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Clinical Pharmacology of Rifampin in Infants and Children

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Abstract

Rifampin is a macrocyclic antibiotic important in the treatment of mycobacterial diseases. This antibiotic is bacteriastatic as inhibits the transcription of DNA to RNA by binding to the β-subunit of bacterial RNA-polymerase (rpoB) to form a stable drug-enzyme complex. Rifampin enters bacilli in a concentration depended manner, achieving steady-state concentration within 15 min. This antibiotic inhibits the growth of most gram-positive and gram-negative microorganisms, and it is used to treat tuberculosis, leprosy, brucellosis, Mycobacterium kansasii, mycobacterium marinum, Mycobacterium uclerans, Mycobacterium malmoense, and Mycobacterium Haemophilus diseases. Rifampin is an effective and safe antibiotic in infants and children. Two formulations of rifampin are available, one for oral and other one for intravenous administration. In infants, the dose of rifampin is 10 to 20 mg/kg every 24 hours (oral administration) and 5 to 10 mg/kg every 12 hours (intravenous administration). To treat tuberculosis rifampin is co-administered with isoniazid. The fixed dose of rifampin/isoniazid is 60/60 mg per dispersible tablets. Concomitant administration of rifampin and isoniazid induces hepatotoxicity in children. Rifampin has been used to treat staphylococcal, bacterial meningitis, tuberculous meningitis, and Haemophilus infections. The pharmacokinetics of rifampin has been extensively studied in infants and children. Rifampin is extensively metabolized by different cytochromes P-450 and the metabolites are: 25-O-desecetyrifampicin and 3-formylrifamycin SV, 25-O-desecetyrifampicin, is the mean metabolite. Rifampin is a potent inducers of several cytochromes P-450. Rifampin, and its metabolites, are mainly excreted in the bile and eliminated with the faeces. Little is known about the bacterial resistance to rifampin, it is approximately < 20% and is higher in younger than older patients (P-value = 0.003). The aim of this study is to review the published data on rifampin-dosing, effects, metabolism, pharmacokinetics, and bacterial-resistance of rifampin in infants and children.

Keywords: Rifampin, Rifampin-dosing, Effects, Metabolism, Pharmacokinetics, Bacterial-resistance, Infants, Children

Introduction

Rifampin is a macrocyclic antibiotic important in the treatment of mycobacterial diseases. Rifampin is bacteriastatic as it inhibits the transcription of DNA to RNA by binding to the β-subunit of bacterial RNA-polymerase (rpoB) to form a stable drug-enzyme complex. Rifampin enters bacilli in a concentration dependent manner, achieving steady-state concentration within 15 min [1]. Rifampin suppresses the formation of RNA synthesis [2]. Rifampin inhibits the growth of most gram-positive bacteria as well as gram-negative microorganisms, such as Escherichia coli, Pseudomonas, indole-positive and indole-negative Proteus, and Klebsiella. Rifampin is very active against Staphylococcus aureus and coagulase negative staphylococci. This drug is also highly active against Neisseria meningitis and Haemophilus influenzae type b. Rifampin inhibits the growth of Legionella species in cell culture and in animal models. This antibiotic inhibits the growth of many Mycobacterium tuberculosis clinical isolates in vitro at concentrations of 0.06-0.25 μg/ml. Rifampin is bactericidal against Mycobacterium leprae. Mycobacterium kansasii are inhibited by 0.25-1 μg/ml. Most strains of Mycobacterium scrofulaceum, Mycobacterium intracellulare, and Mycobacterium avium are suppressed by rifampin at a concentration of 4 μg/ml. Mycobacterium abscessus inactivates rifampin via an ADP-ribosyltransferase and monooxygenase, making the bacteria-MIC isolates at concentrations ranging from 0.25 to 1 μg/ml. Rifampin is used to treat tuberculosis, leprosy, brucellosis, Mycobacterium kansasii, Mycobacterium marinum, Mycobacterium uclerans, Mycobacterium malmoense, and Mycobacterium Haemophilus diseases. Rifampin is also used in the prophylaxis of meningococcal and Haemophilus influenzae meningitis, and in combination with β-lactam antibiotics or vancomycin, is actives against staphylococcal endocarditis or osteomyelitis, especially those caused by staphylococci tolerant of penicillin [2].

After oral administration, rifampin is absorbed at variable extents. Rifampin absorption constant rate, systemic clearance, and the volume of central compartment/volume to peripheral compartment ratio are 1.15 hours^{-1}, 19 L/h,

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and 53 L, respectively [3]. Food decreases the rifampin peak concentration by one-third, thus rifampin should be taken in an empty stomach.

Rifampin is metabolized by microsomal B-esterases and cholinesterases. Rifampin has good penetration into many tissues, but peak concentration and AUC in the nervous central system and pericardial tissue only about 13% to 20% of those in plasma [4, 5]. Rifampin and its metabolites are excreted by bile and eliminated with faeces, with urine elimination accounting for only one-third. The population pharmacokinetics of rifampin is best described by once-compartment model with transit compartment absorption [6]. For each 1-kg weight increase, above 50 kg, the systemic clearance increases by 0.05 L/kg and the distribution volume by 0.69 L. Thus, the peak concentration and AUC decrease with increasing patient weight above 50 kg.

Rifampin is available for oral administration alone and a fixed-dose combination with isoniazid (150 mg isoniazid, 300 mg rifampin) or with isoniazid and pyrazinamide (50 mg isoniazid, 300 mg rifampin, and 300 mg pyrazinamide). A parenteral form of rifampin is also available. The dose of rifampin for treatment of tuberculosis in adults is 600 mg per day given once-daily, either 1 hour before or 2 hours after a meal. Children should receive 15 mg/kg (15 to 20 mg/kg), with the maximum dose of 600 mg, once-daily, given in the same way. This rifampin regimen was recommended by the WHO. Rifampin is also useful for the prophylaxis of meningococcal and Haemophilus influenzae type b meningitis diseases. To prevent meningococcal disease, adults may be treated with 600 mg twice-daily for 4 days; children older than 1 month should receive 10 to 20 mg/kg (mean dose, 15 mg/kg) to a maximum of 600 mg. Combined with β-lactam antibiotics or vancomycin, rifampin may be useful for therapy in selected cases of staphylococcal endocarditis or osteomyelitis, especially those caused by staphylococci tolerant to penicillin. This antibiotic may also be indicated for the eradication of the staphylococcal nasal carrier state in patients with chronic furunculosis. In the treatment of brucellosis, 900 mg per day rifampin can be combined with doxycycline for 6 weeks [2].

In infants, the oral dose of rifampin is 10 to 20 mg/kg per dose every 24 hours, and may be administered with feedings. The intravenous dose of rifampin is 5 to 10 mg/kg per dose every 12 hours, given via syringe pump over 30 min. This antibiotic is used in combination with vancomycin, or aminoglycosides for treatment of persistent staphylococcal infections. Monitoring hepatic transaminase activity and bilirubin is recommended, and periodic complete blood count for thrombocytopenia is suggested [7]. Observe intravenous site for signs of extravasation. Rifampin causes orange/red discoloration (see reference 23) of the face and body secretions (e.g. sweat, urine, tears, sputum). This drug is a potent inducer of several cytochromes P450 enzymes (CYP24A1, CYP3A4, CYP2B6, CYP3A, CYP2C9, CYP1A2, CYO2C9, CYP2C19, and CYP1A2) [26-30]. If administered concomitantly with the following drugs may have decreased pharmacologic effects due to increased metabolism: aminophylline, amiodarone, ecimetidine, corticosteroids, digoxin, enalapril, fluconazole, midazolam, morphine, phenobarbital, phenytoin, propranolol, and zidovudine [7].

Literature Search

The literature search was performed electronically using PubMed database as search engine, the cut-off point was June 2019. The following key words: “rifampin infants effects”, “rifampin children effects”, “rifampin infants metabolism”, “rifampin children metabolism”, “rifampin infants pharmacokinetics”, “rifampin children pharmacokinetics”, “rifampin infants resistance”, and “rifampin children resistance” were used. In addition, the book NEOFAX by Young and Mangum [7] was consulted. The manuscript is prepared according to the “Instructions for Authors”.

Results

Efficacy and safety of rifampin in infants and children

El-Karasksy, et al. [8] verified the safety and efficacy of rifampin in ameliorating pruritus in cholestatic children. Twenty-three Egyptian children, suffering from intractable pruritus of cholestasis were enrolled. Rifampin administration was started at a dose of 10 mg/kg per day in two divided doses and increased gradually to a maximum of 20 mg/kg per day if there was no response. Liver function tests were followed up weekly. Seventeen children (74%) showed improvement of pruritus with rifampin therapy. None of children showed any deterioration of liver functions after up weekly. Rifampin, at a dose of 10 to 20 mg/kg per day is safe and effective in ameliorating uncontrollable pruritus in children with persistent cholestasis.

Arnold, et al. [9] examined the safety of rifampin in hospitalized infants. Overall, 2,500 infants received 4,279 courses of rifampin; the mean gestational age was 27 weeks, and mean birth-weight was 1,125 gram. Thrombocytopenia (121/1,000 infant days, 12.1%) and conjugated hyperbilirubinaemia (25/1,000 infant days, 2.1%) were the most common laboratory adverse events. The most common clinical adverse events were medical necrotizing enterocolitis (64/2,500 infants, 3%) and seizure (60/2,500 infants, 2%). The overall incidence of adverse events among infants receiving rifampin appears low.

The treatment of latent infection with Mycobacterium tuberculosis is important in children because of their vulnerability to life threatening forms of tuberculosis. Diallo, et al. [10] performed a multicenter, open-label trial study, and randomly assigned in 844 children aged < 18 years, with latent Mycobacterium tuberculosis infection, to receive either 4 months of rifampin or 9 months isoniazid. The primary outcome was adverse events of grade 1 to 5 that resulted in the permanent discontinuation of a trial drug. The secondary outcomes were treatment adherence, side-effect profile, and efficacy of rifampin. Children who underwent randomization, 829 (98.2%) were eligible for inclusion in the modified intension to treat analysis. A total of 360 of 422 (85.3%) in

rifampin group completed per-protocol therapy, as compared with 311 of 422 children (76.3%) in the isoniazid group. There were no significant differences between-groups in rates of adverse events, with fewer than 5% of children in the combined groups with grade 1 or 2 adverse events that were deemed to possibly relate to a trial drug. Mycobacterium tuberculosis was found resistant in 2 children treated with isoniazid compared with no children treated with rifampin.

Effects of rifampin in infants and children

Then infants with mean gestational age and body weight of 27 weeks and 900 gram, respectively, were enrolled. Their mean age at the time of infection was 26 days (range, 6 to 64 days). Infants had persistent staphylococcal bacteraemia [11]. The staphylococcal isolates were methicillin-resistant Staphylococcus aureus (5 isolates), methicillin-susceptible Staphylococcus aureus (2 isolates), and coagulase-negative staphylococci (3 isolates). The mean number of bacteraemia days prior rifampin administration was 8.3 days (range, 5 to 15 days). The rifampin intravenous dose varied from 2.5 to 10 mg/kg every 12 hours. The mean rifampin duration course was 9.7 days (range, 3 to 16 days). Eight infants had sterile blood cultures within 24 hours, 1 infant had sterile a blood culture within 48 hours, and 1 infant had a sterile blood culture within 5 days after intravenous administration of rifampin. No adverse effects were noted in these infants. The MIC for rifampin ranged from 0.0013 to 0.04 μg/ml. Other eight infants, with a mean age of 23 days, were treated with a single intravenous or oral rifampin at a dose of 10 mg/kg per day. After rifampin oral administration, the peak and trough rifampin concentrations were 4.02±1.22 and 1.11±0.48 μg/ml, respectively, the trough concentration was measured at 12 hours after oral administration of rifampin, the mean rifampin concentration was 1.86±0.96 μg/kg at 2 hours postingestion, increasing to a peak concentration of 2.8 μg/ml at 8 hours post-ingestion. Rifampin was found to be an effective and safe antibiotic for the treatment of persistent staphylococcal bacteraemia in infants.

