Acute Myocardial Infarction and Related Drugs

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Abstract: As the medical name for a heart attack, acute myocardial infarction (AMI) is a common disease with serious symptoms and no relevant targeted drugs. Extremely critical consequences of AMI in mortality, morbidity, and cost to the society have been the great challenge in the long-term development of human society. In addition, the advent of AMI and results of clinical trials on therapy have major implications from the epidemiological, societal, and patient points of view. Hence, it is of great significance to develop drugs related to acute myocardial infarction with excellent pharmacokinetics. This paper discusses the pathophysiology, evolving drugs on therapy of acute myocardial infarction and incorporates the chemical structure, pharmacology, underlying economics of pertinent drugs and further discussion of the drugs related to the AMI.

1 INTRODUCTION

1.1 Definition and Categories

Acute myocardial infarction, commonly defined as myocardial necrosis due to acute, persistent ischemia and hypoxia of the coronary arteries; Also known as a sudden heart attack, it is a life-threatening condition that occurs when blood flow to the heart muscle is suddenly interrupted, leading to tissue damage (White, Chew, 2008). Furthermore, a new definition of myocardial infarction has been consensus group put forward in 2000 from the European Society of Cardiology and the American College of Cardiology, with the definition being based on myocyte necrosis as determined by troponins in the clinical setting of ischemia (White, Chew, 2008).

Acute myocardial infarction is a major cause of morbidity and mortality worldwide, with two entities. According to the difference between ST segment elevation and non-elevation on electrocardiogram, acute myocardial infarction can be classified as ST segment elevation myocardial infarction (STEMI) and non-ST segment elevation myocardial infarction (NSTEMI) (Boersma, 2003). In addition to distinguishing from by ST segment, the two types of acute myocardial infarction can also be clinically distinguished by coronary angiographic findings (Most of the coronary arteries in NSTEMI are not completely occluded).

1.2 Factors and Symptoms

Acute myocardial infarction can be caused by several factors, such as age, genetics. However, extreme lifestyles may be the biggest culprit. Epidemiological studies have highlighted the role of lifestyle factors in acute myocardial infarction. Poor lifestyle habits, such as obesity and alcohol abuse, can potentially put people at risk for acute myocardial infarction. While chest pain and shortness of breath are typical symptoms of an acute myocardial infarction, there are several different symptoms, including nausea, anxiety, or dizziness (Boersma, 2003).

1.3 The Number of Cases in China and Other Countries

According to incomplete statistics, there are 3 million people suffer from STEMI each year, and there are also more than 4 million cases of NTSEMI (White, Chew, 2008). Acute myocardial infarction, a common disease in developed countries, affects more than 1 million people in the United States each year. However, acute myocardial infarction is also on the rise trend in developing countries at present. For example, acute myocardial infarction has become a major cause of hospitalization and mortality in China. According to incomplete statistics, there are approximately 4 million cases of acute myocardial infarction in China (White, Chew, 2008).

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1.4 Drugs Used to Treat the Disease

As the main potential incentive of acute myocardial infarction, platelet hypperaggregation is constantly devouring human life. Based on extensive pharmacological evidence, antithrombotic medications such as Aspirin and Clopidogrel are the most potentially effective antiplatelet agents contribute to treat platelet hypperaggregation. In addition, Nitrates and Stains as other first-lines medicine are adopted in improving the long-term outlook in survivors of the acute phase. Although, the majority of pharmacological evidence are based on the clinal trials from patients with STEMI, the first-lines medicine also available optional for the NSTEMI patients (Boersma, 2003). In this paper, Aspirin and Clopidogrel are discussed in the next stages as the main treatment agents for acute myocardial infarction in the article.

2 DESCRIPTION OF CHEMICAL STRUCTURE OF DRUGS

In the description, the structures for aspirin and clopidogrel are shown by two figures. In addition, there are two more figures of the chemistry properties for aspirin and clopidogrel.

2.1 Aspirin

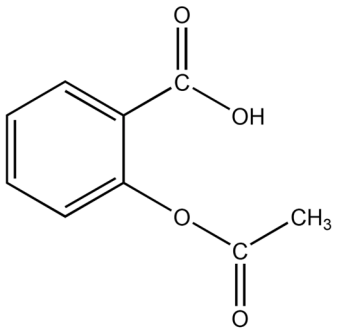

Figure 1: the structure of aspirin

As known as acetylsalicylic acid, with the IUPAC name 2-Acetoxybenzoic acid, is a salicylic acid class of drugs. As a white crystalline or crystalline powder, odorless or with a slight odor of acetic acid, slightly soluble in water, soluble in ethanol, soluble in ether and chloroform, and acidic in aqueous solutions. The structure of aspirin and the properties of Aspirin can be demonstrated as Figure 1 and Table 1:

Table 1: the properties of Aspirin

Formula	$C_9H_8O_4$	Boiling point	321.4°C at 760 mmHg
Molar mass	180.16	Solubility in water	$3.3g/L$
Density	$1.35g\ cm^{-1}$	Vapor pressure	$0.000124mmHg\ at\ 25°C$
Boiling Point	$136-140℃$		

2.2 Clopidogrel

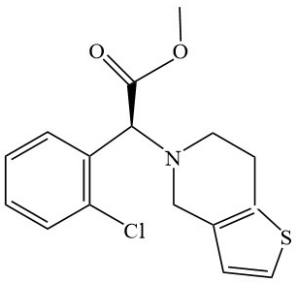

Figure 2: The structure of $clopidogrel$.

