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A Multi-center Comparison of the Safety of Oral versus Intravenous Acetylcysteine for Treatment of Acetaminophen Overdose

The Toxicology Investigator Network Authorship Group

Abstract

Oral and intravenous (IV) acetylcysteine are used for treatment of acetaminophen poisoning. The objective of this multi-center study was to compare the safety of these two routes of administration.

METHODS—We conducted a multi-center chart review of all patients treated with acetylcysteine for acetaminophen poisoning. The primary safety outcome was the percentage of patients with of acetylcysteine-related adverse events.

RESULTS—A total of 503 subjects were included in the safety analysis (306 IV only, 145 oral only and 52 both routes). There were no serious adverse events related to acetylcysteine for either route. Nausea and vomiting were the most common related adverse events and were more common with oral treatment (23% vs 9%). Anaphylactoid reactions were more common with IV administration (6% vs 2%).

Conclusions—Intravenous and oral acetylcysteine are both associated with minimal side effects and are safe for treatment of acetaminophen toxicity.

Introduction

Acetylcysteine is the treatment of choice for acetaminophen overdose. It can be administered by either the oral or intravenous route. Previous studies have shown that both routes are effective and have few significant side effects.^{1,2} However, there are no reports that compare the safety of these treatments in a contemporary, multi-center study. The objective of this study was to describe the current use of oral and intravenous acetylcysteine for treatment of acetaminophen poisoning and to compare the safety of oral and intravenous acetylcysteine in a multi-center setting.

Methods

This retrospective chart review included records of patients who received acetylcysteine for acetaminophen overdose or toxicity at one of 11 centers distributed throughout the United States. The method for identifying cases varied among the sites. Nine sites searched pharmacy records and reviewed cases where acetylcysteine was administered; one site reviewed emergency department logs to identify cases of acetaminophen overdose or

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toxicity; two performed a discharge diagnosis search to identify cases of acetaminophen poisoning; and five sites reviewed medical toxicology service consultations (several sites used more than one method). Cases where the patient was treated with acetylcysteine for acetaminophen overdose or toxicity were included in the analysis. All records were reviewed by trained abstractors using a standardized data collection form. Abstractors were trained on practice cases. The practice cases had been previously abstracted by two senior investigators who produced a “gold standard” used to evaluate the practice cases. All discrepancies between the abstractors and the gold standard were reviewed with the abstractors during a training session. Data were collected at each site for 18 months. Not all sites started at the same time; the data collection periods ranged from June 2006-December 2007 to September 2006-February 2007. This study was approved by the IRB of each center and qualified for a waiver of informed consent.

Data collected included patient demographics, clinical information including type of acetaminophen ingestion/overdose, co-ingestions, medical history, medical outcome, alanine transaminase (ALT) and aspartate aminotransferase (AST) activity and serum acetaminophen concentration. The type of ingestion was defined as acute ingestion (acetaminophen ingested over a period less than 8 hours), repeated supratherapeutic (acetaminophen ingested over more than 8 hours) or other/unknown.

The data collection tool provided a checklist of 14 pre-defined adverse events including gastrointestinal reactions (nausea or vomiting), anaphylactoid reactions (bronchospasm, pruritus, flushing, urticaria, non-urticarial rash, angioedema, stridor, chest tightness, hypotension,) and three other adverse events (tachycardia, presyncope/syncope, anxiety). Adverse events were classified by relatedness (related versus not related) and seriousness (serious versus nonserious) by the site investigators while they were abstracting the case from the medical record. Investigators were instructed to consider adverse events related to acetylcysteine if the event was temporally related to acetylcysteine administration and the investigator could not identify an alternative cause. Adverse events were rated as serious using an adaptation of the FDA definition (an event that results in death, in-patient hospitalization or re-hospitalization or prolongation of hospitalization, persistent or significant disability/incapacity or that required intervention to prevent permanent impairment or damage.)

Our research plan was to have all cases abstracted independently by two reviewers. However not all sites were able to double abstract cases for the entire study so an undetermined proportion of cases were only abstracted by a single reviewer. Differences between abstractors were resolved by discussion between the abstractors and review of the medical record prior to submission to the data management center. If differences could not be resolved, the site investigator made the final determination. At the data management site, we performed a basic data verification to identify invalid results (e.g. reported time of labs occurred before the patient was admitted to a healthcare facility). When invalid results were identified, the cases were returned to the site investigator for correction.