Coagulase negative staphylococci are the most common cause of neonatal sepsis in the neonatal intensive care unit. Van der Lugt, et al. [12] evaluated the use of rifampin in persistent coagulase-negative staphylococci bacteraemia in 137 infants with a coagulase-negative staphylococci infection. Main outcomes were the total duration of bacteraemia and the adequacy of vancomycin and rifampin therapy. Of 17/137 (8.0%) infants who developed a coagulase-negative staphylococci bacteraemia. Eighteen infants were treated with rifampin because of persistent bacteraemia. Duration of bacteraemia prior to rifampin therapy (8.0±3.6 days) was positively correlated (P-value < 0.001) to the total duration of bacteraemia (10.3±3.7 days). After starting rifampin therapy C-reactive protein levels of all infants declined and blood culture became sterile at 2.3±1.6 days. Vancomycin levels were not consistently measured in all infants, resulting in late detection of subtherapeutic trough levels. Rifampin may be effective in the treatment of persistent coagulase-negative staphylococci infections in infants.

The efficacy of rifampin in eliminating Staphylococcus aureus colonization was evaluated in a paediatric peritoneal dialysis population. Six children with documented nasal colonization were treated with rifampin and cloxacillin for 7 days [13]. Although antimicrobial therapy eliminated nasal carriage in all children, recolonization occurred in 66% children. Nasal colonization proved difficult to eradicate negative cultures documented in only 3 of 5 (60%) children after rifampin/cloxacillin therapy. Although Staphylococcus aureus carriage is a risk for Staphylococcus aureus infections, efforts to eradicate carriage with rifampin are hindered by rapid recolonization.

Correct timing and technique of neural tube defect repairs significantly decrease the morbidity and mortality rate of neuronal tube defect cases. However, infections related to surgery are still common. Demir, et al. [14] investigated the effects of topical rifampin combined with routine prophylaxis in infants with open neural defects. Thirty infants were started on topical rifampin before surgery and 56 infants did not receive rifampin. In the postoperative period, meningitis/ventriculoperitoneal shunt infections and surgical site infections were observed in 6.7% and 3.3%, respectively, of the experimental group treated with topical rifampin. Meningitis/ventriculoperitoneal shunt infections and surgical site infections were observed in 37.5% and 21.4%, respectively in the control group. External ventricular drainage not using topical rifampin were identified as important relative risk factors for meningitis/ventriculoperitoneal shunt infections (relative risk = 19.3, 95% confidence interval = 3.5 - 105.3; P-value = 0.001; relative risk = 18.1, 95% confidence interval = 2.4 - 137; P-value = 0.005, respectively). Flap transposition, cerebrospinal fluid leaks, not using topical rifampin were identified as relative risk factors for surgical site infections (relative risk = 22.2, 95% confidence interval = 4.8 to102; P-value = 0.042). No local or systematic adverse effects resulting from the use of rifampin was observed. The use of topical rifampin is an easy and effective method for reducing surgical site infections related to neural tube defect surgery.

Treatment of acute bacterial meningitis in children with bactericidal antibiotics causes cell wall lyses and a surge in inflammation cascade, which in turn contributes to neuronal damage and morbidity. In a pilot study, in children with bacterial meningitis, Uppal, et al. [15] studied markers of inflammatory response and neuronal damage in two groups of children with bacterial meningitis; one group received rifampin pre-treatment with ceftriaxone and the other group received ceftriaxone alone. Forty children with bacterial meningitis, aged 3 months to 12 years, were randomly assigned to receive either a single rifampin dose of 20 mg/kg 30 min before ceftriaxone or ceftriaxone alone was given. The primary outcome variables were cerebrospinal concentration of tumour necrosis factor α, S100B and neuron-specific enolase on days 1 and 5, and the secondary outcome variables were the values of tumour necrosis factor α and interleukin 6 in serum on 1 to 5 years; hearing test and neurologic sequelae at 3 months after recovery from the illness were performed. Children in rifampin pre-treatment group had significantly lower

cerebrospinal fluid tumour necrosis factor α concentrations [median and interquartile range were 15.5 (7.2 to 22.0) versus 53.0 (221 to 804) pg/l, P-value = 0.019] and S100B [median and interquartile range were 145 (54.7 to 450) versus 447 (221 to 804) pg/ml, P-value = 0.048] and neuron-specific enolase [median and interquartile range were 8.6 (5 to 14.7) versus 18.2 (7.0 to 28.7 ng/ml, P-value = 0.035] on day 5 when compared with ceftriaxone alone group. The rifampin treated group had also reduced morbidity and neurologic sequelae; however, were not statistically significant. Pretreatment with a single dose rifampin 30 min before ceftriaxone administration reduced the cerebrospinal fluid concentrations of inflammation markers and neuronal damage in children with bacterial meningitis.

Campos, et al. [16] studied the efficacy of rifampin prophylaxis in reducing the prevalence of ampicillin- and chloramphenicol-resistant Haemophilus influenzae type b in four day care facilities after each center had individual cases of invasive infections (2 meningitis, 1 pneumoniae, and 1 cellulites) caused by multiply-resistant organisms. Rifampin was given in a single intravenous daily dose of 20 mg/kg for 4 days. Cultures were taken pre-treatment and 10 days after the last dose of rifampin. A total of 174 children and 27 adults were included in the study. These authors identified a total of 55 nasopharyngeal carriers; 45 received rifampin and 10 refused treatment. On the 10-day follow-up, cultures in the second sample 95.5% and 20%, respectively, of treatment and untreated children were no longer colonized with Haemophilus influenzae type b (P-value < 0.001, Fisher's exact test). Rifampin was successfully to reduce the prevalence of multiply resistant Haemophilus influenzae type b carriers attending day care centers. Rifampin is recommended as a prophylactic treatment for intimate contacts of young children who developed invasive infections of Haemophilus influenzae type b [17]. A day course of oral rifampin (20 mg/kg per day, not to exceeded 600 mg as a maximum single daily dose) was 95% effective in eradicating pharyngeal colonization with Haemophilus influenzae type b, thus efficiently reducing the risk of both associated children and recurrent illness in index children aged < 2 years. One hundred and sixty-three children with Haemophilus influenzae type b infection were treated with rifampin; prophylaxis was recommended for 128 children. Throat swabs were obtained from contacts prior to therapy, and repeated cultures were obtained on 7 and 10 days after completing therapy with rifampin. Thirty-four families received rifampin for 2 days and 34 families received rifampin for 4 days. This study revealed that 2-day therapy with rifampin is effective as 4-day treatment in the eradicating Haemophilus influenzae type b pharyngeal colonization.

The efficacy of rifampin prophylaxis (20 mg/kg per day divided in two doses for 4 days) in children with invasive Haemophilus influenzae type b infection from household contacts of 38 children with invasive Haemophilus disease was evaluated in a prospective, placebo-controlled fashion [18]. At the end of treatment, efficacy was 91.5% in children aged < 5 years and 100% in those children aged > 5 years. Haemophilus influenzae type b carrier rate of rifampin-treated children was significantly smaller than that of placebo-treated children one month after prophylaxis. However, 22% to 25% of rifampin-treated children aged < 5 years were colonized with Haemophilus influenzae type b, based on cultures obtained one to four weeks after prophylaxis, while approximately 75% of placebo-treated carriers were still positive at this time.

Fifty children with tuberculosis have been treated with rifampin at an oral dose of 10 to 20 mg/kg, and isoniazid 10 to 20 mg/kg daily for one month followed by 10 to 20 mg/kg of rifampin and 20 to 40 mg/kg of isoniazid twice a week for another 8 months [19]. Children ages ranged from 4 months to 15 years with a median age of 3 years. A presumptive diagnosis of tuberculosis was made on the basis of 10 mm or more of induration to 5 TU of purified protein derivative and a chest film or other findings compatible with tuberculosis. Three children had extra-pulmonary disease (2 had cervical adenitis, and 1 had tuberculosis arthritis). Of 47 children with pulmonary disease, 32 (68.1%) were asymptomatic. The results were excellent. Symptoms cleared in 1 to 2 months. Most pulmonary infiltrates were cleared by 10 months, but adenopathy rarely cleared in less than 2 years. Drug toxicity occurred in only one child (vomiting of rifampin). This treatment appears to be safe, effective, inexpensive, short and simple enough to ensure cooperation or to allow personnel to administer drugs directly to children from socially disorganized families.

Children aged < 5 years have the highest age-specific rate of progression from latent tuberculosis infection to active disease. Since 2012, a 4-month regimen of daily rifampin has been the standard recommendation for paediatric patients with latent tuberculosis infection. Using univariate and multivariate analyses, Gaensbauer, et al. [20] compared treatment completion rates between 4-month oral rifampin and 9-month isoniazid regimens for all paediatric patients treated with rifampin for latent tuberculosis infection, and assessed the influence of clinical and demographic characteristics on successfully completion of the 2 regimens. There were 395 children treated with 4 month rifampin and 779 children treated with 9-month isoniazid. Completion rates overall were significantly higher for 4 month rifampin than 9-month isoniazid (83.5% versus 68.8%, P-value < 0.001). Drug toxicity leading to treatment non-completion was low in both groups (1.5% in rifampin-treated children and 0.7% in isoniazid-treated children, P-value = 0.23), and no children progressed to active tuberculosis in either cohorts. The isoniazid treated children were more likely to fail treatment completion because of barriers potentially related to the longer duration of treatment such as relocation or loss to follow-up. Paediatric patients were significantly more likely to complete the latent tuberculosis treatment infection treatment using 4-month rifampin than with 9-month isoniazid regimen. Better completion rates of 4-month rifampin may increase the efficacy to tuberculosis prevention and decrease demand on public health resources.

One hundred and seventeen children with pulmonary tuberculosis underwent treatment with an oral 6-month daily

regimen of rifampin (15 mg/kg per day) and isoniazid (10 mg/kg per day) [21]. The treatment was completed in 97 children (83%). The mean weight gain during therapy was 2,147 gram. There was an excellent clinic-radiologic response to the treatment, and improvement in chest roentgenograms was observed in all children at the end of therapy. No relapses occurred among the children followed for an average of 21 months. The present results indicate that the treatment of primary pulmonary tuberculosis in children with a combination of oral rifampin and isoniazid daily for 6 months is efficacious and does not result in any relapse.

Paediatric tuberculous meningitis is a highly morbid, often a fatal disease. Standard treatment includes isoniazid, rifampin, pyrazinamide, and ethambutol. Current rifampin dosing achieves low cerebrospinal fluid concentrations. In adult trials, higher-dose of rifampin and/or fluoroquinolone reduced mortality rate and disability. To estimate optimal dosing of rifampin and levofloxacillin for children, Savic, et al. [22] compared plasma and cerebrospinal fluid pharmacokinetics and outcomes data from adult tuberculosis meningitis trials plus plasma pharmacokinetic data from children. A population pharmacokinetic/pharmacodynamic model using adult data defined rifampin target exposures ($AUC_{0\text{-}24\ hours}$ = 92 mg.h/l). Levofloxacin targets and rifampin paediatric drug disposition information were literature-derived. To attain target rifampin exposures, children require daily doses of at least 30 mg/kg orally or 15 mg/kg intravenously. From paediatric population pharmacokinetic model, oral levofloxacin doses need to attain exposure targets of 19 to 33 mg/kg. The present study provides data-driven guidance to maximize paediatric tuberculous meningitis treatment.

A cluster of toxic reactions among children inadvertently given excessive doses of rifampin for chemoprophylaxis of invasive Haemophilus influenzae type b disease in a day-care center was investigated [23]. In all 19 children, who received five times the therapeutic dose of rifampin, dramatic adverse reactions developed. A striking “glowing” red discoloration of the skin and facial or periorbital edema was found to be the hallmarks of rifampin toxicity. These clinical signs of acute toxicity contrast sharply with the adverse side effects of rifampin reported with therapeutic doses.

Concomitant administration of rifampin and isoniazid induces hepatotoxicity in children

The incidence and degree of liver injury was prospectively evaluated in 44 children aged from 4 months to 14 years (mean age, 4.5 years) treated for tuberculosis with oral isoniazid at a dose of 15 to 20 mg/kg per day and rifampin 15 mg/kg per day [24]. None of the patients had hepatic dysfunction before initiation of treatment. Elevation of the serum alanine aminotransferase (ALT) concentration (> 100 units) occurred in 36 children (82%). One child with an increase in ALT value had coincidental infection with hepatitis B. The incidence of hepatotoxicity did not correlate with the patient’s age or sex. Fifteen of 36 children (36%) developed clinical hepatitis with jaundice. In 7 children (15.9%), liver enlargement and prolongation of the prothrombin time were also observed. In all, but one child, liver dysfunction was recognized 6 to 30 days (mean, 14 days) after start of treatment. Biochemical signs of hepatic injury in 35 surviving children (79.5%) regressed completely without alteration of the isoniazid-rifampin regimen in 22 children (63%). These results suggest the possibility that hepatocellular damage may due to the effect of tubercle bacilli products liberated in the liver after their destruction by antituberculosis drugs. However, the high rate of hepatotoxic reactions warms that the the isoniazid dose of 10 mg/kg per day should not be exceeded when that drug is combined with rifampin.

