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Conventional and Novel Pharmacotherapy of Angina Pectoris

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1. Introduction

As it has been mentioned in the previous chapters, Angina pectoris, commonly known as angina, is severe chest pain and discomfort due to myocardial ischemia. A lack of blood, hence a lack of oxygen supply for heart muscle, will cause this pain which can be because of narrowed and blocked coronary arteries. In other words, angina can be assumed to play the role of a protective mechanism to signal myocardial ischemia.

There are different kinds of angina. Stable, unstable, Prinzmetal's or variant angina and latterly discovered type called microvascular angina which is caused by small blood vessels, not artery damage.

Although the amount of mortalities and morbidities of heart diseases and additionally the diagnostic techniques in this field underwent drastic improvements, still there are many patients complaining about angina pectoris mostly as a restricting pain. Due to the report of American Heart Association statistics committee and stroke statistics subcommittee in 2010, the prevalence of angina pectoris has become 9.8 million, translating to almost 30 thousand per million. This amount in Europe has been estimated to be around 20 - 40 thousand per million (Fox, Garcia et al. 2006; Fernandez, Tandar et al. 2010; Lioyd-Jones, Adams et al. 2010). In another study performed in US, it has been mentioned that 1 in 4 patients is experiencing angina pectoris following myocardial infarction. With regard to the annual occurrence of MI in US which is 1.5 million cases, there are significant amount of people in each year suffering from angina. Therefore, curing angina pectoris is of high importance (Plomondon, Magid et al. 2007).

Although one of the main goals in angina treatment is relief of symptoms, amelioration of the position, especially pain, will unexpectedly cause the ischemia to proceed and so, the consequence will be cardiac injury. Considering this problem, due to American and European drug regulators the anti-anginal medicines also needs to possess anti-ischemia effects, as well. Other purposes of angina pectoris treatment are slowing progression of the disease and reduction of future events, especially heart attacks and, of course, death by treating the underlying heart condition. Treatments for angina include lifestyle changes, medicines, medical procedures, cardiac rehabilitation, and other therapies and will depend on the severity of the symptoms, severity of the underlying disease, and extent of damage to the heart muscle, if any (Parker and Parker 2002; Fernandez, Tandar et al. 2010).

In recent decades, pharmaceutical scientists focus has been on design of systems which can manage to release the medication with a steady or a controlled speed. These delivery systems are called "novel".

The application of novel drug delivery systems in angina therapy show their importance through controlling release of a medication with short therapeutic index or decreasing the drug dosage intervals which can increase patients' compliance in following up the therapy or even it can control the release of drug according to the chronobiology (Dehghan, Aboofazeli et al. 2010; Mandal, Biswas et al. 2010).

In this chapter, medications and pharmacotherapy of angina pectoris will be mainly discussed. At the end of chapter one will be informed of conventional and novel medications for treatment of angina.

2. Anti-angina currently used medicines

In angina therapy drugs are playing an important role. A variety of medicines with different dosage forms and amounts are prescribed in each type of angina. Since the main cause of angina is lack of oxygen supply in the coronary arteries, the anti-anginal agents usually play their roles through increasing oxygen delivery or decreasing oxygen requirement of the tissue or both. Obviously, ascending the amount of oxygen delivery is possible with vasodilation and reduced oxygen demand can be caused by cardioinhibitors which reduce heart rate and contractility. There are still other mechanisms that may occur in treating angina pectoris. For instance, anti-thrombotic drugs which avoid formation of thrombus, like anticoagulants, are involved in angina therapy. Figure 1 shows a schematic classification of conventional anti-anginal medications.

Regularly, in angina pharmacotherapy, medications are prescribed for three different purposes. 1) To reduce the number of angina attacks by daily use of certain drugs over a
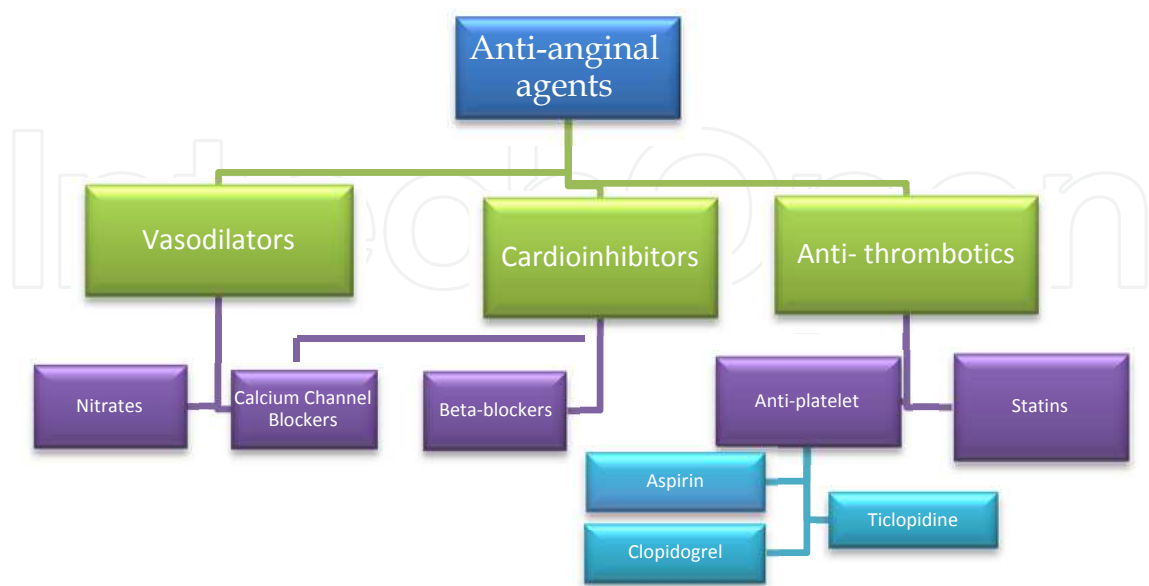
Fig. 1. Conventional medicines used in treatment of angina pectoris

