PAPERS AND ORIGINALS

Rational use of antibiotic therapy after appendicectomy

D J PINTO, P J SANDERSON

Summary and conclusions

A prospective randomised trial was carried out on 263 patients admitted for appendicectomy. In those patients with normal or inflamed appendix only, wound sepsis occurred in five (5%) of the 96 patients receiving metronidazole compared with seven (7%) of the 91 controls. In patients with gangrenous or perforated appendices, however, 15 of the 32 patients (47%) receiving ampicillin and five (16%) of 31 patients receiving metronidazole developed a wound infection ($p < 0.025$).

Therapeutic courses of metronidazole significantly reduced wound sepsis rate in those with gangrenous or perforated appendices. Together with another antibiotic it should form part of the management of such patients, but antibiotics are unlikely to reduce further the low rate of wound infection in patients with normal or inflamed appendices.

Introduction

Wound infection is the commonest complication after appendicectomy, occurring in as many as 30% of patients.[1] Various methods have been used to minimise the incidence of wound infection. Topical application of ampicillin powder into the wound reduced the incidence of wound sepsis,[2,3] while prophylactic systemic ampicillin or tetracycline, though having no effect on the incidence of wound sepsis, reduced intraperitoneal sepsis.[4] Other workers,[5-7] however, have shown a reduction in postoperative wound infection after short-term prophylaxis with parenteral antibiotics. Leigh *et al*[8] found *Bacteroides fragilis* to be the commonest organism in infected appendicectomy wounds, and a recent survey[9] showed anaerobic organisms more often than aerobes. Willis *et al* reported that anaerobic sepsis was abolished by metronidazole.[10] Povidone-iodine sprayed into the wound reduces wound sepsis after abdominal surgery.[11]

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This study was undertaken to formulate a plan for the rational use of antibiotics, so that effective treatment could be given to those at high risk of developing a septic complication.

Patients and methods

All patients admitted to Northwick Park Hospital from June 1977 to November 1978 with a clinical diagnosis of acute appendicitis were entered into the trial. Two hundred and sixty-three consecutive patients were studied but 13 were withdrawn because of failure to adhere to the protocol. A standard form was completed after each operation noting the age and sex of the patient, duration of symptoms, the depth of fat, the presence or absence of free fluid or pus on entering the peritoneum, and the position of the appendix and its macroscopic appearance—that is, normal, inflamed, gangrenous, or perforated. Culture swabs of the paracaecal area and appendix stumps were taken and put into Cary-Blair transport medium.

After operation the wound was inspected daily and classified into four grades: grade 0 was a clean, well-healed wound, grade I a wound with a sterile serous or bloodstained discharge, grade II a wound with a superficial stitch abscess, and grade III a wound discharging pus.

Swabs were taken for culture and sensitivity from all wounds classified as grades I-III. Two weeks after operation each patient was questioned in the outpatient clinic for evidence of wound infection or discharge and the standard form completed.

Treatment—Patients were randomised to receive metronidazole or either ampicillin or no antibiotics depending on the state of the appendix. Each patient received povidone-iodine sprayed into the operation wound as described by Gilmore and Sanderson.[11] Two sets of patients were compared as follows. Group 1 comprised those with a normal or inflamed appendix; one subgroup received no systemic antibacterial agent, while the other subgroup was given a 1-g metronidazole suppository about one hour before operation, followed by the same dose 8 and 16 hours after appendicectomy. Patients aged under 12 years received 500-mg suppositories. Group 2 comprised patients with a gangrenous or perforated appendix, or both. One subgroup received 500 mg of intramuscular ampicillin at operation when the condition of the appendix was diagnosed. This dose was repeated every six hours after operation until the patient could take the same dose orally; treatment was continued for five days. The other subgroup received a 1-g metronidazole suppository about one hour before operation and every eight hours thereafter until the patient could take the drug orally, when the dose was changed to 200 mg eight-hourly; treatment was continued for five days.

Transport of specimens—Swabs of purulent material were

transported from operating theatres deep in a tube of Cary and Blair transport medium.[12] Swabs and samples of pus were examined by Gram film to ascertain the number and proportion of morphological forms present and cultured aerobically and anaerobically.[13] Isolates were identified conventionally[13 14] and antibiotic sensitivities obtained by the comparative method using discs.

