CHAPTER 5

DISCUSSION

In the disc-susceptibility test of Shigella to ceftriaxone, the drug showed a very good activity against the test organisms. All of 30 shigellae isolates (100 %) were susceptible to the drug. The average zone diameter was 30.7 ± 3.76 which was much higher than the indicated sensitive zone diameter for ceftriaxone (16 mm).[33]

For other antibiotics tested, Shigella gave the comparable percentages of sensitive strains to the results of the tests obtained from Ramathibodi Hospital in the same year (1982) as shown in Table 39

Table 39 Comparison of the antibiotic susceptibility test's results of this study to the Ramathibadi Hospital's test results (Rama*) in the same year (1982).

Antimicrobial agents	Percentage of sensitive strains (no. of strains tested)			
	S. flexneri		S. sonnei	
	Rama*	This study	Rama*	This study
ampicillin	13 (220)	11 (56)	3	7 (14)
cephalothin	-	92 (53)	-	64 (14)
chloramphenicol	5 (220)	2 (55)	3	14 (14)
neomycin	-	80 (55)	-	57 (14)
TMP/SMX	67 (220)	73 (56)	96	78 (14)
tetracycline	7 (220)	4 (55)	-	7 (14)

The minimum inhibitory concentrations (MICs) of ceftriaxone against Shigella was very low, the MIC_{50} and MIC_{90} obtained were 0.00465 and 0.0262 µg/ml respectively. In comparison with reports of Lolekha et al (Bangkok, Thailand), Angehrn et al[4] (Basle, Switzerland and Shelton et al (Texas, USA) (table 40), the MIC_{90} of each report was nearly the same while the MIC_{50} of this experiment was relatively lower than the others. This might be due to the larger number of the organisms tested.

Table 40 The Comparison of the MIC_{50}, MIC_{90} and modal MIC of ceftriaxone to shigellae of various experiments.

title	MIC_{50} µg/ml	MIC_{90} µg/ml	modal MIC µg/ml	number of stains tested
This experiment in Bangkok (1982)	0.00465	0.0262	0.00391 and 0.0312	103
Lolekha et al in Bangkok (1982)	0.022	0.03		40
Angehrn et al[4] in Basle, Switzerland (1980)	0.05	0.05		10
Shelton et al[5] in Texas, USA. (1980)		0.03	0.015	94

These in vitro results supported the idea of this research which tried to discover the more active compound against Shigella spp.

In clinical studies, a single dose treatment of ceftriaxone

reduced the diarrhea and systemic symptoms within a satisfactory period. In 58-63 % of the patients, the frequencies of stools per day and the stool characteristics turned to normal within the average of 3.1 and 3.75 days after treatment, respectively. While, in the absence of specific therapy, shigellosis develops spontaneous clinical improvement 5-7 days in most cases, but the abnormal stools persist for 10 days or longer.[62]

Haltarin et al[58,59] and Gilman et al[60] reported the clinical results of ampicillin therapy in various doses and routes of administration. These are shown in comparison with this study's results in table 41.

ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

Table 41 The comparison of clinical results of ampicillin therapy and ceftriaxone therapy in shigellosis

Source of data	Haltarin et al		Haltarin et al			Gilman et al		This study
Year of observations	1968		1969			1980		1983
Country	U.S.A.		U.S.A.			Bangladesh		Thailand
Drug used	ampicillin*		placebo	ampicillin*		ampicillin*		ceftriaxone**
Route of administration	IM.	oral	oral	oral	oral	oral	oral	IM. & IV.
Dose (mg/kg/day)	100	100	-	50	100	50	150	50
No. of patients studied	22	32	16	29	32	7	10	21
Age range (children) (yrs.)	0 - 5					4.6± 1.6	3.2 ± 1.8	1 - 12
Causative organisms	Shigella spp.		Shigella spp.			S. flexneri		Shigella spp.
Clinical observations								
No. of patients with diarrhea for >5 days after initiation of therapy (%)	2(9)	1(3)		2(7)	1(3)			8/19 (42)
Mean no. of days of diarrhea after initiation of therapy (range)	3.1 (<1-6)	3.3 (<1-7)		3.3 (1-7)	3.1 (1-8)	4.0 ± 2.0	3.3 ± 2.3	3.1 (1-5)
First afebrile day	0.4(<1-2)	1.4(<1-4)		1.4(<1-4)	1.4(<1-6)			1.08(1-2)
Mean no. of days after therapy started until stool cultures negative	0.8 (<1-3)	2.1 (<1-4.5)						