Fifteen of 18 children (83%) treated with rifampin and isoniazid showed a rise in ASAT values and 11 (61%) had a rise in ALAT values exceeding 29 U/L [25]. Seven children with maximal ASAT values between 40 and 100 U/L were treated without any changes in the regimen and the transferases normalized later in the treatment. Six out of eight children (75%) with ASAT values over 100 U/L were allowed a three-week pause in their therapy, one was given the same dose of rifampin, and in one the treatment was discontinued entirely. The therapy was discontinued in an additional three children because of a second high rise in the transaminase values. Liver injury can occur at any time during treatment, and thus makes continuous follow-up tests necessary.

To estimate rates of hepatotoxicity in the US among children treated for tuberculosis, O’Brien, et al. [26] conducted a retrospective survey of health department. These authors received 874 reports suitable for analysis of children treated during 1977 to 1979. A total of 16 hepatotoxicity reactions were reported; 14/430 (3.3%) children receiving isoniazid and rifampin had a hepatotoxic reaction, which approximates the rate seen in adults taking these drugs. Half of reactions occurred during the first 10 weeks of treatment. Because the likelihood of hepatotoxicity may be increased with higher doses, limiting the dose of isoniazid to 10 mg/kg and rifampin to 15 mg/kg may help minimize hepatotoxic reactions. Because more serious diseases, especially disseminated tuberculosis, may further increase the risk of hepatotoxicity, close monitoring of such children receiving isoniazid and rifampin should help minimize serious hepatotoxicity. Routine biochemical monitoring may not be necessary for all children, e.g. those with forms of disease and those with normal pre-treatment liver function who are treated with lower drug doses.

Several cytochromes P-450 enzymes are induced by rifampin

The Rifampin is a potent inducer of the following P-450 enzymes: CYP24A1, CYP3A4, CYP2B6, CYP3A, CYP2C9, CYP1A2, CYO2C9, CYP2C19, and CYP1A2 CYP24A1 [27 – 30).

Metabolism of rifampin in children

Koup, et al. [31] studied the metabolism and pharmacokinetics of rifampin in children. The metabolites of rifampin are 25-O-desacetylrifampicin and 3-formylrifamycin SV. 25-O-desacetylrifampicin is the main metabolite. Twenty

children with normal hepatic function and normal renal function were enrolled. Nineteen children were aged 3 months to 2.9 years, and a child was aged 14 years. Eighteen children had documented infection with Haemophilus influenzae type b (16 meningitis, 1 periorbital cellulites, and 1 epiglottises). A child received rifampin for tuberculosis, and another child was treated with rifampin for treatment of a staphylococcal ventriculoperitoneal shunt infection. Children were studied early during their course of therapy with rifampin. Sixteen children were studied within the first 24 hours of rifampin therapy, and four children were studied after 2 and 6 days of therapy. This drug was administered intravenously as a 30-min infusion. The interval between intravenous and oral treatment of rifampin was 24 hours in 17 children and 2 to 7 days in 3 children. Intravenous doses preceded the oral rifampin treatment in 18 children, and in 2 children, rifampin intravenous and oral treatment was administered at the same time of day. Three to five serum samples were obtained following the drug administration. Sampling began 0.5 hours after the end of rifampin infusion and continued over a 6 to 8 hours period of time. The serum was separated from blood and used for rifampin concentration determination.

The extent of absorption (F) was determined according to the following relationship:

$$F = \frac{\text{AUC i.v. . Dose p.o.}}{\text{AUC i.v. . Dose p.o.}}$$

Where: AUC = area under the concentration-time curve, p.o. = concentration of rifampin after oral dose, i.v. = concentration of rifampin after intravenous administration.

The rifampin intravenous administration was well tolerated with no side effects. No evidence of gastrointestinal upset was observed after oral administration of rifampin. The mean elimination half-life were 25-O-desacetylrifampicin following intravenous administration of rifampin was 2.66±1.25 hours following oral administration. The elimination half-life of 25-O-desacetylrifampicin following intravenous administration of rifampin was 3.60±1.82 hours and was significantly longer (r = 4.25, P-level < 0.001) than that of rifampin after oral administration. The extrapolated end of infusion concentration of rifampin was corrected for the standard dose of 300 mg/m^2 and was 27.4±12.1 µg/ml. This value was significantly higher than the dose corrected peak concentration observed following oral administration (9.1±4.5 µg/ml, r = 8.68, P-value < 0.0001). The time to peak rifampin following the oral administration was 2.0±0.88 hours. The extrapolated peak rifampin concentrations following intravenous administration did not correlate with peaks observed following the oral administration. There was a week correlation between the AUCs observed following oral and intravenous administration (r = 0.636, P-value < 0.01). Table 1 summarizes the pharmacokinetic parameters of rifampin after intravenous and oral administrations in 20 children.

Pharmacokinetics of Rifampin in Infants

Pharmacokinetics of rifampin in one extreme premature infant with congenital tuberculosis

The incidence of women of child-bearing age presenting with tuberculosis in London is estimated 252/100.000 (0,52%) deliveries [32]. In the case of anti-tuberculous agents, the major risk is hepatotoxicity and three agents identified by the WHO as essential, isoniazid, rifampin and pyrazinamide, to carry such a risk. In preterm infants where biliary elimination is immature, extra care is needed with dosing. A woman of Somali origin presented at 26 + 2 weeks' gestation with a 3-month history of cough, night sweats and weight loss. She had smear positive Mycobacterium tuberculosis in sputum cultures. The high mortality is associated with congenital tuberculosis in premature infants. The infant was started with a daily treatment with intravenous rifampin (5 mg/kg), isoniazid (5 mg/kg) and amikacin (15 mg/kg) for congenital tuberculosis. In this infant, the peak and trough concentrations of rifampin were 2.4 and < 0.2 µg/ml, respectively, after intravenous administration, and 4.7 and 0.3 µg/ml, respectively, after oral administration.

Pharmacokinetic of rifampin in preterm and term infants

Pullen, et al. [33] studied the pharmacokinetics of rifampin and its mean metabolite 25-O-desacetylrifampicin in the plasma of 123 infants with mean gestational age, post-conceptional age, postnatal age and body weight of 29.9±4.1 weeks, 33.5±5.0 weeks, 24.8±13.4 days, 1,580±1,140 gram, respectively. Rifampin was infused intravenously over 30 min at a dose of 5 to 10 mg/kg once a day. Infants also received vancomycin at a dose of 10 to 20 mg/kg with an interval of 6 to 24 hours. Twelve infants were treated with a combination therapy of intravenous flucloxacillin and gentamicin for 2 to 9 days (mean, 4.5±2.3 days) preceding rifampin therapy. However, this combination therapy turned out to be unsuccessful in all 12 infants and therapy with intravenous vancomycin was started. After 3.3±2.6 days (range, 0 to 8 days), intravenous rifampin was added. The concentrations of rifampin and its rifampin and its mean metabolite 25-O-desacetylrifampicin were measured the plasma samples of 123 infants. Rifampin peak and trough

Table 1: Rifampin pharmacokinetic parameters in 20 children aged 3 months to 2.9 years after rifampin intravenous and oral administration of rifampin. The figures are the mean±SD, by Koup, et al. [31].

	Intravenous administration					Oral administration		
N = 20	Elimination half-life (hours)	Distribution volume (L/m^2)	Clearance (L/h/m^2)	Peak concentration (µg/ml)[a,b]	25DR/R AUC	F	Peak concentration (µg/ml)[b]	25DR/R AUC
Mean	2.25	11.43	3.68	27.4	0.23	0.50	9.1	0.19
SD	0.64	3.83	1.32	12.1	0.13	0.22	4.5	0.09

25DR = 25-O-desacetylrifampicin. R = rifampin. AUC = area under the concentration-time curve.
F = bioavailability after oral administration. [a]Back extrapolated to end of 0.5 hours infusion. [b]Corrected for a dose of 300 mg/m^2.

concentrations after the second dose were 4.66±1.47 µg/ml (range, 2.06 to 6.87 µg/ml) and 0.21±0.20 µg/ml (range, 0.01 to 0.75 µg/ml), respectively, after a rifampicin dose of 8.5±2.1 mg/kg. A significant linear relationship between rifampin dose and rifampin peak plasma concentrations was found (r = 0.556, P-value = 0.009). Plasma concentrations of rifampin and 25-O-desacetylrifampicin were lower after 2 weeks of rifampin therapy due to cytochromes P-450 induction. Table 2 shows the pharmacokinetic parameters of rifampin in 8 infants at the beginning and after two weeks of rifampin therapy.

Smith, et al. [34] enrolled 27 preterm and term infants, and all received at least a dose of rifampin intravenously based on their gestational and postnatal ages. Infant's demographic characteristics are shown in table 3. Table 4 shows the simulated exposure to rifampin by postnatal age group using different dosing regimens. The 1,000 virtual patients generated from pharmacokinetic simulations matched the infant demographic data. A dose of 8 mg/kg once-daily resulted in $AUC_{0\text{-infinite}}$ at steady-state ≥ 55.2 µg.h/l in 92.3% of simulated infants < 14 days of postnatal age with a mean±SD $Cmax_{ss}$ of 8.3±1.8 µg/ml. A dose of 15 mg/kg once-daily resulted in $AUC_{0\text{-infinite}}$ at steady-state ≥ 55.2 mg.h/ml in 91.5% of infants ≥ 14 days of postnatal age with a mean $Cmax_{ss}$ of 13.2 µg/ml. Overall, ≥ 90% of virtual infants with the proposed dosing achieved rifampin exposures comparable to adults treated for Staphylococci infections. Infants aged < 12 months with high-burden tuberculosis and HIV are at high of Mycobacterium tuberculosis exposure infection disease, and mortality rate, emphasizing the need for rigorous evidence from pharmacokinetic studies to guide optimal antituberculosis treatment in this vulnerable population [35]. Up to 50% of infants exposed to rifampin for infection due to Mycobacterium tuberculosis will develop tuberculosis disease in the absence of preventive therapy, with up 39% of these progressing to severe pulmonary or disseminated disease. A 4-fold increase in mortality rate is present among infants with maternal HIV-

Table 2: Differences between rifampicin mean pharmacokinetic parameters at the beginning and after two weeks of rifampicin therapy in 8 infants with postnatal age of 24.8±13.4 days and body of 1,800±1,140 gram. The figures are the mean±SD, by Pullen, et al. [33].

