

Application of Aspirin for Rheumatoid Arthritis and Myocardial Infarction Treatment

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Abstract. With the intensification of the aging process of the population, the disease problems of the elderly are particularly prominent. Rheumatoid arthritis and myocardial infarction are common diseases in the elderly. The main component of aspirin has been used to treat fever since 1763, and then the role of aspirin was discovered by humans. In modern daily life, aspirin is used for anti-inflammation, pain relief, and inhibition of thrombus formation. The subject of this research is how recent experiments demonstrate the effectiveness of aspirin for these two diseases. Research done by different teams has shown that aspirin inhibits a catalyst called COX that catalyzes the production of prostaglandins for rheumatoid arthritis treatment, leading to the relief of skeletal muscle pain and inflammation. In the treatment of myocardial infarction, aspirin prevents the accumulation of platelets to reduce the formation of thrombosis. Among the drug that can treat these two diseases, aspirin can be said to be the most effective drug with the least side effects.

Keywords: Rheumatoid arthritis, Myocardial Infarction, Treatment.

1. Introduction

Aspirin is the most widely used nonsteroidal anti-inflammatory drug nowadays, before it was manufactured by Bayer company, the chemical that has a similar structure has been widely used by people all over the world. The biggest reason this drug has survived so far is that it has very few side effects. The predecessor of aspirin is salicylic acid, which was found in willow [1]. As early as 1763, a priest named Edward Stone discovered that willow bark could be used to cure fever, he used powder ground from willow bark to treat malarial fever in 50 patients [1]. Since then, the world's research has officially started. People worldwide continued to purify salicylic acid from willow, and doctors began to use the purified compounds in pain remission. In 1897, aspirin was first manufactured by a chemist from a German company which is Bayer, it was the first time that people could modify salicylic acid to aspirin, for far, the legend of aspirin began [1].

The metabolize of aspirin is extremely due to its short half-life. Aspirin could be hydrolyzed to salicylic acid in the bowel wall, liver, and RBCs. Salicylic acid then reacts with other chemicals to form new substances. Salicylic acyl glucuronide could be produced when salicylic acid reacts with glycine, and acyl glucuronide could be formed when glucuronic acid conjugate with salicylic acid. Those two products are mainly produced in urinary metabolism. Furthermore, gentistic acid, 2, 3-dihydroxybenz acid, gentisuric acid, and salicyluric aphenolic glucuronide are also formed and excreted from urine [2]. Due to aspirin's short half-life and few side effects, the doctor was willing to prescribe aspirin to their patients. Rheumatoid arthritis is one of the diseases that can be treated with aspirin. It is a chronic autoimmune disease, and the etiology of this kind of disease is still unclear, but the serological marker and asymptomatic synovitis shows that rheumatoid arthritis could be prevented by aspirin [3]. Aspirin is also important in the treatment of myocardial infarction. Aspirin binds with cyclooxygenase and inhibits it, reducing the aggregation of platelet and thrombus formation [4]. More uses for aspirin have yet to be explored by humans, but this drug's potential is limitless. In this research, the mechanism and metabolism of aspirin, the therapeutic use of rheumatoid arthritis, and myocardial infarction will be evaluated, and the future direction of aspirin will be reflected.

2. Application of aspirin for rheumatoid arthritis treatment

Research about the mechanism of aspirin has been done by a scientist named Harry Collier in 1958, Harry Collier wanted to test how aspirin blocked kinins, which are substances released into the blood by damaged biological cells to cause inflammation. He starts his experiment by using the guinea pig, he injected the guinea pigs with bradykinin, a substance that can constrict the trachea of guinea pigs, and he judged the intensity of pain by the state of tracheal constriction. He then gave aspirin to some of the guinea pigs. He found that guinea pigs that had been given aspirin and those that hadn't had breathing difficulties after being injected with bradykinin, while the guinea pigs that had been given aspirin before the experiment had no changes in their trachea. The fact shows that aspirin does work in this situation, but where does it really do its job [3]?

