1 RESPIRATORY THERAPY

2 RESPIRATORY TRAC INFECTIONS

CIPROFLOXACINE IN THE TREATMENT OF LOWER RESPIRATORY TRACT INFECTIONS: A COMPARATIVE STUDY AGAINST PENICILLIN AND CHLORAMPHENICOL

Dr. HOOD ALSAGAFF

Dept. of Pulmonology, Airlangga School of Medicine

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Hood ALSAGAFF,
Dept.of Pulmonology, Airlangga School of Medicine / Dr.Soetomo General Hospital, Surabaya, Indonesia.

A double blind, randomized, controlled study on the efficacy and safety of oral ciprofloxacin (500 mg bid.) in pneumonia as compared to the standard therapy of proc.penicillin G (600.000 U i.m. bid.) plus chloramphenicol (1 gr i.v. bid.) was done. Bacteriologic specimens were obtained by transtracheal aspirations .
Results : N = 80 ; Ciprofloxacin gave a 95 % success rate, v/s 92.5 % for the control group (no p, may be due to type II error). However to be fair the ciprofloxacin group did achieve a quicker defervescence, a shorter hospital stay and better radiological resolution. No side effects were reported in both groups.
Conclusion : Ciprofloxacin is an excellent alternative against the time honored regimen of Penicillin plus Chloramphenicol in lower respiratory tract infections, given their good tissue penetration, good safety record and convenient oral use.
The cost of therapy is not solely related to the purchase of the drug, but also to its route of administration. Par enteral administration will involve considerably more nursing time and supervision, translating into higher cost to the patient.
Empirical treatment must be given before bacteriological result are known. However without epidemiological evidence of pathogens and antibiotic sensitivities provided by sputum cultures, there can be no best guess therapy. Nevertheless given their known bacterologic efficacy, in severe disease and in the immunocompromised host where resistant or multiple pathogens may be involved, ciprofloxacin can be an excellent choice.

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Hood Alsagaff,
Dept. of Pulmonology, Airlangga School of Medicine /
Dr. Soetomo General Hospital - Surabaya - Indonesia

INTRODUCTION :

For most practical purposes lower respiratory tract infection is treated empirically rather than based on bacteriologic and sensitivity test findings.
New drugs are usually compared to time honored regimens as guidelines in each hospital.
The basic therapy for lower respiratory tract infection at the Department of Pulmonology of the Dr.Soetomo Hospital is a Penicillin derivative combined with Chloramphenicol.

BACKGROUND :

Ciprofloxacin is a quinolone antibiotic, which is relatively new in Indonesia, and for the time being at least should not give a problem of drug resistance yet.
The basic treatment of lower respiratory tract infection in the pulmonary ward of the Dr.Soetomo Hospital resulted in a mortality rate of 25.2 % (1988) with an average hospitalization period of 9.3 days. A quinolone group antibiotic, being new on the scene and having a relatively broad spectrum may improved these figures. One other point is that while the standard regimen has been around for many years, seen from the pharmacokinetic view, it has no sound foundation, being the combination of a bacteriosidic drug (penicillin) and a bacteriostatic drug (chloramphenicol)

PURPOSE OF STUDY :

To compare the efficacy and safety of oral ciprofloxacin to parenteral procain penicillin G (i.m.) plus intravenous chloramphenicol, in the treatment of lower respiratory tract infections.

OBJECTIVE :

To obtain an alternative treatment regimen for lower respiratory tract infection, which is superior in efficacy but are comparable in price, to the prevailing standard therapy.

METHODOLOGY :

Double blind, Randomized, Controlled study.
Randomization being achieved by computer generated random numbers and matching them to the order of admission.

Treatment group :
Ciprofloxacin 500 mg b.i.d.
placebo injections representing :
2 ml of Calcium osteilin (a white solution similar to procain penicillin G)i.m. twice daily
and 2 ml of vitamin C i.v. twice daily

Controle group :
Procain Penicillin G 600.000 U, i.m., twice daily
Chloramphenicol 1 gram, i.v., twice daily
Placebo tablets representing :
500 mg Ciprofloxacin b.i.d.

All identification of drugs and placebo is only known to the chief investigator.

Sampling :

Method of sampling : cluster sampling of all patients with lower repiratory tract infection, admitted to the pulmonary ward of the Dr.Soetomo General Hospital, fulfilling the study criteria. Assignment to treatment group or control group is by randomization as explained above.

Due to practical reasons the number of patients allocated to each group of treatment was pre determined before the study, to be 40 each, bearing into mind the possibility of a type II statistical error.

STUDY PARAMETERS and DIAGNOSTIC CRITERIA:

Diagnosis of Lower Respiratory tract infection was based on : Fever, cough, purulent expectoration, dyspnea, tachipneu percussion dullness, bronchial breathing, bronchophony(+)
Leucocytosis, Elevated ESR.
Pathogenic bacteria recovered by transtracheal aspiration
Chest X-ray compatible to consolidation either lobar or patchy.

