Angina Pectoris and Acute Coronary Syndromes

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Learning Objectives

Contrast and compare chronic stable angina, Prinzmetal’s or variant angina and unstable angina with respect to presentation, pathophysiology and approach to treatment.

Describe the clinical effects and differences between agents within and between the classes of drugs used to manage angina (nitrates, beta-blockers, and CCBA’s).

Given a patient case, construct a treatment plan including selection of appropriate medication, dose, monitoring parameters and patient instructions.

Angina: Introduction

Ischemic heart disease accounts for a substantial portion of death, disability and economic loss in most industrialized nations.

Coronary Artery Disease (CAD) is the leading cause of death in the U.S.

Unstable angina is accompanied by an increased risk of cardiac death and MI.

In 1991, the National Center for Health Statistics reported 570,000 hospitalizations for this condition resulting in 3.1 million hospital days.

Angina Defined

Angina pectoris is a clinical syndrome typically characterized by a deep, poorly localized chest or arm discomfort that is reproducibly associated with physical exertion or emotional stress and relieved promptly by rest or sublingual nitroglycerin.

Angina General

Angina pectoris is the development of chest pain due to myocardial ischemia.

Coronary blood flow is inadequate to supply the heart with the needed oxygen and nutrients.

Patients often have underlying coronary artery obstruction.

Diagnosis of angina and its subclassification requires evaluation of the nature of the chest pain and circumstances surrounding its development.

Angina Types

Chronic Stable Angina: - a chronic and predictable development of chest pain upon exertion.

Unstable Angina: - a critical condition characterized by the unpredictable development of chest pain at rest or during minimal exertion. It is either accompanied by an increase in frequency and/or severity of pain within the recent (weeks to 1 or 2 months) past.

Vasospastic Angina or Prinzmetal’s Angina: - is characterized by the unprovoked coronary artery spasm resulting in chest pain.
**Angina Types**

- **Chronic Stable Angina:** - a chronic and predictable development of chest pain upon exertion
  - Patients rely on antianginal medication throughout the day to perform various degrees of activity; however, may prophylaxis with sublingual nitrates based on anticipated exertions.

- **Unstable Angina (UA):** - a critical condition characterized by the unpredictable development of chest pain at rest or during minimal exertion. It is either accompanied by an increase in frequency and/or severity of pain within the recent (weeks to 1 or 2 months) past.
  - Patients with unstable angina are admitted to an acute care setting and managed aggressively with nitrates, beta-blockers, CCBA's, antiplatelets, and anticoagulants.
  - UA is part of the spectrum of acute coronary syndromes (ACS).

- **Vasospastic Angina or Prinzmetal's Angina:** - is characterized by the unprovoked coronary artery spasm resulting in chest pain.
  - Patients with this angina may be relatively young and have few or even no cardiac risk factors.
  - Chest pain is often unpredictable and cyclical in nature, sometimes reverting spontaneously into remission.

- **Silent Myocardial Ischemia:** a phenomenon experienced by a large percentage of patients with ischemic heart disease who for various reasons do not perceive chest pain despite EKG changes consistent with ischemic heart disease.

**Diagnosis of Unstable Angina**

- Requires the determination of the likelihood of CAD and an assessment of the severity of presentation. Assessment of pt symptoms of angina include:
  - Evidence of prior MI or indicators of CAD
  - Considerations of sex, age, and number of major risk factors for ASCVD
  - Known history of variant angina or cocaine use

- Markers of high likelihood of unstable angina include:
  - ST-segment elevation or depression of ≥ 1 mm on a 12-lead EKG with or without pain, and
  - Deep, symmetrical T-wave inversions in multiple precordial leads.
Unstable Angina: Prognosis

- Risk of death or ischemic complications is lower than with MI but higher than with stable angina.
- Prolonged episodes of severe chest pain are important markers of high-risk unstable angina.

Angina Therapy: General

- Therapy may require cardiac catheterization and myocardial revascularization:
  - Goal: to risk stratify and place in context the need for CABG or PTCA or stenting.

