

Clinical Study

The pattern and risk factors associated with adverse drug reactions induced by Reteplase in patients with acute ST-elevation myocardial infarction: The first report from Iranian population

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ABSTRACT

Objective: Acute myocardial infarction (AMI) is one of the main leading causes of mortality and morbidity. Reteplase is a fibrin-specific thrombolytic which is used in the treatment of AMI. There is a limited number of studies reporting the postmarketing adverse drug reactions (ADRs) induced by reteplase. This study was aimed to examine the reteplase pattern of ADR and its associated risk factors in patients with acute ST-elevation myocardial infarction.

Methods: A cross-sectional, prospective study in an 8-month period was done at the University affiliated referral cardiovascular center. The Naranjo probability scale and World Health Organization criteria for severity of ADRs were used for assessing the ADRs. The linear regression and logistic regression tests were used to evaluate the correlation between ADRs and risk factors.

Findings: The all 20 patients who received reteplase during the study period were entered. The majority of patients ($n = 17$) experienced at least one ADR. The results showed that the incidence of ADRs was mainly associated with gender and age, and the number of ADRs was associated with the history of diabetes and taking anti-diabetic agents. The gender was the main predictor in the occurrence of ADRs (odds ratio: 32, 95% confidence interval: 1.38–737.45; $P = 0.030$).

Conclusion: The results showed that gender, age, diabetes mellitus, and using of anti-diabetes medications are the risk factors associated with the incidence of ADRs by reteplase.

Keywords: Acute myocardial infarction; adverse drug reactions; Reteplase

INTRODUCTION

The adverse drug reactions (ADRs) were assumed as one of the main leading causes of mortality and morbidity in the USA with the increased cost to health care system based on Lazarou *et al.* meta-analysis in 1998.^[1] Furthermore, the Pirmohamed *et al.* analysis of

ADRs in the United Kingdom showed that ADRs are responsible to 1 of 16 hospital admissions with the annually cost of up to £466 million, as well as 0.15% of all mortalities, in hospitals.^[2]

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Reteplase is a recombinant nonglycosylated form of human tissue plasminogen activator (t-PA) which catalyzes the cleavage of endogenous plasminogen to generate the plasmin. Reteplase is similar to alteplase, but the modifications give reteplase a longer half-life of 13–16 min. It produces rapid and faster thrombolytic activity and low incidence of bleeding compared to nonspecific thrombolytics. This fast fibrinolytic activity of reteplase can accelerate the reperfusion in ischemic tissue and help to save time to the patient.^[3-5]

In comparison with streptokinase, reteplase has fewer ADRs along with no antigenicity. Moreover, reteplase has a higher patency rate (84% vs. 60–68%) than streptokinase.^[6] Based on Reteplase versus Alteplase Patency Investigation During acute myocardial infarction (RAPID II) trial, reteplase achieved a higher incidence of thrombolysis in myocardial infarction (TIMI) Grade III flow at 60 and 90 min when compared with alteplase. However, the overall rate of TIMI III flow and mortality rate were not different statistically.^[7]

In the large Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO III) trial, reteplase was similar to alteplase regarding 1-month and 1-year mortality, the incidence of stroke at 1-month, and the combined end point of mortality or nonfatal stroke.^[8,9]

In the International Joint Efficacy Comparison of Thrombolytics (INJECT) trial comparing reteplase with streptokinase, reteplase was significantly associated with the lower rate of cardiogenic shock, hypotension, and a lower incidence of heart failure. However, the rate of 35-day mortality, recurrent myocardial infarction (MI), in-hospital stroke, and major bleeding events were similar with two drugs.^[10]

There is a limited number of studies reporting the ADRs induced by reteplase. This study was aimed to examine the reteplase pattern of ADRs and its associated risk factors in patients with acute ST-elevation MI (STEMI).