Table 41 (cont.)

Drug used	ampicillin*		placebo	ampicillin*		ampicillin*		ceftriaxone**
Route of administration	IM.	oral	oral	oral	oral	oral	oral	IM. & IV.
Dose (mg / kg / day)	100	100	-	50	100	50	150	50
No. of patients studied	22	32	16	29	32	7	10	21
No. of culture positive / total (%) on day 0			(100)	(100)	(100)	-	-	20/20(100)
1			(94)	(63)	(61)	-	-	20/20(100)
2			(77)	(24)	(24)	-	-	14/19(74)
3			(67)	(17)	(6)	0/7	0/10	11/17(65)
4			(55)	(14)	(6)	-	-	8/15(53)
5			(45)	(7)	(0)	-	-	11/13(85)
7			(30)	(30)	(0)	1/7	1/8	
14-21						1/3	0/3	

* ampicillin was given as 4 divided doses for 5 days.

**ceftriaxone was given as a single dose therapy.

ศูนย์วิทยทรัพยากร
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From table 41, the clinical results of ceftriaxone therapy were comparable to those of ampicillin therapy, especially in 1968 and 1969 in USA. while ampicillin was still giving very good activity against shigellosis. Ceftriaxone rendered patients afebrile within an average of 1.08 days while the ampicillin groups of patients had nearly the same results of 0.4 to 1.4 days. Diarrhea disappeared almost in the same time after initiation of therapy in every group (within the averages of 3.1 to 4.0 days, see table 41). Ceftriaxone gave a satisfactory clinical results.

In bacteriological observations, the results of bacterial cultures from stools of patients in ceftriaxone group showed no advantage over the placebo group in the report of Haltarin et al in 1969.[59] Thus, the single dose treatment of ceftriaxone could not eradicate the organisms from the stools. There would be a substantial risk of environmental shedding and spreading of the organisms.

Serum concentrations of ceftriaxone obtained by mitrobiological assay, were comparable to those in the study of Schaad et al in children[20] and in the study of Mitsuhashi et al in adults[38] as shown in figure 10,11,12.

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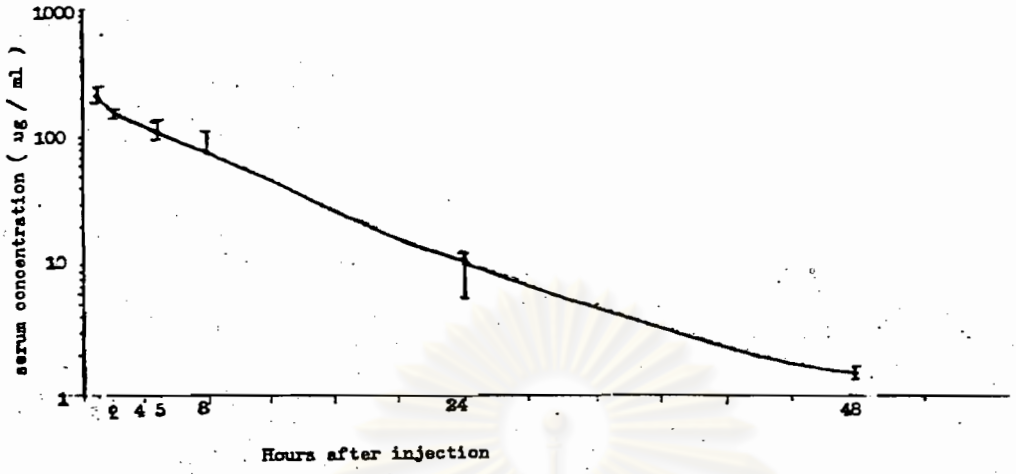

