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Streptokinase and premedication strategies: Incidence of type I hypersensitivity reactions associated with streptokinase in clinical practice

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ABSTRACT

Type I hypersensitivity reactions are observed following the administration of streptokinase, resulting in poor outcomes and increased mortality. Premedication serves as a strategy to prevent these reactions in clinical practice. This study aimed to determine the incidence of type I hypersensitivity reactions associated with patients who received streptokinase and premedication. This retrospective descriptive study collected data from the electronic medical records of Nakhon Pathom Hospital covering the period from January 1, 2019 to July 31, 2021. Seventy-four participants were identified. The incidence of type I hypersensitivity reactions was 459 cases/1,000 patients. The most common type I hypersensitivity reaction was hypotension, followed by anaphylactic shock and respiratory complications. All patients with hypotension fully recovered with appropriate management; however, all patients experiencing anaphylactic shock did not survive. An inferior wall infarction was significantly associated with these reactions. In conclusion, type I hypersensitivity reactions occurred despite the administration of premedication in patients who received streptokinase. Healthcare professionals should closely monitor and carefully manage these cases for desirable clinical outcomes.

Keywords: streptokinase; hypotension; anaphylaxis; anaphylactic shock; respiratory complications

1. INTRODUCTION

Fibrinolytic agents have several indications in patients with thromboembolism disorders, including ST-elevated myocardial infarction (STEMI), acute ischemic stroke, pulmonary embolism, arterial and venous thrombosis, and prosthetic valve thrombosis (Chiasakul and Bauer, 2020). The mechanism of action of fibrinolytic agents is the activation of either fibrin-bound or circulating plasminogen to plasmin, resulting in fibrinolysis (Brogden et al., 1973).

The most common adverse drug reaction is bleeding; however, several studies have reported hypersensitivity reactions to administered fibrinolytic agents, particularly streptokinase (SK), which is derived from beta-hemolytic streptococci (ISIS-2 [Second International Study of Infarct Survival], 1988).

The type I hypersensitivity reactions are hypotension, dyspnea, urticaria, angioedema, anaphylaxis, and anaphylactic shock, while the type 3 hypersensitivity reaction is serum sickness (Davies et al., 1990; Duangmee et al., 2022; Prasitdumrong et al., 2023). Duangmee et al. (2022) established that 6.12% of patients who received SK had suspected adverse drug reactions (one patient had urticaria, two patients suffered from anaphylactic shock, and six patients had hypotension), whereas 0.18% of patients who received alteplase experienced orolingual angioedema, and 0.77% of patients who received tenecteplase became hypotensive. A pharmacovigilance study in Thailand reported a higher incidence of urticaria, angioedema, and type I hypersensitivity reactions after administering SK compared to alteplase (34.11/10,000 and 9.86/10,000 persons, respectively) (Prasitdumrong et al., 2023).

In clinical practices, several hospitals have introduced premedication strategies with corticosteroids and antihistamines to prevent hypersensitivity reactions. However, the evidence-based advantage remains limited, and no peer-reviewed guidelines have recommended this strategy (O'Gara et al., 2013; Ibanez et al., 2018). Moreover, a recent study about bleeding in patients who received a fibrinolytic agent concomitant with corticosteroids established that corticosteroids, even for premedication, were associated with bleeding, particularly in those who received two types of corticosteroids (Ruenroengbun et al., 2024). Duangmee et al. (2022) reported that out of 147 patients, 11 (7.48%) received premedication before the administration of SK, and of those 11 patients, 3 (27.27%) developed hypotension. Furthermore, the mentioned pharmacovigilance study in Thailand did not analyze the incidence of patients who received premedication (Prasitdumrong et al., 2023). Nakhon Pathom Hospital, an 860-bed tertiary care hospital, applies a premedication regimen to all patients with STEMI who receive SK. Consequently, this study aimed to analyze the incidence of hypersensitivity reactions related to SK administration with premedication and evaluate the factors associated with these reactions.

2. MATERIALS AND METHODS

We performed a retrospective observational study spanning from January 2019 to July 2021. Data were retrieved from the electronic medical records of Nakhon Pathom Hospital. The study protocol received approval from the Ethics Committee of Nakhon Pathom Hospital (Approval No. 007/2022) on February 24, 2022, valid until February 23, 2023.

Patients who received a fibrinolytic agent were enrolled. The inclusion criterion was patients who were administered SK during admission at Nakhon Pathom Hospital with drug code 2110020. Exclusion criteria were patients who did not receive a premedication regimen before SK and patients with incomplete or missing data in their medical records. The sample size, estimated for a finite population proportion from n4Studies, was determined to be 96 patients (Ngamjarus, 2016).