As known as a drug that inhibits platelet aggregation, with the IUPAC name $(+)-(S)-methyl\ 2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)acetate$ (J.-M. Pereillo, 2002). The structure of clopidogrel and the properties of Aspirin can be demonstrated as Figure 2 and Table 2:

Table 2: The properties of Clopidogrel

Formula	$C_{16}H_{16}ClNO_2S$	Boiling point	423.7°C at 760 mmHg
Molar mass	321.86	Density	$1.32g\ cm^{-1}$

3 DISCUSSION OF DRUG PHARMACOLOGY

In the discussion of pharmaceutical pharmacology, aspirin and clopidogrel would be discussed in three separate parts, which are pharmacodynamics, Pharmacokinetics, and the Mode of Delivery.

3.1 Aspirin

3.1.1 Pharmacodynamics

As one of the earliest antiplatelet drugs, aspirin was synthesized in the late 19th century, and its antiplatelet action was discovered British pharmacologist John Robert Vane in 1970s.

As an antithrombotic drug, aspirin is an inhibitor of cyclooxygenase (COX) (Warner, 2002). The irreversible acetylation of aspirin with cyclooxygenase leads to the inactivation of COX, which in turn disables the pathway of thromboxane formation and ultimately prevents high platelet aggregation. (The main involved in antithrombotic is COX-1 (Warner, 2002). Studies have shown that COX-2 plays a significant role in prostaglandin production.)

3.1.2 Pharmacokinetics

As a weak acid, aspirin dissociates very slight in the stomach. As a result, aspirin is quickly absorbed by cell membranes in the stomach. Nevertheless, in the small intestine, as the PH value gradually increases, the amount absorbed gradually decreases.

According to long-term clinical trials, only 20 to 50 percent of aspirin is ionized; the rest is absorbed into the bloodstream. Aspirin has a half-life of two to three hours (Bond, 2007). For example, the half-life of a single dose of 0.65g aspirin in breast milk is about 3.8 to 12.5 hours. (Because aspirin is excreted in breast milk, large doses can have an adverse effect on infants.)

3.1.3 Mode of Delivery

Aspirin is mainly taken orally. The daily dose needs to be determined according to the stage of the disease and the patient's constitution. Generally, small doses are given priority to, usually 50 to 150mg per day (Bond, 2007). However, during an acute myocardial infarction, 325 mg of aspirin can be taken orally for the first time, and then 100 mg a day (Ferguson, 1970).

3.2 Clopidogrel

3.2.1 Pharmacodynamics

As one kind of antithrombotic agent, clopidogrel is a P2Y12 purine receptor antagonist (Mega, 2009). P2Y12 receptor plays an important role in mediating the sustained activation of stimulated by ADP, and is a major receptor that mediates platelet adhesion. P2Y12 receptor antagonist can inhibit the activation and amplification of platelet induced by ADP and produce effective antithrombotic effect.

3.2.2 Pharmacokinetics

As a prodrug, clopidogrel in activated in two steps by two enzymes. The enzyme in first step mainly is CYP2C19 (Mega, 2009). There are many different enzymes involved in the second step (Hydrolysis reaction), such as CYP2C19, CYP2C9. The figure 3 briefly describe the progress of pharmacokinetics for clopidogrel.

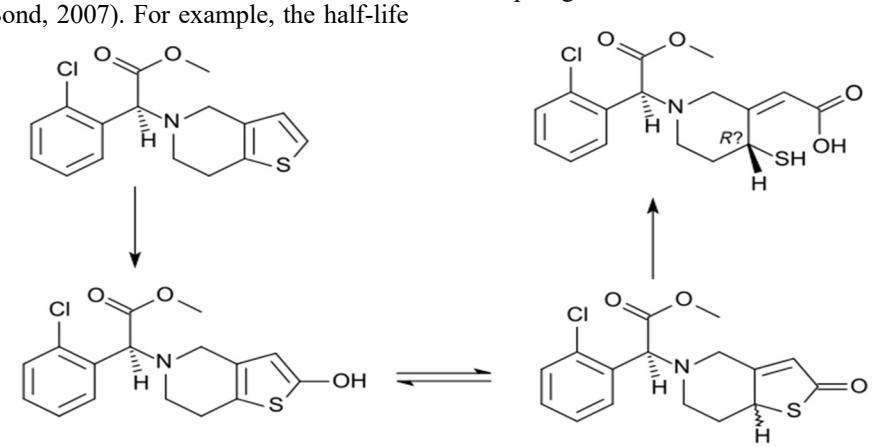

Figure 3: the progress of pharmacokinetics for clopidogrel. The primarily step is oxidation with CYP2C19 enzyme as catalyst. The two structures at bottom are tautomer. Moreover, the second step is reaction of hydrolysis.

