A Cost Effective Approach to Surgical Antibiotic Prophylaxis

Mara M. Pavan and Douglas L. Malyuk

ABSTRACT

Cefoxitin has been the prophylactic antibiotic of choice for appendectomy and colorectal surgery at this institution. Recent information suggests that cefazolin and metronidazole given as a single intravenous preparation could be a cost-effective alternative to cefoxitin or cefotetan for surgical antimicrobial prophylaxis of uncomplicated appendectomies.

This study was conducted to determine the efficacy, toxicity, and cost of the current antibiotic regimens used for prophylaxis of uncomplicated appendectomies, to evaluate the efficacy, toxicity and cost of the cefazolin plus metronidazole combination in uncomplicated appendectomies, and to facilitate a cooperative working relationship between the Departments of Pharmacy and General Surgery.

Although the numbers involved were small, this study suggests that the cefazolin/metronidazole combination is cost-effective. It is suggested that research is warranted in evaluating combinations such as this as cost-effective alternatives to current therapy.

Key Words: *appendectomy, cefazolin, cefotetan, cefoxitin, cost-effective, metronidazole, prophylaxis*

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RÉSUMÉ

À ce jour, dans notre établissement, la céfoxitine est l'antibiotique prophylactique de choix pour l'appendicectomie et la chirurgie colo-rectale. Toutefois, selon des données récentes, une combinaison de céfazoline et de métronidazole administrée sous forme de préparation intraveineuse constituerait peut-être une alternative rentable à la céfoxitine ou au céfotétan dans les cas d'appendicectomie sans complications.

L'étude vise à déterminer l'efficacité, la toxicité et le coût des antibiothérapies employées actuellement pour la prophylaxie des appendicectomies sans complications, à évaluer l'efficacité, la toxicité et le coût d'une combinaison de céfazoline et de métronidazole lors de ces opérations et à faciliter la collaboration entre les services de pharmacie et de chirurgie générale.

Quoique portant sur un petit nombre de cas, les résultats laissent entendre que la combinaison de céfazoline et de métronidazole est rentable. Il serait souhaitable de poursuivre les travaux pour évaluer d'autres combinaisons de ce type comme alternatives rentables des traitements actuels.

Mots clés: *appendicectomie, céfazoline, céfotétan, céfoxitine, métronidazole, prophylaxie, rentable*

Mara M. Pavan, B.Sc.Pharm., at the time of this investigation was a Pharmacy Resident, Royal Columbian Hospital, New Westminster, British Columbia. Mara is currently a Pharmacist, St. Paul's Hospital, Vancouver, British Columbia.

Douglas L. Malyuk, Pharm.D., is the Assistant Director Pharmacy Services (Clinical), Royal Columbian Hospital.

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Address correspondence to: Douglas L. Malyuk, Pharm.D., Pharmacy Department, Royal Columbian Hospital, 330 East Columbia Street, New Westminster, British Columbia V3L 3W7.

INTRODUCTION

Cefoxitin has been the prophylactic antibiotic of choice for appendectomy and colorectal surgery at this 600-bed tertiary care institution. Cefoxitin has activity against certain aerobic and anaerobic bacteria, particularly *Escherichia coli* and *Bacteroides fragilis* which are potential post surgical pathogens.[1,2] Renewed interest in multiple antibiotic regimens has resulted from the high costs associated with single agents such as cefoxitin and cefotetan. In particular, recent information suggests that cefazolin and metronidazole given as a single intravenous preparation could be an equally efficacious and cost-effective alternative to cefoxitin in surgical antimicrobial prophylaxis targeted against *E.coli* and *B. fragilis*.[3,4,5,6,7,8] The advantages of this combination can be summarized as follows:

1. Cefazolin is an effective agent against *E.coli.* Hospital microbiology data indicates that cefazolin has lower Minimum Inhibitory Concentrations (MICs) than cefoxitin and the sensitivity of *E.coli* to cefazolin has been maintained over the last five years.[9,10]
2. Metronidazole has 100% activ-

ity against *B.fragilis* and all subspecies compared to 70-80% activity for cefoxitin.[10,11]

