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A Simplified Review on Isoniazid

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Abstract: *Isoniazid is largely effective for the operation of tuberculosis. Still, it can beget liver injury and indeed liver failure. Tuberculosis (TB) remains a global burden and public health concern. Isoniazid, a top antitubercular medicine (ATD) though effectively used in TB preventive chemotherapy is preferentially available in adult phrasings. Its use thus in paediatric population is challenged with issues of high probability of inaccurate cure administration, low case compliance and adherence. This burden may be advanced in resource limited settings;therefore, development of simple child friendly phrasings is needful. This study aimed to design, develop and estimate an unconsidered formulary model of a paediatric oral dispersible isoniazid tablet for use in a resource-limited setting. Paediatric oral dispersible isoniazid granulation batches with varying attention (0.5-5.5 w/w) of sodium carboxyl methyl cellulose as super disintegrant were prepare by wet granulation system and compressed. Granulation batches were subordinated to pre and post contraction evaluation independently in agreement with established standard styles results were statistically analysed using one way analysis of friction (ANOVA) with significance set at $p<0.5$.*

Keywords: Paediatric Tuberculosis, Isoniazid, Dispersible Tablet, Extemporaneous Compounding

I. INTRODUCTION

There exists an increasing demand for therapeutic effectiveness of dosage formulations through improved patient compliance. Innovative drug delivery technologies as can be found in microencapsulation, nanoencapsulation, sustained / controlled release matrix systems, fast release dispersible systems etc. aim to achieve improved efficacy of the active pharmaceutical ingredients, better patient compliance and the attainment of formulation chemotherapeutic goals. These novel technologies result in either enhanced bioavailability, dose and dosing frequency reduction or minimization of side effects.

Globally, there are increasing efforts to develop the technology of oral fast disintegrating tablet or oral/mouth dissolving drug delivery systems (ODT /ODDDS). This is because comparative to the conventional tablet systems, the technology presents with the advantages of simplicity of design, ease of handling, good stability with offering of therapeutic benefits such as rapid absorption and onset of action, increased bioavailability, accuracy of dose administration, convenience of dosing (reduction), enhanced efficacy, safety, improved patient acceptance, compliance, and adherence. Thus, patient populations such as the geriatrics, paediatrics, mentally ill and those with dysphagia could benefit from ODDDS formulations.

The rationale behind developing oral disintegrating tablet is the availability of larger surface area in the oral dosage form which allows rapid wetting in the moist buccal environment that leads to rapid disintegration and dissolution in the oral cavity. Rapid disintegration of tablet results in fast dissolution and rapid absorption and onset of action, hence improved patient compliance and convenience. The oral or buccal mucosa is highly vascularized; therefore drugs can be absorbed directly and can enter the systemic circulation without undergoing first pass hepatic metabolism.

Dispersible tablets are uncoated or film coated tablets which disintegrate rapidly usually within a matter of seconds when placed in water to form a stabilized homogenous dispersion/suspension and are thus intended to be dispensed in water of about 5-15 mLs. They comprise of totally water-soluble excipients and components. This formulation technology can also be used for APIs that are unstable in liquid formulations but could be re constituted as suspensions prior to use.

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These tablets are expected to have low friability values which infers their good physical strength upon exposure to mechanical shock and attrition that could occur during transportation, storage, and dispensing. As opposed, to a suspension, no refrigeration is required. In more recent years, increasing attention has been paid to formulating not only fast dissolving and/or disintegrating tablets that are swallowed, but also orally disintegrating tablets that are intended to dissolve and/or disintegrate rapidly in water before being swallowed.

Super disintegrants are substances (synthetic, semi synthetic and/ or natural) which are added in small quantities (1-10% w/w) as tablet formulation excipients to effect the fast disintegration of the dosage form in an aqueous environment. The widely used super disintegrants are cross povidone, croscarmellose sodium and sodium starch glycolate. Super disintegrants exert their actions in powder systems through the mechanisms of improved wettability as a result of increased powder porosity which enhances capillary action.

