IJBCP International Journal of Basic & Clinical Pharmacology

doi: 10.5455/2319-2003.ijbcp20131005

Research Article

Sex hormones alter the effect of aspirin on bleeding

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Received: 17 July 2013 Accepted: 4 August 2013

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ABSTRACT

Background: Interaction of aspirin and sex hormones was investigated through bleeding time.

Methods: Bleeding time in 32 males and 105 unmarried females with previous 6 normal menstrual cycles and all aged between 18 to 21 years was found by Duke's method before and after 2 hours of aspirin administration. Phase of menstrual cycle of each female was determined by present menstrual history.

Results: Bleeding time in 32 male was 69.33± 4.94 seconds and in 105 female was 73.03±1.89 seconds which were not statistically different (P>0.05). This time was increased to 107.66±4.76 seconds in males and 113.65±3.73 seconds in females after aspirin administration which were statistically different (P<0.05). The response in males was relatively greater (P<0.0005) as compared to females (P<0.0025). Among females, 44 were in follicular phase while 29 were in luteal phase as per their menstrual histories. Bleeding time in females in Follicular phase was increased from 70.22±2.90 seconds to 109.65±3.82 seconds and in females in luteal phase from 81.13±4.26 seconds to 117.95±7.49 after aspirin administration. The statistics of bleeding time in follicular and luteal Phases shows a statistically significant (P<0.05) difference before aspirin but non-significant (P>0.05) difference after aspirin administration with a greater effect in Follicular phase probably due to estradiol.

Conclusion: Males respond to aspirin more as compared to females which is likely the effect of the drug and testosterone interaction. Similarly females in the follicular phase respond to aspirin more as compared to females in the luteal phase which may be a result of interaction of estrogen and aspirin.

Keywords: Sex hormones, Aspirin, Bleeding time

INTRODUCTION

Hormones and drugs interact with each other as demonstrated by different responses of drugs in variety of individuals. These can either be direct, when drugs and hormones have common locus of action or indirect that is, by modifying some other factors, for example pharmacokinetics of a drug. These phenomena might be the reason behind the gender related dissimilarities in drug responses.

Aspirin which is acetyl-salicylic acid, is the most commonly used antiplatelet drug in the prevention of cardiovascular diseases. The use is attributed to its effect

as irreversible inhibitor of enzymes cyclo-oxygenases, COX-1 and COX-2. Owing to its irreversible inhibition of COX-1 in platelets and decreasing a potent vasoconstrictor and platelet aggregator thromboxane (TX-A2)², aspirin increases bleeding time. Thus bleeding time is considered as the measure of response to aspirin.

Testosterone is the major hormone in a male, while estrogen and progesterone are highly important in a female body. Since, these hormones effect bleeding tendency, they can be the reason of gender related discrepancies in responses to aspirin. Such a relationship is investigated in our study.

METHODS

137 healthy medical college undergraduate volunteers, 105 females and 32 males were randomly recruited for this study. All the participants gave written, informed consent before participation in the study.

A performa was filled by each volunteer, providing information about their name, age and sex.

Stage of menstrual cycle of each female was also determined using a structured interview.

Bleeding time was determined by Duke's method and noted.

The study protocol was approved by the university ethical committee.

SPSS version was used for statistical analysis.

RESULTS

Table 1 shows bleeding time in male and female volunteers. Mean bleeding time in 32 male volunteers is 69.33±4.94 (mean±SEM), while in 105 females is 73.03±1.89 (mean±SEM). Statistically insignificant difference (P>0.05) exists between the two.

Table 1: Bleeding time before aspirin administration in male and female.

Sex	Bleeding time	Significance
Male	69.33±4.94 (32) *	P>0.05
Female	73.03±1.89 (105)	P>0.03

^{*} Mean± SEM (Number of volunteers)

Table 2 depicts the effect of aspirin on bleeding time of different genders. Bleeding time in 32 male volunteers is 107.66±4.76 (mean±SEM) and in 105 females is 113.65±3.73 (mean±SEM) after aspirin administration. There is a statistically significant difference (P<0.05).