3. The addition of cefazolin to a pre-mixed metronidazole minibag is physically and chemically stable for seven days when refrigerated at five degrees Celsius.[3,4,5]
4. Comparison of drug costs shows significant savings when substituting cefazolin plus metronidazole for cefoxitin. Acquisition costs from this institution indicate that one dose of cefoxitin 1g costs $13.00. One dose of cefazolin 1g plus metronidazole 500 mg costs $3.80.[12]
5. Trials using cefazolin plus metronidazole as antibiotic prophylaxis for appendectomies have shown the combination to be an efficacious alternative to the more traditional antibiotics.[6,7,8]

Uncomplicated appendectomies (i.e., no perforation, mass, abscess or peritonitis) were chosen to evaluate cefazolin plus metronidazole for the following reasons. First, several trials indicated the successful use of this combination in uncomplicated appendectomies.[6,7,8] A prospective study involving 400 patients compared placebo, metronidazole alone, metronidazole with cefazolin, and metronidazole with tobramycin in uncomplicated appendectomies. It found that metronidazole with cefazolin or tobramycin was the best regimen.[6] A follow-up study of 270 patients compared a single preoperative dose with that of three doses, and three day courses of metronidazole and cefazolin in uncomplicated appendectomies and found there was no difference in efficacy between the three groups.[7] Second, mortality, morbidity, and subsequent wound infections are rare with this type of surgery.[13] Prophylaxis is recommended in appendectomies because of the potential for bacterial contamination and complicated appendectomies cannot always be identified by clinical signs and symptoms prior to surgery.[1,2,7] Third, a preliminary report from the Department of Health Records indicated 60% of appendectomies performed yearly are uncomplicated (n=158); this would allow a reasonable number of patients for the study.

Therefore, the objectives of the study were:

1. To determine the efficacy, toxicity, and cost of current antibiotic regimens used for prophylaxis of uncomplicated appendectomies.
2. To evaluate the efficacy, toxicity, and cost-effectiveness of the cefazolin plus metronidazole combination in uncomplicated appendectomies.
3. To facilitate a cooperative working relationship between the Departments of Pharmacy and General Surgery.

METHODS

The initial step was to secure support for the cefazolin plus metronidazole combination from the hospital Infectious Disease (ID) consultant. The Department of General Surgery was then approached with a proposal to evaluate the use of cefazolin plus metronidazole in uncomplicated appendectomies. A liaison committee consisting of a surgeon, the ID consultant, a clinical pharmacist, and the pharmacy resident was formed to deal with the implementation of the study. Following liaison committee discussions, the following methodology was formulated.

Phase 1

Fifty randomly selected charts of patients who had uncomplicated appendectomies from October 1989 to October 1990 were retrospectively reviewed by the pharmacy resident. The charts were summarized using data collection forms. Each course of therapy was evaluated for choice of prophylactic antibiotics, length of therapy, occurrence and timing of wound infection, pathogens involved, adverse drug reactions with particular emphasis on pseudomembranous colitis, bleeding diathesis, changes in PT, PTT, platelets, and development of allergic reactions, and cost of antibiotic therapy.

The cost of antibiotic therapy is based on acquisition costs; it does not include intravenous (IV) mixing equipment or nursing administration costs.

Criteria for exclusion were patients less than 12 years of age, as it was felt that dosing in this age group should be based on weight; metronidazole is only available in the 500 mg dose of pre-mixed bags. Also excluded were patients who were pregnant or lactating, or patients who had significant hypersensitivity to penicillin or cephalosporin manifested by anaphylaxis, difficulty breathing, swelling or rash. As well, patients whose primary surgery was not appendectomy, and patients who were immunocompromised due to AIDS, chemotherapy, or steroids were excluded.

