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Research Article

Drug Use Evaluation of Ciprofloxacin at Inpatient and Outpatient Departments of Hiwot Fana Specialized University Hospital, Harar General Hospital and Jagol Hospital in Harar City

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ABSTRACT

Background: Ciprofloxacin has been used for chemotherapy of bacterial infections over the years in Ethiopia. However, not much is understood about the standard of its use regarding the appropriateness of clinical indication, dosage administered, dose frequency, duration and potential for interactions with multivalent cations.

Methods: A retrospective drug use evaluation was conducted based on patient prescription records (cross-sectional study) and standard treatment guidelines, which cover a one-year period. The sample size targeted to use was 400 prescriptions. The data were collected and checked for its clarity and compiled in the form of tables, percentages, and graphs.

Results: From a total of 400 prescriptions, 56% of them were prescribed for females. Only 71 (17.75%) have the diagnosis and the prescribed dose of ciprofloxacin was 500mg with BID based in generic form and frequently for seven days. From the total 75% of prescriptions contain drugs with ciprofloxacin. Mostly two drugs were prescribed with ciprofloxacin 42%. Frequently prescribed drug categories with ciprofloxacin were other Antibacterial which accounts for 121 (40.33%) and doxycycline was dominant.

Conclusion: All prescription evaluated with regards to UTI, STI, enteric fever infections were found to meet the standard criteria appropriate for ciprofloxacin use with respect to dose, dose frequency and use of other drugs. However, in the case of dose duration, the evaluation was found to be largely inappropriate for all the unjustified indications.

Keywords: Drug resistance; Irrational use of drugs; Quality improvement; Antibiotic prescribing and standard treatment guideline

INTRODUCTION

One of the foremost pressing problems facing public health providers and administrators in many countries is ensuring the rational use of medicine or drugs. The conference of experts on the rational use of medicine, convened by the World Health Organization (WHO) in Nairobi in 1985 defined rational drug use as "the rational use of drug requires that patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of some time and at lowest cost to them and their community" (Tessema Tsehay Biru. et al. 2014) [1-3].

Rational drug use implies a private approach to patient treatment. The presence of ordinary treatment guidelines and drug formularies for selected drugs in health facilities doesn't make sure that they are prescribed and used correctly. One mechanism to ensure correct prescribing and use is drug use evaluation (DUE) (American society of hospital pharmacists, 2009).

The discovery and use of antimicrobial agents have brought a serious breakthrough in therapy. A lot of previous intractable infectious conditions have now become amenable to antimicrobial therapy. Various classes of antibiotics are discovered and used with varying degrees of success, among these are the quinolones. An older member of this group like the nalidixic acid, have been available for the treatment of urinary tract infection. However, the limited use of this drug coupled with the rapid development of

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resistant strains becomes a problem. Therefore, the introduction of the fluorinated quinolones like ciprofloxacin has become an important therapeutic breakthrough, since these have broad-spectrum antimicrobial activity and a very good pharmacokinetic profile. Their side effects are comparatively fewer and microbial resistance to their action does not develop rapidly (Hamami. RPH, 2009) [4,5].

Ciprofloxacin atypical member of the quinolones group has been incorporated into the Ethiopian national drug formulary/ Standard treatment guideline since, 1990 to date. It constitutes a large portion of health facility budgetary allocation for drugs and it's also the major drug for the management of typhoid and paratyphoid fevers.

Bacterial resistance to agents due to the increasing use of antimicrobial agents has become a worldwide concern. Thus, drug use evaluation (DUE) is one of the useful methods used to combat development of bacterial resistance to antibiotics and also a means of preventing irrational use of antibiotics within the health institution and drug use evaluation asses the prescriber adherence with the available national treatment guideline, knowledge of pharmacotherapeutic and appropriate use of them for intended pharmacological activity and also the presence of empirical treatment. Drug use evaluation is not one process, but it is a continuing and schematic process intended to maintain appropriate and rational schematic use of the drug. It involves considering the presence of rational antibiotics prescribing, dispensing and patient use through examines the individual patient card, patient prescription at dispensing (American society of hospital pharmacists, 2009) [6].

Ciprofloxacin is employed for various diseases in Ethiopia, like Bacillary Dysentery, Gastroenteritis, Pneumonia, Typhoid fever, Chancroid, and Gonorrhea. On the opposite hand, ciprofloxacin and other antibiotics are often used inappropriately resulting in wastage of scarce healthcare resources as well as increasing the risk of the emergence of bacterial resistance (American society of hospital pharmacists, 2009).

