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Does impairment of renal and hepatic function influence the metabolism of thrombolytics in patients with myocardial infarction?

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Thrombolytic agents activate plasminogen and induce a systemic fibrinolytic and anticoagulant state. Two thrombolytic drugs are used frequently in practice: streptokinase (SK) and alteplase (t-PA). Streptokinase mainly undergoes renal elimination with a half-life of 11–17 min, while alteplase is eliminating by the liver with a half-life of 4–6 min. Our goal was to examine whether renal and hepatic function influence the elimination and metabolism of thrombolytics and the efficacy of percutaneous coronary intervention (PCI) after using alteplase or streptokinase. 416 patients with myocardial infarction (MI) were treated from January 2001 to December 2003 (228 male and 189 female). Alteplase was used in 9 men and 6 women (mean age: 53.88 ± 9.61 vs. 65.33 ± 9.87 years, $p = 0.07$). Patients who underwent rescue PCI after administration of alteplase had slightly higher hepatic enzyme levels/alanine transaminase (ALT): 47.85 vs. 41.4 U/l; gamma-glutamyl transpeptidase (GGT): 69.5 vs. 44.8 U/l/. All patients treated with alteplase survived, rescue PCI was done in 8 cases. Streptokinase was used in 36 men and 28 women (mean age: 63.33 ± 10.51 vs. 63 ± 12.03 years, $p = 0.9$). We did not find a difference between serum creatinine levels of patients who received streptokinase and underwent PCI as compared to those who had not. Rescue PCI was done in 16 cases. 12 patients died in this group. In conclusion we have not found a significant correlation between the use of the thrombolytics and hepatic or renal function; this could indicate that such a slight impairment of liver and renal function does not influence pharmacokinetic properties of thrombolytics.

1. Introduction

Early reperfusion of occluded coronary arteries offers great promise as a method for minimizing myocardial damage. In patients who are not eligible for primary coronary intervention (PCI) thrombolytic drugs are the first choice.

Thrombolytic agents are plasminogen activators that convert plasminogen, the inactive proenzyme of the fibrinolytic system in blood, to the proteolytic enzyme plasmin (Collen et al. 1991). Plasmin dissolves the fibrin clot, but may also degrade other components of the haemostatic system and predispose to bleeding. Thrombolytics are used in myocardial infarction (AMI), deep venous thrombosis, thrombosed vascular graft, peripheral arterial thrombosis, acute ischaemic stroke, or pulmonary embolism (Lutomski et al. 1995).

The most important thrombolytic agents are streptokinase (SK), recombinant tissue-type plasminogen activator or alteplase (t-PA), anisoylated plasminogen streptokinase activator complex (APSAC), single-chain urokinase-type plasminogen activator or prourokinase (scu-PA) and others (reteplase, monteplase, lanoteplase) (Noble et al. 1996; Verstraete 1999). The first generation thrombolytic agents as SK and urokinase are moderately efficacious and they cause extensive systemic fibrinogen breakdown (Collen et al. 1990).

The two drugs used in clinical practice in Hungary are streptokinase and alteplase. SK consists of a single polypeptide chain (414 amino acids) (Lutomski et al. 1995; Stringer 1996). Earlier studies evaluated pharmacokinetics of SK using radiolabelled drug and indicating biphasic elimination with an initial half-life ($t_{1/2}$) of 11 to 17 min, followed by a terminal phase $t_{1/2}$ of 80 min (Lutomski et al. 1995) (Table). The initial rapid clearance from plasma is due to inactivation by circulating anti-streptokinase antibodies (Battershill et al. 1994). SK is degraded to peptides and eliminated mainly by the kidney.

Alteplase (t-PA) is a serine proteinase with a molecular weight of 70 kDa consisting of a single-stranded polypeptide chain (527 amino acids) (Lutomski et al. 1995; Gillis et al. 1995; Stringer 1996). After intravenous bolus administration, alteplase had an initial half-life of 4–6 min and a terminal $t_{1/2}$ of 39–53 min (Lutomski et al. 1995). The initial rapid elimination may result from rapid uptake of the drug by hepatocytes. The liver plays a predominant role in the elimination of alteplase, more than 80% of the drug is cleared within 10 min (Wagstaff et al. 1995) (Table).

There are few data about the elimination and metabolism of thrombolytic agents in patients with myocardial infarction especially with impaired renal or hepatic function. Our goal was to determine whether baseline hepatic or renal status of patients with acute myocardial infarction influence the action and metabolism of thrombolytics and the efficacy of rescue PCI after thrombolysis.

