A RETROSPECTIVE EVALUATION OF CIPROFLOXACIN USE AT KWAME NKRUMAH UNIVERSITY OF SCIENCE AND TECHNOLOGY (KNUST) HOSPITAL, KUMASI

by

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DECLARATION

I hereby declare that this submission is my own work towards the MSc and that, to the best of my knowledge it contains no material previously published by another person nor material which has been accepted for the award of any other degree of the University, except where due acknowledgment has been made in the text.

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ABSTRACT

Back ground

Ciprofloxacin has been used for chemotherapy of bacterial infections over the years in Ghana. However not much is known about the quality of its use regarding the appropriateness of clinical indication, dosages administered, dose frequency, duration and potential for interactions with multivalent cations

Objective

The present study was therefore undertaken to evaluate its use in respect of the above mentioned parameters excluding the first.

Methods

This was a cross-sectional retrospective study involving two thousand patients' charts that covered a three month period (1st Oct 2004 to 31st December 2004) at the KNUST Hospital. Patient records were examined to assess the appropriateness of ciprofloxacin use with respect to the dose, dose frequency, dose duration and the potential for drug – drug interactions with multivalent cations (MVCs).

Results

It was found out that the dose for all the justified indications of UTI, bone and joint infection, enteric fever and enteritis was 500 mg. The dose frequency in all the above cases was twelve hourly. The potential for drug –drug interaction with respect to multivalent cations was virtually absent. However the duration of treatment for all the justified cases did not meet standard criteria.

Conclusion

All the patient folders studied were found to meet the standard criteria appropriate for ciprofloxacin use in respect of dose, dose frequency, and the no-potential for drug –drug interaction. The only exception was dose duration which was inappropriate.

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LIST OF ABBREVIATIONS

AUC	Area under Curve
Bd	Twelve hourly
Cmax	Maximum Serum Concentration
CSF	Cerebrospinal Fluid
DNA	Deoxyribonucleic Acid
DUE	Drug Use Evaluation
GI	Gastrointestinal
IV	Intravenous
KNUST	Kwame Nkrumah University of Science and Technology
MIC	Minimum Inhibitory Concentration
MVC	Multivalent Cation
T_{Max}	Time to Reach Maximum Concentration
UTI	Urinary Tract Infection
WHO	World Health Organization

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DEDICATION

TO GOD BE ALL THE GLORY.

I DEDICATE THIS WORK TO MY DEAR WIFE, ANNE AND PRECIOUS CHILDREN, EMMANUEL, ABIGAIL AND CHARLES NOT FORGETING SARAH, MY NIECE.

CHAPTER 1 INTRODUCTION

1.1 BACKGROUND

The discovery and use of antimicrobial agents have brought a major breakthrough in therapy. A lot of previously intractable infectious conditions have now become amenable to antimicrobial therapy. Various classes of antibiotics have been discovered and used with varying degrees of success. Among these are the quinolones. Older members of this group, like the nalidixic acid, have been available for the treatment of urinary tract infections. However the limited use of this drug coupled with the rapid development of resistant strains became a problem. (Threlfall and Ward, 2001). Therefore, the introduction of the fluorinated 4-quinolones like ciprofloxacin has become an important therapeutic breakthrough since these have broad spectrum antimicrobial activity and have very good pharmacokinetic profile. Their side effects are comparatively fewer and microbial resistance to their action does not develop rapidly (Mandel and Petri 1996).

Ciprofloxacin, a typical member of the group, has been incorporated into the Ghana National Formulary/Standard Treatment Guidelines since the 1990s to date. It constitutes a large portion of health facility budgetary allocation for drugs and it is also the major drug for the management of typhoid and paratyphoid fevers. However research work have indicated that ciprofloxacin and other antibiotics are often used inappropriately leading to a wastage of scarce healthcare resources (Rho and Yoshikawa, 1995; Thoung et al, 2000) as well as increasing the risk of the emergence of bacterial resistance (Motiur *et al*, 2001)

Evaluation of ciprofloxacin use is therefore critical to controlling the emergence of resistant strains as well as cutting down of unnecessary expenditures and also ensuring that patients derive maximum benefit from its use.

The purpose of this study was therefore to evaluate ciprofloxacin use at KNUST Hospital.

1.2 PROBLEM STATEMENT

In most developing countries governments spend about 20-50% of their national budget on drugs and medical sundries (World Bank, 1994). This makes the financial impact of pharmaceuticals on their economies to be substantial. Governments are thus concerned about the rational use of these drugs.

Furthermore, the World Health Organization Policy Perspective on Medicine (2002) also indicates that even when drugs are made available, more than fifty percent are prescribed, dispensed or sold inappropriately while 50% of patients fail to take the medicines correctly resulting in harmful consequences.

One of the major consequences of such inappropriate use of antibiotics is the development of resistance strains of the hitherto susceptible organism.

Inappropriate treatment could also lead to the ultimate; death of the patient.

Indeed the WHO report on infectious diseases 2000 indicates that "without proper treatment typhoid is a serious and frequently relapsing disease that kills up to ten percent of those infected."

