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Intrarectal metronidazole in the prevention of anaerobic infections after emergency appendicectomy: a controlled clinical trial

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SUMMARY

A series of 102 patients with presumptive acute appendicitis entered a prospective, randomized, clinical trial of intrarectal metronidazole given over a 48-h period commencing before surgery. Adequate levels of circulating metronidazole were achieved. A significant reduction in the incidence of anaerobic wound infection was observed in the treated group ($P<0.02$). The convenience and short duration of the prophylactic regimen allowed early discharge from hospital. No untoward effects were observed.

THE success of prophylactic metronidazole in controlling serious wound infection due to Gram-negative anaerobic organisms after elective colonic surgery has already been established (Goldring et al., 1975; Willis et al., 1977), although the importance of simultaneous administration of an antimicrobial agent to control organisms of the coliform group remains uncertain. In acute appendicitis, Willis et al. (1976) have extended this prophylactic antimicrobial approach to emergency surgery, using metronidazole alone over 8 days, commencing just before surgery.

The aim of the present study was to examine further this prophylactic approach and to assess the efficacy of short term metronidazole, given solely as suppositories, in preventing anaerobic wound infection after appendicectomy for acute appendicitis.

Patients and methods

A consecutive series of 102 patients in whom a presumptive diagnosis of acute appendicitis had been made entered the trial. Patients were randomly allocated to receive identically marked suppositories containing either metronidazole 1 g or placebo (Witepsol). The first suppository was inserted at the time of presumptive diagnosis and thereafter a further suppository was inserted 8-hourly for 2 days. Proctoscopy was performed within 24 h of completing the course in the first 41 patients in the series.

Blood metronidazole levels

A venous blood sample was taken at the time of induction of general anaesthesia to measure the circulating level of metronidazole and the time interval between insertion of the initial suppository and blood sampling was noted.

Bacteriology specimens

The following specimens were taken for culture at the time of surgery: (*a*) a swab of peritoneal fluid; (*b*) a swab from the serosal aspect of the appendix; (*c*) after removal of the appendix and wound closure, the appendix was opened in its distal third and a swab of luminal content taken. All swabs were immediately immersed in Stuart's transport medium for transfer to the laboratory. Cultures were incubated both aerobically and anaerobically with 10 per cent added carbon dioxide for at least 48 h. The following culture media were used: 6 per cent horse blood agar, 6 per cent horse blood agar incorporating gentamicin sulphate 15 μg/ml, MacConkey's agar and Robertson's cooked meat broth. Bacteria were identified by standard procedures (Cowan and Steel, 1974).

Pathology

In all cases the appendix was subjected to routine histopathological examination.

Wound inspection

Formal wound inspection was made on the third or fourth day and again on the tenth day; in all cases where early ward discharge had been allowed arrangements were made for wound inspection on the tenth postoperative day. For the purposes of this study 'wound infection' was defined as the presence of pus or a purulent exudate at the wound.

Exclusions

Twelve patients were withdrawn from the study, 4 because of an error in the diagnosis at operation (1 acute cholecystitis, 1 caecal diverticulitis, 1 inflamed Meckel's diverticulum and 1 already established appendix abscess). Six patients were excluded because they had received antibiotics (intra- or postoperatively); in 5 of these cases the surgeon had been unwilling to leave his patients in a double-blind situation and in the sixth case preoperative administration of an antibiotic before hospital admission was discovered. Two patients were excluded because they were given the wrong suppositories. Thus 90 patients remained in the study.

Results

Matching of the groups (Table I)

Comparison of the groups with regard to age and sex showed no significant differences. In this study we classified appendices as normal, inflamed or gangrenous/ruptured. Unlike the earlier study of Willis et al. (1976) we have not recognized lymphoid hyperplasia as a significant pathological entity and have included such appendices in our normal group. Eighty-four per cent of appendices in our series were significantly inflamed. While there was no significant difference between the incidence of inflamed and gangrenous/ruptured appendices in the placebo and metronidazole groups, there were significantly fewer normal appendices in the metronidazole group compared with the placebo group and in this respect there was a slight bias against the metronidazole group (*Table I*). The relative incidence of acute appendicitis in the under-13-year-olds is greater than our figures suggest since most younger children from our area are admitted to a paediatric hospital. The anatomical sites of the appendix at operation were similar in both groups.