METHODS

A prospective cross-sectional study was conducted in Shahid Madani Heart Center, the largest referral center for the cardiovascular disorders in the North-West of Iran for a period of 8 months. The study was approved by the Ethics Committee of the University.

The patients' eligibility criteria included the age of over 18-year-old with a diagnosis of acute STEMI, who candidate for receiving reteplase. Exclusion criteria included patients with chronic kidney and liver disease, pregnant women, patients who were not able to continue the study and the existence of

contraindication to thrombolytic therapy including recent head/ facial trauma and/or ischemic stroke within last 3 months, intracranial tumor, and prior intracranial hemorrhage, suspected aortic dissection, active internal bleeding, or bleeding diathesis, and severe uncontrolled hypertension.^[11]

The reteplase (Retelies®, Osvah Pharmaceutical Co.) was administered with the usual adult dose of AMI as 10 units intravenous (IV) bolus over 2 min as soon as possible after the onset of AMI symptoms, followed by a second 10 unit IV bolus 30 min later over 2 min. If the serious bleeding or anaphylaxis was occurred, the second dose was withheld. All patients concurrently received heparin 60 units/kg bolus (maximum: 4000 units) followed by continues infusion of 12 units/kg/min (maximum: 1000 units/h) by adjusting to aPTT target of 50–70 s. All patients also received a loading dose of 162–325 mg chewable nonenteric coated form of aspirin as well as 300 mg of clopidogrel.^[11]

All patients receiving reteplase that had completed the informed consent form were monitored for ADRs induced by reteplase. Detection and monitoring of ADRs were done through completing a questionnaire by reviewing the patients' medical file and documentation as well as interviewing with the patients.

The questionnaire includes the demographic information, past medical history, drug history, familial, habitual and social history, laboratory, and echocardiographic information.

The causality of ADRs evaluated by Naranjo *et al.* ADR probability scale.^[12] The scores between 1 and 4 ranked as possible, 5–8 ranked as probable, and ≥ 9 ranked as highly probable. The score of ≤ 0 was deemed as doubtful ADR. The severity of ADRs was classified into four levels according to World Health Organization (WHO) system classification: (1) Mild – No need to treatment (2) Moderate – Need to specific treatment, (3) Severe – Cause to prolonged hospitalization, and (4) Very severe – Potential life-threatening or contribute to the death.

Data analysis was done by SPSS 16.0 (SPSS Inc., 2007, Chicago, IL, USA). To identify the normally distribution of data, Kolmogorov–Smirnov test was performed. Spearman test was used to evaluate the correlation between the study parameters. We used the linear regression (stepwise method) to find any relationships between the incidence and number of ADRs and the independent study risk factors. Also, the logistic regression analysis was done to assess the independent predictors involved in the incidence of ADRs. Continues data were showed as a mean \pm standard deviation. $P < 0.05$ were considered statistically significant.

RESULTS

The all 20 patients who received reteplase during the study period were entered. The most number of patients were male ($n = 17, 85\%$). The mean age of study population was 58.8 ± 11.1 years old. All patients spent 3.8 ± 0.8 days in critical care unit. The half of patients experienced the anterior part of MI. The other half experienced the inferior part of MI. The number of ADRs experienced by patients was between 0 and 8. The most patients ($n = 17, 85\%$) experienced at least one ADR. Furthermore, the mean number of ADRs was 3.2 ± 2.7 per patients. In average, each male patient experienced 3.4 ADRs, as well as 2 ADRs, was experienced by females.

The patients' demographics and clinical data are listed in Table 1. The frequency of documented ADRs was presented in Table 2. The most common ADRs were chest pain, nausea, vomiting, and coughing that were occurred in one-third of all patients. Based on Naranjo scale for measuring the probability of ADRs, the most ADRs ranked as "possible ADR" [Table 2]. The anaphylactic reactions as the most serious ADR were documented in two patients that treated by antihistamine and corticosteroid.

