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Review Article

Acetylsalicylic Acid, Cardiovascular Diseases and Nanotechnology

Max S Saito*

Department of Production and Control of Drugs, Federal University of Rio Grande do Sul, Brazil

***Corresponding author**

Max Seidy Saito, Department of Production and Drug, Federal University of Rio Grande do Sul, College of Pharmacy, Av. Ipiranga 2752, Porto Alegre, Rio Grande do Sul, Brazil, Tel: 555133165411; Email: maxsaito@gmail.com

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Abstract

Acetylsalicylic acid (ASA) is the most widespread antiplatelet agent used now a day due to its efficacy and low cost. However, several side-effects are well-known to limit ASA usage. This review covers the recommended guidelines for ASA usage for primary and secondary prevention in cardiovascular diseases, showing when this treatment is recommended, the concomitant usage of proton pump inhibitors in ASA therapy and if enteric-coated ASA is well established. Furthermore, we show promising studies and future perspectives on the exploration of different administration routes as well as the usage of nanotechnology to lower therapy-related side-effects, particularly gastrointestinal bleeding and ASA resistance.

ABBREVIATIONS

ARA: Arachidonic Acid; ASA: Acetylsalicylicacid; COX-1: Cyclooxygenase-1; CVD: Cardiovascular Diseases; FDA: Food and Drug Administration; GBR: Gastrointestinal Bleeding Risk; LDA: Low-dose ASA; NP: Nanoparticles; PEG: Polyethylene Glycol; PGH_2: Prostaglandin H_2; PPI: Proton Pump Inhibitors; PPIs: Proton Pump Inhibitors; RES: Reticule Endothelial System; TXA_2: Thromboxane A_2

INTRODUCTION

Acetylsalicylic acid (ASA - aspirin®), is the most widespread antiplatelet agent used now a days due to its known efficacy and low cost [1,2]. The mechanism of action observed for ASA is the acetylation of the Ser530 residue in the active site of plateletcyclooxygenase-1 (COX-1), thus preventing the proper binding to arach idonic acid (ARA), and further impairing the prostaglandin H_2 (PGH_2) synthesis. Consequently thromboxane synthase (TXS) do not synthetize thromboxane A_2 (TXA_2), a potent platelet activator and inflammatory mediator [3–6]. (Figure 1) Such mechanism renders ASA as one of the main drugs used in the management of thrombotic diseases. Data provided by the Agency for Healthcare Research and Quality(AHRQ) [7] in 2007, reported that nearly 20% of adults in United States were taking ASA daily and literature from several studies [8–16] using different doses of ASA (75mg to 325mg) showed that doses above 160mg is not recommended in any case due to an increased risk of gastrointestinal bleeding (GBR). Nevertheless, Hedberg *et al.* [13] observed in a nationwide cohort study in Sweden that proton pump inhibitors (PPIs) in patients taking low-dose ASA (LDA; 75-160mg/day) failed to reduce GBR.

Furthermore, accordingly to World Health Organization (WHO), cardiovascular diseases are currently among the major causes of death worldwide [17–19]. (Figure 2) Ittaman *et al.*[16] in a very concise review, showed the benefits and problematic associated with ASA usage for the primary prevention of CVDs, mainly showing that ASA usage is uncertain, despite the recommendations of several organizations (American Heart Association/American Stroke Association; American College of Chest Physicians; U.S. Preventive Services Task Force; Canadian Cardiovascular Society and European Society of Cardiology). Overall, the usage of ASA according to those organizations is advised for patients in critical care, in which the therapeutical benefit of ASA is able to surpass the GBR. For the prevention of a secondary episode of CVD, LDA is highly recommended because due to the increased risk of those patients, managing recurrent cardiovascular events is the main priority over GBR itself, especially with a concomitant usage of PPIs [13,16]. Moreover, another promising ASA formulation is the enteric-coated. This formulation is ASA coated with fatty acids, waxes, shellac, plastics, polymers and polysaccharides [20]. A systematic review of Garcia Rodriguez *et al.* [20] Revealed no statistically significant differences in ASA and enteric-coated ASA, suggesting that GBR in that case is because systemic inhibition of PGH_2 rather than local inhibition.