long period. 2) To prevent attacks before some exercises or robust activities. 3) To relief the pain and pressure of an attack when it begins.

Generally, there are five main types of medicines, which help to relief, control symptoms and increase blood flow and oxygen supply to the heart muscle:

- Nitrates
- Beta-blockers
- Calcium channel blockers
- Anti-platelets
- Statin drugs

Moreover, due to the patient's condition, other medications can be prescribed by the specialist, as well. And also these drugs can be prescribed in combination which in most cases it works more efficiently than monotherapy.

2.1 Nitrates and nitrites

Here the term "nitrates" is taken to include both nitrates and nitrites avoiding repetition. But it is presumed that the nitrates can only reduce to nitrites for exerting their action.

Nitrates are one of the oldest medications for angina. They are potent vasodilators that open up the arteries, improving blood flow to the body (including heart) which raises the oxygen supply of myocardium. There are two kinds of nitrates: short acting nitrate preparation and long acting nitrate preparation. Short acting ones usually are used to ease angina pains and/or to prevent developing an anginal attack before an exercise that is likely to cause one. Whilst the long acting productions are prescribed in a regular daily basis for the patients with frequent anginal pains and it is not useful for rapid pain relief.

The most important drug of this group is Nitroglycerin (glyceryl trinitrate) which was the first medication used in 1879 by William Murrell for the treatment of angina pectoris and, its immediate release forms, still remains the therapeutic mainstay for patients suffering from classic and variant angina. Nitroglycerin is often administered sublingually for rapid relief of angina sudden attack (Murrell 1879). The main drugs of this group include: nitroglycerin or glyceyl trinitrate (GTN), isosorbide dinitrate, isosorbide mononitrate, pentaerythritol tetranitrate (PETN) and amyl nitrite.

2.1.1 Mechanism of action

Nitrates in the smooth muscle of both venous and arterial beds, are denitrated into nitric oxide (NO) which is a potent vasodilator. This vasodilatation relieves anginal pain through different mechanisms. Veins dilation will reduce cardiac workload and consequently, oxygen demand. Coronary dilation will increase blood flow to ischemic areas. And finally dilation of arterioles will lower the afterload and so cardiac workload.

The released NO from nitrates activates guanylate cyclase and increases the amount of cyclic guanine monophosphate (cGMP). cGMP which is a second messenger, activates protein kinase. Myosin light chains dephosphorylate by protein kinase. As a result, the smooth muscle becomes relaxed. Additionally, decreased intracellular calcium levels by cGMP are another mechanism of smooth muscle relaxation (Katzung, Masters et al. 2009).

2.1.2 Pharmacokinetics

The nitrates undergo first-pass effect in liver excluding isosorbide mononitrate. Thus, despite their high absorption from the GI, nitrates absorption into the systemic circulation is

incomplete; i.e., oral preparations have slow onset of action (except sublingual tablets) which is not pleasant when quick relief is required. So, there are available dosage forms with short onset time.

Nitrates distribute extensively throughout the body and their bonding to plasma protein has been estimated to be around 60%.

Nitrates undergo metabolism in liver by the enzyme glutathione organic nitrate reductase. For example the yielded active metabolites for nitroglycerin are glyceryl dinitrates and mononitrates.

The metabolites of nitrates are excreted in urine, except isosorbide moninitrate, that less than 1% of it is eliminated in urine. Elimination half-lives of nitrates differ depending on the kind of nitrate and administration route. Table 1 indicates elimination half-lives of some preparation of nitrates.

2.1.3 Adverse reactions

Acute side effects: Throbbing headache and dizziness are the most common side effect of nitrates (these are probably consequences of blood vessles vasodilation). Orthostatic hypotension is another common side effect of using nitrates. There is a rare situation named "nitrite syncope". In which the nitrate-induced hypotension is severe and thus, the lowered blood pressure will cause slowing of heart rate, nausea, shivering and syncope. The adverse effects of gastrointestinal tract include nausea and vomiting.

Nitrate tolerance: Continuous uptake of nitrates (any kind) in high dose may cause tolerance. In tolerance, the nitrate's effect will become weak or disappear completely. Although, the mechanism of tolerance has been poorly understood but diminished amount of nitric oxide and systemic compensation can be partly responsible for this phenomenon. The well-known so called "Monday disease" is a touchable example of nitrate tolerance that has happened in industries, especially where explosives are manufactured(Rutherford 1995; Munzel, Daiber et al. 2005).