Table 2: Bleeding time after aspirin administration in male and female.

Sex	Bleeding time	Significance
Male	107.66±4.76 (32)*	- P<0.05
Female	113.65±3.73 (105)	- r<0.03

^{*} Mean± SEM (Number of volunteers)

Table 3 shows that bleeding time in 32 male volunteers is increased from 69.33±4.94 (mean±SEM) to 107.66±4.76 (mean±SEM) with a t-statistics of 7.124 and a very high significant statistical difference (P<0.0005) after aspirin

administration. The bleeding time in 105 females is increased from 73.03±1.89 (mean± SEM) to 113.65±3.73 (mean±SEM) with a t-statistics of 3.130 and a high significant statistical difference (P<0.0025) after aspirin administration. This clearly indicates that aspirin alters the bleeding time more in males as compared to females.

Table 3: Effect of aspirin on bleeding times in male and female.

Sex	Bleeding Time		t-statistics	Significance
	Before Aspirin	After Aspirin		
Male	69.33± 4.94 (32)*	107.66± 4.76 (32)	t=7.124	P<0.0005
Female	73.03± 1.89 (105)	113.65± 3.73 (105)	t=3.130	P<0.0025

^{*} Mean± SEM (Number of volunteers)

Table 4 compares the bleeding time in two phases of menstrual cycle. In follicular phase, bleeding time in 44 females is 70.22±2.90 (mean±SEM). In luteal phase, this time in 29 females is 81.13±4.26 (mean±SEM). Both the results are statistically significant different (P<0.05).

Table 4: Bleeding time before aspirin administration in different phases of menstrual cycle.

Phase	Bleeding time	Significance
Follicular	70.22±2.90 (44) *	- P<0.05
Luteal	81.13±4.26 (29)	r<0.03

^{*} Mean± SEM (Number of volunteers)

Table 5 compares the bleeding time in two phases of menstrual cycle after aspirin administration. In follicular phase, bleeding time in 44 females, comes to be 109.65±3.82 (mean±SEM).In luteal phase, this time in 29 females is increased up to117.95±7.49 (mean±SEM). Both the results has statistically insignificant difference (P>0.05).

Table 5: Bleeding time after aspirin administration in different phases of menstrual cycle.

Phase	Bleeding time	Significance	
Follicular	109.65±3.82 (44)*	· /	
Luteal	117.95±7.49 (29)	- P>0.05	

^{*} Mean± SEM (Number of volunteers)

Table 6 represents the comparison of bleeding time in different phases of menstrual cycle in females, before and after aspirin administration. Before aspirin, mean bleeding time in 44 females in follicular phase is 70.22±2.90 (mean±SEM) and in 29 females in luteal

phase is 81.13 ± 4.26 (mean \pm SEM). After aspirin, this time is increased in females in follicular phase up to 109.65 ± 3.82 (mean \pm SEM) and in females in luteal phase up to 117.95 ± 7.49 (mean \pm SEM). The difference between bleeding times before giving aspirin is statistically significant (P<0.02) which becomes insignificant (P<0.20) after aspirin administration.

Table 6: Effect of aspirin on bleeding time during different phases of menstrual cycle in female.

Time	Menstrual Cycle		t-statistics	Significance
	Follicular Phase	Luteal Phase		
Before Aspirin	70.22± 2.90 (44)*	81.13± 4.26 (29)	t=2.118	P<0.02
After Aspirin	109.65± 3.82 (44)	117.95± 7.49 (29)	t=0.985	P<0.20

^{*} Mean±SEM (Number of volunteers)

Table 7 further elaborates the effect of aspirin on bleeding time in the two phases of menstrual cycle. After aspirin administration, mean bleeding time in 44 females in follicular phase is increased from 70.22±2.90 (mean±SEM) to 109.65±3.82 (mean±SEM) and of 22 females in luteal phase from 81.13±4.26 (mean± SEM) to 117.95±7.49 (mean±SEM). The effect of aspirin on bleeding time is relatively more pronounced in follicular phase as represented by t statistics.

