Original Research Article

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Analysis of adverse reactions associated with use of fluoroquinolones - a retrospective study

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Abstract

Fluoroquinolones are the most commonly prescribed antibiotics in infections like respiratory tract infections, urinary tract infections. Serious adverse reactions (ADR) reported with certain drugs of this class resulted in withdrawal or restriction to its use. Spontaneous reporting of ADRs has placed a major role in identifying these issues. The present study was aimed to analyze the pattern of ADRs implicated to fluoroquinolone in an ADR monitoring Centre through spontaneous reporting. A total of 24 ADRs associated with the use of fluoroquinolones were reported during the evaluation period. Upon evaluation of the patient characteristics in the reported ADRs, more reports were in females (54.16%). Fluoroquinolone antibiotic most commonly implicated in the reactions included ciprofloxacin (62.5%) followed by levofloxacin (29.1%) and ofloxacin (8.3%). Among the severe reactions (n = 5), the most commonly involved system organ class was skin and appendages. Mild and Moderate reactions involved Neurological and Gastrointestinal disorders. In 83%, the reaction was considered to be preventable. Periodic evaluation of ADR is very essential in a hospital set up and it can complement institutional risk management strategies as well as drug safety evaluation.

Keywords: Fluoroquinolones, spontaneous reporting, drug safety, adverse reactions, retrospective study

1 Introduction

Fluoroquinolones are the most commonly prescribed antibiotics among inpatient and out patients in hospitals [1]. They are used in treatment of various infections like respiratory tract infections, urinary tract infections, sexually transmitted diseases and skin and soft tissue diseases [2]. Increases in the use of fluoroquinolones in recent years have coincided with steady increases in the incidence of fluoroquinolone-resistance among gram-negative bacilli in intensive care units [3]. Some serious adverse reactions reported with certain drugs of this class resulted in withdrawal or restriction to its use. Example temafloxacin, was withdrawn from the market due to hemolysis, renal failure and hypoglycemia; trovafloxacin was withdrawn due to its hepatotoxic nature; grepafloxacin was withdrawn because of torsades de pointes; and sparfloxacin as a result of phototoxicity and torsades de pointes [4-6].

Interestingly, all of these drugs demonstrated safety in preapproval clinical trials. Serious adverse drug reactions (ADRs) were only detected after drugs were administered to a larger patient population. For more than two decades, the safety of fluoroquinolones (FQs) was under investigation. These frequently used antibiotics are now used only when no other alternatives are applicable, due to some serious adverse effects, by the recent warnings, for some common conditions like uncomplicated urinary tract infections (UTIs) and acute bacterial infections of the sinus and bronchi [7]. There are not many published studies which tried to analyze the pattern of ADRs reported on fluoroquinolone drug class. Only few published studies are available which tried to characterize the nature of ADRs to fluoroquinolones encountered in a hospital set up [8].

Spontaneous reporting of ADRs has placed a major role in the identification of these safety issues to fluoroquinolones and thereby help in ensuring safer use of this class of antibiotics. Periodic evaluation of ADR related data generated is equally important in characterizing the pattern of ADRs and thereby help in designing steps to improve the safety of drug use in the working set up. Data generated from the tertiary care hospital contributes to the national and international safety database thereby contributing to the common goal of a safer drug use.

The present study was aimed to analyze the pattern of ADRs implicated to fluoroquinolone antibiotics reported spontaneously to the ADR monitoring centre and to determine whether their route of administration, duration, and dose and form play a significant role in the development of adverse effects.

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2 Materials and methods

This study involved active ADR monitoring for prescribed fluoroquinolones in all departments, Govt. Stanley Medical College and Hospital, Chennai, Tamil Nadu, India. ADR reporting from Pharmacovigilance Programme of India (PVPI) was used to collect the data. This study was approved by the Institutional Ethics Committee and was conducted in accordance with the best practices of good clinical practices (GCP) outlined in ICH guidelines available in https://ichgcp.net/. ADR's related to fluoroquinolones notified over a period of two years (Jan 2018 – Dec 2019) was selected for evaluation. All suspected ADR's were initially assessed by the attending physician and subsequently the information was analyzed by the pharmacologists in the Department of Pharmacology. Collected data were evaluated to understand the pattern with respect to patient demographics, nature of the reactions, characteristics of the drugs involved and outcome of the reactions. Causality, severity, and preventability of reaction were analyzed.

