The African Journal of Medicine and Medical Sciences

Volume 15
1986

BLACKWELL SCIENTIFIC PUBLICATIONS
Oxford London Edinburgh Boston Palo Alto Melbourne

Afr. J. Med. med. Sci. (1986) **15**, 35–40.

Cefoxitin: single agent treatment of septic abortion

O. ABUDU, V. ROTIMI, V. UGURU AND A. AGBOOLA

Departments of Obstetrics and Gynaecology and Microbiology, College of Medicine, Lagos University Teaching Hospital, Lagos, Nigeria

Summary

Using strict diagnostic criteria, a clinical trial of cefoxitin as the only antimicrobial agent in the treatment of twenty-five cases of septic abortion was carried out. The success rate of 77% (seventeen out of twenty-two) was significant in this group of seriously ill patients of low social class. Presence of pelvic abscess does not seem to preclude the use of cefoxitin. While the infections were of mixed bacterial flora, anaerobes were the predominant organisms isolated. Most organisms isolated were sensitive to cefoxitin but *Pseudomonas aeruginosa* was markedly resistant. No untoward reactions were observed. It appears that cefoxitin was successful as a single agent in the treatment of septic abortion.

Résumé

On a employé les critères diagnostiques strictes pour un essai à clinique de céfoxitin comme la seule agente antimicrobiale pour la traitement de vingt-cinq cases d'avortement septique. La pourcentage de 77 (dix-sept/vingt-deux) était significatif chez ce groupe des malades. La présence d'abcès de bassin n'avait pas semblé à empêcher l'emploi de céfoxitin. Pendant que les infections étaient du flore bactériel mélangé, les anaerobes étaient les organismes surtout isolés. La plupart des organismes isolées était sensible à céfoxitin mais *Pseudomonas aeruginosa* était en particulier résistante. On n'avait pas observé n'importe quelles réactions malencontreuses. Il semble que céfoxitin avait de succès comme agente unique pour la traitement d'avortement septique.

Correspondence: O. O. Abudu, Department of Obstetrics and Gynaecology, College of Medicine, University of Lagos, P. M. B. 12003, Lagos, Nigeria.

Introduction

Abortion is a social problem and constitutes one of the major causes of maternal mortality in both developed and developing countries. The two commonest complications of abortion that lead to increased maternal mortality or morbidity are haemorrhage and sepsis. Sepsis accounts for about a third of maternal mortality in Nigeria (Harrison, 1979). The incidence of septic abortion in Lagos is difficult to assess as most cases are not seen in recognized institutions, but we admit about two to three cases of septic abortion per week in our hospital.

Because of the polymicrobial aetiology of septic abortion, treatment is usually by a combination of antimicrobial agents: a penicillin plus an aminoglycoside and metronidazole or clindamycin. Metronidazole and clindamycin have become very useful since the recent awareness of the role of anaerobes in pelvic sepsis.

Cefoxitin, is a semi-synthetic β-lactam antibiotic with a broad spectrum activity against many Gram positive and Gram negative bacteria; anaerobes including bacterides and indole positive *Proteus* strains and *Serratia* species (Birnbaum *et al.*, 1978). Because recent clinical trials have established the efficacy of cefoxitin in the treatment of obstetrics and gynaecological infections (Ledger & Smith, 1979; Sweet *et al.*, 1978), we have carried out an uncontrolled clinical trial to evaluate the efficacy of cefoxitin as the sole antimicrobial agent in the treatment of twenty-five cases of septic abortion in Lagos.

Patients and methods

Patients

Patients who had recent history of abortion and

satisfy the following diagnostic criteria; pyrexia of ≥ 38°C, tachycardia of ≥ 90/min, foul smelling vaginal discharge, uterine tenderness, adnexal tenderness, peritonitis or features of septicaemia (see Table 1) were admitted into the study. The following data were documented: age, marital status, social class, whether abortion was spontaneous or induced, history of use of antimicrobial agents in the last fortnight and of drug allergy.

All patients had pre- and post-treatment haematological, biochemical and full bacteriological investigations. All patients were classified into different social classes using the criteria of Register General of England and Wales (1950).

2OE system and by standard methods described by Cowan (1974); the anaerobes were identified by the methods of Duerden *et al.* (1980) and Rotimi, Faulkner and Duerden (1980). Minimum inhibitory concentration (MIC) tests and sensitivity tests were performed for each significant isolate by standard methods. Semiquantitative assessment of the density of bacterial growth, on a scale of $1^+ - 5^+$, was performed according to the method previously described (Rotimi & Duerden, 1981).

