# DOWNLOAD PDF ISONIAZID MECHANISM OF ACTION

## Chapter 1 : Isoniazid | C6H7N3O - PubChem

*To understand INH action and resistance fully, a synthesis of knowledge is required from multiple separate lines of research - including molecular genetic approaches, in vitro biochemical studies and free radical chemistry - which is the intent of this review.*

Rifampin has also bactericidal activity against slow and intermittently growing M. Isoniazid kills actively growing tubercle bacilli by inhibiting the biosynthesis of mycolic acids which are major components of the cell wall of M. The exact mechanism of action by which pyrazinamide inhibits the growth of M. In vitro and in vivo studies have demonstrated that pyrazinamide is only active at a slightly acidic pH pH 5. Ethambutol diffuses into actively growing M. Rifampin diffuses well to most body tissues and fluids, including the cerebrospinal fluid CSF , where concentrations are increased if the meninges are inflamed; concentrations in the liver, gallbladder, bile, and urine are higher than those found in the blood. Because it is lipid-soluble, rifampin may reach and kill susceptible intracellular, as well as extracellular, bacteria and Mycobacteria species. Isoniazid is widely distributed to all fluids and tissues, including CSF, pleural and ascitic fluids, skin, sputum, saliva, lungs, and muscle. Pyrazinamide is widely distributed to most fluids and tissues, including liver, lungs, kidneys, and bile. Ethambutol is distributed to most tissues and body fluids, except CSF. Hepatic; rifampin is rapidly deacetylated by auto-induced microsomal oxidative enzymes to the active metabolite O-desacetylrifampin. Time to peak serum concentration Rifampinâ€”1. Peak serum concentration Rifampin: Children 6 to 58 months of age: In dialysisâ€” Significant amounts of isoniazid are removed from the blood by hemodialysis. Tuberculosis during pregnancy should be managed on a case-by-case basis because of the complexity of management decisions. It has rarely caused postnatal hemorrhages in the mother and infant when administered during the last few weeks of pregnancy; vitamin K may be indicated. Imperfect osteogenesis and embryotoxicity were reported in rabbits given up to 20 times the usual daily human dose. Isoniazid Isoniazid crosses the placenta, resulting in fetal serum concentrations that may exceed maternal serum concentrations. Studies in rats and rabbits have shown that isoniazid may be embryocidal. Pyrazinamide Adequate and well-controlled studies in humans have not been done; the risk of teratogenicity has not been determined. Studies in mice given high doses of ethambutol have shown that ethambutol causes a low incidence of cleft palate, exencephaly, and vertebral column abnormalities. In addition, studies in rats given high doses of ethambutol have shown that ethambutol causes minor abnormalities of the cervical vertebrae. Pediatrics Ethambutol may cause reversible optic neuritis; therefore, patients should be monitored regularly for visual acuity, visual fields, and red-green color discrimination. Geriatrics Appropriate studies on the relationship of age to the effects of rifampin, isoniazid, pyrazinamide, and ethambutol combination have not been performed in the geriatric population. However, elderly patients are more likely to have an age-related decrease in renal function, which may require an adjustment of dosage in patients receiving ethambutol. Pharmacogenetics Isoniazidâ€”Patients can be divided into two groups: The rate of acetylation does not significantly alter the effectiveness of isoniazid. However, slow acetylation may lead to higher blood levels of isoniazid and, thus, an increase in toxic reactions. Slow acetylators are characterized by a relative lack of hepatic N-acetyltransferase. Patients who are slow acetylators may be more prone to develop adverse effects, especially peripheral neuritis, and may require lower-than-usual doses. Dental Rifampinâ€”The leukopenic and thrombocytopenic effects of rifampin may result in an increased incidence of certain microbial infections, delayed healing, and gingival bleeding. If leukopenia or thrombocytopenia occurs, dental work should be deferred until blood counts have returned to normal. Patients should be instructed in proper oral hygiene, including caution in the use of regular toothbrushes, dental floss, and toothpicks. Combinations containing any of the following medications, depending on the amount present, may also interact with this medication. Those indicating need for medical attention Incidence more frequent Hepatitis dark urine; yellow eyes or skin hepatitis prodromal symptoms loss of appetite; nausea and vomiting; unusual tiredness or weakness peripheral neuritis clumsiness or unsteadiness; numbness, tingling, burning, or pain in hands and feet Note: The risk of developing hepatitis is age related.

