Time to peak effect of aspirin-induced platelet inhibition and ex vivo effects of desmopressin: An observational study

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Abstract

Objective: To investigate the time to maximal platelet inhibition after an oral loading dose of ASA. The effect of ex vivo reversal platelet inhibition by desmopressin (DDAVP) was also studied.

Methods: Ten healthy volunteers were given a 300 mg ASA-tablet. Blood was sampled at 0, 15, 30, 60, 120, and 180 minutes. DDAVP was added to the samples taken at 120 minutes.

Samples were analyzed with a Multiplate® platelet aggregometer (MEA) using arachidonic acid (AA), collagen, and thrombin aggregation agonists.

Results: Platelet inhibition was observed in the sample activated by AA at 15 minutes but not until 120 minutes in the samples activated by collagen. No platelet inhibition was seen in the samples activated by thrombin. The median time to maximal AA-induced platelet inhibition of <30 U was 30 (interquartile range 15-90) minutes. Ex vivo DDAVP did not reverse platelet inhibition. Subgroup analysis did not show any gender differences.

Conclusions: ASA induces a strong platelet inhibition within 30 minutes of oral ingestion, with no gender differences. Ex vivo DDAVP did not reverse ASA's platelet inhibition.

Introduction

Acetylsalicylic acid (ASA) is frequently prescribed in the treatment and prevention of acute coronary syndrome (ACS) and acute ischaemic stroke, even if its role in primary prevention is unclear [1,2]. ASA is also used as an over-the-counter drug for pain and inflammation. ASA-associated haemorrhage risk is an issue regardless of indication [3,4] since it at low doses (75-150mg daily) inhibits platelets, primarily by irreversible inhibition of platelet cyclooxygenase (COX), preventing the formation of thromboxane A2 (TXA2) and thereby, diminishing platelet aggregation. At higher ASA doses, also prostacyclin is inhibited, counteracting the ASA low dose antithrombotic effect [5]. In emergencies, ASA therapy is often started with a loading dose of 300 mg [6].

Standard aspirin therapy is currently often combined with a P2Y12-antagonist, so-called dual antiplatelet therapy in coronary care (DAPT), with strengthened platelet inhibition [7]. There is a variable individual response both to ASA and P2Y12-antagonists, [8] highlighted by the introduction of point-of-care (POC) platelet function devices that are easy to use and rapidly show results [9]. Examples of POC platelet function devices are PFA-100, VerifyNow, PlateletWorks, TEG-PM (Platelet Mapping), ROTEM platelet, and Multiplate Electrode Aggregometry (MEA). Several studies have measured ASA responsiveness with these devices.

MEA has been used for studies of platelet aggregation in different clinical settings [10,11]. MEA reliably measures ASA platelet inhibition and is comparable to standard light transmission aggregometry and other POC platelet function devices [12]. In a study by Karon et al. MEA was the best test for measuring the effects of aspirin at the initiation of treatment as compared to TEG-PM and VerifyNow [13]. It is important to measure the baseline platelet function with MEA before the start of ASA as MEA can show platelet inhibition despite no ASA intake [14]. No study has yet investigated the time to peak platelet inhibition as measured by MEA in healthy volunteers after a normal per-oral loading dose of ASA (300-325 mg): previous studies have investigated either very early inhibition in patients with acute myocardial infarction [15] or a lower ingested dose [16].

Desmopressin (DDAVP) raises the plasma levels of factor VIII and von Willebrand factor (vWF) by stimulating their release from von Weibel Palade bodies on endothelial cells [17]. DDAVP is used clinically in the treatment of mild hemophilia A and von Willebrand disease, in coagulopathies associated with hepatic cirrhosis and uremia, and various congenital and acquired causes of platelet dysfunction [18]. Desmopressin has also been used to reverse ASA effects on platelets [19]. DDAVP has also been proposed to have direct effects on platelets, but in a study from our laboratory, MEA failed to demonstrate any in

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vitro effect of desmopressin on whole blood platelet aggregation in healthy volunteers with no platelet inhibiting drugs [20].

The primary aim of this study was to investigate the time to peak platelet inhibition measured with MEA, in blood from non-fasting healthy volunteers after an oral loading dose of 300 mg of ASA. A secondary aim was to investigate if the ex-vivo addition of DDAVP reversed the ASA-induced platelet inhibition.

**Material and methods**

This prospective observational study was approved by the Swedish Ethical Review Authority (registration numbers DNR 2010/482) and was conducted following the World Medical Association Code of Ethics (Helsinki Declaration 1975). The study was performed in 2019 at the Department of Intensive and Perioperative Care, Skåne University Hospital, Lund, Sweden. The manuscript was prepared following the STROBE guidelines for observational studies.

Ten healthy non-smoking volunteers without any medication 14 days prior to inclusion, were recruited and included after informed and signed consent. Five females and five males were studied, balancing gender effects on platelet function [21].

