The Impact of Formulary Reservations on Drug Utilization: A Controlled Trial

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ABSTRACT

A controlled trial was conducted in two teaching hospitals (A and B), with similar case mixes to determine the impact of reservations, which were educational in nature, on the utilization of oral ciprofloxacin. Over a two-month period the health records of all the patients who received the drug were reviewed, and information on utilization and demographics of patients receiving the drug was recorded. As well, the number of admissions to the two hospitals over this period were compared. If culture and sensitivity (C & S) results were available, appropriateness was assessed in accordance with criteria for use established at site A; in the absence of C & S information, consensus by two microbiologists was used. Over the two-month period a total of 136 patients received ciprofloxacin at the two institutions. At site A, which had reservations, the number of patients who continued to receive ciprofloxacin upon admission was significantly decreased relative to site B, which did not have reservations (14% vs. 36% respectively, p = .029). As well, when assessed by total number of admissions to the institutions, the number of patients receiving ciprofloxacin at site A was less than site B (1.5% vs. 2.6% respectively, p = .003)). While the utilization was decreased at site A vs. site B, the proportion of patients with therapy deemed to be appropriate was not different between the two sites. Educationally based reservations are an effective formulary tool for optimizing drug utilization.

Key Words: *ciprofloxacin, drug use evaluation, formulary reservations.*

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RÉSUMÉ

Une étude comparative a été effectuée dans deux centres hospitaliers universitaires où l'éventail des cas est similaire afin de déterminer les répercussions de certaines restrictions d'origine didactique sur l'usage de la ciprofloxacine administrée par voie orale. Pendant deux mois, on a passé en revue les dossiers médicaux des patients auxquels était prescrit le médicament, pour recueillir les renseignements concernant l'utilisation de ce dernier et les données démographiques sur les patients. On a, en outre, relevé le nombre d'hospitalisations dans chaque établissement durant cette période. Les cas pour lesquels des résultats de culture et d'épreuve de sensibilité (C&S) figuraient au dossier ont été évalués d'après les critères d'utilisation du médicament établis par l'établissement A. Pour les autres cas, on s'est appuyé sur l'opinion concordante de deux microbiologistes. Pendant les deux mois, 136 patients au total ont reçu le médicament. La proportion de patients traités à la ciprofloxacine après l'hospitalisation est nettement plus faible pour l'établissement A, où l'usage du médicament est sujet à des restrictions, que pour l'établissement B où n'existe aucune restriction (14% et 36% respectivement, p = 0,029). En outre, comparativement au nombre d'hospitalisations, la proportion de patients traités à la ciprofloxacine est plus faible pour l'établissement A que pour l'établissement B (1,5% et 2,6% respectivement, p = 0,003). Bien que le médicament soit moins souvent prescrit au site A, la proportion de traitements jugés appropriés est la même dans les deux hôpitaux. Les restrictions d'origine didactique constituent donc un moyen efficace d'optimiser l'utilisation des médicaments figurant sur les formulaires.

Mots clés: *ciprofloxacine, évaluation de l'utilisation des médicaments, formulaire, restrictions.*

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INTRODUCTION

A formulary is a compilation of available drug products developed and maintained in a hospital by the Pharmacy and Therapeutics Committee.[1,2] Formularies are used to encourage the appropriate use of pharmacotherapy, discourage less than optimal drug therapy, and reduce costs.[2]

Formularies may be classified as open, reserved, or restrictive, and pharmacy departments are often given the responsibility of ensuring adherence to the formulary. Open classification means the drug is supplied upon request by a physician. Reserved drugs are usually retained for specific indications, or for use in a certain patient population. At our facility, reserved drugs are identified as such in the formulary along with the use for which they are reserved. In addition, the pharmacist is expected to contact the physician for orders involving reserved drugs. Drugs classified as restricted require that stringent criteria be met before the drug is released for use. This may require, for example, co-signature by the chief of staff in order to obtain the drug; or for antibiotics, an infectious disease consult may be necessary for the drug to be supplied.[2] While many studies have been done to describe the impact of formulary restrictions, there is little data on the impact of reservations which are primarily educational in nature.[3-8]