Pharmacokinetic parameters	Beginning of rifampicin therapy	After two weeks of rifampicin therapy	Statistical analysis: paired-sample t test
Rifampicin first-order elimination constant ($hours^{-1}$)	0.13±0.06	0.18±0.06	- 1.55 (P-value = 0.165)
Distribution volume corrected for body weight (L/kg)	1.77±0.31	2.33±1.19	- 1.30 (P-value = 0.236)
Total body clearance corrected for body weight (L/kg/h)	0.22±0.07	0.36±0.15	- 3.74 (P-value =0.007)
Elimination half-life (hours)	6.1±1.9	4.4±1.7	1.91 (P-value = 0.099)

Table 3: Demographic characteristics of infants. The figures are the mean and range, by Smith, et al. [34]

	Gestational age < 32 weeks		Gestational age ≥ 32 (weeks)		
	Postnatal age < 14 days (N = 11)	Postnatal age > 14 days (N = 6)	Postnatal age < 14 days (N = 4)	Postnatal age > 14 days (N = 1)	Total days (N= 22)
Gestational age (weeks)	27.0 (24 - 30)	25.5 (23 - 28)	38.5 (37 - 41)	37.0	27.5 (23 - 41)
Postnatal age (days)	2.0 (0 - 12)	33.5 (21 - 56)	5.5 (2 -12)	55.0	7.5 (0 - 56)
Postmenstrual age (weeks)	27.6 (29.9 (24.3 - 31.3)	29.9 (27.0 – 33.3)	39.93 (37.3 – 41.3)	44.8	29.9 (24.3 - 44.9)
Body weight (grams)	1,100 (650 -1,700)	1.105 (810 - 1.680)	3,993 (3,390 -3,700)	6,000	700 (300 - 700)

Table 4: Simulated exposure to rifampin by postnatal age group using different dosing regimes. The figures are the mean±SD and range, by Smith, et al. [34]

Rifampin dose (mg/kg)						
	8	8	10	12	15	20
Hours after rifampin dosing						
	24	12	10	12	15	24
Postnatal age < 14 days						
[a]$Cmax_{ss}$ (µg/ml)	8.3±1.8	16.2±4.4	10.4±2.3	12.5±2.7	15.6±3.4	20.7±4.5
[b]$AUC_{0\text{-infinite}}$ (µg.h/ml)	84.8 (30.2 - 193.0)	172 (70.0 – 405)	106 (37.8 - 41.3)	127 (45.3 - 289)	156 (49.5 - 361)	212 (75.5 - 482)
[c]TA (%)	92.3	100	97.8	99.1	99.7	100
Postnatal ≥ 14 days						
[a]$Cmax_{ss}$	6.9±1.6	8.2±1.7	8.6±2.0	10.3±2.4	13.2±3.3	17.1±3.6
[b]$AUC_{0\text{-infinite}}$ (µg.h/ml)	39.2 (151 - 96.7)	68.1 (30.0 - 141)	49.0 (18.9 - 120)	58.8 (22.7 - 145)	72.6 (28.1 - 166)	97.9 (37.8 - 241)
[c]TA (%)	8.9	76.2	30.7	56.7	91.5	97.8

[a]Cmax = Rifampin peak concentration at steady-state. [b]$AUC_{0\text{-infinite}}$ median (min - max). [c]TA% target attainment rate = (number of subjects with $AUC_{0\text{-infinite}}$ > 55.2 µg.h/ml total number of subjects in the group) x 100.

coinfection and tuberculosis. In 2010, the WHO revised paediatric tuberculosis dosing guidelines by recommending considerably higher doses of first-line antituberculosis drugs in children, rifampin 15 to 20 mg/kg versus 8 to 12 mg/kg was recommended. These guidelines were based on evidence from pharmacokinetic studies. HIV-infected and HIV-uninfected infants were eligible after at least 2 weeks of intensive phase first-line antituberculosis treatment. Pharmacokinetic sampling was deferred in critically ill infants with a body weight < 1,800 gram. Rifampin was a granulate for suspension (100 mg/5 ml); manufactured by Eremfat, Germany, and is referred to as formulation 1. A second rifampin suspension R-cin (100 mg/5 ml) was manufactured by Aspen Pharmacare, South Africa, and registered by Medicines Control Council and was referred to as formulation 2. Infants were fasted for 2 hours prior to rifampin dosing to facilitate improved absorption. A nasogastric tube was inserted to ensure accurate dosing. An indwelling peripheral venous catheter was inserted, and a predose (0 hour) blood sample was obtained for rifampin concentration determination and for albumin and alanine aminotransferase (ALT) levels. Five blood samples of 0.6 ml were collected at 1, 2, 4, 6, and 8 hours post-dose. Plasma was separated from blood and used for rifampin concentration determination. Cmax obtained at Tmax was recorded directly from the concentration-time curve. The Cmax, $AUC_{0\text{-infinite}}$, and the elimination half-life were compared by the clinical covariates of age at time of pharmacokinetic study evaluation (0 to 6 versus 7 to 12 months). Prematurity (premature, < 37 weeks, versus term), HIV status, ethnicity (black versus mixed race), and gender as well as, for rifampin pharmacokinetic parameters only, by rifampin formulation and rifampin dose of 15 to 20 mg/kg. Fifteen of 39 (38.5%) infants were premature. Twenty-two (56%) infants were born to HIV-infected. None of the 39 infants achieved the target adult peak rifampin concentration of ≥ 8 µg/ml. Table 5 provides the rifampin pharmacokinetic parameters comparisons for Cmax, $AUC_{0\text{-infinite}}$ and the elimination half-lifefor Cmax, $AUC_{0\text{-infinite}}$, and the elimination half-life by formulation and rifampin dose are also displayed.

Pharmacokinetics of rifampin in infants and children

There is the need to evaluate the pharmacokinetics of rifampin upon which to base rifampin dosages in infants and children. McCracken, et al. [36] compared the bioavailability of three formulations of rifampin in infants and children. The study included 38 infants and children, 19 were infants aged 6 to 58 months (mean, 26 months), weight range was 6.6 to 17.1 kg (mean, 12.4 kg), the average body surface was 0.53^2 meter and 19 were children. A rifampin single oral dose of 10 mg/kg was given to children. All pharmacologic studies were conducted after 10 to 12-hour fasting, and rifampin was withheld for at least 15 hours. Rifampin in an 85% sucrose suspension that contained 10 mg/ml of rifampin power was given to patients (study group A). This was prepared by placing the contents of one capsule (300 mg rifampin) in 30 ml of supalta. The above suspension, admixed with two tablespoons of applesauce, was given to 12 patients (study group B). In five children the rifampin powder was divided into thirds and added to two table spoons applesauce (study group C). The dosage in this group of children was estimated to be 8 to 12 mg/kg. Blood samples were obtained immediately before and 0.5, 1, 2, 4,

Table 5: Rifampin pharmacokinetic parameters of rifampin in 39 infants with tuberculosis and HIV-infected. The body weight was < 1,800 gram. The figures are the mean±SD and range, by Bekker, et al. [35].

	Recommend dose by the WHO (mg/kg)	Actual dose (mg/kg)	Cmax (µg/ml)	Tmax (IQR) (hours)	$AUC_{0\text{-infinite}}$ (µg.h/ml)	Half-life (hours)	Clearance/F (L/h/kg)
Formulation 1 (N = 14)	15 (15 - 20)	12.91 (10.13-18.8)	4.13 (0.65 - 7.96)	2.0 (2.0 - 2.0)	16.77 (1.59-33.01)	2.07 (1.10 - 4.06)	1.55 (0.37 - 7.07)
Formulation 2 (N = 25)		16.75 (10.1-20.51)	2.22 (0.59 - 6.94)	2.0 (2.0 - 2.0)	9.52 (1.78-33.0)	2.04 (1.06 - 3.93)	3.14 (0.58-16.68)

F = fraction absorbed.

Table 6: Rifampin (10 mg/kg) serum concentrations and pharmacokinetic values in 19 infants with a mean age and a body weight of 26 months and 12.4 kg, respectively, and 19 children with average body surface was 0.53^2 meter. The figures are average±SEM and range, by McCracken, et al. [36].

		Time after the dose (hours) Serum concentrations (µg/ml) at different times after the dose							
Study Group	Number of patients	0.5	1	2	4	6	8	Elimination half-life(hours)	AUC (µg.h/ml)
A: Suspension in sucrose	21	7.6±0.78 (0.4-13)	10.7±0.81 (4.6-17.2)	9.2±0.7 (3.9-17.6)	6.1±0.62 (1.8-14.4)	4.2±0.45 (1.2 - 8.0)	1.9±0.56 (0.5-3.4)	2.9	56
B: Suspension in applesauce	12	4.5±1.01 (0.4-12.8)	8.9±1.29 (2.6-14.3)	6.2±0.70 (2.9-10.4)	3.2±0.43 (0.9-3.9)	1.9±0.27 (0.7-3.9)	1.9±0.25 (1.1-2.5)	2.9	38
C: Powder in applesauce	5	9.1±2.9 (2.7-21.0)	11.5±2.3 (5.2-21.0)	8.8±1.1 (5.2-12.8)	6.5±0.91 (3.4 – 10.0)	3.7±0.61 (1.5-5.6)	2.1±0.33 (2.1 – 0.33)	2.9	57
*P-Value		0.5634	0.6193	< 0.05**	0.044§	0.0028&	0.4056	___	___

*Tukey-Kramer Multiple Comparisons Test.
Level of difference among the three study groups: ** A versus B < 0.05, A versus C > 0.05, B versus C > 0.05. §A versus B <0.01, A versus B > 0.05, B versus C < 0.05. &A versus B < 0.01, A versus B > 0.05, B versus C > 0.05.

and 6 hours after rifampin dosing. Specimens were obtained at 8 hours in some patients. Saliva and tears were collected in capillary pipettes at 2, 4, and 6 hours after the dose. A single urine sample was obtained at random times during the six-hour period. Data were analyzed using the Student's t-test and Barrett's test for equal variance. When significant differences were found, the two groups were compared using the Mann-Whitney U-test. The level of difference among the three study groups was tested by the Tukey-Kramer Multiple Comparisons Test. Rifampin pharmacokinetic studies were performed in 19 infants and 19 children. Serum concentrations, half-life, and AUC values for the three study groups are shown in table 6.

Pharmacokinetics of rifampin in children with tuberculosis with and without HIV-coinfection

Thee, et al. [37] studied the pharmacokinetics of rifampin in 11 children aged 1.09+0.49. Rifampin was administered orally at doses of 10 and 15 mg/kg. After a dose of 10 mg/kg, Cmax, Tmax and AUC were 6.36 µg/ml (range, 4.45 to 8.27), 1.49 hours (range, 1.07 to 1.91), 17.78 µg.h/ml (range, 12.81 to 22.76), respectively. After a dose of 15 mg/kg, Cmax, Tmax, and AUC were 11.9 µg/ml (range, 8.71 to 14.67), 1.54 hours (range, 1.16 to 1.93), and AUC was 36.95 µg.h/ml (range, 27.64 to 46.25), respectively. In these two dosages, the P-value of Cmax was 0.005, and the P-value of the AUC was 0.006. No difference was observed for Tmax in these two groups. The HIV status influenced the Cmax of rifampin at a dose of 35 mg/kg. The following results are expressed as the mean and the 95% confidence interval. The mean of Cmax was 1.08 µg/ml (range, 0.79 to 1.37) in not-HIV-coinfected children (N = 15), and 1.50 µg/ml (range, 1.39 to 1.61) in HIV-infected children (N = 5), P-value = 0.009. No difference in Cmax was observed after rifampin doses of 10, 15, and 25 mg/kg. The HIV status did not influence AUC. No difference was observed for the type of tuberculosis: pulmonary and extrapulmunary, for gender, and nutritional status at the various rifampin doses tested.

Schaaf, et al. [38] investigated the effects of HIV status on the pharmacokinetics of rifampin in children. Twenty-one children with a mean age of 3.73 years were HIV-infected and 33 children with a mean age of 4.05 years were not-HIV-coinfected. Rifampin was administered at a dose of 60 mg. Cmax, Tmax, and $AUC_{0\text{-}6\ hours}$ were 4.91±2.03 µg/ml, 1.80±0.87 hours, and 14.88±7.43 µg.h/ml, respectively, in children HIV-infected (N = 21). These values were 6.92±5.88 µg/ml, 1.67±0.93 hours, and 18.07±1.52 µg.h/ml respectively, in children not HIV-coinfected (N = 33). Pharmacokinetic values in children not-HIV-infected and in children HIV-coinfected were not statically different.

Antwi, et al. [39] explored the pharmacokinetics of rifampin in 59 children HIV-infected and 72 children were not-HIV-infected, all children had tuberculosis, 85 children had pulmonary tuberculosis and 28 children had extrapulmunary tuberculosis. Twenty-four children were aged < 2 years and 89 children were aged < 5 years. Mean oral rifampin dose was 15.8 mg/kg (range, 13.6 to 18.8). Cmax, Tmax, AUC0-8 hours, clearance and the distribution volume were normalized for the bioavailability. Cmax, Tmax, AUC0-8 hours, distribution volume, and the clearance were 7.65 µg/ml (range, 5.2 to 9.1), 2.01 hours (range, 1.13 to 2.10), AUC0-8 hours 30.49 µg.h/ml (range, 21.93 to 38.44), clearance 0.11 L/h/kg (range, 0.08 to 0.14)" and the distribution volume 1.37 L/kg (range, 1.08 to 2.05) were found in children not HIV-infected. Rifampin pharmacokinetic parameters in children HIV-coinfected were as follow: Cmax 5.83 µg/ml (range, 3.71 to 8.26), Tmax 1.83 hours (range, 1.02 to 2.08), AUC0-8 hours 24.88 µ.h/ml (range, 15.95 to 35.27), clearance 0.12L/h/kg (range, 0.09 to 0.16)" and the distribution volume 1.37 L/kg (range, 0.73 to 1.19). Cmax, AUC0-8 hours, and the clearance were statistically different in children not-HIV-infected than in children HIV-coinfected. for rifampin, dose, sex, and AUC0-8 hours HIV infection status jointly influenced Cmax (r2 = 0.41; P-value = 0.001), AUC0-8 hours (r2 = 0.17; P-value < 0.001), and the clearance (r2 = 0.26; P-value < 0.001).

