REVIEW ARTICLE

Fluoroquinolone Induced Neurotoxicity: A Review

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ABSTRACT

With increasing use of fluoroquinolones, there have been numerous reports of central nervous system adverse effects differing with individual fluoroquinolones. Structure toxicity relationship shows that the C-7 substituent on the quinolone nucleus plays an important role in the central nervous system effects of these compounds by inhibiting the interaction of gamma amino butyric acid with the receptors. Study done in healthy human volunteers has demonstrated the reversal of increased central nervous system activity induced by ofloxacin with midazolam. Risk factors for the neurotoxicity include elderly age, presence of central nervous system disorder, impaired renal function and drug-drug interactions. While the central effects are more common with ciprofloxacin and ofloxacin, these have also been reported with levofloxacin which has a better structure toxicity profile. Knowledge of these reversible and potentially avoidable adverse effects of fluoroquinolones can prevent misdiagnosis, unnecessary investigation and improper medication. A robust pharmacovigilance mechanism is essential for determining and monitoring the CNS adverse effects of existing and newer fluoroquinolones.

Key words: Fluoroquinolones, neurotoxicity, seizures

Introduction:

Fluoroquinolones (FQs) are commonly used antibiotics both in inpatient and outpatient settings. Their therapeutic use ranges from the common respiratory, urinary tract and gastrointestinal infections to management of drug resistant tuberculosis and febrile neutropenia in immunocompromised patients. [1] Significant features of this group of antibiotics include their wide antibacterial spectrum, less frequent dosing interval and relatively better patient tolerability. A study of antibiotic use in the public and private healthcare facilities and private retail pharmacies in New Delhi, India showed that the betalactam antibiotics and fluoroquinolones were the most commonly prescribed antibiotics. Ofloxacin, ciprofloxacin, levofloxacin, and norfloxacin were the most commonly prescribed fluoroquinolones. [2] A similar study of antibiotic use in acute diarrhea showed inappropriate use of fluoroquinolones, including in children. [3] The high consumption rates of FQs coupled with the problem of potentially inappropriate prescriptions can result in increased incidence of adverse effects and antimicrobial drug resistance besides the economic implications involved.

Of particular importance is the central nervous system (CNS) adverse effect of FQs which seems to be under recognized. [4] With increasing use of fluoroquinolones, there have been numerous reports of CNS adverse effects differing with individual fluoroquinolones. CNS-related adverse events have been reported to be higher in association with quinolone use than with the use of other systemic antimicrobials. [5] Also important is the fact that the CNS adverse events are avoidable to a large extent by knowing the predisposing drug and patient characteristics. The impact of adequate prescriber awareness and the consequent patient education regarding these factors can be enormous considering the widespread use of these antibiotics.

Hence the aim of the present article is to review the literature on the mechanism(s) of neurotoxicity and

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clinical aspects of central nervous system adverse effects of FQs.

Mechanisms of fluoroquinolone induced neurotoxicity

Structure toxicity relationship shows that the C-7 substituent on the quinolone nucleus, particularly pyrrolidine or piperazine, plays an important role in the CNS effects of these compounds. [6] The CNS excitatory action of quinolones is based on the inhibition BDZ-$GABA_A$ receptor complex, particularly binding of gamma amino butyric acid (GABA) to the receptors. This mechanism is also shared by the betalactam antibiotics. [7] Quinolones containing 7-piperazine (e.g., ciprofloxacin, norfloxacin) and those containing 7-pyrrolidine (e.g., tosufloxacin and clinafloxacin) have increased epileptogenic potential while substituted compounds containing 7-piperazinyl– or 7-pyrollidinyl (e.g., levofloxacin) are associated with reduced seizure-causing potential. Gemifloxacin, levofloxacin, and moxifloxacin lack the specific structure-toxicity relationships noted to induce seizures. [8] The nature of C-7 substituent may also determine the interaction with non-steroidal anti-inflammatory drugs (NSAIDs) and theophylline which can potentially increase the chances of seizures. Other receptors possibly involved in the CNS excitatory effects include N-methyl-D-aspartate, adenosine and amino acid receptors while effects on dopamine and opioid receptors has also been suggested. [9]

