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Comparison of the Effects of Different Doses of Acetylsalicylic Acid on Thromboxane B2 According to Gender

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ABSTRACT: Purpose: It is a basic drug with proven antiaggregant and antiplatelate activity in atherosclerotic heart diseases, especially coronary heart disease.Although there are different views on the ideal dose, we aimed to determine whether aspirin (ASA), which we have tried to show its efficacy even at very low doses, creates a difference in efficacy in males and females at very low doses, and therefore we wanted to determine the lowest dose depending on gender.

Method: In this study, 21 female and 19 male patients who applied to the General Internal Medicine Department of ŞişliEtfal Hospital were included.The patient groups included in the study were divided into four groups consisting of 10 patients each receiving 20mg, 40mg, 80mg and 150mg.Blood samples were taken for serum thromboxane (Tx) B2 examination from all patients before ASA. Then, after 14 days of ASA use, blood samples were taken from the patients again for the second time to detect TXB2 decrease.TxB2 levels were determined by ELISA using acetylcholinesterase and Elimin reagent.

Findings: The effects of TXB2 formation were similar in all groups, including 20 mg ASA.This similarity was the same between female and male patients and no statistical significance was found between both genders.In both males and females, the 20 mg ASA dose resulted in the same reduction in TXB2 as the other doses.Statistically, there was no difference between all groups. TXB2 formation was similar at all doses.No statistical significance was found between all groups in TXB2 formation after treatment.

Discussion: The metabolism of some drugs may differ between males and females, especially at very low doses.In our study, we found that the efficacy of a very low ASA dose of 20 mg decreased TXB2 formation at similar and identical rates in both genders. We consider that the use of low dose ASA will be more beneficial in terms of side effects and because it does not cause prostocyclin inhibition.

Keywords: *Antiaggregation ,Acetyl salicylic acid, Prostoglandin, Prostocyclin, Thromboxane*

I. INTRODUCTION

ASA (Acetyl salicylic acid) inhibits the cyclooxygenase (COX) activity of prostaglandin (PG) G/H synthases.It shows this effect by acetylating serine at position 529 in COX-1.Thus, it prevents the formation of Thromboxane A2 (TXA2), and (PGH2) [1].

Aspirin inhibits COX-2.It does this by acetylating serine at position 516. However, its affinity for COX-2 is 170 times lower than COX-1[2].

Antiaggregant activity is dependent on its ability to inhibit prostoglandin synthesis.ASA acts by blocking the COX enzyme that causes arachidonic acid (AA) to metaboliseprostoglandin, thromboxane and prostocyclin (PGI2). ASA causes antiaggregant effect by inhibiting the production of an active molecule in thrombosis by reducing TXA2 formation in platelets.This effect of ASA on platelets is irreversible.Therefore, the effect continues even if ASA is discontinued for 10 days, which is the life span of the platelet [3,4]3).Clustered platelets release TXA2 at the beginning of coagulation and its oxetane ring is rapidly hydrolysed to TXB2.Conversely, PGI2, which has the same opposite effect, is a product formed by the COX enzyme from arachisodonic acid.This has an antogonist effect inhibiting platelet aggregation.**(Fig.1)**

