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Role of Post Approval Clinical Trials for Drug

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ABSTRACT

Anti-tuberculosis drugs, the main aim for improving current treatment should be to optimize the use of the two current drugs, rifampicin and the pro-drug pyrazinamide, which are responsible to a similar extent for the entire sterilizing activity of current therapy. The rifamycin activity could be improved by increasing the dose size of rifampicin or by daily dosing with long acting rifapentine. Increasing the dose size of pyrazinamide is limited by toxicity but an alternative approach is to use inhalation with pyrazinoic acid, as an adjunct to standard oral therapy. This would acidify pulmonary lesions, thus increasing the bactericidal activity of the orally administered pyrazinamide. Because pyrazinoic acid is the active moiety, it should also increase overall pyrazinamide activity and, because most resistance arises in the pncA gene that converts pyrazinamide to pyrazinoic acid, it should act on most pyrazinamide resistant strains. Inhalation technology allows delivery of drug to lesions rapidly and without first pass toxicity. The properties of drug containing microparticles and nanoparticles during inhalation and storage are reviewed. Spray-dried larger Trojan particles in which the smaller encapsulated particles can reside should be able to improve localisation within alveoli and avoid some storage problems.

Keywords – Rifampicin, Prednisolone, Rifampicin Resistance, M. Tuberculosis

I. INTRODUCTION

Rifampicin is one of the most potent and broad-spectrum antibiotics against bacterial pathogens and is a key component of anti-tuberculosis therapy, stemming from its inhibition of the bacterial RNA polymerase (RNAP). It is a semisynthetic derivative of rifamycin B obtained from Streptomyces Mediterranean.

Rifampicin is bactericidal to M. tuberculosis and many other gram-positive and gram-negative bacteria like Staph. aureus, N. meningitidis, H. influenzae, E. coli, Klebsiella, Pseudomonas, Proteus and Legionella. Against TB bacilli, it is as efficacious as INH and better than all other drugs. The bactericidal action covers all subpopulations of TB bacilli, but acts best on slowly or intermittently dividing ones (spurters).

Rifampicin is typically used to treat Mycobacterium infections, including tuberculosis and leprosy; and

also has a role in the treatment of methicillin-resistant Staphylococcus aureus (MRSA) in combination with fusidic acid. It is used in prophylactic therapy against Neisseria meningitidis (meningococcal) infection. Further, it has been used with Amphotericin B in largely unsuccessful attempts to treat primary amoebic meningoencephalitis caused by Naegleria fowleri

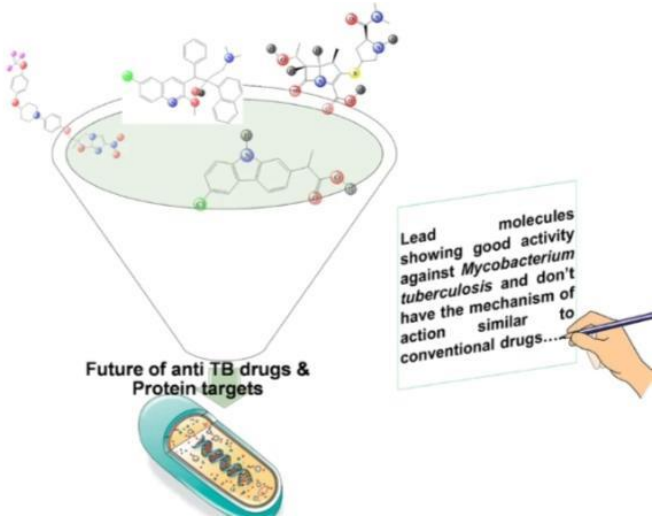

Figure 1 - Shows future of anti TB drugs and protein targets

It is also used to treat infection by Listeria species, Neisseria gonorrhoeae, Haemophilus influenzae and Legionella pneumophila. For these non-standard indications, sensitivity testing should be done (if possible) before starting rifampicin therapy. Rifampicin resistance develops quickly during treatment and rifampicin monotherapy should not be used to treat these infections — it should be used in combination with other antibiotics. With multidrug therapy (MDT) used as the standard treatment of leprosy, rifampicin is always used in combination with dapsone and clofazimine

Pharmacokinetic Interactions with Rifampicin

The antituberculosis drug rifampicin (rifampin) induces a number of drug-metabolising enzymes, having the greatest effects on the expression of cytochrome P450 (CYP) 3A4 in the liver and in the small intestine. In addition, rifampicin induces some drug transporter proteins, such as intestinal and hepatic P-glycoprotein. Full induction of drug-metabolising enzymes is reached in about 1 week after starting rifampicin treatment and the induction dissipates in roughly 2 weeks after discontinuing rifampicin.

