Metronidazole v. cefoxitin in severe appendicitis—a trial to compare a single intraoperative dose of two antibiotics given intravenously

A. P. CORDER
M.B., B.S.

JEAN E. PRIOR
M.B., B.S.

T. BATES
F.R.C.S.

MARGARET HARRISON

P. J. DONALDSON
F.R.C.S.

The William Harvey Hospital, Kennington Road, Ashford, Kent TN24 0LZ

Summary

In severe appendicitis, the effect of a single intravenous dose of metronidazole (500 mg) was compared with cefoxitin (1 g). The antibiotics were given by random allocation once the diagnosis had been established at operation.

In the metronidazole group, 5 out of 48 patients developed a wound infection whilst in hospital compared with 13 out of 48 in the cefoxitin group ($P=0.036$). However, 57% of wound infections became apparent after the patient went home and the overall infection rates were similar.

The mean length of postoperative hospital stay was 5.0 days in the metronidazole group and 6.8 days in the cefoxitin group ($P=0.052$), but of those who did develop a wound infection, the length of stay was almost double in the cefoxitin group. Anaerobic organisms were cultured from the wound in 7 out of 15 patients who received cefoxitin but in none of 5 patients in the metronidazole group. Whilst metronidazole only delayed the discharge of pus from the wound, it did seem to reduce the severity of infection. Cefoxitin appeared to be less effective, given as a single intravenous injection at a dose of 1 g.

KEY WORDS: wound infection, appendicitis, metronidazole, cefoxitin.

Introduction

Sepsis after appendicectomy commonly affects the wound but, when the appendix is gangrenous or perforated, deep sepsis often arises and the length of hospital stay may be prolonged. Prophylactic metronidazole has been shown to be effective in reducing the wound infection rate after appendicectomy

(Foster, Bolwell and Balfour, 1981; Willis *et al.*, 1976) but after severe appendicitis, this may still be in the region of 40% (Foster *et al.*, 1981; Bates, Touquet and Tutton, 1980). Without antibiotics however, the wound infection rate has been reported between 40 and 70% (Foster *et al.*, 1981; Tanner *et al.*, 1980; Donovan *et al.*, 1979; Bates *et al.*, 1974). It is generally accepted that metronidazole is effective only against anaerobic bacteria (Editorial, 1981) and while these are of great importance in the genesis of wound infection after appendicitis (Willis *et al.*, 1976; Kelly, 1980) has shown that considerable synergy can exist between aerobic and anaerobic organisms.

In the present study of severe appendicitis, metronidazole was therefore compared with cefoxitin, an antibiotic effective against both aerobic and anaerobic bacteria (Williams, Geddes and Neveu, 1978). The antibiotics were given as a single intraoperative dose when the diagnosis of severe appendicitis was made. Metronidazole has been shown to be effective in appendicitis given as a single intravenous dose of 500 mg pre-operatively (Greenall *et al.*, 1979) but it was felt that intraoperative administration would be just as effective in providing circulating antibiotic at the time of wound contamination. Peritonitis was not considered to be a contraindication to this regime in view of previous reports of the successful use of single doses of antibiotics in the treatment of perforated appendicitis and peritonitis (Donovan *et al.*, 1979; Tanner *et al.*, 1980; Bates *et al.*, 1974).

Patients and methods

All patients admitted to one firm of a district general hospital, who were found to have severe

appendicitis at operation through a grid-iron incision, were admitted to the study. Severe appendicitis was defined as: (1) gangrenous appendicitis; or (2) perforated appendicitis; or (3) appendicitis with peritonitis.

Once the diagnosis had been made on opening the peritoneum, the patient was randomly allocated to receive either metronidazole or cefoxitin by drawing a numbered card from an envelope, prepared in batches of 10.

A single dose of one antibiotic was then given intravenously by the anaesthetist, either metronidazole 500 mg in 100 ml over 20 min or cefoxitin 1 g over 3 min (maker's dosage recommendation at outset of trial 1-2 g, 8 hourly). Children under the age of 5 years were excluded and those between the age of 5 and 10 years were given half the adult dose. The wound was closed without drainage and no topical application was used. The appendix was examined histologically in all cases.