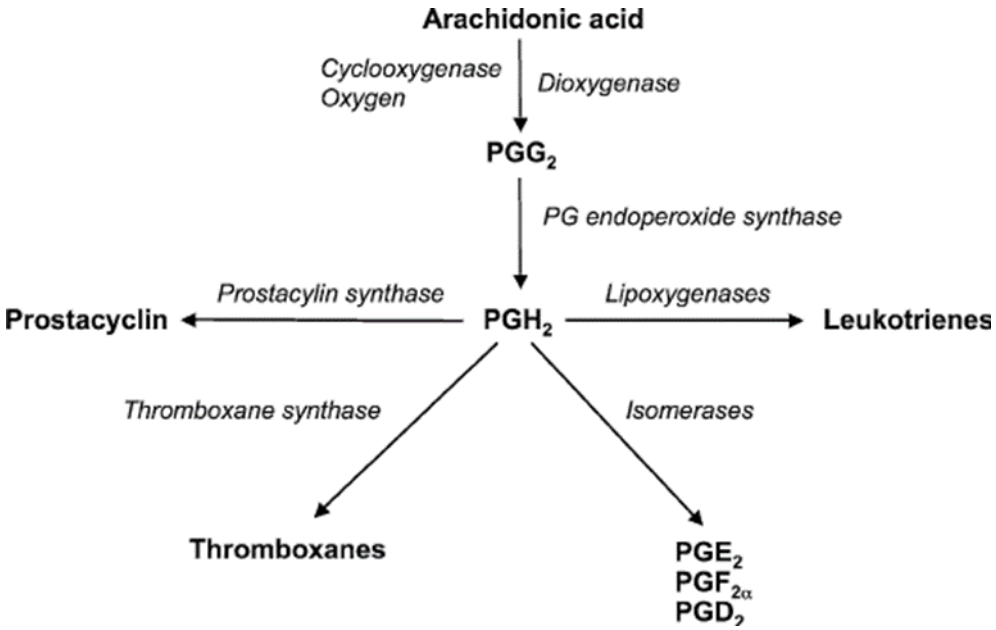

Figure-1Arachidonic Acid Metabolism

Although thromboxanes and prostoglandins have different effects on many tissues other than platelets, it is their effects on platelets that make them special.While inhibition of thromboxane formation by inhibition of the COX enzyme provides antiaggregant properties, the decrease in PGI2 synthesis by blocking the same pathway creates a para-tissue aggregant effect.It is therefore obvious that ASA has an effect on both pathways in this sense.The important point here is that while the formation of TX synthesis is inhibited at low doses, a higher dose of ASA is required for PGI2 inhibition.

As early as 1987, Kyrle et al. [5] found that 7-day ASA administration (30 mg/day) to healthy volunteers reduced the generation of thrombin and FVa[6].Furthermore, it has been suggested that ASA may partially inhibit TF (Tissue Factor) synthesis by nuclear translocation of NF-jB /c-Rel protein in human monocytes in a dose-dependent manner at m RNA and protein levels [7].This effect is a strengthening effect of antiaggregant activity through a different pathway.ASA has also been shown to decrease TF expression in human atherosclerotic plaques [8].

One of the effects of ASA on the coagulation system is that it may decrease thrombin formation by acetylating prothrombin and/or platelet membrane components [9].It has been shown that 20 mg kg ASA administered in three doses per day caused a mild but significant decrease in prothrombin clotting activity measured on days 2-8 [10], but prothrombin or thrombin times were not affected by ASA treatment [11].

Environmental factors may modify the antithrombotic effects induced by ASA.The best example of this is that the inhibitory effect of ASA on thrombin formation is weakened in the presence of marked hypercholesterolaemia[12], whereas the effect on thrombin formation is increased with the concomitant use of ASA and simvastatin, a cholesterol-lowering agent [13]**.**In another effect, in a cell model based on stable transfection with fibrinogen and analysis of clots made from fibrinogen purified from the medium, it has been shown that ASA positively changes the fibrin clot and reduces clot stiffness by 30% by making fibrin networks looser [14].

ASA was approved for the first time in 1989 by the American Thoracic Diseases Association with 325 mg as an antiaggregant in patients with ischaemic heart disease [15]**.**In most individuals, platelet TXA2 synthesis and a daily aspirin dose of 30 to 100 mg ASA per day is considered to be an adequate dose as an anti-aggregant.

In one of the dose determination studies, administration of ASA up to 325 mg daily for 4 weeks blocked platelet function and the development of acute cardiovascular diseases in 94-100% and it was stated that the platelet response to ASA may be related to collagen or ADP-induced aggregation dose[16]**.**It has also been shown that there is no aspirin-induced decrease in platelet P-selectin after stimulation with ADP or thrombin in healthy subjects [17].

