

Double Blind Randomized Controlled Study of Once Daily 400 mg Pefloxacin Short Course in Typhoid and Paratyphoid Fever

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Abstrak

Uji klinik tersamar ganda membandingkan 400 mg pefloksasin/hari selama 7 hari dengan kloramfenikol dosis standard 50 mg/kg BB/hari selama 14 hari pada demam tifoid/paratifoid telah dilakukan dengan menggunakan "double dummy technique" secara acak. Tujuan studi adalah untuk menilai efikasi klinik maupun bakteriologik pada pengobatan jangka pendek dengan jenis obat baru golongan fluorokuinolon untuk demam tifoid. Kasus yang dievaluasi meliputi 20 penderita yang diobati dengan pefloksasin, menghasilkan penurunan panas rata-rata dalam 3,8 hari ($SD \pm 1,6$). Tidak tercatat kematian, komplikasi, relaps maupun pembawa kuman sekretoir dalam kelompok pefloksasin. Semua kasus yang dievaluasi memenuhi kriteria positif untuk *S. typhi*/*S. paratyphi* dalam darah dan patuh mengikuti seluruh penilaian pasca pengobatan sampai selesai. Pada 21 orang penderita yang diobati dengan kloramfenikol tercatat kematian pada satu kasus, komplikasi pada 2 kasus lainnya masing-masing seorang dengan toksemia dan lainnya dengan perdarahan rektal. Panas turun rata-rata dalam 4,5 hari ($SD \pm 1,5$). Dalam kelompok ini, pembawa kuman sekretoir pasca terapi (*carrier*) tercatat pada 2 orang penderita. Pada penilaian pasca terapi ternyata tiga kasus lainnya mengalami infeksi *Salmonella* spp. asimtomatik pasca perawatan, masing-masing 2 kasus dalam kelompok pefloksasin dan seorang dalam kelompok kloramfenikol. Pada studi terbatas tetapi cukup objektif ini dapat disimpulkan bahwa penggunaan pefloksasin dosis tunggal selama satu minggu sangat memuaskan untuk penderita demam tifoid setempat.

Abstract

A 7-day short course of once daily 400 mg pefloxacin (PEF) was compared by a double blind dummy technique against a standard 14 days course of 50 mg chloramphenicol (CAP) /kg BW/day in four divided dosages for treatment of typhoid and paratyphoid fever. The purpose of the study was to evaluate objectively clinical and bacteriological efficacy. A total of 79 patients were enrolled. Only *S. typhi* and *S. paratyphi* positive cases were included in the final analysis. Both groups were comparable for duration of illness, sex, age, body weight and height. Microorganisms were all sensitive to both PEF and CAP. Treatment results were significantly better in the PEF group ($N=20$), fever cleared in an average of 3,8 days ($SD \pm 1,6$). In the CAP group ($N=21$) it was 4,5 days ($SD \pm 1,5$). In the CAP group one patient died and two other cases suffered from complications, rectal bleeding and toxemia respectively. None was seen in the PEF group. There were also no secretory carriers or relapses seen in the PEF group while 2 cases became secretory carriers in the CAP group. A symptomatic newly acquired post treatment *Salmonella* spp. infections were noted in both groups (two in the PEF group and one in the CAP group). It may be concluded that in this limited but very objective study, a short 7-day once daily pefloxacin treatment course in our local population yielded superior results compared to standard chloramphenicol treatment.

Keywords : Typhoid fever, Pefloxacin, Chloramphenicol, Short Course Treatment, Double Blind Study.

INTRODUCTION

Information on the use of pefloxacin for intestinal infections was not available yet in the mid-80s.¹ In the later parts of the 80s it was suggested that a 14 days course of pefloxacin was useful in typhoid fever.² A study with thrice daily 400 mg pefloxacin for 14 days

gave excellent results.³ A comparative study by Hajji et al favored pefloxacin above the control drug used cotrimoxazole.⁴ In the early 90s a short course of one week twice daily 400 mg pefloxacin in typhoid fever cured 94,6 % of the patients.⁵

Serum levels of pefloxacin as published by the international literature as well as in healthy Indonesian

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volunteers was still many times higher than the MICs for Salmonella at 12 hour post oral dosing.^{6,7,8}

A pilot study with a single daily dosage of 400 mg pefloxacin for 7 days in our population group gave very promising results.⁹ A double blind study was designed to compare a one week course of 400 mg pefloxacin against standard chloramphenicol treatment, the present drug of choice used in Indonesia.