2.1.4 Dosage forms

According to different indications of nitrates, considering two main groups of long- and short- acting nitrates, there are a wide range of preparation forms to fulfill the patients' demands (table 1).

Short acting and long acting anti-anginal agents are being prescribed due to their onset and duration of action. For rapid cardiac response, nitroglycerin formulations with short onset (sublingual tablets or pump sprays) are administered. At the commencement of an attach, exactly when the patient starts to feel the chest pain or before starting an activity, one 0.3 or 0.4 mg pill or one metered dose of spray can be taken and patient can repeat it every 5 minutes, if necessary, up to maximum three doses. These dosage ranges for isosorbide dinitrate is fairly different. In this case, sublingual 2.5 to 10 mg tablets should be taken. The repetition dose is every 2-3 hours during acute phase and 4-6 hours for prophylaxis.

Long acting nitroglycerin sustained-release tablets are prescribed 2.5-13 mg every 6-12 hours. Alternatively, the topical form or the patches can be used instead. Isosorbide dinitrate extended-release formulations are administered 40-80 mg twice daily.

In any case, it is necessary to have 10-12 hours nitrate-free interval per day due to prevention of nitrate tolerance (Cutler, Eff et al. 1995; Katzung, Masters et al. 2009).

Kind of nitrate	Dosage form	Amount of active agent	Elimination half-life
Nitroglycerin	Tablets (sublingual)	0.15, 0.3, 0.4 and 0.6 mg	$1/_2$–1 hr
	Tablets (buccal and controlled-release)	1, 2 and 3 mg	3-5 hr buccal
	Capsules (sustained-release)	2.5, 6.5, 9 and 13 mg	5 hr
	Aerosol (lingual)	0.4 mg/metered spray	$1/_2$–1 hr
	I.V.	0.5, 0.8 and 5 mg/ml	3-5 min
	I.V. premixed solutions in dextrose	100, 200 and 400 mcg/ml	
	Topical	2% ointment	2-12 hr
	Transdermal (patches)	0.1, 0.2, 0.4, 0.6 and 0.8 mg/hour systems	24 hr
Isosorbide dinitrate	Tablets	5, 10, 20, 30 and 40 mg	5-6 hr
	Tablets (sublingual)	2.5, 5 and 10 mg	$1/_2$–2 hr
	Tablets (extended-release)	40 mg	5-6 hr
	Tablets (chewable)	5 and 10 mg	$1/_2$–2 hr
	Capsules (extended-release)	40 mg	5-6 hr
Isosorbide mononitrate	Tablets	10 and 20 mg	Unknown
	Tablets (extended-release)	30, 60 and 120 mg	
Amyl nitrite	Solution (inhalation)	50 mg	5 min

Table 1. Commercialized dosage forms of nitrates (Christensen, Comerford et al. 2003).

2.2 Beta blockers

Beta blockers have been used for over 35 years to treat both angina and high blood pressure (hypertension). These medications through beta blockade slow the heart rate, decrease blood pressure, and lessen the force of contraction of the heart muscle, however, the third generation of beta blockers show to have vasodilatory effects through different pathways which will be discussed more in section 2.2.1. When taken regularly, beta-blockers are proven to prevent heart attacks and mortality and reduce the frequency of angina attacks (reinfarction). Because of their effects on the respiratory system, beta-blockers are unsuitable

for angina sufferers who have asthma or bronchitis. Carvedilol, propranolol and atenolol are some of most important beta blockers.

2.2.1 Mechanism of action

There are three types of beta receptors in the body that control several different functions. Beta-1 receptors are located mostly in heart muscle and also in eye and kidneys, whilst the prominent part of beta-2 receptors are in upper respiratory system (bronchial vascular smooth muscle); however, there are a few beta-2 receptors in heart muscle. And finally beta-3 receptors are distributed in adipose tissue. The beta receptors are targets of cathecolamines, especially noradernaline (norepinephrine) and adernaline (epinephrine). In fact, beta blockers induce their effect by preventing the normal ligand (cathecolamines) from binding to beta receptors. Due to their distribution sites in body, beta-1 and beta-2 blockers are of interest in angina therapy. Preventing adrenaline's performance on heart by beta blockers causes lower heart rate, contractility and blood pressure and in one words reduced heart's workload. Thus, the myocardial oxygen demand will decrease and this final effect is assumed to be the most important effect of beta blockers in angina treatment. The final function of beta blockers owing to their ability to be selective or nonselective, cause them to have different indications. The nonselective beta antagonists, blockade both beta-1 and beta-2 receptors, whereas, the selective ones only block beta-1 receptors (cardioselective beta blockers). These two groups of agents that are used in angina pharmacotherapy are listed in table 2, seperately.

