OPEN ACCESS Freely available online

Advances in Pharmacoepidemiology and Drug Safety

Review Article

Safety Review of Quinolone and Fluoroquinolone Containing Medicinal Products: Global Regulatory Scenario and Way Forward

Muhammad Haseeb Tariq[1*], Muhammad Junaid Farrukh[2], Syed Azhar, Syed Sulaiman[1,3], Obaidullah4

[1]*Discipline of Clinical Pharmacy, School of Pharmaceutical Sciences, University Sains Malaysia 11800 Penang, Malaysia*

[2]*Department of Clinical Pharmacy, Faculty of Pharmaceutical Sciences, UCSI, University, Kuala Lampur, Malaysia*

[3]*Advance Medical and Dental Institute, Universiti Sains Malaysia, Bertam, Penang, Malaysia*

[4]*Division of Pharmaceutical Evaluation and Registration (P.E&R), Drug Regulatory Authority of Pakistan (DRAP), G-9/4, Islamabad, Pakistan*

ABSTRACT

Drugs are introduced into the market for use by the patients after year's long drug development processes including extensive clinical trials and stringent approval pathway by drug regulatory authority keeping in view safety, efficacy and quality parameters. Drugs are usually approved after successful completion of phase III clinical trial. Post marketing surveillance or phase-IV clinical trials are focused on long term safety studies and may continue for years. Drugs are withdrawn from the market if serious adverse events appeared even after approvals like withdrawal of rofecoxib [1].

Keywords: Drugs, Quinolones, Nalidixic acid, Catheter-related bloodstream infections (CRBSI)

INTRODUCTION

Quinolones are a class of antibacterial agents which acts by inhibition of bacterial topoisomerase II (DNA gyrase) and topoisomerase IV in Gram-positive species, thus inhibiting tertiary negative supercoiling of bacterial DNA [2]. The history of quinolones started in 1962 with development of Nalidixic acid [3]. Initially, within a decade few quinolones including oxolinic acid, cinoxacin and pipemidic acid were developed which have slightly improved activity towards Gram-negative bacteria. However the breakthrough to broad spectrum activity especially against Gram-negative bacteria waited a further 10 years before development of fluoroquinolones by fluorination at 6-position. Since the mid-1980s much efforts were employed in the synthesis of more potent and broad spectrum quinolones, which resulted in development of ciprofloxacin, ofloxacin and then levofloxacin which have good penetration in most bodily tissues along with acceptable bioavailability thus covering a broad range of indications involving respiratory, genitourinary, gastrointestinal and skin and soft tissues [2].

MATERIALS AND METHODS

The next significant advancement occurred in 1990s with the development of new moieties including temafloxacin, sparfloxacin, trovafloxacin, clinafloxacin, grepafloxacin and sitafloxacin having four to eight folds greater activity against Gram-positive, Gram-negative and anaerobes. However, unexpected toxicity including haemolytic uremic syndrome, photo toxicity, hepatotoxicity, significant QT prolongation and hypoglycaemia led to withdrawal or suspension of all these molecules [4]. Fortunately, new 8-methoxyquinolones including oral, intravenous and ophthalmic moxifloxacin and gatifloxacin were developed which had 10 folds greater activity than previously available second generation agents. Later on the oral and infusion dosage forms of gatifloxacin were withdrawn but the ophthalmic gatifloxacin is still available and is not associated with serious toxicities [5].

Currently the 1st generation quinolone antibiotics are not available in USA, Canada or have been previously withdrawn due to safety concerns, while some quinolones including

***Corresponding author:** Muhammad Haseeb Tariq, Discipline of Clinical Pharmacy, School of Pharmaceutical Sciences, University Sains Malaysia 11800 Penang, Malaysia, Tel: 923008343304; E-mail: haseebrph@gmail.com

Received Date: December 06, 2021; **Accepted Date**: December 20, 2021; **Published Date**: December 27, 2021

Citation: Muhammad HT (2021) Safety Review of Quinolone and Fluoroquinolone containing Medicinal Products: Global Regulatory Scenario and Way Forward. Adv Pharmacoepidemiol Drug Saf Vol.10:621.

cinoxacin, nalidixic acid and pipemidic acid is available in the European market. The fluoroquinolones are recommended as first line drugs in following conditions: treatment of urinary tract infections including acute uncomplicated pyelonephritis, acute complicated cystitis or catheter associated-UTI without upper tract symptoms, Acute Complicated Pyelonephritis or Urosepsis or CA-UTI patients who are severely ill, Acute Bacterial Prostatitis and Chronic Bacterial Prostatitis [6].

