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Prophylactic metronidazole in appendicectomy: a controlled trial

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SUMMARY

Prophylactic metronidazole was compared with no treatment in a randomly allocated study of patients undergoing appendicectomy. A 1-g suppository of metronidazole was given with the premedication and 200 mg t.d.s. orally for 7 days thereafter.

There were 4 hospital wound infections in the 87 patients receiving metronidazole and 11 out of 83 in the no-treament group ($P<0.05$). However, 60 per cent of wound infections occurred at home and the overall infection rates were not significantly different.

The duration of postoperative hospital stay was longer in the control group (5·8 days $\pm$ 3·0 s.d.) than in the treated group (4·8 $\pm$ 2·3; $P<0.01$).

Only one anaerobic infection occurred in a patient receiving metronidazole but late infection was not prevented. Blood levels of metronidazole taken at the end of operation showed a wide variation but there was no correlation with subsequent infection. Culture of the appendix showed aerobic organisms in 88 per cent of cases and anaerobes in 72 per cent.

It is suggested that an antibiotic which is effective against both aerobic and anaerobic organisms might have an advantage over metronidazole in appendicitis.

SEPSIS following appendicectomy still causes considerable morbidity and prolonged hospital stay in spite of the benefit which has been demonstrated from the use of various topical and systemic agents. However, there has been increasing awareness of the importance of non-sporing anaerobes (Bacteroides spp.) as a major cause of sepsis after gastrointestinal and gynaecological surgery (1).

Willis et al. (2) have reported that prophylaxis against anaerobic organisms with metronidazole greatly reduces the morbidity of appendicitis and subsequent studies have so far confirmed this finding. Willis and his colleagues gave metronidazole 1 g by suppository with the premedication followed by oral therapy for 7 days. Rodgers et al. (3) have since reported a significant reduction in wound infection using intrarectal metronidazole for 48 h and Greenall et al. (4) found similar benefit from a single intravenous infusion of 500 mg at operation. Metronidazole given for 3 days has also been found to be superior to topical povidone-iodine in preventing wound infection after appendicectomy (5).

The present study was carried out following the report by Willis et al. (2) and the same dosage regimen of metronidazole was used.

Patients and methods

All patients admitted as an emergency with a clinical diagnosis of appendicitis were entered into the trial. Patients were randomly allocated by the admitting house surgeon to receive either prophylactic metronidazole or no treatment. A grid-iron incision was used in every case without peritoneal drainage.

Treatment cards were prepared in sealed envelopes in equally divided batches of ten. Patients in the treatment group received a 1-g suppository of metronidazole with the premedication, approximately 1 h preoperatively and 8-hourly postoperatively until tolerating oral fluids. Thereafter, metronidazole 200 mg 8-hourly was given orally for 7 days. No specific treatment was given to the control group but the operating surgeon was not informed whether the patient had received metronidazole. Children received half the adult dose up to the age of 12 years.

A peritoneal swab was taken only if pus was present, but during the latter part of the study the appendix tip was immersed in Amies transport medium at the time of operation and then inoculated on to the relevant culture media as soon as possible: these were 8 per cent horse blood agar, MacConkey agar and deoxycholate citrate agar, incubated at 37 °C in 5 per cent carbon dioxide, and 8 per cent horse blood agar and neomycin blood agar anaerobically at 37 °C. The appendix tip was also cultured for Campylobacter spp. on the campylobacter isolation medium (Oxoid) at 43 °C.

The Bacteroides spp. were identified using the Mastring MID8 for the presumptive identification of Gram-negative anaerobes. The β-haemolytic streptococci were grouped by the Phadebact system.

The findings at operation were divided into three categories: normal appendix, acute appendicitis and gangrenous appendicitis, perforation or peritonitis.

Histological examination of the appendix was carried out in all cases and any doubt about the presence of early appendicitis was decided by the pathological findings.

Each wound was inspected daily and the criteria of Ljungqvist (6) were used to indicate an infection, i.e. a frank discharge of pus. The surgeon who examined the patient postoperatively was unaware of the treatment group unless he felt that antibiotic treatment was indicated and made specific inquiry. Patients were examined again at about 4 weeks and questioned about any discharge from the wound. Those failing to attend outpatients were contacted by post.

The height and weight of each patient were recorded and those more than 20 per cent over the ideal weight for a medium frame (Metropolitan Life Insurance tables) were classed as obese. The age, sex, prevalence of obesity, length of postoperative hospital stay and the number of postoperative days in which the temperature was recorded above 100 °F were compared in the two groups.