1.3 OBJECTIVES

a. To analyse the pattern of ciprofloxacin use among patient categories identified by age
b. To identify the illnesses most frequently treated with ciprofloxacin
c. To determine whether ciprofloxacin was appropriately prescribed in respect of dose, dose frequency, and dose duration.
d. To determine whether drugs that potentially decrease ciprofloxacin absorption were co-prescribed

1.4 JUSTIFICATION

Ciprofloxacin is an antimicrobial agent that has virtually replaced chloramphenicol in the management of some life threatening conditions like typhoid fever. It is also indicated in the syndromic management of gonococcal urethritis.

It is important that the appropriateness of its use be evaluated occasionally. Indeed, enteric fever is a major public health problem particularly in the developing countries causing about six hundred thousand deaths yearly (Raveendran et al, 2008)

Inappropriate use of this anti-infective has been identified as one of the preludes to the development of resistant strains hence the need to ensure that it is appropriately used. This study will influence antibiotic policy at the hospital by enabling the institution to identify and correct ciprofloxacin use problems in order to improve patient outcomes.

CHAPTER 2

LITERATURE REVIEW

2.1.0 CLINICAL PHARMACOLOGY

2.1.1 PHARMACOKINETIC PROFILE OF FLUOROQUINOLONES

The fluoroquinolones are rapidly and extensively well absorbed from the small intestines after oral administration. They undergo a minimal first pass metabolism and reach a maximum serum concentration after two hours (AHFS 2003)

The presence of food in the gastro- intestinal tract decreases the rate but not the extent of absorption of the drug administered. Absorption may be substantially affected by concurrent administration with milk or yoghurt alone. Absorption however is not affected significantly by dietary calcium that is part of a meal. (AHFS 2003)

Antacids containing aluminum, magnesium and calcium decrease absorption of oral ciprofloxacin. Hart *et al.,* (1991) reported of a pharmacodynamic interaction between ciprofloxacin and antacid as well as ciprofloxacin and sucralfate. These interactions result in decreased ciprofloxacin absorption that is manifested by decreases in maximum serum concentration (Cmax) and area under the curve (AUC) and increase in the time to maximum concentration (Tmax). Fifty percent decrease in absorption was observed when antacids were administered two to four hours before ciprofloxacin administration and only 20-40% decrease when administered 2-4hrs after ciprofloxacin.

(Schentag *et al*, 1988). These changes in pharmacokinetic properties may potentially compromise antimicrobial efficacy. Even though the mechanism of this reduction has not been fully elucidated, it is believed that, the above named divalent and trivalent ions

may bind to and form insoluble complexes with the quinolones in the gastro intestinal tract.

These negative effects of the antacids can be significantly reduced by administering the antacid doses not within two hours after or in the six hours prior to the next antimicrobial dose (Kastrup, 2000). If an antacid is absolutely required, then an adjunctive therapy e.g. H_2 receptor antagonist or proton pump inhibitor may be used to replace the antacid (Hasten and Horn, 1997, Lomaestro and Bailie, 1995)

The protein binding of ciprofloxacin is low (20-30%) and the substance is present in plasma largely in the non-ionized form. Ciprofloxacin is widely distributed into body tissues and fluids following oral or I.V. administration. The large steady state volume of distribution of 2-3 L/kg body weight shows that ciprofloxacin penetrates into tissues resulting in concentrations which clearly exceed the corresponding serum levels. The highest concentrations of the drug are generally obtained in the bile, lungs, kidney, liver, gall bladder, uterus, seminal fluid, prostatic tissue and fluid, tonsil, endometrium, fallopian tubes and ovaries. Concentration of the drug achieved in most of these tissues and fluids substantially exceed those in serum. (AHFS op cit)

Other areas of drug distribution are the bone, aqueous humor, sputum, saliva, nasal secretion, skin, muscle, adipose tissue, cartilage and pleural, peritoneal, ascitic, blister, lymphatic and renal cyst fluid. It is also concentrated in neutrophils achieving concentrations that may be 2-7 times higher than the extracellular concentration.

The only fluid receiving lower concentration is the cerebrospinal fluid (CSF) which may be 6-10% of peak serum concentration. In adults with meningitis who received

200mg dose of ciprofloxacin every 12 hrs by I.V infusions ever 30 minutes, the ratio of CSF/ serum concentration in sample obtained 1-2 hrs after a dose was 0.11-0.46 during the first 2-4 days of therapy when meninges were inflamed and 0.04-0.3 during days 10-14 when meninges were uninflammed. (AHFS 2003) The drug crosses the placenta and is distributed into amniotic fluid in humans as well as breastmilk. Breastmilk concentration may be higher than concomitant serum concentration. These attained concentrations are sufficient to inhibit the majority of susceptible pathogens (Wiseman and Balfour 1994)

Renal and non-renal mechanisms are involved in the elimination of the drug. It is partially metabolized in the liver by modification of the piperazinyl group to at least four metabolites. They are desethylene ciprofloxacin, sulfociprofloxacin, oxociprofloxacin, and N – formylciprofloxacin

These have microbiologic activity that is less than that of the parent drug but may be similar to or greater than that of some other quinolones. Ciprofloxacin and its metabolites are excreted in urine and faeces. Unchanged ciprofloxacin is eliminated by both glomerular filtration and tubular secretion.

