The African Journal of Medicine and Medical Sciences

Volume 14
1985

BLACKWELL SCIENTIFIC PUBLICATIONS
Oxford London Edinburgh Boston Palo Alto Melbourne

Afr. J. Med. med. Sci. (1985) **14**, 31–35.

Clinical trial of Cefoxitin (Mefoxin) in parenteral therapy of septicemia (postabortal and postpartum) in Ibadan

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Summary

Cases of post-abortal sepsis are admitted every day into the University College Hospital (UCH), Ibadan, Nigeria. This derives from the high incidence of induced (illegal) abortions in this environment. The infections are usually caused by mixed bacterial flora, often resistant to the common antibiotics because of the indiscriminate use of these drugs. Any new drug that can be effective in the treatment of these resistant cases will be welcome. The efficacy of Cefoxitin in the treatment of twenty-five cases of postabortal sepsis was therefore compared with the efficiency of other antibiotics in the management of sixty other cases. Response to Cefoxitin was prompt. Temperatures settled within 96 h and no case of pelvic abscess resulted. It was concluded that Cefoxitin could well be a safe and effective alternative antibiotic to replace the common antibiotics to which many hospital organisms have developed resistance.

Résumé

Des cas de septicémie à la suite d'avortement sont admis tous les jours à l'Ecole Universitaire de Médecine d'Ibadan, Nigeria. Cela vient du taux élevé d'avortements (illégaux) provoqués dans cet environnement. Les infections sont généralement causées par une flore bactérienne mixte, résistant souvent aux antibiotiques courants à cause de l'usage sans distinction de ces drogues. N'importe quelle nouvelle drogue qui peut être efficace dans le traitement de ces cas résistants sera bienvenue. L'efficacité de la Céfoxitine dans le traitement de vingt-cinq cas de septicémie dus à des avortements a donc été comparées avec l'efficacité d'autres antibiotiques dans la conduite de soixante autres cas. La réponse à la Céfoxitine a été rapide. La température s'est stabilisée en l'espace de 96 h et aucun cas d'abcès pelvien n'est apparu. Il fut conclu que la Céfoxitine pourrait bien être un antibiotique alternatif sur et efficace pour remplacer les antibiotiques courants auxquels beaucoup d'organismes hospitaliers ont développé une résistance.

Paper presented at the Symposium on Surgical Infections in Africa at the Intercontinental Hotel, Nairobi, Kenya, 7–9 February 1983.

Introduction

Postpartum and, particularly, postabortal sepsis occur frequently in Ibadan (Control of Infection Committee, UCH, 1982). These problems arise because of the poor delivery facilities available outside the major hospitals, and because of high rate of induced (criminal) abortions which eventually end up in the teaching hospitals. The complications of pelvic sepsis, and generalized septicemia, which follow these procedures account for a very high percentage of cases of sepsis in Ibadan. In many cases, such infections are usually caused by a mixed bacterial flora, both Gram negative aerobes and anaerobes (Ledger, Tee & Lewis, 1975; Ledger & Smith, 1979). There is the need therefore for effective and safe antibiotics for the treatment of these unfortunate patients.

Unfortunately, however, the infecting bacterial organisms, in most of these cases, are

often found to be resistant to the commonly available antibiotics (Finland, 1972; Robertson, 1973; Finland *et al.*, 1976; William, 1977; Moelleing, 1978). This has been due mainly to the indiscriminate use to which the available antibiotics are put in the country. These drugs can be purchased not only across the counter in chemist shops (Osoba *et al.*, 1978), but also most of the strong antibiotics are sold as wares on the streets all over the country.

The search for newer and more potent antibiotics has led recently to the discovery of synthetic and semi-synthetic antibiotics. One of these, Cefoxitin (Mefoxin), a semi-synthetic Cephamycin antibiotic derived from Cephymycin C, and closely related to the Cephalosporins, has been shown to be active against various bacterial strains which are known to be resistant to most of the available Cephalosporin antibiotics (Sweet, Robbie & Hadley, 1979). On the basis of the experience with the drug, a clinical trial was undertaken in Ibadan. The objective of this was the comparison of its efficacy and safety in the parenteral therapy of infections caused by susceptible pathogenic organisms in postabortal or postpartum sepsis.

Materials and methods

Hospitalized patients with untreated acute pelvic infections resulting from septic abortions and postpartum infections were admitted into the study. Patients, mostly with mild to moderate pelvic sepsis, were allocated to the test (twenty-five cases) and control (sixty cases) treatment schedule groups randomly as they were admitted. None was serious enough in either group to warrant pelvic surgery.

