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# Effects of rifampicin and ketoconazole on the pharmacokinetics of a single oral dose of diethylcarbamazine in healthy volunteers

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**Effects of rifampicin and ketoconazole on the pharmacokinetics of a single oral dose of diethylcarbamazine in healthy volunteers**

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**Abstract:**

*Diethylcarbamazine (DEC) is the first-line drug for the control and treatment of lymphatic filariasis caused by the Wuchereria bancrofti and Brugia malayi parasite. DEC is rapidly and extensively metabolised in the liver. Rifampicin and ketoconazole are a potent inducer and inhibitor of hepatic cytochrome P450 enzymes (CYPs) resulting in numerous clinically significant drug interactions. The aim of this study was to examine the effects of co-administration of rifampicin and ketoconazole on the pharmacokinetic parameters of DEC in 12 healthy Thai male volunteers in an open-labeled, randomised 3-phase crossover design experiment. In phase 1 each volunteer received only a single oral dose of 6 mg/kg of DEC. In phases 2 and 3 the subjects received a single oral dose of 6 mg/kg DEC after pretreatment with either 600 mg rifampicin or 400 mg ketoconazole orally for 5 days, respectively. Each phase of each study was separated by a 1-month separation period. The plasma DEC concentrations during a 48 hour period were measured using High Performance Liquid Chromatography (HPLC). Statistical analysis using two-way ANOVA indicated that neither rifampicin nor ketoconazole significantly altered the mean* $C_{max}$, $AUC_{0-48}$, $AUC_{0-\infty}$, $t_{1/2}$, $t_{max}$, $k_a$, $k_e$, $V_d/F$ *and* $Cl/F$ *(*$P > 0.05$*). There were no significant differences among the mean urine pH values of the 3 phases (*$P>0.05$*). The results show that the pretreatment with rifampicin and ketoconazole did not significantly affect any of the pharmacokinetic parameters. In this study, it was not possible to conclude clearly that DEC was not metabolized via the cytochrome P450 enzymes.*

**Key words:** *Diethylcarbamazine, rifampicin, ketoconazole, pharmacokinetics, drug interaction*

**บทคัดย่อ:**

*Diethylcarbamazine (DEC) เป็นยาเลือกลำดับแรกที่ใช้ในการควบคุมและรักษาภาวะการติดเชื้อไมโครฟิลาเรียที่ต่อมน้ำเหลือง (lymphatic filariasis) ที่มีสาเหตุจากเชื้อ Wuchereria bancrofti และ Brugia malayi DEC ถูกแปรรูปอย่างรวดเร็วและมากที่ตับ ในขณะที่ rifampicin และ ketoconazole เป็นยาออกฤทธิ์แรงในการเหนี่ยวนำและยับยั้งเอนไซม์ไซโตโครม พี 450 ตามลำดับ ซึ่งสามารถเกิดปฏิกิริยาระหว่างยาของยาที่ให้ร่วมในระหว่างการรักษาจึงทำให้มีผลต่อการรักษาในทางคลินิกได้ วัตถุประสงค์ในการศึกษาครั้งนี้เพื่อศึกษาผลของการบริหาร rifampicin หรือ ketoconazole ร่วมกับ DEC ในอาสาสมัครชายไทยสุขภาพปกติจำนวน 12 คนต่อค่าพารามิเตอร์ทางเภสัชจลนศาสตร์ของ DEC การศึกษาเป็นแบบสุ่มไขว้และเปิดเผยโดยแบ่งการทดลองออกเป็น 3 ช่วง (phase) โดยช่วงที่ 1 อาสาสมัครรับประทาน DEC ขนาด 6 มก./กก. เพียงอย่างเดียว ส่วนในช่วงที่ 2 และ 3 อาสาสมัครรับประทาน DEC ขนาด 6 มก./กก. ในวันทำการทดลองหลังจากได้รับประทาน rifampicin ขนาด 600 มก./กก. หรือ ketoconazole ขนาด 400 มก./กก. มาเป็นเวลา 5 วันตามลำดับ โดยมี separated period 1 เดือน วิเคราะห์หาความเข้มข้นของ DEC ในพลาสมา ในช่วงเวลา 48 ชั่วโมง โดยเครื่องโครมาโทกราฟฟีสมรรถนะสูง (HPLC) ผลการวิเคราะห์ทางสถิติโดยใช้ two-way ANOVA พบว่า rifampicin หรือ ketoconazole ไม่ทำให้เปลี่ยนแปลงค่าพารามิเตอร์ทางเภสัชจลนศาสตร์ของ DEC (*$C_{max}$, $AUC_{0-48}$, $AUC_{0-\infty}$, $t_{1/2}$, $t_{max}$, $k_a$, $k_e$, $V_d/F$ *และ* $Cl/F$*) อย่างมีนัยสำคัญ (*$P>0.05$*) ค่าเฉลี่ย pH ของปัสสาวะของทั้ง 3 ช่วงของการทดลองไม่มีความแตกต่างกันอย่างมีนัยสำคัญ (*$P>0.05$*) จากผลการทดลองนี้จึงอาจสรุปได้ว่า การรับประทาน rifampicin หรือ ketoconazole ร่วมกับ DEC ไม่ทำให้เปลี่ยนแปลงค่าพารามิเตอร์เภสัชจลนศาสตร์ของ DEC อย่างมีนัยสำคัญและในการศึกษานี้อาจยังไม่สามารถสรุปได้ชัดเจนว่าการแปรรูป DEC จะไม่เกี่ยวข้องกับเอนไซม์ไซโตโครม พี 450*