Postoperatively the wound was inspected for evidence of infection but this was only recorded when there was frank discharge of pus (Ljungquist, 1964). The use of further antibiotics was permitted within the protocol if this was considered necessary by the clinician involved. Permission to undertake the study was given by the local Ethical Committee. Although the study was not double-blind, the surgeon assessing the wound postoperatively and in out-patients was unaware of the antibiotic given. Patients were seen for follow-up 1 month after operation and if they failed to attend, they were contacted either by post or telephone. Specific enquiry was made as to whether there had been any discharge from the wound after the patient left hospital. The age, sex and weight of patients were compared in the two groups.

The length of postoperative stay included the first postoperative day as well as the day of discharge from hospital. If a patient required re-admission to hospital due to a complication of appendicectomy, the postoperative stay was taken to be the sum of the

duration of the 2 admissions. Wound swabs were taken for microscopy and culture in those cases who developed a wound infection in hospital.

Results

A total of 97 consecutive patients with severe appendicitis were admitted to the trial between August 1979 and February 1982. Forty-eight patients were randomly allocated to the metronidazole group and 49 to the cefoxitin group.

The following protocol violations occurred: one patient allocated to the cefoxitin treatment never received the drug but was given postoperative metronidazole. The records of this patient have not been traced so that 48 patients in each group were available for analysis. Further antibiotic treatment was given to 9 patients. In 7 cases (4 in the metronidazole group), this treatment was started immediately postoperatively. Two cases in the cefoxitin group received further antibiotics starting more than 1 week after operation. The patient's weight was not recorded in 10 patients (6 in the cefoxitin group) and 2 patients in the cefoxitin group were lost to follow-up.

Comparisons between the 2 groups with respect to age, weight and sex are summarized in Table 1. There were 11 children under the age of 10 years in the cefoxitin group compared with 2 in the metronidazole group ($P < 0.025$) in spite of random allocation. The children received half the adult dose of either drug but the mean dose of cefoxitin per kg body weight was only marginally higher than in the adults. Patients with a perforated appendix or peritonitis were evenly distributed between the 2 groups (Table 1).

Wound infection in hospital occurred in 5 patients receiving metronidazole and in 13 patients in the cefoxitin group ($P < 0.04$) (Table 2). However, 57% of wound infections occurred after the patient left hospital and the overall number of infections was 22 in the metronidazole group and 20 in the cefoxitin group. Three patients in the cefoxitin group were re-

TABLE 1. Comparison of the 2 groups

	Metronidazole	Cefoxitin	<i>P</i>
Males	27	30	
Mean age (years)	31.5 (48)*	24.1 (48)	0.023 (Mann-Whitney)
Children <10 years	2	11	<0.025 (χ^2)
Mean age (years) excluding those <10 years	31.6 (46)	29.3 (37)	NS
Mean weight (kg)	60.33 (44)	53.5 (42)	NS
Mean weight (kg) excluding those <10 years	60.8 (42)	62.6 (31)	NS
Gangrenous appendix	27	23	—
Perforated appendix	6	8	—
Peritonitis	15	17	—

NS = not significant. *Number in parentheses

TABLE 2. Frequency of wound infection and duration of postoperative stay in the 2 groups

	Antibiotic Group		P
	Metronidazole	Cefoxitin	
Hospital wound infections	5 (48)*	13 (48)	0.037 (test for equality of 2 proportions)
Total number of wound infections	22 (48)	20 (46)	—
Wound swabs yielding <i>Bacteroides</i> sp. on culture	0 (5)	7 (15)	—
Mean duration of post-operative hospital stay (all patients) days	5.0 (48)	6.83 (48)	0.052 (Mann-Whitney)
Mean duration of post-operative hospital stay (excluding all patients <10 years) days	4.83 (46)	7.3 (37)	0.019 (Mann-Whitney)
Mean duration of post-operative hospital stay in patients who did not develop wound infections (days) $\pm$ s.d.	4.15 $\pm$ 1.32 (27)	4.35 $\pm$ 1.35 (26)	NS
Mean duration of post-operative hospital stay in patients who developed wound infections. *	5.90 (21)	10.25 (20)	0.0008 (Mann-Whitney)

NS = not significant. *Number in parentheses

admitted with septic complications compared with one patient in the metronidazole group and 3 cefoxitin patients developed a pelvic abscess compared with one metronidazole patient. No patient was readmitted more than once.