To avoid diurnal variation in platelet function the volunteers were instructed to eat a normal breakfast including 1 bowl of yogurt with cereals and one or two pieces of bread, before starting the study at 8 am [22]. During the study, only ingestion of tea, coffee, or water was allowed. In a recent study conducted by Krekel et al., no significant effect on platelet aggregation was seen after coffee, high-fat meals, or physical exercise [23].

The volunteers were given a single 300mg oral loading dose of non-enteric ASA (4 tablets of Trombly® 75mg, Pfizer, New York, USA). The tablets were swallowed with water, without being chewed, since chewing ASA tablets has been shown to increase absorption and shorten the time to a 50% reduction of serum thromboxane B2 (TXB2) concentration from 12 to 5 minutes [24]. Enteric-coated ASA tablets have poorer absorption from the higher pH environment of the small intestine and may result in less platelet inhibition [25].

**Blood sampling**

A peripheral vein catheter (PVC) (Venflon™, BD, Plymouth, UK) was inserted in an antecubital vein. Venous blood was drawn from the PVC using the Vacutainer System® (BD, Plymouth, UK) immediately before and then at 15, 30, 60, 120, and 180 minutes after ingestion of ASA. The first tube for each sampling was discarded before blood for MEA analysis was drawn using a 3 ml hirudin tube (Roche Diagnostics Scandinavia AB, Bromma, Sweden). The samples were incubated for 30 minutes at room temperature before analysis as recommended by the manufacturer [26] and Würtz et al. [27].

**Multiple Electrode Aggregometry**

MEA analysis was performed using the Multiplate® analyzer (Roche Diagnostics Scandinavia AB, Bromma, Sweden). The analysis is based on whole blood and measures the change in electric impedance between two electrodes over time upon the addition of a platelet activation agonist. Activated platelets stick to the electrodes causing the impedance to increase with increased platelet aggregation. This change in electrical current is plotted in a graph as aggregation units (AU) against time (min). The area under the curve (AUC) represents the extent of platelet aggregation and is expressed as units (U) where 1 U = 10 AU·min. Three tests with different platelet agonists were performed on each sample. The agonists used were ASPItest® with a test concentration of 0.5 mM of arachidonic acid, which initiates platelet aggregation through the COX pathway; TRAPtest® with 32 µM thrombin receptor activating peptide; and COLtest® with 3.2 µg/ml of collagen as described in the manufacturer's instructions [26]. Maximal ASA-effect as measured with the ASPItest was defined as an AUC of <30 U in accordance with the manufacturer’s documentation based on studies using hirudin anticoagulated test tubes [28,29].

**DDAVP spiking**

In addition to the analyses described above, an extra sample was taken 2 hours after ASA ingestion to investigate whether DDAVP added in vitro attenuates the effect of ASA as measured with MEA. The samples were incubated at room temperature for 30 minutes. Each sample was divided in two aliquots with 1.3 ml of blood in each. One of the aliquots was mixed with 0.1 ml of DDAVP with a concentration of 12.6 ng/ml (Octostim®, Ferring Copenhagen, Denmark) to a target concentration of 0.9 ng/ml. This concentration is higher than the average maximal plasma concentration in vivo after a normal dose (0.3 µg/kg) of DDAVP, which is 0.6 ng/ml [30]. The other aliquot was mixed with 0.1 ml of normal saline (Fresenius Kabi, Bad Homburg, Germany) to serve as a control. Both aliquots were then analyzed with MEA using ASPItest®, TRAPtest®, and COLtest® as described above.

**Statistics**

Statistical analysis was done using GraphPad Prism version 8.4.2 for Windows (GraphPad Software, La Jolla, California, USA). All variables were considered non-parametric and were presented as median with (interquartile range). Friedman's test was used to compare MEA AUC values at baseline (0 minutes) with the different blood sampling times (15, 30, 60, 120, and 180 minutes). Wilcoxon's two-tailed matched-pairs rank sum test was used to compare samples taken at each blood sampling time to the baseline, as well as comparing DDAVP ex-vivo spiked blood samples to non-DDAVP spiked samples. A p-value of <0.05 was considered significant. As gender has been described to affect platelet function, [20] a subgroup analysis with a Mann Whitney test of gender differences was also performed, analyzing Delta differences between before ASA and at 120 minutes for ASPItest®, COLtest®, and ASPI* with DDAVP.

**Results**

The median age of the 10 volunteers was 31 years with a range of 21–53 years.