**คำสำคัญ:** *ยาไดเอธิลคาร์บามาซีน, ยาไรแฟมปิซิน, ยาคีโตโคนาโซล, เภสัชจลนศาสตร์, การเกิดปฏิกิริยาระหว่างยา*

## Introduction

Lymphatic filariasis results from infection by the parasitic roundworms *W. bancrofti*, *Brugia malayi*, and *Brugia timori*. More than 120 million people from 80 countries have already been affected by filariasis and over 40 million of them are seriously incapacitated and disfigured by the disease.[1] Diethylcarbamazine (DEC) is the first-line drug used for the control and treatment of lymphatic filariasis and tropical pulmonary eosinophilia caused by the *W. bancrofti* and *B. malayi* parasite.[2] DEC is absorbed rapidly from the gastrointestinal tract and metabolised rapidly and extensively in the liver[3-4] to a major metabolite known as DEC-N-oxide. In a test on five healthy volunteers who received a 50 mg dose, in tablet form, of DEC citrate the DEC absorption was rapid, with peak plasma concentrations similar to the above study being attained within 2 hours.[5] Administrations of 150 mg and 6 mg/kg body-weight produced mean peak plasma concentrations at 500 to 637 ng/ml in 2-3 hours[1] and 1254 to 2348 ng/ml in 2-4 hours.[6] Since no parenteral formulation of DEC exists, the absolute bioavailability of the drug is unknown.

Rifampicin, an antituberculosis drug, is known as a potent inducer of CYP3A4 and other CYP isoenzymes (especially CYP2C9 and CYP2C19)[7] and also P-glycoprotein (P-gp).[8-9] Conversely, ketoconazole, an antifungal drug, is a potent reversible inhibitor of CYP3A4 and P-gp.[10-12] Pharmacokinetic drug interactions have frequently been reported indicating that when either rifampicin or ketoconazole was coadministered with numerous drugs they metabolized via the CYPs. For example, rifampicin significantly decreases plasma concentrations of celiprolol, praziquantel and imatinib mesylate,[7, 9, 13] and ketoconazole has been shown to markedly reduce plasma concentrations of mefloquine and everolimus.[12, 14]

In Thailand, lymphatic filariasis, tuberculosis, and fungal infections are major public health problems and so there is the possibility that rifampicin or ketoconazole and DEC coadministration can occur in clinical practice. This coadministration may lead to rifampicn-DEC or ketoconazole-DEC drug interactions. The purpose of this investigation was to study the effects of rifampicin and ketoconazole on the pharmacokinetics of a single oral dose of DEC in healthy volunteers.

## Materials and methods

### Chemicals and reagents

The standard diethylcarbamazine citrated salt (DEC) (Lot No. 35F-0262) was purchased from the Sigma Chemical Company, USA. The quinidine sulfate, purchased from the Nutritional Biochemicals Corp. DEC tablet (Lot No. 10303123) was kindly donated by the Insect Prevention Center, Songkhla, Thailand. Rifampicin (Lot No. K470138) and ketoconazole (Lot No. A 18288.58.) were purchased from Songklanagarind Hospital, Hat Yai, Thailand. The HPLC grade of methanol and dichloromethane were purchased from J.T. Baker (Phillipsburg, NJ, USA.). Potassium dihydrogen phosphate ($KH_2PO_4$) and disodium hydrogen phosphate ($Na_2HPO_4$) were bought from Merck Darmstadt, Germany. Water was purified for HPLC by the Milli Q Water Purification System (Milipore, Milford, MA, USA.).