The WHO severity classification of ADRs was shown in Table 3. According this table, the most

ADRs were categorized in mild-moderate ADRs and the most ADRs were resolved without the need for treatment. The most severe ADRs were the anaphylactic reactions and bradycardia. The

Table 1: The medical history of patients received reteplase

Characteristics	n (%)
Medical and habitual history	
Myocardial infarction	3 (15)
Cerebrovascular accident	1 (5)
Diabetes mellitus	4 (20)
Ischemic heart disease	4 (20)
Hypertension	7 (35)
Surgery	5 (25)
Percutaneous coronary intervention	4 (20)
Hyperlipidemia	5 (25)
Other diseases	10 (50)
Smoking	7 (35)
Alcohol consumption	1 (5)
Substance abuse	1 (5)
Family history of myocardial infarction	6 (30)
Drug history	
Cardiovascular drugs	5 (25)
Anti-hyperlipidemia drugs	3 (15)
Nonsteroidal anti-inflammatory drugs	2 (10)
Central nervous system drugs	2 (10)
Anti-diabetes drugs	3 (15)

Table 2: Probability of ADRs based on Naranjo scale

Type of ADR	n (%)	Naranjo ADR probability scale				
		No ADR (%)	Doubtful (%)	Possible (%)	Probable (%)	Highly probable
Abdominal cramp	2 (10)	18 (90)	1 (5)	1 (5)		
Allergy	1 (5)	19 (95)		1 (5)		
Anaphylactic reactions	2 (10)	18 (90)			2 (10)	
Back pain	5 (25)	15 (75)		5 (25)		
Blurred vision	3 (15)	17 (85)		3 (15)		
Body numbness	1 (5)	19 (95)	1 (5)			
Bradycardia	3 (15)	17 (85)		3 (15)		
Chest pain	7 (35)	13 (65)	2 (10)	5 (25)		
Chilling	1 (5)	19 (95)		1 (5)		
Constipation	2 (10)	18 (90)		2 (10)		
Cough	6 (30)	14 (70)	1 (5)	5 (25)		
Ecchymosis at injection site	3 (15)	17 (85)		1 (5)	2 (10)	
Edema and pain in extremities	2 (10)	18 (90)		2 (10)		
Fever	2 (10)	18 (90)		2 (10)		
Hard breathing	4 (20)	16 (80)	1 (5)	3 (15)		
Head numbness	1 (5)	19 (95)		1 (5)		
Headache	4 (20)	16 (80)		4 (20)		
Increase in mucosal secretion	1 (5)	19 (95)		1 (5)		
Itching	1 (5)	19 (95)		1 (5)		
Nausea/vomiting	6 (30)	14 (70)		6 (30)		
Stress during sleeping	2 (10)	18 (90)		2 (10)		
Sweating	4 (20)	16 (80)	1 (5)	3 (15)		
Tachycardia	1 (5)	19 (95)		1 (5)		

ADRs=Adverse drug reactions

Table 3: WHO classification of severity of ADRs

Type of ADR	n (%)	Severity of ADRs (%)				
		No ADR	Mild	Moderate	Severe	Highly severe
Abdominal cramp	2 (10)	18 (90)	2 (10)			
Allergy	1 (5)	19 (95)	1 (5)			
Anaphylactic reactions	2 (10)	18 (90)				2 (10)
Back pain	5 (25)	15 (75)	4 (20)	1 (5)		
Blurred vision	3 (15)	17 (85)	3 (15)			
Body numbness	1 (5)	19 (95)		1 (5)		
Bradycardia	3 (15)	17 (85)	2 (10)			1 (5)
Chest pain	7 (35)	13 (65)	4 (20)	3 (15)		
Chilling	1 (5)	19 (95)	1 (5)			
Constipation	2 (10)	18 (90)	1 (5)	1 (5)		
Cough	6 (30)	14 (70)	6 (30)			
Ecchymosis at injection site	3 (15)	17 (85)	3 (15)			
Edema and pain in extremities	2 (10)	18 (90)	1 (5)	1 (5)		
Fever	2 (10)	18 (90)	1 (5)	1 (5)		
Hard breathing	4 (20)	16 (80)	3 (15)		1 (5)	
Head numbness	1 (5)	19 (95)		1 (5)		
Headache	4 (20)	16 (80)	2 (10)	2 (10)		
Increase in mucosal secretion	1 (5)	19 (95)	1 (5)			
Itching	1 (5)	19 (95)	1 (5)			
Nausea/vomiting	6 (30)	14 (70)		6 (30)		
Stress during sleeping	2 (10)	18 (90)	1 (5)	1 (5)		
Sweating	4 (20)	16 (80)	4 (20)			
Tachycardia	1 (5)	19 (95)		1 (5)		