Incidence rates were calculated for new events of any type I hypersensitivity reactions, including hypotension, urticaria, angioedema, anaphylactic reactions, and respiratory complications. Duplicated patients with different adverse drug reactions were excluded from the incidence calculation. The denominator comprised the total number of patients exposed to SK. We also conducted an analysis to identify factors associated with type I hypersensitivity reactions. Hypotension was defined as a decrease in blood pressure below 90/60 mmHg or mean arterial blood pressure below 60 mmHg within 24 hours after receiving SK. The physician's diagnoses were characterized by urticaria, angioedema, anaphylactic reactions, and respiratory complications.

Characteristics were described between patients with and without type I hypersensitivity reactions. Continuous demographic variables, e.g., age, weight, blood pressure, laboratory data, door-to-needle time, and rate of administration, are reported as mean (standard deviation) or median (interquartile range) depending on the data distribution. Frequencies and percentages are used for the categorical variables, i.e., sex, medical history, allergy history, and medication history. These variables were compared between the groups using the Chi-square or Fisher exact test, analysis of variance, or quantile regression, where appropriate. Logistic regression was applied to evaluate the association between covariables and type I hypersensitivity reactions. Simple or univariate logistic regression analysis was initially used to explore the unadjusted association between each covariable and the outcome. Covariables with p-values <0.1 in the univariate analysis were simultaneously considered in a multivariate logistic regression with a backward elimination approach. Finally, significant covariables with p-values <0.05 and clinically associated with the outcome were used in the final logistic regression. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated and reported. All statistical analyses were performed with STATA version 18.0 software (Stata Corp., College Station, TX, USA).

3. RESULTS AND DISCUSSION

A total of 74 patients with a mean weight of 66.61 ± 13.92 kg received SK. The majority of patients (93.24%) had no known history of allergy, while only four patients (5.40%) had a history of drug allergy with no prior exposure to a fibrinolytic agent. The average baseline systolic and diastolic blood pressures were 134.94 ± 32.65 mmHg and 81.69 ± 22.53 mmHg, respectively. Mean eosinophils, basophils, and the estimated glomerular filtration rate were 2.04 ± 2.74%, 0.12 ± 0.33%, and 71.89 ± 31.57 mL/min/1.73 m^2, respectively. Table 1 provides the baseline characteristics of the patients.

Type I hypersensitivity reactions occurred in 34 patients (45.95%); 30 patients (40.54%) developed hypotension, 3 patients (4.05%) suffered from anaphylactic shock, and 1 patient had respiratory complications (dyspnea). The mean onset of these reactions was 142 min or 2.37 hours after receiving SK. The most common probability scale with Naranjo's algorithm was "possible." All patients who developed anaphylactic shock did not survive. Conversely, only one with hypotension died, and the others recovered.

The incidences of type I hypersensitivity, hypotension, anaphylactic shock, and respiratory complications were

459/1,000, 405/1,000, 41/1,000, and 14/1,000 patients, respectively. The factors associated with type I hypersensitivity reactions were baseline systolic blood pressure in the univariate logistic regression and inferior wall infarction in the univariate and multivariate logistic regression (Table 2).

Table 1. Baseline characteristics of the patients receiving SK with a premedication regimen (n = 74)