Figure 10 Sera ceftriaxone concentrations after a 50 mg/kg IV. dose in children. (Fig.7)

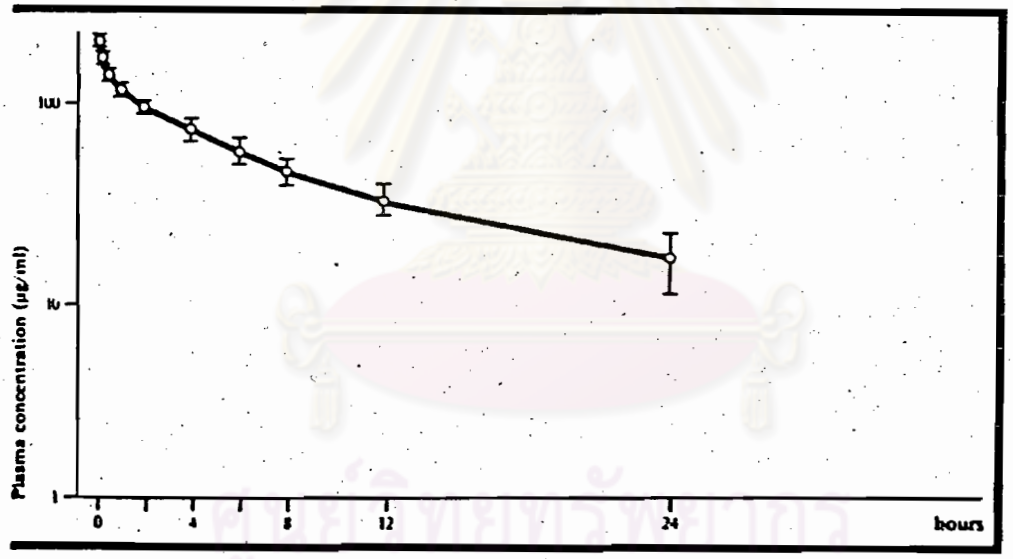

Figure 11 [38] Plasma concentrations after IV. injection of 1 gm ceftriaxone in 5 healthy volunteers. (Mitsuhashi et al [38])