Kwara, et al. [40] investigated the rifampin pharmacokinetics in children without HIV-infection. Twenty-nine children were aged < 5 years and 33 children were aged ≥ 5 years. Forty-eight (77.4%) children had pulmonary tuberculosis and 14 (22.6%) children had extrapulmunary tuberculosis. Dispersible tablets of rifampin/isoniazid (60/60 mg were administered to children on exclusive breastfeeding were allowed to a breakfast 10 to 12 hours throughout the study. Blood samples were collected at times 0 predose, 1, 2, 4, and 8 hours post-dose. The plasma was separated from blood and used for rifampin concentration determination. These authors did not distinguish children with HIV-infection from those without HIV-infection and the pharmacokinetic parameters of rifampin for all children are summarized in table 7.

Rifampin pharmacokinetics in children not-HIV-infected

Arya, et al. [41] studied the pharmacokinetics of rifampin in 20 children aged 5 to 12 years with newly diagnosed pulmonary or lymph node tuberculosis. Children overnight fasting, received a rifampin single oral dose at 6 am. Children weighing 11 to 17 kg were given a rifampin single oral dose of 150 mg, while those weighing 12 to 25 kg received a rifampin single oral dose of 225 mg. A standard breakfast and lunch were given respectively 2 hours and 6 hours after rifampin administration. Venous blood samples were collected at 1, 2, 3, 4, 6, 8, and 12 hours, plasma was separated from blood and used for rifampin concentration determination. The demographic data of the children and the rifampin pharmacokinetic parameters are expressed as the mean±SD. The age was 9.8+1.23 years, the weight was 22.5±4.3/kg, the dose was 9.95±0.97 mg/kg, Cmax was 6.32±0.67 µg/ml, Tmax was 3.42±0.51 hours, $AUC_{0\text{-}12\ hours}$ was 33.24±2.13 µ.h/ml.

Mukherjee, et al. [42] investigated the pharmacokinetics of rifampin in 42 children aged 2 to 5 years and in 212 children aged > 5 years who were newly diagnosed to have tuberculosis (pulmonary or extrapulmoary). Children without severe malnutrition (N = 202) and children with severe malnutrition (N = 64) were enrolled. The rifampin standard dose was 8 to

Table 7: Median (interquartile range) of steady-state pharmacokinetic parameters of rifampin in 62 children aged < 5 years and ≥ 5 years with tuberculosis and with or without HIV-coinfection. Rifampin was administered orally in dispersible tablets containing rifampin/isoniazid 60/60. Figures are the median and range, By Kwara, et al. [40].

Parameters	Number of children = 62
Cmax (µg/ml)	6.3 (3.5 - 8.8)
Tmax (hours)	2.0 (1.0 - 2.1)
$AUC_{0\text{-}8\ hours}$ (µg.h/ml)	26.0 (15.2- 36.1)
$AUC_{0\text{-}12\ hours}$ (µg.h/ml)	28.6 (16.5 - 39.6)
$AUC_{0\text{-}infinite}$ (µg.h/ml)	31.2 (16.9 - 43.6)
Distribution volume corrected for bioavailaty (L)	23.5 (14.7 - 40.0)
Distribution volume corrected for body weight (L/kg)	1.6 (1.2 - 2.5)
Clearance corrected for bioavailability (L/h)	7.7 (5.2 - 11.4)
Clearance corrected for body weight (l.h/kg)	0.5 (0.4 - 0.8)

12 mg/kg (N = 64) and the rifampin dose recommended by the WHO (recommended dose) was 15 mg/kg (15 to 20) (N = 63) were administered to children. Fixed dose combination was isoniazid 75 mg, rifampin 100 mg, and pyrazinamide 250 mg per dispersible tablet. Blood samples for pharmacokinetic study were collected 14 days (up to 30 days) after starting treatment in all children. The first blood sample (0 hours) was collected before administration of rifampin. Next three points of blood samples (0.5 ml) were obtained at 1, 2, and 4 hours. Breakfast was allowed one hour after treatment. The plasma was separated from blood and used for rifampin concentration determination. Rifampin plasma concentration 2 hours after standard dose was 11.2±1.0 mg/kg (standard dose) and 15.2±1.1 (recommended dose), P-value < 0.0001. After the administration of the standard dose Cmax, Tmax and $AUC_{0\text{-}4\ hours}$ were 10.4±7.2 µg/ml, Tmax 1.5±1.2 hours, $AUC_{0\text{-}4\ hours}$ 28.0±19.3 µg.h/ml, respectively. After the administration of the recommended dose, Cmax, Tmax, and $AUC_{0\text{-}4\ hours}$ were 12.0±6.1 µg/ml, 2±2 hours, and 30.5±17.1 µg.h/ml, respectively. In these two groups, Tmax was significantly different, P-value = 0.004.

Verhagen, et al. [43] studied the pharmacokinetics of rifampin in 30 children aged 1 to 15 years with tuberculosis. Blood samples were collected just prior and 2, 4, and 8 hours after witnessed rifampin intake. Plasma was separated from blood and used for rifampin concentration determination. Rifampin doses of 10 mg/kg (8 to 12, standard dose) and the dose recommended by the WHO 15 mg/kg (15 to 20, recommended dose) were administered to children. The actual dose of rifampin was 10.4 mg/kg (range, 9.3 to 11.2). $AUC_{0\text{-}24\ hours}$, Cmax, clearance and distribution volume were corrected for bioavailability, and the elimination half-life were 20.6 µg.h/ml (range, 4.4 to 94.2), 5.1 µg/ml (range, 4.1 to 6.2), 3.0 hours (range, 2.0 to 8.0), 8.1 L/h (range, 2.7 to 45.6), 16.0 (range, 5.8 to 57.4), 1.4 hours (0.4 to 4.6). Apart from Tmax, for which median and range was displayed, geometrical means and range were shown for all pharmacokinetic parameters.

Rifampin serum concentrations in children with tuberculosis

Thee, et al. [44] measured the serum concentrations of rifampin in 27 children aged 2 to 14 years. Children received a rifampin single oral dose10 mg/kg, after an adequate wash-out of 1 week. Rifampin tablets were administered on empty stomach after overnight fasting. Venipunctures were performed at 1, 2, 3, 4, 5, and 24 hours blood samples were collected and the serum collected and serum was separated from blood and used for rifampin determination. Rifampin serum levels were measured by a microbiological method

Table 8: Rifampin serum concentrations among children in different age groups after a single rifampin oral dose of 10 mg/kg. The figures are the mean±SD, by Thee, et al. [44].

	Age and number of children		
	2 - < 6 years (N = 7)	**6 - < 10 years (N = 11)**	**10 - 14 years (N = 9)**
Hours after ingestion	**Serum concentrations of rifampin (µg/ml)**		
1	0.8*	< 0.4*	1.2*
2	1.5*	1.5*	1.9*
3	5.2±1.9	4.1±1.3	5.2±0.2
4	4.7±0.9	5.7±1.1	5.1±0.6
5	3.9±0.6	5.1±0.9	4.3±0.7
7	2.1±0.3	3.0±0.4	2.1±0.2
24	< 0.4	< 0.4	< 0.4
Pharmacokinetic parameters of rifampin			
Cmax 6.1±1.2 µg/ml	6.5±1.2	7.1±1.2	6.6±0.8
Tmax [min-max] 3.8 hours [3.0-5.0]	3.8 [3.0-5.0]	4.0 [4.0-5.0]	3.5 [1.5-5.0]
Elimination half-life (hours)	2.1	2.6	1.9
$AUC_{0\text{-}7\ hours}$	20.15	21.75	22.75

*As variability was high, SD were not calculated.

based on the agar diffusion disk technique. A staphylococcus strain highly sensitive to rifampin was used as the indicator strain. Children were stratified into three based on age groups, and table 8 summarizes the rifampin serum concentrations and the rifampin pharmacokinetic parameters.

Rifampin concentrations in the cerebrospinal fluid

Nahata, et al. [45] measured the concentration of rifampin in the cerebrospinal fluid of 8 infants and children aged 1day to 18 years (mean age, 5.6+6.1). The shunt types were ventriculoatrial (N = 6), bilateral subdural peritoneal (N = 1), ventriculoperitoneal (N = 1), and post fossa peritoneal (N = 1). A single rifampin intravenous dose of 20 mg/kg (maximum, 1,200 mg) was administered one hour before surgery and the dose was infused over 60 min. Blood samples (0.3 to 0.5 ml) were collected by finger/heel at time 0 (prior to drug administration), and 0.5, 1.0, 2.0, 4.0, 5.0, and 8 hours after starting the infusion. A one ml of cerebrospinal fluid sample was collected at the time of shunt. Rifampin dose, rifampin peak serum concentrations, and cerebrospinal fluid rifampin concentrations, clearance, distribution, and the elimination half-life of rifampin in the cerebrospinal fluid are summarized in table 9. The cerebrospinal fluid concentrations exceed the MIC_{90} of rifampin against staphylococci by at least 150-fold. A marked (two-fold) variation was observed in pharmacokinetic parameters of rifampin. All patients had orange-red discoloration of urine after rifampin prophylaxis.

Bacterial resistance to rifampin

The WHO recommended the use of molecular-based tests MTBDRplus and GeneXpertMTB/RIF to diagnose multidrug-resistant tuberculosis in developing and high-burden countries. Both tests are based on detection of mutations in the rifampin Resistance-Determining Region of DNA depended RNA polymerase gene (rpoB). Such mutations were found in 95 to 98% of Mycobacterium tuberculosis strains determined to be rifampin-resistant by the "gold standard" culture-based drug susceptibility testing. Ocheretina, et al. [46] reported the phenotypic and genotypic characterization of 153 consecutive clinical Mycobacterium tuberculosis strains diagnosed as rifampin-resistant by molecular tests. One hundred and thirty-three isolates (86.9%) were resistant to rifampin. However, the remaining 16 isolates (10%) tested were rifampin-sensitive. Five strains with discordant genotypic and phenotypic susceptibility results had rifampin MIC close to the cut-off value of 1 µg/ml used in phenotypic susceptibility assay and were confirmed as resistant by drug susceptibly testing on solid media. Nine strains had sub-critical rifampin MICs ranging from 0.063 to 0.5 µg/ml. Finally, two strains were susceptible to rifampin and harboured a salient rpoB mutation. The present data indicate that not only detection of the presence but also identification of the nature of rpoB mutation is needed to accurately diagnose resistance to rifampin in Mycobacterium tuberculosis. The observed clinical significance of low-level resistance to rifampin supports the re-evaluation of the present critical concentration of the drug used in culture-based drug susceptibility testing. The incidence of antituberculosis drug resistance in South Texas has been tabulated. Age, sex, and ethnic group were not found to significantly influence of resistance. The resistance to rifampin was 10.6%. There was a 7.3% rate of resistance to rifampin for any individual organism (i.e. to 2 and 3 most commonly used antituberculosis drugs). Carpenter, et al. [47] concluded that the incidence of single and multiple antituberculosis drug resistance in South Texas is higher than previously reported. Mucous membrane colonization with type B streptococci frequently persists in infants after treatment of invasive infection and may be associated with recurrent disease. Fernandez, et al. [48] determined the frequency with group B streptococci colonization and persists at mucous membrane sites after treatment of invasive early onset infection and to determine the efficacy of oral rifampin in eradicating colonization in these infants and their mothers. Cultures for isolation of group B streptococci were obtained from infants and their mothers after completion of the infant's parenteral therapy, 1 week later when rifampin therapy was initiated and approximately 1 to 4 weeks after completion of rifampin therapy. Rifampin dose was 10 mg/kg (maximum 600 mg) twice-daily for 4 days. Ten

Table 9: Rifampin pharmacokinetics in the cerebrospinal fluid and in serum in 8 infants and children aged 1 day to 18 years undergoing cerebrospinal fluid (CSF) shunt placement, by Nahata, et al. [45].

