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Original article

Dasatinib significantly reduced *in vivo* exposure to cyclosporine in a rat model: The possible involvement of CYP3A induction

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ABSTRACT

Background: This study was designed to investigate the effects of dasatinib and nilotinib on the pharmacokinetics of cyclosporine in rats, as these drugs have been reported to be cytochrome P450 3A4 (CYP3A4) substrates.

Methods: Control and test groups (n = 5) were treated with vehicle and dasatinib (4 mg/kg, and 16 mg/kg, oral) or nilotinib (94 mg/kg, oral), respectively, for 8 consecutive days. On day 8, all groups were administered cyclosporine (30 mg/kg) 1 h after the last dose of dasatinib or nilotinib. Blood was collected from the retro-orbital plexus in heparinized tubes at different time points (0, 0.5, 1, 1.5, 2, 3.5, 8, 12, and 24 h). The cyclosporine concentration in blood samples was determined by ultra-performance liquid chromatography–tandem mass spectrometry. The effects of dasatinib on CYP3A2 mRNA and protein expression levels were also investigated.

Results: Dasatinib significantly reduced the maximum blood concentration (Cmax) of cyclosporine by 85.7%, and increased hepatic and intestinal CYP3A2 mRNA and protein expression levels by 2.4- and 1.25-fold, respectively, compared to those in the controls ($p < 0.05$). On the other hand, nilotinib had no significant effects on cyclosporine pharmacokinetic parameters.

Conclusions: Dasatinib significantly reduced cyclosporine exposure, which was most probably related to the induction of CYP3A-mediated cyclosporine metabolism.

Introduction

Following the approval of first tyrosine kinase inhibitor (TKI), imatinib, in 2001 by the US Food and Drug Administration (FDA), several TKIs have entered the market. Currently, TKIs are receiving considerable attention in cancer treatment owing to their excellent efficacy and low toxicity compared to those of traditional chemotherapeutic agents [1]. However, a major problem associated with TKI treatment is frequent clinical drug-drug interactions (DDIs) [2–7].

Dasatinib (Sprycel®) and nilotinib (Tasignais®) are orally administered TKIs used for the treatment of chronic myeloid leukemia (CML) [2,5,8]. Both drugs extensively undergo cytochrome P4503A4 (CYP3A4)-mediated biotransformation, with the involvement of other enzymes to a lesser extent. *In vitro* studies have demonstrated their mechanism-based CYP3A4 inhibition [5,9]. Few studies have reported that dasatinib and nilotinib can increase the exposure of CYP3A4 substrates simvastatin and midazolam, respectively, in humans [2,4,5]. However, there is a lack of detailed information on the effect of dasatinib on other CYP3A4 substrates. While some research has been performed to determine the benefit of dasatinib and cyclosporine combination therapy [10,11], considering the chronic prescription patterns for TKIs, the current study was undertaken to fill the gaps in literature with regard to the effects of dasatinib and nilotinib on cyclosporine pharmacokinetics.

Cyclosporine (NEORAL® Oral Solution, Novartis) is an immunosuppressant widely used in organ transplantation and many other clinical conditions [12]. It undergoes extensive hepatic and intestinal biotransformation mainly via the metabolizing enzyme,

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CYP3A4 [12–15]. Considering the narrow therapeutic index of cyclosporine, the change in drug bioavailability may result in serious consequences, either increased toxicity or therapeutic failure [16]. Several reports indicated that CYP3A4 inhibitors or inducers can significantly change the bioavailability of cyclosporine [12].

The aim of this study was to investigate the effect of repeated dasatinib and nilotinib pretreatment on the pharmacokinetics of cyclosporine in healthy rats.

Materials and methods

Chemicals

Cyclosporine oral solution (Neoral®, Novartis) was obtained from the pharmacy of King Khalid University Hospital (Riyadh, Saudi Arabia). Dasatinib monohydrate, nilotinib, and the cyclosporine standard were purchased from (Carbosynth, United Kingdom). TRIzol reagent Invitrogen Co. (Grand Island, NY, USA), High capacity cDNA kits (applied biosystem), SYBR® Green PCR Master Mix (Applied biosystem), Forward and reverse CYP3 A2 primers (Integrated DNA technologies IDT, Coralville, IA, USA), Primary monoclonal antibodies against CYP3 A2 (Detroit R&D), Inc. β-actin (Santa Cruz, CA, USA)

Animals

Healthy Wistar albino rats of either sex, weighing 200 ± 20 g were obtained from the Central Animal House Facility of King Saud University (Riyadh, KSA). They were kept in standard plastic animal cages in controlled, an air-conditioned room (12-h light/dark cycle) with free access to food and water. The study protocol was approved by Research Ethics Committee of College of Pharmacy, King Saud University (Riyadh, KSA).