Angina Therapy: General

- Therapy may require cardiac catheterization and myocardial revascularization:
  - Indications may include:
    - Failure to stabilize with adequate medical therapy.
    - Recurrent unstable angina.
    - High-risk result from a non-invasive test.
    - Prior revascularization procedure.
    - Diagnosis or exclusion of significant CAD with multiple clinical episodes without objective documentation of ischemia.

Beta-Blockers for Angina

- Beta-Blockers should be started in the absence of contraindications (IV for high-risk patients) or oral for intermediate and low-risk patients.
- Consider pt. intolerance due to pulmonary disease, especially asthma, LV dysfunction, risk of hypotension or severe bradycardia, diabetes, lipid disorders.

Beta-Blockers for Angina

- Mechanism: reduce cardiac work by negative inotrope, negative chronotrope and hypotensive (central and renin blocking) effects.
- Pharmacologic Issues: High first pass, modest half-life, variable protein binding, cardioselectivity (dose dependent), intrinsic sympathomimetic activity, alpha-blockade.
- Monitor: SE’s are extension of pharmacologic effects, bradycardia, hypotension, CHF, depression abrupt withdrawal, impotence, diabetes (Sx and Symptoms) lipid effects (decr. HDL, incr. trig), reactive airway disease.
Beta Blocking Agents

- Non-Selective
  - Nadolol
  - Propranolol
  - Timolol
  - Pindolol
  - Carteolol
  - Penbutolol
- Selective
  - Atenolol
  - Metoprolol
  - Esmolol
  - Betaxolol
  - Bissoprolol
- Selective Activity
  - Acebutolol
  - Labetalol
  - Carvedilol

Nitrates for Angina

- Mechanism: reduce cardiac work afterload and preload reduction as well as coronary dilatation and possibly antiplatelet effects.
- Pharmacologic Issues: Variable bioavailability, short half-life, tolerance
- Monitor: SE’s are extension of pharmacologic effects, hypotension, headache, especially post withdrawal
- Other Issues: multiple dosage forms, durations of action, cost, compliance

Nitrates for Angina

- If symptoms not relieved with 3 sl NTG tablets and initiation of β-Blocker therapy (when possible), IV NTG is recommended.
- IV NTG should start at 5-10 mcg/min continuous infusion and titrated up by 10 mcg/min q 5-10 minutes until relief of symptoms or limiting side effects (headache/hypotension SBP <90) or dose exceeds 200 mcg/min
- Switch to oral nitrates within 24 hours when possible

Nitrate Tolerance

- Main limitation of long-term prophylactic nitrate therapy is the development of tolerance (both to hemodynamic effects on exercise capacity)
- Definition: decrease in response to a given amount of nitrate or the need of increased amounts of nitrate to maintain a continuous effect
- Numerous trials, using exercise testing to assess the efficacy of nitrate therapy, have shown an attenuation of antianginal effect with chronic therapy

Nitrate Tolerance

- Tolerance can develop with all forms of nitrate therapy that maintain continuous blood levels of the drug
- Tolerance can develop after only a few doses

Mononitrates

- Issues of Metabolism
  - ISDN has a high first pass effect → low blood levels of ISDN
  - Approx. 26% (F = 26%) enters systemic circ. from po dose
  - Majority of effect from ISDN is IS-5-MN

Mononitrates

- GI Tract
  - ISDN 100%
  - IS-2-MN (19%)
  - IS-5-MN (64%)

- Gut Wall
  - ISDN (26%)
  - IS-5-MN (64%)
  - IS-2-MN (19%)
  - (a) gut wall
  - (b) hepatic
**Isosorbide-5-Mononitrate**

- **Pharmacokinetics**
  - Peak absorption (immed. release) is within 60 min. (longer for sust. release)
  - Absolute bioavailability approx. 100%
  - ISMN half-life approx. 4-5 hours
- **Pharmacodynamics**
  - Peak effect 1-4 hours
  - Duration of effect approx. 12 hours (angina and ETT)
- **Elimination**
  - Hepatic -> inactive metabolites

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**Patient Information: Nitrates**

- Discuss issue of tolerance (rational ISDN-ISMN, importance of following instructions)
- Do not crush or chew IMDUR tablets
- Potential for hypotension and headache with all nitrates
- ISMO or ISDN are not choice for immediate anti-anginal effect
- Eccentric dosing (7 hour separation)
- sl NTG - storage, dating, dosing.

