CHAPTER 5

DISCUSSION AND CONCLUSION

Risperidone is a relatively new antipsychotic available world–wide since the early 1990s. It is a novel antipsychotic with dopaminergic and serotonergic effects. The main pharmacological activities of risperidone include serotonin (5–HT_2) receptor blockade and dopamine (D_2) antagonism (Megens *et al*., 1994). After oral administration of 1 mg of risperidone, 5–HT_2 receptor occupancy is about 60% and D_2 receptor occupancy in the striatum is about 50% (Nyberg *et al*., 1993). Risperidone is rapidly and very well absorbed after administration orally ; less than 1% is excreted unchanged in the faeces (Heykants *et al*., 1994). Risperidone is 90% plasma protein bound (Borison *et al*., 1994). The principal metabolite is 9-hydroxyrisperidone. Hydroxylation of risperidone is subject to the same genetic CYP 2D6-related polymorphism as for debrisoquine and dextromethorphan. In poor metabolizers the half-life of risperidone was about 20 hours compared with about 3 hours in extensive metabolizers (Huang *et al*., 1993). Risperidone exhibits linear elimination kinetics. Steady state is reached within 1 day for risperidone and within 5 days for the active fraction.

Rifampin is a potent inducer of the CYP enzyme system such as CYP 3A4, 1A2, 2C19, 2D6, etc (Strayhorn *et al*., 1997). Clinical studies in healthy volunteers demonstrated a reduction in the plasma concentrations and half-life of ondansetron following treatment with rifampin, and concluded that the interaction is most likely the result of induction of the CYP 3A4-mediated metabolism of ondansetron (Villikka *et al*., 1999). Another clinically important drug interaction with rifampin was concomitant administration with oral contraceptives, and it was found that a 4 fold increase in the rate of hydroxylation of estradiol and ethinylestradiol in patients treated with rifampin was associated with an increases of CYP content in liver biopsies (Lin, 2003). Ridtitid *et al*., (2002) found that 5 days pretreatment with 600 mg of oral rifampin causes a great reduction in plasma concentrations of either a single oral dose (40 mg/kg) or multiple oral doses (25 mg/kg) of praziquantel, which will lead to the failure of treatment if these interactions occur in patients. Backmann and Juregui (1993) found that rifampin induced several cytochrome P 450 isoenzymes, not only CYP 3A4 but also CYP 1A and CYP 2C.

In the present study, rifampin was given to the healthy male volunteers at the dose of 600 mg in a single dose regimen for 5 days, because the dose was sufficient to induce hepatic microsomal enzymes as described in previous studies (Miguet *et al*., 1977; Borcherding *et al*., 1992; Tracy and Webster, 2001). The recommended dose of risperidone for treatment of psychotic patients such as Schizophrenia in Thailand is 2-8 mg. Risperidone was given orally 4 mg in healthy volunteers, because Niemegeers *et al*., (1999) have suggested 4 mg/day as the best minimal dosage regimen. They comment that treatment with risperidone, 6 mg/day, is likely to induce unnecessarily high D_2 receptor occupancy, with a consequent extrapyramidal side effects. They found that high 5-HT_{2A} receptor occupancy did not prevent extrapyramidal side effects completely. To achieve this, they suggested risperidone, 4 mg/day, as a suitable initial dose for antipsychotic effect with a minimal risk of extrapyramidal side effects in most patients.

The present results revealed that when a single oral dose of risperidone was administered with rifampin for 5 days, plasma concentrations of risperidone could be detected in all 10 subjects. In the 10 subjects which were pretreated with rifampin for 5 days, the mean AUC_{0-48}, $AUC_{0-\infty,}$ C_{max} and $MRT_{0-\infty,}$ of risperidone were reduced by 78.38% (4.6 fold), 77.55% (4.5 fold), 51.91% (2.1 fold) and 64.86% (2.8 fold), respectively, while the mean V_d/f and Cl/f increased by 31.17% (1.45 fold) and 88.51% (8.7 fold), respectively, compared with those values when risperidone was administered alone. However, the mean K_e, t_{max} and $t_{1/2}$ were not significant different form control when compared to risperidone alone in the ten subjects.

Pretreatment with rifampin prior to risperidone resulted in increase in clearance of risperidone. These changes led to corresponding largely decrease in C_{max} and AUC of risperidone, suggesting that the biotransformation of risperidone was increased. It is well established that risperidone undergoes extensive first-pass metabolism by the liver since the mean C_{max} , AUC_{0-48}, and $AUC_{0-\infty,}$ of risperidone in this study were markedly decreased after rifampin pretreatment, thus it could suggest that the presystemic metabolism of risperidone was markedly increased. These results were in good agreement with other studies of interindividual variability in cytochrome P 450 induction. For example, Ged *et al*. (1989) reported that there was a large interindividual variation in the changes in protein level of CYP 3A4 in human liver before and