Characteristic	Hypersensitivity reactions (n = 34)	No hypersensitivity reaction (n = 40)	Total (n = 74)
Sex			
Male	24 (70.59%)	30 (75%)	54 (72.97%)
Female	10 (29.41%)	10 (25%)	20 (27.03%)
Age			
Mean ± SD (years)	62.06 ± 11.15	59.13 ± 12.55	60.47 ± 11.94
31–45 years	1 (2.94%)	5 (12.5%)	6 (8.11%)
46–60 years	14 (41.18%)	17 (42.5%)	31 (41.89%)
61–75 years	15 (44.12%)	13 (32.5%)	28 (37.84%)
76–90 years	4 (11.76%)	5 (12.5%)	9 (12.16%)
Underlying disease			
Hypertension	19 (55.88%)	29 (72.5%)	48 (64.86%)
Dyslipidemia	14 (41.18%)	12 (30%)	26 (35.14%)
Diabetes mellitus	9 (26.47%)	18 (45%)	27 (36.49%)
Coronary artery disease	4 (11.76%)	3 (15%)	7 (9.46%)
Others	12 (35.29%)	17 (42.5%)	29 (39.19%)
Medication history			
Calcium channel blockers	3 (8.82%)	7 (17.5%)	10 (13.51%)
Aspirin	6 (17.65%)	4 (10%)	10 (13.51%)
Beta blockers	1 (2.94%)	8 (20%)	9 (12.16%)
Angiotensin-converting enzyme inhibitors	4 (11.76%)	4 (10%)	8 (10.81%)
Angiotensin receptor blockers	3 (8.82%)	4 (10%)	7 (9.46%)
Type of STEMI			
Inferior wall	24 (70.59%)	14 (35%)	38 (51.35%)
Anterior wall	9 (26.47%)	23 (57.5%)	32 (43.25%)
Posterior wall	0	2 (5%)	2 (2.7%)
No data	1 (2.94%)	1 (2.5%)	2 (2.7%)
Door-to-needle time			
Mean ± SD (minutes)	63.35 ± 19.46	61.15 ± 16.29	61.15 ± 16.29
Within 30 minutes	3 (8.82%)	2 (5%)	5 (6.76%)
After 30 minutes	31 (91.18%)	38 (95%)	69 (93.24%)
Rate of administration			
Mean rate (unit/kilogram/minute)	403.36 ± 81.58	381.6 ± 82.46	391.72 ± 82.2
Within 500 units/kilogram/minute	29 (85.30%)	35 (87.5%)	64 (2.5%)
More than 500 units/kilogram/minute	4 (11.76%)	3 (7.5%)	7 (9.46%)
No data	1 (2.94%)	2 (5%)	3 (4.05%)

Table 2. Logistic regression analysis of the association between the covariables and type I hypersensitivity reactions

Factors	Univariate logistic regression			Multivariate logistic regression		
	OR	95% CI	p-value	OR	95% CI	p-value
Baseline SBP	0.98	0.96 – 0.99	0.008*	0.99	0.97 – 1.00	0.252
Inferior wall infarction	4.38	1.59 – 12.08	0.004*	3.22	1.02 – 10.19	0.046*
Infusion rate >500 units/kilogram/minute	1.19	0.34 – 4.10	0.789	0.84	0.19 – 3.79	0.819
Medication history						
Beta blockers	0.12	0.01 – 1.03	0.053	0.14	0.02 – 1.32	0.087
ACEIs	1.20	0.28 – 5.21	0.808	-	-	-
ARBs	0.87	0.18 – 4.20	0.863	-	-	-
CCBs	0.46	0.11 – 1.92	0.285	-	-	-
Age	1.02	0.98 – 1.06	0.292	-	-	-
Female	1.25	0.45 – 3.49	0.670	-	-	-
Body weight	0.98	0.94 – 1.01	0.202	-	-	-
Eosinophils	1.10	0.92 – 1.31	0.290	-	-	-
eGFR	0.99	0.98 – 1.00	0.273	-	-	-
Door-to-needle time	1.02	0.99 – 1.05	0.291	-	-	-
Known drug allergy	0.77	0.12 – 4.91	0.783	-	-	-
Underlying disease						
Hypertension	0.48	0.18 – 1.27	0.138	-	-	-
Diabetes mellitus	0.44	0.16 – 1.18	0.102	-	-	-
Chronic kidney disease	0.35	0.07 – 1.88	0.224	-	-	-

Note: *Significant difference at p-value <0.05

ACEIs: angiotensin-converting enzyme inhibitors, ARBs: angiotensin receptor blockers, CCBs: calcium channel blockers, CI: confident interval, eGFR: estimated glomerular filtration rate, OR: odds ratio, SBP: systolic blood pressure.

Duangmee et al. (2022), who studied a similar hospital level, reported a proportion of 6.12% for type I hypersensitivity with SK, while the proportion in this study was 45.95%. Different data collection processes caused this higher proportion. This study directly identified type I hypersensitivity from the patient records, encompassing physician-reported and diagnosed cases. In contrast, Duangmee et al. (2022) employed a trigger tool to identify type I hypersensitivity reactions, which may have some missing data.

Hypotension is the most common reaction after administering SK. According to a previous study in Thailand, the cumulative incidence of SK-induced hypotension was 28.92/10,000 patients (Prasitdumrong et al., 2023), and the proportion from a pharmacovigilance study in Cuba was 36% (Betancourt et al., 2005). In the present study, the incidence of hypotension were 405/1,000 patients, constituting a proportion of 40.54%. Although the populations in those previous studies did not receive any premedication, the incidence and proportion of SK-induced hypotension were high. Consequently, the premedication regimen may not prevent hypotension owing to several mechanisms of SK-induced hypotension besides type I hypersensitivity mediated by IgE antibodies e.g., reduction in total peripheral resistance caused by the interplay of a reduction in whole blood viscosity and widespread vasodilatation (Khalid et al., 2021). Corticosteroids and antihistamines inhibit the immunological mechanism only. Most patients fully recovered after treatment with either volume replacement or norepinephrine; however, one patient died from other causes after developing hypotension.