## Chapter 2 : Action Mechanism of Antitubercular Isoniazid

*Isoniazid, also known as isonicotinylhydrazide (INH), is an antibiotic used for the treatment of tuberculosis. For active tuberculosis it is often used together with rifampicin, pyrazinamide, and either streptomycin or ethambutol. [2].*

The minimum inhibitory concentrations of rifampicin for several medically significant pathogens are: Mycobacterium tuberculosis â€" 0. The treatment-related adverse effects include hepatotoxicity , nephrotoxicity , hemolysis , and interactions with other drugs. The more common side effects include fever, gastrointestinal disturbances, rashes, and immunological reactions. Taking rifampicin usually causes certain bodily fluids, such as urine, sweat, and tears, to become orange-red in color, a benign side effect that nonetheless can be frightening if it is not expected. This may also be used to monitor effective absorption of the drug if drug color is not seen in the urine, the patient may wish to move the drug dose farther in time from food or milk intake. The discolorization of sweat and tears is not directly noticeable, but sweat may stain light clothing orange, and tears may permanently stain soft contact lenses. Since rifampicin may be excreted in breast milk, breast feeding should be avoided while it is being taken. Liver toxicityâ€" hepatitis , liver failure in severe cases Respiratoryâ€"breathlessness Abdominal â€" nausea , vomiting, abdominal cramps, diarrhea Flu-like symptoms â€"chills, fever, headache, arthralgia , and malaise. Rifampicin has good penetration into the brain, and this may directly explain some malaise and dysphoria in a minority of users. Allergic reactionâ€"rashes, itching, swelling of the tongue or throat, severe dizziness, and trouble breathing [32] Chemical structure[ edit ] Rifampicin is a polyketide belonging to the chemical class of compounds termed ansamycins , so named because of their heterocyclic structure containing a napthoquinone core spanned by an aliphatic ansa chain. The napthoquinonic chromophore gives rifampicin its characteristic red-orange crystalline color. The critical functional groups of rifampicin in its inhibitory binding of bacterial RNA polymerase are the four critical hydroxyl groups of the ansa bridge and the napthol ring, which form hydrogen bonds with amino acid residues on the protein. Other interactions include decreased levels and less effectiveness of antiretroviral agents , everolimus , atorvastatin , rosiglitazone , pioglitazone , celecoxib , clarithromycin , caspofungin , voriconazole , and lorazepam. The activity of rifampicin against some species of mycobacteria can be potentiated by isoniazid through inhibiting mycolate synthesis [39] and ambroxol through host directed effects in autophagy and pharmacokinetics. Mutation of amino acids shown in red are involved in resistance to the antibiotic. The majority of resistance mutations in E. When describing mutations in rpoB in other species, the corresponding amino acid number in E. In Mycobacterium tuberculosis, the majority of mutations leading to rifampicin resistance are in cluster I, in a 81bp hotspot core region called RRDR for "rifampcin resistance determining region". Early detection of such multidrug or extensively drug-resistant tuberculosis is critical in improving patient outcomes by instituting appropriate second-line treatments, and in decreasing transmission of drug-resistant TB. If these two drugs must be used concurrently, they must be given separately, with an interval of 8 to 12 hours between administrations. Rifampicin is easily absorbed from the gastrointestinal GI tract; its ester functional group is quickly hydrolyzed in bile , and it is catalyzed by a high pH and substrate-specific esterases. After about 6 hours, almost all of the drug is deacetylated. Even in this deacetylated form, rifampicin is still a potent antibiotic; however, it can no longer be reabsorbed by the intestines and is eliminated from the body. The half-life of rifampicin ranges from 1. Food consumption inhibits its absorption from the GI tract, and the drug is more quickly eliminated. Antacids do not affect its absorption. Distribution of the drug is high throughout the body, and reaches effective concentrations in many organs and body fluids, including the cerebrospinal fluid. Since the substance itself is red, this high distribution is the reason for the orange-red color of the saliva, tears, sweat, urine, and feces. History[ edit ] In , a soil sample from a pine forest on the French Riviera was brought for analysis to the Lepetit Pharmaceuticals research lab in Milan , Italy. There, a research group headed by Piero Sensi [50] and Maria Teresa Timbal discovered a new bacterium. This new species produced a new class of molecules with antibiotic activity. Because Sensi, Timbal and the researchers were particularly fond of the French crime story Rififi about a jewel heist and rival gangs , [51] they decided to call these compounds "rifamycins". After two