Although antimicrobial drugs are among the safest and least toxic of medicine utilized in medical practice, they are also included under the foremost commonly misused of all drugs. Excessive amounts may result in significant toxicities especially in patients with impaired drug excretion or metabolism. The use of too low a dose may end in treatment failure and is presumably to pick for microbial resistance. Hence dosing errors which can be the wrong frequency of administration or the use of either an excessive or sub-therapeutic dose are common in using antimicrobial agents (Meher B. R. et al 2014) [7-9].

Antibiotics use has been effective in the treatment of infectious disease, but the emergence of resistant bacteria is now becoming a global concern. Patients in many hospitals staffed by highly competent personnel are dying as a result of infection by resistant bacteria in developing and developed countries. Another problem with the use of antibiotics is when use inappropriately results in dangerous adverse drug reaction. One of the major consequences of such inappropriate use of antibiotics is the development of resistant strains of the very susceptible organism. Inappropriate treatment could also lead to the eventual death of the patient. Indeed, the WHO report on infectious disease 2000 indicates that "without proper treatment of typhoid with ciprofloxacin is a serious and frequently relapsing disease that kills up to 10% of those infected" (Goldman, MP., 1990) [10].

Thus, unfortunately, overuse and inappropriate use may erode the clinical utility of fluoroquinolones (FQs) such as ciprofloxacin, sparfloxacin, enoxacin and gatifloxacin. Therefore, drug use evaluation is critical to overcoming this problem. Evaluation of ciprofloxacin use is therefore critical for controlling the emergence of resistant strains also as lowering unnecessary expenditures and also ensuring that patients derive maximum enjoy from its use. Therefore, the objective of this study was to evaluate ciprofloxacin use in the outpatient and inpatient departments of Hiwot Fana Specialized University Hospital (HFSUH), Harar General Hospital (HGH) and Jagol Hospital (JH).

METHODS

Description of the study area

The Harari region is located at 515KM east of the Ethiopian capital city, Addis Ababa. Harari region was surrounded by the State of Oromiya region, Eastern Harerghe Zone and the study was done in three hospitals in Harar Town.

Study design

Institutional based on a retrospective cross-sectional descriptive study design was conducted.

Source population

The source for this study was all the patient prescriptions in the three hospitals during the period of Jan 1, 2016, to Jan 1, 2017.

Study population

The study population for this research was all prescription of outpatients and inpatients containing ciprofloxacin in the three hospitals assessed during the period of Jan 1, 2016, to Jan 1, 2017.

Sample size

The sample size was calculated by using the formula for estimating a single proportion to the patient's service in the three hospitals. The precision of 5% and a confidence limit of 95% were assumed in the sample size determination. The sample size uses the following formula to calculate.

$$n = z^{2}\frac{pq}{d^{2}}$$

q= 1-p which is 1-0.5=0.5

ni= Sample size from finite population.

Z= the standard score (critical value) corresponding to 95% confidence level = 1.96.

d= the proportion of sampling error between the sample and the population = 5% (0.05).

P =ciprofloxacin uses in outpatients and inpatients.

$$ni = \frac{1.96^{2}(0.475)(0.525)}{(0.05^{2})} = 383$$

Since sampling was from a finite population of size (N) less than 10,000, the final sample size, n, was calculated by using finite population correction formula and because sampling is from a finite population of size, N, total number of patient within the area, then the ultimate sample size, n, was calculated by applying finite population correction formula as follows. The previous history

indicates that about 20 prescriptions that contain ciprofloxacin for the patient visiting HFSUH are totally estimated to be about 7500 annually.

$$n = \frac{n_0}{\left(1 + \frac{n_0}{N}\right)},$$

where, no = 383 and N = 7500 monthly

Adding a 10% non-response rate (incomplete prescription), the final sample size was calculated to be, n = 383

n = required sample size when target population is < 10,000

N = Population target

Therefore 383/(1+(383/7500)) = 364.391

= 364

Contingency = Sample size + 10%

= 364.7 X 10%

= 364 x10/100

≈ 36

= 36+364

= 400

The minimum sample size of this study was 400 individuals, where, n = 400

Sampling technique

The systematic random sampling technique was employed to select study respondents from the clients. The study subject was selected using a probability sampling method. So, we selected a prescription from an already arranged setting or from allocated room services until the required sample size allocated 400reached from the three hospitals.