**Results**

**Magnitude of Noncompliance**

Number (%) of Patients Compliant at Low, Medium, and High Categories

- Low Compliance (< 70%)
- Medium Compliance (70% and < 85%)
- High Compliance (85%)

**Distribution of Patients at Various Compliance Rates**

Straka et al 1996; Pharmacotherapy

**Clinician’s Choice**

% of Patients

Mean Days Compliant

**Results**

Primary Endpoints: Concordance
Nitroglycerin Ointment
- Onset 20-60 min, duration 2-6 hrs, dose 0.5 to 1 inch tid with NFP (1 inch (2%) = 15mg)
- Care should be taken by applicant if not patient

Nitroglycerin Patch
- Onset 40-60 min, duration 8 hrs, dose 0.2, 0.4 0.6 mg/hr
- 12 hrs on 12 hrs off (choose off time carefully)

CCBA’s for Angina
- Mechanism: Reduce cardiac work by negative chronotrop, negative inotrop and increase supply (coronary vasodilation)
- Pharmacologic Issues: relative effects on conduction system, negative inotropism, vasodilitation
- Monitor: EKG intervals, HR, BP, PK-PD interactions with drugs

CCBA’s for Angina
- CCBA’s modulate the influx of calcium across cell membranes by affecting calcium channels
- Intracellular Ca++ is controlled by a series of complex gates
- CCBA’s affect the voltage dependent channels decreasing the availability of intracellular Ca++
- Decreasing intracellular Ca++ causes decreased contraction of the myocardial and smooth muscles

CCBA’S Chemical Classification
- Benzothiazepines
  - Diltiazem (Cardizem™, Dilacor™, Tiazac™)
- Phenylalkylamines
  - Verapamil (Calan™, Isoptin™, Covera-HS™)
- Dihydropyridines
  - Nifedipine (Procardia™, Adalat™)
  - Nicardipine (Cardene™) Felodipine (Plendil™)
  - Isradipine (DynaCirc™) Nimodipine (Nimotop™)
  - Amlodipine (Norvasc™) Bepridil (Vascor™)
  - Nisoldipine (Sular™)

Drug Therapy for Angina
- Monitoring Issues (B-blockers, CCBA’s, Nitrates)
- With all agents monitor
  - Blood pressure, clinical signs and symptoms of hypotension (mental status, syncope, etc.)
  - EKG (for HR, intervals, rhythm etc.) -not nitrates
  - Edema (CCBA’s)
  - Potential metabolic complications with B-blockers (lipids, glucose)

Drug therapy for Angina: Cost Issues
- Cost considerations should include both cost of agent and perceived cost-effectiveness of the agent to achieve desired goal safely, stabilize patient, permit long term management of symptoms
- Failure to control symptoms with minimal side effects may lead to non-compliance resulting in costly interventions, re-admissions and/or excessive (perhaps unnecessary) drug use
Drug Therapies for Angina

Pros and Cons of various therapies

- Beta-blockers reduce exercise capacity (CCBA’s may increase it or at least not adversely affect it)
- Both beta-blockers and CCBA’s have negative inotropic effects, however they are often used together - caution should be exercised with pts. exhibiting any degree of CHF

- Beta-Blockers and CCBA’s may be useful for coexisting conditions (afib/flutter, hypertension, post-MI state (beta-blockers)
- Nitrate therapy may be difficult for some patients to take (compliance with necessary regimens, inconvenience of patch/paste etc.)
- Costs issues must be addressed/individualized
- Appropriate counseling for expected side-effects, abrupt withdrawal, storage, onset etc.