

การศึกษาเภสัชจลนศาสตร์และผลทางคลินิกของเมทโทเทรกเสท
ในผู้ป่วยไทยที่เป็นโรคมะเร็งศีรษะและคอ



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วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาเภสัชศาสตรมหาบัณฑิต

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PHARMACOKINETICS AND CLINICAL STUDIES OF METHOTREXATE

IN THAI PATIENTS WITH HEAD AND NECK CANCER

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A Thesis Submitted in Partial Fulfillment of the Requirements
for the Degree of Master of Science in Pharmacy

Department of Pharmacy

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APPENDIX I

Table 18. Clinical responses of patients: Diagnosis, tumor size and tumor response.

Patients no.	Diagnosis for cancer of	Tumor sizes (cm)		Node sizes (cm)		Tumor responses
		before treatment	after treatment	before treatment	after treatment	
1	nasopharynx	NM	NM	10 X 6	7 X 4	NM
2	lower gum	3.3	1.2	-	-	PR
3	base of tongue	1.1	0	-	-	CR
4	soft palate	2.2	0.9	-	-	PR
5	buccal mucosa	5.8	NF	-	-	NF
6	base of tongue	1.2	0	-	-	CR
7	tongue	1.9	0	-	-	CR
8	pharynx	3.0	1.3	6 X 7	5 X 5	PR
9	tongue	1.4	0	-	-	CR
10	metastatic cancer	NM	NM	7 X 6	5 X 5	NM
11	nasopharynx	NM	NM	-	-	NM

NM = tumor size could not be measured

NF = patient did not followed up

CR = complete, PR = partial response

VITAE

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หัวข้อวิทยานิพนธ์	การศึกษาเภสัชจลนศาสตร์และผลทางคลินิกของเมทโทเทรกเสท ในผู้ป่วยไทยที่เป็นโรคมะเร็งศีรษะและคอ
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บทคัดย่อ

การศึกษาเภสัชจลนศาสตร์ของเมทโทเทรกเสท หลังการฉีดยาเข้าทางหลอดเลือดดำ กระทำในผู้ป่วยที่เป็นโรคมะเร็งศีรษะและคอ จำนวน 11 ราย ได้รับยาเมทโทเทรกเสทขนาด 1 มิลลิกรัมต่อน้ำหนักตัว 1 กิโลกรัม ระดับยาเมทโทเทรกเสทในซีรัมวัดโดยวิธีเฉพาะด้วย ไซเฟอร์ฟอร์แมนซ์ลิควิด โครมาโตกราฟี

การศึกษาวิธีวิเคราะห์ระดับยาเมทโทเทรกเสทในซีรัม โดยใช้ ไซเฟอร์ฟอร์แมนซ์ลิควิด โครมาโตกราฟี ได้ถูกทดลองและวิจารณ์ไว้ในการทดลองนี้ พบว่าวิธี วิเคราะห์ที่ง่ายและรวดเร็วคือใช้เรเดียล โมโคร บอนดาแพค คอลัมน์ (Radial μ Bondapak Column), สารละลายเคลื่อนที่ (Mobile Phase) คือ 0.01 โมล ของโปแตสเซียมฟอสเฟต บัฟเฟอร์มีค่าพี.เอช. ของสารละลาย 4.5 ผสมกับอะซีโตไนโตรไนโอตราส่วน 82 ต่อ 18 ไซล ผ่านคอลัมน์ด้วยอัตราเร็ว 0.8 มิลลิเมตรต่อนาที วิธีการสกัดใช้เซพแพค (Sep pak) พบว่า % recovery ของเมทโทเทรกเสทหลังการวิเคราะห์มีค่า 40 % และปริมาณต่ำสุดของ เมทโทเทรกเสทที่สามารถตรวจสอบได้คือ 0.1768 ไมโครกรัมต่อมิลลิกรัม

ผลการวิเคราะห์ข้อมูลโดยใช้โปรแกรมคอมพิวเตอร์ PCNONLIN พบว่า เภสัชจลนศาสตร์ของยาฉีดเมทโทเทรกเสทที่เหมาะสมเป็นแบบ Two-compartment open model โดยมี อัตราการกระจายตัวของยา, อัตราการขจัดยา, ค่ากึ่งชีงของยา เมทโทเทรกเสท, ค่าปริมาตรการกระจายตัวของยา และค่าการขจัดยา วัดได้เท่ากับ