Patient inclusion criteria :
Hospital admission diagnosis of Lower Respiratory Tract Infection.
Age : 18 - 75 years
Willing to give informed consent

Patient exclusion criteria :
Hypersensitivity to penicillin,chloramphenicol or quinolones.
Impairment of Renal, Hepatic or hemostatic function.
Pregnant or nursing women.

note :

The attending physician reserved the rights, to stop the trial anytime, whenever it is deemed detrimental to the patient's well being. The patient is also regarded as a treatment failure and changed over to another regimen, if after 3 days of therapy no clinical improvement is found.

BASELINE DATA :

General :
Patient's name, age, sex, registration number,
Date of admission and discharge

Medical history and general condition.

Clinical parameters :
Body temperature : taken everyday
Cough and expectoration
Dyspnea
Length of hospitalization :
Patient discharge will occur 3 days after the fever has subsided, and no other clinical signs/symptoms are present.

Adverse effects :
All subjective and objective adverse effects occurring during treatment will be recorded and graded. They are classified as mild to moderate if still tolerable, and severe if a change in treatment is required.

Laboratory parameters :

Leucocyte count	: day	0,3,7,10,14
ESR	: day	0, 7, 14
Blood sugar F & PP	:	0
Serum creatinine	:	0, 7, 14
SGOT, SGPT, Bili	:	0, 7, 14
Hemostatic function test	:	0
Blood gases	:	0
Electrocardiography	:	0
Pulmonary function tests	:	0

Microbiologic parameters :
Fluid obtained through transtracheal aspiration will be cultured for identification of pathologic bacteria and antibiotic sensitivity testing using paper discs for ciprofloxacin, penicillin and chloramphenicol.

Radiologic parameters :
Standard PA and Lateral Chest X-ray on day : 0, 7, 14

EVALUATION OF CLINICAL EFFICACY :
Clinically CURED:
resolution of all clinical signs and symptoms at end of therapy
Clinically IMPROVED:
partial resolution of the aboved.
Therapeutic FAILURE
No improvement or deterioriation of clinical signs and symptoms or necessitating a change in antimicrobial therapy

DROPPED OUTS :
All cases not meeting trial protocol, or having less than 3 days of therapy.

TRIAL DESIGN :

Experimental group : Control group :

Day 0
Confirmation of admission diagnosis
Obtaining base data parameters

Day 1

Ciprofloxacin 500 b.i.d.	Placebo tabl. b.i.d.
plus	plus
Placebo injections calc.ost.	Pen.Proc.G 600.000 U bid
Placebo injections vit C	Chloramphenicol 1 gr bid

Obtaining data as outlined in methodology

Day 2
same as day 1

Day 3
same as day 1 and 2
Evaluation of clinical condition of patient:
Improved : continue trial
Worse or unimproved : dropped out and classified as therapeutic failure, to be treated with other drugs.

Day 4 - etc.
same as day 1 and 2
Trial discontinued 3 days after fever has subsided.

CONCOMITTANT MEDICATION :

No antipyretic drugs should be used.
Xanthine bronchodilators were avoided.
All other symptomatic treatment should be used sparingly, if at all and were documented

STATISTICAL ANALYSIS :

Student T test , Pearson Correlation for quantitative data
Chi square test (with Yates correction) for qualitative data, also Wilcoxon rank test where applicable, Alpha = 0.05 and Beta = 20 %.

RESULTS :

Comparison of base line data between the treatment and control group, revealed no statistical difference in age, sex distribution, body temperature and white blood cell count at admission, renal and liver function tests, radiological appearance (Table I.).

Base line data (Table I)

	Ciprofloxacin	Control group
Age	46.71 (S.D.=15.49)	41.23 (S.D.=16.39)
Sex (M / F)	34 / 6	32 / 8
body temp.(adm.)	38.09 (S.D.=0.85)	38.29 (S.D.=2.48)
WBC (adm.)	19778 (S.D.=1890)	18538 (S.D.=1692)
RFT (N / ABN)	40 / 0	40 / 0
LFT (N / ABN)	40 / 0	40 / 0
Radiol. opacities		
> 1 lobus	31	29
= 1 lobus	9	11
< 1 lobus	0	0

(all no p.)

Bacteriological findings: (Culture, on Admission)

	Ciprofloxacin	Control group.	Total
Str.pneumoniae	18	17	35
Str.viridans	2	1	3
Staphylococcus	4	6	10
Klebsiella sp.	4	3	7
Pseudomonas sp.	2	1	3
No growth	10	12	22
All	40	40	80

Clinical response :(table II)

	Cured	Improved	Failed
Ciprofloxacin	29	9	2
Amoxillin + Chloramphenicol	27	10	3

(no p.)