The incidence of anaphylactic reactions due to SK from a study in Thailand was 3.71/10,000 patients (Prasitdumrong et al., 2023), while the incidence from the International Collaborative Study of Severe Anaphylaxis was 284/100,000 patients (International Collaborative Study of Severe Anaphylaxis, 2003). The present study reports an incidence of 41/1,000 suffering anaphylactic shock. The differences may have originated from the various indications of SK in the previous study; however, this study only included STEMI patients.

A case report from Bednarczyk et al. (1989) reported anaphylactic shock leading to pulmonary and cardiac arrest 30 min after the administration of SK, and recovery was induced with hydrocortisone and epinephrine. However, three patients in our study who experienced anaphylactic shock died. One of these patients transiently improved and was rechallenged with SK, resulting in the recurrence of severe anaphylactic shock. Thus, SK rechallenge should be avoided in cases of anaphylaxis or anaphylactic shock.

An association between the inferior wall infarction and type I hypersensitivity reaction was detected. In this study, most patients with type I hypersensitivity reactions were hypotensive. Tisdale et al. (1992) reported that 10 of 13 cases of SK-induced hypotension were inferior wall infarctions. Up to 60% of patients with inferior wall infarction developed hypotension (Aydin et al., 2018), and SK may have precipitated this reaction. The effects of inferior wall infarction and hypotension resulted from right ventricular infarction and dilatation, leading to insufficient right ventricular output volume and consequent systemic hypotension (Ondrus et al., 2013).

Baseline systolic blood pressure was another factor that was significantly associated with type I hypersensitivity when analyzed by univariate logistic regression while underlying disease with hypertension was not.

The rate of administration was significantly associated with SK-induced hypotension in a previous study. Lew et al. (1985) recommended that the SK administration rate should not exceed 500 units/kg/min. In the present study, only 7 patients received SK with an infusion rate of ≥500 units/kg/min, and half of them developed type I hypersensitivity reactions. The recommended SK dose for patients with STEMI is 1.5 million units intravenously over 60 min (O'Gara et al., 2013; Ibanez et al., 2018). Although univariate and multivariate logistic regression analyses failed to detect an association, extending the administration time to 75 min should be considered in patients weighing <50 kg.

Respiratory complications were identified in this study. A 53-year-old female patient exhibited dyspnea 15 min after receiving SK; she had a respiratory rate of about 40 breaths/min, which increased from a baseline of 24 breaths/min. Prasitdumrong et al. (2023) reported a low cumulative incidence of respiratory complications of 1.48/10,000 patients exposed to SK.

The limitations of this research were that no comparative group received premedication. The calculated sample size was not reached; however, we included the total population in this setting. The retrospective design may have resulted in incomplete data. We did not observe any patients with pulmonary embolism, another indication of SK. Moreover, this study was based on a small population and the premedication strategy needs further investigation.

4. CONCLUSION

The findings of this study provide valuable insight into the use of SK and the premedication strategy. The incidence of type I hypersensitivity reactions in patients who received SK was 459/1,000 patients. The most common type I hypersensitivity reaction was hypotension, followed by anaphylactic shock and respiratory complications. Inferior wall infarction was associated with type I hypersensitivity. Therefore, medical professionals should closely monitor these patients. Furthermore, the premedication strategy implemented before administering SK was ineffective in preventing type I hypersensitivity reactions.

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REFERENCES

Aydin, F., Yildirim, O. T., Dagtekin, E., Aydin, A. H., and Aksit, E. (2018). Acute inferior myocardial infarction caused by lightning strike. *Prehospital and Disaster Medicine*, 33(6), 658–659.

Bednarczyk, E. M., Sherlock, S. C., Farah, M. G., and Green, J. A. (1989). Anaphylactic reaction to streptokinase with first exposure: case report and review of the literature. *DICP: The Annals of Pharmacotherapy*, 23(11), 869–872.

Betancourt, B. Y., Marrero-Miragaya, M. A., Jiménez-López, G., Valenzuela-Silva, C., García-Iglesias, E., Hernández-Bernal, F., Debesa-García, F., González-López, T., Alvarez-Falcón, L., López-Saura, P. A., and the Cuban National Network of Pharmacoepidemiology. (2005). Pharmacovigilance program to monitor adverse reactions of recombinant streptokinase in acute myocardial infarction. *BMC Clinical Pharmacology*, 5(1), 5.

