

A double-blind trial of a single intravenous dose of metronidazole as prophylaxis against wound infection following appendicectomy

M. J. GREENALL, A. BAKRAN, I. R. PICKFORD, J. A. BRADLEY, A. HALSALL, J. MACFIE, M. ODELL, E. MARY COOKE, CHRISTINE LINCOLN AND M. J. MCMAHON*

SUMMARY

One hundred patients undergoing appendicectomy through a right iliac fossa incision were randomized to receive normal saline or 500 mg metronidazole as an intravenous infusion during the operation. One patient in the saline group developed an erythematous rash. There were 13 wound infections (as defined by the discharge of pus), 12 (out of 51) in the saline group and 1 (out of 49) in the metronidazole group. *Bacteroides* spp. were frequently cultured from the lumen of removed appendices and from pus obtained from infected wounds. This work supports the value of metronidazole but suggests that a single-dose regimen is adequate for prophylaxis.

AFTER appendicectomy a high proportion of infected wounds has yielded *Bacteroides* spp. (Leigh et al., 1974) and a previous study (Willis et al., 1976) has shown that a regimen of metronidazole suppositories and subsequently tablets given for a period of 1 week significantly reduced the incidence of wound infection.

We felt that the use of suppositories held certain disadvantages, and that treatment for 7 days might be unnecessary. Metronidazole administered as an intravenous infusion has been found safe and effective in the treatment of anaerobic infections (Selkon et al., 1977), and a single 500-mg dose infused over 20 min produced a mean rise of 11.7 µg/ml 30 min after administration had ceased in 14 patients (Eykin and Phillips, 1977). As these serum levels appeared to compare favourably with those achieved by treatment with metronidazole suppositories (Houghton and Templeton, 1978), we have investigated the efficacy of a single intravenous dose of 500 mg of metronidazole administered during appendicectomy as prophylaxis against wound infection.

Patients and methods

Patients who underwent appendicectomy via a right iliac fossa approach in the General Infirmary at Leeds during two periods of time between July 1977 and April 1978 were included in the study. A total of 116 patients aged between 5 and 73 years was included but 16 were rejected before the code was broken (Meckel's diverticulitis, 1; administration of additional antibiotics, 4; data mislaid, 3; failure to administer the infusion or adhere to the protocol, 8). The study was carried out using a randomized, double-blind technique. Identical infusion bottles containing 500 mg metronidazole in 100 ml saline or 100 ml physiological saline were stored in numbered sequence in the operating theatre. When a patient was taken to theatre for appendicectomy the numbered bottle was given to the anaesthetist who commenced the infusion once the anaesthetic had been induced and allowed the 100 ml to run in over approximately 10 min. At the end of the procedure data were recorded by the surgeon on a similarly numbered card. The wound was examined daily by the surgeon whilst the patient was in hospital and also at the first visit to the outpatient department. An infection was defined as the discharge of pus from the wound.

A swab was taken from the lumen of the appendix and also from all wound infections which appeared during inpatient stay. All the lumen swabs but only about half the wound swabs were placed immediately into Robertson's meat broth and plated out within 30 min. The Robertson's meat broth was subcultured at 24 h. The aerobic media used for inoculation and subculture were blood agar and MacConkey agar and the anaerobic pre-reduced media used were blood agar, neomycin blood agar and kanamycin (100 µg/ml) and vancomycin (7.5 µg/ml) blood agar. The wound swabs not transported in Robertson's meat broth were inoculated directly on to these media. The time between taking the swab and inoculation of the media was variable, but on occasions it was in excess of 4 h. Bacteria were identified by standard methods. Anaerobic Gram-negative bacilli were designated *Bacteroides* spp.

The code was broken when 100 patients had satisfactorily completed the trial.

Results

Fifty-one patients received saline and 49 metronidazole. The two groups were well matched except with respect to the frequency of wound drainage (Table I), which was more commonly employed in the control group.

Pus producing wound infection was seen in 1 wound from the metronidazole group (2 per cent) and in 12 from the saline control group (24 per cent). This difference was significant at $P = 0.002$ using Fisher's exact test. Reddening of the wound, which settled without additional treatment and did not result in a discharge of pus, was seen in a further 4 wounds, 2 in the metronidazole group and 2 in the control group.

