History of Aspirin

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Introduction

The discovery and development of antithrombotics, antiplatelets, anticoagulants and fibrinolytics form one of the most fascinating chapters in the history of medicine. It has one of the longest stories in drug discovery. Many of these advancements in the discovery process were made by individuals with little experience in the field. The innovators belonged to diverse backgrounds. The review will be limited to the most important drugs in current use which have a story to tell.

The Fascinating Story of Aspirin

Aspirin is probably the mostly widely used drug world over and most frequently prescribed antithrombotic agent. The precursor of aspirin, salicylates was observed in willow bark and other plant sources as old a 2400 years ago by Hippocrates. The antipretic and antiinflammatory properties of willow leaves were first described by Galen. The modern history of salicylates can be traced to Reverend Edward Stone of Oxfordshire, England in 1757. He described that bark of the white willow tree (salix alba vulgaris) is a cure for febrile illness. The subsequent phase of aspirin development occurred half a century later with the development of chemistry and pharmacology. The active principle in salicylates was isolated between 1826 and 1829 by Italian, chemistry and pharmacology. It was named salicin. In 1838, Piria, a French scientist, isolated salicylic acid from salicin. In 1897, Felix Hoffman, a German Chemist modified salicylic acid to produce acetylsalicylic acid which was named aspirin (a for acetyl, spir for spiraeora or the genus spiraea and in as a popular suffix for drugs). Aspirin was initially rejected because of an erroneous impression that it was cardiotoxic. However, the drug was introduced commercially few months later and was quickly accepted as analgesic / antipretic.

Aspirin as an antithrombotic

As early as 1891, a German Scientist, Binz, observed that salicylic acid caused mucosal bleeding in patients. In 1940 Karl Link showed that acetylsalicylic acid (ASA) can reduce prothrombin activity and published several reports in 1943 related to its anticoagulant effect. Gibson in 1948 first proposed the use of ASA for vascular diseases. LL Craven, an otorhinolaryngologist in private practice in California in late 1940s noted that when his tonsillectomy patients took aspirin containing medicine, they bled excessively. In 1948 he started treating his older male patients with ASA to prevent myocardial infarction (MI). In 1950 he reported that none of 400 patients on ASA had MI. Craven published two more articles in which he reported that of more than 8000 patients on aspirine none had myocardial infarction. He also observed that ASA is useful in secondary prevention of MI and to prevent stroke. Craven initially recommended ASA to all male patients between 30 and 90 years, though subsequently he prescribed aspirin for men between the ages of 45 and 65 years. To verify aspirins antithrombotic action, Craven ingested aspirin tablets daily which resulted in profuse nasal bleeding after 5 days. Unfortunately, Craven died of MI in 1957 less than a year after he published his last paper. By 1950 it was established that aspirin in high doses caused bleeding by prolonging the prothrombin time. However, even low doses of aspirin which did not affect the prothrombin time prevented coronary thrombosis. Because aspirin in high doses was associated with bleeding, many physicians in 1940s were prescribing aspirin together with vitamin K. In 1967, Weiss et al. reported that ASA caused inhibition of platelet activation by collagen. He thought that aspirin antiplatelet effect is due to impaired adenosine diphosphate (ADP) release resulting in defective platelet aggregation. Weiss also noticed that aspirin had rapid and irreversible antiplatelet effect which remained for the duration of the life of platelet. Although the work of Weiss...
and co workers demonstrated the antiplatelet effects of aspirin, the specific molecular mechanism of aspirin effect was reported by John Vane in 1971. He stated that aspirin inhibited prostaglandin synthetase which resulted in its antiplatelet effect. In 1982 Vane won the Nobel Prize in Medicine for this work. Vane observation of antiplatelet effect of aspirin was confirmed by Smith and Willis. Work of these scientists revealed that aspirin effects on platelets is mediated through cyclooxygenase-1 (COX-1) enzyme inhibition thereby reducing thromboxane-A2 synthesis. Harrison et al reported that ASA can prevent cerebral transient ischaemic attacks.

**Aspirin in Clinical trials**

A large number of randomized, multicentric trials were carried out to prove the efficacy of aspirin in preventing and treating cardiovascular disorders. In 1988, the second International Study of Infarct Survival (ISIS-2) proved the value of aspirin in treating acute MI. In 1989, Physicians Health Study established the value of aspirin in primary prophylaxis against cardiovascular disease. The optimal effective dose of aspirin was an area of controversy. A recent review of clinical trials and aspirin dosage by James E Dalen indicates that 160mg/day may be the most optimum dosage.

**Conclusion:**

The history of aspirin spans over two centuries. Salicylates were initially used as analgesic antipyretic. Acetylation of salicylic acid (Aspirin) was a watershed event in the history of salicylates. Aspirin was detected to have antithrombotic property through its antiplatelet action. Aspirin is probably the most widely used medication because of its antiplatelet properties resulting in prevention and treatment of acute coronary syndrome and occlusive stroke. Story of aspirin is unique in the history of drug discovery.

**Other Antiplatelets**

Various other antiplatelets like clopidogrel, prasugrel (thienopyridines) and Glycoprotein IIb/IIIa receptor antagonists like abciximab, tirofiban and eptifibatide have been recently developed. These drugs lack a history like that of aspirin. The oldest antiplatelet drug, aspirin, continues to retain the pride of place as the most frequently used antithrombotic.

**References**

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