Pharmacokinetic experiment

The rats were divided into 5 groups, i.e., control group I and control group II and test group I, II and III (5 rats in each group). The control group I was administered only vehicle (10% propylene glycol in water) and control group II was administered only water for 8 days. The test group I was treated with dasatinib (16 mg/kg, oral) suspended in solvent system comprising 10% propylene glycol in water and test group II was treated with dasatinib (4 mg/kg, oral) suspended in 10% propylene glycol solvent system; while the test group III was treated with nilotinib (94 mg/kg, oral) suspended in solvent system comprising 6% DMSO in water. The test groups I, II and III were treated for 8 consecutive days. On the 8th day, the overnight fasted animals in all groups (control and test groups) were administered a single dose of cyclosporine (30 mg/kg, orally) 1 h after the last treatment dose. Blood from the retro-orbital plexus was collected in heparinized tubes at 0, 0.5, 1, 1.5, 2, 3.5, 8, 12, and 24 h. The blood samples were kept at −80 °C until analysis.

LC–MS bioanalytical method and sample preparation

A calibration curve was prepared using rat whole blood. Standard stock solutions of cyclosporine A (CsA) and cyclosporine D (CsD) (internal standards [ISs]) were prepared in methanol to achieve a final concentration of 1 mg/ml. These stock solutions were stored in a refrigerator. The stock solution of CsA was used to prepare a series of calibration standards. Series of diluted stock solutions or working solutions of CsA were prepared in methanol and a 15-μl aliquot of each working solution was added to 300 μl of blank rat blood. Ten microliters of the diluted internal standard (CsD) was added to each sample. The samples were vortexed for 20 s and then 150 μl of zinc sulfate (0.2 M) was added and vortexed again for another 20 s. The protein was precipitated by adding 525 μl of methanol and then the samples were vortexed again for approximately 30 s. The samples were left for 5 min and then centrifuged at 12,000 rpm (13845 rcf) for 6 min. The test samples obtained from the animals were also prepared according to this method, except that in place of the diluted standard solution, an equal volume of blank methanol (15 μl) was added; the remaining procedure was the same. The supernatant was aspirated and analyzed using a validated ultra performance liquid chromatography–mass spectrometry (UPLC-MS) method [17].

Effect of dasatinib on hepatic and intestinal CYP3 A2 mRNA expression

Total RNA isolation and cDNA synthesis

Total RNA was prepared from liver and intestine tissues by using the TRIzol reagent (Invitrogen®). RNA quality and concentration were assessed by determining the 260/280 ratio (>1.8) by using the NanoDrop™ 8000 spectrophotometer (Thermo Fisher Scientific). Subsequently, cDNA synthesis was completed using the High-Capacity cDNA reverse transcription kit (Applied Biosystems) according to the manufacturer's instruction as described previously [18].

Quantification of CYP3A2 mRNA expression by real-time polymerase chain reaction

A quantitative analysis of *CYP3A2* mRNA expression was performed by real-time polymerase chain reaction (RT-PCR) by subjecting the resulting cDNA to PCR amplification using 96-well optical reaction plates in the ABI Prism 7500 System (Applied Biosystems) [18]. Rat primers for *CYP3A2* (F: 5′-GTCAAACGCCTGTGTTTGCC-3′ and R: 5′-ATCAGGGTGAGTGGCCAGGA-3′) and β-actin (F: CCAGATCATGTTTGAGACCTTCAA and R: TGGTACGACCAGAGGCATACA) were purchased from Integrated DNA Technologies (Coralville, IA, USA). Fold changes in the level of CYP3A2 between the dasatinib-pretreated group and group treated with dasatinib and cyclosporine was corrected based on the levels of β-actin. The RT-PCR data were analyzed using the relative gene expression (i.e., $^{\Delta\Delta}$CT) method [19].