Blood metronidazole levels at the time of surgery

For 36 of the 42 patients who received metronidazole, the time interval between insertion of the first suppository and induction of anaesthesia was recorded and this is plotted against the circulating level of metronidazole in *Fig.* 1. At commencement of surgery following the initial single suppository, the mean

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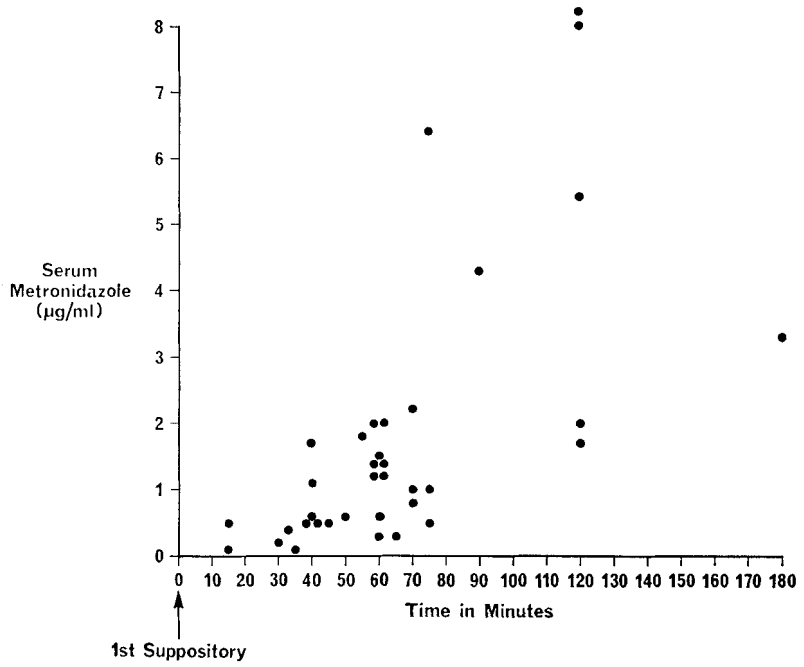

Fig. 1. Levels of circulating metronidazole at the time of surgery after a single 1-g suppository.

Table I: COMPARISON OF GROUPS

	Metronidazole ($n = 42$)	Placebo ($n = 48$)
Male/Female	27/15	27/21
Age		
<13	6	8
13–24	26	27
25–50	7	12
>50	3	1
Pathology		
Normal	2*	12*
Inflamed	30	31
Gangrenous ruptured	10	5

* There are significantly fewer normal appendices in the metronidazole group ($P<0{\cdot}0066$, Fisher's exact test). No other significant differences exist between the groups. The overall incidence of normal appendices in the series was 16 per cent; inflamed appendices 67 per cent; ruptured/gangrenous appendices 17 per cent.

Table II: BACTERIOLOGY

	Metronidazole		Placebo	
	Anaerobes		Anaerobes	
Site	Present	Absent	Present	Absent
Peritoneal fluid	2	40	2	46
Appendix serosa	10	32	13	35
Appendix lumen*	32	8	43	5
Operation wound	0	42	7	41

* Luminal swabs were not obtained in 2 patients.
In every case one or more strain of bacteroides comprised the anaerobic flora. Two instances of purely aerobic wound infection occurred (*see* text).

blood metronidazole level was 1·8 mg/l and the range was 0·1–8·2 mg/l. This indicated that satisfactory absorption from rectal mucosa was taking place, despite the short interval between insertion of the first suppository and sampling of blood. The mean time interval from insertion of the initial suppository to surgery was 64 min. From *Fig.* 1 it is evident that higher blood levels can be attained when this time is longer.