Upon admission to the study, relevant history was obtained and the patient had complete clinical examination. All abnormal signs and symptoms related to the infections were noted. The temperature, pulse rate, blood pressure and respiratory rate were recorded at least every 4 h during the acute phase of the illness, and at least twice daily during the remainder of the drug therapy. Prior to the drug therapy, each patient had at least one set of paired aerobic and anaerobic blood cultures, urine microscopy and cultures, haematologic studies, packed cell volume (PCV), white blood cells (WBC), and differential and blood urea nitrogen, SGOT, SGPT, alkaline phosphatase and total bilirubin.

The study was an open controlled comparison of the efficacy, safety and tolerance of intravenous Cefoxitin on the one hand and Cotrimoxazole/Metronidazole, Gentamycin or Ampicillin on the other hand, in the therapy of the hospitalized adults with pelvic sepsis. Each patient received 6 g/day of intravenous Cefoxitin, in three divided doses of 2 g bolus or the appropriate dosage of the control antibiotics by the same route, for whatever period of time that was deemed clinically appropriate, up to but not beyond 14 days. Response to treatment schedule was determined by how fast the temperatures settled and how soon the symptoms disappeared. If the patient was judged to require further antibiotics therapy, the study was stopped at the end of 14 days and a generally available certified antimicrobial agent, selected on the basis of antibiotics sensitivity test results, was substituted.

Follow-up cultures of blood together with microscopy and cultures of urine, were obtained as often as necessary, depending on the response of the patients. However, all patients had follow-up cultures of specimens from the vagina 48 h after the onset of drug therapy, and 3 days after the conclusion of drug therapy. Also, the haematology and blood chemistry studies were repeated 48 h after onset of drug therapy, and 3 days after conclusion of study.

Results

All the eighty-five patients enrolled into the study completed it. Of the patients admitted into the Cefoxitin study group, twenty were young unmarried students, and many of these have had induced (criminal) abortions. Two of the four patients admitted for postpartum sepsis were allocated to the Cefoxitin treatment schedule group, and the remaining patients had sepsis following spontaneous abortions. The distribution of the cases admitted into the control group was about similar.

The age and parity distribution of the patients in the Cefoxitin treatment schedule group are as shown in Table 1. They were young women, with most of them below the age of 25 years. Also, more than 50% of them had

Table 1. The age-parity distribution of women with postpartum or post-abortal sepsis in Cefoxitin trial

Parity	Age (years)					Total
	15–19	20–24	25–29	30–34	≥35	
0	4	4	—	—	—	8
1	—	—	2	—	—	2
2	—	3	2	—	—	5
3	—	3	2	—	2	7
4	—	1	—	—	—	1
≥5	—	—	—	2	—	2
Total	4	11	6	2	2	25

had two or fewer deliveries. Indeed, eight of them had had no deliveries before, although a few of these admitted to previous pregnancies which terminated in abortions.

Durations of vaginal bleeding in all the patients before reporting in the hospital varied from 2 to 4 days. Other symptoms and signs in the Cefoxitin group included lower abdominal pain and tenderness in twenty patients, mucopurulent offensive vaginal discharge in eight, backache, abdominal distension, vomiting and others. Pyrexia (temperatures ≥ 38°C) was recorded in eight of the patients prior to the commencement of treatment. Corresponding figures for the control treatment schedule groups are shown in Table 2. However, almost all the patients presented with some form of temperature greater than 36.8°C. All the patients, in both groups, also denied any previous history of sexually transmitted disease.

Among those with pyrexia, temperature continued to swing between 38° and 41°C for varying number of days after the commencement of treatment. However, temperatures settled faster (within 48–96 h) among the Cefoxitin treatment schedule patients (mean 54 h) as compared with the controls where temperatures settled between 48 and 120 h (Table 3). There were no cases of pelvic abscess that required surgery and none of the patients died after commencement of therapy with Cefoxitin.

Common bacteriological finding in patients before Cefoxitin treatment included *Klebsiella* species (10 isolates), *E. coli* (8 isolates), *Proteus* species (6 isolates) and *Streptococcus fecalis* (12 isolates). Corresponding isolates for the control group are shown in Table 4. Positive cultures were mostly from the cervix. The commonest organisms cultured from the high vaginal swab were *Klebsiella* species and *Streptococcus fecalis*. Following treatment, however, repeat cultures yielded no growth in the

Table 2. Clinical features on admission of patients with postabortal or postpartum sepsis in Cefoxitin trial

Symptoms*	Cefoxitin group		Control group	
	No. $n = 25$	%	No. $n = 60$	%
Abdominal pain + tenderness	20	(80)	42	(70)
Vaginal bleeding	16	(64)	38	(63)
Offensive vaginal discharge	8	(32)	25	(42)
Pyrexia (temperature 38°C)	8	(32)	20	(33)
Vomiting, backache etc.	4	(14)	10	(16)

*Many patients presented with more than one clinical symptom.

