Isosorbide dinitrate as Anti-Anginal agent

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Abstract: ISDN is an Anti-Anginal agent which is vascular smooth muscle relaxant used to prevent chest ache in patients with a positive coronary heart circumstance[Coronary artery disease]. Belong to class of nitrate, Anti-Anginal drug licensed in 1975, lengthy performing nitrate within the form of isosorbide dinitrate started out to be used for chronic oral therapy. All natural nitrate has same motion but differ only in time course. Nitrates dilate veins as examine to arteries and also produce some arteriolar dilation. ISDN has both brief appearing(sublingual path) as well as long acting actions(oral direction). ISDN comes underneath time table H drug ought to utilized by medical doctor concern and prescription. Nitrate mostly reason arterial and venous vasodilation effects, which boom coronary artery blood supply, and decrease cardiac preload and afterload via enhancing nitric oxide (NO) degree motive healing resistance and tolerance step by step happens. we’re take a look at the ISDN makes use of, approach of management, unwanted results and storage situation of drug on this evaluate article.

Keyword: Anti-Angina, Isosorbide dinitrate, sublingual and oral route.

Abbreviation: ISDN : Isosorbide Dinitrate.

Introduction:
In individuals with coronary heart disease, isosorbide dinitrate is a drug used to treat and prevent angina pectoris. It is a member of the nitrate drug family. Isosorbide research was historically started in Stockholm by Porje, and the medication was introduced in Sweden in 1946. In the 1950s, Harris and colleagues in the United States created isosorbide dinitrate. Amyl nitrate, the first therapeutic treatment for angina, was initially documented in 1867. Nitro-glycerine's advantages were then published in 1879. Propranolol, the first clinically available beta blocker, did not enter clinical use for the long-term oral therapy of chronic stable angina until 1964. Calcium antagonists were discovered in 1964, and they were approved for use in 1975 to treat angina. Around this period, chronic oral therapy using long-acting nitrates in the form of isosorbide dinitrate started to become popular. Isosorbide dinitrate (ISDN) is 1,4;3,6-dianhydro-D-glucitol 2,5-dinitrate, an organic nitrate whose structural formula is

Molecular Formula: C6H8N2O8
Synonyms:
- ISOSORBIDE DINITRATE
- 87-33-2
- Isordil
- Sorbide nitrate
- Sorbidnitate

Molecular Weight: 236.14 g/mol
Medicine Type: Allopathy
Prescription Type: Prescription Required
Approval: DCGI (Drugs Controller General of India)
Schedule: Schedule H
Pharmacological Class: Nitrates
Therapy Class: Antianginal.
Physical Properties of ISDN:
Isosorbide dinitrate is a white, crystalline, odorless chemical with a melting point of 70°C and an optical rotation of +134° (c=1.0, alcohol, 20°C). It is stable in air and in solution. Although it is sparingly soluble in water, isosorbide dinitrate is easily soluble in organic solvents including acetone, alcohol, and ether.

Since more than a century ago, nitrates have been routinely used to treat coronary artery disease (CAD), angina pectoris, congestive heart failure, and hypertension. Nitrates cause the dilatation of both arteries and veins. The most widely used nitrate is isosorbide dinitrate (ISDN), which provides rapid angina pectoris relief after being administered sublingually.

CLINICAL PHARMACOLOGY:
Isosorbide dinitrate's main pharmacological effect is the relaxing of vascular smooth muscle, which leads to the dilation of peripheral arteries and veins. After 24 hours (or less) of continuous therapy, active medicines in the vast majority of these trials were no more efficacious than placebo. Nitrate tolerance has never been successfully overcome by dose escalation, not even to doses that are significantly higher than those used acutely. Nitrates' antianginal potency isn't fully recovered until several hours have passed since they were last in the body.

Pharmacokinetics:
Isosorbide dinitrate absorbs almost completely after oral administration, but bioavailability varies greatly (10% to 90%), with significant first-pass hepatic metabolism. About an hour after consumption, serum levels are at their highest. The bioavailability of ISDN is typically around 25%, and most studies have found that it gradually increases during chronic therapy.

- **Anti-Anginal Drug:**
  - Anti-Anginal medications are those that stop, delay, or prevent angina pectoris attacks.
  - Anginal Pectoris: This pain syndrome is brought on by the imbalance of oxygen supply and demand in the myocardium.
  - Angina pectoris describes acute, excruciating, pressing chest pain under the sternum brought on by myocardial ischemia. Although the pain is typically felt in the substernal region, it can also occasionally be felt in the neck, shoulder, arm, or epigastrium. Comparatively fewer women than men get the typical substernal ache.
  - The two basic tactics that angina medications use are to boost myocardial oxygen delivery and decrease oxygen demand.

Reasons:
- Coronary artery disease (CAD)
- Vasospasm of coronary Arteries

Due to this heart doesn't get enough blood, without blood tissue lose O2 (oxygen) and die.

Risk factors/causes:
- Hyperlipidaemia
- Hypertension
- Diabetes
- Smoking
- Weak lifestyles
- Family history

Symptoms: Patients may also suffer from symptoms like:
1) Weakness
2) Heartburn
3) Cramping
4) Indigestion
5) Sweating
6) Nausea
7) Shortness of breath.