As some subjects received both oral and IV acetylcysteine, we performed our analysis two ways. For our primary outcome, we considered the patient as the unit of analysis. Subjects were categorized by their treatment route as “oral-only group”, “IV-only group” and “both group”. We then calculated the percent of subjects (with 95% CI) who had an adverse event in each of these groups. Our second comparison was conducted using the treatment route as the unit of analysis. For this analysis subjects receiving both IV and oral acetylcysteine could count toward the total number of adverse events in both treatment routes. For example, if a patient had a rash while receiving IV acetylcysteine, and was changed to oral acetylcysteine and has vomiting, that patient would count as an adverse event for the IV

route and as an adverse event for the oral route. This analysis was performed to identify bias due to exclusion of subjects who had their treatment route changed due to an adverse event. In a secondary safety analysis, the by subject and by treatment route analyses were performed with the adverse events categorized as “gastrointestinal” and “anaphylactoid” subtypes using the above described definitions.

For our descriptive analysis, continuous variables were presented as means (with standard deviations-SD)) or medians (with interquartile range-IQR) and categorical variables were presented as counts and percents. Continuous variables were compared among the three treatment groups using ANOVA (for normally distributed continuous data), Kruskal Wallis test (for non-normal continuous data) or X^2 (for proportions). The X^2 test for trend was used to determine if the percentages of patients having anaphylactoid reactions was associated with serum acetaminophen concentration. Absolute risks differences and confidence intervals were used to compare primary safety variables. We considered an absolute risk difference statistically significant if the 95% confidence interval did not include zero. Finally, we used logistic regression to determine the odds ratio (IV versus oral) for a related adverse event after adjustment for potential confounders. The potential confounders we considered were age, gender, prior vomiting, administration of activated charcoal and the occurrence of any co-ingestion. Data were analyzed using SAS Version 9.1.3.

Results

Five hundred and three records were collected from the eleven investigative sites (Figure 1). The characteristics of the population are shown in Table 1. The three groups are of similar age and gender. For all groups, most cases (55%) were classified as acute ingestions, but a proportion of ingestions were repeated ingestions (24%) or could not be classified by the investigator using the documented history (21%). Most patients had a co-ingestion of some type.

The majority of patients (61%) were treated with IV acetylcysteine for their entire course (IV-only group). The next largest group (29%) was those treated with oral acetylcysteine for the entire course (oral-only group). The route of treatment was changed during the course of acetylcysteine treatment in 52 (10%) patients (the both group); 19 patients initially received IV acetylcysteine and were switched to oral acetylcysteine, 28 patients initially received oral acetylcysteine and were switched to IV acetylcysteine, 4 patients were treated with oral-IV-oral and 1 patient received an unknown route of acetylcysteine at a hospital before being transferred to the study hospital and receiving IV acetylcysteine. The most common reasons reported for switching treatment route included the following (more than 1 reason could be selected for each patient): stopped due to an acetylcysteine-related adverse event (12), decreased mental status or too sleepy (3), liver transplant (2), transfer (3), patient leaving the hospital prior to completing the IV protocol (2) and physician discretion (9).

Overall 90.3% of the patients survived without liver transplant, 0.4% had a liver transplant, 5.2% of the patients died and 4.2% had an unknown outcome (Table 1). The median (IQR) duration of treatment was 31.4 (20.4 to 50.7) hours for the oral-only group 26.4 (13.2 to 52.0) hours for the IV-only group and 47.5 (31.7 to 79.5) hours in the both group. Thirty-six percent of patients in the IV-only group were treated within 10 hours of ingestion (the maximum time to treatment recommended on the label) while 41% of those in the oral-only group were treated within 10 hours of ingestion.

Adverse Reactions

Of the 306 IV only patients, 215 experienced a total of 423 adverse events reported in IV-only group (Table 2). Of the adverse events, 81.3% (344/423) were not related to

acetylcysteine, and 18.7% (79/423) were related and non-serious. There were 20 non-acetylcysteine related deaths and no serious and related adverse events reported in this group. Forty-two of the 306 IV-only subjects (13.7%; 10.0 to 18.1%) had one or more non-serious, related adverse events while being treated with acetylcysteine. The percentages of patients having related GI, anaphylactoid and other reactions were 8.8%, 5.9% and 2.9% respectively.

