Concomitant Use of Lisinopril Reduces the Effect of Aspirin on Bleeding

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Abstract

Objective: To determine the Lisinopril and Aspirin interaction through their concurrent effect on bleeding in adult male rabbits.
Methods: Twenty four healthy adult male rabbits were used. Bleeding time of each animal was determined by Duke's Method. They were divided randomly in three groups containing equal number of animals into Control, Aspirin, Lisinopril and Combination groups. After oral administration of the drug(s), the bleeding time of the animals was again determined by same method.
Results: Prolongation of bleeding time was significant ($p<0.05$) in Aspirin and combination groups but insignificant ($p>0.05$) in Lisinopril group after 1 hour. It was significant ($p<0.05$) in Aspirin and Lisinopril groups but insignificant ($p>0.05$) in Combination group after 24 hours. This change was observed after 48 hours too.
Conclusion: Concurrent use of Lisinopril reduces the effect of Aspirin on Bleeding after a certain time period.
Keywords: Aspirin, Lisinopril, drug interaction, bleeding time. (ASH & KMDC 19(1):37;2014).

IIntroduction

Aspirin (Acetylsalicylic acid) is an antipyretic, anti-inflammatory and a potent agent that prolongs the bleeding time and inhibits platelet aggregation[1,2] .Aspirin therapy results in a considerable decline in the risk of nonfatal myocardial infarction, nonfatal stroke, or vascular death in high-risk patients[3,4].

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Lisinopril is a potent, competitive inhibitor of angiotensin-converting enzyme (ACE), the enzyme responsible for the conversion of angiotensin I (ATI) to angiotensin II (ATII)[5]. Angiotensin converting enzyme inhibitors [ACEIs] have reduced the mortality rate in patients with ischemic heart disease & stroke[6,7,8,9,10]. The beneficial effect of ACEIs may result from improvement of endothelial function, increased bradykinin, nitric oxide, prostacyclin (PGI_2) levels & reduced plasma plasminogen activator inhibitor-1 which might explain their antithrombotic effect[11.12].

Wojewodzka-Zelezniakowicz with his colleagues[13] and similarly Sugano with his co investigators[14] have determined the effect of ACE inhibitors on bleeding but our study is planned to explore the interaction of Aspirin and Lisinopril which are co administered in a number of cardiac patients.

Subjects and Methods

After ethical approval of Institutional Ethical and Scientific Research Committee, this study was conducted on 24 healthy adult male rabbits in Experimental Pharmacology Laboratory of Karachi Medical and Dental College as per guidelines of Institutional Animals Ethics Committee (IAEC). The weights of animal were in the range of 1-1.2kg. They were acclimatized for laboratory conditions for a week. All environmental conditions were kept the same throughout the experimentation. Bleeding time of each animal was determined by Duke's Method for base line data. They were divided randomly in three groups containing 6 animals each.

There were four groups; Group A (Control Group); received a suspension containing 10 mg flour in 05 ml distilled water as a single dose orally. Group B (Aspirin Group); received a suspension containing 9.280 mg Aspirin (Reckitt Benckiser) in powdered form in 05 ml distilled water as a single dose orally. Group C (Lisinopril Group); received a suspension containing 0.571 mg Lisinopril (ICI) in powdered form in 05 ml distilled water as a single dose orally. Group D (Combination Group); received a suspension containing 9.280 mg Aspirin (Reckitt Benckiser) and 0.571 mg Lisinopril (ICI) in powdered form in 05 ml distilled water as a single dose.

Each animal received the dose at 08 AM in the morning. No toxicity was noticed during or after drug administration. Bleeding time was noted at 09 AM (after I hour) of the same day and at 08 AM in the morning of the two consecutive days (after 24 and 48 hours). After experimentation the rabbits were observed for one week for any toxicity and then freed.

The data was entered using SPSS version 20 (Statistical Package for Social Science) for data analysis. Bleeding times in the three groups were compared.

Results

Table 1 compares the bleeding time of control group with drug receiving groups after 1 hour of drug administration. It was 2.22 ± 0.25 (Mean ± SE) minutes in control and 4.22 ± 0.44, 3.16 ± 0.21, 3.33 ± 0.23(Mean ± SE) minutes respectively in Aspirin, Lisinopril and Combination groups. The difference is significant ($p<0.05$) in Aspirin and combination groups but insignificant ($p>0.05$) in Lisinopril group if compared with control group.