The prevalence of various species of bacteria recovered from the appendix lumina and from the pus of the infected patients is shown in Tables II and III. All infected wounds discharged pus between 3 and 14 days after appendicectomy.

The patient who was treated with metronidazole and developed an infected wound did not have a drain but 3 of the patients in the saline group who became infected did have wound drains.

Discussion

A wound infection resulting in the production of pus was found in 12 of the 51 patients who received prophylaxis with intravenous saline. This infection rate of 24 per cent is similar to rates reported in other recent series in which no antibiotic prophylaxis was employed (Rickett and Jackson, 1969; Benson et al., 1973; Bates et al., 1974).

Leigh et al. (1974) recovered *Bacteroides* spp. from 90 per cent of infected wounds after appendicectomy. Our overall recovery rate of 40 per cent was due to our failure to isolate *Bacteroides* spp. from dry swabs, but the rate was 80 per cent from the swabs sent in

* University Departments of Surgery and Microbiology, General Infirmary, Leeds.

Correspondence to: M. J. McMahon.

Table I: DATA FROM 49 PATIENTS WHO RECEIVED INTRAVENOUS METRONIDAZOLE AND 51 WHO RECEIVED SALINE DURING APPENDICECTOMY

	Metronidazole	Control
Age (yr \pm s.d.)	22 \pm 15	22 \pm 14
Male/female	25/24	26/25
Appendix		
Normal	9	11
Inflamed	27	25
Gangrenous	7	9
Local pus collection	4	4
Peritonitis	2	2
Drains	5	9
Infected wounds	1	12

Table II: PERCENTAGE FREQUENCY DISTRIBUTION OF BACTERIAL SPECIES RECOVERED FROM THE LUMEN OF REMOVED APPENDICES AND FROM THE WOUND PUS IN THE SALINE GROUP

Organism	Appendix lumen (n = 11)	% in lumina	Wound pus (n = 10)	% in wound pus
<i>Coliform</i> spp.	11	100	8	80
<i>Bacteroides</i> spp.	6	55	4	40
Enterococci	2	18		
<i>Clostridium</i> spp.	2	18	1	10
Diphtheroid	1	9		
<i>Bacillus</i> spp.	1	9		
<i>Lactobacillus</i> spp.	1	9	1	10
<i>Staphylococcus aureus</i>	1	9		
<i>Haemophilus influenzae</i>	1	9		
<i>Pseudomonas aeruginosa</i>			1	10

A bacteriological specimen was not obtained from 2 infections which discharged pus subsequent to the patients' discharge from hospital.

Table III: BACTERIAL SPECIES RECOVERED FROM THE LUMEN OF THE REMOVED APPENDIX AND FROM THE WOUND PUS IN THE SINGLE PATIENT WHO RECEIVED METRONIDAZOLE AND DEVELOPED INFECTION

Organism	Appendix lumen (n = 1)	Wound pus (n = 1)
<i>Bacteroides</i> spp.	Yes	—
<i>Coliform</i> spp.	Yes	Yes
<i>Clostridium</i> spp.	Yes	—
Diphtheroid	Yes	—

Robertson's meat broth. This organism is clearly important in wound infections following appendicectomy. Nevertheless, we cultured a total of four other organisms from the wounds of patients who had not received metronidazole. Although the effectiveness of metronidazole as an agent for use against *Bacteroides* is now well established (Whelan and Hale, 1973; Willis et al., 1974, 1976, 1977), most of the remaining organisms isolated here do not lie within its spectrum of activity. There is evidence, however, that obligate anaerobes such as *Bacteroides fragilis* may inhibit phagocytosis (Ingham et al., 1977) and thereby allow other organisms to multiply. Such a mechanism might explain the effectiveness of metronidazole in reducing the incidence of infections involving a wide spectrum of organisms.