2.1.2 STRUCTURE ACTIVITY PROFILE OF CIPROFLOXACIN

The fluoroquinolones are synthetic broad spectrum bactericidal agents. Their bactericidal activities are an improvement on that of the quinolones. They contain 6-fluoro and 7-piperazine substituents which greatly enhance their antimicrobial efficacy when compared to the quinolones. Ciprofloxacin is a typical member of the group. Its structure is as shown in figure 1 below.

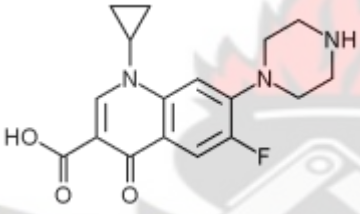

Fig1:1,4-dihydro-1-cyclopropyl-6-fluoro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid

The fluorine molecule provides the increased potency against gram- negative organisms with the spectrum broadened to include gram- positive organism. The piperazine moiety is responsible for the antipseudomonal activity. Their bactericidal activity is mediated through their capacity to interfere with the enzyme Deoxyribonucleic Acid (DNA) gyrase and topoisomerase IV needed for the synthesis of bacterial DNA.

Ciprofloxacin is therefore active against both gram-positive and gram-negative bacteria. Some of the susceptible gram-negative bacteria are salmonella, shegella, campylobacter neisseria and pseudomonas. It however has moderate activity against gram -positive organisms like *Streptococcus pneumoniae* and *Enterococcus faecalis* (BNF March 2003)

It has therefore found use in the treatment of infections caused by susceptible organisms in lower respiratory tact, skin and skin structure, bone and joint, and urinary tract infections, as well as infectious diarrhoea, typhoid fever and sexually transmitted infections.

Anders et *al.* (2001) also reported the successful treatment of ulcerogenital tularaemia with oral ciprofloxacin in 12 paediatric patients. His team also reported the successful treatment of tularaemia in central Sweden where 43 patients with median age 53, range 21-83years were treated with oral ciprofloxacin. The dosage administered was 500-750mg two times daily for 10 days. The response obtained was excellent and no complication or relapse occurred. (Eliason et al, 2002)

Ciprofloxacin is also indicated for inhalational anthrax (post exposure) to reduce the incidence or progression of disease following suspected or confirmed exposure to aerosolized *Bacillus anthracis* spores. The adult dosage is 500mg every 12 hours and children 15mg/kg (maximum 500mg per dose) 12 hourly. If the IV route is used then the adult and children dose are respectively 400mg and 10mg/kg (maximum 400mg) every 12 hours. The duration of treatment is sixty days.

Examples of the fluoroquinolones in current use are ciprofloxacin, enoxacin, lomefloxacin, norfloxacin, gatifloxacin, and sparfloxacin

2.2 THREATS OF RESISTANCE DEVELOPMENT TO CIPROFLOXACIN

The development of resistance by microorganisms is of global concern. This is because microorganisms that were susceptible to some anti-infective agents have now become resistant. Resistance of microorganisms to ciprofloxacin has been observed worldwide in surveillance studies (Rahman *et al,* 2001.) The species of organisms which have been particularly involved in this are *Pseudomonas aeruginosa, Neisseria gonorrhoea, Salmonella enterica, Staphlococcus aureus,E.coli, and. Clostridium jejuni*.

This resistance often causes the Minimum Inhibitory Concentrations (MICS) of these organisms to increase from 4 to 16 fold. Some of these concentrations are often above peak drug concentrations achievable in serum. Rahman *et al*, 2001 detected treatment failure of ciprofloxacin in gonorrheoa management in Bangladesh. Further research revealed that treatment failure with the use of ciprofloxacin for gonorrheoa correlated with the prevalence of fluoroquinolone -resistant *N. gonorrheoa* strain in Bangladesh.

Reyes et al, 2001 also observed a high level of ciprofloxacin resistance of gonococcal isolate recovered from conservative female sex workers in Cebu and Manila in the Phillipines. Tapsall *et al,* 1992 reported of the failure of 500mg ciprofloxacin therapy in male urethral gonorrhoea in Australia

In the US ciprofloxacin resistance to *N gonorrhea* has resulted largely from clonal outbreaks caused by human to human spread (Gordon *et al.,* 1996 and Fox *et al* 1997)). They observed the emergence of *N. gonorrhea* with decreased susceptibility to ciprofloxacin in Cleveland, Ohio.Threlfall and Ward (2001) also reported decreased susceptibility to ciprofloxacin in *S. enterica* serotype *typh*i from UK. They further reported that nalidixic acid resistant *S. typhi* with decreased susceptibility to ciprofloxacin

is endemic in India and neighbouring countries. Indeed Chandel *et al. (2000)* have also noted several cases of treatment failure of enteric fever caused by *S. enterica* serotype Typhi and Paratyphi A in India

In Europe resistance to ciprofloxacin has also been noted in *Clostridium jejuni* and *E coli.* The *E. coli* resistance was particularly noted in urinary tract infections. Faecal carriage of resistant *E coli* however appeared commonly in both healthy adults and children in Spain. Carriage of these resistance strains in children, in whom it is rarely used and in adults who have no prior exposure to quinolones suggested that the population at large had acquired the resistant strains. (Endtz *et al.* 1991, Ena *et al.* 1995, Garau et *al,* 1999).