Results

One hundred and eighty-seven of the 250 patients (75%) presented with a normal or an inflamed appendix. The remaining 63 (25%) presented with a gangrenous or perforated appendix. Twenty-five patients (10%) had a normal appendix removed.

Group 1—Ninety-six patients received metronidazole perioperatively and 91 received no antibiotics. There was no difference in the mean age and range at presentation and the male:female distribution was similar in the two groups (table I), as was the distribution of children aged under 12 years. There was no difference in the duration of symptoms at presentation, depth of subcutaneous fat, or position of appendix. Seven of the 91 controls (7·7%) and five of the 96 treated patients (5·2%) developed postoperative wound infections. Of the seven controls one had a grade I wound infection, one a grade II infection, and two a grade III infection plus pelvic abscesses, which spontaneously discharged through the rectum. In the treated group one patient had a grade I infection and four a grade III infection without intraperitoneal complications.

Group 2—Thirty-two patients received ampicillin and 31 patients metronidazole for five days. The mean ages and ranges were similar in the two groups, as was the male:female ratio (table I). There were

TABLE I—*Distribution of patients between subgroups in groups 1 and 2*

	Group 1		Group 2	
	Control	Treated	Ampicillin	Metronidazole
No of patients	91	96	32	31
Mean age (and range) in years	20·8 (4-71)	20·9 (7-87)	24·4 (8-62)	27·2 (6-76)
Men	49	56	15	18
Women	42	40	17	13
Under 12 years	23	25	6	6

six children under the age of 12 in each of the subgroups. There was no difference between the subgroups in the duration of symptoms, depth of subcutaneous fat, or position of the appendix. There were twice as many perforated appendices in those receiving ampicillin (16:8). On the other hand, there were more patients with gangrenous appendices in the metronidazole group (23:16). Fifteen of the 32 patients receiving ampicillin and five of the 31 receiving metronidazole developed a postoperative wound infection (table II). One patient in the ampicillin subgroup developed a pelvic abscess and one in the metronidazole subgroup a grade II infection. The other wound infections in both groups were grade III. Metronidazole significantly reduced the incidence of postoperative wound infection ($\chi^2 = 5{\cdot}52$; $p < 0{\cdot}025$). Among patients with gangrenous appendices one patient in the metronidazole subgroup developed a wound infection compared with seven in the ampicillin subgroup, and this difference was highly significant ($\chi^2 = 7{\cdot}40$; $p < 0{\cdot}01$; table II). The incidence of wound infection in patients with perforated appendices was 50% in each of the two subgroups.

TABLE II—*Wound infection rates in all patients in group 2 and in subgroup with gangrenous appendices*

	All group 2		Patients with gangrenous appendix	
	Ampicillin	Metronidazole	Ampicillin	Metronidazole
Infected	15 (46·9%)	5 (16·1%)*	7 (43·7%)	1 (4·5%)†
Not infected	17	26	9	22
Total	32	31	16	23

*$\chi^2 = 5{\cdot}52$; $p < 0{\cdot}025$.
†$\chi^2 = 7{\cdot}40$; $p < 0{\cdot}01$

Organisms were cultured from one or both peroperative swabs in 80% of the patients in group 2 but only 10% of those in group 1. Most yielded *Bacteroides fragilis* and *Escherichia coli*; 82% of the *E coli* isolated were sensitive to ampicillin in vitro. In all cases the bacteria isolated from infected wounds were the same as those obtained at the time of surgery. Despite metronidazole, one patient from group 1 and two from group 2 had *B fragilis* in their wounds.

Discussion

The use of prophylactic antibiotics in all cases of acute appendicitis is of questionable value. As in other series,[2] we found a low rate of wound infection (6%) in group 1 patients (75% of the series), which was probably accounted for by the low yield of organisms from the peritoneal cavity (10% positive cultures). Perioperative use of metronidazole did not influence the wound infection rate, and, although two controls developed pelvic abscesses, it is premature to conclude that metronidazole played a significant part in eliminating this problem in the treated group.