From the available prescription that contains ciprofloxacin 7500 within specified study period the select sample by systematic random sampling, N=7500/400 =19 so, the targeted prescription was selected every 19 prescriptions from pre-documented prescription.

Data collection method

A checklist was used to assess patient ciprofloxacin utilization. The checklist was including information on the Ciprofloxacin utilization and relating factors of antibiotic management. The checklist was used to collect the pertinent data from the documented prescription.

Four enumerator drug lists have conducted the filling process of a checklist and they were supervised by the researchers. Data was collected by filling the checklist technique using a checklist that was filled by enumerators.

Data processing and analysis

The responses were systematically tabulated and analyzed using percentages, tables and explanations separately or together depending on the nature of questions by using computer excel and calculator for analyzing the data. Finally, the findings of the study were summarized and discussed based on the nature of the questions.

RESULTS

Socio-demographic characteristics

A total of 400 patient prescriptions containing ciprofloxacin orders were included in the study from the three hospitals. Two hundred thirty-four (56%) of them were females. The age range was between fifteen and seventy-five years with a mean age of 36 Table 1.

From a total of 400 prescriptions, only 71 (17.75%) have the diagnosis. The most common route of administration was oral and the commonly prescribed dose was 500mg 386 (96.5%) with BID based in generic form and frequently for seven days Table 2.

The number of drugs per prescription indicates 42% of the prescription contains two drugs and 5% of the prescription contains four drugs. From the total of 400 prescriptions, 300 (75%) of them contain more drug prescribed with ciprofloxacin about 83% in the oral route of administration. Frequently prescribed drug categories with ciprofloxacin were other Antibacterial which accounts for 121 (40.33%). From the total of 121 antibacterial drugs, 46 (38%) was

Table 1. Age and sex distribution of patients with ciprofloxacin indication in the out Patient and inpatient department of the hospitalsfrom Jan 1, 2016, to Jan 1, 2017, n=400.

Variables	Categories	Number	Percent
Age	<20 year	31	7.80%
	21-30year	80	20.00%
	31-40 year	107	26.64%
	41-50year	97	24.35%
	>51 year	85	21.10%
Sex	Male	166	41.5%
	Female	234	58.5%

Table 2. Prescribing pattern and utilization of ciprofloxacin in the hospitals from Jan 1, 2016 to Jan 1, 2017, n=400.

Variables	Response	Frequency	Percent
Diagnosis	Yes	71	17.75
	No	329	82.25
Route of Administration of ciprofloxacin	Injectables (Iv)	10	2.5
	Oral	384	96
	Eye Drops	6	1.5
Dose	500mg	386	96.5
	250mg	14	3.5
Frequency	BID	367	91.75
	TID	16	4.00
	Stat	17	4.25
Duration	For seven days	181	45.25
	For 10 days	82	20.5
	For five days	98	24.5
	For three days	9	2.25
	For fourteen days	13	3.23
	For once	17	4.75
Prescribed in name	Generic	391	97.75
	Brand	9	2.25
	Total	400	100

Doxycycline followed by Ceftriaxone 36 (30%). From a total of 400 prescriptions, only 71 (17.75%) have the diagnosis.

The most common indication of ciprofloxacin was typhoid's followed by urinary tract infection. In three hundred twenty-nine (82.25%) of the cases, ciprofloxacin was indicated inappropriately based without the diagnosis Table 3.

Regarding the dosage regimen out of 400 prescriptions, 346 (86.5%) had correct ciprofloxacin dosing, 361 (90.25%) had the correct frequency of administration and 368 (92.5%) cards had a correct duration Table 4.

The common disease treated by ciprofloxacin

The most common disease treated by ciprofloxacin was indicated in the diagnosis part of the prescription from a total of 400 prescriptions only 71 (17.75%) of them contain diagnosis. Mostly ciprofloxacin prescribed for Typhoid 33 (46.48%), 21 (29.58%) of ciprofloxacin prescribed for UTI related infectious and 17 (23.94%) of them indicated as STI.

DISCUSSION

The purpose of drug use evaluation is to make sure that drugs are used appropriately, safely and effectively to enhance patient health status. In addition, continual improvement within the appropriate and effective use of medicine has the potential to lower the general cost of care. The success of treatment largely depends on the power of a physician to diagnose the main health problems of patients, select the right drug, dosage form, and route of administration, foresees probable adverse reactions and drug interactions, and stop unnecessary or dangerous duplication of therapy. Drugs need to be prescribed appropriately, on the idea of clinical diseases identified through diagnosis. Hence, prescribers should consider WHO recommendations and up-to-date information while prescribing any drug. The study showed that 86.5% of the Ciprofloxacin indication or diagnosis was not specified as per the WHO indication criterion [11,12].

