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"ASPIRIN VS HEPARIN: A COMPARATIVE REVIEW OF ANTIPLATELET AND ANTICOAGULANT THERAPY"

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Abstract
Aspirin and Heparin are two widely used agents in the prevention and treatment of thromboembolic disorders, yet they differ fundamentally in their mechanisms of action, clinical applications and pharmacological profiles. Aspirin, an antiplatelet agent, primarily inhibits cyclooxygenase-1[COX1] thereby Suppressing thromboxane Az Synthesis and preventing platelet aggregation. It is mainly indicated in arterial thrombosis, such as myocardial infarction and stroke prevention. In contrast, heparin is an anticoagulant that enhances the activity of antithrombin 111, inhibiting thrombin and factor Xa, thus interfering with the coagulation Cascade. It is Commonly used in venous thromboembolism, deep vein thrombosis, pulmonary embolism, and during surgeries or dialysis. This review compares their pharmacodynamics, indications, side effect profiles and clinical outcomes, highlighting the Complementary yet distinct roles of antiplatelet and anticoagulant therapy. The selection between aspirin and heparin is guided by the type of thrombosis, patient risk factors, and therapeutic goals, underlining the importance of individualized treatment strategies in cardiovascular and hematological care.

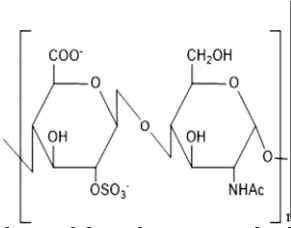
Keywords: Antiplatelet, Anticoagulant, Thrombosis, Pharmacodynamics, Individualized treatment.

INTRODUCTION

Chemical structure of Heparin sodium

Used for Atrial Fibrillation, Deep Vein Thrombosis, Pulmonary Embolism

Heparin has been used as a blood thinner for more than 80 years. However, its exact mode of action wasn't fully understood until the 1960s, and the specific part of the heparin molecule responsible for its anticoagulant effect wasn't identified until almost two decades later. Heparin is a complex and varied molecule, making it challenging to study and work with [1-4]. Besides its well-known role in preventing blood clots, various polysaccharides-some



derived from heparin and others from similar structures—have been shown to affect many biological systems. This suggests that these substances might have medical uses beyond blood thinning, such as treating inflammatory conditions. However, these other potential uses of heparin are not as well understood and are still being researched.

Mechanism of Action

Only about one-third of the heparin dose given actually binds to antithrombin (AT), and this portion is mainly responsible for heparin's blood-thinning effect. The other two-thirds doesn't contribute much to anticoagulation at typical treatment levels [5,6] However, at higher doses-beyond what's normally used-both high- and low-affinity forms of heparin can enhance the AT-related activity of another blood protein called heparin cofactor II [7]. The heparin-AT complex works by blocking several clotting enzymes, including thrombin (factor IIa) and factors Xa, IXa, XIa, and XIIa [8] Among these, thrombin and factor Xa are the most strongly affected, with thrombin being about 10 times more sensitive to the inhibitory effects of the

heparin-AT complex than factor Xa.For heparin to block thrombin, it must attach to both the enzyme and antithrombin (AT). However, when it comes to inhibiting activated factor X (factor Xa), binding directly to the enzyme is less critical.

Pharmacokinetics

Heparin's behavior in the body can vary a lot because it tends to bind to many positively charged proteins, cells, and surfaces—not just its intended target, antithrombin. This non-specific binding can affect how well it works and is a major reason why some patients show a weaker response to heparin (a condition called heparin resistance) (9)

Administration /Dosing

Heparin cannot be absorbed when taken by mouth, so it must be given by injection. The two preferred ways to give it are through an intravenous (IV) line or a subcutaneous (under the skin) injection. Giving heparin into the muscle (IM) is not recommended because it can cause large bruises due to bleeding from blood vessels in the muscle [10-13].

Adverse Effects

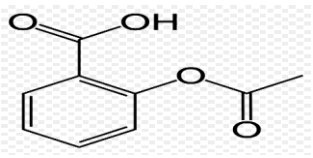
Heparin is commonly associated with side effects like bleeding, low platelet counts (thrombocytopenia), and reactions at the injection site. Long-term use of heparin can lead to additional side effects. Among all the complications, bleeding is the most serious, so it's important to monitor patients closely. Signs of bleeding may include blood in urine or stool, easy bruising, tiny red spots on the skin (petechiae), or nosebleeds [14].

Uses

As mentioned earlier, heparin has shown antitumor and antimetastatic properties, which may be linked to its anticoagulant effects or other direct and indirect mechanisms, such as blocking signaling pathways. These effects vary depending on the type of tumor cell.