PATIENTS AND METHODS

All patients presenting with signs and symptoms suggestive of typhoid fever were screened for inclusion in this double blind randomized study of treatment. Patients received either 400 mg pefloxacin daily for one week or 50 mg chloramphenicol /kg BW for two weeks. Placebos were given in the same form and for the same length of time.

Patients of both sexes between the ages of 16 and 65 years without complications like perforations, intestinal bleeding or coma were admitted to the study except :

1. when fever already lasted for more than 3 weeks,
2. females that were pregnant or lactating,
3. when there was severe impairment of kidney and liver functions,
4. patients with known hypersensitivity against quinolones or chloramphenicol.
5. patients in need of receiving other antimicrobial agents.

Before initiating specific therapy with pefloxacin or chloramphenicol the following investigations were performed : blood, stool and urine cultures, blood counts, renal and liver function tests as well as Widal agglutination titres. Bacterial susceptibility was determined by a disc diffusion procedure.^{10,11,12} The condition of the patients were assessed daily. Passive recordings were done for adverse reactions. Blood culture was repeated on day 15 in the positive cases and repeated weekly until negative. Stool and urine cultures were all performed on day 15, 22 and 28 as well. Patients were assessed for clinical relapse up to a period of two months. Blood chemistry was repeated on day 15.

All patients entered were included in the tolerance and safety evaluation while those who were definitely shown to be initially positive for Salmonella were included in the efficacy analysis.

All patients were asked to give informed consent in full accordance with the Helsinki declaration. Statistics were performed where applicable.

RESULTS

Seventy nine patients passing inclusion and exclusion criteria consisted of 39 patients in the pefloxacin group and 40 patients in the chloramphenicol group. From the 39 patients in the pefloxacin group 22 were positive for Salmonella and from the chloramphenicol group also 22 of the 40 patients were positive for Salmonella. One patient in the pefloxacin group was dropped because of unattendance during the post-treatment period and two patients, one respectively in each group because of transfer to another hospital.

Characteristics of the two evaluated groups were similar (Table 1).

Table 1. Basic data of patients included in the efficacy analysis Pefloxacin (PEF) vs. Chloramphenicol (CAP)

Parameters	PEF (N = 20)	CAP (N = 21)
Male : Female	14 : 6	13 : 8
Age (years) *	22,5 (SD±5,4)	24 (SD±6,4)
Body Height (cm) *	160,5 (SD±6,0)	157,3 (SD±7,6)
Body Weight (kg) *	50,3 (SD±8,5)	46,4 (SD±6,2)
Duration of fever (Pre treatment) *	10,0 (SD±4,5)	8,5 (SD±4,1)

* P > 0,05

Table 2. Clinical efficacy Pefloxacin vs. Chloramphenicol

	Pefloxacin	Chloramphenicol
Defervescence (days)	3,8 (SD ± 1,6)	4,5 (SD ± 1,3)
Side effects	None	None
Complications	None	Yes (2)
Mortality	None	Yes (1)

Clinical efficacy is shown in Table 2. There was no statistical difference in the average number of days before total resolution of fever occurred. The daily follow-up showed that in the chloramphenicol group one patient (female /28 y) deteriorated and died even after corticosteroids were given. Another patient (male/30y) developed rectal bleeding on the 4th day of study. This occurrence lasted for 4 days but did not need to be corrected by blood transfusion or change of treatment. Another case got worse on the 3rd day of treatment with chloramphenicol, developed a toxic state and was treated accordingly. No deaths or complications were recorded in the pefloxacin group of patients. No clinical adverse reaction were registered for both groups.

Table 3. Bacteriological efficacy in Typhoid Fever : Pefloxacin vs, Chloramphenicol

	PEF	CAP
Isolated Pathogens		
<i>S.typhi</i>	20*	20**
<i>S.paratyphi A</i>	2	2
Susceptibility of pathogens	All	All
Convalescent Carriers		
Non-secretory	1	1
Intestinal	-	1
Urinary	-	1
Intercurrent convalescent asymptomatic <i>Salmonella</i> spp.carriage	2	1

* One case defaulted on post treatment follow up and another was transferred on the 4th day of treatment in afebrile condition to another hospital (no follow up possible).