Taking into cognizance documented high rate of fluoroquinolone resistance in *E coli* isolated from poultry (Blanco *et al,* 1997), Hooper 2001 stated that acquisition of resistant strains from food sources may have resulted in substantial colonization of the human population with resistant *E. coli*, creating a reservoir of resistant organisms. He also stated that fluoroquinolone use in humans is a risk factor for having resistant strains.

2.3 DRUG USE EVALUATION (DUE)

Other synonyms for DUE are Drug Use Review (DUR) and Medicine Use Evaluation (MUE). DUR used to be assigned retrospectively while DUE was used prospectively but the terms are now used interchangeably

Drug Use Evaluation (DUE) is one of the major tools employed by institutions in addressing the problems of irrational drug use. It helps to measure the problem as well as analyze and make the institution to understand the causes underlying it.

Health facilities have their Therapeutics Formula and Essential Drug List as important tools in the hospital to ensure that drugs are prescribed appropriately. But after these have been established, one would also need to be guided by the current patterns of usage. This is the role that Drug Use Evaluation studies play.

DUE is a system of ongoing, systematic criteria-based evaluation of drug use that will help ensure that medicines are used appropriately at the individual patient level (WHO 2002) The ultimate purpose of DUE is to ensure the optimization of drug therapy i.e. drug is safe, effective and delivers improved health outcomes. DUE is classified into two or at times three main categories; Retrospective, Prospective and/or at times Concurrent.

In Retrospective DUE, therapy is reviewed long after the patient has received the medication. Information is obtained from patient medical charts or computerized records. These are screened to see whether the drug therapy met approved criteria. Such a review may detect patterns in prescribing, dispensing or the administering of drugs which do not conform to standard. This will enable the necessary measures to be put in place to prevent inappropriate use or abuse. Even though it has the advantage of serving as a

quicker means of evaluation, and is performed away from patient care areas, in most cases interventions that are made, do not go to benefit the case study patients immediately. It however serves as a means for developing prospective standards and target interventions.

Prospective DUE involves evaluating a patient's planned drug therapy before a medication is dispensed. This type enables the pharmacist to identify and resolve problems before the patient receives the medication. Some of the problems commonly addressed here include drug –disease contraindication (Academy of Managed Care, 1999). An ulcer patient will for example, not have to be given a non-steroidal anti-inflammatory agent which will potentially worsen the problem. Others are therapeutic interchange, incorrect drug dosage, inappropriate duration of drug treatment, drug-allergy interactions and clinical abuse/misuse

Concurrent DUE is performed during the course of treatment and involves the on-going monitoring of drug therapy to ensure positive treatment outcomes. It is analogous to case management or health management. It presents pharmacists with the opportunity of alerting prescribers of potential problems and to intervene in areas such as drug-drug interactions, drug-disease interactions, duplicate therapy, over or underutilization, excessive or insufficient dosing, drug–age precautions, drug-gender precaution, and drug-pregnancy precautions. This allows alteration to therapy to be made if deemed necessary.

Procedure for drug use evaluation.

There are five main steps involved in the procedure for DUE. These are establishment of criteria for the review of the medicine, measurement of actual use, comparison and analyses stage, intervention, and evaluation of the DUE programme.

1) Establishment of criteria for review of the medicine

It allows criteria to be defined so that comparisons of optimal drug use can be made with actual drug use. These criteria are statements that define correct drug usage with respect to various components e.g. indication, dosage, frequency and duration of therapy. For example the standard criteria for the management of malaria in an adult non-pregnant person of fifty kilograms body weight and above is 100mg artesunate and 300mg amodiaquine two times daily for three days. Any departure from this would be considered inappropriate. These criteria could be obtained from the hospital's Standard Treatment Guidelines or the national one or the Pharmacy Department and Infectious Disease Section (Goldman, 1990) of the hospital or pooled from internationally acclaimed medical literature.

Holloway and Green (2003), recommend that reviewing many criteria will make the DUE process cumbersome and may impair successful completion of the review. Therefore the number of criteria established for each medicine should be between three and five.

Once the criteria are established, thresholds or benchmarks are decided for each criterion in order to define the expectations or goals for compliance with the criteria. A threshold refers to the percentage of charts or records that will meet or exceed the

established criteria for the drug. Ideally this should have been 100% but in reality 90-95% compliance is set below which corrective measures are instituted.

2) Measurement of Actual Use

Pertinent data are obtained from patient medical records, prescriptions or computerized databases. Depending on the objectives, the data can be gathered retrospectively, prospectively, concurrently or an admixture of all, or either of them.

3) Comparison and Analysis Stage

This stage involves an analysis of the actual data obtained and its comparison with the optimal criteria established. Patterns or aberrations observed are then interpreted.