Ciprofloxacin is a fluoroquinolone antibiotic with a broad spectrum of activity. At Hospital A ciprofloxacin was reserved for infections where there was documented resistance to formulary items, or for the treatment of infections previously amenable to parenteral antibiotic therapy when oral therapy was appropriate.[9]

These reservations were imposed in an attempt to limit the development of resistance to this unique antibiotic. Extensive use of ciprofloxacin in a community hospital has been linked to the increased development of resistance. In 1988, the susceptibility to *Pseudomonas aeruginosa* was 91% but in 1990 it was 55%.[10] A similar trend was seen with other organisms. In Ontario, 49% of methicillin resistant *Staphylococcus aureus* (MRSA) isolates were found to be resistant to ciprofloxacin and norfloxacin.[11] The isolates were collected over a seven-month period starting in July of 1989 and were taken from different institutions throughout the province. It was concluded that there is a need to re-evaluate the use of the fluoroquinolones for treating MRSA, in light of this high resistance pattern.

A drug utilization evaluation (DUE) is defined as an authorized, structured, ongoing program that provides a rational systematic method of defining, assessing, and improving the quality of drug use.[12] Drug use evaluations can be either prospective, concurrent, or retrospective in nature. A prospective evaluation is initiated during the course of therapy and interventions occur before the first dose is administered. During a concurrent evaluation, the order is reviewed as soon as possible without any delay in drug administration, while the retrospective evaluations assess the cause of therapy once it is completed. A disadvantage of a retrospective review is that one is not able to intervene on behalf of the patient when the therapy is inappropriate. Nevertheless, retrospective evaluations are easy to implement and require limited resources.[12]

The objectives of this study were: 1) To perform a DUE of ciprofloxacin at the two teaching hospitals; and 2) To assess the impact of formulary reservations on the utilization of ciprofloxacin at Hospital A versus Hospital B which did not have formulary reservations for this drug.

METHODOLOGY

The demographic information for each hospital was collected so the patient populations being treated could be compared. This information was assessed both globally and by medical/surgical subspecialties. The names of all the patients receiving ciprofloxacin at the two hospitals were recorded by pharmacy for a period of two months, January and February 1992. Through a retrospective health record review those patients who received ciprofloxacin and whose records were available, were studied using a predeveloped DUE data collection form.

The utilization of ciprofloxacin in the two hospitals was determined and compared. Specifically the following were assessed:

1. The quantity used by each facility and by different services therein. The total admissions for the hospitals during the two months were obtained. The quantity utilized was reviewed in terms of the number of patients who received ciprofloxacin and the number of orders for ciprofloxacin that were entered into the pharmacy computer systems at each institution.
2. The site of infection, specifically respiratory tract, skin or skin structure, bone or joint, urinary tract and other category were recorded.
3. The number of culture and sensitivity (C&S) reports and the frequency of ciprofloxacin sensitivity were recorded.
4. The utilization of other antibiotics (parenteral or oral)

prior to and in combination with ciprofloxacin use was recorded.

5. The number of patients who were receiving ciprofloxacin prior to admission and whose therapy was continued were recorded.

6. The number of Infectious Disease (ID) consults obtained were recorded.

7. The dose, dose frequency, and duration of ciprofloxacin were also recorded. The duration of therapy was determined based on continuous therapy which was defined as no more than a day between changes in orders or reorders.

8. A review of the health record to determine adverse reactions and potential drug interactions was performed. To constitute an adverse reaction a specific citation in the medical or nursing notes of toxicity due to ciprofloxacin was necessary. Potential interactions were determined by reviewing drugs taken concomitantly with ciprofloxacin. The potential interactants included antacids, warfarin, ferrous salts, theophylline, and probenecid.

The impact of reservations was assessed by comparing the number of patients who received ciprofloxacin, divided by the number of admissions and adherence to criteria at site A with that of site B which did not have reservations. In order to assess the impact of reservations, the indications for ciprofloxacin orders that did not meet the criteria of having C&S results were assessed by consensus using two microbiologists. The microbiologists were blinded as to the hospital from which the orders originated.