Rifampicin has its greatest effects on the pharmacokinetics of orally administered drugs that are metabolised by CYP3A4 and/or are transported by P-glycoprotein. Thus, for example, oral midazolam, triazolam, simvastatin, verapamil and most dihydropyridine calcium channel antagonists are ineffective during rifampicin treatment. The plasma concentrations of several anti-infectives, such as the antimycotics itraconazole and ketoconazole and the HIV protease inhibitors indinavir, nelfinavir and saquinavir, are also greatly reduced by rifampicin.

The use of rifampicin with these HIV protease inhibitors is contraindicated to avoid treatment failures. Rifampicin can cause acute transplant rejection in patients treated with immunosuppressive drugs, such as cyclosporin. In addition, rifampicin reduces the plasma concentrations of methadone, leading to symptoms of opioid withdrawal in most patients.

Rifampicin also induces CYP2C-mediated metabolism and thus reduces the plasma concentrations of, for example, the CYP2C9 substrate (S)-warfarin and the sulfonylurea antidiabetic drugs. In addition, rifampicin can reduce the plasma concentrations of drugs that are not metabolised (e.g., digoxin) by inducing drug transporters such as P-glycoprotein.

Thus, the effects of rifampicin on drug metabolism and transport are broad and of established clinical significance. Potential drug interactions should be considered whenever beginning or discontinuing rifampicin treatment. It is particularly important to remember that the concentrations of many of the other drugs used by the patient will increase when rifampicin is discontinued as the induction starts to wear off.

Clinical Pharmacokinetics of Rifampicin

Rifampicin is widely used to treat against M. tuberculosis . After oral administration on an empty stomach, the absorption of rifampicin (rifampin) is rapid and practically complete.

With a single 600mg dose, peak serum concentrations of the order of 10μg/ml generally occur 2 hours after administration. The half-life of rifampicin for this dose level is of the order of 2.5 hours.

The amount of rifampicin extracted by the liver during its first passage through the hepatoportal system and transferred to bile is of relevance for the time course of distribution of the antibiotic in the blood compartment. With doses of the order of 300 to 450mg, the excretory capacity of the liver for the antibiotic is saturated. As a consequence, increasing the dose of antibiotic results in a more than proportional increase in serum concentrations.

On repeated administration, and most likely as a consequence of self-induced (autoinduction) metabolism, the rate of disappearance of rifampicin from the blood compartment increases in the early phase of treatment, the phenomenon affecting mainly the levels following the peak, with a consequent reduction in half-life.

Approximately 80% of rifampicin is transported in blood bound to plasma proteins, mainly albumin. Rifampicin is well distributed, although to a different degree, in the various tissues of the human body. Probably in the hepatocyte, rifampicin undergoes a process of deacetylation. The metabolic derivative, desacetylrifampicin, is more polar than the parent compound, and microbiologically active. This metabolite accounts for the majority of the antibacterial activity in the bile. Rifampicin is almost equally excreted in the bile and urine, the recovery in the 2 fluids being of the same order of magnitude.

Administration of rifampicin to new born infants and children is followed by blood levels generally lower than those. Found in adults for the same dose levels. In patients with impaired liver and kidney function the elimination of the antibiotic from the blood compartment is slower than in normal subjects.

Rifampicin has been found to compete with bilirubin and other cholefil substances for biliary excretion, giving rise to transient and reversible increased bilirubin and BSP retention values.

A kinetic model study on the transfer constants between various body compartments has indicated that rifampicin is rapidly absorbed from the intestine and that the absorption rate increases with time. Rifampicin as such is transferred into urine at a rale 3 times higher than the rate of transfer into bile.