Management of community acquired pneumonia in outpatient settings in presence of co-morbidities (i.e. chronic heart, lung, liver or renal disease, diabetes mellitus; alcoholism; malignancies; asplenia; immunosuppressing conditions or use of immunosuppressing drugs; or use of antimicrobials within the previous 3 months, in-patients with non-ICU treatment or in special concerns when pseudomonas is considered to be causative agent [7].

Management of Diabetic Foot Infections (DFI) of moderate severity where hospitalization is warranted, and severe DFI where ICU admission may be required to avoid life or limb threatening condition [8].

Suggested empiric treatment options for clinically suspected ventilator-associated pneumonia in units where empiric methicillin-resistant staphylococcus aureus coverage and double antipseudomonal /gram-negative coverage are appropriate [9].

Empiric antimicrobial therapy in adults with infectious diarrhea [10].

Antibiotic lock therapy in outpatient management of Catheter-related bloodstream infections (CRBSI) [11].

The United States Food and Drug Administration (FDA) first added a boxed warning of increased risk of tendinitis and tendon rupture to fluoroquinolones in July 2008. Another box warning of risk of worsening symptoms for those with myasthenia gravis was added in February 2011. Based on these developments the agency decided to update the label to describe the potential for irreversible peripheral neuropathy in August 2013. FDA Advisory Committee in November 2015 discussed the risks and benefits of fluoroquinolones for the treatment of acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis and uncomplicated urinary tract infections based on new safety information. On May 12, 2016, United States Food and Drug Administration (USFDA) published a safety announcement as a result of safety review, which have demonstrated that systemically used fluoroquinolones are associated with potentially permanent serious side effects involving tendons, muscles, joints, nerves, and central nervous system which may lead to permanent disability. Based on these findings FDA advised that these serious side effects outweigh the benefit for patients with acute sinusitis, acute bronchitis, and uncomplicated urinary tract infections who have other treatment options and thus the use of these drugs should be reserved for those who do not have alternate treatment options [12]. The safety announcement was readily followed by FDA news release warning on July 26, 2016 [13]

Health Canada, the national public health department of Canada also triggered a review of fluoroquinolones after FDA and published the summary safety review on January 23, 2017, which recommended that the safety information for all fluoroquinolone products be updated to include information about this rare but serious risk. The Health Canada also provided list of approved fluoroquinolones which included ciprofloxacin, moxifloxacin, levofloxacin, norfloxacin, ofloxacin [14].

In view of the above, Germany decided to refer the matter to the Pharmacovigilance Risk Assessment Committee (PRAC) on February 01, 2017 for its recommendation to decide the marketing authorizations status of these products. The referral contained 14 drugs including nalidixic acid, pipemidic acid, cinoxacin, enoxacin, pefloxacin, lomefloxacin, ciprofloxacin, levofloxacin, ofloxacin, moxifloxacin, norfloxacin, prulifloxacin, rufloxacin and flumequin in all strengths, and pharmaceutical forms for systemic and inhalational use [15].

PRAC completed its review on October 05, 2018 and recommended restrictions on the use of fluoroquinolones and quinolone antibiotics due to disabling and potentially long-lasting side effects. The PRAC recommended that all quinolone antibiotics should be removed from the market because they are authorized for infections that should no longer be treated with this class of drugs. PRAC further recommended that fluoroquinolone antibiotics should not be used to treat infections that are not severe or for mild or moderately severe infections unless the commonly recommended medicine cannot be used, for preventing traveller's diarrhoea or recurring uncomplicated urinary tract infections. The recommendations of PRAC were forwarded to Committee for Medicinal Products for Human Use (CHMP) for its opinion [16].