years of attempts to obtain more stable semisynthetic products, a new molecule with high efficacy and good tolerability was produced in and was named "rifampicin". Rifampicin is also known as rifaldazine, [52] [53] rofact, and rifampin in the United States, also as rifamycin SV. Santa Cruz Biotechnology Product Block. Archived from the original on 27 November  Retrieved 14 November

## Chapter 3 : Isoniazid - Wikipedia

*Abstract. Activation of the antitubercular isoniazid (INH) by the Mycobacterium tuberculosis KatG produces an inhibitor for enoyl reductase (InhA). The mechanism for INH activation remains poorly understood, and the inhibitor has never been isolated.*

Many of the drugs still used to treat TB were discovered many years ago, Summary before the advent of newer powerful molecular For decades after its introduction, the mechanisms of techniques. Thus, the mechanisms of action of many action of the front-line antituberculosis therapeutic older TB drugs were poorly defined, yet many are still part agent isoniazid INH remained unclear. Recent devel- of first- or second-line therapies. These activities could then be rationally nucleic acid biosynthetic enzymes. A direct role for screened for and optimized in development programmes. The concerted effects highly selective agent that is still a centrepiece of therapy of these activities â€" inhibition of cell wall lipid synthe- Youatt, ; Deretic et al. We use the plural, tivity of this agent. To understand INH action and mechanisms, deliberately, as a range of potent mecha- resistance fully, a synthesis of knowledge is required nisms have recently been uncovered that may act addi- from multiple separate lines of research â€" including tively or synergistically to explain the exceptional and molecular genetic approaches, in vitro biochemical highly selective potency of INH against M. INH itself is not toxic to the bacterial rium tuberculosis, kills over 2 million people per year, with cell, but acts as a prodrug and is activated by the myco- between 1 billion and 2 billion people latently infected bacterial enzyme KatG Zhang et al. Not only tional catalase-peroxidase that has other activities has the unfortunate synergy between TB and HIV including peroxynitritase Wengenack et al. While the protective emergence of multidrug resistant strains, which are both activities of KatG against host phagocyte NADPH difficult and very costly to treat, poses an additional public oxidase-derived peroxides appear important in the health hazard and further roadblock in effective control of absence of INH Ng et al. Although there has been a renewal of activity in the INH-resistant mutants occurs during treatment, with a major site for INH resistance mutations being the katG Accepted 2 October,  Structures of isoniazid 1 , the isonicotinic lhydrazyl radical 2 and the isonicotinoyl radical also termed isonicotinic acyl Reactive species formed by KatG activation of INH radical 3. A range of elegant studies have characterized the stable products of INH oxidation by both KatG and model oxi- mutations that result in a partially active protein that dants Johnsson and Schultz, ; Johnsson et al. ST , although et al. A range of oxi- action. Even in the absence of posed from results of spin trapping experiments Wengen- added oxidants, the in vitro auto-oxidation of INH ack and Rusnak,  It is likely that the oxidant what tentative Buettner,  The spin trap 5,5- in vivo is a low flux of hydrogen peroxide that might form dimethylpyrolline-N-oxide DMPO often allows better within the bacteria as a by-product of aerobic metabolism assignments than PBN, as the range of hyperfine cou- Zhao et al. However, intracellular-formed super- pling constants of its spin adducts are wider. Accordingly, oxide might also have a direct role Ghiladi et al. INH-derived species assigned as carbon-centred and As both these superoxide- and low-flux hydrogen alkoxyl adducts of DMPO have been observed upon KatG peroxide-oxidizing systems show the expected decrease oxidation of INH Timmins et al. The results from other oxidizing systems radish peroxidase Zinner et al. However, it is uncertain whether an initial product with KatG also, although confirmation these model oxidants accurately simulate the exact with authentic KatG is required. Despite these advances, species formed by M. Additionally, a role for man- definitively the production of the isonicotinoyl radical 3 in ganese in vivo is unlikely as although it can reach high Fig. There are several important antimyco-  The crystal structures of KatG Bertrand et al. This results in a high sensitivity of M. However, further delineation of the M. As addition of took some time to determine the mechanisms. InhA is an enoyl acyl carrier protein reductase overall INH action. We further hypothesize that some of Banerjee et al. It was mycobacterial cell and be oxidatively detoxified in the later shown that these adducts could be formed during growth medium Lancaster, ; Thomas et al. Lowered mycothiol levels Miesel et al. The presence of an S-nitrosomycothiol reduc- et al. The InhA Rozwarski et al. Although sub- recently been further clarified by transferring clinically sequent cyclization of these two initial INH-NAD adducts observed mutations, such as inhA S94A into wild-type generates a range