So far, there are many studies on ASA proving its antiaggregant effects in ischaemic heart disease.In the SPAT study, one of the first of these, it was found that 75 mg ASA reduced the risk of acute MI by 30% in patients with stable angina.**36**. Although dose studies have created differences between groups, the dose is currently accepted as 80-100 mg/day.Although it is generally safe in terms of side effects, the most common side effect is on the gastrointestinal system.Depending on the dose, the occurrence of side effects is high.Another important side effect is decreased renal blood flow and renal failure due to inhibition of prostoglandin synthesis.This is particularly noticeable at high doses of ASA. At low doses, there is almost no effect on creatine clearance. After oral administration, ASA is rapidly absorbed from the body.In the stomach and upper small intestine, bioavailability is 40-50% with a catalysed by esterases and a plasma half-life of approximately 18 minutes[18].

In the prevention of primary arterial thromboembolic events, a 12% reduction in serious vascular events was associated with a 20% reduction in non-fatal myocardial disease (MI), but this effect was not demonstrated in cerebral events[19,20].In the secondary prevention study, ASA was shown to have a stronger effect, resulting in an overall absolute reduction in serious vascular events (Stroke and MI) of 20%.

Although ASA has been accepted as the agents of choice in preventing MI risk and CVO in the background of ischaemic heart disease as a result of many studies to date, its effect in atrial fibrillation is limited. This is due to its effect on primary coagulation, i.e. platelets.

Today, it is recommended in all ischaemic heart diseases, post MI, after coronary angioplasty and bypass surgery, in trans ischaemic attack and is included in the guidelines.It is also recommended in patients with hyperlipidaemia, mild hypertension, patients with a family history of thrombosis, smokers, and patients after hip and knee surgery.Contraindications include bronchial asthma, active peptic ulcer, gout, and iron deficiency anaemia.

II. MATERIAL and METHOD

This study was conducted between June 1997 and February 1998 among the patients who applied to the General Internal Medicine and Diabetes outpatient clinic of ŞişliEtfal Hospital and who were hospitalised in the 2nd Internal Medicine clinic because of coronary artery disease.Babyprin 80 mg "pfizer" and Dispril 300 mg were used as acetylsalicylic acid (ASA, aspirin).The doses of these drugs were used by patients as ¼ Babyprin (20mg), ½ Babyprin (40mg), Babyprin 80mg, ½ Dispril (150mg).

The patient groups included in the study were divided into four groups consisting of 10 patients each receiving 20mg, 40mg, 80mg and 150mg.The study included 21 females and 19 males. Patients with a history of gastrointestinal bleeding and peptic ulcer, haematological disease, bronchial asthma, chronic obstructive pulmonary disease and known drug allergy to ASA were excluded from the study.ASA preparations were given as a single daily dose.

2.1.Serum Thromboxane B2 Measurement:

Blood samples for serum thromboxane (Tx) B2 examination were obtained from all patients before ASA.Subsequently, after 14 days of ASA use, blood samples were taken from the patients for the second time to detect TxB2 decrease.The blood samples were centrifuged without waiting, serum was removed and placed in a deep-freezing cabinet at -24 degrees Celsius.All sera were pooled together at the end of the study.

TxB2 levels were determined by ELISA using acetylcholinesterase and Elimin reagent.This test is based on competition between free and bound (acetylcholinesterase-bound forms of TxB2).The levels were determined by measuring the optical density at 412 nm with a spectrophotometer by measuring the yellow colour formed after the Eliman reagent (containing acetylcholinesterase substrate) added to the medium after the rabbit antiserum.

2.2.Statistical Analysis:

Statistical analyses were performed using "IBM SPSS Statistics for Windows. Version 25.0 (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, USA)".Descriptive statistics are presented as frequency and % for categorical variables and Mean ± SD, median (IQR) for continuous variables.The data of the study were determined as n=10 for each dose group and Wilcoxon test was applied for dependent group comparisons and Mann-Whitney U test was applied for independent group comparisons from nonparametric tests to determine whether there was a significant difference between variables.Statistically, $p<0.05$ value was considered statistically significant.