Due to its wide range of chemical actions, heparin and its derivatives have attracted attention in breast cancer research. Studies have shown that heparin-based compounds can significantly reduce breast cancer cell growth and spread, both in lab experiments (in vitro) and in animal models (in vivo). They may also help in targeted cancer therapy by regulating the production of key components of the extracellular matrix [15]

Aspirin



Chemical name: 2-Acetoxybenzoic acid

Aspirin (acetylsalicylic acid) is the most widely used antiplatelet medication around the world, commonly used to prevent heart and blood vessel diseases both before (primary prevention) and after (secondary prevention) they occur. For patients at high risk of vascular problems, aspirin use leads to a 34% drop in nonfatal heart attacks, a 25% decrease in nonfatal strokes, and an 18% reduction in death from any cause.

Mechanism of Action

Aspirin (acetylsalicylic acid) works by adding an acetyl group to certain molecules, which makes it an acetylating agent. It permanently disables the enzyme cyclooxygenase-1 (COX-1), preventing the production of prostaglandin H2, which is needed to form thromboxane A2, a compound involved in blood clotting(16) Aspirin does this by attaching its acetyl group to the amino acid serine at position 529 (Ser529) in COX-1's active site. It also binds to another amino acid, arginine at position 120 (Arg120), which blocks arachidonic acid from entering the enzyme's active site and reaching tyrosine 385 (Tyr385), further stopping prostaglandin H2 productions

Pharmacokinetics

There is considerable discussion around the definition and potential mechanisms underlying aspirin resistance. Reports of aspirin resistance vary widely; the differences may be due to the different definitions employed to characterize the apparent resistance. Of the many proposed causes, the most frequent seems to be simply related to patients either not taking the drug (non-adherence) or taking it but not absorbing it (non-response, low bioavailability) since true 'genetic' resistance to aspirin is exceedingly rare.Upon re-challenge with either immediate-release or enteric-coated formulations, no subjects were found to be resistant to immediate-release aspirin, while some subjects still exhibited low responses to enteric-coated aspirin. Importantly, studies have shown that patients with incomplete response to aspirin do experience higher risk for recurrent thrombotic events. In one study, discontinuation of lowdose aspirin was associated with a > 30% increased risk of CV events [17]. The ability of a novel formulation to deliver predictable levels of aspirin and consistently achieve full (>99%) inhibition of thromboxane production would be helpful in addressing the issue of aspirin resistance.

Administration/Dosing

Aspirin works by permanently blocking platelet TXA2, and its effects build up with daily use. In healthy people, taking just 30 mg of aspirin per day can almost completely stop TXA2 production within a week. However, in certain medical conditions like diabetes, metabolic syndrome, or after coronary artery bypass surgery (CABG), aspirin may not be as effective. That's why typical daily doses of 75–100 mg are used-they're higher than the minimum needed

but help account for individual differences in response.

Adverse Effects

Non-aspirin NSAIDs (nonsteroidal anti-inflammatory drugs), which also block COX enzymes, may lead to kidney problems and worsen blood pressure control. This happens because they interfere with prostaglandins that help dilate blood vessels in the kidneys. Aspirin, however, is a much weaker inhibitor of these kidney-related prostaglandins. When taken at low to moderate doses for heart disease, aspirin usually doesn't affect kidney function or blood pressure.

Uses

Newer Uses for Aspirin

The story of Aspirin is far from over, and according to Elwood et al, "several new uses of the drug are being investigated. Some of these arise from its antithrombotic effects, but others appear to originate from other drug actions. That Aspirin has other activities should not be surprising, because salicylates have many functions in plants that have nothing to do with platelets or thrombosis" [18, 19].

Discussion

Asthma is a chronic inflammatory airway disorder characterized by bronchial hyperresponsiveness and episodic bronchospasm. Since the 1960s, studies have noted that intravenous heparin can subjectively improve asthma symptoms.

More recent clinical models have shown that inhaled heparin or its derivatives possess anti-asthmatic properties in various triggers, including allergens, exercise, adenosine, and distilled water challenges.

Seven randomized controlled crossover trials, mostly with small sample sizes (8 to 25 participants), have explored heparin's anti-inflammatory effects in exercise- or allergen-induced asthma [20,21]