Administration of drug. All patients received initial starting doses of 2 g of cefoxitin sodium by slow intravenous bolus and then 2 g every 6 h subsequently for 5 days. The total daily dose was 8 g. Additional therapy in the form of

Table 1. Clinical criteria used for diagnosis and evaluation of cefoxitin therapy

Clinical features	No. of patients	
	Before treatment	72 h after treatment
Pyrexia ≥ 38°C	22	5
Tachycardia ≥ 90/min	18	4
Foul smelling ± blood stained vaginal discharge	22	5
Uterine tenderness	22	5
Adnexal tenderness	22	5
Peritonitis	10	4

Bacteriological investigations

Blood culture, midstream urine (MSU) specimens, cervical swabs (CS) and high vaginal swabs (HVS) were taken from each patient pre- and post-treatment. When feasible, specimens of pus were obtained by culdocentesis or at laparotomy. All swabs were transported immediately in Amies transport medium to the research laboratory where they were processed within 20 min of arrival. The swabs were inoculated onto a set of selective and non-selective media. For anaerobic culture, BM-k agar (Holbrook, Ogston & Ross, 1978) and neomycin blood agar were used and incubated anaerobically using the gas generating kit system (Oxoid) at 37°C for 48 h. The facultative and aerobic organisms were identified by API

blood transfusion, evacuation of incomplete abortion, colpotomy and laparotomy were performed when indicated (Table 2).

Clinical response. Patients were examined daily to determine clinical response based on improvement in the criteria listed in Table 1. A patient was classified as cured when signs and symptoms of the illness disappeared, and as failed (not improved) if after 72 h treatment it was necessary to stop administration of cefoxitin because there was persistent temperature of ≥ 38°C, persistence or lack of reduction in the count of potential pathogens isolated from the cervix or high vagina, persistence of uterine tenderness or adnexal tenderness. Thereafter patients who did not respond to cefoxitin were treated with a combination of gentamicin, ampicillin and metronidazole or clindamycin as

Table 2. Other therapeutic procedures carried out

Type of management	Total No. of patients	No. of patients that:	
		Improved	Did not improve
Evacuation	17	16	1
Colpotomy	3	3	0
Laparotomy	7	3	4
Right nephrectomy	1	0	1
Blood transfusion	12	7	5

indicated by the sensitivity test results.

Statistical analysis. The data obtained were analysed statistically using the Student's *t*-test.

Results

Out of the twenty-five patients treated with cefoxitin, three did not have a full investigation according to our protocol and although they responded very well to cefoxitin therapy they have been excluded from the detailed analysis presented.

The mean age of the patients studied was 21 ± 4.5 years; eleven (50%) of the twenty-two patients were married with a mean age of 23.8 ± 4.1 years and the remaining eleven unmarried patients had a mean age of 18.2 ± 3 years. All the unmarried patients were included in the fourteen (63.6%) patients who admitted that the abortion was induced. Twenty (89.9%) of the twenty-two patients belonged to social classes IV and V, the remaining two patients were in social class III. Fifteen (68.2%) of the patients had used antimicrobials in the last fortnight preceding admission into the trial. No patient gave a history of allergy.

Table 3 summarizes the clinical data of the patients. Twelve (54.5%) patients had packed cell volume (pcv) of < 25% on admission. Seventeen (77.3%) of the twenty-two patients improved on cefoxitin therapy. The mean duration of hospital stay was 9 ± 4.9 and 21 ± 8.4 days respectively for the cured and 'not improved' groups of patients. There was a

Table 3. Comparison of patients' clinical data and duration of therapy

Clinical features	Mean measurements of patients' clinical data	
	Cured group	Failed group
Mean temperature	38.9°C	39.1°C
Mean white blood cell count × 10^3 ± s.d.	11.4 ± 4.4	17.6 ± 5.5
Mean symptom — institution of therapy interval (days) ± s.d.	3 ± 2.5	4 ± 1.8
Mean duration of cefoxitin therapy (hours) ± s.d.	112.9 ± 46.3	163.2 ± 74.7
Mean duration of hospital stay after institution of therapy (days) ± s.d.	9 ± 4.9	21 ± 8.4

s.d. = Standard deviation.

significant ($P < 0.05$) difference between the two groups in the mean duration of hospital stay after institution of therapy, but there was no significant difference in the other parameters. There was no mortality in this study and no patient suffered any untoward reactions to cefoxitin.