### Subjects

Twelve healthy Thai male volunteers, age 22-40 years (mean age ± SD 28.5 ± 5.78 years) and weighing 51-70 kg (mean weight ± SD 60.46 ± 5.37 kg) participated in the study. All the volunteers were given a detailed explanation concerning the purpose, protocol, and risk of the study. Each was also given a written consent from that had been approved by the ethics committee (ST. No. 0521.1.07/1364, approved 11/07/05), Faculty of Pharmaceutical Sciences, Prince of Songkla University, Hat Yai, Thailand. Prior to the study, a medical history, physical examination, standard biochemical and hematological screening tests (CBC, FBS, BUN, creatinine, SGOT, SGPT, direct bilirubin, total protein and albumin) were carried out for each volunteer. The volunteers did not smoke and none was using continuous medication at the time of the experiment. Drinking of alcoholic beverages, coffee and tea were not allowed for one month prior to and during the entire period of the study.

**Study protocol**

An open-labeled, 3-phase crossover study design was used in this study. Each phase was separated by a one-month period. In all of the phases, a single oral dose of 6 mg/kg of DEC was given on the study day. Phase 1: DEC only, each subject received a single oral dose of 6 mg/kg of DEC with 200 ml water. For Phases 2 and 3, each subject received a pretreatment dose of either 600 mg rifampicin or 400 mg ketoconazole orally once daily for 5 consecutive days. On the sixth day, each subject received a single oral dose of 6 mg/kg of DEC with 200 ml water. All the subjects fasted overnight before the DEC administration and they received a regular meal 2 hours after DEC.

**Blood sampling and urine collection**

Five milliletre (5ml) blood samples of venous blood were collected in 50 µl heparinised saline solution tubes (5,000 U/ml) before drug administration. Samples were taken at (0 hour) and then subsequently at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36, and 48 hours post drug administration. Plasma samples were collected within 30 minutes by centrifuge at 3,000 g for 10 minutes and were then stored at -60 $^{o}$C until analysis.

Urine samples (2 ml) were collected in a container before drug administration (0 hour) and 1, 4, 12, 24, 36, and 48 hours post drug administration for measuring urine pH using a pH meter (Mettler Toledo, Schwerzenbach, Switzerland)

**Determination of diethylcarbamazine concentrations in plasma samples**

Plasma DEC concentrations were determined by the HPLC method using an electrochemical detector as previously described by Bolla et al.[1] In brief, the HPLC system consisted of a Water's 2695 pump and Autosampler (Water Associates, Milford, MA, USA) and a Water's 474 Electrochemical detector. Detection was done with the potential stat +1150 mV and I-range set at 100 nA. The column was a reverse-phase Nova-Pak $C_{18}$ (3.9 mm x 150 mm HPLC column, particle size 4 µm, Water Associates, Milford, MA, USA). The mobile phase consisted of methanol: 0.2 M phosphate buffer pH 6.5 (55:45 vol/vol). The mobile phase was freshly prepared daily and filtered through 0.45 micrometer filter paper (Nylon 66), then degassed by sonification for 10 minutes before using. The flow rate was 0.5 ml/min. All analyses were performed at room temperature (25 ± 1 $^{o}$C).

In a screw-capped test tube, 500 µl of plasma was mixed with 100 µl of 30 µg/ml quinidine sulfate dissolved in methanol, 200 µl of 2 M NaOH, and 5 ml dichloromethane, respectively. The mixture was placed on a mechanical shaker for 15 minutes and then centrifuged for 20 minutes. The organic layer was then transferred to another screw-capped test tube and all the liquid was evaporated. Next the residue was reconstituted in 100 µl of methanol by vortex mixing for 15 seconds and then 20 µl was injected into the HPLC system for analysis. The limit of detection (LOD) and limit of quantitation (LOQ) of the DEC in plasma were 10 and 25 ng/ml, respectively. The intraday and interday assay coefficients of variation of the DEC were 3.66% to 4.66% and 7.28% to 9.78%, respectively at the concentration range of 100 to 2,000 ng/ml. The absolute recovery of DEC in human plasma was 102.35% to 104.96%.