Nonselective Beta blockers useful in angina treatment	Selective Beta blockers useful in angina treatment
Carvedilol	Acebutolol
Labetalol	Atenolol
Nadolol	Betaxolol
Penbutolol	Bisoprolol
Pindolol	Metoprolol
Propranolol	
Timolol	

Table 2. Selective and nonselective anti-anginal beta blockers

As it was mentioned before, the third generation of beta-adrenoceptor antagonists comprises drugs with extra ability of vasodilatation. Most of them play their role by blocking alpha-1 receptor (labetalol, carvedilol and bucindolol). Nebivolol is the exception of third generation; because, the vasodilatation mechanism of this beta-1 highly selective blocker is by stimulating nitric oxide release (Weiss 2006; Karter 2007).

2.2.2 Pharmacokinetics

Most of beta blockers are quickly absorbed after oral administration (generally from small intestine). Moreover, their systemic absorption after topical application has been confirmed to be without significant delay. However, there are pharmacokinetical differences in the

drugs of this category which is mostly because of their hydrophilic or lipophilic affinities. For example the absorption of hydrophilic beta blockers such as nadolol and atenolol from GI is incomplete. Furthermore, this characteristics influence beta blockers indications, as well. Since, the lipophilic beta antagonists can pass blood brain barrier and enter CNS (propranolol), they are used in prophylactic treatment of migraine or vascular headache.

Beta adrenoceptor antagonists' distribution in body is also influenced by this quality. The lipophilic beta blockers are more detected in biologic fluids.

Due to solubility of beta blockers in water or lipid, their metabolism and elimination can be through liver or kidneys; i.e. drugs with low lipophilicity are excreted from kidneys, whilst more lipophilic substances are metabolized in liver.

2.2.3 Adverse reaction

Beta blockers are widely prescribed throughout the world in several remedies and they do not seem to have many severe side effects. Nevertheless, their most important unpleasant effects are due to inhibitory effect of nonselectives on beta-2 receptors. Since beta-2 receptors are mainly in bronchi, beta-2 antagonists hinder opposing the alpha 1 receptor-mediated vasoconstructor tone. Thus the patients with any dysfunction in their airways will experience serious problems. To overcome this disadvantage, new class of beta blockers with beta-1 selectivity and partial beta-2 agonist ability, has emerged. Beta-1 antagonists are preferable to the prior beta blockers, however, since bronchospasm was reported in certain individuals followed by selective beta blockers uptake, they are not considered completely "safe".

Other adverse effects experienced by the patients are dizziness and lightheadedness accompanied by blurred vision. Some people may feel cold in their hands and feet as a result of decreased blood pressure, especially to the extremities. Moreover, beta blocker consumption may cause some allergic reactions like rashes and itching.

2.2.4 Dosage forms

Available formulations of beta blockers have been summarized in table 3.

Among these drugs, betaxolol, bisoprolol, nadolol and penbutolol are prescribed for angina prophylaxis, while others are used in treatment of angina attacks.

Generic name of beta receptor antagonist	Dosage form	Amount of active agent	Dosage range
Acebutolol	Capsules	200 & 400 mg	200 mg twice daily up to 800 mg and even higher, if necessary
Atenolol	Tablets	25, 50 & 100 mg	50 mg once daily and can be adjusted after one week. Maximum daily dose is 200 mg

Generic name of beta receptor antagonist	Dosage form	Amount of active agent	Dosage range
Betaxolol	Tablets (film-coated)	10 & 20 mg	10-20 mg once a day. Can be increased to 50 mg/day after one or two weeks of inadequate response
Bisoprolol	Tablets	5 & 10 mg	5 mg per day, can be increased every three days, up to 20 mg
Carvedilol	Tablets		Started with 6.25mg twice a day and can be continued up to 50mg per day
Labetalol (Quyyumi, Wright et al. 1985)	Tablets (film-coated)	100, 200 & 300 mg	
Metoprolol	Tablets	50 & 100 mg	100 to 400 mg in divided doses
	Tablets (extended-release)	25, 50, 100 & 200 mg	100 to 400 mg daily
Nadolol	Tablets	20, 40, 80, 120 & 160 mg	40 mg per day. Can be increased up to even 240 in certain time intervals
Penbutolol	Tablets	20 mg	20-40 mg once a day
Pindolol	Tablets	5 & 10 mg	15 to 40 mg divided doses per day
Propranolol	Capsules (extended-release)	60, 80, 120 & 160 mg	Tablets or solution can be administered 40-320 mg in three or four doses daily and the long-acting forms are given once a day, however, it can increase
	Tablets	10, 20, 40, 60 & 80 mg	
	Solution	4, 8 & 80 mg/ml	
Timolol	Tablets	5, 10 & 20 mg	10-30 mg twice daily(Arronow, 1980)

Table 3. Beta blockers dosage forms which are used as anti-anginal agents (Christensen, Comerford et al. 2003)

2.3 Calcium channel blockers (CCBs)

Calcium channel blockers, also called slow calcium channel antagonists or slow channel blockers, inhibit calcium ion movement through slow channels in cardiac and smooth muscles. CCBs are mostly used for treatment of classic and variant angina. Also, they are particularly beneficial if angina is caused by arterial spasms (Prinzmetal's variant angina) rather than blockage.