Table 3. Drug therapy response — interval (h) as indicated by fall in temperature among the patients in Cefoxitin trial

Chemotherapeutic agent	Positive response	No. of h range	Mean h
Cefoxitin	23/25 (92%)	48–96	54
Cotrimoxazole/ Metrondazole	15/25 (60%)	48–120	72
Gentamycin	13/25 (52%)	72–120	78
Ampicillin*	0/10 (0%)	96–120	–

*Patients on ampicillin were given the benefit of 4–5 days before changing therapy.

Table 4. Pathogens isolated from vaginal swabs (HVS) and cervix of patients with pelvic infections and were treated with Cefoxitin or other antibiotics

Organisms	Cefoxitin		Other antibiotics	
	Before	After	Before	After
Klebsiella spp.	10	—	32	12
E. coli	8	—	40	15
Proteus spp.	6	—	27	7
Streptococcus fecalis	12	—	15	6

patients in the Cefoxitin treatment schedule, while some cultures from patients in the control treatment schedule still yielded positive results, even when the patients were symptom free.

There were no marked changes in the baseline and repeat haematological and blood chemistry investigations carried out, as most of the results were within normal range. Furthermore, while the WBC and differential tended to fall with the improvement in the patients' conditions, the PCV rose. There were no adverse reactions to Cefoxitin to warrant stoppage of the study and all failed control group cases were given the benefit of alternative drugs after 14 days, following antibiotic sensitivity results.

Discussion

The response of patients with postabortal sepsis to Cefoxitin has tended to confirm the high hopes placed on Cefoxitin (Ledger & Smith, 1972; Sweet *et al.*, 1979) especially when compared with the other locally available drugs in the hospital, as shown in this study. Response to Cefoxitin has been prompt, with pyrexia settling within 96 h (mean 54 h) and the other symptoms clearing within 7 days, compared with the situation among the patients who received the other forms of therapy for similar problems in the study, where pyrexia settled only within 120 h (mean 72 h).

This is of very marked significance in this environment, in view of the large numbers of organisms that have developed resistance to many of the locally available antibiotics. The indiscriminate use of antibiotics purchased across the counter (Osoba *et al.*, 1978) has in no small measure encouraged the development of resistance by many organisms, especially the hospital acquired ones (Finland, 1972; Robertson, 1973; William, 1977). In order to preclude problems with some Gram negative organisms for example, the major reserve drugs, such as Chloramphenicol or Clindamycin, have had to be used concurrently to treat these organisms (Ledger *et al.*, 1975). Cefoxitin, a semi-synthetic Cephamycin antibiotic derived from Cephamycin C, and closely related to the

Cephalosporins, would appear to be a safe single alternative agent. Unlike other Cephalosporins, Cefoxitin is said to be highly resistant to Cephalosporinases (Sweet *et al.*, 1979).

Having such resistance, Cefoxitin is able to penetrate and destroy many of the bacteria which are ordinarily resistant to Cephalosporins because of their production of Cephalosporinases. The drug is thus very effective against infections caused by most of the clinically important Gram negative bacteria other than *Pseudomonas* and *Enterobacter* species (Sweet *et al.*, 1979). This has been well demonstrated in this study, especially with the demonstrated efficacy of Cefoxitin against (for example) *Klebsiella* species, *E. coli* and *Proteus* species.

The timing of the delivery of antibiotics is important. If appropriate antibiotics can be given shortly after the bacterial invasion of the peritoneum, then a marked impact on both the complications of sepsis and the development of abscess can be made and the patient usually is cured (Ledger & Smith, 1979). On the other hand, if this is given later, in the course of disease after abscess formation has occurred, a therapeutic failure may result, and drainage will be necessary for cure (Sweet *et al.*, 1979). Fortunately, most of the patients in the current study reported for treatment in hospital within 3 days of the onset of bleeding, pain and fever. Hence, there were no cases of pelvic sepsis that required surgery.

Cefoxitin is metabolized only minimally in the body and excreted by the kidneys (Schrogie *et al.*, 1979; Humbert *et al.*, 1979). The drug showed no evidence of liver or kidney damaging effects as clearly shown by the blood chemistry studies. Similarly, no significant toxicity or hypersensitivity effects were noticed in the study, thus confirming the safety of the drug. Cefoxitin could thus be a safe and effective alternative antibiotic to replace the common antibiotics to which the many hospital acquired organisms have developed resistance, thus preserving the reserve antibiotics.

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(*Received* 4 *March* 1984; *revision received* 13 *March* 1984; *accepted* 15 *May* 1984)