A study done in healthy human volunteers confirmed the CNS stimulant action of ofloxacin as evidenced by the electroencephalographic changes. [10] After administration of flumazenil following ofloxacin the effects were even pronounced indicating an increased CNS activity. The ofloxacin induced increased CNS activity was completely reversed following administration of midazolam. Hence administration of benzodiazepine (BZD)-agonists might be useful in the treatment of fluoroquinolone induced neurotoxic events.

While the effect on the GABA receptor is well established it is likely that it is coupled with other mechanism(s) that increase the penetration of FQs into the CNS to produce the toxicity. The lipophilicity of FQs depends on the individual compound. However, CNS penetration of FQs does not always correlate with the potential for epileptogenicity. In contrast to ciprofloxacin, ofloxacin has an increased CNS permeability of 50% of the serum concentration, though less cases of neurotoxicity have been reported for ofloxacin than for ciprofloxacin. [4, 11] Ofloxacin has a serum/plasma ratio of 47-87%. However, at therapeutic doses the serum concentration achieved is insufficient to produce adequate CSF levels necessary to produce adverse effects. [10] Abnormal state of blood brain barrier can increase the CNS penetration. Also, uneven distribution of the drug can result in higher concentration in specific areas of the brain. [10] Impaired renal function is associated with increase in elimination half life and area under the curve, and a decrease in renal and total clearance. [12] Accumulation of FQs may occur particularly in the elderly. [10]

Clinical aspects of fluoroquinolone induced neurotoxicity

CNS disturbances are second most commonly reported adverse events with FQs. [13] The overall incidence of these reports varies from 1% to 3.3%. [4, 8, 10] The most commonly reported symptoms include headache, dizziness and drowsiness. These usually occur on the first day of and resolve after discontinuation of the drug therapy. Other, less commonly reported, CNS events have included agitation, delirium, confusion/encephalopathy, acute organic psychosis, seizures and abnormal vision. [4, 8] Seizures have been reported more frequently among individuals predisposed to epileptic seizures, cerebral trauma and anoxia. [8] The reported overall trend in incidence of drug-related CNS adverse events is as followsnorfloxacin>ciprofloxacin>ofloxacin>levofloxacin. [11]

Patients who have received both fluoroquinolones and either theophylline or certain nonsteroidal anti-inflammatory drugs are predisposed to develop seizures. [8] Ciprofloxacin has been shown to decrease the metabolic clearance of theophylline and caffeine. It is advisable to use non-interacting quinolones such as ofloxacin or norfloxacin or to measure theophylline levels and reduce caffeine intake where appropriate. [14] A synergistic inhibitory effect of fluoroquinolones and several NSAIDs has been observed on the binding of the neurotransmitter GABA. [14] Elderly patients should be monitored carefully for the CNS symptoms. It is likely that many signs of possible adverse reactions, such as confusion, weakness, loss of appetite, tremor or depression, are often mistakenly attributed to old age and remain unreported. [15]

Oro-facial dyskinesias have also been reported with ciprofloxacin and ofloxacin, in the absence of a metabolic abnormality and at extremes of age. [16, 17] A tourette-like syndrome has also been described with ciprofloxacin implicating a possible interaction with the central dopaminergic system. [18] While the CNS effects are more common with ciprofloxacin and ofloxacin, these have also been reported with levofloxacin which has a better structure toxicity profile. [4, 19]

Summary

The structure toxicity relationship of fluoroquinolones provides unique opportunity for the design and development of new quinolone derivatives with expanded antibacterial activity and better pharmacokinetics without the CNS effects. The reversal of CNS effects of FQs with the use of BZD in healthy volunteer study provides a therapeutic basis for their use in the management of FQ induced CNS adverse effects. The prescriber should be alert regarding the possibility of drug-drug interaction between FQs and other CNS active drugs, theophylline or NSAIDs. Other risk factors include elderly patients, those with CNS disorder and impaired renal function. Knowledge of these reversible as well as potentially avoidable CNS adverse effects of FQs can prevent misdiagnosis, unnecessary investigation and improper medication. Proper patient education will also help in avoiding unnecessary delay in reporting of symptoms in cases of psychiatric symptoms. Since the structure toxicity relationship alone is inadequate to predict the CNS effects of existing and newer FQs a robust pharmacovigilance mechanism is essential for determining and monitoring the CNS adverse effects.