Wound infection was defined as either the discharge of pus whether pathogenic organisms were isolated or not, or the discharge of serous fluid from which pathogenic organisms were isolated. Early infection was defined as occurring during hospital stay. Late infection was defined as occurring up to three weeks after discharge from hospital.

The objective of this phase was

to serve as a baseline indicator of the current prophylactic management trends of uncomplicated appendectomies with emphasis on efficacy, toxicity and cost-effectiveness.

Phase 2

The collection period for this phase was March 18 to June 1, 1991. Exclusion criteria were those described in Phase 1. In addition, patients who were started on prophylactic antibiotics at another hospital prior to surgery were excluded because physicians at other institutions were not aware of the appendectomy protocol. Patients whose surgeon ordered protocol medications received cefazolin 1000 mg (SKF) admixed by the pharmacy department into a metronidazole 500 mg pre-mixed minibag (Abbott). This was to be administered as a single IV dosage form 30 minutes preoperatively. The one preoperative dose is based on Medical Letter recommendations.[1] If the appendectomy was uncomplicated, no postoperative antibiotics would be ordered. Where the appendectomy was complicated, the surgeon could order his antibiotic regimen of choice.

Postoperative late infection was evaluated using a follow-up questionnaire which was sent home with all patients who were included in the protocol group (Appendix A). This was to be returned to the hospital three weeks following discharge.

The charts of all patients having an appendectomy were reviewed as described in Phase 1.

It is important to note that although the Department of General Surgery agreed to support the study, it was not mandatory for all surgeons to order the preoperative dose of cefazolin plus metronidazole. Compliance with the study protocol would aid in determining the effectiveness of the initial liaisons with the Department of General Surgery.

RESULTS

Phase 1

Of the 50 charts reviewed, seven were ineligible because of allergy to penicillin or pregnancy. All patients who were ordered antibiotics prior to surgery were given either 1 or 2 grams of cefoxitin. In the majority of cases, this was ordered as one dose prior to surgery (70%). Following surgery, 79% of patients were subsequently ordered further antibiotic treatment (Table I). There was documentation of three cases (7%) of wound infection. One was an early infection; two were late infections. A fourth case had indications of a late infection, however, it failed to meet the criteria for wound infection.

There was no documented evidence of adverse drug reactions.

On average, each patient received a total amount of 5.9 grams of cefoxitin (average of four doses). At a cost of $13.00 per gram cefoxitin, the cost per person for antibiotics was approximately $77.00. Based on 158 uncomplicated appendectomies per year, the cost of antibiotic prophylaxis would be $12,166.00.

Phase 2

A total of 64 appendectomies were performed during this phase. Of those, 12 were ineligible for inclusion in the study. The remaining 52 patients were eligible to receive the cefazolin plus metronidazole combination prior to surgery. Of those, four were given no antibiotics, six were given cefotetan (at time of study, the hospital implemented an auto-substitution policy of cefotetan for cefoxitin), and 42 were given cefazolin plus metronidazole (Table II).

Following surgery, 29 patients were found to have uncomplicated appendectomies. Two patients had not received preoperative antibiotics and subsequently were not

Table I: Summary of Phase 1 Antibiotic Utilization in Uncomplicated Appendectomies

	Pre-op (n=43)	Post-op (n=43)
No antibiotics	10 (23%)	9 (21%)
Cefoxitin x1 dose	30 (70%)	5 (12%)
Cefoxitin >1 dose	3 (7%)	29 (67%)
Other antibiotics	0 (0%)	1 (2%)*
Total receiving antibiotics	33 (77%)	34 (79%)

*One patient received gentamicin + cefoxitin post-op.

Table II: Summary of Phase 2 Antibiotic Utilization in Appendectomies

	Pre-op (n=52)	Post-op uncomplicated (n=29)*	Post-op complicated (n=21)*
No antibiotics	4 (8%)	24 (83%)	0 (0%)
Cefazolin/metronidazole	42 (81%)	2 (7%)	9 (43%)
Cefotetan (for cefoxitin)	6 (11%)	3 (10%)	10 (48%)
Other	0 (0%)	0 (0%)	2 (9%)

*Two patients had diagnosis other than appendicitis post-op.

given postoperative antibiotics. Five other patients did not follow protocol. Twenty-two patients did not receive postoperative antibiotics after the initial preoperative dose of cefazolin plus metronidazole.