The failures in the ciprofloxacin group were due to Str. pneumoniae (1) and staphylococcus (1) while in the control group were due to Str.viridans(1), Klebsiella(1) and Pseudomonas (1)

Resolution of Radiological opacities due to pneumonia (table III)

	Mean	S.D.	
Ciprofloxacin	8.54 days	2.26	
Control	8.96 days	3.07	(no p.)

Temperature defervescence :(table IV)

	Mean	S.D.	
Ciprofloxacin	3.36 days	1.26	
Control	3.77 days	1.73	(no p.)

Hospital stay (table V)

	Mean	S.D.	
Ciprofloxacin	10.14 days	3.846	
Control	13.68 days	10.22	(no p.)

Side effects :
Pre and post antibiotic examination of serum creatinine and blood ureum nitrogen levels, serum transaminases levels, revealed no side effects of either the treatment or the control group.
Likewise no gastro intestinal disturbances . hypersensitivi ty reactions or blood dyscrasias were reported.

From the tabulation in table I - V, it can be seen that the 2 treatment groups were comparable in every aspect of treat ment.

DISCUSSION :

Overall no difference could be shown between the two treatment groups, both achieving a success rate of over 90 %, that is 95 % for ciprofloxacin and 92.5 % for penicillin + chloramphenicol.
To be fair, the ciprofloxacin group did achieve a quicker defervescence, a shorter hospital stay and better radiological resolution but unfortunately the limited number of patients did not make it possible to reach statistical significance.
If the sputum reveals predominant gram positive cocci, than str.pneumoniae prevails, so any penicillin derivative can be expected to give a reasonably good result. But if gram negative coccobacillary organisms are dominant or if previous therapy with penicillin derivates or macrolides have proven unsuccessful than ciprofloxacin would be the oral drug of choice.
Previous bacteriological studies done at the Dr.Soetomo Hospital showed that ciprofloxacin is highly effective against staphylococcus aureus (92.6%), Klebsiella sp. (100%), Pseudomonas sp.(81.8%) and moderately effective against streptococcus (66.6 %)

A global report on bacterial resistance in the general practice setting (R.W.Lacey):

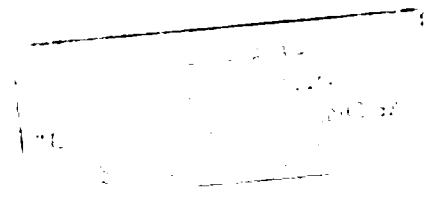
	Percentage of sensitive bacteria tested :			
	Staph.aureus	Strept.pneu.	H.Infl.	Coliforms
Amoxillin	15	100	61	58.5
Chloramph.	85.4	97.4	n.a.	85.4
Quinolone	81.8	100	100	100

As expected, side effects were low. In fact it was non existent in this study, with is not surprising given the safety record of ciprofloxacin.

Safety overview : Adverse experiences to Ciprofloxacin (N=1690)
(R.Stahlmann, H.Lode)

Effect	%
1. Gastro-intestinal	5.0
naussea/vomitting	1.6
diarrhea	1.5
vomitting	0.7
dyspepsia	0.4

abdominal pain	0.3
anorexia	0.2
flatulence	0.2
2. Skin and allergic reactions	1.4
rash	0.8
pruritus	0.5
3. C.N.S.disturbances	1.6
dizziness	0.5
asthenia	0.4
headache	0.3
visus disorder	0.2



The quinolone derivatives are regarded by some experts as the most important advance in antimicrobial therapy, because of their high activity against a wide range of gram (+), gram (-) aerobic and anaerobic pathogens. This is particularly true in respiratory medicine, where quinolones have the added advantage of an excellent penetration into the bronchial tissue, bronchial secretions, sputum and sinus secretions. The penetration from serum into bronchial lumen is approximately 55 - 80 % for ciprofloxacin and easily exceed the MIC by a factor of 20 - 100 for very sensitive pathogens . For at least 3-12 hours after oral administration, blood-free lung tissue concentration is 4-5 times higher than the corresponding plasma concentration, an observation also shared by the macrolide group of antibiotics, which may explain why both drug groups have an excellent record against mycoplasma pneumoniae.

An added benefit of ciprofloxacin is it's oral administration. Because the cost of antimicrobial therapy is not solely related to the purchase of the drug, but also its route of administration. Par enteral adiministration will neccessitate the use of syringes / infusion sets etc. AND will involve considerably more nursing time and supervision, often at periods of greatest stress such as at night. (if the drug has to be given more than once a day). Translating into (a substantial) higher cost to the patient.