of diastereoisomers Nguyen et al. Introduction of a; Broussy et al. However, these in vitro systems used a high Although it appeared that an INH adduct of M. Nat Struct Mol Biol Microbiology Pt 9: The inhibition of â€" J Biol Chem Looking ahead, it would appear that INH is already Oxidation of isoniazid by manganese and Mycobac- an optimal substrate for KatG for conversion to species terium tuberculosis catalase-peroxidase yields a new such as the isonicotinoyl radical, and so logical avenues for mechanism of activation. J Am Chem Soc Org Biomol Chem 3: Aust J Chem N-acetyltransferase, a mycobacterial enzyme that Buettner, G. Free Radic Biol Med 3: J Exp Med Antimicrob Agents Chemother Biochim Biophys Acta Crit Rev Microbiol Bio- Oxidative stress response and its role in sensitivity chemistry Petersburg area in Russia. Nicotin-amide-adenine nucleotides of Mycobacterium â€" Nat Cell culosis beta-ketoacyl ACP synthase by isoniazid. Nat Rev Mol Cell Biol 6: Missense mutations in the catalase-peroxidase gene, Minisci, F. J Infect Dis Antimicrob Agents Maughan, W. Lung Cell Mol Physiol Deretic agents, free radicals, and antibiotics. Antimicrob Agents Thomas, D. Mycobacterium tuberculosis enoyl reductase: Antimicrob Agents Vogt, R. Honer Zu Bentrup, K. Mycobacterium avium-, Mycobacterium tuberculosis-, and Shoeb, H. J Med Microbiol isoniazid-dependent free radical generation catalyzed by Mycobacterium tuberculosis KatG and the isoniazid-Singh, R. J Biol Wengenack, N. Biochem Biophys Res Commun Am Rev Stover, C. Tubercle Lung Dis The formation of an excited product.

## Chapter 4 : Mechanisms of action of isoniazid | Graham Timmins - blog.quintoapp.com

*Isoniazid (INH) is one of the most active compounds used to treat and prevent worldwide. â€¢ Despite its simple structure, the mechanism of action of INH is very complex and involves several different concepts.*