Of interest, in some cases the surgeons ordered cefazolin and metronidazole postoperatively for appendectomies considered complicated (Table II).

Of the 22 patients who followed protocol, one patient spiked a fever of 38.6 one day post-op. Although no blood or wound cultures were taken, the patient was ordered three doses of cefotetan and discharged on Day 3 with no real evidence of infection. No other patients showed evidence of early infections.

Twenty-one patients were sent follow-up letters to determine late infections. Six were lost to follow-up; the remaining 15 (71%) either returned the letter (12 patients) or were contacted by phone (3 patients). None showed evidence of late infection.

There was no evidence of adverse drug reactions noted in the charts.

The average antibiotic cost per patient was $13.55. This was based on the 29 uncomplicated appendectomies, therefore, it includes those patients who did not follow protocol. It also takes into account the cost for cefotetan at $16.35 per gram. Based on n=158, the total annual cost of uncomplicated appendectomies would be $2,141.00 (Table III).

The number of charts reviewed provided insufficient power to conduct statistical analysis of the results.

DISCUSSION

The objectives of this study were; first, to determine the current antibiotic regimens used for prophylaxis in uncomplicated appendectomies and to determine baseline efficacy, toxicity, and cost; second, to compare the efficacy, toxicity, and cost-effectiveness of cefazolin plus metronidazole for antimicrobial prophylaxis of uncomplicated appendectomies; and, third, to facilitate a cooperative working relationship between the Departments of General Surgery and Pharmacy. These three objectives have been achieved.

Phase 1 of the study identified the antimicrobial prophylaxis agent used in uncomplicated appendectomies was cefoxitin. Although current literature recommends preoperative prophylaxis only,[1] 79% of patients received postoperative doses of cefoxitin. There was a 7% incidence of wound infection in this population. This includes both early and late wound infections, however, this did not involve any follow-up monitoring with the patients. There was no evidence of adverse drug reactions such as pseudomembranous colitis, bleeding diathesis, changes in PT, PTT, platelets, or development of allergic reactions.

In Phase 2, the regimen appeared to be efficacious as there was no evidence of early wound infection in the uncomplicated cases which followed protocol. There was one case where a temperature increase prompted the start of postoperative antibiotics but there was no other evidence of infection.

Follow-up contact with patients to determine late wound infection at two to three weeks post-surgery revealed no evidence of subsequent infections. Fifteen patients either returned the follow-up questionnaire (80%) or were contacted by phone (20%) at least three weeks following discharge. The compliance rate of 71% was very good. The reason for the good response may be that the questionnaire was discussed with most of the patients prior to leaving the hospital. This method for determining late wound infections appears to be an effective mechanism for gathering such information.

As in Phase 1, there was no evidence of adverse drug reactions.

Major cost savings were realized with the implementation of the protocol. This was due to the decreased cost of the combination product. The cost of one gram of cefoxitin is $13.00 compared to $3.80 for one gram of cefazolin mixed into a pre-manufactured bag of 500 mg metronidazole.

Additional cost savings were due to decreased usage of antibiotics postoperatively. When one takes into account that only one preoperative dose was ordered compared to a previous average of four total doses, the decrease in cost becomes dramatic. For uncomplicated appendectomies alone, an extrapolated annual cost from the retrospective Phase 1 data of approximately $12,000.00 compares to a cost of approximately $2,100.00 from Phase 2 data. If all patients had been given one dose of cefazolin plus metronidazole the cost would be approximately $600.00.

Table III: Cost Comparison Summary

	Phase 1	Phase 2
Average cost per patient	$77.00	$13.55
Extrapolated annual cost of uncomplicated appendectomy	$12,166.00	$2,140.90

The difference between the latter two cost figures is significant when one considers that only six patients strayed from the protocol regimen.

