Abstract  Objectives: To evaluate the possible pharmacokinetic interaction between nefazodone and lithium.  
Methods: Twelve healthy volunteers received nefazodone 200 mg b.i.d. for 5 days. A 4-day washout phase followed from day 6 to day 9. From day 10 to day 20, escalating doses of lithium 250 mg b.i.d. to 500 mg b.i.d. were given; the daily dose of 1000 mg was obtained on day 13. From day 16 to day 20, nefazodone 200 mg b.i.d. was added to the lithium dosing regimen. Venous blood sampling was performed on days 5, 15 and 20 for 0- to 48-h-pharmacokinetic analysis. Nefazodone and its metabolites, hydroxynefazodone, mCPP and triazoledione were assayed by high-performance liquid chromatography (HPLC). Lithium was assayed by flame photometry.  
Results: Co-administration of nefazodone did not modify pharmacokinetic parameters of lithium at steady-state. Comparison of the area under the plasma or serum concentration-versus-time curve calculated from 0–12 h (AUC0–12) of nefazodone and hydroxynefazodone revealed no significant differences when nefazodone was administered alone or with lithium. The mean maximum peak plasma concentration Cmax and AUC0–12 of meta-chlorophenyl-piperazine (mCPP) were significantly reduced by 27% (P < 0.001) and 16% (P < 0.001) with the co-administration. The mean Cmax and AUC0–12 of triazoledione were reduced by 23% (P < 0.005) and 16% (P < 0.01) by the co-administration.  
Conclusion: Since there were no clinically significant changes in the pharmacokinetics of the parent compounds or metabolites, and the combination was well tolerated, no dosage adjustments of nefazodone or lithium are necessary when they are co-administered.  
Key words  Nefazodone · Lithium · Steady-state pharmacokinetics · Healthy subjects  

Introduction  
Nefazodone, 2-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-5-ethyl-2,4-dihydro-4-(2-phenoxy-ethyl)-3H-1,2,4-triazol-3-one hydrochloride, is an antidepressant drug.  

Clinical studies show that many depressed patients treated with nefazodone experience effective antidepressant response within several weeks of the initiation of the treatment [1–3]. Nefazodone has a pharmacological profile distinct from selective serotonin reuptake inhibitors (SSRIs) and is both a potent 5-HT2 antagonist and a moderate inhibitor of neuronal reuptake of 5-HT and norepinephrine [4]. After oral administration, nefazodone is extensively metabolized by N-dealkylation and aliphatic and aromatic hydroxylation to its major metabolites, hydroxynefazodone, meta-chlorophenylpiperazine (mCPP) and a triazoledione metabolite [5, 6].
In vitro studies have shown nefazodone to be metabolized by cytochrome P450 3A1 (CYP3A4), while mCPP is metabolized by CYP2D6 [7, 8]. Importantly, nefazodone in only a very weak inhibitor of CYP2D6. All three metabolites are pharmacologically active. Hydroxynefazodone and triazoledione metabolites may contribute significantly to the therapeutic efficacy of nefazodone, while mCPP has a minor role with a low systemic exposure (≤8%) [5, 9, 10]. Nefazodone and hydroxynefazodone exhibit nonlinear kinetics for both dose and time with AUC and peak plasma concentration (Cmax) increasing disproportionally as the dose increases, while the pharmacokinetics of mCPP and triazoledione appear to be linear [9, 11].

As lithium salts share some characteristics with those of Na⁺ and K⁺, they are able to substitute for these ions at a variety of sites in the body. In addition to their effects on electrolyte and ion transport, their primary mode of action is believed to be on neurotransmitters like serotonin, norepinephrine, dopamine and acetylcholine and their effects on second messengers [11, 12, 13]. Lithium pharmacokinetics have been extensively studied [14, 15]. Lithium has a Cmax occurring 1–2 h after ingestion. It is initially distributed in the extracellular fluid and gradually enters the intracellular compartments. Lithium is excreted almost entirely in the urine [16]. The preventive activity of lithium towards the relapses of manic-depressive illness is well known [17–19]. Concomitant use of an antidepressant drug is required for the control of severe bipolar disorders and the augmentation therapy has proven to be of good efficacy [20–22], but this combination sometimes results in the occurrence of adverse events including lithium toxicity from increased lithium serum levels [23]. A few case reports of drug interactions associated with neurotoxicity symptoms have been described, either with tricyclics [24, 25] or with SSRIs [26–30]. However, controlled pharmacokinetic studies with fluvoxamine [31], sertraline [32] and citalopram [33], did not show a significant effect on lithium serum levels. The objective of this study was to evaluate the potential for a pharmacokinetic interaction between nefazodone and lithium.