RESULTS & DISCUSSION

The CHMP through its publication dated November 16, 2018 endorsed the recommendations for PRAC and concluded that the marketing authorization of quinolone antibiotics including cinoxacin, flumequin, nalidixic acid, and pipemidic acid should be suspended. The CHMP further confirmed that the use of remaining fluoroquinolones should be restricted and the prescribing information and the Patient Information Leaflet (PIL) should be updated regarding the disabling and potentially permanent side effects. CHMP described that the restrictions in the use of these antibiotics will mean that they should not be used to treat infections that are not severe (such as throat infections) or to treat mild or moderate infections unless other antibiotics recommended for these infections cannot be used to treat non-bacterial infections, e.g. non-bacterial (chronic) prostatitis; for preventing traveller's diarrhoea or recurring uncomplicated lower urinary tract infections in patients who previously had side effects with these drugs along with systemic corticosteroids.

CHMP confirmed that fluoroquinolones can produce tendon swelling and injury just within 2 days of initiation of the therapy and can even occur several months after stopping the treatment. Special caution should be considered while prescribing these drugs to elderly, patients with a kidney disease and those who have had an organ transplantation since these patients are at

higher risk of tendon injury. The recommendations of CHMP have been forwarded to European Commission, which gave its final decision on March 11, 2019 endorsing the recommendations of CHMP, this decision is now a legal binding applicable in all EU countries [17]. Medicines and Healthcare products Regulatory Agency (MHRA) of UK also decided to adopt the decision of EC as a result of the EMA review [18].

Protecting public health is the prime responsibility of the respective drug regulatory authorities in each country and the drug safety is one of the key factor which can be acquired through effective pharmacovigilance systems, interdisciplinary scientific team work, proactive decision making and regulatory actions. Fluoroquinolones are widely used worldwide and have now been proven to be associated with disabling and potentially long lasting side effects, its use should be restricted throughout the world even in under developed countries which do not have robust pharmacovigilance systems. Drug regulatory bodies throughout the world should take immediate actions to restrict the use of fluoroquinolones and spread the information in a proper way to each and every healthcare professional and patients. Global pharmacovigilance programs should be conducted across the regulatory bodies to share information and reviews so that drug safety could be assured worldwide. Furthermore, national and global plans should be developed for prescription control focusing on rational use of antibiotic therapy and development of national antibiograms on annual basis to recommend the use of antibiotics for next year and to monitor the effectiveness of control programs.

CONCLUSION

Pharmaceutical companies marketing the medicines should be encouraged to develop their pharmacovigilance departments and training of healthcare professionals should be conducted so that they may be able to report every side effect either reported by the patient or observed by any health care professional viz. doctor, pharmacist, and nurse. National and regional pharmacovigilance system should play a vibrant role for establishment of an effective and accessible reporting mechanism for patients and healthcare professionals with more organized collection of Adverse Drug events from all sources including healthcare facilities, health programs, immunization programs, active surveillance studies etc. The problem of anti-microbial resistance is becoming a global medical threat since it has already led to increased treatment costs with prolonged hospital stays and higher mortality rate. 19 Among many, problem of Multi drug resistant (MDR) Tuberculosis and Extended drug resistant (XDR) Typhoid has potentially emerged as a real threat in developing countries. The medical fraternity instantly needs to change the way it prescribes and uses antibiotics. The situation draws more attention due to development of very few new antibiotics in past and thus without paradigm shift in behaviour and prescriptions pattern, anti-microbial resistance will remain a major pandemic emergency threats.