Patient's age and sex were considered for evaluation. In agreement with previous published research articles [9], patients were subdivided into six age groups; infants, children and adolescents (0–15 years), young adults (16– 30 years), adults (31–45 years), older adults (46–60 years), elderly adults (61–75 years), and very elderly adults (over 75 years).

Individual reactions were classified depending on the type of reaction as type A (Augmented) and type B (Bizarre) based on the classification by Rawlins and Thompson [10]. ADR's for which frequency is available in the literature were classified into very common, common, uncommon, rare, and very rare based on the reported frequency of the reaction [11].

Reactions were codified and were further classified to various system organ classes depending on World Health Organization Adverse Reaction Terminology (WHO-ART) [12].

Causality assessment was carried out using the ''WHO causality assessment scale''. In the WHO causality assessment, the drug reaction is classified as certain, probable/likely, possible, unlikely, inaccessible/unclassifiable. For preventability assessment, ADR's were categorized into definitely preventable, probably preventable and not preventable using the criteria of Schumock and Thornton modified by Lau et al [13]. Depending upon the severity, ADRs were classified into mild, moderate and severe reactions using the criterion developed by Hartwig et al. for severity assessment [14].

3 Results and discussion

Fluoroquinolones group of antibiotics have made a major contribution in the care of infected patients and they are widely prescribed. Even though they are generally considered as safe drugs, there have been concerns regarding the safety of agents in this class of Drugs. The present study was aimed at analyzing the pattern of ADRs implicated to fluoroquinolone antibiotics reported spontaneously to the ADR reporting unit of a tertiary care teaching hospital in India. An analysis of spontaneous reporting data on ADRs to fluoroquinolones in three Italian regions demonstrated that this class of agent was attributed to 4.3% of total ADRs reported and 22.5% of ADRs attributed to systemic antimicrobials [15]. In our study, a total of 24 ADRs associated with the use of fluoroquinolones were reported during the evaluation period. Upon evaluation of the patient characteristics in the reported ADR's, more reports were in females (54.16%), and the details were tabulated in Table 2. When considering the age criteria, more cases were reported in young adults (29%) and the details were tabulated in Table 1.

Table 1. Age wise distribution of ADR's

Age group	Number (%) of ADR reports
0-15	3 (12.5%)
16-30	5 (20.8%)
31-45	7 (29.1%)
46-60	4 (16.6%)
61-75	2 (8.3%)
>75	3 (12.5%)
Total	24

Earlier studies suggest that incidence of adverse effects with fluoroquinolones is not higher in the elderly than in the younger population [16]. And considering the nature of the reactions reported, type A reactions (66.6%) accounted for majority and more were described to be common (Table 3). Fluoroquinolone antibiotic most commonly implicated in the reactions included ciprofloxacin (62.5%) followed by levofloxacin (29.1%) and ofloxacin (8.3%). The results were given in table 4.

The system organ class most commonly affected was skin and appendages (75%) and the most reported reactions were skin rash and itching (Table 5). The pattern was similar to the data reported in earlier studies [17, 18].

In majority (87%) of the reactions, the suspected drug was withdrawn for the management of the ADR and an additional treatment for the reaction was instituted in 50% of the reactions. Rechallenge of drug was not done in any condition. In 69% of the reactions, the patient recovered from the reaction at the time of evaluation of the ADR report. Upon causality assessment, majority of the reports were rated as possible (58.3%) followed by probable (33.33%) (Table 6).

Moderate and mild reactions accounted for 50% and 25% of the reactions respectively. On severity assessment, 25% of the reactions were deemed to be severe as presented in Table 7.

Among the severe reactions (n = 5), the most commonly involved system organ class was skin and appendages. 'Mild and Moderate reactions' involved neurological and gastrointestinal disorders. In 83%, the reaction was considered to be preventable (definitely or probably preventable) as depicted in Table 8.