ADRs=Adverse drug reactions, WHO=World Health Organization

results showed a significant correlation between the incidence of anaphylactic reactions and history of hypertension ($r = 0.572$; $P = 0.008$) and cerebrovascular accident (CVA) ($r = 0.545$; $P = 0.013$). The results of Spearman analysis showed that the incidence of reteplase ADRs was associated with the age ($r = 0.604$; $P = 0.005$) and male gender ($r = 0.608$; $P = 0.004$). Furthermore, the number of reteplase ADRs was linked with the history of diabetes mellitus ($r = 0.659$; $P = 0.002$) and use of anti-diabetes agents ($r = 0.516$; $P = 0.020$) [Table 4].

The linear regression analysis (stepwise method) showed the two models of correlation between the incidence of ADRs and study risk factors including age and gender of patients. In the linear regression model, a significant relation between the number of ADRs and age of patients was documented. The logistic regression analysis showed the gender as the main predictor factor in the incidence of reteplase ADRs (odds ratio: 32, 95% confidence interval: 1.38–737.45; $P = 0.030$).

DISCUSSION

In this study, 20 patients with STEMI were studied. The key finding of this study may be that the gender was identified as the main predictor in the incidence

Table 4: Correlation between study parameters and ADRs

Variable	Study factors	Correlation coefficient (r)	P
Incidence of ADRs	Age	0.604	0.005
	Gender	0.608	0.004
Number of ADRs	Diabetes mellitus	0.659	0.002
	Use of anti-diabetic drugs	0.516	0.020
Anaphylactic reactions	Hypertension	0.572	0.008
	Cerebrovascular accident	0.545	0.013

ADRs=Adverse drug reactions

of ADRs induced by reteplase. Moreover, the most ADRs ranked as “possible” indicating the mild pattern of ADRs induced by reteplase. However, anaphylaxis to the reteplase was higher than the other reports.

In the study conducted by Shah *et al.*^[13] the incidence of bradycardia in the studied group was reported 31.25% while in our study it was 15%. Moreover, the incidence of ecchymosis at the site of injection was 26.25%, while in our study it was 15%.^[13] In precise study by Singh *et al.* which evaluated postmarketing safety and efficacy of reteplase on 228 Indian patients with STEMI, the incidence of ADRs was reported in 5.3% of patients. However, this rate was higher in our study (85%). In this study, arrhythmia, epistaxis, hematuria, ventricular fibrillation, and tachycardia

were the reported ADRs. However, the rates of these ADRs were not reported.^[14]

Several studies have described the role of gender in the incidence of ADRs. Domecq *et al.*^[15] in a prospective drug surveillance study of 1920 hospitalized patients showed the longer period of hospitalization among men with ADRs than women. In contrast, in the UK study of 48 cohort studies with 513,606 patients females were more prone to showing ADRs (60% more than males).^[16] In the present study, the logistic regression analysis indicated the factor of male gender accounting in the incidence of reteplase ADRs with the odds ratio of 32. However, this result should be interpreted with a caution due to some limitations of the study that was mentioned in the limitation part.