**Pharmacokinetic analysis**

The pharmacokinetic parameters were analyzed by a one-compartment model, with the use of the WinNonlin version 3.1 (Pharsight, Mountain View, CA). The plasma DEC concentration-time curve (semilogarithmic curve) was fitted with the one-compartment model. The area under the concentration-time curve from time zero to the end time of the collection interval ($AUC_{0-48}$), the area under the concentration-time curve extrapolated to infinity ($AUC_{0-\infty}$), the absorption rate constants ($k_a$), the elimination rate constants ($k_e$), the terminal disposition half-life ($t_{1/2}$), maximum plasma concentration ($C_{max}$), time to reach $C_{max}$ ($t_{max}$), the apparent oral clearance (Cl/F), and the apparent volume of distribution ($V_d$/F) were obtained.

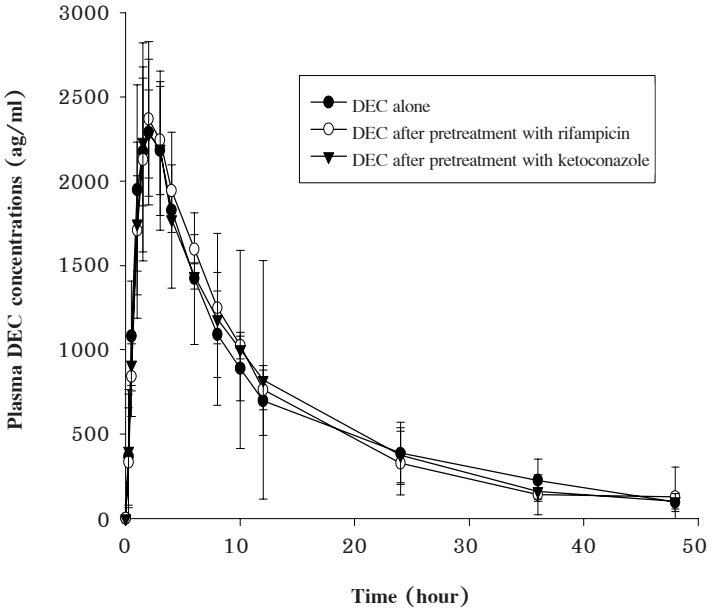
**Statistical analysis**

All pharmacokinetic parameters were expressed as mean ± SD. The differences in pharmacokinetic parameters among these groups were tested using two-way ANOVA, with a significance level of 0.05.

## Results

All subjects completed the study. No adverse effects or significant signs and symptoms were observed or reported throughout the study period. The mean plasma concentration-time profiles of the DEC and the mean urine pH in each phase are shown in Figure 1. The pharmacokinetic parameters are summarised in Table 1.

The results showed that rifampin and ketoconazole did not alter the pharmacokinetic parameters of DEC (P>0.05), and the mean urine pH values measured in all the study phases did not show any significant difference (P>0.05).

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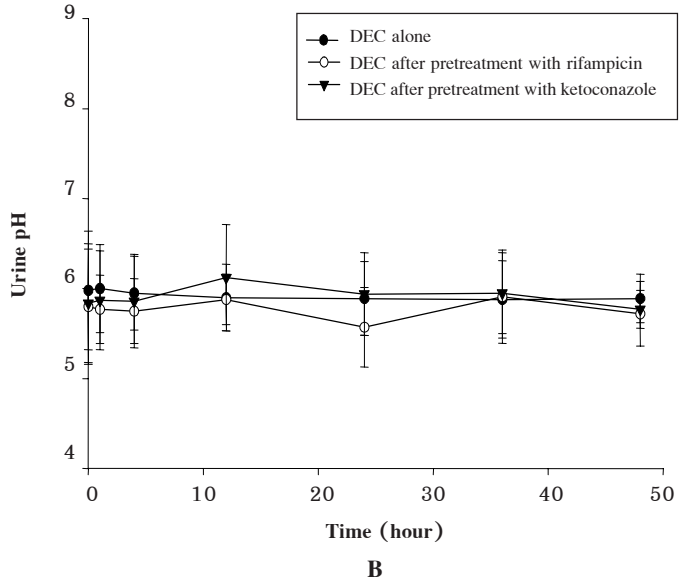


