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QUINOLONE ANTIBIOTICS: LIMITATIONS FOR USE IN CHILDREN AND ELDERLY

Pharmacology

Dr Soumya N M First Year Resident, Department of Pharmacology, SBKS MI&RC, Sumandeep Vidyapeeth, Piparia.

Dr BM Sattigeri* Prof & Head, Department of Pharmacology, SBKS MI&RC, Sumandeep Vidyapeeth, Piparia. *Corresponding Author

ABSTRACT

Summary: Quinolones are preferred for their wide therapeutic range to treat infections of respiratory tract, urinary tract, etc. Birth of these antibiotics occurred in 1960's while George Lescher and coworkers identified them as effective antibiotics while working on the synthesis of antimalarial drug.

Then evolved various generations of these antibiotics with the fluorine substitution at the position 6 or 7, making them have more advantages, pharmacokinetic benefits and extended spectrum of activity over the earlier generation quinolones.

However, limitations in the use of these class of antibiotics in children and the elderly occurred due to various adverse drug reaction that were caused by them. The seriousness of these adverse drug reactions caused by fluoroquinolones led to the withdrawal of these preparations from the market while, their use is still being considered on weighing the risk benefit ratio in some of the chronic infections including tuberculosis and in conditions with multidrug resistance.

KEYWORDS

Adverse drug reactions, Children, Elderly, Quinolones

INTRODUCTION:

Adverse drug reactions following the use of antibiotics contribute to 40.9%, thus prolonging the duration of hospital stay increasing the economic burden to family & Health care system. [1] Hence, it is considered as a major health concern. Since, the birth of quinolones in 1960s, the evolved generation benefitted with their use in treating the bacterial infections. Unlike other antibacterial drugs, quinolones have been preferred by the practitioners to treat respiratory infections, gastro intestinal infections, urinary tract infections, sexually transmitted diseases, diseases of skin and soft tissues. [2]

With the changes in the structure of the basic molecule discovered serendipitously in 1962, as a quinolone compound during the synthesis of chloroquine, the emerged molecules have fluorine substitutions at position 6&7 which added their spectrum of activity, good therapeutic potential, bioavailability and their use in treating the bacterial infections. [3]

Initially the quinolone preparations were freely used for treating various bacterial infections until the harm caused by these preparations in the form of tendonitis in children was realized which was considered as a major limitation for current use. Several studies have reported the common potential adverse effects with quinolones such as the musculoskeletal, skin, gastrointestinal, nervous system of which the musculoskeletal reaction is more frequent with Pefloxacin (18.2%) than Ciprofloxacin (3.3%) as reported by Chalumeau et al (2003). [4]

EVOLUTION OF FLUROQUINOLONES:

George Lischer & Coworkers (1962) on their serendipitous discovery of quinolone molecule with antibacterial activity during the synthesis of antimalarial drug chloroquine introduced Nalidixic acid as the first parent compound for the class of antibiotics. [5] Further, the substitution of fluorine molecule at position 6&7 led to the development of the remaining generation of quinolones (second, third & fourth). These preparations were developed with better antibacterial activity, excellent oral bioavailability, therapeutic potential, wide distribution in the body fluids, long half-life, once daily administration, increased patient compliance, low incidence of resistance development as compared to the member of earlier generation.

Considering the limitations of 1st generation due to their notifiable oculotoxicity, the second generation were developed with wider spectrum of activity, which however failed in effectiveness against the pneumococcal infections. Later, the Third generation preparations were limited with use for severe phototoxicity they caused. While the use of Fourth generation drugs got restricted for the severe cardiotoxicity and phototoxicity caused by them.

Though several preparations were introduced after the introduction of Nalidixic acid very few were available for clinical use as the disadvantages and adverse effects caused by the drugs were identified during the post marketing surveillance for which they were introduced.

Table No 1: Shows the quinolone related adverse drug reaction on post marketing Surveillance.