Table: Characteristics of thrombolytics

Variable	Streptokinase	Alteplase
$T_{1/2}$ (min)	11 – 17	4 – 6
Plasma clearance (ml/min)	11 ± 9	516 – 998
Volume of distribution (L)	1.1 ± 0.7	3.8 – 6.6
Fibrin specificity	Minimal	Moderate
Plasminogen binding	Indirect	Direct
Potential allergenicity	Yes	No
Elimination	Renal	Hepatic

2. Investigations and results

Streptokinase was used in 36 men and 28 women (mean age: 63.33 ± 10.51 vs. 63 ± 12.03 years, $p = 0.9$). Men, treated with SK had a significantly higher serum creatinine level than women treated with SK (102.42 ± 32.3 vs. 79.29 ± 18.35 μmol/l, $p = 0.001$). We did not find a difference between serum levels of ALT (men: 62.58 ± 72.97 vs. women: 66.9 ± 74.77 U/l, $p = 0.84$) and GGT (men: 48.55 ± 36.62 vs. women: 40.11 ± 33.82 U/l, $p = 0.43$) in patients treated with SK. Rescue PCI was done in 9 men and 7 women, and a total of 12 patients died in this group (5 men and 7 women). We have also found a positive correlation between the use of streptokinase and high serum creatinine (>116 μmol/l) level ($p = 0.001$).

Alteplase was used in 9 men and 6 women (mean age: 53.88 ± 9.61 vs. 65.33 ± 9.87 years, $p = 0.07$). There was no difference between genders in serum creatinine level (98.11 ± 29.7 vs. 75.4 ± 23.22 μmol/l, $p = 0.14$). Hepatic enzyme levels were higher but not significant in men than in women (ALT: 51.62 ± 42.15 vs. 32.25 ± 8.18 U/l, $p = 0.24$; GGT: 74.2 ± 70.87 vs. 32.75 ± 15.1 U/l, $p = 0.26$). All patients treated with alteplase survived, rescue PCI was done in 8 cases. Patients, who underwent rescue PCI, after administration of alteplase, had slightly higher, but not significant hepatic enzyme level/alanine transaminase (ALT): 47.85 vs. 41.4 U/l; gamma-glutamyl transpeptidase (GGT): 69.5 vs. 44.8 U/l/ and no correlation was found between the use of alteplase and hepatic enzymes.

3. Discussion

In this study we examined the correlation between the use of different thrombolytics, namely streptokinase and alteplase, and serum creatinine, hepatic enzyme levels in 416 patients treated with acute myocardial infarction, moreover to determine the frequency of rescue PCI. Our hypothesis was that renal and hepatic dysfunction could affect the metabolism of these drugs used in patients with AMI.

Streptokinase is eliminated mainly by the kidney, in our patients the serum creatinine level of men was significantly higher than in women. 15.85% of men and 14.81% of women received SK, 25% in each group underwent rescue PCI after drug administration, but no correlation was found between serum creatinine levels of patients who received SK and underwent PCI as compared to those patients who had not. In the literature, we could not find earlier studies examining the correlation between renal function and SK administration, Lnych et al. (1995) found a significant early onset proteinuria after streptokinase administration.

Alteplase, which is known to have a higher opening potency of infarct-related coronary artery (average 74.2% of patients vs. for SK 48.2% of patients) (Gillis et al. 1995; Collen et al. 1989) was underused in our patients, only 3.96% of men and 3.17% of women received t-PA. We have not found a significant difference between hepatic enzyme levels of patients, men had a tendency to have higher levels of GGT. Half of the patients treated with alteplase underwent rescue PCI and they had slightly but not significantly higher hepatic enzyme levels. It is known that alteplase mainly undergoes hepatic elimination, but such moderate impairment of hepatic function does not influence pharmacokinetic properties of t-PA, whereas it was shown that in fibrotic and cirrhotic liver the clearance of t-PA was decreased (Nagaoka et al. 2003).

The lower opening potency of coronary arteries in our alteplase treated patients could be due to extrahepatic clearance of the drug and interindividual variation in metabolism.

In conclusion we established, based on our findings, that there is no significant correlation between renal and hepatic function and use of thrombolytic drugs, but to confirm this statement larger studies must be done in the future.

4. Experimental

We assessed retrospectively the medical records of 416 patients (228 male and 189 female) admitted with acute myocardial infarction (AMI) to the 1st and 3rd Department of Internal Medicine of University of Debrecen Medical and Health Science Center, from first of January 2001 to 31st of December 2003. Hepatic function was characterized using serum alanine transaminase (ALT) (normal level: < 40 U/L) and gamma-glutamyl transpeptidase (GGT) (normal level: < 40 U/l) level, while renal function with serum creatinine level (normal level < 116 μmol/l). The use of each thrombolytic drug (SK or t-PA) was studied and the frequency of rescue percutaneous coronary intervention (PCI) was analyzed.

Statistical analysis was made by SPSS program Version 11.0 and Microsoft Excel. $P < 0.05$ was considered statistically significant.

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