2.1. The Discovery of RCS

Harry fell into a research bottleneck. At this time, he and his assistant, Ms. Priscilla Piper, thought of looking for John Vane, who was working in a laboratory under the Royal College of Surgeons of England. Vann invented a method similar to the bioassay called the cascade surface perfusion assay [3]. The specific operation is to soak two pieces of biological tissue in a neutral solution called Krebs solution for a period of time and keep the liquid flowing during soaking to form an upstream and downstream [5]. Upstream are the lungs of guinea pigs that have been injected with some allergen in egg whites, these lungs usually contain other drugs, and then it produces a hormone, which reaches another tissue of other animals through the solution. If the downstream tissue shows obvious changes such as trembling and writhing, it means that it is allergic to a certain component of the hormone secreted by the upstream guinea pig. Then one day Piper and Van discovered that a section of the rabbit's aorta was trembling for about 30 seconds, indicating that a secretion had not been neutralized. They named this substance rabbit aortic-contracting substance. They re-conducted the experiment and added some aspirin to the lung tissue of guinea pigs. The lungs that encountered Krebs' solution were still allergic, but the rabbit's aorta did not tremble. The true identity of RCS was suddenly realized two years after the experiment was completed. It is a prostaglandin. The substance that produces prostaglandin is unknown, but the arachidonic acid in the human body is also produced by this substance. When the cells are stimulated, the human body will produce arachidonic acid, followed by a series of chemical reactions, prostaglandins are the products of the reaction. The real role of aspirin has also been discovered, and it may be an important factor in blocking the production of prostaglandins. Vann ran the experiment again, and this time he was sure of his idea. When cells are stimulated, arachidonic acid is produced, which produces prostaglandins, which cause fever and pain in the body, and aspirin blocks the follow-up of this series of reactions. Within more research people did in the following years, people found that aspirin is blocking a substance called cyclooxygenase, or COX for short. This enzyme acts as a catalyst in the chemical process that produces prostaglandins. Other NSAIDs could have the same function as aspirin, but the reason why scientists choose aspirin is that aspirin irreversibly blocks COX through eternal acetylation [6].

2.2. Inhibition of COX

Research about how aspirin acts as an inhibitor has been done by Stephen's team. 5 males and 5 females are chosen to be participants for this research, as shown in Fig. 1. They complete a questionnaire about their medical history, exercise, and food habits. And all of them are healthy. Among those ten participants, 1 of them are chosen to use aspirin. The scheme below shows what should participants do before the experiment.

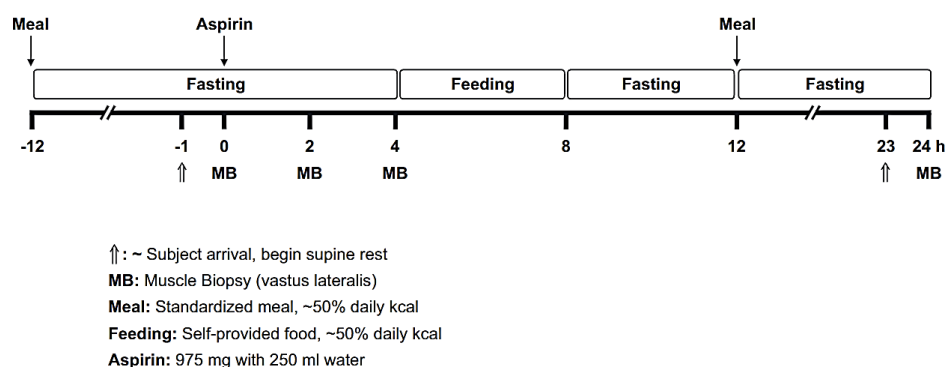


Figure 1. Timetable for participants and dose of aspirin [6, <https://doi.org/10.1152/jappphysiol.01119.2016>]

The detail of the muscle biopsy was given a local anesthetic (lidocaine HCL, 1%) to participants, and took two biopsies from each leg, the second of which was performed through a fresh incision close to the first. In order to split the muscle for investigation carried out inside the body, and experiment carried out outside the body, extra blood, visible fat, and connective tissue were removed following the biopsy. Stephen's team incubates skeletal muscle and recorded data of in and ex-vivo skeletal muscle PGE₂ (product of metabolism of COX) production after participants used a single dose of aspirin. Fig. 2 compares the data researchers get from these two kinds of body skeletal muscles.