4) Intervention

This is the step for the implementation of corrective measures. Action should be targeted to areas of concern such as inappropriate prescribing patterns, economic considerations, quality of drug therapy, and changing standard treatment guidelines. The importance of such a recommendation cannot be overemphasized. An intervention of such nature by Hammerman *et al.* (1997) indicates that performing drug use evaluation and distributing the result to prescribers concerned has a beneficial effect on the appropriateness of drug use and provides an important tool for identifying the main problems of prescribing.

5) Evaluation of the DUE Programme

This final step involves an assessment of the effectiveness of the DUE programme. Any deficiencies observed are noted and corrected to enhance future programmes.

Table 2.1: PROTOCOLS FOR CIPROFLOXACIN USE AT KNUST HOSPITAL

DISEASES CONDITION	DRUGS USED	DOSAGE	FREQUENCY OF ADMINISTRATION	DURATION
Acute Prostatis	Ciprofloxacin Doxycycline	750 mg 100 mg	Twelve hourly Twelve hourly	14 - 21 days 14 - 21 days
Scrotal Masses	Ciprofloxacin Doxycycline	500 mg 100 mg	Single dose Twelve hours	- 10 days
Urethral Discharge	Ciprofloxacin Doxycycline	500 mg 100 mg	Single dose Twelve hourly	- 7 days
Gonoccocal Vaginitis	Ciprofloxacin	500 mg	Single dose	-
Lower Abdominal Pain in women	Ciprofloxacin	500 mg	Single dose	-
Chancroid	Ciprofloxacin	500 mg	Single dose	-
Prophylaxis of meningitis	Ciprofloxacin	500 mg	Single dose	-
Gonoccocal Arthritis	Ciprofloxacin	250 mg	Twelve hourly	14 - 21 days
Enteric Fever	Ciprofloxacin	500 mg	Twelve hourly	10 - 14 days

The above protocols were not essentially different from what is in the Ghana Standard Treatment Guidelines. Most of the indications above were not common occurrences at

KNUST Hospital except for enteric fever. Pooled criteria using the KNUST protocol, Ghana Standard Treatment Guidelines, the Management Sciences for Health guidelines found at www.msh.org/rpmplus, and Goodman and Gilman were used for benchmarking. This is shown below.

Table 2.2 DRUG USE EVALUATION CRITERIA FOR CIPROFLOXACIN

INDICATOR	**CRITERIA**	**THRESHOLD %**
Dose and dose frequency	Uncomplicated UTI : 500mg Complicated or recurrent infection: 500 mg – 750 mg bd G1 infection : 500 mg bd Bone and joint infection: 500mg bd Enteric Fever: 500 mg bd Gonorrhoea: 500 mg in one dose.	90
Duration	Uncomplicated UTI : 1-3 days Complicated UTI : 10-21 days G1 infection : 5 days Bone and joint infection: 4-6weeks Enteric fever : 10-14 days	95
Potential for drug – drug interaction.	Medicine – antacids, Irons, calcium other mineral-multivitamins	90

Credit www.msh.org/rpmplus with adaptation

2.4 PREVIOUS WORK CIPROFLOXACIN USE EVALUATION

Ciprofloxacin use evaluations have been done both retrospectively and prospectively. These have been with respect to appropriateness of its use and pharmacoeconomic benefits. The purpose of these was to ensure that society derives maximum benefit from the use of these drugs without creating unnecessary avenues for the development of resistant strains.

Appropriateness of use

Goldman, (1990) using 40 patient charts, discovered that all charts from the retrospective review met the criteria for appropriateness of use and the patients had either micro or clinical cure upon review.

However, Koo and Renner (1993) also discovered that only 17% of patients prescribed ciprofloxacin had infections that were appropriately treated with the antibiotic. On average it was reported that $20500 per year could be saved by prescribing equally efficacious oral antibiotics at the centre. He recommended that ciprofloxacin be restricted to its proven indications in ambulatory setting in order to ensure considerable cost saving.

Pickering et al (1994) also discovered in a retrospective chart review of ciprofloxacin-prescribing in a large academically oriented long- term care facility that only 25% of orders were appropriate. Twenty three percent of orders were less than appropriate based on indication and 49% due to the availability of a more effective and /or less expensive alternative antibiotic choice. They concluded that prescribing of fluoroquinolones was less than optimal. This had the potential of leading to development of resistant bacteria strains and increased health care cost.

Balfour and Faulds (1993) concluded that oral ciprofloxacin use in serious infection offers considerable scope for cost avoidance when appropriately substituted for parenteral therapy. It does not necessitate therapeutic drug monitoring and can be administered on an outpatient basis.

In a similar pharmacoeconomic review, Marchbanks *et al.* (1991) asserted that a successful clinical outcome was achieved in approximately 90% of patients treated with ciprofloxacin and this resulted in an estimated cost avoidance of $165 per course.

These various work indicate a wide variety of outcomes in the use of ciprofloxacin, particularly with respect to appropriateness of use. It is therefore important that every health facility or nation must occasionally conduct DUE to determine the appropriateness of use of ciprofloxacin as well as other drugs.