The study was reviewed by the Medical Records Committees at both hospitals. The data were expressed both descriptively and statistically. Mean data were analyzed using the student's 't' test and difference in proportion by Chi-Square analysis and Fisher's Exact test as appropriate. A value of $p<.05$ was considered significant.

RESULTS

Drug Utilization Evaluation

Over a two-month period from January 1, 1992 to February 29, 1992, 136 patients received 153 courses of oral ciprofloxacin at the two facilities. Seventy-nine patients (58.1%) were from site A and 57 patients (41.9%) were from site B. By the third of July only 50 of 79 (63.3%) health records were available at site A and 42 of 57 (73.7%) from site B and DUE data is provided on those patients. Data on the services using ciprofloxacin, the dose, the interval, and the duration of therapy are based on the entire 136 patients since health record review was not needed to obtain this information.

The mean age of the patients at site A was 64.2 ± 19.2 years versus 51.5 ± 16.4 years (NSS). The percentage of male patients receiving ciprofloxacin at site A and B were 58% and 55%, respectively (NSS). The suspected site of the infection being treated is shown in Table I for each site. The services prescribing ciprofloxacin at site A and B are shown in Table II. The highest user at both institutions was surgery accounting for 57.0% and 45.6% of the orders at site A and B, respectively.

Culture and sensitivity results were obtained at site A in 18 of 50 patients (36%) with 16 of 18 (89%) reporting sensitivity to ciprofloxacin. The remaining two (11%) did not report ciprofloxacin sensitivities. For 15 of 50 patients

TABLE I: Site of infection being treated

Site of Infection	Site A # patients (n = 50)	(%)	Site B # patients (n = 42)	(%)
Respiratory	13	(26)	7	(17)
Skin/Skin Structure	8	(16)	7	(17)
Bone Joint	0	(0)	3	(7)
Urinary Tract	4	(8)	5	(12)
Other	25	(50)	20	(47)

TABLE II: Service Utilization

Site A	# patients (n = 79)	(%)	Site B	# patients (n = 57)	(%)
Surgery Services+	45	(57.0)	Surgery Services+	26	(45.6)
Medicine Services*	16	(20.3)	Medicine Services*	21	(37.0)
Oncology	11	(13.9)	Hematology	3	(5.3)
Psychiatry	4	(5.1)	ICU	2	(3.5)
Ophthalmology	2	(2.5)	Neurology	2	(3.5)
Unknown	1	(1.3)	Transplant Unit	2	(3.5)
			Extended ICU	1	(1.8)

+ Surgery Services include general, vascular, thoracic/cardiothoracic, ENT, obstetrics/gynecology, urology, plastics, orthopedics, and neurosurgery.

* Medicine Services include general medicine, chest medicine, nephrology, family medicine, cardiology, rheumatology, endocrinology, gastroenterology.

(30%) no cultures were drawn during their course in hospital. The remaining 17 of 50 patients (34%) had cultures drawn but no bacterial growth was reported. At site B, C & S results were reported in 14 of 42 patients (33%). Of these, seven of 14 (50%) were reported sensitive to ciprofloxacin while six of the 14 (43%) had no sensitivity reported to ciprofloxacin and one of 14 (7%) was reported as resistant to ciprofloxacin. One of the initial seven infections which was sensitive to ciprofloxacin later developed resistance. For nine of 42 patients (21%) no cultures were drawn. Twenty of 42 patients (48%) had cultures drawn but no bacterial growth was reported. In one case, a culture of *Pseudomonas aeruginosa* had no sensitivity reported.

The dose frequency used at site A and B is shown in Table III. Sixty-nine of 94 orders (73%) were written for 500mg bid at site A vs 37 of 76 orders (49%) at site B. The mean duration of therapy in hospital was 4.6 ± 3.8 days at site A and 5.0 ± 3.3 days at site B.

