Ceftizoxime Alone or in Combination with Metronidazole as Prophylaxis in Elective Colorectal Surgery

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Summary

In a prospective double-blind randomised trial, 200 patients undergoing elective colorectal surgery received ceftizoxime 2g with either placebo or a single dose of metronidazole 500mg followed by a single dose of ceftizoxime 2g two hours later in both treatment groups. There was no difference in the rate of wound infection (9 of 85 vs 7 of 89), distal site infection (16 of 85 vs 18 of 89) or noninfective complications between the 2 treatment groups. Duration of hospital stay was also similar for the 2 groups (mean 11.3 vs 12.3 days). The low incidence of wound infection in this study is particularly impressive, as 13 of 16 wound infections were delayed, minor superficial discharges occurring after the patient left hospital. These results suggest that intravenous ceftizoxime offers effective prophylaxis in colorectal surgery and may be used without metronidazole.

The use of antibacterial agents for prophylaxis against wound infection is well established in patients undergoing operations on the gastrointestinal tract, particularly those involving the large bowel, which are associated with a high risk of infection (Eykyn et al. 1979). A wide range of antibacterial regimens are currently used for surgical prophylaxis (Fry 1988). The ideal prophylactic regimen for large bowel surgery should provide protection against both aerobic and anaerobic bacteria, with a consequent low incidence of wound infection; it should also be well tolerated, convenient to administer and cost-effective. A single agent that is as effective as commonly used combined agent regimens would be particularly advantageous.

Ceftizoxime is a third generation cephalosporin with a broad spectrum of activity, including activity against Bacteroides spp., and a long half-life of between 1.7 and 1.9 hours (Solomkin 1988).

This study assessed the efficacy of ceftizoxime alone and in combination with metronidazole in the prophylaxis of infections following elective colorectal surgery.

1. Patients and Methods

Eligible patients were at least 16 years of age and had been admitted to the Queen Elizabeth Hospital or General Hospital, Birmingham, for elective colorectal surgery. Patients were not included if they had a history of allergy to penicillins or cephalosporins, had received antibiotics within 48 hours of surgery, had evidence of existing infection before, or at the time of, the operation, or were undergoing surgery for inflammatory bowel disease. Patients received mechanical bowel preparation only. Any patients who failed to complete the specified prophylactic regimen, or who were given additional antibiotics within 48 hours of surgery, were excluded from analysis.
The study was of prospective, randomised and double-blind design. At study entry, demographic information, reason for surgery, clinical history and examination findings were recorded, and written informed consent was obtained. Patients were randomised to receive either ceftizoxime 2g + metronidazole 500mg or ceftizoxime 2g + placebo (normal saline 100ml), by intravenous infusion at induction of anaesthesia. Both groups received a further 2g of ceftizoxime 2 hours later. A computer-generated randomisation list was provided by the pharmacy at the Queen Elizabeth Hospital, where the trial drugs were dispensed in identical packages, identified only by their randomisation number. Both the surgeon and the patient were unaware of which regimen was given.

The surgical procedure and duration of surgery were recorded. Patients were observed for evidence of local or systemic adverse reactions or postoperative complications. Surgical wounds were examined and patients were assessed postoperatively on days 3, 7 and 10, and again after 4 to 6 weeks. Patients who died without developing a wound infection before completion of follow-up were excluded from analysis of wound infection rates. A wound was considered infected if it discharged pus. Infection was classified as minor where there was superficial pus in the incision, and major if there was wound dehiscence, or infection was associated with intra-abdominal or pelvic abscess and/or systemic disturbance. Swabs were taken from patients whose wounds drained pus, and were cultured aerobically and anaerobically. Identification of any organism cultured and testing for sensitivity to the trial drugs were performed whenever possible.

Details of length of hospital stay, distal site infections (i.e. urinary tract, chest, pyrexia of unknown origin) and noninfective complications were also recorded.

It was considered that the study required at least 160 patients, 80 in each group. This sample size was based on an assumed infection rate of 25% in the group receiving ceftizoxime + placebo to have an 80% chance of obtaining a statistically significant result (p = 0.05), 80 patients per group would be required if the true difference between the groups was 20%. Results were analysed using a $\chi^2$ test. On completion of the study, all clinical data sheets were sent to Parexel International Ltd for independent analysis. Written agreement to the study protocol was obtained from the Birmingham Hospitals Ethical Committee.

### Results

During the 2-year period ending in February 1991, 200 patients were recruited into the study. Of these, 8 were excluded from analysis (2 ceftizoxime + metronidazole, 6 ceftizoxime + placebo) because of death before completion of follow-up. None of these patients showed evidence of wound infection. A further 18 patients were excluded at the request of the operating surgeon, who considered that a prolonged course of antibiotics was necessary because of technical difficulties (n = 10) or severe contamination (n = 8). Demographic features of the 200 patients entered into the study are shown in Table I. The 2 treatment groups were similar with regard to age, sex and bodyweight. Table I also shows that similar surgical procedures were performed in each treatment group. Patients undergoing colonic resection included those with carcinoma of the colon and those undergoing colectomy for severe constipation or familial ade-

<table>
<thead>
<tr>
<th>Surgical Procedure</th>
<th>Ceftizoxime + metronidazole (n = 100)</th>
<th>Ceftizoxime + placebo (n = 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colonic resection</td>
<td>66</td>
<td>62</td>
</tr>
<tr>
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<td>11</td>
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<td>Pelvic floor repair</td>
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<td>25</td>
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<tr>
<td>Other</td>
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</tr>
</tbody>
</table>

Table I. Patient demographic data and surgical procedures in 200 patients undergoing elective colorectal surgery and randomised to receive either ceftizoxime + metronidazole or ceftizoxime + placebo as surgical prophylaxis