Patients with gangrenous or perforated appendices continue to pose a different and serious problem. Such patients are open to infection, as some 80% of ours had organisms isolated from the peritoneal cavity. Although 82% of *E coli* cultured from these patients were sensitive to ampicillin in vitro, the wound infection rate in those receiving the drug was high (48%). This indicates the important role of anaerobic organisms, which are often resistant to ampicillin. Instillation of ampicillin powder into the wound after appendicectomy significantly reduces wound infection.[2 3] Systemic use of the drug, as in our study, failed to provide a similar beneficial effect. Nevertheless, metronidazole reduced the overall rate of wound infection to 16%, though in those patients with a perforation, and widespread intraperitoneal contamination, the wound infection rate was 50% despite its use.

Based on the results of our present study and a review of published studies we suggest that the following policy should be adopted in managing acute appendicitis. If a normal or only inflamed appendix is encountered, then appendicectomy should not be followed by any antibiotic treatment. If, however, the appendix is gangrenous or perforated then metronidazole 500 mg intravenously should be given during the operation together with cephazolin 1 g intramuscularly or an aminoglycoside, with appropriate doses for children. After operation the drugs should be administered in these therapeutic doses every eight hours for five days. Metronidazole may be given by suppository until the patient can take it by mouth.

We hope that treatment with therapeutic courses of drugs effective against both aerobes and anaerobes of the minority of patients who have major infections will further reduce septic complications after appendicectomy.

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References

1 Anonymous. *Lancet* 1971;ii:195.
2 Bates T, Down RHL, Houghton, MCV, Lloyd GJ. Topical ampicillin in the prevention of wound infection after appendicectomy. *Br J Surg* 1974;**61**:489-92.
3 Andersen B, Bendtsen A, Holbraad L, Schantz A. Wound infections after appendicectomy. 1. A controlled trial on the prophylactic efficacy of topical ampicillin in non-perforative appendicitis. 2. A controlled trial on the prophylactic efficacy of delayed primary suture and topical ampicillin in perforated appendicitis. *Acta Chir Scand* 1972;**138**: 531-6.
4 Magarey CJ, Chant ADB, Rickford CRK, Magarey JR. Peritoneal drainage and systemic antibiotics after appendicectomy. *Lancet* 1971; ii:179-82.
5 Polk HC Jr, Lopez-Mayor JF. Postoperative wound infection: a prospective study of determinant factors and prevention. *Surgery* 1969;**66**:97-103.

[6] Evans C, Pollock AV. The reduction of surgical wound infection by prophylactic parenteral cephaloridine. A controlled clinical trial. *Br J Surg* 1973;**60**:434-7.
[7] Stokes EJ, Waterworth PM, Franks V, Watson B, Clark CG. Short-term routine antibiotic prophylaxis in surgery. *Br J Surg* 1974;**61**:739-42.
[8] Leigh DA, Simmons K, Norman E. Bacterial flora of the appendix fossa in appendicitis and postoperative wound infection. *J Clin Pathol* 1974;**27**:997-1000.
[9] Sanderson PJ, Wren MWD, Baldwin AWF. Anaerobic organisms in postoperative wounds. *J Clin Pathol* 1979;**32**:143-7.
[10] Willis AT, Ferguson IR, Jones PH, *et al.* Metronidazole in prevention and treatment of bacteroides infections after appendicectomy. *Br Med J* 1976;i:318-21.
[11] Gilmore OJA, Sanderson PJ. Prophylactic intraperitoneal povidone-iodine in abdominal surgery. *Br J Surg* 1975;**62**:792-9.
[12] Cary SG, and Blair EB. New transport medium for shipment of clinical specimens. I. Fecal specimens. *J Bacteriol* 1964;**88**:96-8.
[13] Wren MWD, Baldwin, AWF, Eldon CP, Sanderson PJ. The anaerobic culture of clinical specimens: a 14-month study. *J Med Microbiol* 1976;**10**:49-61.
[14] Cowan ST, ed. *Cowan and Steel's manual for the identification of medical bacteria.* 2nd ed. London: Cambridge University Press, 1974.