Statistics

Differences in wound infection rates were examined by the χ^2 test and statistical comparison of the length of hospital stay in the two groups was estimated by Student's t test.

Results

Two hundred patients were admitted to the trial between August 1977 and March 1979.

Exclusions

Thirty patients were subsequently excluded from the study, 12 from the metronidazole group and 18 from the control group (*Table I*). The severity of the appendicitis was responsible for additional treatment being given to 5 patients in the treatment group and 7 in the control

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Table I: PATIENTS EXCLUDED FROM STUDY

	Metronidazole ($n = 12$)	Control ($n = 18$)
Pregnant	0	3
Diverticulitis	1	0
Antibiotics given for unrelated infection (e.g. urinary tract)	6	8
Antibiotics given for postop. fever	1	2
Antibiotics given at operation for peritonitis	3	5
Tube drainage	1	0

Table II: COMPARISON OF GROUPS

	Metronidazole ($n = 87$)	Control ($n = 83$)
Male/female	51/36	39/44
Age		
0–10	16	13
11–20	34	38
21–40	21	22
41–60	13	8
61–90	3	2
Obesity		
>20% average	9	12
Appendix		
Normal	24	21
Inflamed	46	50
Gangrenous/peritonitis	17	12

Table III: RESULTS

	Metronidazole ($n = 87$)	Control ($n = 83$)
Wound infection		
In hospital	4	11 $P<0.05$
At home	13	10 n.s.
Total	17	21 n.s. ($P>0.2$)
Normal appendix	4 (4)*	2 (2)
Acute appendicitis	7 (4)	14 (8)
Severe appendicitis	6 (5)	5 (0)
Total	17 (13)	21 (10)
Length of postop. hospital stay (d ± 1 s.d.)	4·8 ± 2·3	5·8 ± 3·0 $P<0.01$
No. of postop. patient days in which temp. > 100 °F	37 ($n = 22$)	32 ($n = 16$) n.s.

* Figures in brackets represent home infections.

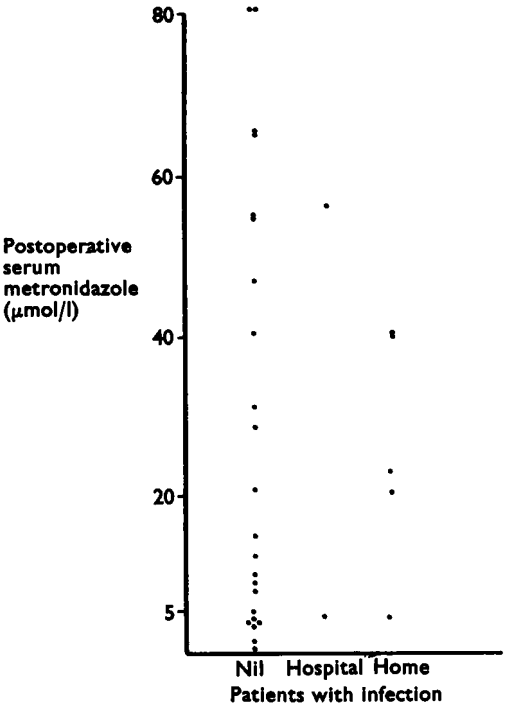

Fig. 1. Serum metronidazole levels in patients with and without postoperative wound infection.

group. There were 3 wound infections in the excluded group, of which 1 occurred in a patient receiving metronidazole.

Comparison of groups

Eighty-seven patients received metronidazole and there were 83 patients in the control group (*Table II*). There were 16 patients over 40 years old in the metronidazole group and 10 in the control group. Fifty-nine per cent of the patients in the treatment group were female compared with 47 per cent of the controls. There were 17 patients in the treatment group with severe appendicitis and 12 in the control group.

Wound infection

There were 4 wound infections in the metronidazole group and 11 in the control group whilst the patients were in hospital ($P<0.05$) (*Table III*). However, 60 per cent of wound infections occurred after the patients went home, making an overall infection rate of 19·5 per cent in the metronidazole group and 25 per cent in the untreated patients (n.s.). Ten wound infections that occurred at home were not actually witnessed by a doctor, although the history was considered to be clear (8 of these were in the control group). When only those patients with severe appendicitis were considered, the overall wound infection rate was 5 out of 12 (42 per cent) in the control group compared with 6 out of 17 (35 per cent) in the metronidazole group. However, only 1 of those in the metronidazole group occurred in hospital compared with all 5 in the control group.