after rifampin treatment. Fourteen patients were included in the study, in which liver biopsies were collected before and after rifampin treatment (600 mg/day for 4 days). After rifampin treatment, there were an 18 fold difference in the induction of CYP 3A4 protein. The extent of increase ranged from 160% to 2900% among these patients. Similar to the hepatic enzyme induction, considerable interindividual variability in human CYP 3A4 induction in small intestine by rifampin was reported by Kolars *et al*. (1992), using endoscopic biopsies in five healthy volunteers. The extent of increase in mRNA of CYP 3A4 in enterocytes during rifampin treatment (600 mg/day for 7 days) ranged from no change in one volunteer to 12 fold in other volunteers. Like the variability in CYP 3A4 induction, a large variation was also seen in intestinal CYP 1A induction by omeprazole (Mc Donnel *et al*., 1992). Endoscopic tissue specimens from 6 healthy volunteers were analyzed for mRNA and enzymatic activity measured by deethylation of ethoxyresorufin before and after omeprazole treatment (20 mg/day for 1 week). The extent of increases in both mRNA and enzymatic activity of CYP 1A was quite variable among individual and ranged from 0% to 600%. The individual who did not initially respond (20 mg/day) had a marked increase in both mRNA and enzymatic activity after receiving 60 mg of omeprazole daily for 1 week, suggesting that enzyme induction is dose dependent.

Although direct measurements of enzyme concentration and catalytic activity by induction are limited in humans, the reduction in plasma AUC of drugs has commonly been used as an indirect index for enzyme induction when concomitantly administered with inducers. As mentioned earlier, the basic study is that induction leads to an increase in the amount of existing enzymes but not to qualitatively different enzymes. Therefore, enzyme induction always causes an increase in the intrinsic clearance, as a result of increased V_d/f and the concept of intrinsic clearance is the cornerstone for relating the changes in plasma AUC to enzyme induction. Using the indirect approach, large individual variations in the decreases in plasma AUC have been reported for many drugs during enzyme induction, for example the verapamil – rifampin interaction. The extent of decrease in oral AUC of S- verapamil caused by rifampin induction ranged from 5 to 60 fold with a mean value of 30 fold in 8 healthy volunteers (Fromm *et al*., 1996). In another study involving 10 subjects, rifampin treatment decreased oral AUCs of midazolam by 11.6 to 55 fold (Backman *et al*., 1996). Similarly, a large inter individual variability was observed for the inductive effect of rifampin on triazolam in 10 healthy

volunteers (Villikka *et al*., 1996). A significant interindividual variability was also observed for cyclosporin. Daily administration of rifampin (600 mg/day) for 11 day resulted in a 2.5 to 6.6 fold increase in oral clerance of cyclosporin (Hebert *et al*., 1992). Rifampin also induces theophylline metabolism. In a clinical study involving six healthy subjects, pretreatment with rifampin resulted in a significant decrease in oral AUC of theophylline, ranging from 23% to 150% (Robson *et al*., 1984). O′Reilly (1974) reported that treatment with rifampin caused a significant reduction of warfarin plasma concentration in patients. As expected, the extent of decreases in the AUC of warfarin. For example, Villikka *et al*. (1997) reported that rifampin also has a marked pharmacokinetic and pharmacodynamic effect on triazolam, reduced triazolam AUC by 95% and C_{max} by 88%. For zolpidem, the C_{max} of zolpidem was decreased by 58%, the total AUC averaged only 27% and the half life was shortened from 2.5 ± 0.5 to 1.6 ± 0.1 hours by rifampin. The risk for potential interaction between risperidone and other drugs has not been evaluated systematically. Rifampin is a potent enzyme inducers, carbamazepine and other enzyme inducers have been shown to decrease substantially the plasma levels of risperidone and its active metabolite, 9-hydroxyrisperidone. Similar effects may be observed with other hepatic enzyme inducers.

In conclusion, results of the present study have suggested that 5 days pretreatment with 600 mg of oral rifampin causes a great reduction in plasma concentrations of a single oral dose of risperidone, which will lead to the failure of treatment. In fact, the possibility of these two drugs to be prescribed by the physicians for the same patient is not frequent. However, in the developing countries such as Thailand, psychosis (especially schizophenia) and Mycobacterium tuberculosis infection are still the important problems especially in the metropolis of the country. Risperidone is atypical antipsychotic drugs and widely used for psychosis while rifampin is widely prescribed to patient with tuberculosis in the short-course therapy. Thus, clinicians should consider monitoring of the dose of risperidone in the patient who is taking rifampin especially in the patient who does not respond to an initial treatment with risperidone, the dose of risperidone may have to be adjusted. Anyway, although plasma level of risperidone is decreased but the active metabolite, 9-hydroxyrisperidone, is increased. Therefore, the therapeutic outcome may not be changed in the early phase of the treatment. However, as the active metabolite will be finally metabolized to inactive form. Enzyme induction by rifampin should result in significant reduction of risperidone.

Additionally, CYP 2D6 is the most likely enzyme that play a major role in the metabolism of risperidone in the liver. The possibility of other mechanism may be due to the induction of other CYP 450 isoforms that involved in risperidone biotransformation or induction of P-glycoprotein. Further studies are needed to clarify the mechanism of this interaction.