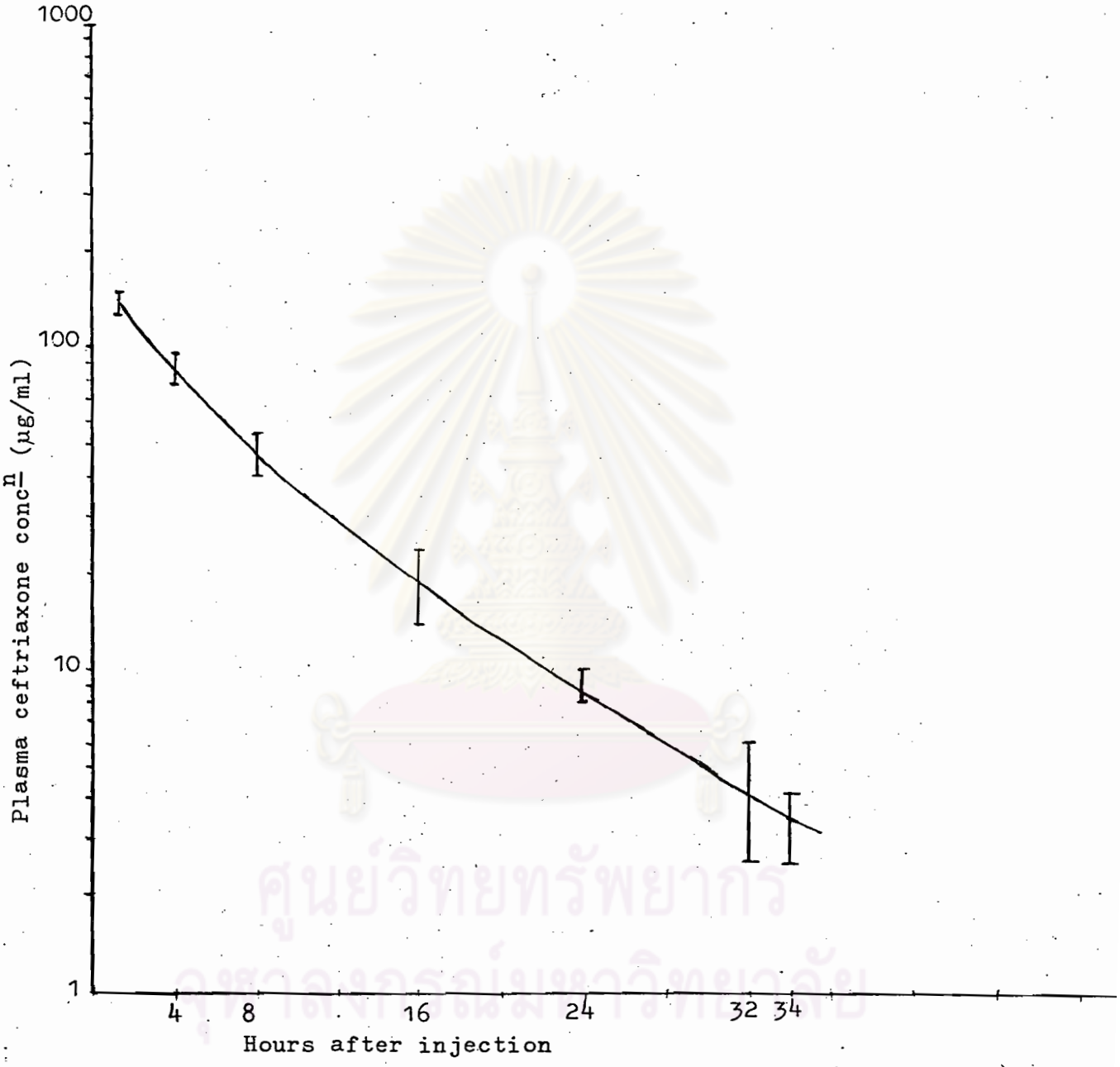

Figure 12 Plasma concentrations of ceftriaxone after a 50 mg/k
IV dose in children (Schaad et al)[20].

At 1 hour after injections the serum levels of ceftriaxone ranged from 160 to 307 µg/ml with a mean of 221.3 ± 39 µg/ml. At 48 hours after injection, serum ceftriaxone levels were still more than 50 times higher than the MIC_{90} of ceftriaxone against Shigella spp. From the curve in figure 10, the ceftriaxone concentration could be estimated to be above the MIC_{90} against Shigella spp. for more than 72 hours. The important factor in shigellosis' pathogenesis is the epithelial cell penetration by the organism. The intestinal fluid secretion induced by the Shigella's enterotoxin[65], appears to be less important in comparison to the colonic disruption produced by bacterial invasion.[64] Improvement in diarrhea and systemic symptoms after a single dose of ceftriaxone might be due to the high serum and tissues ceftriaxone concentration and its long half life. This might eradicate all the organisms in the submucosa which cause tissue damage, and the organisms in the epithelial cells were temporalily disappeared. But, the concentration of the drug in the intestinal lumen may not be enough to eradicate the organisms in stool because the decomposition of the drug excreted from the bile.[33] So, the organisms in the lumen may re-infect and penetrate into the epithelial cell in some patients, this may be the cause of clinical failure in these patients (see table 30, 31). In these cases which clinical symptoms did not improved within 48 hours, the second dose of ceftriaxone may be given, then the other oral antibacterial drugs may be given to eradicate the organisms in the lumen.