

Minocycline 長期投與後 對大腸桿菌抗生素反應之影響

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Minocycline 經長期投與後致大腸桿菌對多種抗生物質之反應發生變化，與投藥經 8 週後所得之大腸桿菌加以比較，它們對 Minocycline 之 geometric mean MIC 之差異由 $1.3 \mu\text{g/ml}$ 提高到 $7.4 \mu\text{g/ml}$ 相差 5.7 倍，其他 tetracycline 類抗生素如 doxycycline 由 $1.9 \mu\text{g/ml}$ 提高到 $22.9 \mu\text{g/ml}$ 相差 12 倍，demethylchlortetracycline 由 $2.0 \mu\text{g/ml}$ 到 $36.1 \mu\text{g/ml}$ 相差 18.1 倍，tetracycline 由 $3.4 \mu\text{g/ml}$ 到 $70.7 \mu\text{g/ml}$ 相差 20.8 倍，chlor tetracycline 由 $5.3 \mu\text{g/ml}$ 到 $74.3 \mu\text{g/ml}$ 相差 14 倍，methacycline 由 $2.7 \mu\text{g/ml}$ 到 $92.2 \mu\text{g/ml}$ 相差 34.1 倍及 oxytetracycline 由 $7.9 \mu\text{g/ml}$ 到 $102.7 \mu\text{g/ml}$ 相差 13 倍。對 cefamezine, chloramphenicol 及 nalidixic acid 則較無明顯差異，但對 ampicillin, neomycin, kanamycin 及 streptomycin 則相差 1.9 倍，2.5 倍，4.1 倍及 14.5 倍。以整個菌株對藥物之 geometric mean MIC 來看，對 7 種 tetracycline 類之抗生素則由 $3.5 \mu\text{g/ml}$ 提高到 2 週後之 $8.5 \mu\text{g/ml}$ 及 8 週後之 $58.0 \mu\text{g/ml}$ 相差 2.4 倍及 16.6 倍；對其他 7 種抗生素分別是 $4.3 \mu\text{g/ml}$ ， $5.5 \mu\text{g/ml}$ 及 $16.0 \mu\text{g/ml}$ 相差 1.3 倍及 3.7 倍。

對 7 種 tetracycline 類抗生素之耐性株分別由 9 株 (25.0%)，提高到 17 株 (47.2%) 及 30 株 (88.2%)，對其他 7 種抗生素亦有明顯的提高，分別是 13 株 (36.1%)，29 株 (80.6%) 及 31 株 (91.1%)。

Minocycline 投與後雖不易誘導大腸桿菌對 minocycline 本身 MIC 之提高，但仍易引起菌株對其他抗生素，尤其是其他同類衍生物之 tetracycline 類抗生素及一些 aminoglycoside 抗生素耐性限閥及耐性株數的提高。固然對革蘭氏陽性球菌作用效果很好但對大腸桿菌及綠膿桿菌之抑制作用則較差。

緒 論

Tetracyclines 在 infectious disease 之治療藥物中是最被重視的，它是一群 broad-spectrum 抗生素，對大部份之革蘭氏陽性及陰性細菌具靜菌作用 (Bacteriostatic action) 而被廣泛使用於臨床。1967 年 Ma-

rtell 及 Boothe 氏(1)等發表更具療效之半合成的 tetracycline 衍生物 minocycline (7-dimethyl amino-6-demethyl-6-deoxy tetracycline) 其靜菌能力強於其他 tetracyclines，不但對感受性細菌具抑制作用，而且對耐性菌株更具明顯的效果，如 tetrac-

Table 1 . Susceptibility to The Tetracyclines of *Escherichia coli* from Chickens with Minocycline Treatment (In Vivo)