Desacetylrifampicin, the more polar metabolic derivative of rifampicin, behaves in the opposite way since its rate of transfer into bile is 4 times higher than that into urine. The rate of biotransformation of rifampicin into desacetylrifampicin is of the same order of magnitude as that of biotransformation of the latter into a further metabolic derivative, which could be a glucuronide conjugate.

Administration of rifampicin to man is associated with proliferation of the smooth endoplasmic reticulum of the hepatocyte and with a state of induction of the drug metabolising enzyme system in the liver. As a result, drug metabolism interactions of clinical significance have been found between rifamipicin and drugs such as oral anticoagulants, oral contraceptives, oral sulphonylurea, hypoglycaemic agents, corticosteroids and digitoxin.

Mechanism of action

Rifampicin inhibits DNA-dependent RNA polymerase in bacterial cells by binding its beta-subunit, thus preventing transcription of messenger RNA (mRNA) and subsequent translation to proteins. Its lipophilic nature makes it a good candidate to treat the meningitis form of tuberculosis, which requires distribution to the central nervous system and penetration through the blood-brain barrier.

The mechanism of rifampicin inhibition of Escherichia coli RNA polymerase was studied with a newly developed steady state assay for RNA chain

initiation and by analysis of the products formed with several 5'- terminal nucleotides. The major effect of rifampicin was found to be a total block of the translocation step that would ordinarily follow formation of the first phosphodiester bond. These effects were incorporated into a steric model for rifampicin inhibition. Additional minor effects of the enzyme bound inhibitor were to increase slightly the lifetime of RNA polymerase on the XPK promoter and to increase by two the apparent Michaelis constants of the initiating triphosphates. The products formed by RNA polymerase in the presence of rifampicin belong nearly exclusively to the class pppPupN. No evidence for the accumulation of such molecules was obtained in viuo.

M. leprae is highly sensitive, while MAC and some other mycobacteria, but not M. fortuitum, are moderately susceptible. Both extra- and intracellular organisms are affected. It has good sterilizing and resistance preventing actions.

Rifampin interrupts RNA synthesis by binding to β subunit of mycobacterial DNA-dependent RNA polymerase (encoded by rpoB gene and blocking its polymerizing function. The basis of selective toxicity is that mammalian RNA polymerase does not avidly bind rifampin.

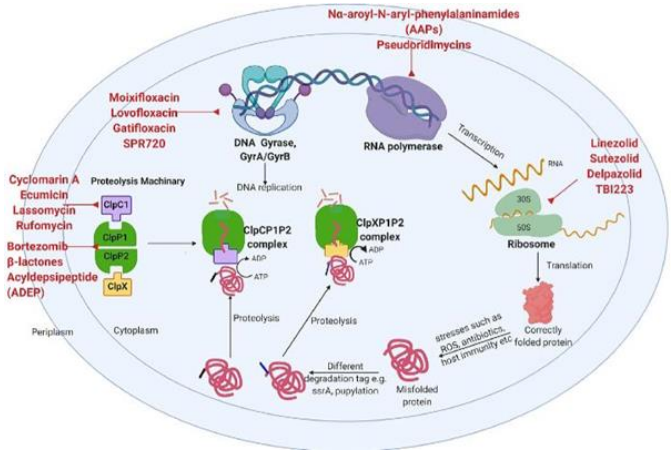

Figure 2- Schematic diagram for inhibition of m. Tuberculosis sites

Mycobacteria and other organisms develop resistance to rifampin rather rapidly. However, the incidence of resistant bacilli is less than 10–7 and it is quite unusual for a patient to have primary rifampin resistant tubercular infection. In India it is estimated to be 2%. Rifampin resistance is nearly always due to mutation in the rpoB gene reducing its affinity for the drug. No cross resistance with any other antitubercular drug, except rifampin congeners, has been noted.

Pharmacokinetics It is well absorbed orally, (bioavailability is ~ 70%), but food decreases absorption; rifampin is to be taken in empty stomach. It is widely distributed in the body: penetrates intracellularly, enters tubercular cavities, caseous masses and placenta. Though it crosses meninges, it is largely pumped out from CNS by P-glycoprotein. It is metabolized in liver to an active deacetylated metabolite which is excreted mainly in bile, some in urine also. Rifampin and its desacetyl derivative undergo enterohepatic circulation. The t½ of rifampin is variable (2–5 hours).