Table 3. Co-administer drugs with ciprofloxacin in the hospitals fromJan 1, 2016, to Jan 1, 2017, n=400.

Variables	Response	Frequency	Percent
Co-administer	Yes	300	75.00
	No	100	25.00
Route of administration with	Injectable	19	6.33
	Oral	250	83.33
	Injectable and Oral	31	10.33
Type of co-administrated drug	Antibacterial	121	40.33
	Antacids	67	22.33
	Anti-helmets	23	7.67
	Anti-protozoa	42	14.00
	Vitamins and Minerals	23	7.67
	Analgesics only	16	5.33
	Endocrine Drugs	8	2.67
Antibacterial frequently prescribed	Ceftriazone	36	29.75
	Gentamycin	8	6.61
	Azithromycin	25	20.66
	Erythromycin	6	4.96
	Doxycycline	46	38.02

Table 4. Dosage regimen (dose, frequency, duration) of ciprofloxacin in the hospitals from Jan 1, 2016 to Jan 1, 2017, n=400.

Indicators	Categorical	Frequency	Percent
Dose	Correct	346	86.50
	Incorrect	54	13.50
Frequency	Correct	361	90.25
	Incorrect	39	9.75
Duration	Correct	368	92.50
	Incorrect	32	7.50

This study was performed based on the indicators about 90% which was lower when compared to a study from Boru Meda Hospital, Ethiopia (95%) (TessemaTsehay Biru. et al. 2014) and Kwame Nkrumah University of science and technology Hospital, Kumasi (100%).

Different doses of ciprofloxacin are used for a variety of infections and age groups. Under-dose use of the drug results in ineffective control of infectious diseases while overdosing results in toxicity problems. Therefore, an optimal dose has to be used for optimal treatment outcomes. 87% correct dose, practices were revealed in the study. This is less than the percentage revealed from a retrospective study conducted in Boru Meda Hospital which showed that 92.5% ciprofloxacin dosing was correct, 7.5% regimens were an overdose and there was no under dose (Tessema Tsehay Biru et al. 2014). Drug resistance has become an exceptional problem related to the utilization of antimicrobial agents. Prolonged or short duration use of ciprofloxacin, can lead to the emergence of microbial drug resistance.

Therefore, it should be used appropriately and properly as directed to stop resistance. Inappropriate duration of therapy was another major problem revealed by this study. 92.5% ciprofloxacin use was with the correct duration of therapy which is lower from the criteria set for ciprofloxacin duration of therapy (95%).

This study indicates about 3% of the indications were with longer treatment periods of ciprofloxacin used while short treatment periods accounted for 2.25% of indications which can lead to the development of resistance.

This result showed the higher percentage of correct duration as compared with a retrospective study wiped out at Boru Meda hospital, South Wollo Zone, which revealed 45% long duration and a couple of 2.5% short duration of therapy (Tessema Tsehay Biru. et al. 2014). The simultaneous use of two or more drugs is suggested in specifically defined situations as supported in pharmacological rational. However, the choice of an appropriate combination requires an understanding of the potential for interaction between the drugs. Interactions may, otherwise, affect the patient negatively, from the study; it was found that 300 (75%) of ciprofloxacin use had one or more interacting drugs of which antacids accounted 67 (22.33%) which have potential interactions. The study showed a high percentage of drug interaction as compared with a retrospective study done in Boru Meda Hospital which revealed 40% and antacid interaction 12.5%. Absorption of the drug may have interfered with an antacid containing Al or Mg because it forms a complex with ciprofloxacin and decreases ciprofloxacin absorption.

Prescribing drugs against contraindications should be avoided unless the advantage of doing so outweighs the danger. Ciprofloxacin was used in the cases, which is a contraindication, children under 18 years old when other drugs are available but it is not absolutely contraindicated.

The analysis of actual performance versus the set criteria indicated that there was poor performance compared to the set criteria. A similar result was obtained from the study from Boru Meda Hospital apart from indication which was better performance.