Although not determined in this study, the decreased number of doses would also be expected to decrease costs in the areas of decreased minibags and other equipment, decreased pharmacy personnel time for IV mixing, and decreased nursing time in drug administration and monitoring. The actual cost saving will vary from institution to institution depending on the distribution system utilized.

The third objective, to facilitate a cooperative working relationship between the Departments of General Surgery and Pharmacy, has also been met. The degree of compliance with this voluntary protocol is one example of how the objective has been achieved. Preoperatively, the surgeons ordered the protocol combination 81% of the time. Following surgery, in those cases which were uncomplicated, the surgeons did not order postoperative antibiotics 83% of the time. It is of interest to note that cefazolin and metronidazole were ordered postoperatively in those cases which were deemed complicated although not part of the original protocol. As this was not protocol, the two antibiotics were not combined in the same minibag.

Subsequent to the completion of the study, the Department of Pharmacy has, with the support of the Department of General Surgery, provided a pharmacist as a consultant to the surgical area on a daily basis. Additionally, the concept of having a pharmacist involved with Drug Use Evaluation (DUE) activities was supported by the surgeons. This study will be used as a DUE report for the Departments of General Surgery and Pharmacy. Further cooperative efforts are planned to utilize the cefazolin/metronidazole combination in colo-rectal surgery and on other projects.

The following are other concerns or problems identified during the study. First, it is interesting to note that although the combination was always ordered to be given 30 minutes preoperatively, this never occurred. As appendectomies are not elective surgery, booking for the operating room (OR) is based on availability. This makes it difficult to schedule an infusion 30 minutes prior to surgery. Most infusions were started when the patient was called to the OR. A recent study has confirmed that the timing of antibiotic administration does affect the risk of surgical wound infection in actual clinical practise.[14] Achievement of adequate tissue concentrations at the time of surgery could be ensured by having the anesthetist start the infusion.

Second, in the situation where cefazolin and metronidazole were ordered postoperatively if the appendectomy was considered complicated, there was some confusion over the dosing frequencies. The present automatic dosing interval substitution policies at this institution caused problems in prescribing the combination (e.g., metronidazole q8h is changed to q12h). If the use of the cefazolin plus metronidazole combination is to be continued, these problems will need to be addressed.

Finally, at the same time this study was being completed, an automatic substitution of cefotetan for cefoxitin was implemented. On a gram for gram basis, cefotetan is more expensive than cefoxitin ($16.35/1g cefotetan vs $13.00/1g cefoxitin). Its cost saving is realized by a longer dosing interval. Nonetheless, the protocol regimen is more cost-effective.

Although the numbers involved in this study were small, the apparent success of this innovative combination is not surprising. In the pre-cefoxitin/cefotetan era, combination antibiotics were successfully used in the prophylaxis of appendectomy and other types of surgery. New information concerning the stability of mixing these antibiotics together removes the advantage offered by products such as cefoxitin and cefotetan. This study demonstrates further research is warranted in evaluating combinations such as cefazolin/metronidazole as cost-effective alternatives to current therapy.

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Appendix A: Questionnaire

Name: _____ Date: _____

1. Has your incision site remained dry and intact?

   Yes ____ No ____

2. If not, what does it look like? i.e., is there pus or fluid?

   _____

   _____

3. When did this occur?

   _____

4. Indicate by circling whether the incision site is:

   a) sore b) reddened c) warm d) not healing well

5. Have you had any episodes of fever?

   Yes ____ No ____ Could not say ____

6. Have you had any bouts of diarrhea?

   Yes ____ No ____

7. How long have they lasted? Have you visited your physician with regards to this problem?

   _____

   _____

8. Have you gone back to your family physician or surgeon regarding a problem with your incision?

   Yes ____ No ____

9. If so, what was the problem?

   _____

   _____

10. Have you been prescribed any antibiotics since your surgery?

    Yes ____ No ____