The mean length of postoperative hospital stay was 1 day shorter in the treated group and this was significantly different ($P<0.01$). There was no demonstrable difference in the incidence of postoperative fever in the two groups.

Bacteriology

There was only 1 proved anaerobic infection in a patient receiving metronidazole. In 6 of the 8 cases in which both appendix and wound cultures were available, the same organism was isolated from both sites. Cultures of the appendix grew anaerobic organisms in 72 per cent of

cases and aerobes in 88 per cent. Both anaerobic and aerobic organisms were found in 65 per cent of cases.

Metronidazole levels

Serum metronidazole levels were taken in 26 patients who had received the drug and in 5 controls; 9 of the treated patients (35 per cent) had levels of 5·3 μmol/l or less at a minimum of 90 min after administration. Two control patients had reported levels of 1·8 and 4·1 μmol/l. The range in the treated group was <0·6 to 82 μmol/l. There was no demonstrable correlation between serum levels of metronidazole and the incidence of infection (*Fig.* 1) or the length of hospital stay in the treated group.

Follow-up

Eight patients failed to attend the outpatient department for follow-up examination but replied to a postal questionnaire that there had been no discharge from the wound since leaving hospital. One patient in each group failed to attend outpatients or to reply to a letter (99 per cent follow-up).

Discussion

The present study confirms that metronidazole significantly reduces the incidence of wound infection occurring in hospital after appendicectomy. However, when careful follow-up was carried out, the number of wound infections occurring after the patient left hospital was much the same in both groups. In the present series 60 per cent of wound infections occurred after discharge from hospital which compares with an incidence of 65 per cent found by Salem et al. (5).

The severity of infections occurring at home is not easy to judge and culture of the wound is difficult to obtain. However, it was clear from the patients' histories that these infections were not always trivial but often started with the profuse discharge of pus which required the district nurse to attend for several days. If those cases of late infection which relied on the patients' histories alone are excluded the incidence in the control group is reduced, but this does not affect the overall results. There were more patients with severe appendicitis in the treated group but this does not appear to have unduly biased the results. Metronidazole seemed most effective in preventing hospital infection in severe appendicitis but in several of these cases onset of infection was delayed until after the patient went home. The follow-up in previous studies has varied between 10 days (3) and 3–5 weeks (5), but only the latter study has indicated the proportion of wound infections occurring after the patient has left the hospital. Willis et al. (2) suggested that deep anaerobic infections give rise to high fever, but this was not shown th the present study. The reduction in the length of stay in the treated group was small but significant.

Serum metronidazole levels were only estimated in 26 patients in the treatment group but in 2 the level was less than 0·6 μmol/l. Similar levels were found in 2 patients in the study conducted by Rodgers et al. (3) using the same assay at 15 and 35 min after insertion of a suppository. The time interval was not recorded in our cases, but since the levels were taken at the end of operation this must have been at least 90 min after administration. Rodgers et al. (3) found serum metronidazole levels of 5·3 μmol/l or less in 41 per cent of their cases at up to 75 min after intrarectal administration. Thirty per cent of patients had levels of 5·3 μmol/l or less at a minimum of 90 min in the present series. Houghton and Templeton (7) have also shown wide variation in serum levels after intrarectal administration.

However, Willis et al. (2) found a minimum preoperative level of 4·7 μmol/l and minimum postoperative one of 26 μmol/l: no metronidazole was found in the blood of any of their control patients. In the present study, however, 2 of 5 control patients had reported blood levels greater than some patients who had been given metronidazole. A polarographic assay, carried out in the same laboratory, was used in all these studies. Although we failed to demonstrate a correlation between wound infection in the treated group and low serum levels, it seems possible that a high level of metronidazole from an intravenous infusion at the time of wound inoculation might be superior to intrarectal administration. Eykyn and Phillips (8) found a range of 76–241 μmol/l 30 min after intravenous infusion of 500 mg metronidazole, and Selkon et al. (9) found a range of 124–282 μmol/l at 1–1½ h after 600 mg i.v. metronidazole.

What has been left unanswered is the role of aerobic organisms in the late wound sepsis seen in patients receiving metronidazole. Willis et al. (2) have dismissed facultative aerobic infection as superficial and mild but prophylactic metronidazole did not completely protect against late postoperative septic morbidity in the present study. Ampicillin, whilst principally active against aerobic Gram-negative organisms, may also have an anaerobic effect as well. In a previous study (10) topical ampicillin was found to reduce the incidence of hospital wound infection from 16 to 3 per cent, which compares closely with the present findings of 13 per cent in the control group and 4·6 per cent in patients who received metronidazole. Margery et al. (11) and Pollock et al. (12) did not find ampicillin as effective but others (13–16) did.

