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COMPARATIVE CLINICAL EVALUATION OF A NEW CEPHAMYCIN ANTIBIOTIC, CEFOXITIN, IN ACUTE BACTERIAL INFECTIONS

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SUMMARY

An open, comparative, preliminary clinical trial, bacteriologically controlled, in hospitalized patients with susceptible infections treated by intravenously administered cefoxitin vs. cephalothin is reported. The 20 cases included in the study presented, clinically, acute, moderate to severe infections, of various organ systems caused by Gram-negative and Gram-positive aerobic and anaerobic bacteria, some with underlying infectious or parasitic diseases common in Brazil. Cefoxitin therapy was given to 11 patients, 9 of which were cured, including two with anaerobic pathogens, and 2 improved. Of the 9 subjects receiving cephalothin, 5 were cured, 2 improved and 2 not improved. Both antimicrobial drugs were locally very well tolerated and adverse reactions were limited to a case of severe allergic manifestation (cutaneous) that led to discontinuation of therapy, another case of significant elevation of eosinophils, and a third patient with transient elevation of transaminases, blood urea and serum creatinine, all in the cephalothin treated group. With cefoxitin, a case of transitory leukopenia and two cases of transitory eosinophilia occurred but in the latter, worm infection was present. Although the number of patients managed are relativelly small, not permitting statistical analysis, the various pathogens and infectious entities carefully studied have convinced us of the apparent excellent tolerance and efficacy of the new cephamycin, a promising antibiotic seeming to represent a therapeutic advance as a single drug in the management of aerobic and anaerobic infections caused by a wide range of different microorganisms.

INTRODUCTION

Cefoxitin is a member of a new family of antibiotics, the cephamycins, with a unique and prominent feature: its high resistance to hydrolysis by beta-lactamase from Gram-positive [9] and specially Gram-negative [14] microorganisms. Cephamycins represent a radical new departure from the cephalosporins and are differentiated by having a methoxyl group at the 7-α-position of the aminocephalosporanic acid nucleus. Cefoxitin is the semisynthetic compound resulting from the chemical modification of cephamycin C, produced by **Streptomyces lactamdurans** [5].

The main pharmacological properties of cefoxitin, compared with cephalosporins, are: 1) high resistance to cephalosporinases; 2) very well tolerated in high doses parenterally; 3) free from nephrotoxicity in contrast to cephaloridine; 4) higher and more prolonged serum antibiotic levels than cephalothin with significantly longer serum life-time; 5) only minimally metabolized whereas cephalothin is degraded (20-30%) to inactive "desacetyl" form [12,16].

Cefoxitin is active **in vitro** and in experimental infections in animals against all bacte-

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rial species sensitive to the various available cephalosporins. Furthermore, because of its resistance to bacterial cephalosporinases, it is highly active against the majority of bacterial strains and species resistant to cephalosporins. These latter include: indol-positive **Proteus** species, the anaerobic **Bacteroides** species, **Serratia marcescens** and resistant strains of **E. coli, Klebsiella-Enterobacter, Providentia, Salmonella** and **Shigella** [6,13,17,18]. However, cefoxitin is inactive against **Pseudomonas aeruginosa** and **Enterococci.** Cefoxitin is rapidly excreted in the urine in ranges up to 90% or greater in the chimpanzee and human following intravenous, intramuscular or subcutaneous injection [2,3].

It is found in body fluids such as cerebrospinal fluid, ocular fluid, and milk of the rat after subcutaneous injection of radioactive cefoxitin. The drug is poorly absorbed after oral dosing of rats, mice and monkeys.

Evaluation of the parenteral safety of cefoxitin was based on chronic and/or subacute studies in the rat, dog, monkey and rabbits; teratogenic studies in the mouse and rat and reproduction studies in the rat [11].

Some clinical trials, comparative or not, have been carried out so far in various countries [4,8,10,15]. The favourable preliminary results justify further clinical studies with the new antibiotic.

We developed an open, comparative preliminary clinical trial in hospitalized patients with susceptible infections using intravenously administered cefoxitin vs. cephalothin.

MATERIALS AND METHODS

Patients — All patients were adult of both sexes, hospitalized in the Infections and Parasitic Disease wards of the Hospital das Clínicas, School of Medicine, University of São Paulo, Brasil. Signed informed consent was obtained from all patients included in the study.

Both cefoxitin and cephalothin were used intravenously, and patients were allocated to one or other antibiotic in an alternate fashion.