Disintegration process is thus enhanced by super disintegrants. The super disintegrant type and the concentration used are critical to the effectiveness as well as an integral to the functionality of the formulated dispersible tablet. Thus, for poorly soluble drugs whose absorption rate is challenged due to its low wettability that results in poor disintegration and dissolution rate. The faster disintegration of tablets delivers fine suspension of drug particles resulting in a higher surface area and faster dissolution. Poorly soluble drugs can thus be formulated as dispersible tablets to improve their therapeutic effectiveness.

Tuberculosis (TB) is a chronic infectious disease characterised with high mortality and morbidity. It is caused by Mycobacterium tuberculosis, a slender, or slightly curved acid-fast bacillus, ranging in length from 1-4 µm. It has been declared by (WHO, 2010) as a global burden and public health issue as it affects both the adult and paediatric population. However, childhood Tuberculosis is neglected because treatment and clinical care have been mostly extrapolated from studies in the adult population. Furthermore, even in the early years of anti-TB drug development, children were largely excluded from major clinical trials, thus the evidence base on which treatment of childhood TB isdetermined is weak and the recommendations in childhood TB is mainly based on extrapolation from the observations in adult patients.

The present standardized chemotherapy of drug sensitive TB consists of two phases; the first entails a two-month intensive therapy with the principal drugs; isoniazid, rifampicin, pyrazinamide and ethambutol (the latter depending on the healthcare setting and type of disease). This is followed by a continuation phase with isoniazid and rifampicin for at least four months. (WHO, 2017). HIV-infected children with TB require antiretroviral therapy (ART) and co-trimoxazole preventive therapy (CPT) in addition to TB treatment. Preventive therapy which is highly effective in children exposed to TB is treated with a daily intake of rifampicin with isoniazid for three months, alternatively for six-months using isoniazid monotherapy for both adults and children, but with caution to people living with HIV who are on ART because of potential drug-drug interactions. Isoniazid (INH) is isonicotinyl hydrazine or isonicotinic acid hydrazide (4-Pyridinecorboxylic acid hydrazine).

It has an empirical formula of C6H7N3O and a molecular weight of 137.14; pH of 6 -8. INH is a colourless, odourless, white crystalline powder that has an anti-mycobacterial (bactericidal) property against both extracellular and intracellular organisms. It is a first line agent in the treatment of pulmonary and extra pulmonary tuberculosis in combination with rifampicin, pyrazinamide and ethambutol. It is a component of all combined anti-tuberculosis chemotherapy recommended by World Health Organization (WHO). INH may be used for tuberculosis prophylaxis, as obtainable in the intermittent prophylactic therapy (IPT) for HIV positive patients. Isoniazid is used in the treatment of pulmonary and extra pulmonary tuberculosis. The usual daily dose is 10-14mg/ kg for adult/children; the maximum daily dose is 300 mg.

The chemotherapy of TB for the paediatric population is however challenged by preferential focus on adult formulations which results in treatment with unsuitable split / broken / divided / crushed adult formulations /tablets as (halves, quarters) or opening of capsules with the addition of the powder to a palatable drink or sprinkling onto food. These protocols are unsuitable because they lead to potential high probability of inaccurate and erroneous dose administration, drug exposure and medicine related toxicity as a result of the physiological development (immaturity) of the organs. Furthermore, consideration should be given to the issues such as differences in pharmacotherapy, taste preferences, age, weight, efficacy, ease of use (dose flexibility, drug acceptability, handling convenience, correct use), safety (bioavailability of active substances, safety of excipients, medication stability.