Length of hospital stay

The mean length of postoperative stay was 6.8 days in the cefoxitin group compared with 5.0 days in the metronidazole group ($P=0.052$) (Table 2). If children under the age of 10 years are excluded, the difference was more marked: 7.3 days (cefoxitin) compared with 4.8 days (metronidazole) ($P<0.02$).

Of those patients who did not develop a wound infection, the mean length of postoperative stay was the same in both groups (cefoxitin 4.35 days, metronidazole 4.15 days). However, in those who did develop a wound infection the mean length of stay was almost double in the cefoxitin group (cefoxitin 10.3 days, metronidazole 5.9 days) ($P<0.001$), and this difference remained whether or not patients treated with additional antibiotics were included.

Bacteriology

Wound cultures were obtained in all 13 hospital wound infections occurring in the cefoxitin group and in 3 out of 5 in the metronidazole group. Of the patients who developed a wound infection at home, only 2 in each group had a wound swab taken.

In the cefoxitin group, 7 out of 15 cultures grew *Bacteroides* species compared with none of the 5 in the metronidazole group (Table 2). All but one culture of *Bacteroides* sp. also grew aerobic organisms. Those cultures which did not show *Bacteroides* sp. grew mixed aerobic faecal organisms except for one pure growth of *Staphylococcus aureus* in the

metronidazole group and one swab which showed no growth in the cefoxitin group.

Discussion

There was no difference between the overall incidence of wound infection in the 2 groups but more patients who received cefoxitin developed a wound infection whilst in hospital and their length of stay was consequently prolonged. There were fewer pelvic abscesses in those patients receiving metronidazole and although the difference was not significant, infection seemed to be less severe in this group. This difference may well be due to the absence of anaerobic organisms after metronidazole treatment noted in the present study and by Foster *et al.* (1981) and Willis *et al.* (1976).

However, 57% of wound infections did not become apparent until after the patient had gone home, a finding previously noted by Salem, Johnson and Devitt (1979) and by Bates *et al.* (1980). It is therefore important that any study of postoperative wound infection should include adequate follow-up but such late infections are usually relatively minor and seldom require re-admission to hospital.

In the present study, an antibiotic was given at the time of discovery of severe appendicitis and was given intravenously to achieve high serum levels at the time of wound inoculation. It is possible that a longer course of treatment would have been beneficial, especially in the cefoxitin group but both Rodgers *et al.* (1979) and Tanner *et al.* (1980) have shown a single dose of metronidazole to be effective. Burke (1961) has demonstrated the inadequacy of antibiotic treatment given more than 3 hr after wound contamination in an animal model and it is possible that similar considerations apply to doses of

antibiotics, other than the initial one, in a prophylactic regime.

Cefoxitin has been shown to be effective in colorectal surgery by Hoffman, McDonald and Watts (1981a) and in appendicitis by Hoffman *et al.* (1981b) and Panichi, Pantosi and Marsiglio (1980) but in a dose of 2 g, 8 hourly, for 1 to 5 days. Both metronidazole and cefoxitin are given 8 hourly when used intravenously but the half-life of cefoxitin is only 50 min (Broden *et al.*, 1979) compared with 7.3 hr for metronidazole (Houghton, Smith and Thorne, 1978).

Therefore, before accepting that cefoxitin is less effective than metronidazole in severe appendicitis, it is possible that a dose of 2 g should be used and that a single intravenous dose may be inappropriate in view of its short half-life. However, Taylor *et al.* (1982) did find a single dose of 1 g cefoxitin effective prophylaxis before abdominal surgery when given pre-operatively into the incision site.

When severe appendicitis is found at operation and no pre-operative prophylaxis has been given, a single dose of intravenous metronidazole given at this time appears to be satisfactory treatment.

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