CHAPTER 1

INTRODUCTION

Schizophrenia is generally considered to be a syndrome, probably a group of disorders, which produces diverse disturbances in cognition, reality testing, mood, interpersonal relations, social and work function. Schizophrenia is found all over the world. The severity of the symptoms and long-lasting, chronic pattern of schizophrenia often cause a high degree of disability. Medications and other treatments for schizophrenia, when used regularly and as prescribed, can help reduce and control the distressing symptoms of the illness. However, some people are not greatly helped by available treatments or may prematurely discontinue treatment because of unpleasant side effects or other reasons. Even when treatment is effective, persisting consequences of the illness - lost opportunities, stigma, residual symptoms, and medication side effects - may be very troubling. In recent years, the possibility that additional neurotransmitters, acting in concert with dopamine (DA), contribute to the etiology of schizophrenia and action of antipsychotic drugs has received more attention than DA (Bersani *et al*., 1990). The serotonin (5-HT) antagonists such as methysergide, cyproheptadine and ritanserin are not psychotomimetic and may possibly have beneficial effects on specific aspects of psychosis. Furthermore, antipsychotics such as clozapine, risperidone, olanzapine and ziprasidone antagonize at multiple 5-HT receptors and have some adventages over selective DA receptor antagonists. There is now considerable evidence form studies of schizophrenia and other forms of psychoses, that the atypical antipsychotic drugs such as clozapine, risperidone, olanzapine and ziprasidone are more effective with fewer extrapyramidal symptoms (EPS). These drugs have higher potencies as 5-HT_{2A} antagonists than as D_2 antagonists or at almost any other receptor (Cutler *et al*., 2000). At clinically effective dose, they all produce fewer EPS than typical neuroleptic drug. However, marked EPS can occur with risperidone if the dose is increased. Risperidone is an atypical antipsychotic agent chemically classified as a benzisoxazole derivative. It is a selective monoaminergic antagonist with high affinity for serotonin type II (5-HT_2) and dopamine-D_2 antagonists or at almost any other receptor (Nyberg *et al*., 1993). Clinical trials in psychotic patients have shown that risperidone is effective in the treatment of the positive, negative, and affective symptoms of schizophrenia (Marder *et al*.,

1997) Furthermore, risperidone therapy is associated with reduced extrapyramidal symtoms. Recently, the U.S. Food and Drug Administration (FDA) approved the use of risperidone for the treatment of residual schizophrenia, and a large prospective clinical study comparing risperidone with haloperidol has demonstrated that patients treated with risperidone have a lower risk of relapse than those treated with haloperidol. Due to the favorable clinical effects of risperidone, a substantial increase has occurred in its use during the last few years. Risperidone is rapidly and very well absorbed after administration orally; less than 1% is excreted unchanged in the faeces (Heykants *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 metbolizers the half - life of risperidone was about 20 hours compared with about 3 hours in extensive metabolizer (Huang *et al*., 1993). Plasma concentrations of risperidone, 9-hydroxyrisperidone, and risperidone plus 9-hydroxyrisperidone are dose proportional over the dosing range of 1 to 16 mg daily (0.5 to 8 mg twice a day). Risperidone exhibits linear elimination kinetics. Steady state is reached within 1 day for risperidone and within 5 days for the active fraction (Leysen *et al*., 1988).

Rifampin is a semisynthetic derivative of rifamycin B, a complex macrocyclic antibiotic. It is mainly used as an antituberculotic drug, which is usually administered for 6 to 24 months with other antituberculotic drugs. A potential for drug interactions often exists because rifampin is a potent inducer of the CYP 450 enzyme system such as CYP 3A4, 1A2, 2C19, 2D6, etc. (Villikka *et al*., 1999), as evidenced by a proliferation of smooth endoplasmic reticulum and an increase in the cytochrome P 450 content in the liver. The enzyme induction caused by rifampin affects the metabolism of many drugs, increasing their metabolism and reducing their effects. The induction is a highly selective process and not every drug metabolized via oxidation is affected (Venkatesan, 1992). Dilger *et al*. (2000) reported that rifampin induced both phase I metabolism (N – dealkylation) and phase II metabolism (glucuronidation) of oral propafenone, resulting in a clinically relevant drug interaction.

Since risperidone is metabolized by CYP 2D6 (Huang *et al*., 1993) and this enzyme is also involved in the metabolism of several other drugs (such as thioridazine, haloperidone, tricyclic antidepressants, beta – blockers, etc.), pharmacokinetic interactions due to competitive

inhibition of the enzyme may occur. Furthermore, the activity of the CYP 2D6 enzyme is genetically impaired in around 7% of Caucasians (Kondo *et al*., 2002), thus, in this patient group, the disposition of risperidone and other drugs metabolized by this enzyme is genetically impaired. In vitro studies showed that drugs metabolized by other CYP isozymes, including 1A1, 1A2, 2C9 and 3A4, are only weak inhibitors of risperidone metabolism.

Due to the increase in prescribing rifampin, the possibility of rifampin and risperidone coadministration tends to have a chance to occur in clinical practice, and may lead to cause rifampin – risperidone drug interaction. To our knowledge, there are no reports studied on the possible interaction between rifampin and risperidone, and the possible role of cytochrome 450 enzymes in the metabolism of risperidone. Therefore, the purpose of this investigation is to study the effect of rifampin on the pharmacokinetics of a single oral dose of risperidone in healthy Thai male volunteers, and the present study may be the guidance and useful data for decision making in case of coadministration of risperidone and rifampin in clinical practice.