Three potential adverse reactions, two rashes, and one of nausea due to ciprofloxacin were reported at site A in two patients. Three potential adverse reactions, two citations of rash, and one of drug fever were reported at site B.

Twelve potential drug interactions were reported at site A in 10 patients. The drugs involved and the number of reports were antacids (7), warfarin (2) and iron salts (3). Eleven potential drug interactions were reported at site B in nine patients involving antacids(6), warfarin (4) and iron salts (1).

Utilization

At site A, 79 patients of the 5,097 patient admissions (1.5%) received ciprofloxacin. At site B, 57 patients of the 2,195 patient admissions (2.6%) received ciprofloxacin. The difference was significant (p=.003).

At site A, 31 of 50 patients (62%) received parenteral antibiotics prior to the first order of ciprofloxacin, while five of 50 (10%) received at least one other oral antibiotic prior to the first order of ciprofloxacin. Seventeen of 50 patients (34%) started on ciprofloxacin as their first antibiotic in hospital. At site B, 23 of 42 patients (55%) received parenteral antibiotics prior to the first order of ciprofloxacin, while nine of 42 (21%) received at least one other oral antibiotic prior to the first order for ciprofloxacin. Nineteen of 42 (45%) of the patients were started on ciprofloxacin as their first antibiotic in hospital. There were no differences in terms of use of parenteral or oral antibiotics prior to ciprofloxacin nor the initial use of ciprofloxacin between the two hospitals.

At site A, one infectious diseases (ID) consultation (2%) was obtained for one of the patients who received ciprofloxacin and at site B, nine of 42 patients (21%) had ID consultations (p=.003).

At site A, seven of 50 patients (14%) were continued on their outpatient ciprofloxacin therapy subsequent to admission versus 15 of 42 patients (36%) at site B (p= .029).

Eighteen patients from site A and 14 from site B had C&S available and were assessed for compliance with site A's criteria. The remainder were sent to the microbiologists for assessment. The overall appropriateness assessed by either site A's criteria or by consensus of the microbiologists was 22% (11/50) at site A versus 33% (14/42) at site B (NSS).

TABLE III: Dose Frequency

Dose Frequency	Site A # orders (%) (n = 94)	Site B # orders (%) (n = 76)
daily, stat	4.3	13.2
bid	93.6	86.8
tid	2.1	0

DISCUSSION

The results of the DUE indicate that surgical services at both hospitals were the major user of ciprofloxacin with 57% of all orders from site A and 46% of all orders from site B being written by surgical disciplines. Although there was a larger proportion of orders from surgery at site A vs site B, this was not statistically significant. A report from site A indicated that educational interventions directed toward surgeons were often less successful than those directed toward medical specialties.[13] This may explain some of the increased use by surgeons at site A.

The duration of ciprofloxacin therapy was relatively short and likely reflects changes to oral therapy prior to discharge, or improvement secondary to antibiotics allowing for discharge. This interpretation of duration of therapy is limited by the fact that many patients were discharged home on the drug and the true duration of ciprofloxacin use could not be determined.

It would appear that C & S data are not being routinely used to select therapy. Thirty percent of patients at site A and 21% of patients at site B did not have C &

S obtained. Even when obtained and alternate therapy was appropriate, a change was rarely made. Other studies have also found that C & S are not always used to direct therapy.[14] This may mean that formulary reservations which include C & S criteria may need to be altered. Indeed, in practice it is difficult to suggest changes in therapy irrespective of culture results if the patient is responding. Nonetheless, our current criteria would consider therapy in which C & S was not obtained as inappropriate. As well, ciprofloxacin in some instances was ordered empirically, subsequently changed to another antibiotic possibly due to C & S information. While this may indicate a rational practice, according to our criteria, ciprofloxacin was to be used for documented resistance and not for empiric therapy and hence was deemed inappropriate.