4.15 ต่อชั่วโมง (1.8 - 6.2 ต่อชั่วโมง), 0.19 ต่อชั่วโมง (0.09 - 0.3 ต่อชั่วโมง),
4.2 ชั่วโมง (2.3 - 7.5 ชั่วโมง), 23.7 ลิตร (11.4 - 31.5 ลิตร) และ 4.5 ลิตร
ต่อชั่วโมง (1.9 - 9.4 ลิตรต่อชั่วโมง) ตามลำดับ เมื่อผู้ป่วยได้รับยาทางหลอดเลือดดำใน
ขนาด 1 มิลลิกรัมต่อน้ำหนักตัว 1 กิโลกรัม ค่าเฉลี่ยของระดับยาสูงสุดในซีรัมวัดได้ 6.7
ไมโครกรัมต่อมิลลิลิตร (3.6 - 8.4 ไมโครกรัมต่อมิลลิลิตร)

การรักษาโรคมะเร็งศีรษะและคอในผู้ป่วยไทยด้วยยาเคมีบำบัดตามด้วยรังสี
รักษา ปรากฏว่าคนไข้มีการตอบสนองต่อการรักษา 100 % โดยมีการตอบสนองสมบูรณ์
57.1 %

using Sep pak, resulted in analytical recovery of 40% for methotrexate. The minimum detectable quantity with this assay was 0.1768 mcg/ml.

Individual serum profile was analyzed using the PCNONLIN computer program. Results demonstrated that the pharmacokinetic of methotrexate following intravenous injection was best described by mean of a two-compartment open model. The distribution rate constant, elimination rate constant, biological half-life, volume of distribution and total clearance of methotrexate were 4.15 hr^{-1} ($1.8 - 6.2 \text{ hr}^{-1}$), 0.19 hr^{-1} ($0.09 - 0.3 \text{ hr}^{-1}$), 4.2 hours ($2.3 - 7.5 \text{ hours}$), 23.7 liters ($11.4 - 31.5 \text{ liters}$), and 4.5 liters/hour ($1.9 - 9.4 \text{ liters/hour}$), respectively. Following intravenous administration dose of 1 mg/kg of methotrexate, the mean individual peak serum concentration was 6.7 mcg/ml ($3.6 - 8.4 \text{ mcg/ml}$).

Tumor responses for methotrexate subsequent by irradiation in Thai patients suffering from head and neck cancer were 100% with complete response rate of 57.1%.



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LIST OF ABBREVIATION

$^{\circ}\text{C}$	=	degree Celcius
kg(s)	=	kilogram(s)
g	=	gram
mg	=	milligram
mcg	=	microgram
L	=	liter
ml	=	milliliter
μl	=	microliter
M	=	mole/liter
rpm	=	revolutions per minute
cm	=	centimeter
nm	=	nanometer
min(s)	=	minute(s)
hr(s)	=	hour(s)
N	=	normal/liter
C _t	=	serum concentration at time t
C ₀	=	peak serum concentration
V _d	=	apparent volume of distribution
V _c	=	volume of central compartment
AUC	=	area under the serum concentration-time cuve
$\alpha t_{1/2}$	=	distribution half-life
$\beta t_{1/2}$	=	elimination half-life
Cl _T	=	total clearance
MTX	=	methotrexate

LIST OF ABBREVIATION (cont.)

PAAP	=	p-aminoacetophenone
8-CT	=	8-chlorotheophylline
TMP	=	trimethoprim
TCA	=	trichloroacetic acid
IS	=	internal standard
MeOH	=	methanol
BS	=	blood sugar
BUN	=	blood urea nitrogen
Cr	=	serum creatinine
UA	=	uric acid
TP	=	total serum protein
Alb	=	albumin
T.Bili	=	total bilirubin
D.Bili	=	direct bilirubin
Chol	=	cholesterol
SGOT	=	serum glutamic oxaloacetic transaminase
AP	=	alkaline phosphatase
Hct	=	hematocrit
Hb	=	hemoglobin
WBC	=	white blood cell
D/C	=	differential count
Ne	=	neutrophils
E	=	eosinophils
B	=	basophils
Ly	=	lymphocytes
Mo	=	monocytes