REFERENCES

1. Greener M. Drug safety on trial. Last year's withdrawal of the anti-arthritis drug Vioxx triggered a debate about how to better monitor drug safety even after approval. EMBO Reports. 2005;6(3): 202-204.
2. Andriole VT. The quinolones [book] Elsevier. 2000.
3. Lesher GY, Froelich EJ, Gruett MD. 8-Naphthyridine derivatives. A new class of chemotherapeutic agents. J Med Chem. 1962;5:1063-1065.
4. Takahashi H, Hayakawa I, Akimoto T (2003) The history of the development and changes of quinolone antibacterial agents. Yakushigaku Zasshi. 2003;38:161-179.
5. Wolfson JS, Hooper DC (1989) Fluoroquinolone antimicrobial agents. Clinical microbiology reviews. 1989;2:378-424.
6. Helen SL, Jennifer L, Urinary Tract Infections, in Pharmacotherapy Self-Assessment Program, Infectious Disease Society of America. America, Editor. 2018: USA, https://www.accp.com/docs/bookstore/psap/p2018b1_sample.pdf (accessed, 14 February 2019).
7. Mandell LA, Wunderink RG, Anzueto A. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clinical infectious diseases. 2007;44: S27-S72.
8. Scott B, Shah PJ (2016) Diabetic Foot Infections, in Pharmacotherapy Self-Assessment Program, Infectious Disease Society of America. America, Editor. 2016: USA. https://www.accp.com/docs/bookstore/acsap/a2016b3_sample.pdf (accessed, 14 February 2019).
9. Kalil AC, Metersky ML, Klompas M. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clinical Infectious Diseases. 2016;63:e61-e111.
10. Shane AL, Mody RK, Crump JA. Infectious Diseases Society of America clinical practice guidelines for the diagnosis and management of infectious diarrhea. Clinical Infectious Diseases 2017;65:e45-e80.
11. Mermel LA, Allon M, Bouza E. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. Clinical infectious diseases. 2009;49:1-45.
12. US Food and Drug Administration. FDA Drug Safety Communication: FDA advises restricting fluoroquinolone antibiotic use for certain uncomplicated infections; warns about disabling side effects that can occur together 2016: USA. https://www.fda.gov/Drugs/DrugSafety/ucm500143.htm (accessed, 15 February 2019).
13. US Food and Drug Administration, FDA updates warnings for fluoroquinolone antibiotics. [press release] 2016: USA.
14. Health Canada. Summary Safety Review - Fluoroquinolones - Assessing the potential risk of persistent and disabling side effects, Editor. 2017: Canada. https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/safety-reviews/summary-safety-review-fluoroquinolones-assessing-potential-risk-persistent-disabling-effects.html (accessed, 15 February 2019).
15. BfArM Germany. Notification to the PRAC / EMA secretariate of a referral under article 31 of Directive 2001/83/EC DMDI, Editor. 2017: Germany. https://www.ema.europa.eu/documents/referral/quinolone-fluoroquinolone-article-31-referral-notification_en.pdf (accessed, 15 February 2019).
16. European Medicines Agency (EMA). Fluoroquinolone and quinolone antibiotics: PRAC recommends restrictions on use.

UK, 2018. https://www.ema.europa.eu/documents/referral/quinolone-fluoroquinolone-article-31-referral-prac-recommends-restrictions-use_en.pdf (accessed, 16 February 2019).

17. European Medicines Agency (EMA). Disabling and potentially permanent side effects lead to suspension or restrictions of quinolone and fluoroquinolone antibiotics. UK, 2018. https://www.ema.europa.eu/documents/referral/quinolone-fluoroquinolone-article-31-referral-disabling-potentially-permanent-side-effects-lead_en.pdf (accessed, 16 February 2019).
18. Drug Safety Update. Fluoroquinolone antibiotics: new restrictions and precautions for use due to very rare reports of disabling and potentially long-lasting or irreversible side effects UK, 2019. https://www.gov.uk/drug-safety-update/fluoroquinolone-antibiotics-new-restrictions-and-precautions-for-use-due-to-very-rare-reports-of-disabling-and-potentially-long-lasting-or-irreversible-side-effects (accessed, 7th April 2019).
19. Smith, Richard, and Joanna Coast. The true cost of antimicrobial resistance. BMJ 2013;346: f1493.