CONCLUSION :

Ciprofloxacin is a excellent alternative against time honored regimens of Penicillin derivatives (with Chloramphenicol) in lower respiratory tract infections, given their good tissue penetration, good safety record and convenient oral use.
Unfortunately their relatively high cost makes it unlikely that the quinolones will prove competitive in community acquired lower respiratory tract infection where penicillin remains effective.
Nevertheless, in severe disease and in the immunocompromised host, where resistant or multiple pathogens are involved, ciprofloxacin may be a very useful and excellent alternative.

Opinions may vary on the value of sputum bacteriology in pneumonia, however a well known chicken - egg paradox exist, that EMPIRICAL TREATMENT must be given BEFORE the results of the bacteriolo-

gy are known. BUT without EPIDEMIOLOGICAL EVIDENCE of pathogens and their antibiotic sensitivities provided by sputum culture, there can be NO, BEST GUESS THERAPY.

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Table 1. OVERVIEW

	MALE				FEMALE				TOTAL			
	86	87	88	89	86	87	88	89	86	87	88	89
Total (N)	93	171	157	139	62	53	86	107	155	224	243	247
Fatalities	28	44	45	44	14	13	22	42	42	57	67	86
Percentage									27.1	25.4	27.6	34.8
Mean age (yr)	40.3	44	44.8	44.2	35.7	39.1	37.2	42.5	38.4	42.9	42.1	43.5
Fatal cases	50.2	50.2	51.4	48.8	46.2	43.5	42.5	45.7	48.9	48.6	48.5	47.3
L.O.S. (mean) (days)	11.5	9.6	9.1	9.3	12.7	10.1	10	7.8	12	9.7	9.4	8.6
Fatal cases	6.8	5.3	3.4	4.3	3.9	4.1	4.9	3.5	5.8	5	3.9	3.9

Table 2

Age distribution

Range	Sex: M/F				Mortality (%)				Total			
	86	87	88	89	86	87	88	89	86	87	88	89
10-20 yrs	18/8	14/11	16/15	13/14	2 11.1	3 12	2 6.5	7 25.9	18	25	31	27
20-30 yrs	28/18	30/7	28/20	26/22	7 15.2	5 13.5	10 20.8	11 22.9	46	37	48	48
30-40 yrs	9/12	24/9	18/15	22/14	3 14.3	9 27.3	11 33.3	11 30.6	21	33	33	36
40-50 yrs	11/13	25/6	20/10	13/13	5 20.8	4 12.9	10 33.3	10 38.5	24	31	30	26
50-60 yrs	11/4	30/9	34/13	26/16	8 53.3	14 35.9	12 25.2	18 42.9	15	39	47	42
60-70 yrs	18/3	32/9	26/9	24/17	12 57.1	15 36.6	14 40	20 47.6	21	41	35	42
70-80 yrs	4/3	12/2	14/2	13/6	4 57.1	5 35.7	8 50	6 31.6	7	14	16	19

Risk of dying Pneumonia/Range Umur

10-20 = 17.5 %

Table 3.

MORTALITY

OVERVIEW	1986	1987	1988	1989
All	42 (27.1%)	57 (25.4%)	67 (27.6%)	86 (34.8%)
Mean age (yrs)	48.9	48.6	48.5	47.3
L.O.S.(days)	5.8	5	3.9	3.9
SEPTICAEMIA				
- all	24	32	35	61
- died (%)	22 (52.4%)	30 (52.6%)	33 (49.3%)	60 (69.8%)
- died <48hr	13	19	22	40
RESPIRATORY FAILURE				
- all	11	6	8	8
- died	11	5	7	8
- died <48hr	5	3	5	3
DIED < 48 HR				
- all (%)	23 (54.8%)	31 (54.4%)	42 (62.7%)	50 (58.1%)
- age	48.4	48	47.9	50.6
- septicaemia	13	19	22	40
- Resp.Fail.	5	3	5	3

Table 4.

CO MORBID
(total - fatal cases)

	1986	1987	1988	1989
KP	35 - 15	87 - 16	77 - 27	92 - 42
DM	-	15 - 4	9 - 5	12 - 9
COPD	6 - 2	11 - 2	21 - 14	13 - 2
Lung cancer	4 - 2	4 - 3	7 - 2	9 - 3
Asthma	5 - 2	7 - 1	2 - -	8 - -
Typh.Fev.	1 - -	1 - -	3 - -	3 - 2

Table 5.

COMPLICATIONS
(total - fatal cases)

	1986		1987		1988		1989	
Septicaemia	24	22	32	30	35	33	61	60
Resp.Fail.	11	11	6	5	8	7	8	8
Pleural Effusion	29	1	19	5	30	3	20	2
Empyema	4	-	3	1	10	-	2	1
Pn.thorax	1	-	2	1	3	-	1	-
Hemoptysis	7	-	24	1	12	-	26	3
Abscess pulm.	-	-	2	1	2	1	3	-