Interactions Rifampin is a microsomal enzyme inducer—increases several CYP450 isoenzymes, including CYP3A4, CYP2D6, CYP1A2 and CYP2C subfamily. It thus enhances its own metabolism (area under the plasma concentration-time curve is reduced by ~35%) as well as that of many drugs including warfarin, oral contraceptives, corticosteroids, sulfonylureas, steroids, HIV protease inhibitors, nonnucleoside reverse transcriptase inhibitors (NNRTIs), theophylline, metoprolol, fluconazole, ketoconazole, clarithromycin, phenytoin, etc. Contraceptive failures have occurred. It is advisable to switch over to an oral contraceptive containing higher dose (50 μg) of estrogen or use alternative method of contraception.

On the Mechanism of Rifampicin Inhibition of RNA Synthesis

E. coli RNA polymerase was studied with a newly developed steady state assay for RNA chain initiation and by analysis of the products formed with several 5'- terminal nucleotides. The major effect of rifampicin was found to be a total block of the translocation step that would ordinarily follow

formation of the first phosphodiester bond. These effects were incorporated into a steric model for rifampicin inhibition. Additional minor effects of the enzyme bound inhibitor were to increase slightly the lifetime of RNA polymerase on the XPK promoter and to increase by two the apparent Michaelis constants of the initiating triphosphates. The products formed by RNA polymerase in the presence of rifampicin belong nearly exclusively to the class Punp. No evidence for the accumulation of such molecules was obtained in viuo.

Effect of rifampicin on liver function in man

Liver function and serum concentrations of rifampicin, a highly cholephilic antibiotic, have been studied after ingestion of a single dose of 600 mg of rifampicin in 12 patients, six of them having a normal liver and six a cirrhotic, and during treatment with 600 mg of rifampicin per day for 17 days in eight patients, four of them having a normal liver and four a cirrhotic. Rifampicin produced competition for the elimination of bilirubin and bromsulphalein by the liver.

This competition, which seemed to involve mainly the uptake by the liver cell, was always rapidly reversible when treatment was discontinued. It makes it impossible, however, to interpret a bromsulphalein test during treatment with rifampicin. In the eight patients treated for 17 days, apart from the competition already mentioned, no clinical, biological, or morphological abnormalities of the liver were ascertained. But in this limited number of patient's, it is not possible to exclude the fact that rifampicin could provoke jaundice by idiosyncrasy in a small percentage of cases.

The serum concentrations of rifampicin were higher in cirrhotic patients than in patients with normal livers, especially after one or two weeks of treatment. It is suggested that efficient blood concentrations of rifampicin would be achieved with small doses in case of previous hepatocellular insufficiency.

Rifampicin reduces effectiveness and bioavailability of prednisolone

Rifampicin is an inducer of hepatic drug metabolising enzymes. This results in interactions with several drugs including oral anticoagulants, hypoglycaemics, and contraceptives. Concurrent treatment with prednisolone and rifampicin is given when tuberculosis coexists with a disease that is sensitive to steroids, when the diagnosis is uncertain, or occasionally in the treatment of severe tuberculosis. Two patients with respiratory disease were treated with both drugs:

Their condition improved considerably after rifampicin was withdrawn. Seven patients were then studied to assess the effect of rifampicin on the pharmacokinetics of prednisolone. Overall, rifampicin increased the plasma clearance of prednisolone by 45% and reduced the amount of drug available to the tissues (area under the plasma concentration time curve) by 66%. The effectiveness of prednisolone may be considerably reduced when rifampicin and prednisolone are used in combination.

Rifampicin is an inducer of the hepatic mixed function oxygenase enzymes involved in drug metabolism. Needle biopsy specimens of the liver from patients receiving rifampicin show an increase in cytochrome P4503 and proliferation of smooth endoplasmic reticulum in the hepatocytes.

Rifampicin induces its own metabolism' during continuous treatment as demonstrated by a shortened half-life. In addition, rifampicin can accelerate the elimination of the contraceptive pill, leading to menstrual disturbance and unwanted pregnancy. Tolbutamide, hexobarbitone, and oral anticoagulants are other drugs whose metabolism is similarly affected.