Drugs of this category are classified into two classes, dihydropyridines (DHPs) and non-dihydropyridines (non-DHPs). The non-DHPs are again comprises of three further compounds: phenylalkylamines, benzothiazepines and tertralols (Ryman and Gurk-Turner 1999). The most selective calcium channel blockers belong to dihydropyridines.

2.3.1 Mechanisms of action

CCBs blockade the calcium ion influx into vascular smooth muscle cells and cardiac myocytes across the voltage gated slow channels. Thus the intracellular calcium levels will diminish. Since, the most important ion for muscle contractility is assumed to be calcium, as a result of decreased calcium levels, vasodilatation of both coronary and peripheral arteries and lower cardiac conduction will be observed. Vasodilatations will cause low blood pressure and consequently, less heart afterload and oxygen demand.

2.3.2 Pharmacokinetics

CCBs are usually well absorbed following oral administration, although they can have different bioavailability due to their metabolism.

They are widely distributed in body fluids with a high protein-binding affinity. It is proved that protein binding percentage of dihydropyridines is higher than non-dihydropyridines.

Most of Calcium channel blockers are metabolized and cleared hepatically and less than 5% is secreted unchanged in urine. And some of them undergo extensive first-pass metabolism which will influence drug's plasma level and half life. Thus, it should be taken into account in dose adjustment.

Elimination half-lives of old CCBs are rather short (3-8 hours), whereas the newer ones (esp. new DHPs) have been designed to last longer in body (Opie 1989; Piepho 1991).

2.3.3 Adverse reactions

Generally, the side effects of CCBs are not really common but still the incidence of some adverse reactions has been reported in a number of patients. Peripheral vasodilatation accounts for the major side effects of DHPs like flushing, headache, rashes, excessive hypotension, peripheral edema (esp. Pedal edema) and palpitation (reflecting reflex tachycardia) (Sirker, Missouris et al. 2001). The later effect is the reason that most of DHPs are not preferred in treatment of angina pectoris.

Non-DHPs side effects are mostly because of the muscle relaxation effect; for instance, they can cause severe bradycardia, or can influence electrical conduction system of heart. This relaxation in smooth muscles of intestine and colon may cause constipation. Constipation is followed by verapamil administration.

2.3.4 Dosage forms

Two main classes of slow channel blockers, have different mode of actions and thus, diverse indications. Although all calcium channel blockers seem to be effective in treatment of stable

angina, causing reflex tachycardia, the dihydropyridines usually are not administered for this purpose. The only FDA approved DHPs as the treatments for angina are nifedipine, amlodipine, nicardipine and biperidil of which nifedipine and amlodipine are used in both vasospastic and chronic stable angina, while biperidil and nicardipine's application is limited to just chronic stable angina (Ryman and Gurk-Turner 1999; Helms, Quan et al. 2006). Table 4 displays dosage forms of some CCBs which are used in angina therapy.

Mibefradil, of tertralol subgroup, was used as an anti-anginal agent but was withdrawn from the market because of serious interactions with other drugs.

Dihydropyrodines			
Generic name of beta receptor antagonist	Dosage form	Amount of active agent	Dosage range
Amlodipine	Tablets	2.5, 5 & 10 mg	5-10 mg daily
Nicardipine	Capsules	20 & 30 mg	20-40 mg three times a day
Nifedipine	Capsules	10 & 20 mg	10-20 mg three times a day, can increase due to patients position
	Tablets (extended-release)	30, 60 & 90 mg	30 to 60 mg once daily
Bepridil	Tablets (film-coated)	200 & 300 mg	200 up to maximum 400 mg daily
Non-dihydropyridines			
Generic name of beta receptor antagonist	Dosage form	Amount of active agent	Dosage range
Diltiazem	Tablets	30, 60, 90 & 120 mg	Start with 30 mg three times a day and can be increase up to 360 mg divided doses per day
	Capsules (extended-release) (Containing multiple 60-mg units of diltiazem)	120, 180 & 240 mg	120-480 mg once daily(Cutler, 1995)
	Capsules (sustained-release)	60, 90, 120, 180, 240, 300, 360 & 420 mg	
Verapamil	Tablets	40, 80 & 120 mg	
	Tablets (sustained-release and extended-release)	120, 180 & 240 mg	

Capsules (sustained-release)	100, 120, 180, 200,240, 300 & 360 mg
Capsules (extended-release)	120, 180 & 240 mg

Table 4. Calcium channel blockers administered in angina therapy (dosage forms and dosing ranges) (Christensen, Comerford et al. 2003)

2.4 Anti-platelets

These anti-thrombotic drugs prevent platelet clumping and so thrombus formation in blood circulation. There are several subgroups of antiplatelets such as: cyclooxygenase inhibitors, adenosine diphosphate (ADP) receptor inhibitors (contains thienopyridines), glycoprotein IIB/IIIA inhibitors and adenosine reuptake inhibitors. Anti-plateletes, dislike anti-coagulants, have the most anti-clot effect in arterial circulation. Since aspirin and clopidogrel are this group's mainly prescribed drugs in angina, in this section they will be discussed in details. Ticlopidine is another thienopyridine that has been shown to have effects on treatment of unstable angina. But according to the results of some studies, ticlopidine have more adverse effects than clopidogrel (Hankey, Sudlow et al. 2000).