Drug *	Tested strains	Duration of treatment (week)	MIC ($\mu\text{g/ml}$)										Geometric mean MIC ($\mu\text{g/ml}$)
			0.8 $\geq$	1.6	3.2	6.3	12.5	25	50	100	>100	**	
MIM	36	0	28 #	2	2	3	1						1.3
	36	2		1	2	1	4	6					2.2
	34	8	4	1	9	4	5	9	1	1			7.4
DOX	36	0	23	5	1	2	2	1	2	2			1.9
	36	2	18	2	2		1	3	6	4			4.3
	34	8	2	2	1	1	4	8	11	4	1		22.9
DCT	36	0	27	2						5			2.0
	36	2	19	1	2					9			5.2
	34	8	4	2			1			13	3		36.1
TC	36	0	8	21					2		7		3.4
	36	2	11	10	1				5		14		8.5
	34	8	1	3	3		1	1	1	1	25		70.7
CTC	36	0		14	13	2				3	4		5.3
	36	2	4	1	15	2				3	11		13.0
	34	8		4	4	1		1	1	8	19		74.3
MC	36	0	27				1	1			7		2.7
	36	2	20			1	1	1			14		7.7
	34	8	3	1			1	1			28		92.2
OTC	36	0	1	4	22						9		7.9
	36	2		3	16			2			15		18.7
	34	8			3	1			1	1	28		102.7

* MIM = minocycline, DOX = doxycycline, DCT = demethylortetracycline, TC = tetracycline, CTC = chlortetracycline, MC = methacycline, OTC = oxytetracycline.

** For calculation of the geometric mean MIC, a value of 250 $\mu\text{g/ml}$ was used in all cases where the MIC was $>100\mu\text{g/ml}$.

Number of positive strains.

Table 2. Susceptibility to Antibiotics of *Escherichia coli* from Chickens with Minocycline Treatment (In Vivo)

Drug *	Tested strains	Duration of treatment (week)	0.8 $\geq$	MIC ($\mu\text{g/ml}$)							Geometric mean	
				1.6	3.2	6.3	12.5	25	50	100	>100	MIC ($\mu\text{g/ml}$)
CEF	36	0	20 #	10	6							1.2
	36	2	21	11	4							1.1
	34	8	13	10	3	3	4				1	2.1
NA	36	0		10	20	6						2.9
	36	2	1	3	30	2						3.9
	34	8		9	17	8						3.1
AP	36	0		16	18	2						4.8
	36	2		19	13	3					1	5.1
	34	8		7	22						5	9.0
NEO	36	0		15	21							4.7
	36	2		16	19				1			5.0
	34	8		16	7	1			4		6	11.8
CM	36	0							16	20		147.0
	36	2							4	32		185.2
	34	8							3	31		188.1
KA	36	0		1	25	10						7.4
	36	2		2	12	21				1		9.9
	34	8		1	8	9	1	3	1	11		30.7
SM	36	0		32	3				1			3.6
	36	2		23	3	2	1	4	4	3		7.3
	34	8		6	2	1	1	4	5	15		52.1

* CEF = Cefamezine; NA = nalidixic acid; AP = ampicillin; NEO = neomycin; CM = chloramphenicol ;

KA = kanamycin ; SM = streptomycin.

** For calculation of the geometric mean MIC, a value of 250 $\mu\text{g/ml}$ was used in all cases where the MIC was $> 100 \mu\text{g/ml}$.

Number of positive strains.

ycline 耐性株，它和其他 tetracycline 衍生物無交叉耐性，不易獲得藥物耐性 (a step-wise fashion) 而且易得到較高且長時間的有效血中濃度及較少的副作用 (2-6)，故它在臨床治療上較其他 tetracyclines 具良好之治療效果，如對 otorhinolaryngologic，皮膚，呼吸道及其他外科等感染之治療 (5, 7-10)，尤其對革蘭氏陰性細菌感染疾患中之尿道感染治療更被稱道 (11-14)。

故本文擬就 minocycline 長期投與後對腸道正常菌叢尤其是對大腸桿菌之影響，包括菌株對其他抗生素之感受性及交叉耐性，來探討 minocycline 在化學療法中所佔之角色及其可能之副作用。

材料及方法

以 American Cyanamid Company 所贈與之 minocycline 每膠束 (100 mg/cap) 添加於一公斤之台糖飼料，每天無限制給與，連續飼養 8 週。雛雞經台糖飼料 4 週飼養後，在投藥前及投藥後 2 週及 8 週各以肛門拭子 (Rectal swab) 採取直腸之檢體，以 EMB (Difco) 加以分離，再經純化及 IMViC 試驗及其他生化學方法 (15-16) 確認後，接種於普通琼脂半固體培養基 (Difco) 保存於冰箱中。

