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Review Article

AUTOINDUCTION PROPERTIES OF RIFAMPICIN ON JAVANESE TUBERCULOSIS WITH VARIANT TYPE CYP3A4*1G

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ABSTRACT

Rifampicin is one of the first-line anti-tuberculosis drugs. Rifampicin is metabolized by cytochrome P450 (CYP) 3A4. Polymorphisms of the CYP3A4 gene will affect gene expression. This leads to impaired of formation of the enzyme. The purpose of this review is to explore the effect of self-induction of Rifampicin. The results of this review showed that Rifampicin was metabolized by the CYP3A4 enzyme. Rifampicin has self-induction properties since Rifampicin also induces CYP3A4 enzyme. Rifampicin treatment repeated for 14 days leads to a shortening elimination half-life. Self-induction of CYP3A4 by Rifampicin maximum is reached after 21 days of use. Bioavailability of Rifampicin decreased from 93% to 68% after 3 weeks of treatment single dose orally. After 7 days administration of Rifampicin will increase clearance but decrease the area under the curve and C_{min}. The effect of autoinduction of Rifampicin is estimated occurs after the first 6 days of administration. In individual with the variant type of CYP3A4 namely CYP3A4*1G/*1G, the effect of self-induction of Rifampicin is minimal.

Keywords: Autoinduction, Rifampicin, Cytochrome P450 3A4*1G.

INTRODUCTION

Drug in the body undergoes metabolic processes. The purpose of the metabolism is to make the drug becomes more polar making it easier excreted in the kidneys. There are two stages of metabolism. The metabolic phase is: The Phase I metabolism involves cytochrome P450 (CYP) enzymes (CYP enzymes), while in Phase II metabolism involves the enzyme N-asetyiltransferase, thiopurine S-methyltransferase, and glutathione transferase [1]. Most drugs undergo the two stages, and some others only through one stage. Induction and inhibition of this enzyme would lead to changes in metabolism. This will cause changes in the kinetic and dynamic profile of drugs [2].

CYP

CYP is a superfamily of enzymes group containing heme. More than 90% of drugs are metabolized by this enzyme. This enzyme group categorized into families and subfamilies based on amino acid sequence [3]. This enzyme plays an important role in the metabolism of the substrate indogenous (steroids, fatty acids) or exogenous (such as drugs or carcinogen and toxin) [4,5]. CYP is a hemoprotein that acts as a terminal oxidase in Phase I of metabolism [6]. This enzyme is expressed mainly in the liver and a small portion in the small intestine, lung, placenta, and kidney [7].

CYP3A4

CYP3A4 isoenzyme is found in the liver, gastrointestinal tract and kidney parenchyma and prostate [8,9]. This enzymes consists of 18 isoform and 502 amino acid. The molecular weight (MW) of this isoenzyme is 57.1 kDa [9].

CYP3A4 is involved in the metabolism of more than 50% of drugs in humans [10,11], among others: Alprazolam, amiodarone, amlodipine, amitriptyline, atorvastatin, dexamethasone, dektrometorpan, diazepam, digoxin, diltiazem, ketoconazole, ondansentron, terfenadine, progesterone, nateglinid and others. CYP3A4 activity varies greatly among individuals. Polymorphisms in CYP3A4 genes may lead to different responses to drugs in the substrates of CYP3A4. The response variation can reach 20 times [12].

Several drugs have been known to be inhibitors and inductors of CYP3A4. One case the interaction of CYP3A4 substrates with CYP3A4 inhibitors or inductor will contribute to the success of the treatment. On the other case this may lead to side effects. Drugs known as inductors CYP3A4 among others: Antiepileptic drugs (phenobarbital group, phenytoin, carbamazepine, felbamat, lamotrigine, oxcarbazepine, primidone, rufinamid and topiramate), cyclophospamide, erythromisine, griseofulvine, lansoprazole, nevirapine, omeprazole, phenitoin, phenobarbital, pioglitason, prednisone, rifampin, troglitason, while the drugs that are inhibitors of CYP3A4 include: Chlorampenicol, cimetidine, ciprofloxacin, fluconazole, itraconazole, nevirapine, norfloxacin, voriconazole, estradiol and others [9].

INDUCTION OF CYP

Induction of an enzyme causes a relative slow process involving the activation of transcription of the gene or mRNA or protein stabilization. This process will change pharmacokinetics and pharmacodynamics of drugs [13,14]. The change of pharmacokinetic and dynamic of drugs can cause over effects or less of effect [15]. The factors influence the induction are genetic variant of host (CYP or receptor genes) that causes changes in the nature of induction. Host physiological factors (such as hepatic dysfunction, infection) and the environmental factors such as diet can alter the response to the inductor [16]. The influence of induction can be seen from the presence of drug metabolites (induced by inductor) in the urine [17] and a decrease in area under the curve [18,19]. The induction activity can cause an increase in mRNA, protein or P450 CYP enzyme activity in the body [13,20,21].

Auto induction/self-induction of rifampicin

Rifampicin is a semisynthetic derivative of Rifampicin B. This substance is produced by Streptomyces mediterranei. MW of these drugs is 823. Rifampicin is soluble in organic solvents and acidic pH water [22,23]. Rifampicin is bactericidal both the intracellular and the extracellular. *In vitro*, rifampicin has activity inhibiting the growth of Gram-positive and Gram-negative (such as *Escherichia coli* and *Pseudomonas*) and indole positive and negative, such as *Proteus* and *Klebsiella*. This drug is also very active against *Staphylococcus aureus* with bactericidal concentrations varied between 3 and 12 ng/mL. Bacterium *Neisseria meningitidis* and *Haemophilus influenzae* are inhibited by rifampicin

with the minimal inhibitory concentration (MIC) from 0.1 to 0.8 mg/mL [24].