CHAPTER 3

MATERIALS AND METHOD

3.1 **Study site**

The setting for the study was KNUST Hospital. It is a District Hospital with hundred beds and second in status to only Okomfo Anokye Teaching Hospital in the Kumasi metropolis. It serves as the medical arm of the Kwame Nkrumah University of Science and Technology (KNUST), Kumasi, in the Ashanti region of Ghana.

The hospital was primarily set up to cater for the health needs of staff, their dependents and students of the University. However it has now extended its services to about thirty surrounding communities with a rapidly increasing population. Since it is located on the Kumasi- Accra express road, it also serves as the port of call for road traffic accidents and other emergencies. It thus serves as the District Hospital.

The Out-patients department is made up of the medical records unit, laboratory, X-ray, ultra sound scanner and electrocardiogram, pharmacy, ambulance emergency units, and blood bank. The In –patient department is made up of theatre, surgery, female ward, male wards, paediatrics, obstetrics and gynaecology, dental clinic, and maternity wards. Services provided at the hospital include laboratory X–ray ultrasound scanner and electrocardiogram. Others departments surgery, theatre female, paediatric, obstetrics and gynaecology dental and finally pharmaceutical, ambulance

The average daily outpatients were about one hundred and fifty with three medical officers at post with visiting specialists from the Komfo Anokye Teaching Hospital. The pharmacy was manned by a pharmacist with three dispensing technicians.

3.2. Study Design

This was a retrospective study involving one hundred and sixty five (165) patient charts purposively selected from two thousand patient charts at the KNUST Hospital. Charts of patients of the hospital who were put on ciprofloxacin from 1st October to 31st December 2004 were examined. This period was chosen because it was a period that students would be in session and it was also to reflect current trends in the prescription of ciprofloxacin at the hospital

The data collection tool was a questionnaire, titled AUDIT OF CIPROFLOXACIN USE AT KNUST HOSPITAL (appendix 1). It was pretested on twenty patients' charts and the necessary changes made.

3.3 Data Collection

The patient folders were selected at night with the assistance of a technician at the biostatistics department of the hospital. Night time was chosen in order to avoid interferences from patients and other staff members. The folders were numbered sequentially as they have been arranged. The first two thousand folders yielded one hundred and sixty five patient charts in which ciprofloxacin had been indicated. About forty charts were examined daily. Patient confidentiality was maintained. Each chart was

examined looking at key issues like indications, dose, dose frequency, dose duration, and the potential for drug –drug interaction with polyvalent cations

3.4 Analyses

The data was input into SPSS for easier analysis. The drug use criteria shown on page 16 were used for the evaluation. Appropriateness of use was determined by comparing the drug prescribed for the indication with the treatment guidelines.

CHAPTER 4

RESULTS

During the period a total of 165 cases of ciprofloxacin use were identified out of 2000 patient charts. They were made up of 104 males (63%) and 61 (37%) females. It is interesting that pregnancy status in females was not indicated in any of the cases. The age range was between eleven and seventy years. Individuals of age 30 and below constituted 93.3%. (Table 4.1)

The morbidity profile for the patients on ciprofloxacin is shown in Table 4.2 Enteric fever was the most common indication; constituting 42%.This was followed by enteritis 15%, urinary tract infection 9% and bone and joints infection of about 2%. Other indications for which the drug was used unjustifiably to an insignificant level were malaria, dysentery, amoebic liver abscess, piloanal sinus and upper respiratory tract infection .In some cases the indications were not specified.

Duration of treatment varied for the various indications as expected and even for the same indication there were variations. For example out of the 15 cases of UTI 6 (40%) had 4-6 days and 9 (60%) had 7-10 days duration of treatment. In enteric fever 27 (38.57%) cases out of 70 had 4-6 days duration of treatment while 41 (58.57%) had 7-10 days (generally 7 days). In enteritis the 4-6day duration of treatment constituted 6 (24%) while 7-10 days accounted for 19 (76%).

The basis for putting a patient on ciprofloxacin was purely empirical with culture and sensitivity testing accounting for less than 1%.

Generally the dosage administered was 500mg orally and 400mg if treatment was parenteral (Table 4.3)

TABLE 4.1 Age Distribution of Patients

Age of patients		Frequency	Percent	Valid Percent	Cumulative Percent
	11-20	75	45.5	45.7	45.7
	21-30	78	47.3	47.6	93.3
	31-40	5	3.0	3.0	96.3
	41-50	3	1.8	1.8	98.2
	51-60	2	1.2	1.2	99.4
	61-70	1	.6	6	100.0
	Total	164	99.4	100.0	
Missing	System	1	.6		
Total		165	100.0		

TABLE 4.2: Indications for which drug was given

Indications	Frequency	Percent	Valid Percent	Cumulative Percent
UTI	15	9.1	9.1	9.1
Bone & Joint	1	.6	.6	9.7
Enteric Fever	70	42.4	42.4	52.1
Enteritis	25	15.2	15.2	67.3
*Unjustified use	54	32.7	32.7	100.0
Total	165	100.0	100.0	

TABLE 4.3: Indications for which drug was given versus dosage administered.