The goal of anti-anginal medication therapy is to balance the oxygen supply and demand in the myocardium's ischemic region once again.

Types of Angina:
1. Stable angina
2. Variant angina
3. Unstable angina

1) Stable Angina:
- Also known as Classical angina.
- It is most common type of angina.
- These attacks are predictable and caused by Exercise, Emotions and Higher work load.
- The main reason behind classical angina is severe arteiosclerotic in coronary artery which supply blood to the deeper tissue of heart.
- This result in decrease coronary artery prefusion.

2) Variant angina:
- Also known as vasospastic and prinzmetal angina
- Uncommon an Unpredictable.
- Attacks occurs during rest.
- Caused by coronary vasospasm.
3] Unstable angina:

- Rapid increase in duration and severity of attack which occurs during rest.
- In this atheromatous plaque rupture which attract platelet deposition, occlusion of coronary artery.

**Treatment of angina:**
- Surgery
- Drugs (anti-anginal)
- Medical procedure and therapies
- Selfcare (Physical exercise, weight loss, avoid smoking).

**Classification:**
Isosorbide Dinitrate classified in Nitrate class as a long acting drug as well as short acting by sublingual route. It is used to abort or terminate attack by ISDN(sublingually). Come under the second line drug which are less effective and have higher toxicity as compare to first line drug.

**Moa:**
The smooth muscle cell quickly dinitrates organic nitrates to release the reactive free radical nitric oxide (NO), which activates cytosolic guanylyl cyclase, increases cGMP, and dephosphorylates myosin light chain kinase (MLCK) through a cGMP dependent protein kinase (Fig.2). Reduced phosphorylated (active) MLCK availability prevents myosin from contracting because it is unable to connect with actin. As a result, relaxation takes places. Additionally, increased intracellular cGMP may inhibit Ca2+ entrance, which would promote relaxation.

- The predominant venodilator effect may be explained by the fact that veins express more of the enzyme that produces NO from GTN than arteries. According to research, nitrate metabolizing enzymes are distributed differently in these blood vessels, which may also explain why epicardial conducting arteries preferentially enlarge over autoregulatory arterioles.
- Platelets: The cGMP production in platelets is activated by the NO produced by nitrates, which has a modest antiaggregatory effect. In cases of unstable angina, this action might be helpful.

**Pharmacokinetics:**
- Organic nitrates are fat soluble and easily absorbed through the skin, gut, and buccal mucosa.
- The partially dinitrate metabolites have longer half-lives but are less active.

**Isosorbide dinitrate:**
It is solid yet has qualities comparable to GTN; it can be taken orally for chronic prophylaxis as well as sublingually during an attack (it acts slightly more slowly than GTN, peaking in 5-8 min). On oral administration, pre-systemic metabolism is noticeable and erratic. Although the sustained release formulation may provide protection for 6–10 hours, the t12 is 40 min. To allow for nitrate levels to drop naturally during sleep at night, the last dose shouldn’t be taken after 6 PM.

**Preparation:**
- SORBITRATE 5, 10 mg tab, ISORDIL 5 mg sublingual & 10 mg oral tab. DITRATE 5, 10 mg tab; 20, 40 mg 20–40 mg SR tab

**Dose and route:**
- 5–10 mg sublingual
- 10–20 mg oral

**Duration of action:**
- 20–40min(sublingual)
2-3hr(oral).

Uses:

✔ Isosorbide Dinitrate is used in the prevention and treatment of angina (chest pain that occurs when your heart muscle is not receiving enough oxygen-rich blood). Blood veins that carry blood to your heart narrow, which results in angina.

✔ The following instructions should be followed when using isosorbide dinitrate: Isosorbide dinitrate is available as an oral tablet, sublingual tablets, and oral capsules.

✔ Oral tablets and capsules containing isosorbide dinitrate are taken orally two to three times a day.

Proper use of isosorbide dinitrate:

- Always take medication as prescribed by your doctor. Never take it in larger amounts, more frequently, or for a longer period of time than recommended by your doctor.

Special Warnings and Precautions for Use:

- In sensitive people, isosorbide dinitrate may have paradoxical side effects that worsen ischemia, exacerbate myocardial damage, or possibly result in severe congestive heart failure.

- Pneumocapillary pressure and systolic blood pressure in patients with normal or hypertensive blood pressure should not be permitted to drop below the physiological range while treating acute or chronic heart failure. Patients with pre-existing hypotension in the range of 90–100 mm Hg should maintain systolic pressure.

➤ Method of administration of isosorbide dinitrate:

1) Angina Pectoris;
   a. Sublingual: 0 to 5 mg sublingually 15 minutes prior to activity likely to cause an anginal episode

Immediate release: Initial dose: 5 to 20 mg orally 2 or 3 times a day

Maintenance dose: 10 to 40 mg orally 2 or 3 times a day.

Extended-release: 40 to 160 mg/day orally.