Bacteriological findings

The facultative and anaerobic organisms isolated are shown in Table 4. Anaerobes were the predominant organisms both qualitatively and quantitatively. They were isolated from all twenty-two patients. The commonest anaerobe was *Bacteroides bivius* which was isolated from all patients before treatment and from sixteen patients after treatment. Other commonly isolated species were *B. asaccharolyticus* (fourteen out of twenty-two patients), *B. fragilis* (White, Gee & Ledger, 1978) and *B. melaninogenicus* (Sweet *et al.*, 1978). The commonest facultative species were *E. coli* and *Streptococcus faecalis*.

There was significant difference in the semi-quantitative count of vaginal isolates before and after treatment in the majority of patients as demonstrated in Table 5. The count of the anaerobes was 5^+ before treatment but went down to 1^+ or 0 after treatment. This reduction in count was also noticed with the aerobes; *E. coli* and *Kebsiella aerogenes* reduced from 4^+ before treatment to 1^+ after treatment. Group B streptococci and *Staphylococcus aureus* were completely eliminated. *Pseudomonas aeruginosa* persisted and replaced colonization occured in one other patient.

The minimum inhibitory concentrations of the potential pathogens are shown in Table 6. All the anaerobes including *B. fragilis* were sensitive to cefoxitin with MIC range of 0.25–16 μg/ml. Ninety percent (90%) of the individual anaerobe was inhibited by cefoxitin on a weight basis of 1 μg/ml with the exception of *B. fragilis* that had MIC_{90} of 4 μg/ml, which is far less than the accepted break-point of susceptibility, 16 μg/ml. The most resistant facultative organism, *E. coli*, had MIC_{90} at 16 μg/ml. However, *P. aeruginosa* was markedly resistant with MIC_{90} of 128 μg/ml, (Table 6).

Of the five patients that did not improve on cefoxitin, two had *P. aeruginosa* infection, another two had *E. coli* infection that showed

Table 4. The microorganisms isolated from the specimens of the twenty-two patients studied

Microorganisms	Number of patients				
	HVS	CS	MSU	Blood	Pus
(a) Anaerobes					
B. bivius	21	22	0	0	0
B. asaccharolyticus	14	14	0	0	2
B. fragilis	10	11	0	2	2
B. melaninogenicus	10	10	0	0	2
B. disiens	7	8	0	0	0
Ano$_2$ *Streptococcus*	6	6	0	1	1
Cl. perfringens	4	4	0	0	0
Bacteroides spp.	3	3	0	0	0
(b) Aerobes					
E. coli	18	16	6	0	0
K. aerogenes	10	9	4	0	0
Strep. faecalis	13	13	1	0	0
Staph. aureus	3	3	0	2	0
P. mirabilis	3	3	1	0	0
Group B *streptococci*	3	3	0	0	0
C. albicans	3	3	0	0	0
N. gonorrhoeae	0	2	0	0	0
P. aeruginosa	2	2	0	0	0

Table 5. The semi-quantitative count of important isolates

Organisms	Pre-treatment		Post-treatment	
	HVS	CS	HVS	CS
B. bivius	5+	5+	1+	1+
B. asaccharolyticus	5+	5+	1+	1+
B. fragilis	5+	5+	0	0
B. melaninogenicus	5+	5+	2+	1+
B. distens	5+	5+	2+	2+
Bacteroides spp.	5+	5+	0	0
Anoy *streptococci*	4+	4+	0	0
Cl. perfringens	3+	2+	0	0
Lactobacillus	5+	5+	2+	2+
E. coli	4+	4+	1+	1+
K. aerogenes	4+	4+	1+	1+
Group B *streptococci*	4+	4+	0	0
P. aeruginosa	3+	3+	4+	3+
Staphylococcus aureus	4+	4+	0	0

Table 6. Minimum inhibitory concentrations of cefoxitin for the significant vaginal isolates

Bacterial isolates	MIC (μg/ml) of cefoxitin		
	Range	MIC_{50}	MIC_{90}
B. bivius	0.25 – 4	0.5	1
B. asaccharolyticus	0.25 – 2	0.5	1
B. melaninogenicus	0.25 – 2	0.25	1
B. fragilis	0.5 – 8	4	4
B. distens	0.25 – 1	0.25	0.5
E. coli	0.25 – 64	8	16
Klebsiella spp.	0.5 – 32	4	8
S. aureus	0.25 – 4	1	2
P. aeruginosa	> 128	> 128	> 128

relative resistance to cefoxitin: the last patient had a right nephrectomy performed for a pyonephrosis.