A new approach to these problems can be solved by proper application of nanotechnology. This area is relatively new, with the first attempt being made in 1972 [21]. Nanoparticles (NP) are colloidal particles, which are less than 1 μm in diameter and can be loaded with several drugs [22]. Modifications in the NP structures and composition can produce nanocapules

Figure 1 Platelet activation pathways, induced by Collagen, von Willebrand Factor, Serotonin, Epinephrine, Thrombin, ADP and Arachidonic Acid, leading to increased calcium concentration. PLA_2 = Phospholipase A_2; ARA = Arachidonic Acid; PGH_2 = Prostaglandin H_2; TXS = Thromboxane Synthase; TXA_2 = Thromboxane A_2; cAMP = Cyclic adenosine monophosphate; AMP = Adenosine monophosphate; COX-1 = Cyclooxygenase-1.

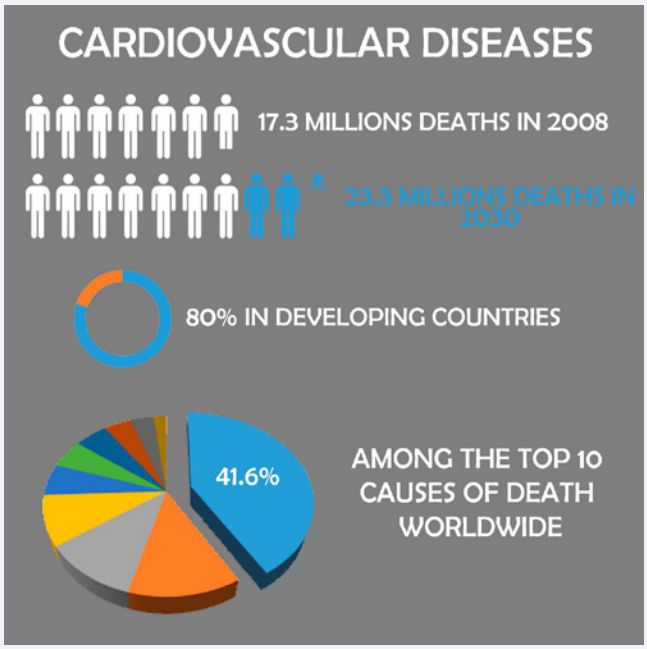

Figure 2 Cardiovascular diseases chart accordingly to WHO (2014).

or nanospheres. Nanocapsules consist in a reservoir system in which oilcore in present surrounded by a polymeric wall, where the drug can be dissolved in this oil core or adsorbed in the wall. Regarding to nanospheres, this system does not show oil in their composition and the drug can be retained or adsorbed in the polymeric matrix [22,23] (Figure 3).

The polymers can be divided in natural and synthetic. Natural polymers can be proteins (i.e. collagen, albumin); polysaccharides (i.e. chitosan, fucoidan, alginate) and synthethic, like polyesters [24]. Additionally, biodegradable polymers approved by the Food and Drug Administration (FDA) can be used to produce NPs, like acrylates, carboxyvinil, methacrilates, Poly (ethylene glycol) [25]. NPs can lead to targeted drug-delivery [26], leading to reduced side effects, higher bioavailability and sustained release [24,27]. (Figure 4) Furthermore, NPs can have so-called "stealth" properties, using biodegradable and biocompatible polymers like polyethylene glycol (PEG) to systematically escape from macrophages of the reticuloendothelial system (RES), leading to prolonged NP in blood circulation that further increases the chance to reach its biological target [28].

This technology can to improve the efficacy of LDA, diminishing the GBR and targeting specific elements present at sites of local thrombosis, like the lesioned endothelium or activated platelets.

Few studies using ASA reached this area, such as Das et al. [26] who made NPs loaded with ASA and albumin for sustained release by the coacervation method. They observed that ASA was released in a sustained and prolonged manner maintaining the antiplatelet activity of ASA. However, this work was not focused on the management of CVDs. Jin *et al.*[29], in 2013, developed a nano sized system of ASA-RGDV (acetylsalicylic acid-Arg-Gly-Asp-Val) targeting activated platelets and binding to receptor GPIIb/ IIIa and then, releasing aspirin inside the thrombus, successfully overcoming ASA resistance and non response, showing high antithrombotic effects due to blockade of ARA pathway. In vivo studies with a thrombus rat model showed that this system was 16,700 fold higher than ASA alone [30]. More studies of the mechanism of action of this nanosized system needs to be investigated as the RGDV is covalently linked to ASA, thus modifying the structure and substantial amount of *in vivo* studies will be necessary before the successful basic research can be translated into clinical trials.