The intravenous infusions were carried out by registered nurses and given through 19 to 22 — gauge butterfly needles. The intravenous site was changed every 48 to 72 hours (in most of the patients 48 hs.) or whenever local conditions required.

Age, sex, race and weight of the patients, besides their clinical diagnosis upon hospitalization are indicated on Tables I and II.

Type of Study — An open, bacteriologically controlled, comparative trial of intravenously administered cefoxitin vs. cephalothin, in hospitalized patients, with moderate to severe infections of several organ systems, caused by pathogenic Gram-positive cocci, Gram-negative rods, aerobic and anaerobic.

Cultures of blood, urine, sputum, body fluids and purulent secretions were performed before, sometimes during, and after treatment was completed. All bacteria isolated as possible causative agents of infection were identified and all were submitted to antibiotic sensitivity tests by the Bauer-Kirby-Sherris-Turck method [1].

Besides susceptibility tests to cefoxitin and cephalothin, the microorganisms were submitted to other antimicrobial agents in general use (namely: Penicillin G; cloxacillin, erythromycin, kanamycin, ampicillin, gentamicin, lyncomycin, chloramphenicol, tetracycline, sulfamethoxazole-trimethoprim and eventually nitrofurantoin, colimycin and streptomycin).

For cefoxitin and cephalothin sensitivity tests 30 mcg BBL discs were used.

A through laboratory study of all patients was performed before, during and after antibiotic therapy using the following tests: complete hemogram, including platelet quantitative determination; ESR first hour; urinalysis with quantitative sediment; blood urea; serum creatinine; alkaline phosphatase; total bilirubin; SGOT and SGPT.

Antibiotic dosage — The dose of cefoxitin or cephalothin was 2 g every 8 hours for each patient, diluted in a volume of 100 ml of 5% dextrose in water and administered by intermitent intravenous 30 minute infusion periods.

According to HESSELTINE et al. [7], cefoxitin serum concentrations (of 72 mcg/ml 30 min.) after 2 g infusion, are higher than cephalothin concentrations; and administration of 6 g of cephalothin/day seems to be a reasonable dose for treatment of most infections [10].

TABLE I

Cefoxitin treated patients, identification, clinical, bacteriological diagnosis and therapeutic results

Number and initials	Sex	Age	Race	Weight (KG)	Diagnosis	Duration of treatment (days)	Temperature °C		Probable causative microorganism	Sensitivity to		Result
							Initial	Final		Cefoxitin	Cephalothin	
1. JPS	F	23	C	61.200	Endometritis plus bilateral anexitis	9	39.4	36.7	**Peptostreptococcus anaerobius**	*	*	Cured
3. MDVB	F	51	N	43.800	Lobar pneumonia	7	40.0	36.5	**Staphylococcus aureus**	S	S	Cured
5. ASC	F	60	N	32.900	Bronchopneumonia	6	38.8	36.5	**Staphylococcus aureus**	I	S	Cured
7 VP	F	63	C	57.100	Acute pleuro-pneumopathy	14	38 5	37.2	**Proteus mirabilis** **E. coli**	I I	R S	Improved
8. MBI	F	18	C	52.300	Acute pyelonephritis	9	39.4	36.5	**Enterobacter cloacae**	R	S	Cured
10. OCD	F	57	C	47.000	Acute urinary tract infection	8	38.3	36.2	**E. coli**	I	S	Cured
12. MCOM	F	20	C	47.700	Septic abortion	5	39.0	36.5	**Veillonella parvula**	S	S	Cured
14. JAA	M	45	N	40.000	Lung abscess plus pleural effusion	11 and 10 (**)	38.1	36.0	Not isolated (probably **S. aureus**)	—	—	Cured
16. JFS	M	56	N	62.500	Acute urinary tract infection	7	39 0	36.2	**E. coli**	I	S	Cured
18. MLS	F	30	C	60.400	Wound infection plus bacteremia	10	39.5	39.0	**E. coli**	R	R (***)	Improved
20. CEL	F	38	C	54.000	Acute urinary tract infection	7	39 3	36.0	Not isolated	—	—	Cured

F = Female M = Male C = Caucasian N = Negro

S = sensitive
R = resistant
I = intermediate

(*) Culture not maintained — susceptibility test not performed

(**) Two treatment courses with a four day interval

(***) A case of probable superinfection; **E. coli** (resistant to both antibiotics) was isolated from blood 9 days after treatment when patient had improved. Drug withdrawn following day and changed to Gentamycin (to which microorganism was sensitive)

TABLE II

Cephalothin treated patients, identification, clinical, bacteriological diagnosis and therapeutic results