以 Heart infusion (HI, Difco) 琼脂平板稀釋法，測定菌株對各種藥物之最低生長抑制濃度 (MIC)，以 18 小時 HI broth (Difco) 培養稀釋液 (Mac Farl and nephelometer standards No 1)，以帶狀接種法接種於 100, 50, 25, 12.5, 6.3, 3.2, 1.6 及 0.8 $\mu\text{g}/\text{ml}$ 之各種不同藥物濃度之 HI 琼脂平板培養基，經 37°C, 24 小時培養觀察其生長情形，並以 12.5 $\mu\text{g}/\text{ml}$ MIC 做為菌株耐性及感受性之指標濃度。測定之抗生素包括 minocycline (MIM; 立達)，oxytetracycline (OTC; 輝瑞)，methacycline (MC; 輝瑞)，demethylchlortetracycline (DCT; 立達)，chlortetracycline (CTC; 氰胺)，tetracycline (TC; 立達) 及 doxycycline (DOX; 輝瑞) 等 7 種 tetracyclines，其他抗生素包括 streptomycin (SM; 明治)，kanamycin (KA; 明治)，chloramphenicol (CM; 中國化學)，neomycin (NEO; 西德有機)，ampicillin (AP; 必治妥)，nalidixic acid (NBC) 及 cefamezine (CEF; 藤澤) 等。

結果

本試驗使用之肉雞包括實驗組 10 隻及對照組 2 隻，每隻肉雞每次分離之大腸桿菌保留 3 或 4 株，試驗前總得 36 株，投藥後 2 週及 8 週各得 36 株及 34 株。由於試驗組之分離株經藥物耐性測定結果與實驗組之分離菌株之藥物耐性型態互相類似，故未加以分開計列。此種結果可能由於同室而受 minocycline 之污染所致，故對抗生素之使用於養雞事業之生長促進劑，有加以慎重考慮及限制的必要，因為此種污染不但影響動物且及於附近活動之人類，常導致耐藥性菌株之增加而嚴重影響抗治療之效果及增加公共衛生之困擾 (17-18)。

以 MIM 投藥後對大腸桿菌的影響來看，它不但導致大腸桿菌對 tetracyclines 同類衍生物之耐性 (表一) 而且對其他抗生素多少亦有交叉耐性之現象 (表二)，投藥 2 週後大腸桿菌對 tetracyclines 藥物之耐性以 CTC 之 MIC 提高較多，8 週後除 MIM 本身外都有相當顯著的提高，對其他抗生素產生之交叉耐性則較不顯著，但一些 aminoglycoside 抗生素如 NEO, KA 及 SM 投藥 8 週後則其 MIC 具較顯著之提高。故 MIM 之投與後大腸桿菌對 MIM 本身不易引起其耐性，但 MIM 仍易導致大腸桿菌對其他 6 種同類衍生物及 aminoglycoside 抗生素之交叉耐性 (Fig. 1)。

MIM 投與後以 geometric mean MIC 來觀察大腸桿菌對 tetracycline 之交叉耐性如表三，投藥 2 週後其 geometric mean MIC 由 1.7 倍到 2.9 倍不等之增加，其中 MIM 提高 1.7 倍最低，而以 MC 2.9 倍最

Table 3. Relation of Antibiotics Resistance (Geometric Mean MIC) to
The Duration of Minocycline Treatment (In Vivo).

Drug *	Duration of treatment (week)			MIC ratio 0:2/2:8/0:8	Drug	Duration of treatment (week)			MIC ratio 0:2/2:8/0:8
	0	2	8			0	2	8	
NA	2.9	3.9	3.1	1.3/ 0 /1.1	MIM	1.3	2.2	7.4	1.7/3.4/5.7
CM	147.0	185.2	188.1	1.3/1.0/1.3	DOX	1.9	4.3	22.9	2.3/5.2/12.0
CEF	1.2	1.1	2.1	0/1.9/1.8	OTC	7.9	18.7	102.7	2.4/5.5/13.0
AP	4.8	5.1	9.0	1.1/1.8/1.9	CTC	5.3	13.0	74.3	2.5/5.7/14.0
NEO	4.7	5.0	11.8	1.1/2.4/2.5	DCT	2.0	5.2	36.1	2.6/6.9/18.1
KA	7.4	9.9	30.7	1.3/3.1/4.1	TC	3.4	8.5	70.7	2.5/8.3/20.8
SM	3.6	7.3	52.1	2.0/7.1/14.5	MC	2.7	7.7	92.2	2.9/12.0/34.1

* See tables 1 and 2 for definition of antibiotics abbreviation.