S No	Quinolone	Adverse Drug Reaction
1	Clinafloxacin	Hypoglycemia, Extremely toxic reaction to sunlight.
2	Grepafloxacin	Prolongation of QT interval, Deadly arrhythmias
3	Sparfloxacin	Extremely toxic reaction to sunlight.
4	Trovafloxacin	Hepatotoxicity
5	Temafloxacin	Nephrotoxicity
6	Pefloxacin	Toxic reactions to sunlight, Tendon problems
7	Fleroxacin	Toxic reaction to sunlight, neurological disturbances.
8	Tosufloxacin	Kidney inflammation

LIMITATIONS FOR USE OF FLUROQUINOLONES IN CHILDREN:

Owing to the common musculoskeletal reactions which were considered as the major limitations for their use in children as indicated to carry a risk of 3.2 cases of tendonitis per 1000 patient treatment years. [6] Similarly Leone et al has shown the fluoroquinolones to be accountable for 14.7 % of musculoskeletal reactions.

The use of these antibiotics in this special population is very selective. They are known to cause common adverse events including skin rashes, allergies, photosensitive reactions, gastrointestinal system related adverse effects such as nausea, vomiting, diarrhea & abdominal pain, along with infrequent neutropenia, eosinophilia and elevated liver enzymes indicating wide range of toxicity. These preparations are known to cause relatively serious toxicity associated with their use in children include prolongation of the QT interval, photosensitivity reaction and acute liver failure. [7]

Despite the range of adverse reactions caused by the class of antibiotics which limited their use to specific conditions was based on the risk benefit ratio as evaluated by the treating clinician. They are preferred in the treatment of respiratory infections in patients with cystic fibrosis, immunocompromised patients with infections caused by multidrug resistant diseases and infections caused by multidrug resistant organisms. [3]

Further, the ability of fluoroquinolones to penetrate into the

cerebrospinal fluid exceeding more than 50% of plasma drug concentration result in the use of these agents in the treatment of meningitis in pediatric patients, which is proved by several studies for single oral dose of Ciprofloxacin to eradicate the nasopharyngeal carriage of N meningitidis thus preventing the meningococcal infections. [8] This has also given way for their use as second line agents in the treatment of Tuberculosis as indicated with the greatest bactericidal effect of Moxifloxacin and Gatifloxacin against M tuberculosis. Hence, they have been extensively used with their therapeutic potential in MDR Tuberculosis. [9]

In addition, Ciprofloxacin has been successfully used as monotherapy treatment in low risk febrile neutropenic patients suffering with malignancy followed by a single intravenous dose of beta lactam. Further fluoroquinolones as prophylactics, could reduce the incidence of gram negative bacteremia in individuals with o=long standing neutropenia. However, the emergence of resistance remains the major limitations for their use. [10,11] Oral Ciprofloxacin and intravenous beta lactam is effectively used in pediatric patients with solid tumors and low risk Non Hodgkins lymphoma.

LIMITATIONS & USE OF FLUOROQUINOLONES IN ELDERLY:

The infectious diseases including pneumonia, influenza, septicemia is considered as among the 10 leading causes of death among the elderly in which the use of antimicrobials is considered as the contributing factors. Further, the practice of polypharmacy and use of non-prescriptive drugs /over the counter preparations lead to adverse drug reactions among the fragile population. [12]