Number and initials	Sex	Age	Race	Weight (KG)	Diagnosis	Duration of treatment (days)	Temperature °C		Probable causative microorganism	Sensitivity to		Result
							Initial	Final		Cephalothin	Cefoxitin	
2. INS	F	23	C	53.900	Lobar pneumonia	9	39.7	36.8	**S. aureus**	S	S	Cured
4. CA	F	50	C	42.000	Bronchopneumonia	14	39.0	37.0	**S. aureus**	S	S	Improved
6. PMG	M	18	C	50.700	Lobar pneumonia	7	39.1	36.4	**S. aureus**	S	S	Cured
9. CG	M	56	N	67.900	Lobar pneumonia	9	39.0	38.7	**S. pneumoniae** **Enterobacter cloacae**(*)	S R	S R	Not improved
11. EVB	F	28	C	47.000	Acute gastrenterocolitis	3	38 4	39.2	**S. enteritidis**, sero-type **typhimurium**	R	S	Not improved (**)
13. DC	F	26	C	56.000	Septic abortion	7	39.9	37.2	Not isolated	—	—	Improved
15. AEA	F	19	N	48.500	Septic abortion	5	39.0	36.4	**Enterobacter aerogenes**	R	S	Cured
17. MLJR	F	21	N	55.200	Septic abortion plus acute urinary infection	8	40.3	36.3	**E. coli** **E. coli**	S S	S S	Cured Cured
19. EGR	F	48	N	56.000	Bronchopneumonia	8	38.0	36.5	**Enterobacter aerogenes**	S	S	Cured

F = Female M = Male C = Caucasian N = Negro

(*) Superinfection due to resistant strain (both antibiotics) of **E. cloacae** originated from IV catheter

(**) The isolated **Salmonella** was sensitive to cefoxitin but resistant to cephalothin; however, antibiotic not changed because of development of intense cutaneous allergic manifestation

Definitions — According to the followed protocol, the severity of infection on entry into study was moderate (10 cases), moderate to severe (4 cases), and severe (6 cases); in none could the infections be considered clinically mild. The inclusion in any of the above groups was based on clinical grounds, chiefly considering grade of toxemia and fever, underlying diseases common in our country (hepatosplenic schistosomiasis, hookworm infection with severe anemia, strongyloidiasis, tuberculosis, etc.), impaired consciousness and systemic involvement. The symptoms and signs were followed personally in each patient by the investigator during treatment. A cure was defined as disappearance of fever, pronounced resolution of anatomical abnormalities and eradication of causative organism (whenever specimens available). If none of the above parameters were reached, the case was considered as not improved; and if only one or two of them subsided, as improved.

RESULTS

The data below derived from preliminary observations in 20 patients, 11 of whom received cefoxitin and 9 cephalothin. Further observations with cefoxitin are in course at our Service.

Two cases of the cefoxitin group and two of the cephalothin group received pre-cefoxitin and pre-cephalothin antibiotic therapy subsequently proven to be ineffective against the infecting microorganism based on disc susceptibility testing.

The average days of treatment with cefoxitin was 8.6 and that of cephalothin 7.8, being 56.2 grams the average total dose of the first antibiotic (range 30-84 g) and 46.7 g the average total dose of the latter (range 18-84g).

Eight out of the eleven cefoxitin treated patients presented important underlying diseases or conditions: three with mansoni schistosomiasis (one with the hepatosplenic form), two of hookworm infection, one of alcoholism, one of strongyloidiasis and one of healed fibrotic tuberculous lesions in the lungs.

Tables I and II indicate the outcome of cefoxitin and cephalothin treatments respectively, for the small population studied so far. Of particular interest were two cases of anaerobic infections treated by cefoxitin. One of them was a case of acute endometritis plus bilateral anexitis with **Peptostreptococcus anaerobius** isolated from uterine secretion; the other one was a patient with septic incomplete abortion caused by **Veillonella parvula** from uterine secretion; in both cases, response to treatment was very good.

Local tolerance at the injection site was extremely good with both antibiotics. No erythema, induration or thrombophlebitis occurred in any patient whatsoever. With the careful technique employed by us and the permanent examination and questioning of patients we only obtained one complaint of mild pain during injection with cephalothin.

A rather severe allergic cutaneous manifestation occurred in one case receiving cephalothin at the third day of therapy, leading to drug withdrawal.