Prior use of parenteral antibiotics was comparable at site A and B. One of the criteria for use was switching from parenteral to oral antibiotics. This did not occur more often at site A than at site B. However, fewer patients admitted to hospital were continued on their (pre-admission) outpatient therapy of ciprofloxacin at site A versus site B (14% vs. 36%, respectively). This reduced utilization was likely due to the formulary reservation that existed at site A which would result in changing the order prior to entry in the pharmacy computer, and hence, prior to identifying the patient for study. Changes in methodology which would identify both active orders and altered orders would be necessary to definitively address this issue. Unfortunately, this methodology was not in place at the time of study and represents a limitation of the study. Despite this, the most plausible reason for this difference in utilization continues to be the formulary reservations.

Infectious disease consults were obtained more often in site B patients receiving ciprofloxacin than in site A patients. This likely contributed to the trend towards increased appropriateness rate (33% at site B vs. 22% at site A) as ID consultants would likely both obtain C & S and use results of that to direct therapy. The lack of prescribing of ciprofloxacin by ID consultants at site A, (the only consultation suggested discontinuing ciprofloxacin), and the use of ciprofloxacin at site B may reflect individual prescribing patterns or compliance with the guidelines for use at the respective hospitals.

Despite the fact that the proportion of appropriateness and adherence to the established criteria was similar at the two sites, the utilization of ciprofloxacin was lower at site A than at site B. There were several possible reasons for this including differences in prescribing practice, the availability of norfloxacin at site A only, and the reserved formulary status of ciprofloxacin. Differences in prescribing practices are always difficult to rule out. However, since most of the housestaff who do the prescribing rotate between the hospitals, this is unlikely to be the reason. Since data were collected shortly after a change in housestaff (i.e., January - February) previous prescribing practices may still have been followed. This transmigration of housestaff would tend to minimize these differences.

Norfloxacin was a nonformulary agent at site B. However, urinary tract infections, the only approved indication for norfloxacin, were infrequently encountered at both institutions (see Table I). Also, the use of norfloxacin was very limited at site A. Although it is unlikely, it could be argued that more norfloxacin, and hence less ciprofloxacin, could have been used at site A.

The final issue is the formulary status of ciprofloxacin. It would appear that formulary reservations decreased the usage of ciprofloxacin at site A both in terms of total utilization and the change in patients admitted on ciprofloxacin who continued that therapy in hospital. At site A pharmacists are required to contact the physician to discuss the indication for ciprofloxacin suggesting formulary alternatives. Our results would indicate that this process was successful at site A in reducing the utilization although not necessarily improving the proportion of patients who would meet the criteria for appropriateness.

Comparing the populations of the two hospitals, site A is larger than site B and had 31,698 admissions last year compared to 13,834 admissions at site B. Based on discharges from physician services in 1989-90, it would appear that the proportion of discharges from the various services of site A and B were similar with the exception of endocrinology, neurology, hematology, and pulmonology being greater at site B. At site A, oncology was a large user of ciprofloxacin and site B does not have oncology as such, but a hematology service which cares for oncology patients.

Limitations of this study, in addition to those already stated, include the use of retrospective data as well as the limited sample size and failure to retrieve all the health records. As well, since several patients received more than one course of ciprofloxacin during the two-month time period,

appropriateness was assessed in terms of patients and not in terms of courses (one patient from site B was admitted twice). The rationale for this was that once appropriateness or inappropriateness was established, to include subsequent courses would only serve to potentially skew the data.

It is important to reserve valuable agents such as ciprofloxacin because widespread use may lead to resistance. Of note, one patient who was started on ciprofloxacin for *Pseudomonas aeruginosa* infection developed resistance during treatment. Another patient who was being treated with ciprofloxacin had C & S which indicated resistance to ciprofloxacin further underscoring the need for judicious use to minimize resistance.

In conclusion, formulary reservations may be a useful tool in order to control drug use in a hospital. They enable the pharmacy to utilize reservation guidelines approved by the Pharmacy and Therapeutics Committee to improve drug use. This study lends further support to the concept that educational reservations as well as the more confining restrictions are effective in encouraging appropriate drug use and containing costs.

Finally, collaborative work with other institutions as illustrated by this study, provides information to the individual institutions on drug utilization and opportunities for both the control group and the intervention group to develop strategies for assessing drug utilization.

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