INDICATION	Dosage administered		Total
	400 mg iv	500 mg	
UTI		15	15
Bone & Joint		1	1
Enteric fever	1	69	70
Enteritis		25	25
*Unjustified use	3	51	54

Table 4.4: Indications versus dose frequency

Indications	Dose frequency	Total
UTI (15)	Twelve hourly	15
Bone and joint infections(1)	Twelve hourly	1
Enteric fever (70)	Twelve hourly	70
Enteritis(25)	Twelve hourly	25
*Unjustified use (54)	Twelve hourly	54

TABLE 4.5: Indications for which drug was given versus duration of treatment

Indications	Duration of treatment					
	1 daily	2-3 days	4-6 days	7-10 days	11-14 days	Total
UTI			6	9		15
Bones & Joint			1			1
Enteric Fever	1		27	41	1	70
Enteritis			6	19		25
*Unjustified use		2	20	30	2	54
Total	1	2	60	99	3	165

TABLE 4.6: Indications for which drugs was given versus potential drug – drug interactions.

	Drug – drug interactions						
INDICATION	Ca salts	Fe salts	Zn salts	Minerals multivitamin preparations	(x) Not applicable	(z) Total	No potential for drug – drug interaction
UTI				1	14	15	93.3%
Bone & joint					1	1	100.0%
Enteric fever		1	1	4	64	70	91.43%
Enteritis	1		1		23	25	92.00%
Unjustified use			1	3	49	53	92.45%
Total	1	1	3	8	151	164	

No potential for drug – drug interaction with MVCs = Not applicable (x) x 100%

Total (z)

TABLE 4.7: Adherence to benchmarks for UTI

INDICATOR	Benchmark %	% Of Correct Indicator
Dose	100	100
Dose Frequency	95	100
Dose duration	95	40
No potential drug – drug interaction	90	93.3%

TABLE 4.8: Adherence to benchmarks for bone and joint infection

INDICATOR	Benchmark %	% Of Correct Indicator
Dose	100	100
Dose frequency	95	100
Dose duration	95	Nil
No potential drug – drug interaction	90	100

TABLE 4.9: Adherence to benchmarks for enteric fever

INDICATOR	Benchmark %	% Of Correct Indicator
Dose	100	100
Dose frequency	95	100
Dose duration	95	60.0
No potential drug – drug interaction	90	91.42

TABLE 4.10: Adherence to benchmarks for enteritis

INDICATOR	Benchmark %	% Of Correct Indicator
Dose	100	100
Dose frequency	95	100
Dose duration	95	40
No potential drug – drug interaction	90	92

CHAPTER 5

DISCUSSION

It has been noted through other previous studies undertaken in evaluating antibiotic use in hospitals that up to 50% of prescriptions can be inappropriate (Gould and Jappy 1996). But without the appropriate use of antibiotics/anti-infectives, the ultimate objective of improving the quality of life of patients would be jeopardized.

In this research, the criteria of appropriateness of ciprofloxacin use, was limited to looking at the dose, dose frequency, dose duration and the potential for interaction with multivalent cations.

The dose of ciprofloxacin given was 500mg orally or 400mg when given parenterally. In all the indications studied, they met the benchmark requirement of 90%. Indeed it was 100%.Therefore ciprofloxacin was used appropriately so far as dose was concerned.

Dose frequency was also appropriate as it was 100% in all the cases thus meeting the benchmark requirement of 100%. The dose frequencies were twelve hourly for all the indications studied.

Dose durations were inappropriate for all the justified indications studied. Bone and joint infections had six days instead of the 4- 6 weeks duration. In UTI it was longer for uncomplicated UTI and shorter for complicated UTI. Such a longer duration for uncomplicated UTI has also been noted by Druckenbrod et al 1997. For uncomplicated UTI the maximum duration is usually three days while for complicated UTI it is 10 – 21

days. The benchmark criterion of 95% was not also met in enteric fever. It was 60% for both the 7-10 days and 10-14 days duration. Four to six day duration constituted 38.6%. This is certainly inappropriate and has serious public health implications. This means that there would be a lot of carriers in the system and the disease would continue to be transmitted from person to person. Again it facilitates the development of resistant strains to ciprofloxacin. The development of resistance strains in enteric fever has been noted globally (Motiur et al, 2001) and one of the causes for the development of this is inadequate exposure of organism to the antibiotic (Raveendran 2008). Therefore if the minimum period of 10 days is not adhered to, cure will not be complete. Without proper treatment, typhoid is a serious and frequently relapsing disease that kills up to 10% of those infected (WHO, 2000)

Enteritis is a broad category of diseases that have been put together. The Illustrated Medical Dictionary of the British Medical Association, 2002, defines it as an inflammation of the small intestine. It says the inflammation may be the result of infection due particularly to giardiasis and tuberculosis or Crohn's disease. In each of these instances ciprofloxacin would be a wrong choice of drug. However the same dictionary makes reference to gastroenteritis which is defined as inflammation of the stomach and intestine causing sudden upsets that last for two to three days. Dysentery, typhoid fever, cholera, food poisoning and travelers' diarrheoa are all forms of gastroenteritis. Since typhoid fever is implicated and no culture test was done to disprove that, then one would have expected that the minimum dose duration of ten days for enteric fever would have been used. It is recommended that culture test should be

requested when treatment is initiated this way for enteritis, so that the appropriate chemotherapeutic agent could be administered for the appropriate duration.