Regarding toxicity one case of the cephalothin group presented transitory elevation of blood urea, serum creatinine and SGOT. In another cephalothin patient a significant elevation of blood eosinophils occurred (no worm infestation was apparent in this patient). As for the cefoxitin treated group, a case of transitory leukopenia (11,700 — 4,000) and two cases of post-therapy eosinophilia were registered, however, in these latter worm infection was present. Finally, in two cases (No. 12 and 20) a mild elevation of transaminases could be detected although within the normal range values.

COMMENTS

Although we did manage a relatively small number of patients, through the present investigation, we had the opportunity to deal with various infectious pathologies in a carefully conducted study which convinced us of the excellent tolerance and efficacy of the new cephamycin and prompted us to proceed investigating cefoxitin as the first single antibiotic alternative in a broader number of aerobic and anaerobic infections, including those where combinations of aminoglycosides and other Beta-lactam antibiotics are commonly used.

Our results are in agreement with the very well conducted trial of McCLOSKEY, published in 1977 [10].

In our limited number of clinical observations both antibiotics proved to be effective **in vitro** and **in vivo** against Gram-positive microorganisms, namely **Staphylococcus aureus**, although disc susceptibility studies showed smaller inhibition zones with cefoxitin when compared with other Beta-lactam antibiotics against Gram-positive bacteria [6].

It seems appropriate to emphasize that one case of the cefoxitin group (No. 14), bearer of a lung abscess, not submitted to surgical drainage received two successive series of the antimicrobial agent (11 and 10 days respectively) with four days interval, totalling 84 g of the drug. Tolerance was excellent and the patient recovered entirely after the second series.

According to our results, we concluded that intravenous cefoxitin is a well tolerated antibiotic, even in 14 day courses of therapy and 8 hour intervals administration of 2 g of the drug (30 minute infusion/dose). We had small alterations of a few laboratory tests in a couple of patients, with both drugs, devoid of any impairment to the patient's health during or after treatment. In the above cited case of allergic reaction, the causative agent was **Salmonella typhimurium** (acute gastroenterocolitis) under cephalothin therapy. The isolated **Salmonella** strain was resistant to cephalothin but sensitive to cefoxitin; however, patient was not switched to this latter because of the chemical similarities of both antibiotics, with the possibility of persistence of the adverse reaction; chloramphenicol was introduced subsequently.

We have come to a preliminary conclusion that cefoxitin is a promising new cephamycin antibiotic that may represent a therapeutic advance in the management of serious or moderately severe Gram-positive and Gram-negative, aerobic and anaerobic, systemic infections, with very good tolerance and apparently devoid of toxicity.

RESUMO

Avaliação clínica comparativa de uma nova cefamicina, cefoxitin, em infecções bacterianas agudas

O presente trabalho é o relato de ensaio clínico preliminar, aberto, comparativo, com controle bacteriológico, em pacientes hospitalizados, tratados com cefoxitin ou cefalotina, endovenosamente. Foram observados 20 pacientes, portadores de infecções agudas, moderadas a severas, causadas por bactérias Gram-positivas e Gram-negativas. Cefoxitin foi administrado a 11 pacientes, dos quais 9 curaram-se, incluindo dois com patógenos anaeróbios, e 2 melhoraram. Dos 9 pacientes que receberam cefalotina, 5 curaram, 2 melhoraram e 2 mantiveram-se inalterados. Ambos os antibióticos foram muito bem tolerados localmente e com ambos ocorreram alguns efeitos colaterais, levando à suspensão do medicamento apenas em um caso, de manifestação alérgica, no grupo da cefalotina. Embora o número de pacientes tratados seja relativamente pequeno, não permitindo análises estatísticas, os vários patógenos e as respectivas entidades cuidadosamente estudadas convenceram-nos da aparente excelente tolerância e eficácia da nova cefamicina, antibiótico promissor no tratamento de infecções aeróbicas e anaeróbicas determinadas por largo espectro de microrganismos.

REFERENCES

1. BAUER, A. W.; KIRBY, W. M. M.; SHERRIS, J. C. & TURCK, M. — Antibiotic susceptibility testing by a standard single disc method. **Amer. J. Clin. Path.** 45: 493-496, 1966.

2. BRUMFITT, W.; KOSMIDIS, J.; HAMILTON-MILLER, J. M. T. & GILCHRIST, J. N. G. — Cefoxitin and cephalothin: antimicrobial activity, human pharmacokinetics, and toxicology. **Antimicrob. Agents Chemother.** 6: 290-299, 1974.