Brogden, R. N., Speight, T. M., and Avery, G. S. (1973). Streptokinase: A review of its clinical pharmacology, mechanism of action and therapeutic uses. *Drugs*, 5(5), 357–445.

Chiasakul, T., and Bauer, K. A. (2020). Thrombolytic therapy in acute venous thromboembolism. *Hematology-American Society of Hematology Education Program*, 2020(1), 612–618.

Davies, K. A., Mathieson, P., Winearls, C. G., Rees, A. J., and Walport, M. J. (1990). Serum sickness and acute renal failure after streptokinase therapy for myocardial infarction. *Clinical and Experimental Immunology*, 80(1), 83–88.

Duangmee, K., Boonmuang, P., Santimaleeworagun, W., and Prasitdumrong, H. (2022). Urticaria, angioedema, and type I hypersensitivity reactions associated with fibrinolytic agents. *Asian Pacific Journal of Allergy and Immunology,* 40(4), 379–385.

Ibanez, B., James, S., Agewall, S., Antunes, M. J., Bucciarelli-Ducci, C., Bueno, H., Caforio, A. L. P., Crea, F., Goudevenos, J. A., Halvorsen, S., Hindricks, G., Kastrati, A., Lenzen, M. J., Prescott, E., Roffi, M., Valgimigli, M., Varenhorst, C., Vranckx, P., Widimský, P., and ESC Scientific Document Group. (2018). 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *European Heart Journal*, 39(2), 119–177.

International Collaborative Study of Severe Anaphylaxis. (2003). Risk of anaphylaxis in a hospital population in relation to the use of various drugs: An international study. *Pharmacoepidemiology and Drug Safety*, 12(3), 195–202.

ISIS-2 (Second International Study of Infarct Survival) Collaborative Group1). (1988). Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. *The Lancet*, 332(8607), 349–360.

Khalid, K., Ahmad, R. E., Y.H. Tong, A. Y. H., Lui, S. Y., and Abidin, I. Z. Z. (2021). Pathophysiology of streptokinase-induced hypotension in acute myocardial infarction: A systematic review of clinical evidence. *Archives of Medical Sciences. Atherosclerotic Diseases*, 6, e85–e94.

Lew, A. S., Laramee, P., Cercek, B., Shah, P. K., and Ganz, W. (1985). The hypotensive effect of intravenous streptokinase in patients with acute myocardial infarction. *Circulation*, 72(6), 1321–1326.

Ngamjarus, C. (2016). n4Studies: Sample size calculation for an epidemiological study on a smart device. *Siriraj Medical Journal*, 68(3), 160–170.

O'Gara, P. T., Kushner, F. G., Ascheim, D. D., Casey, D. E., Jr, Chung, M. K., de Lemos, J. A., Ettinger, S. M., Fang, J. C., Fesmire F. M., Franklin, B. A., Granger, C. B., Krumholz, H. M., Linderbaum, J. A., Morrow, D. A., Newby, L. K., Ornato, J. P., Ou, N., Radford, M. J., Tamis-Holland, J. E.,… Zhao, D. X. (2013). 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. *Journal of the American College of Cardiology*, 61(4), e78–e140.

Ondrus, T., Kanovsky, J., Novotny, T., Andrsova, I., Spinar, J., and Kala, P. (2013). Right ventricular myocardial infarction: From pathophysiology to prognosis. *Experimental and Clinical Cardiology*, 18(1), 27–30.

Prasitdumrong, H., Duangmee, K., Boonmuang, P., Santimaleeworagun, W., Oppamayun, Y., Sonsupap, C., and Nakkaratniyom, T. (2023). Incidence of urticaria, angioedema, and type I hypersensitivity reactions associated with fibrinolytic agents in Thailand using the database of the health product vigilance center. *Asian Pacific Journal of Allergy and Immunology*, 41(1), 67–72.

Ruenroengbun, N., Kongsuwan, K., Dokkaewklang, M., Lakkasorn, A., Ardsean, A., Srimanee, P., Kanchanakomala, N., and Duangmee, K. (2024). Incidence and factors associated with bleeding in patients receiving concomitant fibrinolytic agents and corticosteroids therapy. *Thai Bulletin of Pharmaceutical Sciences*, 19(1), 53–65. [in Thai]

Tisdale, J. E., Colucci, R. D., Ujhelyi, M. R., Kluger, J., Fieldman, A., and Chow, M. S. (1992). Evaluation and comparison of the adverse effects of streptokinase and alteplase. *Pharmacotherapy*, 12(6), 440–444.