Specifically, clopidogrel was not effective in treating acute myocardial infarction for about 2 hours after oral administration, since clopidogrel itself is not effective in inhibiting platelets. However, after being activated by cytochrome P450 enzyme (CYP2C19) in liver, clopidogrel structure is destroyed (thiophene ring is opened), resulting in the formation of new substances that can fight thrombosis (Simon, 2009). The entire clopidogrel is digested in the human body, and it takes about 3.5 to 4.5 hours for the drug to take effect and wear off.

3.2.3 Mode of Delivery

Clopidogrel was mainly taken orally once a day and can be taken for a long time. Dosages vary from 50mg to 150mg, depending on age (best taken after meals). For rapid action, clopidogrel can also be taken orally in 300 to 600mg doses at a time (Collet, 2009).

4 DISCUSSION OF DRUG ECONOMICS

In order to discuss the drug Economics, the cost and the number of prescription and sales of aspirin and clopidogrel are briefly shown.

4.1 Aspirin

According to Clinical (2018), aspirin prescription costed around $4.48 in the United States and as little as £1.28 in the UK. It proves that aspirin is within the reach of almost everyone. Meanwhile, In the United States, there are more than five million patients who need aspirin and a staggering 19 million aspirin prescriptions (Boersma, 2003).

4.2 Clopidogrel

Clinical (2017) stated that nearly all clopidogrel is covered by most Medicare and insurance plans and each patient effectively treats acute myocardial infarction for about $10 per month (Boersma, 2003). In 2018, this is projected to be more than 4 million AMI patients in America and number of prescriptions in the United States is exceeding 20 million.

In a word, the low cost of aspirin and Clopidogrel is an appropriate guarantee for acute myocardial infarction. At the same time, the large number of patients and prescriptions suggests that there still be a large market and a sound momentum of growth for them.

5 FURTHER DISCUSSION

As same as the other drugs, clopidogrel and aspirin own side effects as well. In the further discussion, both adverse effects are discussed and other types of antithrombotic drugs for acute myocardial infarction is briefly covered as well.

5.1 Aspirin

Serious side effect associated with aspirin treatment include:

Gastrointestinal reaction. Oral aspirin can directly affect the stimulation of gastric mucosa and cause nausea and vomiting, and long-term use will lead to gastritis membrane damage and gastric ulcer and gastric bleeding and other symptoms (Vishweshwar, 2005).

Allergic reaction to aspirin. Aspirin can cause rashes, angioedema, asthma, and other allergic reactions in allergic people.

Aspirin may also influence the central nervous system. Generally, when taking a large dose, there will be headaches, vertigo, tinnitus and other symptoms, and there will be coma and other symptoms when taking too much.

Liver and kidney damage. Side effects of aspirin include toxicity to the liver and kidneys. Aspirin is broken down in the liver and then excreted through the kidneys, resulting in decreased liver and kidney function.

5.2 Clopidogrel

As an inhibitor of platelets, clopidogrel affects the lifespan of platelets by irreversibly changing the ADP receptor of platelets, leading to thrombocytopenia, and the lack of platelets is the culprit of the bleeding. Therefore, the main side effect is bleeding, such as subcutaneous bleeding, gingival bleeding. Side effects includes gastrointestinal reactions, allergies, liver and kidney dysfunction, and leukopenia are usual in clinical treatment as well (Diener, 2004).

Platelet membrane glycoprotein IIb/IIIa (GPIIb/IIIa) receptor antagonists are also antithrombotic agents (GPIIb/IIIa antagonists are ligand mimics that prevent fibrinogen from binding to activated platelets, thereby directly inhibiting platelet aggregation) (Kaufman, 1972). Three drugs

are currently on the market: tirofiban, a small non-peptide molecule that mimics fibrinogen binding sites; Etibateptide, a cyclic heptapeptide with a lysine-glycine-aspartic acid (KGD) sequence, also mimics the fibrinogen binding sequence in GPIIb/IIIa; And accimab, a humanized antigen-binding fragment of a murine monoclonal antibody (Simon, 2009).

6 CONCLUSION

This article provides a brief overview to acute myocardial infarction from the perspective of its definition and introduces two drugs for the prevention and treatment of AMI from an antithrombotic perspective——aspirin and 1.

chemical structure, and corresponding chemical properties of these two drugs are described in detail in the follow section. Furthermore, through the parts of pharmacodynamics and pharmacokinetics, the pharmacology of these two drugs is referred at length.

However, these two drugs also own assignable underlying adverse effects. Unfortunately, there is still no specific drug to treat or prevent acute myocardial infarction. These two points are cursorily discussed likewise in further discussion.

Overall, as a common cardiovascular disease, acute myocardial infarction owns a higher mortality rate than the parallel diseases. Nevertheless, due to the understanding of its pathogenesis and the timely investment of related drugs, it has declined significantly in the past decades. On the contrary, both number and the age range of the acute myocardial infarction are increasing year by year. Therefore, as a kind of cardiovascular disease, acute myocardial infarction is still a kind of disease should not be ignored and worthy of study.

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