Another new approach is to modify the administration route. Using NPs for either parenteral, rectal, topical or respiratory routes [31,32]. The most promising approach is the respiratory/ pulmonary route, because of its rapid distribution in the bloodstream, avoiding gastrointestinal complications and the

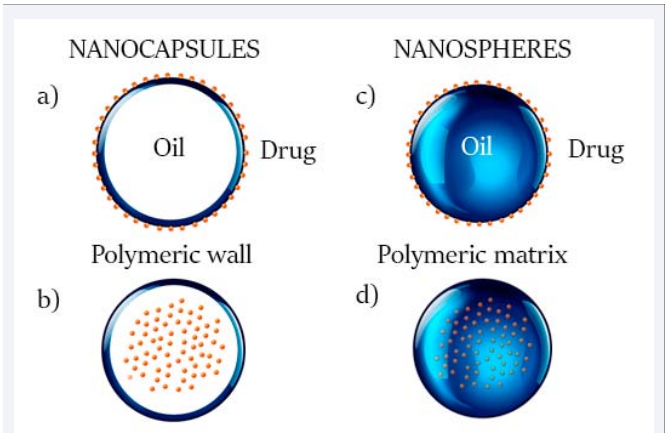

Figure 3 Schematic representation of polymeric nanocapsules and nanospheres: a) adsorbed drug in the polymeric wall; b) dissolved drug in the oil core; c) retained drug in the polymeric matrix and d) adsorbed or disperse drug in the polymeric matrix.

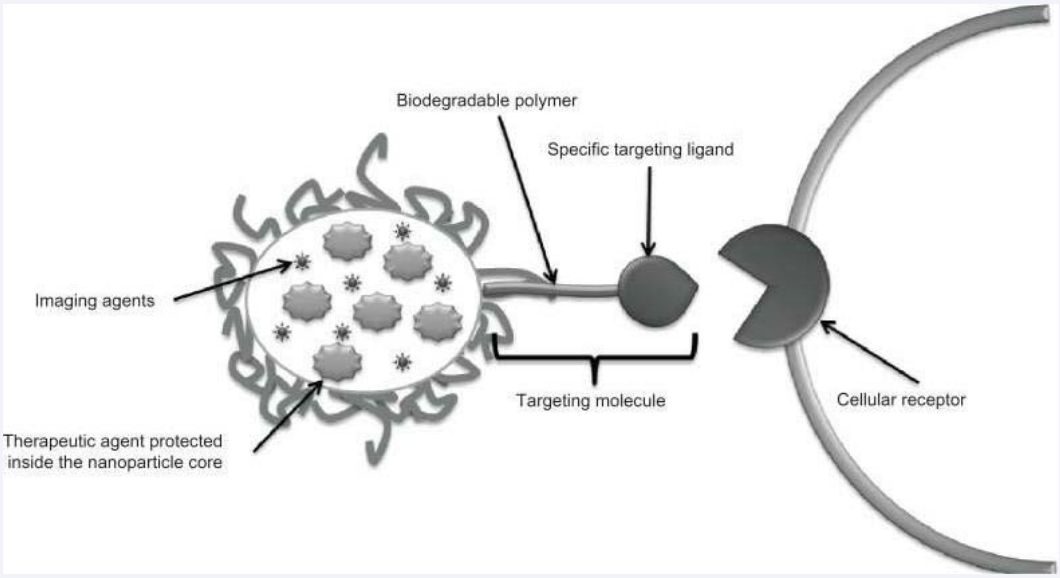

Figure 4 Example of target drug delivery system. In the example, imaging or therapeutic agents are nanoencapsulated in the core. Additionally, specific targeting ligand (i. e. antibodies, peptides, proteins) can be in the nanoparticle surface to specific ligation with the chosen cell.
Figure from: Critical evaluation of biodegradable polymers used in nanodrugs, Copyright © 2013 Marin *et al.*

first pass effect [31]. Moreover, the main problem on ASA usage is the GBR. Through this route, we can avoid the digestive system and the first pass effect, thus lowering ASA dosage, consequently, their toxicity. However several precautions will need to be considered not to induce inflammatory, toxically and pathological disorders in the lungs as a consequence [30,31].

CONCLUSION

ASA is the most used antiplatelet agent, but several complications, i.e. gastrointestinal complications like bleeding and ulcers limits this treatment. It is well knowing that LDA is widely recommended to secondary prevention of CVDs despite the increased GBR. For primary prevention, it is not clear their benefits and some countries have their own protocol. Nevertheless, ASA still be used and will be used in the future because their safety and well-known pharmacokinetics and pharmacodynamics. For this reason, new approaches will be need to surpass these side effects, especially the GBR for optimal treatment and adherence to long-term usage of ASA. Nanotechnology can be the answer for this question, especially modifying to the pulmonary route, but negligible efforts were made in this area.

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