In this trial we have found that a single intravenous injection of metronidazole produced a reduction in the incidence of infection similar to that achieved by a

combined suppository and tablet regimen lasting 7 days. Although Willis et al. (1976) 'considered it inappropriate, however, to use the intravenous route for evaluating the drug as a prophylactic agent', we feel that it has certain advantages in routine practice.

The value of antibiotics for the prevention of wound infection after appendicectomy is at present rather unclear. Although some reports claim marked benefit from their use (Rickett and Jackson, 1969; Longland et al., 1971; Bates et al., 1974), this impression has not been universal (Magarey et al., 1971). There is at least agreement between reports upon the value of metronidazole, although no trial has yet set out to compare this drug with an antibiotic.

We conclude that a single intravenous dose of metronidazole administered at the time of appendicectomy is a convenient, safe, cheap and effective method of reducing wound sepsis rates.

Acknowledgements

We would like to thank Mr E. A. Benson, Mr R. L. Doig, Mr G. L. Hill, Professor D. Johnston, Mr J. H. Shoesmith and Mr F. G. Smiddy for permission to carry out this trial upon patients admitted under their care. We thank the anaesthetic and theatre staff of the General Infirmary at Leeds for their cooperation, and Dr J. Collier and Miss E. M. Colhoun of May and Baker Ltd for the supplies of metronidazole and placebo and for their help with the organization of the trial.

References

- BATES T., DOWN R. H. L., HOUGHTON M. C. V. et al. (1974) Topical ampicillin in the prevention of wound infection after appendicectomy. *Br. J. Surg.* **61**, 489-492.
- BENSON E. A., BROWN G. J. A. and WHITTAKER M. (1973) Prevention of wound infection in acute appendicitis. *Lancet* **2**, 322.
- EYKYN S. and PHILLIPS I. (1977) Intravenous metronidazole in the treatment of anaerobic sepsis. *Excerpta Med. Int. Congr. Ser.* **438**, p. 393.
- HOUGHTON G. W. and TEMPLETON R. (1978) Statistical analysis of serum metronidazole levels in patients receiving the drug mainly by suppository. *J. Antimicrob. Chem.* **4**, Suppl C, pp. 91-96.
- INGHAM H. R., SISSON P. R., THARAGONNET D. et al. (1977) Inhibition of phagocytosis in vitro by obligate anaerobes. *Lancet* **2**, 1252-1254.
- LEIGH D. A., SIMMONS K. and NORMAN E. (1974) Bacterial flora of the appendix fossa in appendicitis and postoperative wound infection. *J. Clin. Pathol.* **27**, 997-1000.
- LONGLAND C. J., GRAY J. G., LEES W. et al. (1971) The prevention of infection in appendicectomy wounds. *Br. J. Surg.* **58**, 117-119.
- MAGAREY C. J., CHANT A. D. B., RICKFORD C. R. K. et al. (1971) Peritoneal drainage and systemic antibiotics after appendicectomy. *Lancet* **2**, 179-182.
- RICKETT J. W. S. and JACKSON B. T. (1969) Topical ampicillin in the appendicectomy wound. *Br. Med. J.* **4**, 206-207.
- SELKON J. B., INGHAM H. R. and HALE J. H. (1977) Experience with intravenous administration of metronidazole in man. *Excerpta Med. Int. Congr. Ser.* **438**, p. 390.
- WHELAN J. P. F. and HALE J. H. (1973) Bactericidal activity of metronidazole against *Bacteroides fragilis*. *J. Clin. Pathol.* **26**, 393-395.
- WILLIS A. T., BULLEN C. L., FERGUSON I. R. et al. (1974) Metronidazole in the prevention and treatment of bacteroides infections in gynaecological patients. *Lancet* **2**, 1540-1543.
- WILLIS A. T., FERGUSON I. R., JONES P. H. et al. (1976) Metronidazole in prevention and treatment of bacteroides infections after appendicectomy. *Br. Med. J.* **1**, 318-321.
- WILLIS A. T., FERGUSON I. R., JONES P. H. et al. (1977) Metronidazole in prevention and treatment of bacteroides infections in elective colonic surgery. *Br. Med. J.* **1**, 607-610.

Paper accepted 15 December 1978.