Metronidazole in the Prophylaxis and Treatment of Anaerobic Infection

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SUMMARY

The influence of prophylactic metronidazole on vaginal carriage rates of anaerobes and the development of postoperative anaerobic infection was studied in 104 women who underwent abdominal hysterectomy. Metronidazole prophylaxis in 54 patients led to a decrease in the anaerobe vaginal carriage rate from 65% pre-operatively to 17% and 28% on the 3rd and 7th postoperative days respectively. In the control group (50 patients) no significant decrease in anaerobe yield was noted, corresponding percentages being 72%, 64%, and 74%. Postoperative infection occurred in 36 patients (28 controls; 8 on prophylactic metronidazole). Wound swabs from all 8 patients in the latter group yielded aerobes, and in 1 patient mixed infection (aerobes/anaerobes) occurred. In 7 of these patients (including the patient with mixed infection), the infection resolved spontaneously, while the 8th patient responded to therapy with metronidazole, kanamycin and ampicillin. In the control patients, 21 cases of postoperative wound infection and 4 of vault infection were seen; wound swabs from patients in the former group yielded aerobes in only 6 cases, and mixed growth of aerobes/anaerobes in 10 cases. Postoperative wound/vault infections in control patients cleared spontaneously in 18 cases and responded to imidazole therapy, with or without ampicillin and kanamycin, in 7 cases.

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Anaerobes have been strongly implicated in the pathogenesis of postoperative abdominal infections.[1-4] It has been shown that the prophylactic administration of metronidazole decreases the incidence of such infections, especially after colorectal or gynaecological surgery.[5-7]

In this report the effect is described of prophylactic oral and intravenous metronidazole on the anaerobe vaginal carriage rate and development of postoperative anaerobic infection in 104 patients (54 with metronidazole prophylaxis, 50 controls) who underwent abdominal hysterectomy. The effect of metronidazole therapy on postoperative anaerobic infections was also studied in these patients.

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PATIENTS AND METHODS

Patients

Women who were to undergo elective abdominal hysterectomy and who had not taken any antimicrobial preparation in the 2 weeks before surgery were included in the trial. Patients who showed any signs of significant haematological, renal, hepatic or cardiac disease, a history of severe upper gastro-intestinal disturbance, or peripheral sensory neuropathy were excluded from the trial.

Drug Administration

A double-blind trial was run in which patients were randomly allocated to either the metronidazole or the placebo group. Patients were given 2 g on admission, 24 - 48 hours before operation, the drug course being interrupted during the period of pre-operative starvation. Postoperatively 200 mg was given 3 times a day for 7 days. Prophylactic therapy was in the oral form except immediately after operation, when the drug was administered intravenously.

Patients were carefully observed for signs and symptoms of infection during a 6-day postoperative period, after which time most patients were sent home to convalesce. They were told to return after 14 days for a follow-up examination, but to return earlier if signs or symptoms of infection developed during the period of convalescence.

Grade I and II postoperative infections[8] were usually treated with 'watchful expectancy'. In more severe cases of sepsis,[8] antimicrobial therapy consisted of oral metronidazole (200 mg 3 times daily) initially, with or without drainage for the first 36 hours; if no clinical response was seen after this time therapy with appropriate antiaerobic agents was instituted, pending results of bacteriological culture. Criteria of infection included: high, irregular fever (2 or more temperature readings of $\geqslant 38°C$ during the postoperative period, with temperatures taken 4-hourly), wound discharge/abscess, pelvic inflammatory disease, septicaemia, urinary tract infection, or pneumonitis. Wound infections were graded according to the method of Gibbs and co-workers.[8]

Bacteriology

High vaginal swabs were taken pre-operatively (before commencement of antimicrobial therapy) and on the 3rd and 7th postoperative days. Swabs reached the laboratory

within 20 minutes and were cultured aerobically and anaerobically with methods designed to optimalize bacterial yields.[9-11] Semiquantitative bacterial counts from vaginal swabs were done according to the method of Willis *et al.*,[5] and bacteria were identified by standard methods.[9-11] Blood was cultured[13] pre-operatively and on the 3rd post-operative day. In cases of wound infection, pus was aspirated into glass syringes or gassed-out tubes, transported to the laboratory within 5 - 10 minutes, and plated.[11] Other bacteriological specimens were examined when indicated.