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Role of pituitary hormones in regulating renal vitamin D metabolism in man

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Summary and conclusions

Studies in animals and tissue culture have shown the importance of prolactin and growth hormone in regulating renal 1α-hydroxylase activity and plasma concentrations of 1,25-dihydroxycholecalciferol (1,25(OH)$_2$D$_3$). Evidence for a similar role for these hormones in man was sought by using a radioreceptor assay to measure plasma 1,25(OH)$_2$D$_3$ concentrations in 20 normal subjects, 12 patients receiving dialysis, 11 patients with primary hyperparathyroidism, 10 pregnant women, seven women with prolactinoma, and 14 patients with acromegaly. Circulating 1,25(OH)$_2$D$_3$ concentrations were appreciably raised in the patients with primary hyperparathyroidism and the pregnant women ($P < 0.001$), slightly but significantly increased in the patients with prolactinoma ($P < 0.05$), and greatly raised in those with acromegaly ($P < 0.001$).

These results suggest that prolactin and growth hormone are important regulators of renal vitamin D metabolism in the physiological conditions of pregnancy, lactation, and growth in man.

Introduction

Renal regulation of vitamin D metabolism has been controversial, but the concept of parathyroid hormone as the only important regulatory factor is now clearly completely untenable.[1] Considerable evidence indicates that the increased calcium demands made during physiological conditions of calcium stress, such as pregnancy, lactation, and growth, are met by increased production of 1,25-dihydroxycholecalciferol (1,25(OH)$_2$D$_3$).[2] The recent findings that prolactin[3] and growth hormone[4] stimulate the production of 1,25(OH)$_2$D$_3$ in experimental animals indicate that these pituitary hormones may be important regulators of renal vitamin D metabolism in natural (as opposed to experimental) calcium stresses. We present here the results of studies of circulating 1,25(OH)$_2$D$_3$ concentrations, which strongly suggest that these hormones fulfil the same role in man as in experimental animals.

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Subjects and methods

We studied the following groups of subjects: 20 normal subjects (11 men, nine women) aged 19-48 (mean 29·4); 12 patients receiving dialysis (nine men, three women) aged 21-25 (mean 23·8); 10 healthy women at 33-34 weeks of pregnancy, aged 23-39 (mean 26·9); 11 patients with primary hyperparathyroidism (three men, eight women) aged 29-72 (mean 49·8); 14 patients with acromegaly (seven men, seven women) aged 36-61 (mean 49·9); and seven women with prolactinomas, aged 18-47 (mean 29·3). Seven of the 14 patients with acromegaly had received treatment, but all had raised concentrations of growth hormone at the time of the study. Two of the women with acromegaly were postmenopausal as shown by stimulation with luteinising hormone-releasing hormone, but the other women with acromegaly or prolactinoma had normal gonadotrophin response. Stimulation with thyrotrophin-releasing hormone was performed in 10 of the patients with acromegaly and all those with prolactinoma. All patients were euthyroid, although the response of thyroid-stimulating hormone was depressed in the seven who had received treatment for acromegaly. All patients were taking their normal diet. None were taking vitamin D preparations or had evidence of vitamin D deficiency.

Morning samples of plasma were stored at −20°C until assay. Our assay for plasma 1,25(OH)$_2$D$_3$ concentrations was developed from that of Brumbaugh *et al*[5] but entailed using an intestinal receptor preparation and Sephadex column chromatography[6] and high-pressure liquid chromatography modified from the method of Matthews *et al.*[7] The precision of the method is ±4 pg/ml.

The results in each group were compared with normal values by means of a two-sample *t* test.

Results

The figure shows the results in the different groups of subjects. The mean ± SE of mean plasma 1,25(OH)$_2$D$_3$ concentration in normal subjects was 29·4±1·9 ng/l; in patients with chronic renal failure receiving dialysis < 10 ng/l; in patients with primary hyperparathyroidism 55·0±5·5 ng/l ($P < 0.001$); in pregnant women 87·7±11·2 ng/l ($P < 0.001$); in patients with prolactinomas 40·4±3·25 ng/l ($P < 0.05$); and in patients with acromegaly 47·7±4·6 ng/l ($P < 0.001$).

Thus the 1,25(OH)$_2$D$_3$ concentration was altered in primary hyperparathyroidism, prolactinoma, and acromegaly and in pregnancy. The ranges in normal subjects and patients with chronic renal failure were similar to those reported.