3. BUHS, R. P.; MAXIM, T. E.; ALLEN, N.; JACOB, T. A. & WOLF, F. J. — Analysis of cefoxitin, cephalothin and their deacylated metabolites in human urine by high-performance liquid chromatography. **J. Chromatography** 99: 609-618, 1974.

4. DAIKOS, G. K.; GIAMARELLOU, H.; KANELLAKOPOULOU, K. & PIPERAKIS, G. — Clinical evaluation of cefoxitin. Chemotherap. Vol. 5: Penicillins and Cephalosporins. J. D. WILLIAM & A. M. GEDDES (eds.), New York, Plenum Press, 1976, pp. 229-234.

5. DAOUST, D. R.; ONISHI, H. R.; WALLICK, H.; HENDLIN, D. & STAPLEY, D. O. — Cephamycin, a new family of beta-lactam antibiotics: antibacterial activity and resistance to beta-lactamase degradation. **Antimicrob. Agents Chemother.** 3: 254-261, 1973.

6. FRANCISCO, W.; GODOY, C. V. F.; YANAGUITA, R. M. & DEL NEGRO, G. — Suscetibilidade "in vitro" a um novo agente antimicrobiano — cefoxitina — de 900 patógenos recentemente isolados. Apresentado ao

VI Congresso Brasileiro de Microbiologia, 27-31 de julho, 1975.

7. HESSELTINE, P. N. R.; BUSCH, D. F.; MEYER, R. D. & FINEGOLD, S. M. — Cefoxitin clinical evaluation in thirty-eight patients. **Antimicrob. Agents Chemother. 11:** 427-434, 1977.

8. LEVI, G. C.; PASTERNAK, J.; AMATO NETO, V. & SILVA, M. L. R. — Observações sobre a atividade da cefoxitina, um novo antibiótico cefalosporínico, no tratamento de infecções bacterianas. **Rev. Brasil. Clín. Terap. 6:** 295-298, 1977.

9. MAHONEY, D. F.; KOPPEL, G. A. & TURNER, J. R. — Substrate inhibition of betalactamase, a method for predicting enzymatic stability of cephalosporins. **Antimicrob. Agents Chemother. 10:** 470-475, 1976.

10. McCLOSKEY, R. V. — Results of a clinical trial of cefoxitin, a new cephamycin antibiotic. **Antimicrob. Agents Chemother. 12:** 636-641, 1977.

11. MERCK SHARP & DOHME RESEARCH LABORATORIES REPORT — MK-306 three-month parenteral toxicity studies in monkeys, dogs and rats, May 13, 1974.

12. MILLER, A. K.; CELOZZI, F.; KONG, Y.; PELAK, B. A.; HENDLIN, D. & STAPLEY, E. O. — Cefoxitin, a semisynthetic cephamycin antibiotic: in vivo evaluation. **Antimicrob. Agents Chemother. 5:** 33-37, 1974.

13 NEU, H. C. — Cefoxitin, a semisynthetic cephamycin antibiotic — antibacterial spectrum and resistance to hydrolysis by Gram-negative beta-lactamases. **Antimicrob. Agents Chemother. 6:** 170-176, 1974.

14. ONISHI, H. R.; DAOUST, D. R.; ZIMMERMAN, S. B.; HENDLIN, D. & STAPLEY, E. O. — Cefoxitin, a semisynthetic cephamycin antibiotic: resistance to betalactamase inactivation. **Antimicrob. Agents Chemother 5:** 38-48, 1974.

15. SCHWARTZ, S.; PAZIN, G. J. & PASCULLE, A. W. — Clinical and pharmacologic experience with cefoxitin in patients with normal and abnormal renal function ABST. 16TH INTERSCIENCE CONFERENCE ON ANTIMICROBIAL AGENTS AND CHEMOTHERAPY 27-29 Oct. 1970, Chicago, Ill.

16. SONNEVILLE, P. F.; KARTODIRDJO, R. R.; SKEGGS, H.; TILL, A. E. & MARTIN, C. M. — Comparative clinical pharmacology of intravenous cefoxitin and cephalothin. **Europ. J. Clin. Pharmacol. 9:** 397-403, 1976.

17. TALLY, F. P.; JACOBUS, N. B.; BARTLETT, J. G. & GORBACH, S. H. — Susceptibility of anaerobes to cefoxitin and other cephalosporins. **Antimicrob. Agents Chemother. 7:** 128-132, 1975.

18. WALLICK, H. & HENDLIN, D. — Cefoxitin, a semisynthetic cephamycin antibiotic: susceptibility studies. **Antimicrob. Agents Chemother. 5:** 25-32, 1974.

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