- Side effects of isosorbide dinitrate:

  - The common side effect of Isosorbide dinitrate include the following

  - Common
    1. Headache,
    2. Flushing (warmth, redness, or tingly feeling)

  - Rare
    1. Light-headedness
    2. Worsening chest pain
    3. Fast or slow heart rate
    4. Pounding heartbeats
    5. Fluttering in your chest
    6. Hives
    7. Difficulty breathing
    8. Swelling of your face, lips, tongue, or throat.

- Adverse reactions:

  - The majority of isosorbide dinitrate's adverse events are caused by the substance's vasodilator activity and are often dose-related.

  - The most frequently reported side effect is a headache, which can be extremely painful. With each dose taken each day, especially at greater doses, headaches could return.

  - There may also be brief spells of dizziness that are occasionally brought on by fluctuations in blood pressure. Although hypotension is uncommon, it can be severe enough in certain individuals to call for stopping treatment.

  - Although not common, syncope, crescendo angina, and rebound hypertension have been documented. Rarely have common dosages of organic nitrates led to methemoglobinemia in persons who appeared to be healthy.

  - The occurrence of methemoglobinemia at these doses is so rare that further discussion of its diagnosis and management is postponed (see OVERDOSAGE).

  - The frequency of adverse effects during therapy with Isordil Titradose tablets cannot be estimated based on existing data.

- Undesirable effects of ISDN:

  i. There may be cutaneous vasodilation and flushing.

  ii. Vascular headaches are frequent, severe, and sometimes permanent. After the first week or two of use, headaches typically go away with the use of adequate analgesics or a temporary dosage reduction.

  iii. There may occasionally be brief episodes of weakness and dizziness, as well as other indications of cerebral ischemia linked to postural hypotension. Even at the standard therapeutic dosage, certain people may occasionally show severe sensitivity to the hypotensive effects of nitrates. There can be severe reactions, including nausea, vomiting, weakness, restlessless, pallor, sweating, and collapse. Alcohol may make this effect stronger. The syndrome will typically go away if you take steps to encourage venous return, such as lowering your head or lying in the Trendelenburg position while deep breathing into your extremities.

  iv. There may occasionally be drug rash and/or exfoliative dermatitis.

  v. Vomiting and nausea don't seem to happen often.

- Therapeutic Indication of ISDN:

  a) Isosorbide dinitrate oral tablet:
i. For the prevention of ischemic heart discomfort brought on by coronary insufficiency. Isosorbide dinitrate may lessen angina attacks' frequency, length, and intensity. There may be an increase in exercise tolerance and a decrease in the demand for nitroglycerin. The treatment of an angina attack is not recommended for the oral tablets.

b) Isosorbide dinitrate sublingual tablets:

- **Overdose of Isosorbide dinitrate:**

  Isosorbide dinitrate overdose symptoms may include a sharp drop in blood pressure, a throbbing headache that won't go away, vertigo, palpitations, visual disturbances, flushed and perspiring skin that later turns cold and cyanotic, nausea, vomiting, and syncope (especially when standing up), methemoglobinemia with cyanosis and anoxia, initial hyperpnea, dyspnea, and slow breathing.

- **Precautions:**

  If you may be taking this medication for a long term, it's miles very essential that your physician take a look at your progress at everyday visits to make certain that this remedy is working properly. Blood tests can be needed to check for unwanted consequences.

  Do not now take avanafil (Stendra®), riociguat (Adempas®), sildenafil (Viagra®), tadalafil (Cialis®), or vardenafil (Levitra®) even as you're the usage of this medication. The usage of those drugs collectively can also reason blurred vision, dizziness, lightheadedness, or fainting. if you are taking those drug treatments and also you experience an angina assault, you ought to go to the clinic right now.

  This medication may additionally motive complications. these complications are a sign that the medication is working. Do no longer prevent the use of the medicine or alternate the time you o

  Getting up slowly may additionally assist.

  Dizziness, mild-headedness, or faintness may occur, particularly when you get up quick from a mendacity or sitting position. Getting up slowly may additionally assist.

  Dizziness, light-headedness, or fainting is also much more likely to occur if you drink alcohol, stand for lengthy periods of time, exercise, or if the climate is warm. at the same time as you take this medication, be cautious to restrict the quantity of alcohol you drink. also, use greater care in the course of exercise or warm climate or if you need to stand for lengthy durations of time.

  Do not forestall the use of this medicine with out checking first together with your medical doctor. Your medical doctor may also want you to regularly lessen the quantity you are the use of earlier than stopping it absolutely.

### Storage:

- Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light. Keep from freezing.
- Keep out of the reach of children.
- Do not keep outdated medicine or medicine no longer needed.
- Ask your healthcare professional how you should dispose of any medicine you do not use.

### Conclusion:

The above mentioned data is concise collective information about Isosorbide Dinitrate used as anti-anginal drug. Its physical and pharmacological properties, Reason behind disease, Risk, Symptoms and method of administration for effective action, precautions during using the drug. The uses of ISDN on Children, Geriatric, During pregnancy the safety and effectiveness has not been established. There may be pharmacological tolerance as well as cross tolerance to other nitrates and nitrates. It is unknown how crucial tolerance is to the proper administration of isosorbide dinitrate in the treatment of angina pectoris patients.

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