Table 2 depicts the bleeding time of control group and of drug receiving groups after 24 hour of drug administration. It was 2.18 ± 0.24 (Mean ± SE) minutes in control and 4.09 ± 0.39, 3.94 ± 0.66 and 3.50 ± 0.91 (Mean ± SE) minutes respectively in Aspirin, Lisinopril and Combination groups. The prolongation of bleeding time is significant ($p<0.05$) in Aspirin and Lisinopril groups but insignificant ($p>0.05$) in combination group if compared with control group.

Table 3 compares the bleeding time of control group and of drug receiving groups after 48 hour of drug administration. It was 2.22 ± 0.25 (Mean ± SE) minutes in control and 4.20 ± 0.45, 3.16 ± 0.46 and 2.67 ± 0.43 (Mean ± SE) minutes respectively in Aspirin, Lisinopril and Combination groups. The change in bleeding time is significant ($p<0.05$) in Aspirin and Lisinopril groups but insignificant ($p>0.05$) in Combination group if compared with control group.

Discussion

Our study shows that the prolongation of bleeding time, a characteristic effect of Aspirin[2] and one of the basis of its extensive therapeutic and prophylactic use in coronary artery disease[3,15-18] is reduced when lisinopril is co administered with it.

Therefore, a statistically significant ($p<0.05$) prolongation of bleeding time is observed throughout 1st to 48th hours by Aspirin and only at 1st but not at 24th and 48th hours by combination of both. This result is somewhat unexpected because potential anti-thrombotic effect of ACE Inhibitors[13] or Lisinopril like drugs is well established. This is supported by our result too, as a statistically significant ($p<0.05$) prolongation of bleeding time is observed at 24 and 48 hours by Lisinopril.

The synthesis of Angiotensin II is prevented locally by high affinity of ACE Inhibitors to endothelium.This may result in attenuation of prothrombotic action of Angiotensin II by inducing oxidative stress[17], inhibiting Nitric Oxide (NO) synthesis[18] & enhancing leukocytes infiltration & adhesion to vascular wall[20]. Angiotensin II also inhibits fibrinolysis by increasing plasminogen activator inhibitor type 1 expression[14] Similarly these drugs increase bradykinin concentration which enhances the release of NO, Prostaglandin I_2 (PGI_2,) & Tissue Plasminogen Activator (t-PA) which are strong antithrombotic agents[3,5].

Table 1. Effect of Aspirin, Lisinopril and their combination on bleeding time after 1st hour in adult male rabbits.

Drug(s)	Bleeding time(Minutes)		p-value
	Control	Drugs	
Aspirin	2.22 ± 0.25(06)*	4.22 ± .44(06)	0.001
Lisinopril	Same	3.16 ± .21(06)	0.064
Combination	Same	3.33 ± .23(06)	0.025

*Mean ± SE (No of Animals)

Table 2. Effect of Aspirin, Lisinopril and their combination on bleeding time after 24th hour in adult male rabbits.

Drug(s)	Bleeding time(Minutes)		p-value
	Control	Drugs	
Aspirin	2.18 ± 0.24(06)*	4.09 ± .39(06)	0.001
Lisinopril	Same	3.94 ± .66(06)	0.040
Combination	Same	3.50 ± .91(06)	0.077

*Mean ± SE (No of Animals)

Table 3. Effect of Aspirin, Lisinopril and their combination on bleeding time after 48th hour in adult male rabbits .

Drug(s)	Bleeding time(Minutes)		p-value
	Control	Drugs	
Aspirin	2.22 ± 0.25(06)*	4.20 ± .45(06)	0.001
Lisinopril	Same	3.16 ± .46(06)	0.034
Combination	Same	2.67 ± .43(06)	0.419

*Mean ± SE (No of Animals)

It has also been recently shown that tissue ACEIs caused experimental thrombolysis in rats by the mechanism which involved bradykinin release from endothelium[21]. However, even in the presence of all these favorable activities, co administration of the two drugs reduces the characteristic effects of both rather to enhance. Perhaps antagonizing action of the two drugs at prostaglandin levels looks to play a pivotal role. Lisinopril, as discussed already, stimulates prostaglandin biosynthesis[13] by increasing bradykinin levels while Aspirin irreversibly inhibits the platelet-dependent enzyme cyclo-oxygenase (COX)[17] thereby prevents the synthesis of prostaglandins. The biosynthesis of prostaglandin seems to be more potent as compared to its inhibition when the two drugs are co administered. Therefore we see the weakening of Aspirin effect on bleeding time in an orderly manner at all stages so p=0.025 at 1st hour, 0.077 at 24 hour and 0.419 at 48 hour for combination of two drugs. This gradual loss may be a result of short half-life of Aspirin as compared to Lisinopril.