Discussion

The result of this study showed that cefoxitin as a single agent was very effective in 77% of the twenty-two cases of septic abortion. Previous studies by Ledger and Smith (1979) and White *et al.* (1978), in which cefoxitin was used as a single agent in the treatment of obstetric and gynaecological infections, a relatively higher success rate was reported. This may be due to the fact that patients with pelvic abscesses were excluded which was not the case in our study.

Six (54.5%) out of eleven of our patients with pus collection complicating septic abortion responded to cefoxitin given on an average of 8 g

per day; all the patients had surgical drainage of pus as additional management. Five patients did not improve after 72 h treatment. Four out of these five that did not respond harboured organisms that were resistant or relatively resistant to cefoxitin particularly *Ps. aeruginosa*. It was pleasing to note that none of the patients who did not have an abscess on admission and who were treated with cefoxitin, progressed to abscess formation. This would suggest that the use of cefoxitin appears to prevent the development of pelvic abscess.

This study confirms the polymicrobial aetiology of septic abortion and defines the role of anaerobes, particularly the Gram- negative non-sporing bacilli in the disease process. Significant reduction in the count or complete elimination of anaerobes post-therapy among the patients that improved surely implicates these organisms as important causative agents in septic abortion. All the anaerobes were susceptible to cefoxitin with MIC values below the break-point of their susceptibilities. Majority of the facultative species were also sensitive. However, usage of this agent should be carefully monitored to prevent the development of replacement colonization by *P. aeruginosa* which is highly resistant to cefoxitin as was the case in two of our patients. In this group of seriously ill young patients from low social class, cefoxitin success as a single agent is significant. The drug was well tolerated by all patients with no single side effect.

We believe that cefoxitin has a place as a single antimicrobial agent in the treatment of septic abortion and with possibly an advantage over the use of a combination of antimicrobials, as commonly practised.

Acknowledgments

We thank Associated Pharmaceutical Products of Nigeria (formerly MSD) for providing the grant and the cefoxitin used for this study; and our house surgeons Drs Kuyebi, Essien and Awonuga for their assistance.

References

Birnbaum, J., Stapley, E.O., Miller, A.K., Wallick, H., Hendlin, D. & Woodruff, H.B., (1978) Cefoxitin a semi synthetic cephamycin: a microbiological overview. *J. Antimicro Chemother.* **4**, (suppl. B), 15–32.

Cowan, S.T., (1974) *Identification of Medical Bacteria*. 2nd edn, London, Cambridge University Press.

Duerden, B.I., Collee, J.G., Brown, R., Deacon, A.G. & Holbrook, W.P. (1980) A scheme for the identification of clinical isolates of gram negative anaerobic bacilli by conventional bacteriological tests. *J. Med. Microbiol.* **13**, 231–245.

Harrison, K.A. (1979) Approaches to reducing maternal and perinatal mortality in Africa. In: *Maternity Services in the Developing World — What the Community Needs*. RCOG 7th Study Group publication. (ed. by R. H. Philpott), pp. 52–69.

Holbrook, W.P., Ogston, S.A. & Ross, R.W. (1978) a method for the isolation of *Bacteroides melaninogenicus* from the human mouth., *J. Med. Microbiol.* **11**, 203–207.

Ledger, W.J. & Smith, D. (1979) Cefoxitin in obstetrics and gynaecologic infections. *Rev. Infect. Dis.* **1**, 199–201.

Registrar-General of England and Wales Classification of occupations 1950. H.M.S.O. London.

Rotimi, V.O., Faulkner, J. & Duerden, B.I. (1980) Rapid methods for the identification of clinical isolates of gram-negative anaerobic bacilli. *Med. Lab. Sci.* **37**, 331–339.

Rotimi, V.O. & Duerden, B.I. (1981) The development of bacterial flora in normal neonates. *J. Med. Microbiol.* **14**, 51–62.

Sweet, R.L., Hadley, K.W., Mills & J. Robbie, M. (1978) Cefoxitin in the treatment of pelvic infections. In: *Current Chemotherapy, Proceedings of the 10th International Congress of Chemotherapy*. (ed. by Siegenthaler, W., Luthy, R), American Society for microbiology Washington D.C. Vol. 11, pp. 767–768.

White, J.S., Gee, C. & Ledger, W.J. (1978) The use of intravenous cefoxitin sodium in patients with obstetric/gynaecologic infections. *J. Antimicrob. Chemother.* **4**, (suppl. B), 239–240.

(*Received* 7 *November* 1984; *revision received* 4 *April* 1985, *accepted* 16 *May* 1985)