高，投藥8週後由MIM之5.7倍到MC之34.1倍，雖然以MIM加以誘導但菌株對MIM之MIC增加最少，其次是DOX，OTC，CTC，DCT，TC及MC。大腸桿菌雖經8週之MIM誘導，但菌株對CEF，NA及AP仍具有相當的感受性，其MIC甚少提高，僅提高1.8，1.1及1.9倍，但NEO，KA及SM則增加到耐性的程度，尤其是後兩者，它們之geometric mean MIC分別提高2.5，4.1及14.5倍。

以12.5 µg/ml 做菌株耐性標準濃度來觀察誘導株對各種抗生素之耐性株及其耐性型態之差異(表四)，對tetracyclines類藥物之耐性株數或耐性劑數，隨MIM誘導時間之延長而增加，如未處理前9株(25.0%)產生耐性而處理後2週增加到17株(47.2%)及8週之30株(88.2%)，故MIM處理時間與藥物之耐性株及多劑耐性株數之增加成正比例關係，對其他抗生素亦有類似的結果如處理前之13株(36.1%)，處理2週後29株(80.6%)及8週之31株(91.1%)產生藥物耐性。以耐性株數加以觀察，tetracyclines類藥物之耐性株似乎較其他抗生素之耐性株少，此乃由於大腸桿菌誘導株對tetracyclines類藥物之MIC高低分佈較為懸殊，而對其他抗生素之MIC雖然不高，但誘導株之MIC則普遍提高所導致之結果。

討論

有關具廣效性抗菌譜之minocycline之應用於革蘭氏陽性及陰性細菌，包括E. coli，P. mirabilis，Klebsiella-Enterobacter，Pseudomonas aeruginosa，Haemophilus influenzae，Staphylococcus aureus，及Streptococcus pneumoniae等細菌感染患者之臨床實際應用及實驗室(In vitro)之感受性試驗都較其他衍化物為優，且耐性及交叉耐性較不易獲得(2-6, 9, 19, 20)，如Holloway氏應用minocycline於16件急性及26件慢性尿道感染之治療，各15件獲得好之

治療結果，並以10株大腸桿菌做藥物感受性試驗結果，minocycline之平均MIC是3.05 µg/ml，優於tetracycline之42.8 µg/ml及doxycycline之15.6 µg/ml。Frisk氏(5)等報告minocycline對250株大腸桿菌及paracolon之感受性亦優於其他同類藥物，minocycline之geometric mean MIC是1.44 µg/ml而doxycycline是7.93 µg/ml及tetracycline之8.16 µg/ml，此種結果類似Holloway氏(14)之報告。Fedorko氏(3)等以18株大腸桿菌探討minocycline與其他tetracyclines衍生物的抗菌能力結果minocycline優於demethylchlorotetracycline，chlorotetracycline，oxytetracycline及tetracycline。

Minocycline對臨床分離之S. aureus (geometric mean MIC, 0.9 µg/ml)之抑制力較oxytetracyclines (18.7 µg/ml)強(21-22)，對Shigella及Serratia marcescens亦具較好之抗菌力價，分別對minocycline及oxytetracycline之geometric mean MIC是19.0與40.3 µg/ml及11.7與94.0 µg/ml，但minocycline對P. aeruginosa及E. coli之capsular-polysaccharide-synthesizing strains (CPS)及non-cps株之geometric mean MIC分別是51.3，82.6及18.3 µg/ml與oxytetracycline之25.4，86.6及14.4 µg/ml具類似或較低之制菌作用。

作者前測定49株臨床腸來源大腸桿菌對tetracyclines之感受性結果(21)，其geometric mean MIC分別是minocycline 79.7 µg/ml，doxycycline 30.3 µg/ml，chlorotetracycline 62.7 µg/ml，demethylchlorotetracycline 61.3 µg/ml，tetracycline 4.3 µg/ml，methacycline 64.7 µg/ml及oxytetracycline 81.6 µg/ml，以感受性而言，doxycycline最佳，其次是tetracycline，demethylchlorotetracycline，chlorotetracycline，methacycline及minocycline，

Table 4. Resistance Patterns of *Escherichia coli* to The Antibiotics from Chickens with Minocycline Treatment (In Vivo).