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References

1. Andriole VT. The Quinolones: Past, Present, and Future. *Clin Infect Dis* 2005;41 (Supplement 2):S113-S119.
2. Kotwani A, Holloway K. Trends in antibiotic use among outpatients in New Delhi, India. *BMC Infect Dis* 2011;11:99.
3. Kotwani A, Chaudhury RR, Holloway K. Antibiotic-prescribing practices of primary care prescribers for acute diarrhea in New Delhi, India. *Value Health* 2012;15(Supplement 1):S116-9.
4. Grill MF, Maganti RK. Neurotoxic effects associated with antibiotic use: management considerations. *Br J Clin Pharmacol* 2011;72(3):381–393.
5. Leone R, Venegoni M, Motola D, Moretti U, Piazzetta V, Cocci A, Resi D, Mozzo F, Velo G, Burzilleri L, Montanaro N, Conforti A. Adverse drug reactions related to the use of fluoroquinolone antimicrobials: an analysis of spontaneous reports and fluoroquinolone consumption data from three Italian regions. *Drug Saf* 2003;26:109–20.
6. Domagala JM. Structure-activity and structure-side-effect relationships for the quinolone antibacterials. *J Antimicrob Chemother* 1994;33(4):685-706.
7. Thomas RJ. Neurotoxicity of antibacterial therapy. *South Med J.* 1994;87(9): 869-74.
8. Owens RC, Ambrose PG. Antimicrobial Safety: Focus on Fluoroquinolones. *Clinical Infectious Diseases* 2005;41:S144–57.
9. Takayama S, Hirohashi M, Kato M, Shimada H. Toxicity of quinolone antimicrobial agents. *J Toxicol Environ Health* 1995;45(1):1-45.

10. Unseld E, Ziegler G, Gemeinhardt A, Janssen U, Klotz U. Possible interaction of fluoroquinolones with the benzodiazepine-GABAA-receptor complex. *Br J Clin Pharmacol* 1990;30(1):63-70.
12. Lipsky BA, Baker CA. Fluoroquinolone toxicity profiles: a review focusing on newer agents. *Clin Infect Dis* 1999;28(2):352-64.
13. Neuman M. Clinical pharmacokinetics of the newer antibacterial 4-quinolones. *Clin Pharmacokinet* 1988;14(2):96-121.
14. Wolfson JS, Hooper DC. Overview of fluoroquinolone safety. *Am J Med* 1991;91(6A):153S-161S.
15. Janknegt R. Drug interactions with quinolones. *J Antimicrob Chemother* 1990;26:7-29.
16. Stahlmann R, Lode H. Safety considerations of fluoroquinolones in the elderly: an update. *Drugs Aging* 2010;27(3):193-209.
17. De Bleecker JL, Vervaet VL, De Sarro A. Reversible orofacial dyskinesia after ofloxacin treatment. *Mov Disord* 2004;19:731-2.
18. Pastor P, Motinho E, Elizalde I, Cirera I, Tolosa E. Reversible oro-facial dyskinesia in a patient receiving ciprofloxacin hydrochloride. *J Neurol* 1996;243:616–7.
19. Thomas RJ, Reagan DR. Association of a Tourette-like syndrome with ofloxacin. *Ann Pharmacother* 1996;30:138–41.
20. Moorthy N, Raghavendra N, Venkatarathnamma PN, Levofloxacin-induced acute psychosis. *Indian J Psychiatry* 2008;50(1):57–58.

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