- Ahmed et al. (n=12) demonstrated that inhaled heparin (1000 µg/kg) reduces exercise-induced asthma symptoms but does not prevent histamine-induced bronchoconstriction.
- Stelmach et al. found that inhaled heparin (5000 IU) significantly decreased bronchial hyperreactivity to histamine and leukotriene D4 compared to placebo ($p=0.043$ and 0.005, respectively), though changes in FEV1 were not significant ($p=0.064$).
- The reduction in airway responsiveness by heparin may be due to its suppressive effect on mast cell degranulation rather than bronchodilation [22].
- A double-blind randomized study with 10 asthmatic subjects showed that inhaled heparin attenuates airway response to adenosine 5'-monophosphate (AMP) but not to methacholine ($p<0.01$), supporting the idea that heparin acts primarily through anti-inflammatory pathways rather than direct bronchodilation [23].
- This analysis highlights the complexity in assessing the association between the PlA1/A2 polymorphism and aspirin resistance, particularly due to variability in measurement techniques. Our findings suggest that the effect of the PlA2 allele on aspirin resistance differs depending on the method used to assess platelet function. Specifically, studies employing thrombin generation or bleeding time reported a significant association between PlA2 carriage and aspirin resistance. However, this subanalysis was limited by a relatively small sample size (n = 220), which may affect the generalizability of these findings [24].
- In contrast, no significant association was observed in studies using PFA-100 and light transmission aggregometry (LTA). Interestingly, our analysis suggests a trend-albeit non-significant-towards aspirin sensitivity in PlA2 carriers when PFA-100 was used, while LTA-based studies indicated a possible increase in aspirin resistance among PlA2 carriers.
- The inconsistency between different testing modalities has been emphasized in previous studies. For example, Fontana et al. demonstrated a striking discrepancy: in a cohort of 96 healthy individuals, only one subject was classified as aspirin-resistant by arachidonic acid-induced aggregation, compared to 28 subjects by PFA-100. These findings indicate that PFA-100 may lack specificity in identifying true aspirin resistance, potentially leading to misclassification and dilution of genotype-phenotype associations. Moreover, PFA-100 assesses platelet function through multiple agonist pathways (ADP, collagen, epinephrine), which are not directly inhibited by aspirin. Therefore, it may be more reflective of general platelet activity rather than specific aspirin effect.
- On the other hand, LTA-particularly when using arachidonic acid-provides a more direct assessment of aspirin's inhibitory effect on COX-1. However, its low sensitivity and technical demands limit its widespread applicability. As such, the variability in defining aspirin resistance across different platforms complicates efforts to determine whether genetic polymorphisms, such as PlA1/A2, are true determinants of aspirin efficacy.
- Supporting this, Lordkipanidze et al. found wide-ranging prevalence rates of aspirin resistance among 201 patients with stable coronary artery disease, depending on the test used: 4% with arachidonic acid-induced aggregation, 6.7% with VerifyNow®, 51.7% with ADP-induced aggregation, and 59.5% with PFA-100. These results underscore the methodological challenges in defining aspirin resistance and the implications for identifying genetic associations.
- Beyond the PlA1/A2 polymorphism, we also examined four additional variants (GPIa C807T, COX-1 A842G/C50T, P2Y12 H1/H2, and P2Y1 A1622G). None showed a clear association with aspirin resistance, although limited sample sizes prevent definitive

conclusions. Given aspirin's primary action on COX-1, this gene remains a logical focus for future investigations. Nonetheless, recent studies (e.g., Frelinger et al., Meen et al.) suggest that aspirin resistance may occur independently of both COX-1 and COX-2 pathways, pointing to alternative or multifactorial mechanisms.

- A recent systematic review by Krasopoulos et al. concluded that aspirin-resistant individuals are at increased risk of recurrent cardiovascular events compared to aspirin responders. Therefore, elucidating the underlying mechanisms of aspirin resistance, including genetic contributions and methodological limitations, is crucial for identifying at-risk individuals and improving clinical outcomes.

Conclusion

In this review, we examined the potential anti-inflammatory effects of heparin, as supported by various clinical trials conducted in different settings. Heparin and its derivatives have shown beneficial outcomes in patients with asthma, as well as in those undergoing cardiopulmonary bypass or cataract surgery. However, results from studies on other inflammatory conditions, such as inflammatory bowel disease (IBD), particularly ulcerative colitis, remain inconsistent and varied.

Most trials reported no adverse effects from heparin when used as an anti-inflammatory agent, whether administered systemically or locally-via inhalation, irrigation, or heparin-coated devices. Nonetheless, due to the generally low methodological quality of these studies, it is not yet possible to draw firm conclusions regarding the efficacy of heparin in this role.

Aspirin has been clearly shown to reduce mortality and the risk of reinfarction when used as short-term treatment during acute myocardial infarction (AMI), in patients with unstable angina, and as a long-term secondary preventive measure in those with established cardiovascular disease. Despite strong evidence supporting its effectiveness, aspirin remains underutilized in both acute coronary syndrome management and secondary prevention. Research shows that over 10% of AMI patients do not receive aspirin even when there are no contraindications, and between 20% and 50% of patients who have had an infraction are not maintained on long-term aspirin therapy. The rates are even more concerning in older populations—for instance, nearly 30% of Medicare patients hospitalized with unstable angina do not receive short-term aspirin therapy, and up to 80% of nursing home residents with a prior myocardial infarction are not given aspirin.

Given this evidence, aspirin use should be considered standard practice in these settings unless a clear contraindication exists. The recommended dose should be the lowest effective amount: 160–325 mg for acute events, and 75–160 mg daily for long-term primary or secondary prevention. Higher doses are linked to increased risk of adverse effects and should be avoided.

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Conflict of Interest

No Conflict of Interest

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Inform Consent and Ethical Statement

Not Applicable

Author Contribution

All authors are contributed equally.

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