Pattern	Drug combination*	Duration of treatment (week)		
		0	2	8
1	OTC	-	2 (5.6)#	-
2	OTC & MC	2 (5.6)	1 (2.8)	1 (2.9)
4	OTC, MC, CTC, & DCT OTC, MC, CTC, & DOX	- -	- -	1 (2.9) 1 (2.9)
6	OTC, MC, TC, CTC, DCT & DOX	3 (8.3)	4 (11.1)	11 (32.6)
7	OTC, MC, TC, CTC, DCT, DOX & MIM	4 (11.1)	10 (27.8)	16 (47.1)
Positive numbers		9 (25.0)	17 (47.2)	30 (88.2)
1	SM	1 (2.8)	5 (13.9)	5 (14.7)
	KA	10 (27.8)	17 (47.2)	5 (14.7)
	AP	2 (5.6)	-	-
2	SM & KA	-	2 (5.6)	5 (14.7)
	SM & AP	-	2 (5.6)	-
	KA & AP	-	2 (5.6)	-
3	SM, KA & NEO	-	1 (2.8)	8 (23.5)
	SM, KA & CEF	-	-	3 (8.8)
	SM, AP & CEF	-	-	1 (2.9)
4	SM, KA, AP & NEO	-	-	3 (8.8)
	SM, KA, AP & CEF	-	-	1 (2.9)
Positive numbers		13 (36.1)	29 (80.6)	31 (91.1)
Tested strains		36	36	34

* See tables 1 and 2 for definition of antibiotics abbreviation.

Number of positive strains; figures in parentheses show the percentage.

而以 oxytetracycline 之 MIC 最高，此種高 MIC 耐性結果與以往之報告略有出入 (2-6, 9, 14, 19, 20)，除操作上可能之差異外，與藥物使用頻率及濫用似乎亦具有密切的關係，故以 minocycline 做為大腸桿菌或其細菌感染之治療，應做藥物感受性試驗。以另一個角度來探討 minocycline 與菌株耐性之關係，作者 (22) 以 NTG 處理對抗生素感受性及非莖膜多醣類產生株 (Non-CPS 株) 的大腸桿菌，而獲得 spectinomycin 耐性莖膜多醣類產生變異株 (SP^r -CPS strains)，雖然 minocycline 對此等變異株之 geometric mean MIC ($65.5 \mu\text{g/ml}$) 相當高，但仍優於其他 tetracyclines 衍生物平均 geometric mean MIC $134.2 \mu\text{g/ml}$ ，包括 oxytetracycline, methacycline, demethylchlortetracycline, chlortetracycline, tetracycline 及 doxycycline。相反的若以 SP^r -non-CPS 株加以觀察，它們對 tetracyclines 之感受性 ($3.2 \mu\text{g/ml}$) 類似母株，並不受變異劑處理而影響其 MIC，包括 Minocycline。

但以 chloramphenicol 及 oxytetracycline 處理後之 CPS 變異株 (23)，變異株 (CM^r -or OTC^r -CPS strains) 對 minocycline 之 MIC 改變甚少，由原來母株之 geometric mean MIC $6.3 \mu\text{g/ml}$ 提高到 $7.6 \mu\text{g/ml}$ ，而其他同類衍生物則提高較多，以它們之 geometric mean MIC 與母株之 MIC 加以比較，doxycycline 提高 18 倍，oxytetracycline 39.7 倍，chlortetracycline 46.8 倍，demethylchlortetracycline 67.2 倍，tetracycline 53.3 倍及 methacycline 156.3 倍。

由以往之報告及大腸桿菌經各種誘導劑誘導之變異株對各種藥物之耐性及交叉耐性獲得能力加以探討，不論以 minocycline 本身或其他變異劑如 N-methyl-N'-nitro-N-nitrosoguanidine, chloramphenicol 及 oxytetracycline 等加以誘導，變異株對 minocycline 之耐性獲得較其他同類衍生物慢而低，但

它仍能誘導菌株對其他同類衍生物及部份 aminoglycoside 抗生素之交叉耐性，故此種副作用應予特別的關注，以免影響由於 minocycline 之投與而誘導大腸桿菌或其他細菌對其他藥物耐性限閥的提高，因而導致化學療法之困擾或失敗，甚或引起菌株之生化特性，抗原性，產毒性或病原性的改變 (23)。故 minocycline 對本省目前之大腸桿菌感染症之治療，在 tetracycline 中並非良好之藥品，但它對於其他傳染性疾病之治療仍具有崇高地位。