The inappropriate use of ciprofloxacin in these conditions will require an intervention to rectify the situation. This intervention may involve education including letters to prescribers, in-service education, workshops, and face to face discussions. (WHO DUE participants' guide). For example Hammerman et al (1997) discovered that performing DUE and distributing the results to the doctors concerned improved appropriateness of ciprofloxacin use in UTI from 65 to 85%. Prescribing restrictions could also be instituted so prescribers would have to refer all suspected cases of typhoid fever to a specialist. (White et al, 1997)

The potential for ciprofloxacin interaction with multivalent cations (MVC) was quite minimal as only a few numbers of cases received co –prescriptions with MVC; 6.7% and 0% in UTI and bone and joint infections respectively. In enteric fever and enteritis the no-potential for interactions were 91.43 and 92.00% respectively. These meet the benchmark criteria of 90%. There is therefore no major need for measures to be put in place to avoid the delivery of less amount of ciprofloxacin to the systemic circulation due to the formation of complexes in the gastric lumen. If the MCVs are required, then they should be administered not within two hours after or six hours prior to the next ciprofloxacin dose (Krastrup, 2000)

CHAPTER 6

CONCLUSIONS AND RECOMMENDATION

6.1 CONCLUSION

All patient folders evaluated with regards to UTI, enteritis, enteric fever and bone and joint infections were found to meet the standard criteria appropriate for ciprofloxacin use with respect to dose, dose frequency and use of multivalent cations. However, in the case of dose duration the evaluation was found to be largely inappropriate for all the justified indications. In addition, about thirty three percent of ciprofloxacin use for unjustified indications was noted. This should be addressed by education and also making the national standard treatment guidelines available to prescribers.

6.2 RECOMMENDATION

Further research should be done to evaluate the appropriateness of ciprofloxacin use for the unjustified indications noted in this study. It is further recommended that the hospital's management attention be drawn to the draw backs observed regarding the inappropriate use of ciprofloxacin, so that specific interventions could be initiated to improve its use for excellent outcomes. Following the implementation of the interventions, another DUE should be conducted to determine the level of adherence to the acceptable standards and its impact on patient outcomes.

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APPENDIX 1

AUDIT OF CIPROFLOXACIN USE AT KNUST HOSPITAL DATA COLLECTION FORM

NUMBER

PATIENT CHART NO

WARD SEX M ☐ F ☐

If female Pregnant ☐

Breastfeeding ☐

Not pregnant ☐

WARD……

AGE 1 – 5 ☐ 6 – 10 ☐ 11 – 15 ☐ 16 – 20 ☐ 21 – 30 ☐

31 – 40 ☐ 41 – 50 ☐ 51 – 60 ☐ 61 – 70 ☐ 71 – 80 ☐

CLINICAL INFORMATION ON CIPROFLOXACIN USE

Infection Diagnosis

Respiratory TI ☐ UTI ☐ Skin &Soft tissue Inf. ☐ Bone & Joint ☐

Enteric Fever ☐ Other GI Infection_____ Others _____

Pre – Ciprofloxacin Antibiotic used? Yes ☐ No ☐

If yes reason for stopping antibiotics_____

Ciprofloxacin use Empirical ☐ Culture ☐

Sample taken for culture Yes ☐ No ☐

If Yes, sample type Blood ☐ Urine ☐ Sputum ☐ CSC ☐ Stool ☐

Others ☐ Specify_____

Culture Results; Growth ☐ No Growth ☐

If growth type of organism Ps aeruginosa ☐ E. coli ☐ Staph aureus ☐

H. influenza ☐ N. gonorrhea ☐ S. typhi - paratyphi ☐

Others_____

Culture sensitivity to ciprofloxacin Yes ☐ No ☐

Ciprofloxacin used alone or in combination? Alone ☐ with one antibiotic ☐

Triple therapy ☐ Others_____

Concurrent antibiotics used Amoxyl/Augmentin ☐ cephalosporin 3rd gen ☐

2nd gen ☐ Metronidazole ☐ Tetracycline ☐ Others (specify)_____

_____

Drug Interaction

Drug – drug AI ☐ Ca salts ☐ Fe salts ☐

Mineral & Multivite prep ☐

Theophylline

Adverse Reaction

Evidence of Adverse Reaction Yes ☐ No ☐

If yes specify_____

Dosage

Dosage determined according to body weight? Yes ☐ No ☐

Dosage regimen continuous infusion ☐ Once daily ☐ Twice daily ☐

Any other_____

Duration of treatment 1 day ☐ 2 – 3 days ☐ 4 – 6 days ☐

7 – 10 days ☐ 11 – 14 ☐ ≤ 14 days ☐

Total No. of cipro doses_____

Treatment complied with protocol Yes ☐ No ☐

Outcome of treatment Death ☐ Survival from serious infection ☐

Improved but died later ☐ Unknown (no feedback) ☐

Clinical cure Resolution of Infection ☐

Bacteriological cure Yes ☐ No ☐

Treatment failure Death from Infection ☐ Dev Resist strain ☐

Death from other causes ☐