Organisms undergo another divisions before growth is arrested. Use of isoniazid as a sole agent is, therefore, not advised. The drug appears to be taken up by an active process and only sensitive organisms contain significant quantities of drug. Mechanism of action Not definitely known, but hypotheses include effects on: Isoniazid may prevent elongation of the "very-long-chain fatty acid precursors" of mycolic acid. Isoniazid also inhibits the first Step that is specific for mycolic acid synthesis, a desaturase enzyme. Biotransformatin is by acetylation to acetylisoniazid major and hydrolysis to isonicotinic acid minor. This results in blood levels that vary by a factor of 4 to 6 fold. Isoniazid inhibits hepatic mixed function oxidases. Isoniazid increases the elimination of pyridoxine. Signs related to this are: At a microscopic level, synaptic vesicles disappear, there is mitrochondrial alteration; axon terminal fragmentation; and occasionally, alterations in the spinal cord and various ganglia. Mostly occurs 4 to 8 weeks after start of therapy. Must monitor hepatic function e. May result from metabolite, acetylhydrazine. There is some contribution from alcoholic hepatitis. Reversible vasculitis may occur and arthritic symptoms at various joints may be observed. Other mycobacteria have variable sensitivity. Gram negative bacilli require 0. Many chlamydiae are sensitive. Resistance Can develop quickly. Must not use the drug alone because of this. Resistance has developed in as little as 2 days in meningococcal carrier states. Elongation is not inhibited. Rifampin binds to the beta-subunit of the holoenzyme. Higher concentrations are required to inhibit mammalian mitochondrial RNA synthesis. Pharmacokinetics Rifampin is well absorbed after PO administration, usually q1d. Rifampin is broadly distributed, even into the CSF. Its presence in many body fluids is shown by the orange-red color it gives to urine, feces, saliva, sputum, tears, and sweat GG8th90,p The half-life of rifampin is 1. Rifampin is deacetylated to a form that is still active as an antibacterial. Rifampin and its deacetylated form are eliminated in the bile, but the deacetylated form is less bioavailable so, despite the enterohepatic circulation, rifampin is eventually eliminated. Elimination is slowed by hepatic dysfunction and slow acetylators taking isoniazid. Hepatic microsomes which deacetylate the drug are induced. Most common are rash 0. Jaundice Most notable problem and has resulted in death. Hepatitis is rare in patients with normal liver function, but chronic liver disease, alcoholism, and old age appear to increase the incidence. Flu-like syndrom includes fever, chills, and arthralgias and, in some cases, eosinophilia, interstitial nephritis, acute tubular necrosis, thrombocytopenia, hemolytic anemia and shock. It has precipitated methadone withdrawal. Redman syndrome -- caused by marked overdosage, and shown by severe liver damage, bright red urine, tears, saliva; skin resembles that of broiled lobster. Miscellaneous Other effects include gastrointestinal disturbances e. Currently being investigated for M. May need to do periodic hematologic screening. Permanently stains contact lenses. Drug interactions Induces hepatic isoforms of cytochrome P, but half to a third as potent as rifampin. Kinetics of didanosine and fluconazole appear unaffected. Because is similar to rifampin, should suspect of altering pharmacokinetics of many compounds. Death due to hepatic necrosis can occur. Resistance to ethambutol develops slowly. May appear as early as 24 h or 90 days after start therapy. May be worsened by isoniazid and pyridoxine.

## Chapter 5 : Ethambutol and Isoniazid Drug Information, Professional

*For decades after its introduction, the mechanisms of action of the front-line antituberculosis therapeutic agent isoniazid (INH) remained unclear. Recent developments have shown that peroxidative.*