There were 114 adverse events reported by 80 of the 145 patients treated in the oral-only group (Table 2). Of these adverse events, 52.6% (60/114) were judged not related to acetylcysteine treatment, while 47.4% (54/114) were judged as non-serious and related. There was one non-acetylcysteine related death and no serious and related adverse events reported in this group. Thirty-seven subjects (25.5%; 95% CI: 18.7 to 33.4%) in the oral-only group had one or more non-serious, related adverse events. The percentages of patients having GI, anaphylactoid and other reactions judged as related to acetylcysteine were 22.8%, 2.1% and 2.1% respectively.

There were 103 adverse events reported in the both group (Table 3). Of the adverse events, 65.0% (67/103) were judged as not related to acetylcysteine, while 35.0% (36/103) were judged as related and non-serious. There were five non-acetylcysteine related deaths and no serious and adverse events were judged as related to acetylcysteine. Twenty of the 52 subjects (38.5%) in the both group had one or more related adverse events. The percentages of patients having related GI, anaphylactoid and other reactions during IV administration were 13.5%, 5.8% and 5.8% respectively. The percentages of patients having related GI, anaphylactoid and other reactions during oral administration were 26.9%, 0% and 0% respectively.

The percentage of subjects with related adverse events was 11.8% (95% CI 3.7 to 19.9%) higher for the oral-only group than for the IV-only group. In the final model only age, gender, co-ingestion and vomiting prior to NAC were significantly and independently associated with related adverse event. After adjustment for these factors, the odds ratio of a related adverse event for the IV versus the oral group was 0.45 (0.27 to 0.75).

The 11.8% difference in the percentage of adverse events between the oral-only and IV-only groups was primarily due to a higher percentage of subjects with related GI adverse events in the oral-only group (absolute risk difference 13.9%, 95% CI 6.4 to 21.5%). In an analysis adjusted for the confounders listed above, the odds ratio for a related GI adverse event in the IV-only group was 0.31 (95% CI 0.18 to 0.55) compared to the oral-only group.

As the relatedness of nausea and vomiting may be difficult to determine retrospectively, we also compared the proportions of subjects with any vomiting reported (unrelated or related). In this analysis, the risk of any vomiting was 28.1% for the IV group and 17.9% for the oral group, giving a risk difference of 10.6% (95% CI 2.2 to 18.2%) in favor of oral acetylcysteine. However, the rate of vomiting prior to acetylcysteine was 9.1% higher for the IV group. The rate of antiemetic use was similar between the two groups.

The risk of a patient having a related anaphylactoid reaction in the IV-only group was 5.9% while the risk in the oral-only group was 2.1%, giving a risk difference of 3.8% (95% CI 0.3% to 7.3%). Finally, as the risk of an anaphylactoid reaction may be related to the serum acetaminophen concentration³, we determined the percent of subjects having related anaphylactoid adverse events for each quartile of acetaminophen concentration for the IV route. The percentage of patients in each quartile having an anaphylactoid reaction was similar among the quartiles (5%, 11%, 3%, 6% for the lowest to highest quartiles, $p=0.53$ χ^2 test for trend). However, these results are limited because the number of related events was small in each quartile.

When comparing adverse event mentions by their associated route of NAC administration (i.e. the patients in the both route group are counted as events by the route of administration when the event occurred), the IV-route group had a rate of 26.3% (94/358) related adverse events per treatments administered, while the oral-route group had a rate of 37.5% (75/200) related adverse events per treatments administered (absolute risk difference 11.2%, 95% CI 3.3 to 19.2%; Table 4).

Discussion

Oral and intravenous acetylcysteine are both safe for treatment of acetaminophen ingestion. As the results obtained in the “by route” analysis produced similar findings to the “by patient” analysis, our discussion will focus on the oral versus IV comparison in the by “route analysis”.

No serious adverse reactions were judged related to either treatment. The rate of related nausea and vomiting was higher in the oral acetylcysteine group than in the IV group, but the rate in the IV group was also clinically significant (approximately 10%). The percentage of patients with any related anaphylactoid reaction in the IV group was higher than the oral group. This percentage (6%) is similar to the percentage reported in another retrospective study⁴, but was much lower than the 15 to 50% reported in prospective studies⁵⁻⁸, where minor reactions are more likely to be detected. Overall, very few patients had their route of treatment changed due to adverse reactions, further confirming the overall safety and tolerability of both routes.