Aspirin has clot-preventing properties within the coronary arteries or other blood vessels. Daily aspirin therapy is advised to patients, unless they have problems tolerating it. In this case, clopidogrel can be used instead. However, one recent study showed that in patients suffering stable angina, treatment with aspirin and clopidogrel indicates greater platelet formation blockade rather than monotherapy with aspirin alone (Saha, Berglund et al. 2008).

2.4.1 Mechanism of action

Since aspirin has many indications, it can act through different biologic pathways. Aspirin anti-platelet and with less importance anti-inflammatory effects are believed to be the main mechanisms in treating angina pectoris.

Anti-platelet and anti-inflammatory: While administered in low doses, aspirin inhibits prostaglandin synthetase action and therefore avoid clotting followed by preventing thromboxane A_2, the platelet-aggregating substance, formation. Aspirin owes this ability of prostaglandins and thromboxanes suppression to irreversible inactivation of the cyclooxygenase (COX) enzyme. As the chemical structure of aspirin can be observed in fig.2, its free acetyl group is attached to a serine residue in the active site of COX enzyme through a covalent bond. This is the reason of difference between aspirin and the similar anti-inflammatory NSAIDs group which are reversible inhibitors.

Although if the dose of aspirin rises, it will interferes with prostacyclin production and so this will negate the anticlotting properties.

The exact mechanism of aspirin's anti-inflammatory action is not completely understood but it is mostly believed that the ability to inhibit prostaglandin synthesis can influence synthesis or action of other mediators of inflammation by restraining them.

Clopidogrel is a selective adenosine diphosphate (ADP) antagonist. It irreversibly blocks the ADP receptor on the platelet cell membrane and consequently the glycoprotein IIb/IIIa cannot be activated and so platelet aggregation will be avoided (Savi, Nurden et al. 1998).
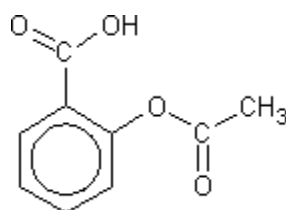
Fig. 2. Chemical structure of aspirin

2.4.2 Pharmacokinetics

Since aspirin is a weak organic acid with a pK_a equal to 3.5, in oral dosage form it is expected to absorb in stomach and proximal small intestine in nonionized form; because in these areas the acidic environment dominates.

Suddenly after absorption it is metabolized into acetic acid and salicylate. This rapid metabolism is resulting in high concentrations of salicylates in most body liquids and fluids. Therapeutic salicylate blood level for anti-inflammatory effect is 150 to 300 mcg/ml. Salicylates have rather high protein binding ranged from 75 to 90% depending on blood level.

Salicylate is excreted by the kidneys with first-order kinetics and its elimination half-life has estimated to be between 2 and 4.5 hours depending on the aspirin administered dose (in toxic doses this range reaches 15 to 30 hours) (Hartwig-Otto 1983).

Clopidogrel is a prodrug and after rapid oral absorption, it is converted to the active agent in liver. The half life of this active agent is 8 hours.

Clopidogrel is eliminated almost equally from urine and feces.

2.4.3 Adverse reactions

One of the main adverse effects of aspirin is gastric upset. Especially when taken in high doses the risk of gastrointestinal bleeding increases. Aspirin uptake can be also accompanied by nausea and heartburn.

The patient taking aspirin is advised to be monitored frequently; the main reason is because it may cause leucopenia, thrombocytopenia and prolonged bleeding time.

Other rare but severe side effects include Rey's syndrome, anaphylaxis and angioedema.

Some of clopidogrel's side effects are neutropenia, hemorrhage and skin rash.

2.4.4 Dosage forms

There are several dosage forms of these medications available in the market. As aspirin is considered to be multifunctional, the only forms that can be used in treatment of angina are in table 5.

2.5 Statins

Statins or HMG CoA reductase inhibitors, lower cholesterol and have been shown to stabilize the fatty plaque on the inner lining of the coronary artery, even when the blood cholesterol is normal or minimally increased. Due to recent research statins can atorvastatin, fluvastatin, lovastatin, pravastatin, and simvastatin (Dehghan, Aboofazeli et al. 2010; Dvir and Battler 2010).

2.5.1 Mechanisms of action

Since hyperlipidemia has been proved to be one of the main reasons for coronary heart diseases, lowering lipid levels in bloods can decrease the incidence of cardiovascular

disease. The most effective impact of statins on the patients suffering from anginal attacks is believed to be through lowering the LDL cholesterol level in plasma (Khan 2006).

HMG CoA reductase is an enzyme responsible for mevalonate production. In lipid forming pathway, mevalonate is finally transformed to cholesterol. Statins which have some structural similarities with this HMG CoA, can competitively attach to the enzyme and block it. Therefore, the speed of cholesterol biosynthesis will decline. Statins play their role in angina therapy through other mechanisms, as well.

Researchers have defined some other modes of actions for statins, rather than lipid lowering, in managing heart related diseases like anti-inflammatory, plaque stability and prevention of clotting. These beneficial effects are independent from lipid lowering characteristics (Furberg 1999).