ADVERSE DRUG REACTION

Reaction	**Frequency of occurrence**	**Management**
1. To either daily or intermittent rifampicin administration		
1.1 Cutaneous	Uncommon	Usually mild and self- limiting.

	(<5%)	
1.2 Gastrointestinal	Variable	Give rifampicin during or immediately after a meal
1.3 Hepatitis	Uncommon (<1%)	Stop all drug treatment. Adult patient to hospital. Give alternative chemotherapy if hepatitis recurs or if liver function tests again become abnormal.
1.4 Purpura	Very uncommon	Stop rifampicin treatment and never resume it.
2. To intermittent rifampicin administration only		
2.1 "Flu" syndrome	Uncommon during first 12 weeks of administration, thereafter more frequent; varies with dose size and interval between doses	Reduce dose size of rifampicin. If this is unsuccessful change to daily administration.
2.2 Shock	Rare	Stop rifampicin treatment and never resume it. Admit patient to hospital.
2.3 Shortness of breath	Rare	Stop rifampicin treatment and never resume it. Admit patient to hospital if blood pressure falls or if shock sets in.
2.4 Haemolytic anaemia	Rare	Stop rifampicin treatment and never resume it. Admit patient to hospital
2.5Renal failure	Rare	Stop rifampicin treatment and never resume it. Admit patient to hospital

II. LITERATURE REVIEW

SR. NO.	TITLE	AUTHOR	YEAR	DISCRIPTION	REF .NO
1	The effect of rifamycin SV on bile pigment excretion in rats.	Acocella, G., and Billing, B. H.	1965	Anti-tuberculosis drugs, the main aim for improving current treatment should be to optimize the use of the two current drugs,	1
2	Biliary excretion of antibiotics in man	Acocella, G., Mattiussi, R., Nicolis, F. B., Pallanza, R., and Tenconi, L. T.	1968	The rifamycin activity could be improved by increasing the dose size of rifampicin or by daily dosing with long acting rifapentine.	2
3	The effect of an intravenous infusion of rifamycin SV on the excretion of bilirubin,	Acocella, G., Nicolis, F. B., and Tenconi, L.	1965	Increasing the dose size of pyrazinamide is limited by toxicity but an alternative	3

	bromsulphalein and indocyanine green in man	T.		approach is to use inhalation with pyrazinoic acid,	
4	Excretion of unconjugated bilirubin in rat bile.	Gastroenterology, 49, 521-525. Berthelot, P	1967	, thus increasing the bactericidal activity of the orally administered pyrazinamide. Because pyrazinoic acid is the active moiety,	4
5	In Bilirubin Metabolism.	, I. A. D. Bouchier, and B. H. Billing,	2004	it should also increase overall pyrazinamide activity and, because most resistance arises in the pncA gene that converts pyrazinamide to pyrazinoic acid,	5
6	Effect of bunamiodyl on hepatic uptake of sulfobromophthalein in the rat.	Berthelot, P., and Billing, B. H.	1966	The properties of drug containing microparticles and nanoparticles during inhalation and storage are reviewed.	6
7	Measurement of urinary 6-3 hydroxycortisol excretion as an in vivo parameter in the clinical assessment of the microsomal enzyme inducing capacity of antipyrine, phenobarbitone and rifampicin	.Ohnhaus EE, Park BK.	2001	Spray-dried larger Trojan particles in which the smaller encapsulated particles can reside should be able to improve localisation within alveoli and avoid some storage problems.	7
8	. Differential induction of antipyrine metabolism by rifampicin	Toverud EL, Boobis AR, Brodie MS, et al.	1981	This would acidify pulmonary lesions, thus increasing	8
9	Determination of drug metabolising enzymes in needle biopsies of human liver.	.Schoene B, Fleischman RA, Remmer H, Von Oldershausen HF.	1973	Rifampicin is one of the most potent and broad spectrum antibiotics against bacterial pathogens	9
10	Changes of the smooth endoplasmic reticulum induced by rifampicin in human and guinea pig hepatocytes.	.Jezequel AM, Orlandi F, Tenconi LT	1971	It is a semisynthetic derivative of rifamycin B obtained from Streptomyces mediterranei.	10
11	. Kinetics of rifampicin and isoniazid administered alone and in combination to normal subjects and patients with liver disease	Acocella G, Bonollo L, Garimoldi M, Mainardi M, Tenconi T, Nicolis FG.	1972	Rifampicin is bactericidal to M. tuberculosis and many other gram-positive and gram-negative bacteria like Staph.	11
12	Effects of antibiotics on	Nocke-Finck L,	1973	aureus, N. meningitidis, H.	12