**Methods**

After approval was obtained from the Ethics Committee, 13 healthy volunteers aged between 18 and 41 years, including 11 male and two female subjects, were enrolled in this open-label multiple-dose study, after signing an informed consent form. The study was carried out in accordance with the Declaration of Helsinki. The subjects had previously been screened for dextromethorphan oxidative phenotype. The result of this test was not used as an inclusion or exclusion criterion. The subjects were selected on the basis of good general health as determined by no clinically significant deviations from normal in baseline measurements of medical history, physical examination, clinical laboratory determination and electrocardiogram (ECG) conducted within 14 days prior to study enrollment. Any subject with evidence of cardiovascular, hepatic, renal, thyroid or metabolic dysfunction as well as recent drug or alcohol abuse and/or positive urine screening for drugs of abuse was excluded. Individuals who had donated blood within 3 months prior to the beginning of the study could not be enrolled. The subjects were also checked for thyroid function by free thyroxine (FT₄) and thyroid-stimulating hormone (TSH) tests. No concomitant medication other than contraceptives for women of child-bearing age or medication for the treatment of any adverse events was permitted for the duration of the study. Laboratory tests were performed again within 48 h prior to day 1 and at discharge. Vital signs including respiratory rate, sitting blood pressure and pulse rate, which were recorded during pre-study screening, each day before study drug administration and at the completion of the study. A complete physical examination and an ECG were done again at discharge. Following the daily investigators’ questioning and examination of the subjects, all clinical adverse events, whether believed by the investigator to be related or unrelated to the treatment, were recorded from the time the subjects entered the investigators clinic on day 1 of the study until their discharge on day 23. Moreover, neurological tests such as the segmental coordination test, Romberg sign and the occurrence of tremors, were performed daily from day 10 to day 21, 2 h after the morning dose intake in order to assess any neurological signs or symptoms. Body temperature was measured from day 10 to day 21.

The study was carried out in three sequential stages. First the subjects were administered nefazodone tablets 200 mg b.i.d. (at 0800 hours and 2000 hours) from day 1 to day 5. The dose of 400 mg d⁻¹ is the target dose for nefazodone in practice. A 4-day washout period then followed from day 6 to day 9. From day 10 to day 15, subjects received an ascending dose of lithium carbonate tablets 250 mg b.i.d. (at 0800 hours and 2000 hours). The starting dose was 250 mg b.i.d. and it was adjusted to achieve a serum level of lithium within the recommended therapeutic range (i.e. 0.5–0.8 mmol l⁻¹) by increasing daily with half a tablet up to 500 mg b.i.d. Finally, from day 16 to day 20, nefazodone 200 mg b.i.d. was co-administered with lithium. Subjects stayed at the investigation clinic from the evening of day 4 until the morning of day 7 and from the evening of day 14 until the morning of day 23. For other days, the subjects went to the clinic for dosing and blood sampling. All dosings were administered 30 min before breakfast and dinner with 200 ml of tap water.

**Measurement of nefazodone and its metabolite plasma concentrations**

A venous blood sample of 5 ml was collected at 0 h of day 1. Blood samples for the determination of the trough concentrations observed just before the morning dose (Cmin) were obtained prior to the dose given at 0800 hours on days 3 and 4, 18 and 19. Prior to the dose given at 0800 hours on days 5 and 20, serial blood samples were taken for 0- to 48-h-pharmacokinetic analysis at 0, 1, 2, 3, 4, 6, 8, 12, 24, 36 h and 48 h. Venous blood samples (5 ml each) for evaluation of nefazodone and its metabolites hydroxynefazodone, mCPP and triazoledione plasma concentrations were collected using Becton-Dickinson vacutainers with tripotassium EDTA as the anticoagulant. The separated plasma was stored frozen at or below −20 °C until analysis.

Concentrations of nefazodone and its metabolites in plasma were determined by an HPLC method. The analytes were detected using UV absorbance at 254 nm. The validated limits of quantification were 10 ng ml⁻¹ for nefazodone and triazoledione, 2.5 ng ml⁻¹ for mCPP and 5 ng ml⁻¹ for hydroxynefazodone.

**Measurement of lithium serum concentrations**

Daily monitoring for lithium serum levels was performed to ensure that subjects remained within the therapeutic range (i.e. 0.5–0.8 mmol l⁻¹). Prior to the dosing at 0800 hours from day 10 to day 20, venous blood samples for determination of lithium level were collected. Moreover, venous blood samples for the determination of lithium Cmin were obtained prior to the dose at 0800 hours from day 13 to day 15 and on days 18 and 19. Prior to the dose at 0800 hours on days 15 and 20 serial blood samples were