**Time to maximal effect after oral ingestion of ASA: MEA AUC using ASPItest® decreased significantly after the loading dose of 300 mg ASA (p<0.001) (Figure 1). The median MEA AUC using ASPItest® before ASA ingestion was 99 U (Q1-Q3:94-103). At 15 minutes there was a significant decrease to 87 U (19-94 U), (p=0.006), and at 30 minutes there was a further decrease to 23 U (19-81 U), (p=0.002). The median of all subsequent measures was below the cut-off value for maximal platelet inhibition of 30 U. The median time to maximal ASA-induced platelet inhibition measured with the ASPItest was 30 minutes (15-90 minutes). All but 2 of the 10 volunteers showed maximal platelet inhibition on ASPItest within 60 minutes after ASA ingestion. One was a 53-year-old male reaching <30 U at 180 minutes; the other a 31-year-old male reaching <30 U at 120 minutes. Three of the volunteers already showed maximal platelet inhibition at the first sampling at 15 minutes: 2 females both 21 years old and one male 23 years old. On COLtest the decrease in platelet aggregation compared to baseline was not
significant at 15, 30, or 60 minutes. There was, however, a statistically significant decrease from baseline to 120 minutes (p=0.002) and 180 minutes (p=0.002) (Figure 2).

TRAPtest showed no significant difference between MEA AUC at baseline and sampling after ingestion of ASA (p=0.27) (Figure 3).

The addition of DDAVP ex vivo did not increase the MEA AUC using ASPItest compared to the controls (Figure 4) or the other MEA tests (Table 1).

A subgroup analysis of gender differences did not detect any significant differences in Delta response to ASA (before and at 120 minutes after the loading dose) for ASPItest: p = 0.14; COL: p = 0.06 and ASPItest-DDAVP: p = 0.11.

Discussion

In this prospective observational study, a peroral loading dose of 300 mg (non-chewed) ASA to healthy volunteers induced demonstrable and significant platelet inhibition within 30 minutes with considerable interindividual differences. Ex vivo desmopressin did not reverse this platelet inhibition.

Zeymer et al. studied platelet inhibition with the MEA ASPItest 5 and 20 minutes after patients with suspected or confirmed acute myocardial infarction were given either 250 mg or 500 mg of intravenous (iv) ASA or 300 mg oral chewed ASA tablets [15]. They also measured arachidonic acid (AA) induced thromboxane B₂ (TxB₂) synthesis as a gold standard marker of COX-1 inhibition by ASA. The baseline mean ASPItest AUC was 86 U. Maximal MEA platelet inhibition was on average already reached at 5 minutes when ASA was given intravenously (mean±SD ASPItest AUC 20.6±12 for 250 mg and 23.0±19 for 500 mg respectively) with no significant changes thereafter. In the per-oral group, the platelet inhibition was on average minimal.
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They found a 90% decrease in TxB₂ from the baseline after a 25.7±4.6 min for buffered ASA tablets swallowed intact, 13.6±1.9 min for chewed buffered tablets, and 15.8±1.8 min for buffered tablets dissolved in water (all mean±SD).

The results of our study seem to corroborate the above studies regarding the approximate time to maximal platelet inhibition after oral ASA administration. There were considerable inter-individual variations among our volunteers, with six of the participants responding with maximal platelet inhibition within half an hour, whereas two of the participants had not reached full inhibition until after 2 and 3 hours, respectively. Due to our small sample size, it is not possible to say if this accurately reflects the proportion of the population who have a delayed response to oral ASA, or whether variations depend on age or gender. Rubak et al. could not demonstrate a relationship between age and MEA ASPItest* and COLtest* in 121 healthy volunteers between 17 and 66 years [32]. MEA AUC was higher in females, probably reflecting estrogen effects on platelets. In our subgroup analyses, we could not show any gender differences in baseline values or in the ASA or ex vivo DDAVP responses, but our study is underpowered for this.

The results from the study of Zeymer et al. indicate that gastrointestinal absorption is an important factor affecting the onset of action of ASA-mediated platelet inhibition [15]. Of note is that the gastrointestinal absorption is an important factor affecting the onset of action of platelet inhibition by three different oral formulations of ASA in healthy fasting volunteers using optical aggregometry on platelet-rich plasma. Platelet inhibition was defined as a 50% decrease in optical density, which occurred in all volunteers within 25 minutes [31]. Feldman et al. studied early pharmacokinetics of ASA and changes in serum TxB₂ concentration after oral administration of loading doses of 325 mg in three different formulations, to twelve healthy, fasting volunteers [24]. They found a 90% decrease in TxB₂ from the baseline after a 25.7±4.6 min for buffered ASA tablets swallowed intact, 13.6±1.9 min for chewed buffered tablets, and 15.8±1.8 min for buffered tablets dissolved in water (all mean±SD).

Conclusion

In conclusion, a peroral loading dose of 300 mg (non-chewed) ASA induced demonstrable and significant platelet inhibition as measured by the Multiplate® platelet aggregometer, within 30 minutes. Ex vivo desmopressin did not reverse this platelet inhibition. There were considerable interindividual differences in the onset of peak
platelet inhibition, which should be considered when studying ASA responsiveness. Desmopressin's suspected reversal effect on decreased platelet function caused by ASA should be studied in vivo in future studies with advanced platelet function tests.

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**Conflict of interests**

The Authors declare(s) that there is no conflict of interest.

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