	oestrogen excretion in women taking oral contraceptives. Acta Endocrinol	Breuer H, Reimers D		influenzae, E. coli, Klebsiella, Pseudomonas, Proteus and Legionella.	
13	. Induction of drug metabolism in man after rifampicin treatment measured by increased hexobarbitone and tolbutamide clearance	Zilly W, Breimer DD, Richter E	1975	It is also used to treat infection by Listeria species, Neisseria gonorrhoeae, Haemophilus influenzae and Legionella pneumophila	13
14	. Interaction of sodium, warfarin and rifampicin studies in man. Ann Intern Med	O'Reilly RA	1975	For these non-standard indications, sensitivity testing should be done (if possible) before starting rifampicin therapy. Rifampicin resistance develops	14
15	Rifampicin-induced non-responsiveness to corticosteroid treatment in nephrotic syndrome.	Hendrickse W, McKiernan J, Pickup M, Lowe J.	1979	it should be used in combination with other antibiotics.	15
16	Interaction of rifampicinand glucocorticoids.JAMA	Buffington GA, Dominguez JH, Piering WF, Herbert LA, Kaufman HM, Leman J.	1976	With multidrug therapy (MDT) used as the standard treatment of leprosy, rifampicin is always used in combination with dapsone and clofazimine	16
17	Plasma prednisolone levels from enteric and non-enteric coated tablets estimated by an original technique.	"Morrison PJ, Bradbrook ID, Rogers HJ.	1977	The antituberculosis drug rifampicin (rifampin) induces a number of drug-metabolising enzymes, having the greatest effects on the expression of cytochrome P450 (CYP)	17
18	Comparison of radioimmunoassay and thin layer chromatography assay methods for	Al-Habet SMH, McAllister WAC, Collins JV, Rogers HJ.	1999	such as intestinal and hepatic P-glycoprotein. Full induction of drug-metabolising enzymes is reached in about 1 week after starting rifampicin treatment and the induction dissipates in roughly 2 weeks after discontinuing rifampicin.	18
19	estimation of plasma prednisolone concentrations	, Halliday J,	1981	Rifampicin has its greatest effects on the pharmacokinetics of orally administered drugs that	19

20	Pharmacokinetics.	Gibaldi M, Perrier D	1975	Thus, for example, oral midazolam, triazolam, simvastatin, verapamil and most dihydropyridine calcium channel antagonists are ineffective during rifampicin treatment.	20
21	. Dose dependent prednisolone kinetics.	Tanner A, Bochner F, Caffin J, Halliday J, Powell L	1979	The plasma concentrations of several anti-infectives, such as the antimycotics itraconazole and ketoconazole and the HIV protease inhibitors indinavir, nelfinavir and saquinavir, are also greatly reduced by rifampicin	21
22	Pharmacokinetics of intravenous and oral prednisolone. Br J Clin Pharmacol	Al-Habet S, Rogers HJ.	1980	The use of rifampicin with these HIV protease inhibitors is contraindicated to avoid treatment failures.	22
23	Pharmacokinetics and bioavailability of prednisone and prednisolone in healthy volunteers and patients: a review	Gambertoglio JG, Amend WJC, Benet LZ	1980	Rifampicin can cause acute transplant rejection in patients treated with immunosuppressive drugs, such as cyclosporin.	23
24	Changes in cortisol metabolism following rifampicin therapy.	Edwards OM, Courtenay-Evans RJ, Galley JM, Hunter J, Tait AD	1974	Rifampicin also induces CYP2C-mediated metabolism and thus reduces the plasma concentrations of,	24
25	plasma prednisolone concentrations	Acta crystallogr. Korzheva, N., Mustaev, A., Nudler, E., Nikiforov, V., and Goldfarb,A47	1987	In addition, rifampicin can reduce the plasma concentrations of drugs that are not metabolised (e.g. digoxin) by inducing drug transporters such as P-glycoprotein	25
26	Mechanistic model of the elongation complex of Escherichia coli RNA polymerase.	Korzheva, N., Mustaev	2000	such as cyclosporin. In addition, rifampicin reduces the plasma concentrations of methadone, leading to symptoms of opioid withdrawal in most patients.	26
27	A structural model of transcrip tion elongation	Korzheva, N., Mustaev, A., Kozlov, M.,	1978	Thus, the effects of rifampicin on drug metabolism and transport are broad and of	27