It has been observed that the adverse effects caused fluoroquinolones are more harmful than benefits, Thus, increase in the risk among the population has been attributed to the alteration in the pharmacokinetic properties on account of doubled body fat with decreased muscle mass, that are associated with the absorption, distribution, metabolism and excretion of all the drugs, all of which would contribute to the adverse drug reaction. [13] The most common adverse effects in elderly on the use of fluoroquinolones is neurotoxicity which includes delirium, psychosis, which are mistaken generally as the underlying psychiatric illness / the poor prognosis of the clinical condition. [14] Although not a usual side effect, neurotoxicity occurs in 1-2% of the elderly individuals receiving these class of antibiotics. Further, the popular neurotoxic adverse effects also include those of insomnia, headache and dizziness. [15] Their structural relation to the inhibitory neurotransmitter Gamma amino butyric acid (GABA) and their ability to displace GABA have been considered to be responsible for the epileptogenic neurotoxicity. [16,17] Further, the invitro toxicity studies have also shown the activation of excitatory neurotransmitter, N-Methyl -D- Aspartate (NMDA) receptor to be attributive to the epileptogenic toxicity. [18] Their feature which enables the penetration through the blood brain barriers explains their increase of neurotoxicity which has been prominent with the use of trovafloxacin. [19]

Practice of polypharmacy and the drug interactions contribute to increase the risk of adverse drug reactions among the elderly. Similarly, considering the age, multiple factors such as infections, comorbid conditions, such as cardiovascular diseases, metabolic disorders all contribute and increase the number of adverse drug reactions among the elderly. [20]

Thus, neurotoxicity is considered as a major limitation for the use of fluoroquinolones in elderly. Further, prolongation of QT interval, a notable adverse effect with Sparfloxacin (3%) is related with the cardiac events which include bradycardia, Torsade de Pointes which are associated with the methyl/ amino moiety substitution at C5 position. Sparfloxacin and Ciprofloxacin are of those fluoroquinolones which present with more cardiotoxic effects as compared to Levofloxacin. [21]

Fluoroquinolones are known to alter the levels of certain parameters indicating the hepatic damage that could present in the form of necrosis/degeneration. Several case reports and the post marketing surveillance indicated the severity o& the extent of hepatic damage that was caused by Trovafloxacin which led to its withdrawal from the market. [22,23] It has been stated that the oxidative radicals causing mitochondrial damage, the RNA processing, & transcription along with the covalent adducts to the proteins and inflammation are considered as the involved mechanisms in hepatotoxicity induced by these antibiotics. Of recent Ciprofloxacin has also been reported to induce hepatotoxicity as marked with the elevated liver enzymes, cholestatic jaundice and increased degenerative cells. [24,25]

These antibiotics are known to cause dangerous glycemic disturbances which are though uncommon, life threatening but potentially reversible. The hypoglycemia that occurs involves the pharmacokinetic and pharmacodynamic mechanisms. Pharmacokinetic mechanism includes the Drug- Drug interactions while the Pharmacodynamic mechanism includes stimulation of beta cells with increased release of insulin. Though the mechanism is not clear, blockade of the ATP sensitive K+ channel in the pancreatic beta cells, activation of Ca ++channels with subsequent release of insulin causing hypoglycemia. [26] This problem is more common among the elderly patients particularly among the diabetics receiving the oral sulfonylureas. Levofloxacin was found to be responsible in worsening the cases followed by Ciprofloxacin, Moxifloxacin & Ofloxacin. [27]

WITHDRAWAL OF FLUOROQUINOLONES:

The limitations caused by the class of antibiotics forced the withdrawal of certain preparations such as; 1) Temafloxacin due to Hypoglycemia, Hemolysis, Renal Failure, 2) Trovafloxacin due to hepatotoxicity, 3) Grepafloxacin due to Torsade de Pointes & Arrhythmias, & 4) Sparfloxacin due to Phototoxicity 7&Torsade de Pointes.

CONCLUSIONS & FUTURE PROSPECTS WITH THE USE OF QUINOLONES:

The future prediction of quinolones though difficult, the nucleus of the molecule provides wide opportunity for the development of more beneficial compounds, thus it remains as an open field of research.

It would yield to the development of highly effective quinolone pump inhibitors for the use in treatment of Patients and thus provide a key advantage in future.

Despite the risk involved fluoroquinolones remain the class of antibiotics in treatment of Multi Drug Resistant infections, Respiratory infections and gasrto intestinal infections.

However, they need to be continually monitored to realize their therapeutic potentials.

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