This study provides a broad picture of how acetylcysteine is used in academic centers in the U.S. Previous studies of acetylcysteine have focused only on acute ingestions with a known time of ingestion.⁹⁻¹⁶ We found a high percentage of patients in this study that were treated for repeated supra-therapeutic ingestions or an unknown type of ingestion (most commonly due to inability to obtain an ingestion history in a patient with altered mental status due to co-ingestion or liver failure). Patients with repeated ingestions or an unknown time of ingestion represent a clinical challenge because they cannot be risk stratified using the Rumack-Matthew nomogram. Given the high number of patients who cannot be adequately risk stratified using standard methods, our findings suggest that there is a need for alternative methods of risk stratification that can be used in these populations. We also discovered that most patients treated with oral acetylcysteine were not treated for the full 72-hour course. Also, over half of patients treated with intravenous acetylcysteine were treated with more than the standard 20-hour protocol. This suggests that clinicians at these institutions are not using time-based treatment protocols, but rather are determining the duration of treatment using some other approach (such as treating to an undetectable serum acetaminophen concentration and normal or improving serum ALT).¹⁷

We also found that a minority of patients were being treated using a combination of oral and IV acetylcysteine. This group of patients has not previously been characterized in a large study. The proportion of subjects experiencing an adverse event in this group was higher than the rate observed for either the oral or IV group. A comparison of the rate of adverse events in this group (Table 3) suggests that the main source of adverse events was an increased rate of vomiting during the oral route. This may reflect a pattern of care where patients were started on oral NAC and then changed to IV NAC once they developed vomiting.

There are limitations to the interpretation of the results of this study. The most obvious is that this was an observational study where the treating physician determined treatment. This limits definitive comparisons between the two treatment routes as there are measured and

unmeasured differences in the baseline characteristics of the groups that may account for the differences in adverse events. For example, the rate of single substance ingestions was approximately 8% higher in the group treated with oral acetylcysteine, and the oral-only group had a median duration of treatment that was 5 hours longer than the IV-only group, and therefore they were “at risk” for a treatment-related adverse event longer than the IV-only group. More importantly, there were substantially more non-acetylcysteine related deaths in the IV-only group suggesting that they were sicker than the oral-only group. Our design does not allow us to determine what role these differences may play in our results. However, our study provides a “real world” picture of the complications observed during acetylcysteine therapy. This study shows how often patients with acetaminophen poisoning suffer nausea and vomiting (Table 2) and suggests that the mechanism is both overdose and antidote. The use of antiemetics was high in both groups (Table 1), further emphasizing how common and significant these symptoms are. Our logistic model suggests that the risk of vomiting after treatment is increased for patients who have vomiting prior to antidote administration and patients who report co-ingestions.

A second limitation was that the abstractors were not blinded to the study hypotheses and were simultaneously determining risk factors and outcomes. This may have introduced a misclassification bias; for example patients treated with oral acetylcysteine may have been more likely to have vomiting categorized as related than those treated with IV acetylcysteine. An alternative analytic approach would be to simply count all events without consideration of relationship to acetylcysteine. This type of analysis would minimize the potential for bias introduced by investigator classification, but in an observational study there is a high probability that measured and unmeasured patient characteristics would be associated with treatment selection and with adverse events (confounding). Thus, the observed associations between adverse events and treatment route would not be causal. Ultimately, we felt that the investigators could make reasonable judgments regarding the relatedness of the adverse event so we made our conclusions regarding safety by considering related events. We recognize that an evaluation based on the overall rate of adverse events may lead to alternative conclusions.

Our estimation of the rate of anaphylactoid reactions is limited by our definition of anaphylactoid reactions. Given our retrospective design, we developed a very broad definition of anaphylactoid reactions, and it is possible that a more structured definition applied prospectively would produce different results. Additionally, our retrospective design may fail to capture some cases or accurately characterize other. It is likely that unidentified cases would be less severely poisoned than the cases included in our series as more severely poisoned patients are more likely to generate a toxicology consultation or treating clinician's attention. It is also possible that the use of different case-finding methods among the centers may have resulted in different case characteristics among the centers. Finally, the validity of our estimate of all adverse reactions is limited by the documentation of adverse events. It is likely that our findings are an underestimate; however, there is no reason to believe that there would be differential misclassification between the oral and IV routes, so we believe our comparisons between the routes are valid.

