Functional Living Index-Emesis (FLIE) questionnaire was used to determine the impact of CINV on patient daily living. This included 9 questions on both nausea and vomiting, which were on a 7-point VAS. Any score >108 was defined as having no effect on daily living.

Safety was another endpoint of all studies included. In all three studies safety was assessed based on clinical review of adverse events reported by patients. When a patient reported any adverse event patients received a work-up including vital signs, physical examination, electrocardiogram, and other clinically relevant lab value readings.

RESULTS

All three studies were conducted using the methods outlined previously. In Rapoport et al.¹ 454 patients were treated with rolapitant (or placebo) at varying doses. Doses of 9mg, 22.5mg, 90mg, and 180mg were administered. All patients were randomly assigned to treatment groups. 90 total patients were given 180mg rolapitant vs. 91 patients who received placebo. In this study most patients were male by chance. 38 patients withdrew from the study most commonly due to adverse events. In Rapoport et al.², 526 patients (264 rolapitant and 262 active control) were randomized into two treatment groups which received either 180mg rolapitant or

placebo. This study, like the first, included more males than females by chance and the most common primary malignancy was lung cancer. 25 patients withdrew from the study most commonly due to withdrawal of consent. In Schwartzberg et al.³, 1,332 patients were randomly assigned into two treatment groups. The groups received either 180mg rolapitant or placebo. In this study, patients were mostly women with a primary malignancy of breast cancer. 34 patients withdrew from each treatment group. Withdrawal of consent was the most common reason.

Efficacy of Rolapitant

In all three of the included studies, the efficacy of rolapitant was proven to be statistically significant as compared to placebo in achieving a complete response in the overall phase. These data are highlighted below by Table 02.

Table 02. Efficacy of Rolapitant on CINV in the Overall Phase

Study	Intervention (% of pts with CR)		Odds Ratio (95% CI)	p-value
	Rolapitant 180mg	Active Control		
Rapoport et al. ¹	62.50%	46.70%	NA	0.032
Rapoport et al. ²	70%	56%	1.8 (1.3-2.6)	0.0013
Schwartzberg et al. ³	62%	53%	1.4 (1.2-1.8)	0.0012

In Rapoport et al.¹ the primary endpoint of the study was those patients receiving a CR in the overall phase. They also measured CR in the acute phase (0-24h) and the delayed phase (24-120h). Rolapitant was more effective than placebo in achieving a CR in all three phases. Furthermore, patients who received 180mg of rolapitant had greater rates of no emesis or significant nausea and overall fewer patients required the use of rescue medications in the acute,

delayed, and overall phases as compared to placebo. Through use of the FLIE questionnaire it was also determined that patients who received 90mg and 180mg rolapitant had significantly improved quality of life as compared to placebo.

In Rapoport et al.² the primary endpoint of the study was those patients receiving a CR in the delayed phase (24-120h). They also measured CR in the acute phase (0-24h) and the overall phase (0-120h). Rolapitant was more effective than placebo in achieving a CR in all three phases. When comparing results of the acute phase CR and delayed phase CR it was discovered that there was a correlation of CR in acute and delayed phases. If a patient had a CR in the acute phase that patient was more likely to continue to achieve a CR within the delayed phase as well.

In Schwartzberg et al.³ the primary endpoint of the study was those patients receiving a CR in the delayed phase (24-120h). Patients in the rolapitant study group achieved a significantly greater rate of CR in the delayed phase as compared to placebo. They also measured CR in the acute phase (0-24h) and the overall phase (0-120h). Rolapitant was more effective than placebo in achieving a CR in the overall phase but in the acute phase there was no significant difference. In patients who did not need rescue medication or vomit within the first 48 hours, they were more likely to remain protected in the overall phase as compared to placebo.

Each individual study proved the efficacy of rolapitant in achieving a CR in the overall phase. The number needed to treat (NNT) was determined for each individual study and then converted into one final NNT relevant to the data for all 3 studies. This final NNT came to 7. These data are displayed below in table 03.