	Dose (mg)	Serum		CSF					
Subject		Cmax (µg/ml)	Post infusion sampling time (hours)	CSF conc. (µg/ml)	CSF/ Cmax x 100	Post infusion Time (hours)	Clearance (L/h/kg)	Distribution volume (L/kg)	Half-life (Hours)
1	960	16.6	0.5	3.0	18.1	1.9	0.41	0.8	1.7
2	200	26.7	0.5	0.78	2.90	1.2	0.38	1.9	3.6
3	160	22.9	1.0	1.9**	8.23	2.3	0.22	1.1	3.6
4	175	25.6	0.6	0.12	0.47	1.9	0.22	0.7	2.1
5	150	22.6	0*	---	---	---	0.26	0.8	2.1
6	57	13.5	0.5	0.51	2.34	1.5	0.30	1.3	3.1
7	320	21.8	0*	0.73	3.34	1.9	0.30	1.1	2.5
8	570	19.5	1.5	1.5	7.57	1.3	0.20	0.9	3.5
Mean±SD (range)	320±300 (57 - 960)	21.5±4.4 (13.5-26.7)	0.45±0.32 (0 -1.0)	1.5±0.98 (0.12-3.0)	6.22±6.1 (0.47-7.6)	1.5±0.9 (1.2-2.3)	0.29±0.07 (0.20-0.41)	1.07±0.3 (0.7-1.3)	2.77±0.79 (2.1-3.6)

*End of infusion. **Cerebrospinal fluid collected from left subdural space. CSF/Cmax x 100 = rifampin concentrations in the cerebrospinal fluid to serum rifampin Cmax concentration in serum ratio x100.

of 21 infants (48%) and 13 (65%) of 20 mothers were colonized with group B streptococci at throat or rectal (infant) or vaginal, rectal or breast milk (mother) sites before rifampin was initiated. One week or less after treatment, 7 (70%) infants and 4 (31%) mothers remained colonized by group B streptococci. At study completion 6 infants and 7 mothers had group B streptococci colonization. Persistent colonization was not related to group B streptococci serotype, to initial rifampin MIC or to the development of rifampin resistant strains. Rifampin treatment for four days utilized as a single agent after completion of parenteral therapy failed to reliable eradicate group B streptococci colonization in infants. The United States has a low burden of drug resistance among tuberculosis cases compared with other world regions. Tuberculosis is increasingly concentrated among foreign-born individuals who have higher rates of drug resistance than U.S born individuals [49]. While universal drug susceptibility testing is detecting active tuberculosis, there are limited guidelines for latent tuberculosis infection treatment based on risk factors for drug resistance. To quantify the variable risk of drug resistance among foreign-born individuals, all tuberculosis cases in Washington State between 1994 and 2014 with drug resistance data for rifampin were divided into eight regions of birth. Genotypic cluster and lineage data were compared against drug resistance in a subanalysis. Rifampin resistance was slightly among individuals foreign-born individuals (1.9% versus 1.1%; P-value = 0.063). Multivariate logistic regression demonstrated that older age was associated with a lower risk of resistance to isoniazid and rifampin (odds ratio = 0.86; P-value = 0.006 and odds ratio = 0.64; P-value = 0.003 for each 20-year interval, respectively). These data suggest that the drug resistance in latent tuberculosis infection will remain a challenge and that rifampin-based regimens for treatment of latent tuberculosis infection in non-human HIV-infected adults may be preferable for individuals born in regions with high levels of rifampin resistance. Microbial drug resistance has become a major public health concern worldwide. To acquire epidemiologic data on drug-resistant tuberculosis among children is a major cause of illness and death for this population. Tao, et al. [50] conducted a retrospective study in 2006 to 2015 data from 36 tuberculosis prevention and control institutions in Shandong Province, China. A total of 14,223 new tuberculosis cases, among children (aged < 5 years) accounted for only 5.5%, and were caused by culture-confirmed Mycobacterium tuberculosis. Over the past decade, the percentage of drug-resistant tuberculosis; multidrug-resistant tuberculosis; and overall rifampin-resistant among children increased significantly at least 12%. Understanding the long-term trends of drug-resistant tuberculosis among children can shed light on the performance of tuberculosis control program, thereby contributing to global tuberculosis control. Antibiotic-resistant pneumococci, especially penicillin-resistant strains, are being increasingly isolated. Pneumococci with intermediate penicillin-resistance (MIC 0.1 to 1.0 μg/ml) have been reported from many parts of the world over the past decades, and highly resistant strains (penicillin MICs ≥ 2 μg/ml) have also appeared [51]. Infection may be acquired in the hospital or community, and nosocomial outbreed and may occur in children with diminished host responses. Disease caused by pneumococci with intermediate penicillin-resistance may be treated with high doses of penicillin, but disease caused highly resistant strains, especially meningitis, may require alternative therapy. Pneumococci resistant to several antibiotics, including rifampin, have also appeared. Strains resistant to sever, including all β-lactam antibiotics tested, have been reported in South Africa and Spain. Alternative therapy for resistant strains may include vancomycin, cefotaxime, cefotaxime, cefoperazone, ceftriaxone and imipenem. Pneumococci isolated from sites suggestive of infection, especially blood and cerebrospinal fluid should be routinely tested for penicillin-susceptibility. Driver, et al. [52] assessed the drug susceptibility patterns among tuberculosis patients reported to the New York City Department of Health in the first quarters of 1991 and 1992. Resistance to one or more drugs was seen in 26.3% (137 divided by 520) in 1991. Resistance to rifampin was 15%. Combined resistance to four first-line drugs (isoniazid, rifampin, streptomycin, and ethambutol) was seen in 6% in 1991 and 8% in 1992. Patients with organisms resistant to both isoniazid and rifampin were likely among U.S born and among foreign born, and younger patients were more likely than older patients to have isoniazid and rifampin resistant organisms. These findings underscore the importance of obtaining susceptibility testing in all patients who have culture positive for Mycobacterium tuberculosis. A prospective study of primary drug-resistant strains of Mycobacterium tuberculosis among children was begun at the Kings County Hospital Medical Center of Brooklyn in 1961 and reported in 1961 at a 5 4-years period through 1980, Steiner, et al. [53]. The present report extends the author's observations of primary drug-resistant tuberculosis in children through 1984. The salient finding in the present report was the increase in primary drug resistance to rifampin, 3 of 19 (15.8%) strains isolated in the last period of study (1969 to 1980).This increase was statistically significant (P-value < 0.02) even though the number of strains isolated was small. There were continued low resistance rates to ethambutol and para-aminosalicylic acid and stable resistance rates for isoniazid and streptomycin. Two children in a day care facility developed Haemophilus influenzae type b meningitis. The second child was enrolled in the facility after rifampin had been administered to the other attendees. The isolate from the first child was susceptible to rifampin, but the isolate from the second child was resistant to rifampin. Both isolates had identical outer membrane protein PAGE profiles. To investigate the virulence of these isolates McCarty et al. [54] inoculated infant rats intranasally with either rifampin-resistant or rifampin-susceptible cerebrospinal fluid isolate. The rates of nasal colonization 14 of 20 (70%) and eight of eight animals inoculated with the rifampin-resistant and rifampin-susceptible isolates, respectively, did not differ significantly. However, bacteraemia occurred less frequently in pups inoculated with rifampin-resistant strain than in animals inoculated with the susceptible strain (4 of 20 versus 8 of 8, P-value < 0.0001). Nasal washings, blood, and

cerebrospinal fluid obtained from animals inoculated with the rifampin-resistant isolate were divided and plated on media containing rifampin 1 µg/ml or without rifampin. Except for those from one animal, organisms isolated from blood and cerebrospinal fluid grew only on medium lacking rifampin, whereas Haemophilus influenzae type b growing from nasal washing was frequently found on both media. These authors concluded that mutation of Haemophilus influenzae to rifampin resistance is a hazard of rifampin chemoprophylaxis. Rifampin-resistant isolates have the potential to cause disease in patients and experimental animals, although they may be relatively less pathogenetic than the parent, susceptible organisms.

Discussion

Rifampin is a macrocyclic antibiotic important in the treatment of mycobacterial disease. This antibiotic is bacteriastatic as inhibits the transcription of DNA to RNA by binding to the β-subunity of bacterial RNA-polymerase (rpoB) to form a stable drug-enzyme complex. The mechanism of action of rifampin is typified by the action against Mycobacterial tuberculosis. Rifampin enters bacilli in a concentration-depended manner, achieving steady-state concentrations within 15 min [1]. Rifampin suppresses the RNA synthesis [2]. This antibiotic inhibits the growth of most gram-positive bacteria as well as gram-negative microorganisms, such as Escherichia coli, Pseudomonas, indole-positive and indole-negative microorganisms, Proteus, and Klebsiella. This antibiotic is also highly active against Neisseria meningitis and Haemophilus influenzae. Rifampin is used to treat tuberculosis, leprosy, brucellosis, Mycobacterium kansasii, Mycobacterium marinum, Mycobacterium uclerans, Mycobacterium malmoense, and Mycobacterium Haemophilus influence type b diseases. Rifampin is used in the prophylaxis of meningococcal diseases, and Haemophilus diseases [2]. Two formulations of rifampin are available, one for oral and the other one for intravenous administration. In infants, the dose of rifampin is 10 to 20 mg/kg every 24 hours (oral administration) and 5 to 10 mg/kg every 12 hours (intravenous administration) [7]. In children, the recommended dose by the WHO is 15 mg/kg (15 - 20). Rifampin is an effective and safe antibiotic [8-10]. This antibiotic is used to treat staphylococcal bacteraemia, coagulase-negative staphylococcal infection, Staphylococcus aureus colonization, bacterial meningitis, tuberculous meningitis, tuberculosis infection, and Haemophilus influenzae type b infections [11-23]. Tuberculosis is treated with a combination of rifampin and isoniazid. The combination of rifampin/isoniazid is 60/60 mg in dispersible tablets. Concomitant administration of rifampin and isoniazid induces hepatotoxicity in children with tuberculosis [24-26]. Rifampin is a potent inducer of different cytochromes P-450 CYP24A1, CYP3A4, CYP2B6, CYP3A, CYP2C9, CYP1A2, CYO2C9, CYP2C19, and CYP1A2, [27 - 30]. The metabolites of rifampin are: 25-O-deseacetylrimampicin and 3-formylrifampicin SV, 25-O-deseacetylrimampicin is the mean metabolite [31]. Rifampin and its metabolites are mainly excreted in the bile and eliminated with the faeces. The pharmacokinetics of rifampin was extensively studied in infants and children. Koup et al. [31] studied the pharmacokinetics of rifampin after intravenous and oral administrations to 20 children. There was no difference in the elimination half-life after intravenous and oral administration. The extrapolated end of intravenous infusion corrected for a standard dose of 300 mg/m^2 was significantly higher than the peak concentration after oral administration. The 25-O-deseacetylrimampicin concentration to the rifampin concentration ratio was similar after intravenous and oral administration. An extreme premature infant with congenital tuberculosis was treated with 5 mg/kg rifampin, 5 mg/kg isoniazid, and 15 mg/kg amikacin, the peak and trough concentrations of rifampin were 2.4 and < 0.2 µg/ml, respectively, after intravenous, and 4.7 and 0.3 µg/ml, respectively, after oral administration [32]. One hundred and twenty-three children with a mean postnatal age and body weight of 24.8 days and 1,580 gram, respectively, were treated with 5 or 10 mg/kg rifampin intravenously [33]. Plasma rifampin peak and trough concentrations were 4.66±1.47 and 0.21±0.20 µg/ml, respectively. Twenty seven preterm and term infants received at least one dose of rifampin intravenously based on their gestational and postnatal ages [34]. The 1,000 virtual children generated from pharmacokinetic simulations matched the infants demographic data. A dose of rifampin 8 mg/kg once-daily resulted in a $AUC_{0\text{-infite}}$ at steady-state ≥ 55.2 µg.h/ml in 92.3% of simulated infants aged < 14 days of postnatal age. A dose of rifampin 15 mg/kg once-daily resulted in $AUC_{0\text{-infinite}}$ at steady-state ≥ 52.5 µg.h/ml in 91.5% infants aged ≥ 14 days of postnatal age. Thus, the two doses used and the different infant ages, did not influence $AUC_{0\text{-infinite}}$ and a dose of 8 mg/kg should be used. This in contrast with the dose recommended by the WHO which recommended a rifampin dose 15 mg/kg (15 to 20). Bekker, et al. [35] investigated the rifampin pharmacokinetics in 39 infants, 15 of 39 (38.5%) were premature, and 22 infants (56%) were born to HIV-infected mothers. A formulation of rifampin, referred to as formulation 1 was a granulate suspension (100 mg/5 ml); manufactured by Eremfat, Germany. A second rifampin suspension R-cin (100 mg/5 ml) was manufactured by Aspen Pharmacare, South Africa, and registered by Medicines Control Council and was referred to as formulation 2. The dose of rifampin was 12.91 mg/kg in the formulation 1 and it was 16.54 mg/kg in the formulation 2. Mean Cmax and $AUC_{0\text{-infinite}}$ were 4.23 µg/ml and 16.77 µg.h/ml, respectively for the formulation 1, and 2.22 µg/ml and 9.52 µg.h/ml, respectively, for the formulation 2. Cmax and $AUC_{0\text{-infinite}}$ were greater for formulation 1 than formulation 2. None of the 39 infants achieved the target adult peak rifampin concentration of ≥ 8 µg/ml. The results of this investigation show that the pharmacokinetic parameters of rifampin are depended by different types of rifampin administered. McCracken, et al. [36] compared the bioavailability of three formulations of rifampin in 19 infants and 19 children. Rifampin in 85% sucrose suspension contained 10 mg/kg of rifampin power (study group A). Rifampin was suspended in applesauce solution at a final concentration of 10 (study group B). Two tablets of rifampin powder were placed in two tablespoons of