** One case was transferred to another hospital on the 4th day of treatment still in febrile condition.

Bacteriological efficacy

In both groups pathogens isolated before treatment were identified as *S.typhi* in 20 and *S.paratyphi A* in 2 patients. All strains were sensitive *in vitro* to both pefloxacin as well as chloramphenicol. During the convalescence period samples were taken from the blood (after treatment) and 3 times from the faeces and urine up to one month.

It could be shown that there was no convalescent excretory carrier in the pefloxacin group, but in one bacteriologically severe case where *S.typhi* could be isolated from the blood, urine as well as faeces before treatment the microorganisms persisted on the post treatment m.o. blood check. This patient's condition already returned to normal, and his blood was cleared on a subsequent blood test. There were non-secreting as well as secreting carriers both urinary and faecal in the chloramphenicol group. This has been a well known observation in the majority of studies done with chloramphenicol. Besides that during the convalescence period isolation of other *Salmonella* (spp) from the stools were noted in 3 patients, two in the pefloxacin group and one in the chloramphenicol group. However there were no signs or symptoms of clinical illness (Table 3). Laboratory results showed that there were leucopenic patients in the chloramphenicol group after treatment compared to none in the pefloxacin group. There were no relapse seen in both groups.

DISCUSSION

The development of short term treatment schedules for typhoid fever was initiated in the 80s when more potent bactericidal antimicrobials became available.^{13, 14, 15}

Not only for typhoid fever but for many other infections short term courses were developed and applied with some form of success.¹⁶ The essence of a short course is that the duration of treatment given is not longer than half the time of the universally accepted duration of treatment for the particular infection.

This study was carried out in a double blind fashion with double dummies using a randomized method to secure the most objective results, avoiding bias or doubt in evaluating new ways of treatment. As could be seen in this study we did not encounter a single adverse reaction in contrast to previous reports when higher daily dosing schedules of pefloxacin were used. Clinical efficacy was faultless in the pefloxacin group compared to one demise and two cases with complications in the chloramphenicol group. Bacteriological efficacy favored the pefloxacin group where one non-secreting convalescent carrier was noted, in contrast to the chloramphenicol group where besides a non-secreting carrier, faecal and urinary carriers were also noted.

If we consider the individual cases in both groups where *S.typhi* could still be found in the blood after the treatment period, the patient in the pefloxacin group on admission had *S.typhi* not only in the blood, but also in the stool and urine denoting a severe type of overwhelming infection. This patient had a body weight of 65 kg, while the average in the group was 50,3 kg and probably this daily dose/BW ratio of 400 mg pefloxacin / 65 kg against the average 400 mg pefloxacin / 50,3 kg may have caused this delayed clearance. On the other hand the body weight of the patient that still had *S.typhi* in the blood in the chloramphenicol group was 41 kg, which was below the average of 47,3 kg for the whole group and thus may be assumed that the drug levels in the blood were adequate. It could be suggested that patients with a body weight of 50 kg or more may need BID pefloxacin dosing or higher single daily dosing with pefloxacin especially when encountering cases with overwhelming infections in order to obtain faster clearance of bacteremia.

An interesting point for discussion should be the newly contracted *Salmonella* spp. infection that did not cause any complaint in both groups. Usually salmonellosis is associated with a clinical syndrome of enteritis. The patients were spared probably by way of cross-immunity due to the previous infection with *Salmonella typhi* and *S.paratyphi A*.

Short treatment courses for typhoid fever other than pefloxacin at the moment have been recorded with ciprofloxacin^{17,18} with ofloxacin¹⁹ and fleroxacin.²⁰

CONCLUSION

A 7 days single 400 mg pefloxacin (8 mg/kg BW) course gave superior results in terms of clinical as well as bacteriological efficacy compared to a full 14 days standard course of 50 mg/kg BW chloramphenicol daily and may be regarded as an excellent substitute for standard treatment with chloramphenicol used at present.