In this study three hundred twenty-nine (82.25%) of the cases, ciprofloxacin was indicated without the diagnosis. Regarding the dosage regimen out of 400 prescriptions, 346 (86.5%) had correct ciprofloxacin dosing, 361(90.25%) had the correct frequency of administration and 368 (92.5%) cards had correct duration. This study was in line to a study conducted in Dessie Referral Hospital on the bases of dose 275 (87%) and frequency two hundred ninety-seven (93.99%) were consistent with the WHO indicators. Two hundred four (64.56%) of the cases had the correct duration of treatment (Oumer Muhammed, 2015). Except for diagnosis this study was consistent with the study done in Netherlands on the appropriateness of the ciprofloxacin utilization with these appropriate prescriptions significantly increased and only fewer inappropriate prescriptions were prescribed at this time, 23 ciprofloxacin prescriptions per admissions were prescribed, an entire reduction of 71.3% compared with baseline (Chandel, D.S. et al. 2000). This study was also sharing some findings consistent with the retrospective study conducted in Central North Carolina indicates from 10 community there was inappropriate use of ciprofloxacin was identified (Richard W Druckenbrod, et al 2014).

Only 17.75% of the prescription has a diagnosis as ciprofloxacin was proper and this result was in line to (Goldman, MP., 1990) which indicates only 17% was with appropriate indication and lower than (Pickering. et al, 1994) with 25% appropriate indication to choose ciprofloxacin. This inappropriateness of prescribing ciprofloxacin leads to drug resistant as showed in some study resistant organisms may emerge as a result of many factors, including irrational use of drugs one form of which is irrational prescribing practice. Studies have shown that 22-65% of antibiotic prescriptions are inappropriate (Raveh D. et al, 2006) [9].

Proper prescribing indicated by the most common route of administration of ciprofloxacin was oral and the commonly prescribed dose was 500mg 386 (96.5%) with BID based in generic form and frequently for seven days. This result was inconsistent with Lebanon studies those shows only dosing of these agents was adequate in only 74.6% of treatment. Based on the results of this study, the most clinical interventions for the long run were involved adjusting the dose and duration of fluoroquinolones (Wissam K Kabbara, et al., 2015) [12,13].

CONCLUSION

Few prescriptions evaluated with regards to UTI, STI, typhoid's as common disease prescribed ciprofloxacin for and this study indicates only 17.75% of the prescription has the diagnosis that indicates why ciprofloxacin was prescribed. These were found to meet the standard criteria appropriate for ciprofloxacin use with respect to dose, dose frequency and use of other drugs. However, in the case of dose duration, the evaluation was found to be largely inappropriate for all the unjustified indications. In addition, many of ciprofloxacin use for unjustified indications were noted. This should be addressed by education and also making the national standard treatment guidelines available to prescribers.

Further research should be done to guage the appropriateness of ciprofloxacin use for the unjustified indications noted during this study. It is further recommended that the hospital's management attention be drawn to the drawbacks observed regarding the inappropriate use of ciprofloxacin in order that specific interventions might 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 acceptable standards and its impact on patient outcomes.

LIST OF ABBREVIATIONS

AFI: Acute Febrile Illness; CFX: Ciprofloxacin; DUE: Drug Use Evaluation; DUR: Drug Use Review; ENDF: Ethiopian National Drug Formulary; FQ: Fluoroquinolones; HFSUH: Hiwot Fana Specialized University Hospital; HGH: Harar General Hospital; JH: Jagol Hospital; LRTI: Lower Respiratory Tract Infection; RDU: Rational Drug Use; STD: Sexually Transmitted Disease; STG: Standard Treatment Guideline; UTI: Urinary Tract Infection; URTI: Upper Respiratory Tract Infection.

DECLARATIONS

Ethical Consideration

Prior to data collection, a formal letter was written from Haramaya University, College of Health and Medical Science School of pharmacy to Hiwot Fana Specialized University Hospital, Harar General Hospital and Jagol Hospital in order to get permission to conduct the study. Then we conducted the study using patient prescriptions' data in these hospitals. The institutional review boards at Haramaya University and each participating hospital approved the study protocols.

Consent for Publication

Not applicable. Because the source of data in this study was all the patient prescriptions in the three hospitals

Availability of data and materials

All the data that support the findings of our study are available at Hiwot Fana Specialized University Hospital, Harar General Hospital, and Jagol Hospital but restrictions apply to the availability of these data, which were used only for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of these hospitals.

Competing Interests

The authors declare that they have no competing interests

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Authors' contributions

Mr. Alemu Tadesse and Mr. BirhanuMotbaynor contributed to the design and implementation of this research, to the analysis of the results and to the writing of the manuscript.

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