The generalizability of our findings may be limited as all centers had medical toxicology consulting services guiding therapy, potentially introducing deviations from “standard” treatment protocols such as shorter or longer duration of treatment or changing between administration routes. Clinicians with less experience may not be willing to deviate from standard treatments. As our study did not enroll any children younger than 13 years of age, our results may not be generalizable to younger pediatric patients.

In summary, while minor adverse events were relatively common with both routes, there were no serious related adverse events associated with either treatment. Previous studies have reported that efficacy for prevention of hepatotoxicity is similar for the two routes.^{2,18} As the safety and efficacy of oral and IV acetylcysteine are similar, we believe either route of treatment is acceptable and the selection of route should be based on physician and patient preference.

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Figure 1.
Characterization of Subjects – Safety Population

Table 1

Baseline characteristics and outcomes for patients treated with acetylcysteine by oral, intravenous or both routes. IV= intravenous, RSTI= repeated supratherapeutic ingestion, ALT=alanine aminotransferase, AST= aspartate amino transferase, APAP= acetaminophen.

Characteristics	IV (n=306)	Oral (n=145)	Both (n=52)	P Value
Age (years), median (IQ Range)	33 (23-45)	35 (23-45)	35 (20-43)	0.8869
Weight (kg), median (IQ Range)	70 (61-84)	71 (61-83)	71 (59-82)	0.2200
Gender, n (%)				
Male	106 (34.6)	52 (35.9)	19 (36.5)	0.9462
Female	200 (65.4)	93 (64.1)	33 (63.5)	
Ethnicity, n (%)				
African American	44 (14.4)	26 (17.9)	6 (11.5)	
Asian	12 (3.9)	0 (0.0)	3 (5.8)	
Caucasian	193 (63.1)	74 (51.0)	29 (55.8)	0.0212
Hispanic/Latino	28 (9.2)	19 (13.1)	7 (13.5)	
Native American	0 (0.0)	0 (0.0)	0 (0.0)	
Unknown	29 (9.5)	26 (17.9)	7 (13.5)	
Type of ingestion n (%)				
Acute	158 (51.6)	86 (59.3)	34 (65.4)	
RSTI	60 (19.1)	48 (33.1)	11 (21.1)	<0.0001
Unknown	88 (28.8)	11 (7.6)	7 (13.5)	
Co-Ingested Agent, n (%) *				
Antihistamines	82 (26.8)	33 (22.8)	12 (23.1)	0.6080
Alcohol	76 (24.8)	31 (21.4)	13 (25.0)	0.7085
Opiates	123 (40.2)	52 (35.9)	18 (34.6)	0.5692
None listed	90 (29.4)	54 (37.2)	21 (40.4)	0.1195
Clinical History, n (%) *				
Viral hepatitis	23 (7.5)	13 (9.0)	4 (7.7)	0.8661
Chronic alcohol abuse	77 (25.2)	31 (21.4)	13 (25.0)	0.6705
Malnutrition	5 (1.6)	2 (1.4)	1 (1.9)	0.9599
Other liver disease	5 (1.6)	1 (0.7)	1 (1.9)	0.6843
Asthma	33 (10.8)	13 (9.0)	5 (9.6)	0.8292
None listed	188 (61.4)	97 (66.9)	31 (59.6)	0.4699
Decontamination Method, n (%) *				
Activated charcoal	53 (17.3)	34 (23.5)	16 (30.8)	0.0488
Gastric lavage	7 (2.3)	3 (2.1)	2 (3.9)	0.7590
Whole bowel irrigation	0 (0.0)	0 (0.0)	1 (1.9)	0.0130
Other	6 (2.0)	1 (0.7)	1 (1.9)	0.5896
None	245 (80.1)	111 (76.6)	34 (65.4)	0.0604
Antiemetic, n (%)	81 (26.5)	37 (25.5)	20 (38.5)	0.1664
Lab Values at Presentation, median				
APAP Level (mcg/mL)	41.8	33.2	93	0.0205

Characteristics	IV (n=306)	Oral (n=145)	Both (n=52)	P Value
ALT (IU/L)	54.0	34.0	84.0	0.0005
AST (IU/L)	56.0	30.0	72.0	0.0002
Median time to acetylcysteine (hr)	9.1 [#]	10.0 [#]	10.2 [#]	0.8115
Peak ALT or AST >1000 IU/L [†] n(%)	102 (33.3)	21 (14.5)	25 (48.1)	<0.0001
Outcome, n (%)				
Condition Resolved	273 (89.2)	137 (94.5)	44 (84.6)	
Death	20 (6.5)	1 (0.7)	5 (9.6)	0.0001
Organ Transplant	0 (0.0)	0 (0.0)	2 (3.9)	
Unknown	13 (4.3)	7 (4.8)	1 (1.9)	

* Percentages do not add up to 100 because they are not mutually exclusive categories.