III. FINDINGS

	Dose Group	$\bar{X} \pm SD$	
Age	**20 mg**	55.80±10.19	
	40 mg	59.70±8.24	
	80 mg	47.20±12.99	
	150 mg	49.50±16.02	
	Dose Group		**Frequency (%)**
Gender	**20 mg**	**Female**	5 (%50.0)
		Male	5 (%50.0)
	40 mg	**Female**	5 (%50.0)
		Male	5 (%50.0)
	80 mg	**Female**	6 (%60.0)
		Male	4 (%40.0)
	150 mg	**Female**	5 (%50.0)
		Male	5 (%50.0)

Table 1: Distribution of sociodemographic and clinical variables of the patients

As shown in Table 1, among the patients who participated in the study, 5 (50%) of the 20 mg dose administration were female, 5 (50%) were male and the mean age was 55.80 years with a deviation of 10.19 years, and 5 (50%) of the participants in 40 mg dose administration were female, 5 (50%) were male and the mean age was 59.70 years with a deviation of 8.24 years, and 6 (60%) of the participants in 80 mg dose administration were female, 4 (40%) were male and their mean age was 47.20 years with a deviation of 12.99, and 5 (50%) of the participants in 150 mg dose administration were female, 5 (50%) were male and the mean age was 49.50 years with a deviation of 16.02.

Variable	Dose	ASA Status	Median (IQR)	p*
TXB2	20 mg	Before ASA	310.00 (64.5)	**0.005**
		After ASA	270.50 (48.25)	
	40 mg	Before ASA	365.00 (91.75)	**0.005**
		After ASA	206.50 (109.5)	
	80 mg	Before ASA	314.50 (47.5)	**0.005**
		After ASA	198.00 (42.75)	
	150 mg	Before ASA	306.50 (33.75)	**0.005**
		After ASA	198.50 (13.5)	

**Wilcoxon test, p<0.05.*

Table 2: Before and After ASA Comparisons of TXB2 by Doses

As seen in Table 2, there is a statistically significant difference between before and after ASA in 20 mg dose administration for TXB2 variable.In 20 mg dose administration, the mean values of TXB2 variable after ASA were found lower than the mean values before ASA.

There is a statistically significant difference between before and after ASA in 40 mg dose administration for TXB2 variable.In 40 mg dose administration, the mean values of TXB2 variable after ASA were found lower than the mean values before ASA.

There is a statistically significant difference between before and after ASA in 80 mg dose administration for TXB2 variable.In 80 mg dose administration, the mean values of TXB2 variable after ASA were found lower than the mean values before ASA.

There is a statistically significant difference between before and after ASA in 150 mg dose administration for TXB2 variable.In 150 mg dose administration, the mean values of TXB2 variable after ASA were found lower than the mean values before ASA.

Table 3: Age by Gender, Before ASA and After ASA comparisons As seen in Table3, no statistically significant difference was found in age, before and after ASA values according to doses (20-40-80-150mg) and gender variable (p>0.05).

	Dose Groups	Gender	Median (min-max)	p*
Age	20 mg	Female	64.0 (40.0-70.0)	0.463
		Male	51.0 (43.0-67.0)	
	40 mg	Female	60.0 (48.0-70.0)	0.916
		Male	63.0 (47.0-70.0)	
	80 mg	Female	52.5 (27.0-58.0)	0.520
		Male	53.0 (32.0-60.0)	
	150 mg	Female	50.0 (29.0-64.0)	0.984
		Male	50.0 (28.0-75.0)	
Before ASA	20 mg	Female	321.0 (277.0-401.0)	0.463

		Male	306.0 (296.0-402.0)	
	40 mg	Female	392.0 (316.0-412.0)	0.165
		Male	344.0 (288.0-421.0)	
	80 mg	Female	309.0 (266.0-336.0)	0.831
		Male	314.5 (272.0-329.0)	
	150 mg	Female	304.0 (281.0-321.0)	0.116
		Male	308.0 (290.0-329.0)	
After ASA	20 mg	Female	280.0 (231.0-241.0)	0.346
		Male	261.0 (242.0-319.0)	
	40 mg	Female	201.0 (116.0-309.0)	0.917
		Male	212.0 (192.0-298.0)	
	80 mg	Female	207.5 (184.0-243.0)	0.088
		Male	179.5 (148.0-201.0)	
	150 mg	Female	196.0 (142.0-209.0)	0.600
		Male	202.0 (191.0-216.0)	

*Mann-Whitney U test, p<0.05.