RESULTS

The influence of prophylactic metronidazole therapy on anaerobe vaginal carriage rates is presented in Table I. By metronidazole administration the percentage of anaerobes was decreased from 65% pre-operatively to 17% ($P<0,001$) and 28% ($P<0,001$) on the 3rd and 7th postoperative days respectively. In the control group, pre- and postoperative vaginal anaerobe yields did not differ significantly. Pre-operative anaerobic growth was usually ± or + in both patient groups.[5] In the metronidazole group, postoperative anaerobic growth was usually ± or +, while control patients usually yielded ++ or +++ growth.[5]

TABLE I. VAGINAL CARRIAGE RATE OF ANAEROBES IN GYNAECOLOGICAL PATIENTS

		Isolation rates of anaerobes from high vaginal swabs		
			Post-operative	
Group	Number of patients	Pre-operative	Day 3	Day 7
Metronidazole	**54**	**35**	**9**	**15**
Placebo	**50**	**36**	**32**	**37**

The pattern of anaerobes isolated from the 104 patients can be seen in Table II. *Bacteroides melaninogenicus*, the most common anaerobe cultured, was isolated from 106 specimens, other *Bacteroides* spp. (including *B. fragilis*) from 96, fusobacteria from 8, and anaerobic/micro-aerophilic cocci from 53. Miscellaneous Gram-positive anaerobic rods were isolated from 33 specimens. Vaginal aerobes comprised a spectrum of the usual aerobic flora in that site.

During their period of hospitalization and subsequent convalescence, 8 patients who had received prophylactic metronidazole therapy developed infection; wound swabs from all 8 yielded a variety of aerobes, but only in patient 1 (Table III) were aerobes and anaerobes cultured together. In 7 of these 8 patients (including the patient with mixed aerobic/anaerobic infection) sepsis resolved spontaneously; the 8th patient (clinically but not bacteriologically proven vault infection) responded to metronidazole with kanamycin and ampicillin.

In 28 of the control patients postoperative infection occurred, comprising wound infection (21 cases), vault infection (4 cases), urinary tract infection (2 cases) and chest infection (1 case). Wound swabs from patients with postoperative wound infection yielded aerobes in only 6 cases, mixed cultures of aerobes/anaerobes in 10 cases, and no growth in 1 case; in 4 cases absence of pus precluded bacteriological investigation. Among patients with postoperative wound infections from whose infection sites no anaerobes were isolated, 8 infections resolved spontaneously, 1 responded to metronidazole alone, and 2 responded to a combination of metronidazole, ampicillin, and kanamycin. Details of postoperative anaerobic wound infections are presented in Table III (patients 2 - 11). Therapy with metronidazole, with or without ampicillin and kanamycin, was effective in 2 patients, while in 8 patients infections cleared spontaneously.

TABLE II. PATTERN OF ANAEROBES MOST COMMONLY ISOLATED FROM VAGINAL SWABS FROM 104 PATIENTS

	Number
Bacteroides melaninogenicus **only**	**27**
B. melaninogenicus + *Bacteroides* **spp.***	**34**
B. melaninogenicus + **anaerobic cocci†**	**6**
B. melaninogenicus + *Bacteroides* **spp.*** + **anaerobic cocci†**	**17**
B. melaninogenicus + *Bacteroides* **spp.*** + **anaerobic cocci†** + **anaerobic Gram-positive rods**	**3**
Bacteroides **spp.* only**	**21**
Bacteroides **spp.*** + **anaerobic cocci†**	**8**
Anaerobic cocci† only	**13**
Anaerobic Gram-positive rods only *(Eubacterium, Propionibacterium, Actinomyces, Lactobacillus, Clostridium)*	**9**

* Includes *B. fragilis*.
† Includes micro-aerophilic cocci.

Vault infections either resolved spontaneously (2 cases) or responded to imidazole therapy (2 cases). The 2 patients with urinary tract infection responded to therapy with appropriate urinary antiseptics, while the chest infection in 1 patient cleared with sulphonamide therapy.

No cases of severe postoperative pelvic inflammatory disease or septicaemia were seen.

DISCUSSION

This study confirms that prophylactic metronidazole therapy effectively lowers the anaerobe vaginal carrier rate during the immediate postoperative period when anaerobic infections are prone to develop.[5] In addition, postoperative wound infections from which anaerobes could be cultured occurred in 1 patient under metronidazole prophylaxis, compared with 10 in the control group.