Rifampicin concentration 0.005-0.2 mg/mL could inhibit the growth of *Mycobacterium tuberculosis in vitro*. Some species *Mycobacterium* non-tuberculosis such as *Mycobacterium kansasii* is inhibited at concentrations of 0.25 to 1 mg/mL. *Mycobacterium scrofulaceum*, *Mycobacterium*. *intracellulare* and *Mycobacterium avium* are inhibited at a concentration of 4 mg/mL but certain strains of resistant bacteria can be inhibited at a concentration of 16 mg/mL. *In vitro*, rifampicin may increase the activity of streptomycin and isoniazid [24].

Rifampicin undergoes deacetylation and within 6 hrs all medicines are becoming metabolites (deasetyl rifampicin). C_{max} of Rifampicin given orally is 2-4 hrs. Dose of 450 mg Rifampicin resulted rifampicin levels 6-16 mg/mL after 2 hrs (1-4 hrs) [23]. A single dose of rifampicin 600 mg resulted plasma rifampicin levels about 7 mg/mL. MIC of Rifampicin against *M. tuberculosis* is 0.005-0.2 µg/mL [25]. Metabolism of Rifampicin is deacetylation in which the process in conducted by microsomal oxidative enzymes. The active metabolite of Rifampicin are 25-O-deasetyl rifampicin (major) [26], quinine rifampicin, desacetyl rifampicin quinine, and 3-formylrifampin [27]. Rifampicin is a CYP3A4 substrate, so that is metabolized by CYP3A4. Besides the substrate of CYP3A4, Rifampicin is a potent CYP3A4 inductors [28,29]. Rifampicin has auto-induction/self-induction properties since the drug induces its own metabolites [30-34]. The repeated treatment of Rifampicin will cause induction of CYP3A4 (auto-induction/self-induces), which cause shortening of t½. Rifampicin treatment repeated for 14 days leads to a shortening elimination t½ 40%. Autoinduction CYP3A4 by Rifampicin maximum is reached after 21 days of use [28]. Bioavailability of Rifampicin decreased from 93% to 68% after 3 weeks of treatment single dose orally. After 7 days administration of Rifampicin will increase clearance but decrease of half-life of its elimination [35]. Repeated administration of Rifampicin will decrease the AUC and C_{min}. Auto-induction of Rifampicin cause decreased elimination half-life. It is estimated that this condition occurs after the first 6 days of administration [36]. Mechanism of action of Rifampicin was suspected by pregnant X receptor. Rifampicin was suspected regulating drug metabolizing enzyme and drugs transporter [37].

Auto-induction of rifampicin on variant type CYP3A4*1G

Several studies have identified a variation on this CYP3A4 genes. Wild type of CYP3A4 is CYP3A4*1 (*1/1) (38,39). It were mapped about 40 haplotypes/variant type on CYP3A4. Variant type of CYP3A4 include: CYP3A4*1B, 1C*, *1D, 1E*, *1F, *1G, 1H*, *1I, 1J*, *1K, 1L*, *1M, 1N*, *1P, *1Q, *1R, 1S*, *1T, *2, *3, *4, *5, *6, *7, *8, *9, *10, *11, *12, *13, *14, *15, *16A, 16B*, *17, *18A, 18B*, *19 and CYP3A4*20. The common of variant type in Asian populations are CYP3A4*1G (18.9%), CYP3A4*1H (1%), CYP3A4*1J (0.4%), CYP3A4*1K (0.1%), CYP3A4*1L, *M, *N, *P, *Q, *R, *S, *T (0.1%) [38]. One type of variant CYP3A4*1 is CYP3A4*1G. It was found that the substitution 82266 G>A in individuals with CYP3A4*1G gene causes the substitution of isoleucine in to valine (I369V) [39]. Frekuensi CYP3A4*1G pada populasi china adalah 0,269 [40].

Research by Sutrisna *et al.* in 2011 showed that prevalence of CYP3A4*1G/*1G in Javanese tuberculosis is 20% [41]. The oral administration of Rifampicin in tuberculosis patients with type CYP3A4*1G/*1G genes for 56 days did not cause decrease in the plasma levels of Rifampicin. The individuals with CY3A4*1G/*1G shows the plasma levels of Rifampicin on days 0 is 3.77±2.16 mg/mL while on day 14, 28 and 56 respectively 3.91±1:41; 3.99±1.64 and 3.83±1.95 mg/mL [42]. It is suspected that the effect of auto-induction in individuals with CYP3A4*1G/*1G reduced or lost. This is due to the individual with this variant type have reduced CYP3A4 enzyme activity [39,40]. The homozygous CYP3A4*1G/*1G have lower activity of enzyme CYP3A4 than wild type (CYP3A4*1/*1) and heterozygous CYP3A4*1/*1G [40]. The low activity of CYP3A4 decrease metabolism of Rifampicin. This causes plasma Rifampicin level did not reduced after repeated treatment.

CONCLUSION

Rifampicin is metabolized by the CYP3A4 enzyme. Rifampicin has autoinduction properties as rifampicin also induces CYP3A4 enzyme. The autoinduction properties of Rifampicin is minimal in individuals with type variant of CYP3A4*1G/*1G.

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