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**Figure 1 Mean plasma DEC concentration-time profiles (A), and mean urine pH values (B) for each study phase after administration of only a single oral dose of 6 mg/kg DEC or after pretreatment with 600 mg rifampicin and 400 mg ketoconazole orally once daily for 5 days. There were no significant differences in any pharmacokinetic parameters or urine pH values among 3 phases (P>0.05).**

**Table 1 Pharmacokinetic parameters of the DEC and urine pH measured values (mean ± SD) in 12 subjects after receiving a single oral dose of 6 mg/kg alone or pretreatment with 600 mg rifampicin and 400 mg ketoconazole orally for 5 days.**

| Parameters | DEC | DEC+Rifampicin | DEC+Ketoconazole | P-value (ANOVA) |
|---|---|---|---|---|
| $C_{max}$ (ng/ml) | 2243.54 ± 393.83 | 2274.38 ± 526.55 | 2211.99 ± 335.63 | P > 0.05 |
| $t_{max}$ (h) | 2.31 ± 0.66 | 2.64 ± 0.78 | 2.42 ± 0.65 | P > 0.05 |
| $AUC_{0-48}$ (ng.h /ml) | 20484.81 ± 8931.84 | 23610.91 ± 5790.97 | 24027.14 ± 8239.23 | P > 0.05 |
| $AUC_{0-\infty}$ (ng.h /ml) | 21287.97 ± 9176.35 | 24249.57 ± 6097.74 | 24718.18 ± 8490.30 | P > 0.05 |
| $k_a$ ($h^{-1}$) | 1.126 ± 0.604 | 0.953 ± 0.697 | 1.075 ± 0.623 | P > 0.05 |
| $k_e$ ($h^{-1}$) | 0.154 ± 0.063 | 0.164 ± 0.072 | 0.152 ± 0.067 | P > 0.05 |
| $t_{1/2}$ (h) | 5.14 ± 1.84 | 4.83 ± 1.62 | 5.48 ± 2.54 | P > 0.05 |
| $V_d$/F (L) | 117.79 ± 24.87 | 108.02 ± 34.80 | 118.08 ± 30.97 | P > 0.05 |
| Cl/F (L/h) | 17.16 ± 5.02 | 16.01 ± 3.52 | 16.36 ± 4.06 | P > 0.05 |
| Urine pH | 5.93 ± 0.44 | 5.77 ± 0.44 | 5.91 ± 0.50 | P > 0.05 |

$C_{max}$ = maximal plasma concentration; AUC = area under the concentration-time curve; $k_a$ = absorption rateconstant; $k_e$ = elimination rate constant; $t_{1/2z}$ = elimination half-life; $t_{max}$, time to maximal plasma concentration; Cl/F = apparent oral clearance; $V_d$/F = volume of distribution
P-value > 0.05; non-significant difference when compared with control (DEC alone)

## Discussion

Diethylcarbamazine (DEC), a piperazine derivative, is the drug of choice for the control and treatment of lymphatic filariasis, and also for the therapy of tropical pulmonary eosinophilia (TPE) caused by *W. bancrofti* and *B. malayi* parasites.[2] DEC is rapidly and extensively metabolised in the liver.[3] It has been found that over 50% of an oral dose appears as the unchanged drug in acidic urine, but this value decreases when the urine is alkaline.[4] A major metabolite of DEC in humans is DEC-N-oxide, of which a bout 10% is excreted mainly in urine and between 4 to 5% was recovered in the faeces. Ilondu et al.[15] reported that DEC was found in saliva. The metabolic pathway of DEC is not clearly understood but Tracy and Webster[4] have indicated that DEC metabolism occurs in the liver. Generally cytochrome P450 (CYP) has previously been viewed as a major contributor to drug metabolism especially CYP3A4, which was the most common type found in liver (about 25% of all CYP types).[16] Rifampicin and ketoconazole are potent CYP3A4 inducers and inhibitors, respectively. Consequently, we have investigated the effects of rifampicin and ketoconazole on the pharmacokinetics of DEC in healthy volunteers.

Rifampicin is the most potent inducer of the CYP450 enzymes. Backman and Juregui[17] found that rifampicin induced several cytochrome P-450 isoenzymes, not only CYP3A4 but also CYP1A and CYP2C. These findings were consistent with the highly significant interactions that have been reported in the literature for drugs metabolised by these isoenzymes.[18] For example, glyburide and glipizide are metabolized by CYP2C9,[19] and theophylline by CYP1A2. Zhou et al.[20] has also recently reported the induction of CYP2C19 by rifampicin.