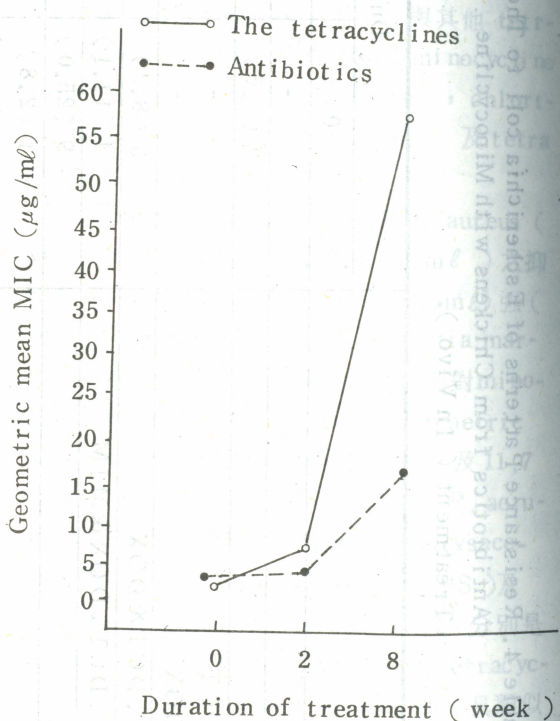


Fig. 1. Susceptibility to the Antibiotics of *Escherichia coli* from Chickens with Minocycline Treatment (In Vivo)

參考文獻

- 1 MARTELL MJ, BOOTHE JH: The 6-deoxy-tetracycline VII. Alkylated aminotetracyclines possessing unique antibacterial activity. *J Med Chem* 10; 44-46, 1967.
- 2 RODIN GS: Antibacterial activity in

- mice of minocycline, a new tetracycline. *Antimicrobial Agents and Chemotherapy* 1966;371-376, 1967.
3. FEDOKO J, KATZ S, ALLNOCH H: In vitro activity of minocycline, a new tetracycline. *Am J Med Sci* 255; 252-258, 1968.
4. PEREZ LC: Effectiveness of minocycline in bacterial infection. *Bol Asoc Med P Rico* 64; 81-83, 1972.
5. FRISK AR, TUNEVALL GA: Clinical evaluation of minocycline. *Antimicrobial Agents Chemotherapy* 1978;335-339, 1969.
6. STEIGBISEL NH, REED CW, FINLAN M: Absorption and excretion of five tetracycline analogues in normal young men. *Am J Med Sci* 255; 296-312 1968.
7. JALAN VO, SHAH BH, DIXIT CV: Pyogenic infections of skin treated with minocycline. *Indian J Dermatology Venereology* 37; 99-103, 1971.
8. MARRA UD: Minocycline in the treatment of bacterial respiratory infections. *Brazil Revista Brasileira de Medicina* 28; 544-550, 1971.
9. ANLYAN AJ: Use of minocycline in the prophylaxis and treatment of surgical infections. *Am Surgeon* 43; 413-416, 1977.
10. SHIBATA K, HANAI T, KATO T, ITO T, FUJII M: Laboratory and clinical studies on minocycline in the surgical field. *Japanese J Antibiot* 22; 458-462, 1969.
11. TWASAWA T, KIDO T: Clinical and experimental studies on minocycline. *Japanese J Antibiot* 22; 511-521, 1969.
12. KAWAMORI Y: Clinical and laboratory research on minocycline. *Japanese J Antibiot* 22; 430-434, 1969.
13. OKUBO H, FUJIMOTO Y, OKAMOTO Y, TSUKADA J: Laboratory and clinical experiments on minocycline. *Japanese J Antibiot* 22; 430-434, 1969.
14. HOLLOWAY WJ: Minocycline in the treatment of urinary tract infections. *Delaware Med J* 42; 333-336, 1970.
15. EDWARDS PR, EWING WH: Identification of Enterobacteriaceae, ed 3, Minneapolis, Burgess Publishing
16. FINEGOLD SM, MARTIN WJ: SCOTT EG: *Bailley and scott's diagnostic microbiology*, fifth edition. The C.V. Mosby Co. Saint Louis P. 148-194, 1978.
17. LINTON AH, KATHERINE H, OSBORNE AD: The effects of feeding tetracycline, nitrovin and quindoxin on the drug-resistance of coli-aerogenes bacteria from calves and pigs. *J Appl Bacteriol* 38; 255-275, 1975.
18. TSENG CC, CHEN MI: Studies on coagulase-negative staphylococci. (III) Biological characteristics and drug susceptibility of the chicken origin strains. *Bulletin of Taipei Medical College* 7-8; 29-38, 1978.
19. KLASTERSKY J, DANEAU D: Comparative study of minocycline and ampicillin in the treatment of urinary tract infections. *Int J Clin Pharmacol* 9; 125-131, 1974.
20. KLASTERSKY J, DANEAU D: Bacteriologic evaluation of minocycline, a new tetracycline. *Chemotherapy* 17; 51-58, 1972.
21. TSAN YC & TSENG CC: (unpublished data)