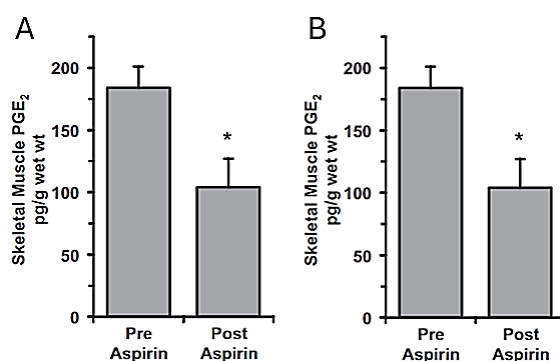


Figure 2. Inside body skeletal muscle (A) and outside body skeletal muscle (B) PGE₂ level before and after using 975 mg of aspirin [6, <https://doi.org/10.1152/jappphysiol.01119.2016>]

The trend of PGE₂ production in both two kinds of skeletal muscle is the same, therefore the experiment result shows that the aspirin can be used to inhibit COX and decrease inflammatory and metabolic regulator PGE. Aspirin could remit skeletal muscle diseases like rheumatoid arthritis [6].

2.3. Application of Aspirin for Myocardial Infarction Treatment

The main cause of myocardial infarction is coronary thrombosis, a substance called thromboxane that causes platelets to clump, which leads to the formation of blood clots in the large arteries. People find that aspirin could inhibit thromboxane, which means it could prevent myocardial infarction [3].

A randomized, double-blind, multicenter research has been set up in seven countries by Michael's team, in this research, all participants will receive 100mg of enteric-coated aspirin or 100mg placebo, and the main goal of this research is to find how efficient is aspirin in the treatment of different diseases such as congestive heart failure [7].

The mean age of participants is about 63.9, people in this age group are most prone to heart disease, and a similar age allowed the experiment to yield more accurate results. In this research, Michael's team carried test by two-sided log-rank test, in this test treatment, country, and sex has already been stratified. For researchers to adjust country and sex, the Cox proportional hazards model is used.

Between 2007 to 2016, each participant completed at least 9 visits over an approximately period of 6 years, except 29.6% of participants were terminated for different kinds of reasons like death or loss of follow-up. Information in Fig. 3 shows that aspirin does lower the risk of myocardial infarction, although the result isn't significant, this difference could be significant in the pre-protocol analysis.

The aspirin dose setting is not suitable for everyone in this research, cardiovascular benefits must be evaluated based on the risk of clinical complications associated with aspirin therapy, such as gastrointestinal bleeding (or other bleeding).

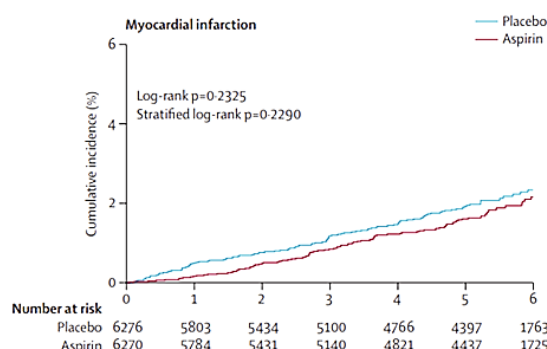


Figure 3. Compare the number of risks between the placebo group and the aspirin group [7, [https://doi.org/10.1016/S0140-6736\(18\)31924-X](https://doi.org/10.1016/S0140-6736(18)31924-X)]

3. Metabolism

Here the metabolism is analyzed. Aspirin is hydrolyzed to salicylic acid in the human body after being taken by patients. And then, the salicylic acid can be conjugated with glycine and glucuronic acid to produce two different urinary metabolites which are salicyluric acid and salicyl acyl glucuronide. Besides these two main products, other minor metabolites are also been produced and excreted into the urine [8].