IV. DISCUSSION

ASA is currently the antithrombolytic agent of choice for the prevention of thrombus in coronary artery disease and cerebrovascular disease, both in acute and chronic treatment.Data from studies involving antiplatelet therapy trials have shown that daily aspirin doses of <160, 160 to 325 and 500 to 1500 mg have approximately similar benefits[21].

Recent guidelines recommend ASA doses of 50 to 100 mg for secondary prevention of non-cardioembolic ischaemia, given the apparent equivalent benefit of different ASA doses in preventing ischaemic stroke and the increased risk of bleeding complications with high-dose ASA.This recommendation is supported by the 2012 guidelines of the American College of Chest Physicians [2], which recommend 75 to 100 mg/day, and the American Heart Association/American Stroke Association 2021 guidelines, which recommend a daily dose of 50 to 325 mg [22].

The optimal daily dose of ASA for long-term, secondary prevention of cardiovascular events is uncertain.Aspirin in the dose range of 75 to 325 mg/day has been evaluated in numerous studies and their meta-analyses, although 81-100 mg is generally accepted.In a meta-analysis of these studies, the Association for Antithrombotic Studies found that benefits were similar at all aspirin doses between 75 and 1300 mg/day [23].However, they have shown that the risk of bleeding starts to increase at doses above 325 mg/day.

ASA inhibits COX and decreases TXA2 formation, on the other hand it inhibits prostacyclin formation by inhibition of the same enzyme.As it is known, TXA2 is a strong vasoconstrictor and a factor that increases platelet aggregation, while prostacyclin is an antiaggregant and vasodilator and shows antagonist effect.Therefore, ASA inhibits two substances with opposite effects.

Studies have shown that ASA inhibits COX in vascular tissue as well as platelets and inhibits vascular prostacyclin[24].However, the important question here is whether ASA is more effective against COX in vascular tissue or in platelets.Again, these effects vary according to dose, so the state of the balance between TXA2 and prostacyclin is important.

If the inhibitory effect of ASA on prostacyclin is more prominent than that of TxA2, then ASA would be expected to increase thrombus rather than prevent it.While ASA irreversibly re-inhibits COX in platelets throughout platelet life, vascular tissues have the ability to re-synthesise COX after exposure to ASA differently from platelets [25].

In a study, arterial and venous prostacyclin levels before and after ASA in patients exposed to coronary bypass operation and TXB2 levels were also examined to investigate the effect of ASA on platelets.In the study, 80-325 mg ASA was used, and as a result, venous prostacyclin levels decreased by 85% with 80 mg ASA, while arterial prostacyclin levels decreased by 35% after 40 mg and 71% after 325 mg ASA [26,27].

In another study, it was argued that ASA dose below 100 mg was not effective in prostacyclin inhibition and platelet antiaggregation [28].On the contrary, in another study, it was shown that 20 mg very low dose aspirin inhibited platelet TXA2 release and aggregation compared with 75 mg aspirin [29].In our study, we observed a decrease of up to 40% in TXB2 in both males and females with the use of 40 mg ASA and above, whereas this decrease in TxB2 was less than 15% with the use of 20 mg ASA.In our study, we wanted to examine whether different doses vary according to gender. We found no difference between male and female genders at all doses.

Perhaps the most important effect of ASA that causes problems in the clinic is its effects on the gastrointestinal system, gastric and duodenal ulcer and gastrointestinal haemorrhage[30].This is extremely important because once gastrointestinal side effects occur in a patient using ASA, neither the patient nor the physician wants to use the drug again and as a result, the patient loses the chance to use an important antithrombotic agent.

Bleeding may also occur from other sites outside the gastrointestinal tract. The most important example of this is catastrophic intracranial haemorrhage.

In a 2019 meta-analysis including the ASCEND, ARRIVE and ASPREE clinical trials, even low-dose aspirin use (≤100 mg per day) increased the risk of intracranial haemorrhage compared with placebo [31].

It is still not clear which dose reduces the maximum TxB2 formation both as an ideal antithrombotic and without causing gastrointestinal side effects or bleeding complications.