On the other hand ketoconazole, an azole antifungal agent with broad-spectrum antifungal activity, has been shown to reduce the metabolism of other drugs sharing the CYP3A4 pathway. Drugs that have been observed with this phenomenon include alprazolam, triazolam, midazolam, nifedipine, nicardipine, amprenavir, cocaine, and opioids.[21-24] In addition, ketoconazole has also been found to be a potent P-glycoprotein inhibitor.[10]

In the study reported here, plasma DEC concentration profiles and the derived pharmacokinetic parameters in healthy subjects who received a single dose of 6 mg/kg DEC orally were similar to those previously reported.[6] The mean peak

plasma DEC concentration in each study depended on the oral dose of DEC. Nevertheless, the variation of these pharmacokinetic parameters may be influenced by inter-individual variations and environmental factors (e.g. sex, race, diet, smoking, coffee and alcoholic drinking). The amount of renal DEC excretion depends on the urine pH. The mean pH values of the urine were not significantly different when compared between the three phases. Therefore, it can be concluded that the urine pH of each subject in this investigation did not influence the plasma concentrations of DEC. Generally, the tmax of DEC was 1-2 hours.[25], 4 Our study showed that $t_{max}$ is 1-3 hours, which was the same as the findings of Shenoy et al.[6] and Bolla et al.[1]

Joseph et al.[26] suggested that CYP was at least partly involved in the oxidation pathway of DEC. Li et al.[27] studied "in vitro" systems using rat liver microsomes (RLM), human liver microsomes (HLM), and recombinant cytochrome P450 (rCYP). It was difficult to estimate the relative contributions of CYPs to the elimination of DEC in HLM because of the immeasurably long $t_{1/2}$ in rCYPs even at high enzyme concentration of 20 pmol per incubation.

The cytochrome P450s constitutes a "superfamily" of isoforms that have an important role in the oxidative drug metabolism. Each CYP isoform possesses a characteristic broad spectrum of catalytic activities of substrates.[16] Flavin-containing monooxygenases (FMOs) have been previously viewed as minor contributors to drug metabolism. However, the advantages associated with using FMOs to diversify the metabolism of a drug are now being recognised.[28] FMOs oxidise the nucleophilic nitrogen, sulfur and phosphorus-containing xenobiotics.[29] Currently, five forms of FMO genes are known, but FMO3 is the major form in adult human liver that is likely to be responsible for the majority of FMO-mediated metabolism.[30] Of the five functional human FMOs known, FMO3 appears to be the most important FMO present in an adult human liver. Based on immunoreactivity investigations FMO3 is expressed at levels approaching 60% of the expression levels of the major CYPs present in adult liver (CYP3A4).[28] The role of FMOs is involved with metabolism of N-containing xenobiotics (This is an incomplete idea. It is technically a sentence but does, however not contain a full thought leading to an idea making your following examples confusing). For example, the neurotoxicant 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) is readily N-oxygenated by FMO to the N-oxide. Another example is N-deacetylketoconazole which is N-hydroxylated by a number of FMOs.[31] Thus, there is the possibility that the FMOs may contribute to the N-oxidation of DEC. However, FMOs-mediated DEC metabolism has not yet been studied and it needs further investigation. Mushiroda et al.[32] indicated that ketoconazole was not a FMOs inhibitor because it could not decrease a primary metabolite of itopride. Other FMOs inhibitors (methimazole and thiourea) could inhibit itopride N-oxide formation. The study showed that itopride meta-bolism was involved with FMOs but not with CYP3A4. However, in the present study, we could not exclude the possibility that FMOs were not involved with or did not affect plasma DEC concentrations. Thus, we have suggest that further investigation of DEC metabolism pathways correlated with FMOs using *in vivo* and *in vitro* study should be done.

Although the involvement of the P-gp pathway has not been studied with DEC metabolism, the present study used rifampicin and ketoconazole, which are respectively P-gp inducer and inhibitor. The study results show that all the pharmacokinetic parameters are unchanged, suggesting that P-gp does not play an important role in DEC metabolism.