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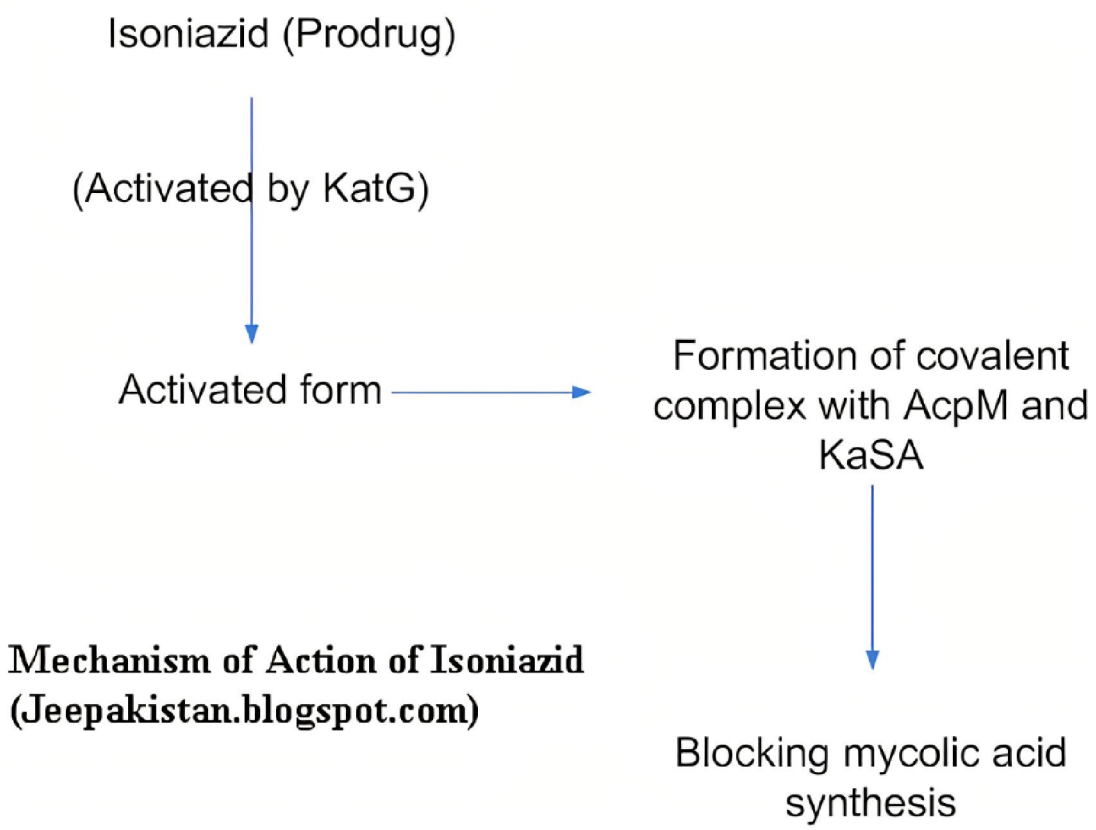
II. MECHANISM OF ACTION OF ISONIAZID

Isoniazid has been the most important drug used in TB treatment rules since 1952. It's a prodrug actuated by the catalase- peroxidase KatG, creating a variety of revolutionaries and adducts that inhibit the mycobacterium's product of the mycolic acids that make up its cell wall. This exertion lends INH to being a potent bactericidal agent. It also appears to be synergistic with other species produced by KatG and other specifics used to treat TB. Still, mutations in the katG, inhA, kasA, and ahpC genes may beget resistance in isoniazid remedy. This resistance in M. tuberculosis develops hastily when only monotherapy of isoniazid is used for the treatment.



Mechanism of Action of Isoniazid (Jeepakistan.blogspot.com)

PHARMACOKINETICS

- Immersion Rapid and complete immersion occurs after oral or intramuscular administration.
- Time of peak tube attention 1 to 2 hours • Distribution fleetly into all body apkins chambers, including cerebrospinal fluid
- Tube protein binding 10 to 15 • Metabolism Metabolized primarily by acetylation and dehydrogenation in liver
- Excretion A maturity(75 to 95) of unchanged medicine and it's metabolites are excreted in the urine, while small quantities are excreted in feces and slaver.

ADMINISTRATION

Lozenge Forms Isoniazid phrasings are available as tablets(100 mg and 300 mg), saccharinity(50 mg/ 5 ml), or through IV or IM injection(100 mg/ ml). Cure In grown-ups, 5 mg/ kg over to 300 mg daily as a single cure daily, or 15 mg/ kg over to 900 mg per day in two to three divided boluses per week is recommended. One course of treatment for active TB infections with medicine-susceptible strains consists of two months of isoniazid, rifampin, pyrazinamide, and

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ethambutol, followed by four and a half months of only isoniazid and rifampin. Although rifampin- grounded short courses are the current recommendation, idle tuberculosis infection can also be treated with isoniazid.