The high rate of spontaneous resolution of post-operative wound and vault infections precludes firm decisions on the therapeutic role of metronidazole in these cases. Response of some patients to imidazole therapy in the absence of demonstrable anaerobic growth from infection sites may reflect failure to culture these organisms owing to inadequate culture techniques.

TABLE III. FEATURES OF PATIENTS WITH POSTOPERATIVE ANAEROBIC INFECTIONS

Group	Patient	Nature of infection	Post-operative day on which infection developed	Pyrexia	Bacteria isolated	Course and treatment
M	1	Grade II wound cellulitis	2	38°C	*B. fragilis* ++ *S. aureus* +++ *Strep. faecalis* + *E. coli* +++	Resolved spontaneously
P	2	Grade III wound cellulitis	2	38°C	*B. melaninogenicus* ++ *Peptostreptococcus anaerobius* ++ *Peptococcus asaccharolyticus* ++ *Gaffkya anaerobia* + *S. aureus* ± *Strep. faecalis* +++	Resolved spontaneously
P	3	Grade II wound cellulitis	2	38,4°C	*B. melaninogenicus* +++ *Proteus* +++ *Klebsiella* + *S. epidermidis* ++ Diphtheroids +	Resolved spontaneously
P	4	Grade II wound cellulitis	3	38°C	*P. asaccharolyticus* + *S. aureus* +	Resolved spontaneously
P	5	Wound cellulitis + infected drain site	3	38°C	*B. capillosus* + *S. aureus* +	Resolved spontaneously
P	6	Infected drain site	3	Nil	*B. capillosus* + *P. anaerobius* ++ *B. bivius* + *B. melaninogenicus* + *S. epidermidis* ±	Resolved spontaneously
P	7	Grade II wound cellulitis	3	38,8°C	*P. magnus* ++ *P. asaccharolyticus* ++ *Gaffkya* ++ *S. aureus* +++ Diphtheroids + *S. epidermidis* ±	Resolved spontaneously
P	8	Grade II wound cellulitis	3	39°C	*Fusobacterium* ++ *B. bivius* ± Unidentified anaerobic Gram-positive rod +++ Diphtheroids +	Resolved spontaneously
P	9	Grade II wound cellulitis	9	38°C	*B. melaninogenicus* ++ *B. bivius* ++ *B. capillosus* + *B. ruminicola* ++ *Klebsiella* +++	Resolved spontaneously
P	10	Wound cellulitis + infected drain site	3	39°C	*B. capillosus* +++ *B. pneumosintes* + *E. lentum* +++ *Fusobacterium* + *S. aureus* +++ *Strep. faecalis* ±	Responded to metronidazole + ampicillin + kanamycin
P	11	Grade III wound cellulitis	2	39°C	*B. melaninogenicus* +++ Lactobacilli +++ Diphtheroids + β-haemolytic streptococci (not A) + *S. aureus* ±	Responded to metronidazole

M = metronidazole prophylaxis; P = placebo.

The overall vaginal anaerobe carriage rate in our study is higher than that described by Willis and co-workers.[5] High vaginal yields of *B. melaninogenicus* subspecies have been emphasized by the latter workers.[5]

We have confirmed the efficacy of metronidazole in the prophylaxis and possibly in the treatment of anaerobic infections associated with abdominal hysterectomy. In the light of evidence at present available,[5-7] it seems questionable whether imidazole prophylaxis should be withheld in patients submitted for gynaecological or colorectal surgery.

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Computed Axial Tomography in Intracranial Aspergillosis

A Report of 2 Cases

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SUMMARY

The findings in 2 patients with intracerebral aspergillosis who underwent computed axial tomography (CAT) are presented for the first time. CAT allows rapid and accurate localization and delineation of the lesion, although the features are nonspecific.

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Cerebral aspergillosis is an uncommon form of intracranial infection. However, in patients with an altered immune response due to primary disease or drugs such as steroids, immunosuppressants or antibiotics, or due to malnutrition, invasive fungal diseases are becoming more common. The majority of cases have been reported since 1950.[1]

Two of our patients with cerebral aspergillosis recently underwent computed axial tomography (CAT) scans.

The results of CAT scans of patients with this condition have not yet been documented, and we should like to report our findings.

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CASE REPORTS

Patient 1

A 24-year-old man was involved in a traffic accident in which he sustained a fracture through the base of the skull as well as a fracture of the right parietal bone. Later, he developed otorrhoea in his right ear. In the ward he developed a secondary meningitis, and a *Klebsiella* organism was cultured. The results of a lumbar