Table 7: Effect of aspirin on bleeding time in different phases of menstrual cycle in female.

Phase	Bleeding Time		t-statistics	Significance
	Before Aspirin	After Aspirin		
Follicular	70.22± 2.90 (44)*	109.65± 3.82 (44)	t=11.246	P<0.0005
Luteal	81.13± 4.26 (29)	117.95± 7.49 (29)	t=9.621	P<0.0005

^{*} Mean± SEM (Number of volunteers)

DISCUSSION

Drug and hormone interactions have been proved in various studies. Aspirin and sulfamethoxazole-trimethoprim suppresses thyroid hormone concentration in dogs. ^{3,4}

Lithium salt also has similar depressive effects on thyroid function.⁵ Diazepam reduces cortisol levels⁶, while chlorpromazine increases prolactin in body.⁷ So, different amount of major hormones in the two genders leads to sex based different responses to certain drugs. For instance, antipsychotics and beta blockers are more effective in women⁸, males are more sensitive to propofol⁹ and pentazocine produces more post-operative analgesia in females.¹⁰ Our study has further supported

these differences by studying the sex related disproportionate effects of aspirin on bleeding time.

Bleeding time increases significantly in males as compared to females after aspirin administration possibly because of testosterone, which up regulates the thromboxane A2 receptors and platelet aggregability. This means male are more sensitive to thromboxane inhibition of aspirin because of greater number of receptors and hence more activity, thus leading to more bleeding as compared to females. This effect is further supported by reduced level of testosterone in older adults after castration which reduces thromboxane A2 receptor density and platelet aggregation potential. ¹²

Furthermore, androgen at physiological levels inhibits oxidative-stress-induced platelet aggregation by reducing thromboxane release from platelets.¹³ Augmentation of this effect by aspirin would decrease the platelet assembly even further, leading to more bleeding in males. Moreover, prostaglandin F2 alpha is a platelet aggregator inhibitor that produces its effect even in aspirin treated cells¹⁴ is present in greater amount in males¹⁵, hence producing more significant bleeding as compared to the opposite gender.

Increased cyclooxygenase activity and thromboxane production in males as compared to females¹⁵ also suggest the significant effect of aspirin in the former group.

However, result of increased bleeding time in females was less significant than males.

Studies have shown that female sex hormones exert negative effect on platelet aggregation 16-18, but the effect was not remarkably increased after aspirin administration in our research, possibly because of the females being partial responders of aspirin¹⁹ or some other compensatory mechanism in their body not yet known. For instance, cyclooxygenase activity was found to be higher after overiectomy but lower after castration²⁰, indicating the probable role of female sex hormones in depressing cyclooxygenase activity. Contradictory to this phenomenon is the research proving an increased production of prostacyclin (PG-I2) by up regulating COX-2 activity²¹, supporting a normally increased bleeding time in females (Table 1), and at the same time supporting decreased effect of aspirin which also inhibits the production of prostacyclin, a potent platelet aggregator inhibitor.

Our research also compared the bleeding time in different phases of menstrual cycle after considering the fluctuations in female hormones during different phases. Data showed more bleeding in the follicular phase of the cycle, characterized by increase level of estradiol. Likely cause might be the lower platelet aggregability and higher fibrinolytic activity in the follicular phase.²² Since, estradiol inhibits platelet aggregability by increasing nitric oxide²³, the effect of aspirin further reduces the

aggregation in the follicular phase. Literature does not support any significant effect of progesterone on bleeding time.

CONCLUSION

Thus, it can be concluded that response to aspirin is dependant on gender, which must be taken into account when administering aspirin to the patient. Lower doses in males producing the same effect as little higher doses in females can reduce the incidence of toxicity.

Funding: None

Conflict of interest: None declared

Ethical approval: Approved by the university ethical

committee

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doi:10.5455/2319-2003.ijbcp20131005

Cite this article as: Aftab MT, Shakeel S, Tariq H, Shaikh S. Sex hormones alter the effect of aspirin on bleeding. Int J Basic Clin Pharmacol 2013;2:537-40.