22. TSENG CC, CHEN MI, LEE LW: Studies on pathogenic *Escherichia coli*. III. Multiple drug resistance of capsular polysaccharide-synthesizing *Escherichia coli*. J Formosan Med. Assoc 78; 7-16, 1979.

23. TSENG CC: Studies on pathogenic *Escherichia coli* (V) Characteristics of spectinomycin-resistant-CPS mutants of *Escherichia coli* induced

by N-methyl-N'-nitro-N-nitrosoguanidin. (In press) data.

24. Tseng CC: Studies on pathogenic *Escherichia coli* (IV) The relation of capsular poly-saccharide synthesis to antibiotics susceptibility, biochemical properties and pathogenicity of *Escherichia coli*. (J. Formosan Med. Assoc. In press) o.

Effectiveness to Antibiotics Response of *Escherichia coli* by Long-Term Administration of Minocycline (In Vivo)

Cheng-Chuang Tseng and Ling-Wen Lee

Minocycline causes after its long-term administration, a considerable change in *Escherichia coli*'s response to various antibiotics. When we compared the *E. coli* isolated from the hosts after 8 weeks administration with the strains obtained before minocycline administration, their geometric mean MIC for minocycline rose from 1.3 µg/ml to 7.4 µg/ml i.e. 5.7 times high. The geometric mean MICs for other tetracyclines also showed a considerable rise: MIC for doxycycline from 1.9 µg/ml to 22.9 µg/ml i.e. 12 times high, for demethylchlortetracycline from 2.0 µg/ml to 36.1 µg/ml i.e. 18.1 times high, for tetracycline from 3.4 µg/ml to 70.7 µg/ml i.e. 20.8 times high, for chlortetracycline from 5.3 µg/ml to 74.3 µg/ml i.e. 14 times high, for methacycline from 2.7 µg/ml to 92.2 µg/ml i.e. 34.1 times high, and for oxytetracycline from 7.9 µg/ml to 102.7 µg/ml i.e. 13 times high. The MICs for cefamezine chloramphenicol and nalidixic acid showed little change, but the MICs for ampicillin, neomycin, kanamycin and streptomycin increased to 1.9 times, 2.5 times, 4.1 times and 14.5 times respectively. The average geometric mean MIC for seven tetracyclines increased from 3.5 µg/ml to 8.5 µg/ml for the strains obtained after 2 weeks minocycline administration, to 58.0 µg/ml for the strains after 8 weeks administration, a 2.4 times and 16.6 times rise respectively; for the other seven antibiotics from 4.3 µg/ml to 5.5 µg/ml and 16.0 µg/ml, a 1.3 times and 3.7 times rise respectively.

The number of resistant strains to seven tetracyclines increased from 9 (25.0%) to 17 (47.2%) and 30 (88.2%) for the strains after 2 weeks and 8 weeks minocycline administration respectively, the resistant strains to the other seven antibiotics also distinctly increased from 13 (36.1%) to 29 (80.6%) and 31 (91.1%) respectively.

Therefore, although the administration of minocycline induced not very significant rise of MIC for minocycline itself, but readily caused a rise of resistance threshold, and an increase of the number of resistant strains to other antibiotics especially to other tetracyclines and some aminoglycoside antibiotics. Though minocycline is very effective to Gram-positive cocci, but against *E. coli* and *Pseudomonas aeruginosa* its inhibitory effect is less satisfactory.