SPECIFIC PATIENT POPULATION

- Case with Hepatic Impairment There's no cureadaptation guidance in the manufacturer marker for cases with hepatic impairment. still, isoniazid is metabolized in the liver, so the medicine should be used with caution in these cases. It's also apparent that cure adaptation may be needed for cases with acute or habitual liver complaint to avoid adverse goods.
- Case with Renal Impairment There's no cure adaptation demanded for cases with renal impairment. Although there was a extension in half- life, it was recommended to administer a full cure of isoniazid in cases with disabled renal function. Cases should be managed conservatively or by haemodialysis.
- Pregnant Women It's considered as gestation order C drug. Isoniazid may cross the placental hedge. Although it may not beget teratogenic goods, it's recommended to cover cases precisely. It's recommended to use isoniazidremedy to treat active tuberculosis during gestation if the benefit overbalanced the implicit threat to the fetus. Pyridoxine supplementation is a recommended intervention for these cases.
- Breastfeeding Women The manufacturer recommends not discouraging breastfeeding as the small quantum of isoniazid in bone milk don't produce toxin in the invigorated. Pyridoxine supplementation is recommended for these cases.
- Pediatric Cases 10 to 15 mg per kg over to 300 mg daily as a single cure; or 20 to 40 mg per kg over to 900 mg per day in two to three divided boluses per week is recommended.
- Senior Cases There's no specific cure adaptation guidance in the manufacturer marker for senior cases.

ADVERSE EFFECTS

- Sudden weakness or ill feeling, or fever for 3 days or longer.
- Pain in your upper stomach (may spread to your back), nausea, loss of appetite.
- Dark urine, clay-colored stools, jaundice (yellowing of the skin or eyes).
- Vision changes, pain behind your eyes.
- Confusion, memory problems, unusual thoughts or behaviour.
- A seizure (convulsions).
- Pale skin, easy bruising or bleeding (nosebleeds, bleeding gums).
- Numbness, tingling, or burning pain in your hands or feet.
- Nausea, vomiting, upset stomach.
- Abnormal liver function tests.

CONTRAINDICATION

Isoniazid can be administered to cases with stable liver complaint, although the threat for medicine accumulation and medicine- convinced hepatitis may increase. These cases should have further frequent monitoring. It's contraindicated for cases who develop severe acuity responses to isoniazid or any other factors of phrasings. It's also contraindicated for the cases with medicine- convinced hepatitis or cases who preliminarily reported isoniazid- associated hepatic injury.

TOXICITY

Isoniazid is metabolized primarily by the liver by acetylation of N-acetyl transferase 2 (NAT2). Three metabolites have implications that correlate with the liver injury associated with the drug: acetyl hydrazine (AcHz), hydrazine (Hz), and a metabolite from the bioactivation of isoniazid itself. There is considerable variation in acetylation rate and elimination half-life from individual to individual, which is not accounted for by dose and concentration. This appears to contribute to the risk for hepatotoxicity and the other adverse effects associated with isoniazid.

The mild liver injury will occur in up to 20% of patients taking isoniazid. Clinical manifestations of hepatotoxicity include fever, fatigue, nausea, and vomiting. However, most patients experiencing isoniazid-induced liver injury are

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asymptomatic. Usually, it is detected only by measuring increased levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), which may rise to as high as five times the normal limit. In a process called "adaptation," the hepatic markers will return to normal in most of these patients, even with continued administration of the drug. About 1% of patients will experience severe liver injury, and isoniazid therapy should stop immediately. Reintroducing isoniazid in these cases is contraindicated as it can cause rapid symptom onset, and fatal hepatitis during isoniazid treatment is associated with continued use after symptoms of hepatitis present.

INTERPRETATION

Treatment of isoniazid-resistant tuberculosis with first-line drugs resulted in suboptimal outcomes, supporting the need for better regimens. Standardised empirical treatment of new cases could be contributing substantially to the multidrug-resistant epidemic, particularly in settings where the prevalence of isoniazid resistance is high.

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