		Malhotra, A., Nikiforov, V., Goldfarb, A.,		established clinical significance	
28	Structure-activity relationships in rifamycins. In Structure-Activity Relationship in Semisynthetic An tibiotics, D. Perlaman, ed.	Lancini, G., and Zanichelli, W.	1977	Potential drug interactions should be considered whenever beginning or discontinuing rifampicin treatment.	28
29	Amino acid changes in conserved regions of the beta-subunit of Escherichia coli RNA polymerase alter transcription pausing and termination. Genes Dev	Landick, R., Stewart, J., and Lee, D.N	1990	It is particularly important to remember that the concentrations of many of the other drugs used by the patient will increase when rifampicin is discontinued as the induction starts to wear off.	29
30	Nucleotide substitutions in the rpoB gene leading to rifampicin resistance of E. coli RNA polymerase.	forov, V.G.	1984	The amount of rifampicin extracted by the liver during its first passage through the hepatoportal system and transferred to bile is of relevance for the time course of distribution of the antibiotic in the blood compartment.	30
31	Danilevskaya, O.N., and Nikiforov	Lisitsyn, N.A., Sverdlov, E.D., Moiseyeva, E.P.	1984	With doses of the order of 300 to 450mg, the excretory capacity of the liver for the antibiotic is saturated.	31
32	Mutation to rifampicin resistance at the beginning of the RNA polymerase beta subunit gene in Escherichia coli	Mol. Gen. Genet	1977	As a consequence, increasing the dose of antibiotic results in a more than proportional increase in serum concentrations.	32
33	On the mechanism of rifampicin inhibition of RNA synthesis.	McClure, W.R., and Cech, C.L	1978	the phenomenon affecting mainly the levels following the peak, with a consequent reduction in half-life.	33
34	Bacterial RNA polymerase subunit and eukaryotic RNA polymerase subunit RPB6 are sequence, structural, and functional homologs and promote RNA polymerase assembly. Proc.	Minakhin, L., Bhagat, S., Brunning, A., Campbell, E.A., Darst, S.A., Ebright, R.H.,	2001	Probably in the hepatocyte, rifampicin undergoes a process of desacelylation. The metabolic derivative, desacetylrifampicin, is more polar than the parent compound, and	34

				microbiologically active.	
35	Recombinant Thermus aquaticus RNA polymerase-A new tool for structure-based analysis of transcription	Minakhin, L., Nechaev, S., Campbell, E.A., and Severinov, K	2001	Administration of rifampicin to newborn infants and children is followed by blood levels generally lower than those.found in adults for the same dose levels. In patients with impaired liver and kidney function the elimination of the antibiotic from the blood compartment is slower than in normal subjects.	35
36	RNA polymerase unveiled.	Mooney, R.A., and Landick, R.	1999	Rifampicin has been found to compete with bilirubin and other cholefil substances for biliary excretion, giving rise to transient and reversible increased bilirubin and BSP retention values.	36
37	Isolation of rifampin-resistant mutants of Listeria monocytogenes and their characterization by rpoB gene sequencing, temperature sensitivity for growth, and interaction with an epithelial cell line	Morse, R., O'Hanlon, K., Virji, M., and Collins, M.D.	1999	A kinetic model study on the transfer constants between various body compartments has indicated that rifampicin is rapidly absorbed from the intestine and that the absorption rate increases with time.	37
38	Topology of the RNA poly merase active center probed by chimeric rifampicin-nucleotide compounds.	Proc. Natl. Acad. Sci.	2008	Administration of rifampicin to man is associated with proliferation of the smooth endoplasmic reticulum of the hepatocyte and with a state of induction of the drug metabolising enzyme system in the liver.	38
39	Modular organization of the catalytic center of RNA polymerase.	.Mustaev, A., Kozlov, M., Markovtsov, V., Zaychikov, E., Denissova, L,	1997	Rifampicin inhibits DNA-dependent RNA polymerase in bacterial cells by binding its beta-subunit, thus preventing transcription of messenger RNA	39
40	Rifampicin resistance in Neisseria meningitidis: evidence from a study of sibling strains, description of	Nolte, O.	1997	Pharmacokinetics It is well absorbed orally, (bioavailability is ~ 70%), but food decreases absorption; rifampin is to be	40