3.1. Overdose And Therapeutic Dose

The metabolism disposition of aspirin is different when patients take a therapeutic dose and overdose [8]. Patel and his team carried out a study. A group with a mean age of 39.71 ± 2.35 y were using the therapeutic dose of aspirin. And another group with a mean age of 24.5 ± 2.4 y were taking the overdose of aspirin. The therapeutic dose group take the aspirin healthily and suitable, they emptied their bladders of urine the night before and then took soluble aspirin (600mg dissolved in 200ml of water). All normal activities, as well as fluid intake, were allowed for two hours after taking the dose. Within 8 hours after they started taking aspirin, their urine was collected as every single sample, and the cubic measure and acidity of urine is recorded, and those samples were stored at a suitable temperature. The basic data the overdose group should record is the same as the therapeutic dose group, the differences were the frequency they took samples. In the overdose group, the initial salicylic acid concentration in patients' bodies is about 240-630mg, and urine samples were taken from patients 2 hours once in the first 12 hours, and in the next 12 hours, urine samples were taken 4 hours once.

The result this team get shows that the urine excretion of salicyluric acid in the overdose group is lower than the group which uses a therapeutic dose. According to Patel's team's findings, they said that the formation of SUA under conditions of overdose is more variable than the therapeutic use.

3.2. Different Genders of Patients

Different gender may also metabolize aspirin differently. A study about how gender relates to metabolism is carried out by Montgomery et al. In this experiment, 44 healthy participants were included, 21 of them were men, and twenty-three of them were women. The subjects were forbidden to eat for a night, and then the researcher inserted a plastic intravenous cannula into their forearm vein, using heparin in saline (10U/ml) to maintain the cannula. After that 300mg aspirin was given orally with 150ml water, and 13 different time periods of blood collection in the next 24 hours, and urine collection every two hours, the collection of urine will become a 12-hour collection in the later

period, the collection of urine stop after 72 hours. HPLC was used to determine aspirin and its metabolites.

The final result shows women had excreted less resistant glucuronide than men, the concentration of this metabolite is too low and it could only be detected in urine but not serum. The concentration of metabolites could be different in concentration between different gender, but this difference is not too large.

4. Side Effects

As aspirin was a medicine, we know it could damage the human body.

For main side effect, Aspirin work in the intestine, its coat starts to dissolve due to the acidic environment the stomach has, so the side effect is mainly gastrointestinal [10]. Large-dose aspirin can prolong the working time of thrombin. According to the survey, 10 to 20 percent of patients have symptoms such as gastric bleeding or mild indigestion after taking aspirin, and that's because the acidic environment makes the aspirin to be nonionized continued, and aspirin accumulates in gastric mucosal cells and changes the permeability of the gastric mucosal cell, LDA also motivates the bleeding of Gastrointestinal tract through an antiplatelet effect [11].

For weight risk and benefit, in the case of aspirin, the benefits this kind of drug brings to the human body far outweigh the harm it brings to the human body, many drugs that have an effect with aspirin could not reach this high standard. Gao et al. had made an investigation on risk assessment of aspirin [12]. They first analyzed patients who use aspirin for a long time, and they found if the dose of aspirin is lower (e.g., 163mg/day), the risk of gastrointestinal tract could be lower. And then they found more than fifty thousand patients and those patients have a mean duration of treatment of more than 30 months and the average dose of aspirin they used is 273mg/day, there was only 12 risk of event per ten thousand people. Their analysis shows that aspirin has a large benefit for the population at risk.

5. Conclusion

This research analyzed the role of aspirin for rheumatoid arthritis and myocardial infarction treatment. And the research also discussed the side effect of aspirin during use. Aspirin can relieve the inflammatory symptoms caused by rheumatoid arthritis by inhibiting COX, and can also prevent myocardial infarction by reducing the formation of thrombus through its anti-platelet aggregation effect. The salicylic acid formed by the breakdown of aspirin can cause some damage to the stomach, the extent of this damage depends on the individual's physique, but most of the time, aspirin's benefits outweigh its disadvantages. Since the advent of aspirin, this drug has continuously discovered its own use, from the beginning of the treatment of fever to the prevention of heart disease, aspirin across the field is very large, and its functions are still being developed.

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