Effect of dasatinib on hepatic and intestinal CYP3 A2 protein expression

Immunoblot analyses were conducted by according to the method of Towbin et al. [20,21] with minor modification to quantify the effect of dasatinib on hepatic expression of CYP3A2 and β-actin. Briefly, 25 μg of liver and intestine proteins from each group was electrophoresed on 10% sodium-dodecyl sulfate (SDS)-polyacrylamide gel electrophoresis (PAGE), and then electrophoretically transferred to nitrocellulose membranes. The membranes were then blocked overnight at 4 °C in a blocking solution. After blocking, the blots were washed several times with TBS Tween-20 before being incubated with a goat CYP3A2 polyclonal antibody for 2 h at room temperature in Tris-buffered saline (TBS) solution. Incubation with a peroxidase-conjugated rabbit anti-goat immunoglobulin (Ig)G secondary antibody was performed in blocking solution for 1 h at room temperature. Bands were visualized using Luminata™ Western Chemiluminescent horseradish peroxidase (HRP) Substrates (Millipore, Billerica, MA, USA), and a densitometric analysis of the immunoblots was performed using LI-COR C-DiGit Blot Scanners (Lincoln, NE, USA).

Pharmacokinetic and statistical analysis

The blood concentrations were utilized to describe the pharmacokinetic profiles by plotting drug concentration–time curves. The non-compartmental model was used to determine the pharmacokinetic parameters of cyclosporine by using PKsolver

(EXCEL-embedded pharmacokinetic software) [22]. All data are expressed as mean ± SD values. Statistical significance was assessed by unilateral, unpaired *t*-test using EXCEL (Microsoft, USA); $p < 0.05$ indicated statistical significance.

Results

Effects of dasatinib and nilotinib on the pharmacokinetics of cyclosporine

The results of cyclosporine pharmacokinetic interaction study with dasatinib are presented in Table 1. Pharmacokinetic profiles of cyclosporine control group I and test groups I and II are presented in Fig. 1. The results of cyclosporine interaction study with nilotinib are presented in Table 2. Pharmacokinetic profiles of cyclosporine control group II and test groups III are presented in Fig. 2. In this study, the blood concentration of cyclosporine decreased significantly in dasatinib pre-treated test groups I and II groups. In dasatinib treated group I (16 mg/kg) and II (4 mg/kg), the maximum blood concentration (Cmax) decreased by 81.3 and 85.7% respectively. (See Table 1 and Fig. 1). Pre-treatment with dasatinib decreases the cyclosporine blood level to such extent, that in some of the samples the blood concentration of cyclosporine was less than lower limit of quantitation (250 ng/ml) of analytical method.

On contrary, the pre-treatment with nilotinib, did not show any statistically significant effect on the cyclosporine blood concentration pharmacokinetic parameters (see Table 2 and Fig. 2).

Effects of dasatinib on hepatic and intestinal CYP3A2 protein expression

Hepatic and intestinal expression of CYP3A2 mRNA and protein expression significantly increased following dasatinib treatment for 8 days compared to that in β-actin controls (Fig. 3). Dasatinib pretreatment led to a significant increase in hepatic and intestinal CYP3A2 protein expression level by 2.4- and 1.25-fold, respectively, compared to that in the controls ($p < 0.05$).

Discussion

DDI is one of the main problems with serious clinical consequences in clinical settings. Several reports have highlighted the role of modulation of drug-metabolizing enzymes, especially CYP450 s, as a major mechanism involved in clinical DDIs [3,4,7]. The present study aimed to investigate the effect of dasatinib and nilotinib on the bioavailability of cyclosporine A in a rat model. Furthermore, we examined the effect of dasatinib on mRNA and protein expression of the CYP3A2 enzyme in rat liver and intestine.

Rats are frequently used as *in vivo* models for DDIs based on the inhibition/induction of CYP450 isoenzymes, although considerable variations were reported in the activity of CYP450 isoenzymes among different species. The activity of CYP450 isoenzymes in mice and male rats showed the most similarity to that in humans [23–26]. However, studies reported a little effect of rifampicin on the metabolism of testosterone in rat hepatocytes, although dexamethasone showed a significant effect in the same study [27].