The results can further be supported if Serum levels of Lisinopril are measured in the presence of Aspirin periodically with the effect of combination on bleeding.

Conclusion

Concurrent use of Lisinopril reduces the effect of Aspirin on Bleeding after 24 hours.

Conflict of Interest

None

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References

1. Ulm EH, Hichens M, Gomez HJ, Till AE, Hand E, Vassil TC, et al. Enalapril maleate and a lysine analogue (MK-521): disposition in man. Br J Clin Pharmacol 1982;14:357-62.
2. Weiss HJ. The discovery of the antiplatelet effect of aspirin: a personal reminiscence. J Thromb Haemost 2003;1:1869-75.
3. Awtry EH, Loscalzo J. Aspirin. Circulation 2000;101:1206-18.
4. Gasparyan AY, Watson T, Lip GY. The role of aspirin in cardiovascular prevention. J Am Coll Cardiol 2008;51:1829-43.
5. Abdelmalek M, Douglas DD. Lisinopril-induced isolated visceral angioedema: review of ACE-inhibitor-induced small bowel angioedema. Dig Dis Sci 1997;42:847-50.
6. Pfeffer MA, Braunwald E, Moye LA, Basta L, Brown EJ, Cuddy TE, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. N Engl J Med 1992;327:669-77.
7. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high risk patients. The HOPE Study Investigators. N Engl J Med 2000;342:145-53.
8. Fox KM, European trial on reduction of cardiac events with perindopril in stable coronary artery disease investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomized, double-blind, placebo-controlled, multicentre trial (the EUROPA study). Lancet 2003;362:782-8.
9. Pilote L, Abrahamowicz M, Rodrigues E, Eisenberg MJ, Rahme E. Mortality rates in elderly patients who take different angiotensin-converting enzyme inhibitors after acute myocardial infarction: a class effect? Ann Intern Med 2004 ;141:102-12.
10. Pretorius M, Rosenbaum D, Vaughan DE, Brown NJ. Angiotensin-converting enzyme inhibition increases human vascular tissue type plasminogen activator release through endogenous bradykinin. Circulation 2003;107:579-85.
11. Kubo-Inoue M, Egashira K, Usui M, Takemoto M, Ohtani K, Katoh M, et al. Long term inhibition of nitric oxide synthesis increases arterial thrombogenecity in rat carotid artery. Am J Physiol Heart Circ Physiol 2002;282:478-84.
12. Vaughan DE. Angiotensin and vascular fibrinolytic balance. Am J Hypertens 2002;15:3-8.
13. Wojewodzka-Zelezniakowicz M, Chabielska E, Mogielnicki A, Kramkowski K, Karp A, Opadczuk A, et al. Antithrombotic effect of tissue and plasma type angiotensin converting enzyme inhibitors in experimental thrombosis in rats. J Physiol Pharmacol 2006;57:231-45.
14. Sugano T, Tsuji H, Masuda H, Nishimura H, Yoshizumi M, Kawano H, et al. Adrenomedullin inhibits angiotensin II–induced expression of tissue factor and plasminogen activator inhibitor-1 in cultured rat aortic endothelial cells. Arterioscler Thromb Vasc Biol 2001;21:1078-83.
15. Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-Elevation myocardial infarction. J Am Coll Cardiol 2007;50:1-157.
16. 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. Circulation 2004;110:588-636.
17. Griendling KK, Minieri CA, Ollerenshaw JD, Alexander RW. Angiotensin II stimulates NADH and NADPH oxidase activity in cultured vascular smooth muscle cells. Circ Res 1994;74:1141-8.
18. Baigent C, Sudlow C, Collins R, Peto R. Collaborative meta-analysis of randomized trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002;324:71-86.
19. Wolf G, Ziyadeh FN, Schroeder R, Stahl RA. Angiotensin II inhibits inducible nitric oxide synthase in tubular MCT cells by a posttranscriptional mechanism. J Am Soc Nephrol 1997;8:551-7.
20. Pastore L, Tessitore A, Martinotti S, Toniato E, Alesse E, Bravi MC, et al. Angiotensin II stimulates intercellular adhesion molecule-1 (ICAM-1) expression by human vascular endothelial cells and increases soluble ICAM-1 release in vivo. Circulation 1999;100:1646-52.
21. Dzau VJ, Bernstein K, Celermajer D, Cohen J, Dahlof B, Deanfield J, et al. The relevance of tissue angiotensin-converting enzyme: manifestations in mechanistic and end point data. Am J Cardiol 2001;88:1-20.