The mechanism for INH activation remains poorly understood, and the inhibitor has never been isolated. We have purified the InhA-inhibitor complex generated in the M. The complex was devoid of enoyl reductase activity. The inactive complex can be reconstituted from InhA and the isolated inhibitor. By monitoring the formation of the InhA-inhibitor complex, we have found that manganese is not essential to the INH activation by M. Tuberculosis due to Mycobacterium tuberculosisinfection is the leading cause of death worldwide among known infectious diseases. A sizeable increase of tuberculosis cases in the United States since 1 is followed by a decrease in more recent years. INH has been the cornerstone in tuberculosis chemotherapy for almost half a century since its discovery as a potent antituberculosis drug in  INH is a prodrug, and its antituberculosis function requires in vivo activation by KatG, an enzyme with dual activities of catalase and peroxidase. The involvement of KatG in the INH action was first implied by an apparent correlation between the loss of KatG catalase activity and INH resistance 8 and confirmed by a genetic study 9. INH activation leads to inhibition of the synthesis of mycolic acid, a long chain fatty acid-containing component of the mycobacterial cell wall 13 ,  Progress made thus far notwithstanding the mechanisms of INH action and resistance are still poorly understood. Purified KatG from eitherM. The crystal structure of the resulting InhA-inhibitor complex has been determined, which shows that the bound inhibitor is an isonicotinic acyl NADH  It is, however, uncertain whether or not the inhibitor generated by this nonenzymatic activation is identical to that formed in the KatG-dependent process. Moreover, the inhibitor derived from INH by either the nonenzymatic or the KatG-dependent activation has never been isolated, and no simple method has been developed for the detection and quantification of the inhibitor. Consequently, biochemical or biophysical characterizations of the nature and consequences of the inhibitor binding by InhA have been greatly hindered by these limitations. We are interested in the mechanisms of the INH action and resistance. This work was carried out to isolate for the first time the InhA inhibitors generated by the nonenzymatic and the M. Octenoic acid, 2,4,6-trimethylpyridine, and ethyl chloroformate were purchased from Aldrich. Escherichia coli UM, a katG-deficient strain, was kindly provided by Dr. Loewen University of Manitoba  All phosphate Pi buffers were at pH 7. Cloning The inhA gene 15 was cloned by the polymerase chain reaction method using M. However, the clone so obtained did not express KatG efficiently. The resulting construct, pKAG2, can be efficiently expressed in E. In order for the recombinant KatG to be expressed in E. To 30 g of wet cell paste, ml of 25 mm Pi was added and the suspension was sonicated for 20 min. The column was eluted with 50 ml of 35 mm Pi followed by ml of 50 mm Pi. InhA, identified by SDS-polyacrylamide gel electrophoresis, was associated with the majorA peak obtained in the 50 mmPi wash. The InhA pool was diluted 1: The column was sequentially eluted with 60 ml of 40 mm Pi, 50 ml of a linear gradient from 40â€”50 mm Pi, and lastly 50 mm Pi. InhA was recovered under a single major peak, and the constituent fractions were pooled. Four grams of ammonium sulfate were added to ml of the InhA sample so obtained. The column was washed first with 50 ml of 0. The identity of InhA was confirmed by N-terminal amino acid sequencing. The level of catalase activity was followed throughout the growth, and cells were harvested when the catalase activity in cells from 1 ml of culture reached about 0. About 30 g of the wet cell paste were sonicated in ml of 25 mm Pi and cooled on ice for 20 min. KatG was recovered by elution with mm Pi. Ammonium sulfate was added to the KatG pool for a final concentration of 0. The sample was then loaded on a 2. The column was sequentially eluted with 50 ml of 0. The column was eluted with ml of a linear gradient of 30â€” mm Pi. The peroxidase activity of KatG was measured as the oxidation rate of 0. Octenoyl CoA was synthesized according to the method of Goldman and Vagelos  The quality of the octenoyl CoA so obtained was essentially the same as that reported earlier  The gel filtration was repeated once more for the pool of the protein fractions. The UV-visible spectrum of the protein peak was measured. The column was first washed with 10 mm Pi until no absorbance in the range of to nm was present in the filtrate. The InhA-inhibitor complex, freed from KatG, was then recovered by elution

with 50 ml of a linear gradient from 50â€” mm Pi. The sample was heated in boiling water for 40 s. Denatured protein was separated from the inhibitor by centrifugation of the sample through Microcon 3 with a molecular weight cut-off of Millipore. The inhibitor was concentrated by lyophilization. Alternatively, urea was added to the InhA-inhibitor complex sample to 8 m, and the sample was loaded on a Sephadex G column preequilibrated and eluted with 8m urea. Two peaks in the A profile of the gel filtration were observed. The first peak was denatured InhA, and the second one was the released inhibitor. The InhA-inhibitor complex in a glass tube was heated in boiling water for 40 s and then put on ice. The treated sample was transferred into a Microcon 3 centricom filter unit and spun to recover the released inhibitor in the filtrate, which was used for spectral measurements and HPLC analysis. Assay and Time Course of Inhibitor Formation The reactions were performed in triplicate in 4 ml of 50 mmPi containing 0. After 30, 60, , and min, 1 ml of the reaction mixture was withdrawn each time and freed from KatG by spinning for 20 min through two Micron 30 filters. A and A of the isolated complex were used to calculate the amounts of the inhibitor formed using 7. The A of InhA was negligible. Isonicotinic acid and INH had retention times of 4. A was used for the detection. Both inhibitor samples were also analyzed by mass spectrometry. The spectra were analyzed in the negative mode. Other Measurements Protein concentrations were determined by the method of Lowry et al. A Milton Roy Spectronic absorption spectrophotometer was used for absorption spectra and single-wavelength measurements. The N-terminal sequence of InhA was determined by automated Edman degradation with a gas sequencer. In the determination of heme content by the pyridine hemochrome assay, the ratio of A of the purified KatG overA developed in the assay was found to be 0. These measurements gave 1. The KatG catalase activity displayed a K m of 2. The specific peroxidase activity of KatG was 0. The UV-visible spectrum of the protein sample so obtained displayed substantial absorption in the range of â€” nm and a smaller absorption peak at nm due to the KatG-bound heme Fig. The â€” nm absorption was absent in control samples obtained the same way but without the addition of KatG Fig. The extra absorption in the â€” nm range were, as will be shown later, associated with an InhA inhibitor formed in this INH activation. Therefore,A provides a convenient indicator for following the INH activation and the inhibitor formation. The inhibitor was apparently bound by InhA very tightly. Repeated gel filtrations easily removed other small molecules such as NADH but not the inhibitor from the protein samples.