[†] Indicates at any time point before, during or after NAC treatment.

[#] Time to acetylcysteine could be determined for 206 patients in the IV group, 115 patients in the oral group and 33 patients in the both group

Table 2

Number of adverse event mentions among patients treated with either the oral or the intravenous route.

		IV (n=306)		Oral (n=145)	
		Related	Not Related	Related	Not Related
Gastrointestinal	Nausea	22 (7.2%)	82 (26.8%)	29 (20.0%)	8 (5.5%)
	Vomiting	20 (6.5%)	66 (21.6%)	19 (13.1%)	7 (4.8%)
Anaphylactoid	Bronchospasm	1 (0.3%)	3 (1.0%)	1 (0.7%)	1 (0.7%)
	Pruritus	10 (3.3%)	0 (0%)	1 (0.7%)	1 (0.7%)
	Flushing	6 (2.0%)	2 (0.7%)	0 (0%)	0 (0%)
	Urticaria	4 (1.3%)	1 (0.3%)	0 (0%)	0 (0%)
	Non-urticarial rash	3 (1.0%)	4 (1.3%)	0 (0%)	2 (1.4%)
	Chest tightness	3 (1.0%)	4 (1.3%)	0 (0%)	1 (0.7%)
	Hypotension	1 (0.3%)	39 (12.7%)	1 (0.7%)	8 (5.5%)
Other	Tachycardia	7 (2.3%)	103 (33.7%)	3 (2.1%)	18 (12.4%)
	<u>Pre-syncope/syncope</u>	<u>1 (0.3%)</u>	<u>0 (0%)</u>	<u>0 (0%)</u>	<u>0 (0%)</u>
	Anxiety	1 (0.3%)	40 (13.1%)	0 (0%)	14 (9.7%)

Table 3

Adverse event mentions among patients treated with both oral and intravenous acetylcysteine. The counts are presented to show the route of administration during the adverse event. N=52

Clinical Effect		IV		Oral	
		Related	Not Related	Related	Not Related
Gastrointestinal	Nausea	6 (11.5%)	13 (25.0%)	11 (21.2%)	7 (13.5%)
	Vomiting	3 (5.8%)	4 (7.7%)	10 (19.2%)	3 (5.8%)
Anaphylactoid	Flushing	1 (1.9%)	0 (0%)	0 (0%)	1 (1.9%)
	Non-urticarial rash	0 (0%)	2 (3.8%)	0 (0%)	0 (0%)
	Chest tightness	2 (3.8%)	1 (1.9%)	0 (0%)	0 (0%)
	Hypotension	0 (0%)	7 (13.5%)	0 (0%)	3 (5.8%)
Other reaction	Tachycardia	3 (5.8%)	10 (19.2%)	0 (0%)	7 (13.5%)
	Anxiety	0 (0%)	5 (9.6%)	0 (0%)	4 (7.7%)

Table 4

Related adverse event mentions for all patients using a by route of administration. The counts are presented to show the route of administration during the adverse event. Patients who received both intravenous and oral acetylcysteine and who had adverse reactions during both routes are counted under each route.

Clinical Effect		Total	
		IV ROUTE (N=358)	Oral ROUTE (N=197)
<i>Gastrointestinal</i>	Nausea	28 (7.8%)	40 (20.3%)
	Vomiting	23 (6.4%)	29 (14.7%)
<i>Anaphylactoid</i>	Bronchospasm	1 (0.3%)	1 (0.5%)
	Pruritus	10 (2.8%)	1 (0.5%)
	Flushing	7 (2.0%)	0
	Urticaria	4 (1.1%)	0
	Non-urticarial rash	3 (0.8%)	0
	Chest tightness	5 (1.3%)	0
	Hypotension	1 (0.3%)	1 (0.5%)
	Tachycardia	10 (2.8%)	3 (1.5%)
<i>Other reactions</i>	Pre-syncope/syncope	1 (0.3%)	0
	Anxiety	1 (0.3%)	0
TOTAL		94	75