A synergy between aerobic and anaerobic organisms has been demonstrated by Kelly (17), and it seems possible that the low serum levels of metronidazole at the time of wound inoculation with intrarectal administration may leave enough viable anaerobic organisms to allow the delayed appearance of a clinical infection. There seems to be little doubt that some form of prophylaxis is indicated in acute appendicitis but it is suggested that it would be valuable to compare metronidazole with an antibiotic active against aerobic as well as anaerobic organisms.

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References

1. LEIGH D. A., SIMMONS K. and NORMAN E.: Bacterial flora of the appendix fossa in appendicitis and post-operative wound infection. *J. Clin. Pathol.* 1974; **27**: 997–1000.
2. WILLIS A. T., FERGUSON I. R., JONES P. H. et al.: Metronidazole in prevention and treatment of bacteroides infections after appendicectomy. *Br. Med. J.* 1976; **1**: 318–21.

3. RODGERS J., ROSS D., MCNAUGHT W. et al.: Intrarectal metronidazole in the prevention of anaerobic infections after emergency appendicectomy: a controlled clinical trial. *Br. J. Surg.* 1979; **66**: 425–7.
4. GREENALL M. J., BAKRAN A., PICKFORD I. R. et al.: A double-blind trial of a single intravenous dose of metronidazole as prophylaxis against wound infection following appendicectomy. *Br. J. Surg.* 1979; **66**: 428–9.
5. SALEM R. J., JOHNSTON J. and DEVITT P.: Short term metronidazole therapy contrasted with povidine-iodine spray in the prevention of wound infection after appendicectomy. *Br. J. Surg.* 1979; **66**: 430–1.
6. LJUNGQVIST U.: Wound sepsis after clean operations. *Lancet* 1964; **1**: 1095–7.
7. HOUGHTON G. W. and TEMPLETON R.: Statistical analysis of serum metronidazole levels in patients receiving the drug mainly by suppository. *J. Antimicrob. Chemother.* 1978; **4**: Suppl. C: 91–6.
8. EYKYN S. and PHILLIPS I.: Intravenous metronidazole in the treatment of anaerobic sepsis. *Excerpta Med. Int. Congr. Ser.* 1977; **438**: 393–9.
9. SELKON J. B., INGHAM H. R. and HALE J. H.: Experience with intravenous administration of metronidazole in man. *Excerpta Med. Int. Congr. Ser.* 1977; **438**: 390–2.
10. BATES T., DUNN R. H. L., HOUGHTON M. C. V. et al.: Topical ampicillin in the prevention of wound infection after appendicectomy. *Br. J. Surg.* 1974; **61**: 489–92.
11. MARGERY C. J., CHANT A. B. D., RICKFORD C. R. K. et al.: Peritoneal drainage and systemic antibiotics after appendicectomy. *Lancet* 1971; **2**: 179–82.
12. POLLOCK A. V., LEAPER D. J. and EVANS M.: Single dose intra-incisional antibiotic prophylaxis of surgical wound sepsis: a controlled trial of cephaloridine and ampicillin. *Br. J. Surg.* 1977; **64**: 322–5.
13. RICKETT J. W. S. and JACKSON B. T.: Topical ampicillin in the appendicectomy wound: report of a double-blind trial. *Br. Med. J.* 1969; **4**: 206–7.
14. MOUNTAIN J. C. and SEAL P. V.: Topical ampicillin in grid-iron appendicectomy wounds. *Br. J. Clin. Pract.* 1970; **24**: 111–15.
15. ANDERSEN B., BENDTSEN A., HOLBRAAD C. et al.: Wound infections after appendicectomy. *Acta Chir. Scand.* 1972; **138**: 531–6.
16. HOOGBERGEN J. A. M.: Decreased incidence of post-appendicectomy wound abscesses due to local application of ampicillin. *Arch. Chir. Neerl.* 1973; **25**: 19–25.
17. KELLY M. J.: Wound infection: a controlled clinical and experimental demonstration of synergy between aerobic (*Escherichia coli*) and anaerobic (*Bacteroides fragilis*) bacteria. *Ann. R. Coll. Surg. Engl.* 1980; **62**: 52–9.

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