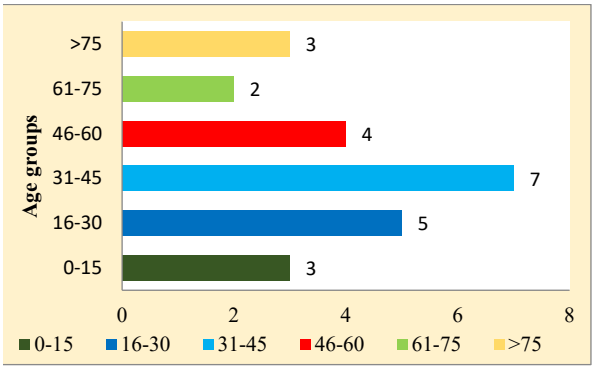

Fig. 1. Graphical Presentation of ADR's based on Age

Table 2. Analysis of ADRs based on Gender

Gender	Number (%) of ADR reports
Male	11(45.83%)
Female	13(54.16%)
Total	24

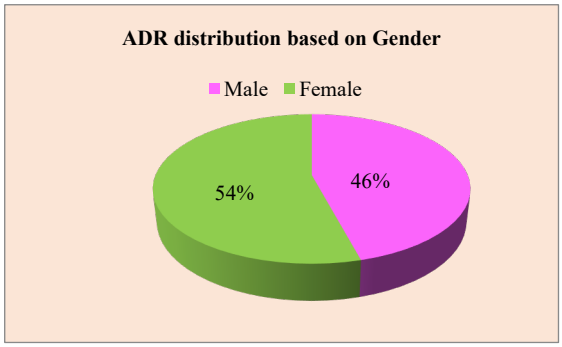

Fig. 2. Graphical Presentation of ADR's based on Gender

Table 3. Analysis of ADRs based on Type of Reaction

Gender	Number (%) of ADR reports
Type A	16 (66.66 %)
Type B	8 (33.33%)
Total	24

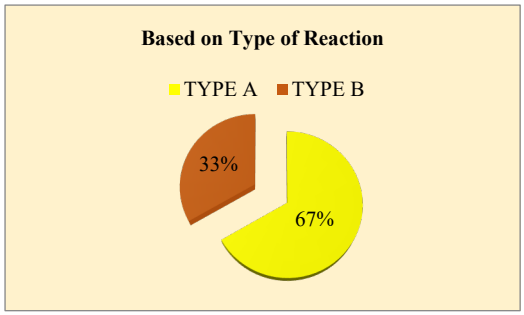

Fig. 3. Graphical presentation of ADR's based on Type of Reaction

4 Limitations of the study

As the denominator data on the patients who received fluoroquinolone is not available, due to missing drug consumption data especially outside the hospital, we could not assess the overall incidence of ADRs to fluoroquinolones as well as based on the patient demographics. Under reporting, was one of the well-known limitation in spontaneous reporting method should be taken into consideration while analyzing the data.

Table 4. Analysis of ADRs based on Individual Drugs involved

Drugs	Number (%) of ADR reports
Ciprofloxacin	15 (62.5%)
Levofloxacin	07 (29.1%)
Ofloxacin	02 (8.3%)
Total	24

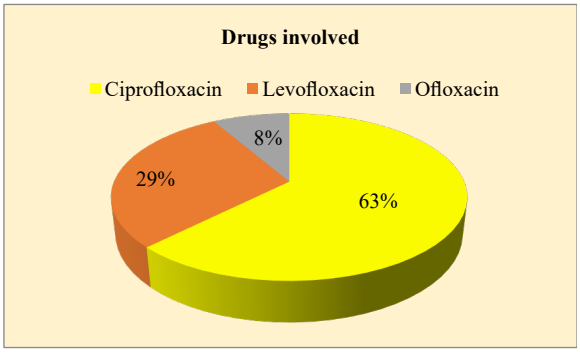

Fig. 4. Graphical presentation of ADR's based on Drugs Involved

Table 5. Analysis of ADRs based on system organ classes affected and reactions reported