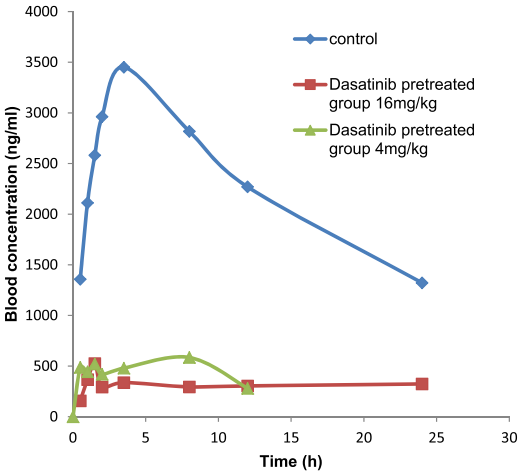

Fig. 1. The plasma concentration *versus* time profiles for cyclosporine control and dasatinib monohydrate-treated groups.

Table 2
Pharmacokinetic parameters for nilotinib pretreated group control and test groups.

Parameter	Control group II Cyclosporine only	Test group III Pre-treated with Nilotinib [94 mg/kg]
Cmax (ng/ml)	4177.5 ± 438.5	4431.5 ± 839.7
Tmax (h)	2.3 ± 0.7	2.3 ± 1.2
Kel (1/h)	0.04 ± 0.01	0.06 ± 0.02
t1/2 (h)	17.4 ± 4.1	13.8 ± 4.8
AUC 0-t (ng/ml·h)	61921.0 ± 4586.7	68964.7 ± 7730.1

All results were expressed as mean ± SD.

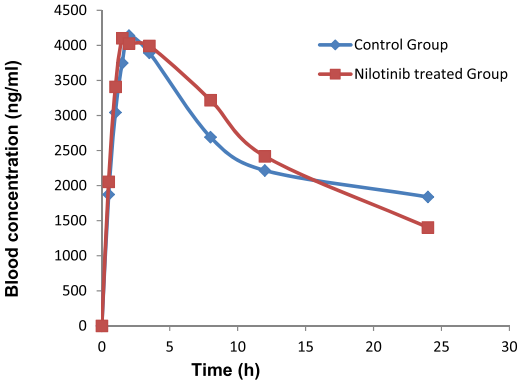

Fig. 2. The plasma concentration *versus* time profiles for cyclosporine control and nilotinib-treated groups.

TKIs are an important group of drugs that have recently emerged as effective oral anticancer therapy. However, due to their extensive interactions with CYP450 s and their chronic prescription pattern, TKIs are frequently involved in clinical DDIs. Dasatinib and nilotinib are among the TKIs approved by the US-FDA for the

Table 1
Pharmacokinetic parameters for dasatinib pre-treated group control and test groups.

Parameter	Control group I Cyclosporine only	Test group I Pre-treated with Dasatinib [16 mg/kg]	Test group II Pre-treated with Dasatinib [4 mg/kg]
Tmax (h)	2.3 ± 0.3	4.4 ± 1.8	4.9 ± 1.3
Cmax (ng/ml)	3735.1 ± 138.6	695.8 ± 232.8*	533.3 ± 102.2438*

* $p < 0.05$, All results were expressed as mean ± SD.