applesauce (study group C), Rifampin dosage in this group of children was estimated to be 8 to 12 mg/kg. The rifampin serum concentrations were different in the tree groups studied, but the elimination half-life and the AUC were similar in the tree groups. The results of this investigation indicate that the serum concentrations of rifampin varied with the type of rifampin administration. Thee et al. [37] studied the pharmacokinetics of rifampin in 11 children with a mean postnatal age of 1.0±0.46 years. Rifampin was administered orally at doses of 10 and 15 mg/kg. After a rifampin dose of 10 mg/kg, the mean values of Cmax, Tmax, and AUC were 6.36 µg/ml, 1.49 hours, and 17.78 µg.h/ml, respectively. After a dose of 15 mg/kg, Cmax and AUC were significantly higher than those obtained with a rifampin dose of 10 mg/kg. Schaaf, et al. [38] investigated the effects of HIV status on the rifampin pharmacokinetics; rifampin was administered orally at a dose of 60 mg to 54 children with tuberculosis, the mean age of 4.05 years, and 21 children were HIV- coinfected. The mean values of Cmax, Tmax and $AUC_{0\text{-}6\ hours}$ were 4.91µg/ml, 1.80 hours, and 14.88 µg.h/ml respectively. In children not-HIV-infected (N = 33), the pharmacokinetic parameters of rifampin were not statistically different than dose obtained in children HIV-coinfected. These authors concluded that the HIV status does not affect the pharmacokinetic parameters of rifampin. Antwi, et al. [39] explored the rifampin pharmacokinetics in 131 children; rifampin was administered orally at a mean dose of 15.8 mg/kg. Fifty-nine children aged < 2 years were HIV-coinfected and 72 children aged < 5 years were not-HIV-coinfected. In children HIV-coinfected the mean values of Cmax, Tmax, and $AUC_{0\text{-}8\ hours}$ clearance, and the distribution volume were 7.65 µg/ml, 2.01 hours, $AUC0_{\text{-}0\text{-}8\ hours}$ 30.49 µ.h/ml, clearance 0.11 L/h/kg, and the distribution volume 1.37 L/kg. The clearance and distribution volume were normalized for the bioavailability and the body weight. Cmax, $AUC_{0\text{-}8\ hours}$, and the clearance, were statistically different in children HIV-coinfected than in children not-HIV-coinfected. The results of this study are in contrast with results reported by Schaaf, et al. [38] who did not observe differences in rifampin pharmacokinetic parameters of HIV-coinfected from those not-HIV-coinfected. The comparison of rifampin pharmacokinetic parameters in the two groups of children is difficult to carry out because the different ages of children. Kwara, et al. [40] investigated the pharmacokinetics of rifampin in 62 children with tuberculosis and with and without HIV-infection. Twenty-nine children were aged < 5 years and 33 children were aged ≥ 5 years. These authors did not distinguish children with HIV-infected and children not-HIV-coinfected, and all children were included in the study. Dispersible tablets of 60/60 mg isoniazid/rifampin were administered to all children. The median values of Cmax, Tmax, $AUC_{0\text{-}infinite}$, clearance, and distribution volume were 6.3 µg/ml, 2.0 hours, 31.2 µ.h/ml, 0.5 L.h/kg, and 1.6 L/kg, respectively. The clearance and the distribution volume were corrected for body weight. Arya, et al. [41] studied the pharmacokinetics of rifampin in 20 children aged 5 to 12 years with tuberculosis and without HIV-infected. A rifampin single oral dose of 150 mg was administered to children weighing 11 to 17 kg and children weighing 12 to 25 kg received a single oral dose of 225 mg. The mean values of Cmax, Tmax, and $AUC_{0\text{-}infinite}$ were 6.32 µg/ml, 3.42 hours, and $AUC_{0\text{-}infinite}$ was 33.24 µg.h/ml. Mukherjee et al. [42] investigated the rifampin pharmacokinetics in children aged 2 to 5 years (N = 42) and in children aged > 5 years (N = 212). The rifampin standard dose was 8 to 12 mg/kg (N = 63) and the rifampin dose recommended by WHO (recommended dose) was 15 mg/kg (15 to 20) (N = 64) were administered to children. The mean rifampin plasma concentrations were 11.2 µg/ml (standard dose) and 15.2 µg/ml (recommended dose) (P-value < 0.0001). The mean values of Cmax, Tmax, and $AUC_{0\text{-}4\ hours}$ were 10.4 µg/ml, 1.5 hours, and 28.0 µg.h/ml, respectively, after the standard dose, and 12.0 µg/ml, 2 hours, and 30.5 µg.h/ml, respectively, after the recommended dose. Tmax was different (P-value = 0.004) in these two groups. Thee et al. [44] measured the serum concentrations of rifampin in 27 children aged 2 to 14 years. The mean serum levels of rifampin ranged from 0.8 to < 0.4 µg/ml at times of 1 and 24 hours after rifampin administration in children aged 2 - <6 years (N = 7), and < 4 to <4 µg/ml in 11 children aged 6 - < 10 years, and 1.2 to < 0.4 µg/ml in 9 children aged 10 to 14 years. The Cmax, half-life, and $AUC_{0\text{-}7\ hours}$ were not statistically different in the three groups of children. Nahata, et al. [45] measured the rifampin concentrations in the serum and cerebrospinal fluid of 8 infants and children aged 1 day to 18 years. Rifampin dose ranged from 57 and 960 (mean, 320 mg). Mean Cmax of rifampin concentration in serum was 21.5 µg/ml and the mean rifampin concentration in the cerebrospinal fluid was1.53 µg/ml. The mean concentration of rifampin in cerebrospinal fluid to the serum ratio was 6.22 x 100.

Little is known on the bacterial resistance to rifampin [46-54], it is approximately < 20% and is higher in younger than older patients (P-value = 0.003). The mechanism of bacterial resistance to rifampin has been described by Gumbo [2]. The prevalence of rifampin-resistant isolates is 1 in every 10^7 to 10^8 bacilli, and is due to an alteration of the target of this drug, rpoB, with resistance in 86% of cases due to mutations at codons 526 and 531 of the rpoB gene [55]. Rifamycin monoresistance occurs at higher rates when patients with HIVs and multicavitary tuberculosis are treated with either rifapentine or rifabutin [56]. Efflux pump induction, and mutations in efflux pumps, have now been demonstrated to be associated with Rifamycin [57].

In conclusion, rifampin is a macrocyclic antibiotic, it is a bacteriastatic as inhibits the transaction of DNA to RNA by binding to the β-subunity of bacterial RNA-polymerase (rpoB) to form a stable drug-enzyme complex. Rifampin enters bacilli in a concentration-depended manner, achieving steady-state concentration within 15 min. This antibiotic inhibits the growth of most gram-positive bacteria and as well as gram-negative microorganisms. Rifampin is used to treat tuberculosis, leprosy, brucellosis, Mycobacterium kansasii, Mycobacterium marinum, Mycobacterium uclerans, Mycobacterium malmoense, and Mycobacterium Haemophilus diseases. Rifampin is metabolized by different cytochromes P-450

and the metabolites of rifampin are 25-O-deseacetylrifampin and 3-formylrifamycin SV, 25-O-deseacetylrifampin is the mean metabolite. Rifampin and its metabolites are excreted in the bile and eliminated with the faeces. Rifampin is potent inducer of CYP24A1, CYP3A4, CYP2B6, CYP3A, CYP2C9, CYP1A2, CYO2C9, CYP2C19, and CYP1A2. This drug is used to with to treat tuberculosis rifampin is co-administered with isoniazid. The concomitant administration of rifampin and isoniazid induces hepatotoxicity. The recommended dose of rifampin by the WHO is 15 mg/kg (15 to 20) in children. The pharmacokinetics of rifampin are extensively studied in infants and children. In infants the elimination half-life is 2 to 4 hours and in children and is about 2 hours. Little is known of the bacterial-resistance to rifampin it is approximately < 20% and is higher in younger than older patients (P-value = 0.003).

Conflict of Interests

The author declares no conflicts of financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employments, gifts and honoraria.

This article is a review and drugs have not been administered to men or animals.

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References

1. Gumbo T, Louie A, Deziel MR, Liu W, Parsons LM, et al (2007) Concentration-dependent Mycobacterium tuberculosis killing and prevention of resistance by rifampin. *Antimicrob Agents Chemother* 51:3781-3788. [View Article]

2. Gumbo T. Chemotherapy of tuberculosis, Mycobacterium avium Complexe Disease, and Leprosy. In the Goodman & Gilman's The Pharmacological Basis of Therapeutics. 13th Edition. Brunton LL, Hilal-dandan, Knollmann BC, editors. Mc Graw Hill, New York, 2018, pp 1067-1070. [View Article]

3. Burman WJ, Gallicano K, Peloquin C (2001) Comparative pharmacokinetics and pharmacodynamics of the rifamycin antibacterials. *Clin Pharmacokinet* 40:327-341. [View Article]

4. Nau R, Prange HW, Menck S, Kolenda H, Visser K, et al. (1992) Penetration of rifampicin into the cerebrospinal fluid of adults with uninflamed meninges. *J Antimicrob Chemother* 29:719-724. [View Article]

5. Shenje J, Ifeoma Adimora-Nweke F, Ross IL, Ntsekhe M, Wiesner L, et al (2015) Poor Penetration of Antibiotics Into Pericardium in Pericardial Tuberculosis. *EBioMedicine* 2:1640-1649. [View Article]

6. Wilkins JJ, Savic RM, Karlsson MO, Langdon G, McIlleron H, et al (2008) Population pharmacokinetics of rifampin in pulmonary tuberculosis patients, including a semimechanistic model to describe variable absorption. *Antimicrob Agents Chemother* 52:2138-2148. [View Article]

7. Young TE, Mangum B. NEOFAX. Antimicrobials. Penicillin G. Twenty-third edition 2010. Thomson Reuters. pp. 86-87. [View Article]

8. El-Karaksy H, Mansour S, El-Sayed R, El-Raziky M, El-Koofy N, et al. (2007) Safety and efficacy of rifampicin in children with cholestatic pruritus. *Indian J Pediatr* 74:279-281. [View Article]

9. Arnold CJ, Ericson J, Kohman J, Corey KL, Oh M, et al (2015) Rifampin use and safety in hospitalized infants. *Am J Perinatol* 32:565-570. [View Article]

10. Diallo T, Adjobimey M, Ruslami R, Trajman A, Sow O, et al (2018) Safety and Side Effects of Rifampin versus Isoniazid in Children. *N Engl J Med* 379:454-463. [View Article]