Bacteriology (Table II)

The presence of organisms in the peritoneal cavity, serosa of the appendix or indeed the lumen of the appendix gave little indication as to whether wound infection was likely to occur. Likewise, the presence or absence of turbid or clear peritioneal fluid was a poor guide to the development of an infected wound.

Wound infection

Seven of the 48 patients in the control group had severe anaerobic wound infection. In 5 of these patients a cellulitis developed which spread into the flank. In 3 this was associated with marked postoperative paralytic ileus and abscess formation requiring surgical drainage. In all 7 cases pus from the wound yielded bacteroides and in all instances the organisms were present in the lumen of the appendix. All 7 wounds yielded coexisting coliform organisms (*Escherichia coli* 6; *Klebsiella aerogenes* 1). Blood cultures were negative. All cases responded to a course of intramuscular gentamicin and lincomycin. The minimum inpatient stay was 18 days.

By contrast, there was no instance of anaerobic wound infection in the group that received metronidazole suppositories and this advantage for patients in the treated group is statistically significant ($P<0{\cdot}02$, Fisher's exact test).

There were 2 patients in the series who had aerobic wound infection, both in the metronidazole group. (One severe wound infection due to *Staphylococcus aureus* resulted in a 2½ week stay in hospital.) One of these cases was a patient who developed a stitch

abscess on the tenth day having been discharged on the third postoperative day with an initially satisfactory wound. One millilitre of pus was aspirated from the wound and this yielded a non-haemolytic streptococcus.

The use of peritoneal drains
Twelve patients in the series had peritoneal drains brought out through a separate stab wound. The usual indication for drainage was the finding of purulent peritoneal exudate and/or a gangrenous or ruptured appendix. Of the 12 patients, 4 had received placebo (3 of whom developed wound infection) and 8 had received metronidazole (none developed infection).

Exclusions
Of the 12 patients excluded from the study, 5 were withdrawn from the trial by the surgeon at the time of operation after administration of the initial preoperative suppository (metronidazole, 2; placebo, 3). All 5 had ruptured appendices, all had separate stab wound drains and received parenteral gentamicin and lincomycin for at least 3 days. Wound infection occurred in 2 of these cases (placebo and metronidazole one each) and in both cases culture yielded coliforms and bacteroides.

Proctoscopy
Forty-one patients (19 placebo; 22 metronidazole) had proctoscopy performed after completing the course of suppositories. No patient showed any abnormality. No practical difficulties arose in the administration of suppositories in the early postoperative period.

Discussion

This study of emergency appendicectomies clearly shows the ability of metronidazole to prevent wound infection from endogenous anaerobic bowel microflora. Use of the intrarectal route to administer the drug is safe and convenient and has clear advantages in the preoperative and immediate postoperative situation where the oral route is not always feasible and where intravenous administration would be unnecessary. Our results confirm that metronidazole is rapidly and satisfactorily absorbed via the rectal mucosa and that therapeutic blood levels can be attained even when there is only a short time interval between insertion of the first suppository and commencement of the operation. Willis et al. (1976) have had similar success using metronidazole suppositories as part of an 8-day course of therapy. In the light of our results, this longer course involving postoperative oral administration would appear to be unnecessary provided that the patient receives protective antimicrobial therapy during the peroperative period, i.e. the period during which surgery is exposing tissues to contamination from endogenous bowel flora. One further practical advantage of a short 2-day course of metronidazole is that it does not interfere with early hospital discharge around the third or fourth postoperative day.

Since there has been no significant evidence for strict anaerobes developing resistance to metronidazole over many years of widespread and varied use, a short course of the drug seems unlikely to precipitate the emergence of bacterial resistance.

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References

COWAN S. T. (1974) *Cowan and Steel's Manual for the Identification of Medical Bacteria.* London, Cambridge University Press.

GOLDRING J., SCOTT A., MCNAUGHT W. et al. (1975) Prophylactic oral antimicrobial agents in elective colonic surgery. *Lancet* **2**, 997–999.

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**, 318–320.

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**, 607–609.

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