	new muta tions and notes on population genetics. J. Antimicrob.			taken in empty stomach.	

Discussion

There is a wide range of conditions that is responsive to steroids and during the course of which tuberculosis may develop and treatment with rifampicin be added. Such conditions, for which steroids are often essential, are as varied as asthma, systemic lupus and other connective tissue disorders, fibrosing alveolitis, and glomerulonephritis; the problem also arises in patients receiving post-transplantation regimens and cancer chemotherapy.

Corticosteroids are occasionally used temporarily as part of the treatment of tuberculosis or in reducing oedema in those with a cerebral or spinal tuberculous abscess impinging dangerously on neurological structures. Alternatively, the combination of rifampicin and prednisolone may be used when the diagnosis is not clear and tuberculosis cannot be excluded.

In particular, it can be difficult to distinguish histologically and clinically between tuberculosis and sarcoidosis. If rifampicin and prednisolone are used in combination in any of these circumstances the steroid is exerting considerably less effect than might be expected. The case histories above illustrate this point and underline how easily failure to respond to treatment may be ascribed to the severity of the illness rather than to drug interaction.

It is important to note that once rifampicin was stopped in case 8 the patient's condition improved despite continued treatment with ethambutol and isoniazid, implying that rifampicin alone was exerting the deleterious effect. Possible clinical effects of rifampicin in patient’s dependent on prednisolone have been reported.9 10 Edwards et a 17 described a patient with Addison's disease who required an increased corticosteroid dose while receiving rifampicin. However, reduced half-life of prednisolone in a young boy determined by using a radiolabelled tracer no quantitative studies of the effect of rifampicin on the metabolism of prednisolone have been carried out.

Our pharmacokinetic study shows a pronounced effect of rifampicin on the metabolism of prednisolone. Although rifampicin is a hepatic enzyme inducer, the precise mechanism of the interaction cannot be distinguished. The core observation is that the area under the prednisolone curve, which is a model independent variable based solely on observations without any interpretation as to mechanism, is reduced with rifampicin.

The area under the curve roughly represents the amount of drug available to the tissues, and a 66% reduction in this might have serious consequences if not compensated for by adjustment of the dosage. Not only may patients in whom disease control depends on prednisolone suffer exacerbation of disease, but a condition that responds to steroids may be overlooked if rifampicin is administered concurrently. The consequences are particularly important as in many cases there are no viable alternatives to corticosteroid treatment and the findings above are probably qualitatively true for all steroids. Rifampicin remains an extremely useful antituberculosis agent, and an alternative to changing to other chemotherapy would be to at least double the dose of prednisolone if rifampicin is to be administered simultaneously.

III.CONCLUSION

During the recent decade, significant progress has been made in reinvigorating the almost nonexistent pipeline of novel agents for the treatment of tuberculosis and in re-establishing the infrastructure for the conduct of clinical trials of new tuberculosis

drugs and treatment regimens. Recent studies of long-acting rifamycin derivatives and potent tluoroquinolone antibiotics are leading to improved regimens for the treatment of active and latent tuberculosis. A number of other compounds in late preclinical and early clinical development show great promise. The rapid increase in knowledge of mycobacterial pathogenesis is leading to the identification of new drug targets, including those believed to playa role in latent infection or in the phenomenon of persistence. A major challenge will be to sustain and increase funding for continued developmental and clinical work if the promise of tuberculosis elimination, or at least significant lessening of the global tuberculosis epidemic, is to be achieve.

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