REFERENCES

- Bergan T. Quinolones. In: Petersen PK and Verhoef J. Antimicrobial Agents Annual. 1st ed Amsterdam Elsevier Science Publ. BV, 1986; 174
- Auvergnat JC. Present epidemiological and therapeutic aspects of enteric fever. *Med Mal Infect* 1986; 16:344
- Criatiano P, Morelli G, Briante V, Lovene MR, Simioli T, Altucci P. Clinical experience with pefloxacin in the treatment of typhoid fever. *Infection* 1989; 17:86
- Hajji H, El Mdaghri N, Benbachir M, El Filali KM, Himmich H. Prospective randomized comparative trial of pefloxacin versus cotrimoxazole in the treatment of typhoid fever in adults. *Eur J Clin Microb* 1988; 7: 361
- Ait Khaled A, Zidane L, Amrane A, Aklil R. The efficacy and safety of pefloxacin in the treatment of typhoid fever in Algeria. *J Antimicrob Chemoth* 1990; 26 (suppl B) : 181
- Setiabudi R, Kunardi L. Pharmacokinetics of pefloxacin. Proceedings of the 1st Asian Symposium on Pefloxacin, April 1, 1989 Jakarta, Excerpta Medica Asia Pacific Congress Series No.95; 6
- Auckenthaler R, Michea-Hamzehpour M, Pechere JC. In-vitro activity of newer quinolones against aerobic bacteria. *Antimicrob Chemoth* 1986; 17 (Suppl B) : 29
- Clarke AM, Zemcov SJV, Campbell ME. In vitro activity of pefloxacin compared to enoxacin, norfloxacin, gentamicin and the new betalactams. *J Antimicrob Chemoth* 1985; 15 : 39
- Nelwan RHH, Hendarwanto, Zulkarnain I. Open Clinical study of once daily oral pefloxacin (400 mg) in typhoid fever. *Acta Medica Indonesiana* 1992; 24 : 25
- Isenberg HD, Washington JA, Balows A, Sonnerwith AC. Collection, handling and processing of specimens. In: Lennete E et al (eds). *Manual of Clinical Microbiology*. Washington DC: Am Society for Microbiology, 1985; 73
- Barry AI, Throtonberry C. Susceptibility Testing: diffusion, test procedures. In: Lennete EH et al (eds). *Manual of Clinical Microbiology*. Washington DC: Am Soc Microb, 1985; 978
- Diagnostics Pasteur: Antibiotic sensitivity testing procedures for pefloxacin
- Lan CK, Cheng DL, Lassere R. Two to three Days Treatment of Typhoid Fever with Ceftriaxone. *SEAJ Trop Med Publ Hlth* 1986; 17 : 119
- Ranoa C, Santiago L, Sangla RP, Lassere R. Randomized study of 3 days treatment of typhoid fever with Ceftriaxone in comparison to a 14 days course of chloramphenicol. *International Society of Chemotherapy. Proceedings of the 14th Int Congress of Chemotherapy; Kyoto 1985; 1986*
- Nelwan RHH. Pengobatan antimikrobia jangka pendek untuk demam tifoid. Proceedings of the Nat Congress Internal Med; PAPDI; 1987, Ujung Pandang; Vol III: 117
- Goldstein FW. Short term treatment of bacterial infection. Western Pacific Society for Chemotherapy. Abstract WPCCID; 1989; Kuala Lumpur; PL I
- Chew SK, Monteiro EHA, Lim YS, Wong SY, Lam MS and Allen DM. Ciprofloxacin in Enteric Fever. An open clinical trial (Abstract). Institute for Advanced Studies, University of Malaya. First Asia Pacific Symposium on Typhoid Fever; 1991; Kuala Lumpur; S3
- Nelwan RHH, Zulkarnain I, Hendarwanto, Widodo D, Herdiman and Soemarsono H. Short course treatment with Ciprofloxacin in Typhoid Fever. A Preliminary Report. *JAMA SEA* 1992; 8 (suppl) : 59
- Tanpaichitra D, Srimuang S. In vitro and Clinical Evaluation of Ofloxacin in Urinary Tract Infections and Enteric Fever. *Rev Inf Dis* 1989, II (suppl S) : 175
- Nelwan RHH, de Garis S, Herzog Ch. One and Two Weeks Oral Fleroxacin vs Standard Chloramphenicol Treatment for Typhoid Fever (Abstract). *Infect Disease Assoc of Thailand and Western Pacific Society of Chemotherapy. 2nd WPCCID; 1990; Pattaya-Thailand; 308*