Anaphylactic reactions were the most severe side effect that occurred immediately after the injection of reteplase by documenting in two cases. However, the incidence of anaphylactic reactions in these patients substantially was higher than the other reports. In the INJECT trial among 2965 patients received reteplase, anaphylactic shock was noted only in three cases.^[10] The other trials reported anaphylactic reactions between 0 and 3 cases as a very rare incidence ADR.^[17] Many factors are associated with the occurring drug anaphylaxis. Drug-related factors such as immunogenicity (acting as a hapten), intermittent, and repeated administrations, as well as parenteral route of administration, are associated with the incidence of drug-related allergies. Moreover, female gender, older age, genetic and ethnicity, and concomitant underlying diseases are the main host related participating factors.^[18] In our study, the incidence of anaphylactic reactions associated with the history of hypertension and CVA. Of note, ethnicity, and genetic roles can be the other participating factors, which need to confirm by pharmacogenomic evaluations.

Furthermore, our analysis showed that the number of side effects increased with the increasing of age that is in agreement with the several previous reports. This finding may be due to the aging phenomenon with decreasing kidney and liver function.^[19,20] On the other hand, in these patients pharmacodynamic interactions increased due to the polypharmacy along with the existence of one or more underlying diseases.^[12,13] Therefore, aging is a pivotal factor in occurring ADRs which was shown in our study regarding reteplase.

The other main finding of the present study is the significant correlation between the number of ADRs induced by reteplase and history of diabetes mellitus as well as the using of anti-diabetic agents.

As mentioned in previous studies, background diseases are one of the main predictor in the incidence of ADRs along with the using of various medications.^[1] In fact the special conditions of diabetes such as diabetic nephropathy and decreased the kidney function, as well as poly pharmacy in this population, may cause to increase the numbers of ADRs. In this line, in one study on diabetic patients one-third of observed ADRs were related to the anti-diabetic agents.^[21]

This study contains many strength points. First, this study is the first report from Iran that has investigated the postmarketing ADRs of reteplase. Second, the significant correlation between the reteplase ADRs and some study risk factors such as gender, age, history of diabetes, and taking of anti-diabetes agents was identified in this study. Finally, the study showed a higher rate of anaphylactic reactions among Iranian population that could be associated with genetic and ethnicity factors which could address for conducting further studies to confirm these findings.

The partially small sample size of the study may be the major limitation of the study. However, it was not an avoidable problem. On the other hand, currently in our heart center the use of reteplase is very limited based on the higher cost. Additionally, the major parts of patients with STEMI are undergone to the primary percutaneous coronary intervention. Therefore, the total numbers of patients giving a thrombolytic are limited.

In summary, the results showed that gender, age, diabetes mellitus, and using of anti-diabetes medications are the risk factors associated with the incidence of ADRs by reteplase.

AUTHORS' CONTRIBUTION

NA and NS; supervised and supported the study, FS; collect data, write manuscript, MRTS and NKA; attended in emergency room, SOM and HH; consults and supervised the study, HF and SD; and revised the manuscript; TEM designed and supervised the study, analyzed data, and write the manuscript.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

- Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: A meta-analysis of prospective studies. *JAMA* 1998;279:1200-5.
- Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, *et al.* Adverse drug reactions as cause of admission to hospital: Prospective analysis of 18 820 patients. *BMJ* 2004;329:15-9.
- Wu Z, Van de Werf F, Stassen T, Mattsson C, Pohl G, Collen D. Pharmacokinetics and coronary thrombolytic properties of two human tissue-type plasminogen activator variants lacking the finger-like, growth factor-like, and first kringle domains (amino acids 6-173) in a canine model. *J Cardiovasc Pharmacol* 1990;16:197-203.
- Smalling RW, Bode C, Kalbfleisch J, Sen S, Limbourg P, Forycki F, *et al.* More rapid, complete, and stable coronary thrombolysis with bolus administration of reteplase compared with alteplase infusion in acute myocardial infarction. RAPID investigators. *Circulation* 1995;91:2725-32.
- Bode C, Smalling RW, Berg G, Burnett C, Lorch G, Kalbfleisch JM, *et al.* Randomized comparison of coronary thrombolysis achieved with double-bolus reteplase (recombinant plasminogen activator) and front-loaded, accelerated alteplase (recombinant tissue plasminogen activator) in patients with acute myocardial infarction. The RAPID II investigators. *Circulation* 1994;94:891-8.
- American College of Emergency Physicians; Society for Cardiovascular Angiography and Interventions, O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, *et al.* 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013;61:e78-140.
- Bode C, Smalling RW, Berg G, Burnett C, Lorch G, Kalbfleisch JM, *et al.* Randomized comparison of coronary thrombolysis achieved with double-bolus reteplase (recombinant plasminogen activator) and front-loaded, accelerated alteplase (recombinant tissue plasminogen activator) in patients with acute myocardial infarction. The RAPID II investigators. *Circulation* 1996;94:891-8.
- Topol EJ, Ohman EM, Armstrong PW, Wilcox R, Skene AM, Aylward P, *et al.* Survival outcomes 1 year after reperfusion therapy with either alteplase or reteplase for acute myocardial infarction: Results from the Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO) III Trial. *Circulation* 2000;102:1761-5.
- A comparison of reteplase with alteplase for acute myocardial infarction. The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO III) Investigators. *N Engl J Med* 1997;337:1118-23.
- Hampton JR, Schroder R, Wilcox RG, Skene AM, Meyer-Sabellek W, Heikkila J, *et al.* Randomized double-blind comparison of reteplase double-bolus administration with streptokinase in acute myocardial infarction (INJECT): Trial to investigate equivalence. *Lancet* 1995;346:329-36.
- Antman EM, Anbe DT, Armstrong PW, Bates ER, Green LA, Hand M, *et al.* ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction – Executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to revise the 1999 guidelines for the management of patients with acute myocardial infarction). *J Am Coll Cardiol* 2004;44:671-719.
- Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, *et al.* A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;30:239-45.
- Shah K, Apsangikar P, Allu J, Chaudhry S. Clinical retrospective and prospective evaluation of efficacy and safety of reteplase in STEMI patients. *Indian Med Gaz* 2012;146:479-87.
- Singh RK, Trailokya A, Naik MM. Post-reteplase evaluation of clinical safety and efficacy in Indian patients (Precise-In Study). *J Assoc Physicians India* 2015;63:30-5.
- Domecq C, Naranjo CA, Ruiz I, Busto U. Sex-related variations in the frequency and characteristics of adverse drug reactions. *Int J Clin Pharmacol Ther Toxicol* 1980;18:362-6.
- Martin RM, Biswas PN, Freemantle SN, Pearce GL, Mann RD. Age and sex distribution of suspected adverse drug reactions to newly marketed drugs in general practice in England: Analysis of 48 cohort studies. *Br J Clin Pharmacol* 1998;46:505-11.
- Retavase product insert monograph. Germany: Boehringer Mannheim GmbH, Centocor, Inc.; 1999.
- Thong BY, Tan TC. Epidemiology and risk factors for drug allergy. *Br J Clin Pharmacol* 2011;71:684-700.
- O'Mahony MS, Woodhouse KW. Age, environmental factors and drug metabolism. *Pharmacol Ther* 1994;61:279-87.
- Routledge PA, O'Mahony MS, Woodhouse KW. Adverse drug reactions in elderly patients. *Br J Clin Pharmacol* 2004;57:121-6.
- Zaman Huri H, Fun Wee H. Drug related problems in type 2 diabetes patients with hypertension: A cross-sectional retrospective study. *BMC Endocr Disord* 2013;13:2.