## Chapter 6 : Rifampin, Isoniazid, Pyrazinamide, and Ethambutol Drug Information, Professional

*Although delineation of the mechanisms of action of isoniazid required many years, it can be seen that convincing progress has been made in the last decade through the combined approaches of bacterial genetics, biochemical work and detailed free radical chemistry.*

Tuberculosis[ edit ] Isoniazid is approved for latent and active tuberculosis infections. For the latter, it must be used in combination with other tuberculosis medications to prevent the development of drug resistance. Isoniazid has been approved as prophylactic therapy for the following populations: The introduction of macrolides led to this use greatly decreasing. However, since rifampicin is broadly underdosed in M. Preventive therapy should be delayed until after giving birth. Both pregnant women and infants being breastfed by mothers taking INH should take vitamin B6 in its pyridoxine form to minimize the risk of peripheral nerve damage. Pyridoxal phosphate a derivative of pyridoxine is required for d-aminolevulinic acid synthase, the enzyme responsible for the rate-limiting step in heme synthesis. Therefore, isoniazid-induced pyridoxine deficiency causes insufficient heme formation in early red blood cells, leading to sideroblastic anemia. Isoniazid is thought to induce a liver enzyme which causes a larger amount of acetaminophen to be metabolized to a toxic form. People taking carbamazepine should have their carbamazepine levels monitored and, if necessary, have their dose adjusted accordingly. This is seen with the simultaneous use of rifampin, isoniazid, and ketoconazole. The doses of phenytoin may need to be adjusted when given with isoniazid. There are some cases of theophylline slowing down isoniazid elimination. Both theophylline and isoniazid levels should be monitored. Valproate levels should be monitored and its dose adjusted if necessary. This complex binds tightly to the enoyl-acyl carrier protein reductase InhA, thereby blocking the natural enoyl-AcpM substrate and the action of fatty acid synthase. This process inhibits the synthesis of mycolic acids , which are required components of the mycobacterial cell wall. A range of radicals are produced by KatG activation of isoniazid, including nitric oxide , [35] which has also been shown to be important in the action of another antimycobacterial prodrug pretomanid. It is metabolized in the liver via acetylation into acetylhydrazine. Two forms of the enzyme are responsible for acetylation, so some patients metabolize the drug more quickly than others. Hence, the half-life is bimodal , with "slow acetylators" and "fast acetylators". A graph of number of people versus time shows peaks at one and three hours. The height of the peaks depends on the ethnicities of the people being tested. The metabolites are excreted in the urine. Doses do not usually have to be adjusted in case of renal failure. History[ edit ] Three pharmaceutical companies unsuccessfully attempted to patent the drug at the same time, [40] the most prominent one being Roche, which launched its version, Rimifon, in  It is manufactured using 4-cyanopyridine and hydrazine hydrate.

## Chapter 7 : Mechanisms of action of isoniazid.

*Mechanism of action â€" The antimicrobial activity of isoniazid (INH) is selective for mycobacteria, likely due to its ability to inhibit mycolic acid synthesis, which interferes with cell wall synthesis, thereby producing a bactericidal effect.*

## Chapter 8 : Rifampicin - Wikipedia

*Abstract. The mechanism of action of isoniazid (INH) on Mycobacterium bovis strain BCG was studied. The rates of synthesis of deoxyribonucleic acid (DNA), ribonucleic acid (RNA), and protein after the addition of INH to growing cultures were followed by measuring the incorporation of 3 H-thymidine, 3 H-uridine, and 14 C-l-valine, respectively.*

## Chapter 9 : Ethambutol - Wikipedia

*Rifampin, isoniazid, pyrazinamide, and ethambutol combination is indicated in the initial phase of the short-course treatment of tuberculosis. During this phase, which should last 2 to 3 months, rifampin, isoniazid, pyrazinamide, and*

*ethambutol combination should be administered on a daily, continuous basis {02}.*