CONTENTS

	Page
CONTENTS	viii
LIST OF TABLES	ix
LIST OF FIGURES	X
LIST OF ABBREVIATIONS AND SYMBOLS	xi
1. INTRODUCTION	1
2. LITERATURE REVIEW	5
Diethylcarbamazine	5
Rifampicin	16
Ketoconazole	40
Cytochrome P450	58
Flavin-containing monooxygenase	66
P-glycoprotein	71
Organic cation transporter, Organic anion transporter	81
3. MATERIALS AND METHODS	90
4. RESULTS	96
5. DISCUSSION AND CONCLUSION	120
BIBLIOGRAPHY	127
APPENDIX	158
VITAE	173

LIST OF TABLES

Ta	ble	Page
1.	The intra-day variations of diethylcarbamazine (DEC)	99
2.	The inter-day variations of DEC	99
3.	Relative recovery of standard DEC	100
4.	The accuracy of DEC	100
5.	Pharmacokinetic parameters of DEC in each of twelve subjects receiving	107
	a single oral dose of 6 mg/kg DEC alone	
6.	Pharmacokinetic parameters of DEC in each of twelve subjects receiving	108
	a single oral dose of 6 mg/kg after pretreatment of 600 mg/day for 5 days rifampicin	
7.	Pharmacokinetic parameters of DEC in each of twelve subjects receiving	109
	a single oral dose of 6 mg/kg after pretreatment of 400 mg/day for 5 days ketoconazole	;
8.	Pharmacokinetic parameters and urine pH (mean \pm SD.) of DEC in twelve	110
	subjects after receiving a single oral dose of 6 mg/kg alone, pretreatment	
	with 600 mg/day rifampicin, or 400 mg/day ketoconazole orally for 5 days	
9.	Plasma concentrations of DEC at 0-48 hour interval in each of twelve	111
	subjects receiving a single oral dose of 6 mg/kg DEC alone	
10.	Plasma concentrations of DEC at 0-48 hour interval in each of twelve	112
	subjects receiving a single oral dose of 6 mg/kg DEC after pretreatment	
	with 600 mg/day for 5 days rifampicin	
11.	Plasma concentrations of DEC at 0-48 hour interval in each of twelve	113
	subjects receiving a single oral dose of 6 mg/kg DEC after pretreatment	
	with 400 mg/day for 5 days ketoconazole	
12.	Plasma concentrations and urine pH of DEC at 0-48 hour interval in	114
	each of twelve subjects receiving a single oral dose of 6 mg/kg DEC alone	
13.	Plasma concentrations and urine pH of DEC at 0-48 hour interval in	115
	each of twelve subjects receiving a single oral dose of 6 mg/kg DEC after	
	pretreatment with 600 mg/day for 5 days rifamnicin	

LIST OF TABLES (CONTINUED)

Table	Page
14. Plasma concentrations and urine pH with of DEC at 0-48 hour interval in	116
each of twelve subjects receiving a single oral dose of 6 mg/kg DEC after	
pretreatment with 400 mg/day for 5 days ketoconazole	
15. Urine pH of DEC at 0-48 hour interval in each of twelve subjects receiving	117
a single oral dose of 6 mg/kg DEC alone	
16. Urine pH of DEC at 0-48 hour interval in each of twelve subjects receiving	118
a single oral dose of 6 mg/kg DEC after pretreatment with 600 mg/day rifampicin	
17. Urine pH of DEC at 0-48 hour interval in each of twelve subjects receiving	119
a single oral dose of 6 mg/kg DEC after pretreatment with 400 mg/day ketoconazole	

LIST OF FIGURES

Figure	Page
1. Structure of diethylcarbamazine (DEC)	5
2. Structure of rifampicin	16
3. Structure of rifampicin metabolite pathway	20
4. Structure of ketoconazole	40
5. Cytochrome P450 cycle in drug oxidations	59
6. Structure of ferric protoporphyrin IX	60
7. Catalytic cycle of FMO	67
8. Structure of P-glycoprotein	73
9. Model of organic secretory transporters in the proximal tubule	82
10. Model of organic anion secretory transporters in the proximal tubule	87
11. Mean calibration curve of standard DEC in plasma	97
12. Representative chromatograms of 20 µl human plasma.	100
Key: (A) blank human plasma; (B) spiked with standard DEC 1,000 ng/ml	
13. Representative chromatograms of 20 µl human plasma.	101
Key: (A) blank human plasma; (B) plasma obtained from a subject receiving	
6 mg/kg DEC alone at 0.25 hour	
14. Representative chromatograms of 20 µl human plasma.	102
Key: (A) plasma obtained from a subject receiving 6 mg/kg DEC at 0.25 hour	
after pretreatment with rifampicin; (B) plasma obtained from a subject receiving	
6 mg/kg DEC at 0.25 hours after pretreatment with ketoconazole	
15. Mean plasma DEC concentration (A) and urine pH (B) after a single oral dose of	106
6 mg/kg DEC administration alone or after pretreatment with 600 mg/day rifampicin	
and 400 mg/day ketoconazole for 5 days	

LIST OF ABBREVIATIONS AND SYMBOLS

AUC = area under the concentration-time curve

BUN = blood urea nitrogen

 C_{max} = maximal plasma concentration

CBC = complete blood count

°C = degree Celsius

Cl/F = apparent oral clearance

CV = coefficient of variation

e.g. = example gratia

FBS = fasting blood sugar

g = gram h = hour

kg = kilogram

k_a = absorption rate constant

k_e = elimination rate constant

L = litre

mg = milligram

min = minute

ml = millilitre

mm = millimeter

mV = millivolt

mol = molar

nA = nanoampere

ng = nanogram

No. = number

P = P-value

 r^2 = coefficient of determination

SGOT = serum glutamic oxaloacetic transaminase

LIST OF ABBREVIATIONS AND SYMBOLS (CONTINUED)

SGPT = serum glutamic pyruvic transaminase

SD = standard deviation

 t_{max} = time to maximal plasma concentration

 $t_{1/2} / t_{1/2} \lambda_z$ = elimination half-life

 V_z/F = volume of distribution

vol/vol = volume by volume

vs. = versus

 $\mu m = micrometer$

 $\mu g = microgram$

% = percent