Name	Drug Form	Amount of Active Agent	Dosage Ranges
Aspirin	**Tablets**	81 and 325 mg	Prevention doses: 81 to 325mg daily or every other day; Treatment doses: 160 to 325mg once daily
	Tablets (enteric-coated)	81, 100, 162, 165 and 325 mg	
	Tablets (chewable)	81 and 100 mg	
	Tablets (effervescent)	100 mg	
	Suppositories	120, 125, 200 and 300 mg	
Clopidogrel	**Tablets**	75 mg	75 mg once a day

Table 5. Available dosage forms of aspirin and clopidogrel for angina treatment

2.5.2 Pharmacokinetics

The pharmacokinetic characteristics of statins vary widely due to their different structures which determine their water or lipid solubility. Quite lipophilic statins are atorvastatin, simvastatin, lovastatin, fluvastatin, cerivastatin and pitavastatin; whereas pravastatin and rosuvastatin are relatively hydrophilic. Obviously, the lipophilic compounds have rapid absorption and distribute easily in biologic fluids.

Almost all of lipophilic statins are metabolized hepatically by cytochrome P450 enzymes and due to their efficient first-pass effect their bioavailability varies from 5% to 60%. Whilst, the hydrophilic statins have longer half lives and excreted both through liver and kidneys.

HMG CoA reductase inhibitors have half lives ranged from less than 5 hours in simvastatin up to 22 hours in pravastatin and 20 – 30 hour in some metabolites of atorvastatin (Garcia, Reinoso et al. 2003; Schachter 2004).

2.5.3 Adverse reactions

Although statins considered being among the safest drugs, the most important but infrequent side effect of statins is because of their metabolism pathway (cytochrome P450) which can cause myopathy and hepatotoxicity and of course serious interactions with other

substances. Myopathy appears as pain and weakness in muscles and rarely rhabdomyolysis. One of statins called cerivasatin was withdrawn from the market due to fatal rhabdomyolysis reports, in 2001.

Other side effects address the liver. Statins can increase amount of hepatic enzymes. This increase, if severe, will cause liver damage. Therefore, the medication can be changed to another statin.

2.5.4 Dosage forms

Atorvastatin, fluvastatin, pravastatin, rosuvastatin and simvastatin are frequently prescribed as treatments of angina pectoris. More information about the different formulations and dosage of these drugs can be found in table 6.

Generic name of beta receptor antagonist	Dosage form	Amount of active agent	Dosage range
Atorvastatin	Tablets (film-coated)	10, 20, 40 & 80 mg	Starting with 10-40 mg once a day, can be increased up to 80 mg daily for maintenance dose
Fluvastatin	Capsules	20 & 40 mg	20 to 80 mg divided doses
	Tablets (extended-release)	80 mg	80 mg once a day
Pravastatin	Tablets	10, 20, 40 & 80 mg	Usually 40 or 80 mg/day, however, it can be 10 or 20 mg in renal or hepatic dysfunction
Rosuvastatin	Tablets	5, 10, 20 & 40 mg	5 to 40 mg once daily (max starting dose is 20 mg)
Simvastatin	Tablets	5, 10, 20, 40 & 80 mg	Starting from 5 or 10 mg and continue with up to 80 mg

Table 6. Statins used in angina therapy.

3. New drugs with novel mechanisms of action

3.1 Ranolazine

Ranolazine is a piperazine derivative which has been proved as an anti-anginal and anti-ischemic agent. Although its mode of action is totally different from other anti-anginal medications and is not clearly understood, some studies show that ranolazine main mechanism in angina is through blockade of late Na current in sarcolemma (late I_{Na}).

In patients with heart failure and chronic angina, in addition to normal Na flow into cells there is a late Na ion current which increases intracellular Na levels. Elevated levels of Na in the cell influence Ca flow and finally contractility of myocardium, leading to incomplete

relaxation and heart muscle dysfunction. Ranolazine by inhibition of late Na current helps the ischemic condition to recover (Maier 2009).

Ralolazine has a variable absorption after oral administration. It is highly metabolized in liver and intestine. Ranolazine excreted into both feces and urine.

This drug is available as extended-release tablets and usually is prescribed 500 to 1000 mg once daily (FDA 2006; Dvir and Battler 2010).

3.2 Nicorandil

Nicorandil is a nicotinamide ester that is classified as an ATP- sensitive potassium channel opener and it has also some nitrate-like activating effects. This medication is a vasodilator able to dilate both arterial and venous systems resulting in reduced pre- and afterload.

Nicorandil's nitrate component is responsible for venous vasodilatation and the arteries and arterioles vasodilatation is developed by opening K^+ channels.

This potassium channel agonist is highly absorbed from GI. It is not seriously undergo first-pass effect thus it is expected to have high bioavailability (75-100%). Its major route of elimination is kidneys.

Gastrointestinal ulceration and discomfort, headache, flushing and weakness have been reported to be main adverse reactions to nicorandil (Frydman 1992; Hiremath, Valluru et al. 2010).