Table 03. Efficacy of Rolapitant on CINV: NNT

% of patients with CR on placebo	% of patients with CR on rolapitant	Relative risk reduction (RRR)	Absolute risk reduction (ARR)	Number needed to treat (NNT)
CER	EER	$\frac{EER - CER}{CER}$	EER - CER	1/ARR
53.6%	67.2%	25.4%	13.6%	7

Safety of Rolapitant

In Rapoport et al.¹ there were incidences of both mild and severe adverse events (AE). The mild AEs were dizziness, headache, constipation, and fatigue. Serious AEs occurred in 11% of patients and included nausea, vomiting, dehydration, febrile neutropenia, neutropenia, pneumonia and renal failure. AEs occurred equally amongst all treatment groups and were most likely due to underlying progression of malignancy or the chemotherapy itself. 12 deaths occurred in patients during this study, which were all attributed to cancer progression or chemotherapy. In Rapoport et al.² the incidence of AEs was randomly split between the rolapitant study group and the placebo study group. The most common AEs included headache, dyspepsia, constipation, and hiccups. There were no treatment related deaths amongst either study group. In Schwartzberg et al.³ the incidence of AEs was randomly split between the rolapitant study group and the placebo study group. The most common AEs included dizziness, headache, constipation, and, fatigue. There were few incidences of neutropenia and febrile neutropenia across both study groups but there were no treatment related deaths amongst either study group.

Table 04. Common Mild Adverse Events Organized by Study

Adverse Event		
Rapoport et al. ¹	Rapoport et al. ²	Schwartzberg et al. ³
dizziness	headache	dizziness
headache	dyspepsia	headache
constipation	constipation	constipation
fatigue	hiccups	fatigue

DISCUSSION

In all three studies rolapitant achieved statistical significance in reducing the incidence of CINV in the overall and delayed phases. In the acute phase this was true of both studies done by Rapoport et al. but Schwartzberg could not prove this. It was also true of two studies, Rapoport et al.² and Schwartzberg et al.³, that when patients achieved a CR in the acute phase they were more likely to continue to achieve a CR in the overall phase. This could indicate that preventing CINV in patients acutely could help to eliminate it in the overall phase as well.

Rolapitant has known drug interactions that can limit its use. Since the liver metabolizes it, it is also limited in those patients with significantly decreased liver function.⁷ It can still be given if need be, but those patients need to be carefully monitored throughout therapy.⁷

The most common AEs during treatment were mild and included constipation, fatigue, headache, and dizziness. Patients tolerated these side effects well. It was supposed that most of the AEs were a result of worsening underlying disease or the chemotherapy treatment. There were a number of deaths across all studies but none that could be contributed to treatment with rolapitant.

One of the main limitations of my search was that rolapitant has been very minimally studied. Therefore, the number of studies fitting my criteria was few. All of the studies included

had some of the same authors involved and also had virtually identical study designs. It may have been helpful to have different methods used in order to get a better understanding of how effective rolapitant can be in different patient populations as well as in combination with different concomitant therapies. A limitation common to all three studies was the use of concomitant 5-HT₃ receptor antagonists. Rolapitant was proven to be more beneficial in achieving a CR than using a 5-HT₃ receptor antagonist alone. Now, the question remains; would rolapitant still be as effective without concomitant use of a 5-HT₃ receptor antagonist?

CONCLUSION

This systematic review indicates that rolapitant can be used to achieve significantly greater relief from CINV in patients receiving either moderately or highly emetogenic chemotherapy. In all three studies patients received a CR in the overall phase meaning that they were adequately protected from CINV the entire time they were at risk. Patients experienced some mild side effects but it was not discernable if this was due to rolapitant. It was presumed that rolapitant was well tolerated in all individuals and that patients suffered side effects from either their cancer or the chemotherapy. Future studies should be focused on the efficacy of rolapitant without concomitant 5-HT₃ receptor antagonists. It is true that rolapitant offers better overall protection from CINV but it should be tested alone. If this were done it could lessen the pharmacologic burden on patients. Rolapitant should also be tested alongside other NK-1 receptor antagonists to prove its efficacy as compared to other medications in the same class. Limitations aside, it has still been shown that rolapitant is a step in the right direction for the improvement of CINV.

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