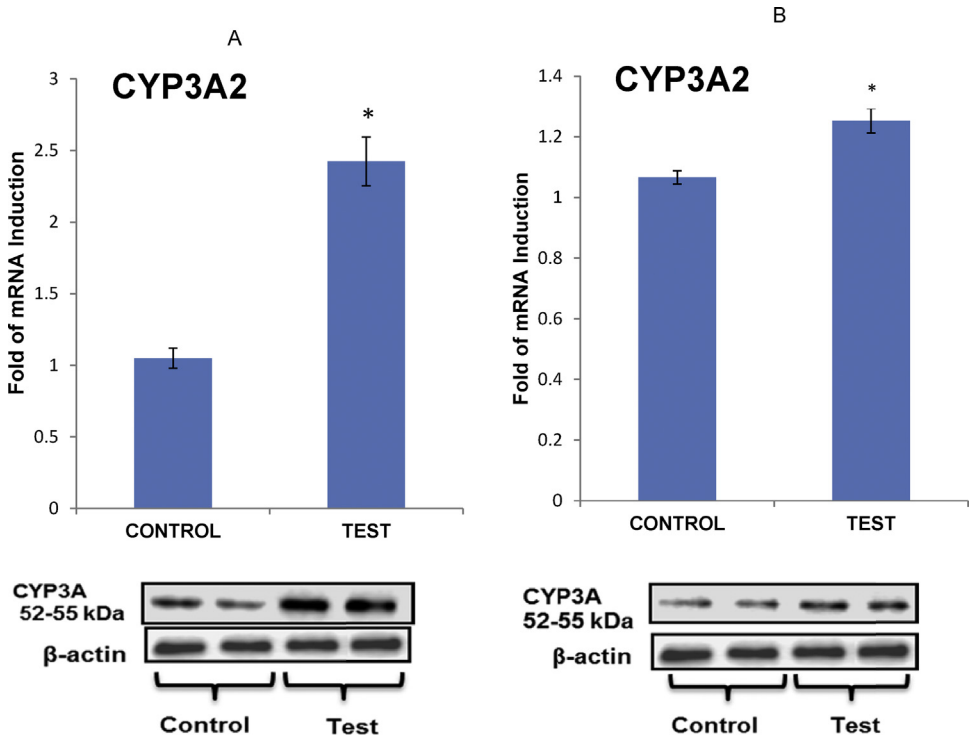

Fig. 3. Effect of dasatinib on hepatic and intestinal CYP3A2 protein expression. A: liver, B: intestine. All values represent mean ± SEM; $^{*}p < 0.05$.

treatment of chronic myeloid leukemia. Their CYP3A4 mechanism-based inhibition has been reported in *in vitro* studies [9]**.** In a healthy human, dasatinib increased the exposure of simvastatin, a CYP3A4 substrate [5]. Another study showed an increased bioavailability of midazolam after single and repeated administration of nilotinib [2,4]. However, the exhaustive information on the *in vivo* impact of these TKIs on CYP3A4 and P-glycoprotein substrates is lacking. In particular, the impact of these TKIs on cyclosporine, which is a known CYP3A4 and P-glycoprotein substrate and undergoes extensive hepatic and intestinal metabolism, has not been reported [12–15]. Moreover, altered bioavailability has been reported in instances of cyclosporine co-administration with drugs that modulate CYP3A4 isoenzyme activity [16,28,29].

In this study, the pretreatment with dasatinib for 8 consecutive days revealed an extraordinary finding regarding the impact of dasatinib on cyclosporine bioavailability. Pretreatment of rats with 16 mg/kg dasatinib markedly decreased the cyclosporine blood concentration (81.3%), as clearly demonstrated in Fig. 1. The pre-treatment with dasatinib (4 mg/kg) also significantly decreased the Cmax of cyclosporine (85.7%) (Fig. 1 and Table 1). The effect of nilotinib on cyclosporine blood levels was insignificant (Fig. 2, Table 2) although previous studies have reported an increase in the bioavailability of some CYP3A substrates when coadministered with nilotinib.

To explore the possible mechanism for this significant dasatinib-CsA interaction, we investigated mRNA and protein expression, which clearly demonstrated a significant CYP3A2 induction.

Our results might explain the failure of cyclosporine to inhibit *in vitro* T cell proliferation when it was concomitantly used with dasatinib in experiments performed by Stephen et al. (2012), which showed a reversal of the inhibition of T cell proliferation by cyclosporine and an increase beyond that in untreated cells [11]. On the other hand, dasatinib and some other TKIs have reported *an in vitro* mechanism-based inhibition of CYP3 A4; however, this effect is a substrate-dependent. For example, although gefitinib and erlotinib are CYP3A4 inhibitors, but they stimulated the metabolism of CYP3A substrates such as midazolam; however, the underlying mechanism remains unclear [30–32].The study showed the differential effect of TKIs on cyclosporine bioavailability, which clearly demonstrates the need for great caution when these drugs are co-administered with cyclosporine and other CYP3A4 substrates, particularly those with a narrow therapeutic index.

The use of the animal model to study DDIs is a major limitation of this study since the results cannot be directly extrapolated to humans. However, the results provide a strong rationale for conducting similar studies in humans.

Overall, the evidence and the results from *in vivo* studies clearly indicate that cyclosporine biotransformation can be induced by dasatinib co-administration through induction of CYP3A expression. However, further studies are needed to explore the role of P-gp modulation in DDIs.

Conclusion

In vivo pharmacokinetic studies showed that dasatinib monohydrate pretreatment significantly decreased the blood level of CsA in rats, which was most probably due to the induction of CYP3A2 isoenzymes. The nilotinib pre-treatment had no significant effects on cyclosporine pharmacokinetics in rats.

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This research doesn't receive any specific financial support from any source.

Conflict of interest

The authors declare that there are no conflicts of interest.

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