3.3 Ivabradine

Ivabradine is the first specific and selective inhibitor of the I_f channel in the sinus node become commercialized (I_f is a name for mixed Na+-K+ inward flow). This drug has bradycardic effects and lowers the heart rate that may prevent myocardial ischemia and angina pectoris; however its pharmacologic benefits have not been proved to be useful in the whole patients suffering from stable angina. It may be used in patients who have beta-blockers intolerance.

Ivabradine is being absorbed completely and has a bioavailability around 40% due to first-pass effect. Its elimination is mainly through hepatic metabolism.

Since the f channels are located in the retina as well, the major side effects accompanying ivabradine consumption are visual symptoms like headache, dizziness and luminous/visual phenomenon. Thus, ivabradine may influence driving task (Macher and Levy 2009; Dvir and Battler 2010; Farrer 2010; Fernandez, Tandar et al. 2010).

3.4 Trimetazidine

Trimetazidine is a metabolic agent which is considered as the first cytoprotective anti-ischemic compound. This drug inhibits fatty acid metabolism by partially blocking 3-ketoacyl CoA thiolase. And by this means, enhances the glucose consumption of myocardium, exactly opposed to what happened in ischemia. Therefore, increased glucose oxidation will result in decreased oxygen demand.

Trimetazidine is widely used outside North America as an effective agent for treatment of stable angina; however it is not proved to be used in US (Di Napoli and Taccardi 2009; Fernandez, Tandar et al. 2010).

3.5 Fasudil

Fasudil is a potent rho-kinase inhibitor, Ca^+ antagonist and vasodilator. Inhibiting rho-kinase will influence the contractility of vascular smooth muscle.

One of indications of fusadil is in adjunct therapy of vasospasdic and stable angina (Vicari, Chaitman et al. 2005).

More anti-anginal drugs are under development and further studies and longer follow ups are required to establish their place in treatment of patients with coronary artery disease.

4. Current researches

Traditional therapies for angina pectoris have focused largely on heart rate reduction and coronary vasodilation. On the other hand, considering the pharmaceutical aspect, the conventional dosage forms are not sufficient for all medications and in some cases there are progressive demands on novel drug formulations to reduce the dose intervals, to obtain drug levels constant in patients' blood and release the medication following biological rhythm. Additionally, route of administration plays an important role in efficacy and even toxicity of the drug.

4.1 Timed-release drug delivery system

Drug delivery systems (DDS) that can precisely control the release rates have had an enormous impact on the health care system. Of this category controlled-release or sustained-release drug delivery systems are one of the most beneficial and advantageous drug delivery technologies that are used in particular medications to control their release. In the last two decades there has been a remarkable improvement in the field of novel drug delivery systems. Carrier technology offers an intelligent approach for drug delivery by coupling the drug to a carrier particle such as microspheres, nanoparticles, liposomes, etc, which modulates the release and absorption characteristics of the drug (Vasir, Tambwekar et al. 2003; Dehghan, Aboofazeli et al. 2010).

The candidates for being embedded in these systems should meet some qualifications, of which, short half life, narrow therapeutic index and high first-pass effect can be mentioned.

As it was shown previously in this chapter, there are several timed-controlled formulations available for use in angina therapy.

4.2 Pulsatile drug delivery system

It has been proved that in cardiovascular disease there are some morning increases in capillary resistance, vascular reactivity and platelet agreeability which decrease latter in the day. Therefore, there is a higher possibility (or risk) of myocardial infarction and sudden cardiac death before noon rather than evening. Furthermore, the obtained data from several studies show that the time of medication administration can influence its pharmacodynamic and pharmacokinetic.

Considering these facts, scientists have developed a novel drug delivery system named pulsatile drug delivery based on chronobiology in which drug is released from supporting carriers in response to different stimuli. The carriers can react to pH, temperature, magnetic or electric field, ultrasound, light and mechanic forces. Carriers are usually polymers which own certain characteristics such as safety, biocompatibility ability to respond to external stimuli.

There are some FDA approved chronotherapeutic products. Verapamil and propranolol are two samples of this category which is specifically designed to lower morning increased blood pressure. In the near future, there will be medications possessing this technology for treatment of angina (portaluppi, 2007 & Mandal, 2010).

5. Conclusion

Decades of research in these fields results in promising achievements. Still there are several studies aiming to develop new agents with novel mechanisms of action, to develop agents overcoming the problems and limitations of traditional and conventional medications and or their dosage forms more, to carry clinical trials focusing on combination therapy for reduction of adverse effects and finally to select the new agents which have mortality benefit when added to standard therapy.

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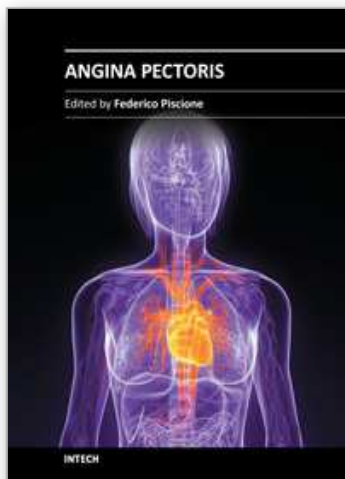
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