Low-dose ASA intake can be used to reduce the risk of colorectal cancer.It is important to always consider both the risks and benefits of aspirin administration.Especially in the prevention and treatment of neurological disorders such as Alzheimer's disease or in the prophylaxis of myocardial infarction, it is important to use the same dose in both genders without any dose difference [32].Since the first evidence of the obstetric efficacy of ASA in females appeared in 1985, numerous studies have been conducted to determine the effect of low-dose aspirin on the incidence of pre-eclampsia, and large meta-analyses including individual patient data have shown that ASA is effective in preventing pre-eclampsia in high-risk patients, especially those with a history of pre-eclampsia[33].

In a study in healthy volunteers, significant platelet inhibition was observed 3 days after a single ASA 81 mg administration.We investigated prostaglandin E2 (PGE2) antrum concentrations and gastrointestinal symptoms in two treatment groups:The first group received 50 mg losartan and 81 mg ASA every day and the other group received losartan every day and ASA every 3 days.Treatment was administered for 30 days for both groups. Gastric endoscopy and biopsies for PGE2 measurement were taken before and after treatment.TXB2 release was measured before and during treatment. A low-dose ASA regimen every 3 days provided complete inhibition of platelet aggregation compared to daily treatment.

Thromboxane B2 release was significantly eliminated for both groups during treatment.No significant difference was found between the endoscopic scores of both treatment groups after 30 days of treatment.In volunteers receiving acetylsalicylic acid every day, suppression of antrum PGE2 content by more than 50% was observed (P = .0016), whereas no significant difference was found between pre- and post-treatment antrum PGE2 doses for every 3-day dosing regimen (P = .4193).Since PGE2 plays a role in gastric healing, this new approach may be safer in the long term and as effective as standard daily treatment. In the study, the number of male and female volunteers was equal, and no difference was found between genders[34].

It has been suggested that some plant-based foods contain milligram amounts of ASA that may have anti-thrombotic effect. A randomised, double-blind, placebo-controlled cross-over study investigated whether a daily intake of 3 mg acetylsalicylic acid causes a measurable reduction in platelet cyclo-oxygenase activity, assessed by in vitro thromboxane B2 production.Ten healthy volunteers (5 males, 5 females) aged 22 +/- 3 years (mean +/- s.d) participated in the study. Participants received 3 mg acetylsalicylic acid or placebo daily for 2 weeks each.At the end of each treatment period, venous blood was collected, and platelet-rich plasma was stimulated with arachidonic acid.ASA treatment has been shown to cause a 39 +/- 8% decrease in maximal thromboxane B2 production. No difference in results was found in both genders (P = 0.000).*(9)*

In another study aimed at evaluating the correlation between AA platelet aggregation (PA) and serum TxB2 inhibition, serum levels of ASA were analysed 10 times over 24 hours in seventeen healthy volunteers receiving a single dose of 162 mg chewed and swallowed ASA (n = 6), 50 mg inhaled ASA (n = 6) or 100 mg inhaled

ASA (n = 5).The correlation between serum TxB2 inhibition and AA-PA was gradual and AA-PA decreased to <5% after 30-40% inhibition of serum TXB2. Again, there was no difference between genders.
In a new study, platelet aggregation levels 2 hours after acetylsalicylic acid intake on day 3 of acute coronary syndrome (early) and 24 hours after the first dose of acetylsalicylic acid (late) were evaluated with the VerifyNow® acetylsalicylic acid test.In the comparison, the values measured at the 2nd hour were found to be 402.4±29.3 acetylsalicylic acid reaction units in 300 mg acetylsalicylic acid daily, 440.4±36.7 acetylsalicylic acid reaction units in 100 mg acetylsalicylic acid 3 times a day and 418.2±41 acetylsalicylic acid reaction units in 100 mg acetylsalicylic acid daily (p=0.04).Although it was found that the values monitored in the second hour increased in the 24th hour measurements in all groups, this increase was at least in patients receiving 3x100 mg and no difference was found in 24th hour values between groups and genders [35].

V. CONCLUSION

In conclusion, the basis of our study was to investigate the effects of ASA on thromboxane synthetase at varying doses according to gender. Studies with low dose ASA revealed that this effect of ASA was dose dependent.When the use of low dose ASA is considered in all aspects, it seems to be more beneficial in both genders without any dose difference.

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