System-organ class affected and the specific suspected ADRs in preferred term	Number (%) of ADR	Reaction	Number (%) of ADRs
Skin and appendages disorder (SOC code 0100)	18	Skin rash	3 (12.5%)
		Itching	3 (12.5%)
		Stevens-Johnson syndrome	3 (12.5%)
		Toxic epidermal necrolysis	2 (8.3%)
		Erythema multiformae	1 (4.16%)
		Fixed drug eruption	6 (25%)
Neurological disorders (SOC code 0400	01	Drowsiness	1 (4.16%)
Gastrointestinal disorders (SOC code 0600)	05	Diarrhea	2 (8.3%)
		Gastritis	3 (12.5%)

5 Conclusion

Our study was based on the reactions obtained by spontaneous reporting program and includes patients who

Table 6. Analysis of ADRs based on Causality

Category	Number (%) of ADRs
Certain	2 (8.3%)
Probable	8 (33.33%)
Possible	14 (58.33%)
Unlikely	0 (0%)

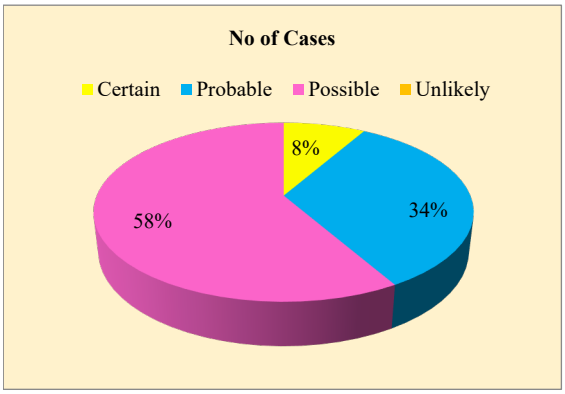

Fig. 5. Graphical presentation of ADR's based on Causality

Table 7. Analysis of ADRs based on Severity

Category	Number (%) of ADRs
Mild	6 (25%)
Moderate	12 (50%)
Severe	6 (25%)

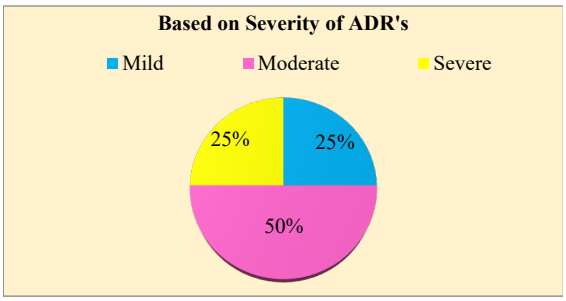

Fig. 6. Graphical presentation of ADR's based on Severity

developed ADR after receiving the fluoroquinolone antibiotic during hospital stay as well as patients who received the drug outside the hospital, developed an ADR. Fluoroquinolone antibiotics contributed to good number of ADR's. Periodic evaluation of ADR is very essential in a hospital set up and it can complement institutional risk management strategies as well as drug safety evaluation.

Table 8. Analysis of ADRs based on its Preventability

Category	Number (%) of ADRs
Definitely preventable	12 (50%)
Probably preventable	8 (33.33%)
Not preventable	4 (16.6%)

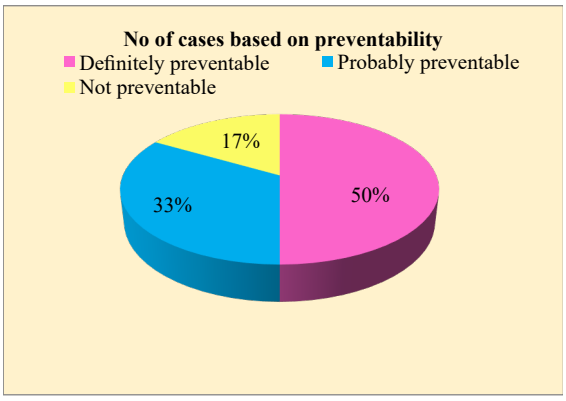

Fig. 7. Graphical presentation of ADR's based on Preventability

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Conflict of interest

None.

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