11. Tan TQ, Mason EO Jr, Ou CN, Kaplan SL (1993) Use of intravenous rifampin in neonates with persistent staphylococcal bacteremia. *Antimicrob Agents Chemother* 37:2401-2406. [View Article]

12. van der Lugt NM, Steggerda SJ, Walther FJ (2010) Use of rifampin in persistent coagulase negative staphylococcal bacteremia in neonates. *BMC Pediatr* 10:84. [View Article]

13. Hanevold CD, Fisher MC, Waltz R, Bartosh S, Baluarte HJ (1995) Effect of rifampin on Staphylococcus aureus colonization in children on chronic peritoneal dialysis. *Pediatr Nephrol* 9:609-611. [View Article]

14. Demir N, Peker E, Gülşen İ, Kocaman S, Tuncer O, Kırımi E (2016) Powder Topical Rifampin for Reducing Infections After Neural Tube Defect Surgery in Infants. *World Neurosurg* 95:165-170. [View Article]

15. Uppal L, Singhi S, Singhi P, Aggarwal R (2017) Role of Rifampin in Reducing Inflammation and Neuronal Damage in Childhood Bacterial Meningitis: A Pilot Randomized Controlled Trial. *Pediatr Infect Dis J* 36:556-559. [View Article]

16. Campos J, Garcia-Tornel S, Roca J, Iriondo M (1987) Rifampin for eradicating carriage of multiply resistant Haemophilus influenzae b. *Pediatr Infect Dis J* 6:719-721. [View Article]

17. Green M, Li KI, Wald ER, Guerra N, Byers C (1992) Duration of rifampin chemoprophylaxis for contacts of patients infected with Haemophilus influenzae type B. *Antimicrob Agents Chemother* 36:545-547. [View Article]

18. Murphy TV, Chrane DF, McCracken GH Jr, Nelson JD (1983) Rifampin prophylaxis v placebo for household contacts of children with Hemophilus influenzae type b disease. *Am J Dis Child* 137:627-632. [View Article]

19. Abernathy RS, Dutt AK, Stead WW, Moers DJ (1983) Short-course chemotherapy for tuberculosis in children. *Pediatrics* 72:801-806. [View Article]

20. Gaensbauer J, Aiona K, Haas M, Reves R, Young J, et al. (2018) Better Completion of Pediatric Latent Tuberculosis Treatment Using 4 Months of Rifampin in a US-based Tuberculosis Clinic. *Pediatr Infect Dis J* 37:224-228. [View Article]

21. Reis FJ, Bedran MB, Moura JA, Assis I, Rodrigues ME (1990) Six-month isoniazid-rifampin treatment for pulmonary tuberculosis in children. *Am Rev Respir Dis* 142:996-999. [View Article]

22. Savic RM, Ruslami R, Hibma JE, Hesseling A, Ramachandran G, et al (2015) Pediatric tuberculous meningitis: Model-based approach to determining optimal doses of the anti-tuberculosis drugs rifampin and levofloxacin for children. *Clin Pharmacol Ther* 98:622-629. [View Article]

23. Bolan G, Laurie RE, Broome CV (1986) Red man syndrome: inadvertent administration of an excessive dose of rifampin to children in a day-care center. *Pediatrics* 77:633-635. [View Article]

24. Tsagaropoulou-Stinga H, Mataki-Emmanouilidou T, Karida-Kavalioti S, Manios S (1985) Hepatotoxic reactions in children with severe tuberculosis treated with isoniazid-rifampin. *Pediatr Infect Dis* 4:270-273. [View Article]

25. Linna O, Uhari M (1980) Hepatotoxicity of rifampicin and isoniazid in children treated for tuberculosis. *Eur J Pediatr* 134:227-229. [View Article]

26. O'Brien RJ, Long MW, Cross FS, Lyle MA, Snider DE (1983) Hepatotoxicity from isoniazid and rifampin among children treated for tuberculosis. *Pediatrics* 72:491-499. [View Article]

27. Hawkes CP, Li D, Hakonarson H, Meyers KE, Thummel KE, et al. (2017) CYP3A4 Induction by Rifampin: An Alternative Pathway for Vitamin D Inactivation in Patients With CYP24A1 Mutations. *J Clin Endocrinol Metab* 102:1440-1446. [View Article]

28. McIlleron HM, Schomaker M, Ren Y, Sinxadi P, Nuttall JJ, et al (2013) Effects of rifampin-based antituberculosis therapy on plasma efavirenz concentrations in children vary by CYP2B6 genotype. *AIDS* 27:1933-1940. [View Article]

29. Luo G, Cunningham M, Kim S, Burn T, Lin J, Sinz M, et al (2002) CYP3A4 induction by drugs: correlation between a pregnane X receptor reporter gene assay and CYP3A4 expression in human hepatocytes. *Drug Metab Dispos* 30(7):795-804. [View Article]

30. Dixit V, Hariparsad N, Li F, Desai P, Thummel KE, et al. (2007) Cytochrome P450 enzymes and transporters induced by anti-human immunodeficiency virus protease inhibitors in human hepatocytes: implications for predicting clinical drug interactions. *Drug Metab Dispos* 35:1853-1859. [View Article]

31. Koup JR, Williams-Warren J, Viswanathan CT, Weber A, Smith AL (1986) Pharmacokinetics of rifampin in children. II. Oral bioavailability. *Ther Drug Monit* 8:17-22. [View Article]

32. Le Doare K, Barber N, Doerholt K, Sharland M (2013) Rifampicin pharmacokinetics in extreme prematurity to treat congenital tuberculosis. *BMJ Case Reports.* [View Article]

33. Pullen J, Stolk LM, Degraeuwe PL, van Tiel FH, Neef C, et al. (2006) Pharmacokinetics of intravenous rifampicin (rifampin) in neonates. *Ther Drug Monit* 28:654-661. [View Article]

34. Smith PB, Cotten CM, Hudak ML, Sullivan JE, Poindexter BB, et al (2019) Pharmaceuticals for Children Act-Pediatric Trials Network Steering Committee. Rifampin Pharmacokinetics and Safety in Preterm and Term Infants. *Antimicrob Agents Chemother* 63(6). [View Article]

35. Bekker A, Schaaf HS, Draper HR, van der Laan L, Murray S, et al. (2016) Pharmacokinetics of Rifampin, Isoniazid, Pyrazinamide, and Ethambutol in Infants Dosed According to Revised WHO-Recommended Treatment Guidelines. *Antimicrob Agents Chemother* 60:2171-2179. [View Article]

36. McCracken GH, Ginsburg CM, Zweighaft TC, Clahsen J (1980) Pharmacokinetics of rifampin in infants and children: relevance to prophylaxis against Haemophilus influenzae type b disease. *Pediatrics* 66:17-21. [View Article]

37. Thee S, Seddon JA, Donald PR, Seifart HI, Werely CJ, et al (2011) Pharmacokinetics of isoniazid, rifampin, and pyrazinamide in children younger than two years of age with tuberculosis: evidence for implementation of revised World Health Organization recommendations. *Antimicrob Agents Chemother* 55:5560-5567. [View Article]

38. Schaaf HS, Willemse M, Cilliers K, Labadarios D, Maritz JS, et al (2009) Rifampin pharmacokinetics in children, with and without human immunodeficiency virus infection, hospitalized for the management of severe forms of tuberculosis. *BMC Med* 7:19. [View Article]

39. Antwi S, Yang H, Enimil A, Sarfo AM, Gillani FS, et al (2017) Pharmacokinetics of the First-Line Antituberculosis Drugs in Ghanaian Children with Tuberculosis with or without HIV Coinfection. *Antimicrob Agents Chemother* 61:e01701. [View Article]

40. Kwara A, Enimil A, Gillani FS, Yang H, Sarfo AM, et al (2016) Pharmacokinetics of First-Line Antituberculosis Drugs Using WHO Revised Dosage in Children With Tuberculosis With and Without HIV Coinfection. *J Pediatric Infect Dis Soc* 5:356-365. [View Article]

41. Arya A, Roy V, Lomash A, Kapoor S, Khanna A, Rangari G (2015) Rifampicin pharmacokinetics in children under the Revised National Tuberculosis Control Programme, India, 2009. *Int J Tuberc Lung Dis* 19:440-445. [View Article]

42. Mukherjee A, Velpandian T, Singla M, Kanhiya K, Kabra SK, Lodha R (2015) Pharmacokinetics of isoniazid, rifampicin, pyrazinamide and ethambutol in Indian children. *BMC Infect Dis* 15:126. [View Article]

43. Verhagen LM, López D, Hermans PW, Warris A, de Groot R, et al (2012) Pharmacokinetics of anti-tuberculosis drugs in Venezuelan children younger than 16 years of age: supportive evidence for the implementation of revised WHO dosing recommendations. *Trop Med Int Health* 17:1449-1456. [View Article]

44. Thee S, Detjen A, Wahn U, Magdorf K (2009) Rifampicin serum levels in childhood tuberculosis. *Int J Tuberc Lung Dis* 13:1106-1111. [View Article]

45. Nahata MC, Fan-Havard P, Barson WJ, Bartkowski HM, Kosnik EJ (1990) Pharmacokinetics, cerebrospinal fluid concentration, and safety of intravenous rifampin in pediatric patients undergoing shunt placements. *Eur J Clin Pharmacol* 38:515-517. [View Article]

46. Ocheretina O, Escuyer VE, Mabou MM, Royal-Mardi G, Collins S, et al (2014) Correlation between genotypic and phenotypic testing for resistance to rifampin in Mycobacterium tuberculosis clinical isolates in Haiti: investigation of cases with discrepant susceptibility results. *PLoS One* 9(3):e90569. [View Article]

47. Carpenter JL, Obnibene AJ, Gorby EW, Neimes RE, Koch JR, et al. (1983) Antituberculosis drug resistance in south Texas. *Am Rev Respir Dis* 128:1055-1058. [View Article]

48. Fernandez M, Rench MA, Albanyan EA, Edwards MS, Baker CJ (2001) Failure of rifampin to eradicate group B streptococcal colonization in infants. *Pediatr Infect Dis J* 20:371-376. [View Article]

49. Furukawa NW, Haider MZ, Allen SJ, Carlson SL, Lindquist SW (2017) Resistance to First-Line Antituberculosis Drugs in Washington State by Region of Birth and Implications for Latent Tuberculosis Treatment Among Foreign-Born Individuals. *Am J Trop Med Hyg* 96:543-549. [View Article]

50. Tao NN, He XC, Zhang XX, Liu Y, Yu CB, et al. (2017) Drug-Resistant Tuberculosis among Children, China, 2006-2015. *Emerg Infect Dis* 23:1800-1805. [View Article]

51. Appelbaum PC (1987) World-wide development of antibiotic resistance in pneumococci. *Eur J Clin Microbiol* 6:367-377. [View Article]

52. Driver CR, Frieden TR, Bloch AB, Onorato IM (1994) Drug

resistance among tuberculosis patients, New York City, 1991 and 1992. *Public Health Rep* 109(5):632-6366. [View Article]

53. Steiner P, Rao M, Mitchell M, Steiner M (1986) Primary drug-resistant tuberculosis in children. Emergence of primary drug-resistant strains of M. tuberculosis to rifampin. *Am Rev Respir Dis* 134:446-448. [View Article]

54. McCarty J, Glodé MP, Granoff DM, Daum RS (1986) Pathogencity of a rifampin-resistant cerebrospinal fluid isolate of Haemophilus influenzae type b. *J Pediatr* 109:255-259. [View Article]

55. Somoskovi A, Parsons LM, Salfinger M (2001) The molecular basis of resistance to isoniazid, rifampin, and pyrazinamide in Mycobacterium tuberculosis. *Respir Res* 2:164-168. [View Article]

56. Burman W, Benator D, Vernon A, Khan A, Jones B, et al (2006) Acquired rifamycin resistance with twice-weekly treatment of HIV-related tuberculosis. *Am J Respir Crit Care Med* 173:350-356. [View Article]

57. Li G, Zhang J, Guo Q, Wei J, Jiang Y, Zhao X, et al (2015) Study of efflux pump gene expression in rifampicin-monoresistant Mycobacterium tuberculosis clinical isolates. *J Antibiot (Tokyo)* 68:431-435. [View Article]

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