The normal pH range in human urine is 5-6.5 but the present study showed a urine pH of 5.93 ± 0.44, 5.77 ± 0.44 and 5.91 ± 0.50 in the subjects during the test period. Awadzi et al.[33] has studied the effects of moderate alkalinisation on low dose DEC therapy on patients with onchocerciasis. The plasma elimination half-life and the total urinary excretion of DEC were significantly less in patients receiving sodium bicarbonate than in the control group. In another study patients received DEC at either 6 mg/kg or 3 mg/kg with or without $NaHCO_3$ at 75 mg/kg body weight. The study found that there was a significant difference between the $t_{1/2,\lambda z}$ for the patients receiving DEC at 3 mg/kg plus NaHCO at 75 mg/kg body weight, while there was a general tendency for $t_{1/2,\lambda z}$ and $AUC_{0-\infty}$ to increased in patients treated with DEC at 6 mg/kg plus $NaHCO_3$ at 75 mg/kg body weight.[34] In this study, the results showed that after a single oral dose of DEC

was coadministered with rifampicin or ketoconazole for 5 days, the mean pH of the urine over the three phases of the study was not significantly different. Thus, urine pH measured values at each of the specific time points in the present study did not affect the plasma concentrations of DEC throughout the study.

Interestingly, the organic anion transporter (OAT) family plays a critical role in the renal excretion and detoxification of a wide variety of compounds including drugs, toxins, hormones, and neurotransmitter metabolites. Every OAT identified so far is expressed in the kidney where their function is a major determinant of toxicity and the therapeutic action of drugs. In addition to the kidney, active OAT is also an important function of other barrier epithelia including liver, placenta, brain capillaries, and choroid plexus. For organic anions, active transepithelial transport across the renal proximal tubule followed by elimination via the urine is a major pathway in this detoxication process. Accordingly, a large number of organic anion transport proteins belonging to several different gene families have been identified and found to be expressed in the proximal nephron. The function of these transporters, in combination with the high volume of renal blood flow, predisposes the kidney to increased toxic susceptibility.[35] Wright and Dantzler[36] suggested that the OAT substrate is the acidic compounds.

Organic cations (OC) constitute a diverse array of compounds of physiological, pharmacological, and toxicological importance.[37] The majority of drugs for therapeutic use including many antihistaminines, antacids, antiarrhythmics, antihypertensives and anticholinergics are organic cations or weak bases.[38] Organic cations (OCs) are positively charged at physiological pH.[39] It is very well known, however, that membrane transporters play an important role in drug absorption across the gastrointestinal tract. One of the best known examples is the cephalosporin and prodrug transport via the intestinal proton-coupled peptide transporter PEPT1. The main candidates as membrane transporters for cationic drugs are the organic cation transporters (OCT) of the SLC22 family; OCT1, OCT2 and OCT3. In humans, OCT1 is expressed primarily in the liver, with some expression in the heart, intestine, and skeletal muscle, whereas OCT2 is expressed in abundance in human kidneys. Human OCT3 is expressed in the liver, kidneys, intestine, and placenta.[40]

DEC is a basic compound.[4, 41] Müller et al.[38] indicated that OCT substrates are organic cations or weak bases. As previous mentioned, the elimination of DEC in both patients and healthy subjects is by renal and extrarenal routes so there is a possibility that DEC excretion by OCT might occur.

Theoretically, DEC is the drug of choice of lymphatic filariasis used both for prophylaxis and the treatment of *W. bancrofti* and *B. malayi* parasites. The therapeutic range is 800 to 1,000 ng/ml.[6] Oral administration of 6 mg/kg of DEC gives enough plasma concentration for antifilarial activity because peak plasma concentration is above the therapeutic level. The present study showed that administration of DEC only, DEC plus rifampicin, or DEC plus ketoconazole did not alter the plasma DEC concentration, and that in each phase of the study the $C_{max}$ was higher than the therapeutic concentration range. Therefore, DEC co-administration with rifampicin or ketoconazole may not alter the efficacy of prophylaxis and treatment of lymphatic filariasis.

## Conclusion

**This study has shown that neither rifampicin nor ketoconazole made any considerable change on the plasma DEC concentrations by CYPs induction, P-gp induction, CYPs inhibition or P-gp inhibition. The metabolic pathway of DEC is unknown. This study indicates that CYPs and P-gp are not likely to be involved in DEC metabolism. Thus the co-administration of these two drugs with DEC does not affect plasma DEC concentrations. FMOs and OCTs are two factors of interest in the DEC metabolic pathway. Further studies are needed to clarify the DEC metabolic pathway.**

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