Fluoroquinolones-Associated Disability

Subjects: Others
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Fluoroquinolones (FQs) are one of the most commonly prescribed antibiotics within the United States. FQs are typically included in the treatment protocols of several illnesses such as urinary tract infections, bacterial bronchitis, bacterial gastroenteritis and other infectious diseases. However, it is clear now that FQs lead to severe, long-lasting side effects that require further investigation to ensure better disease management.

Keywords: fluoroquinolones ; fluoroquinolones-associated-disability ; vagus ; gastrointestinal ; digestion ; DMV ; NTS ; FQAD

1. Overview

Fluoroquinolones (FQs) are a broad class of antibiotics typically prescribed for bacterial infections, including infections for which their use is discouraged. The FDA has proposed the existence of a permanent disability (Fluoroquinolone Associated Disability; FQAD), which is yet to be formally recognized. Previous studies suggest that FQs act as selective $GABA_A$ receptor inhibitors, preventing the binding of GABA in the central nervous system. GABA is a key regulator of the vagus nerve, involved in the control of gastrointestinal (GI) function. Indeed, GABA is released from the Nucleus of the Tractus Solitarius (NTS) to the Dorsal Motor Nucleus of the vagus (DMV) to tonically regulate vagal activity. The purpose of this review is to summarize the current knowledge on FQs in the context of the vagus nerve and examine how these drugs could lead to dysregulated signaling to the GI tract. Since there is sufficient evidence to suggest that GABA transmission is hindered by FQs, it is reasonable to postulate that the vagal circuit could be compromised at the NTS-DMV synapse after FQ use, possibly leading to the development of permanent GI disorders in FQAD.

2. Fluoroquinolones

Fluoroquinolones (FQs) are one of the most commonly prescribed antibiotics within the United States. FQs are typically included in the treatment protocols of several illnesses such as urinary tract infections, bacterial bronchitis, bacterial gastroenteritis and other infectious diseases [1]. In 2014, FQs were prescribed to 31.5 million people across the country [2]. The most common demographic to receive a prescription for FQs usually consists of individuals who are 45 years of age or older [3]. FQs are extremely efficacious in treating bacterial infections through inhibition of bacterial type II DNA topoisomerases, specifically DNA gyrase and topoisomerase IV. Physiologically, gyrases and topoisomerase IV generate double-stranded breaks in the bacterial chromosome, which is essential for their survival. FQs, by binding these enzymes, increase the concentration of enzyme–DNA cleavage complexes, resulting in bacterial cell death [4]. Based on their antibacterial efficacy, four generations of FQs have been identified: classes one and two are active against gram-negative bacteria and have been used to treat common infections such as those to the urinary tract. Classes three and four have expanded efficacy against gram-positive bacteria and are typically prescribed to treat respiratory tract infections [5]. Within these four classes, only six FQs are commonly prescribed to date, including ciprofloxacin (second generation) and levofloxacin (third generation) [6].

While their therapeutic efficacy is clearly recognized and valuable for severe life-threatening infections, it is now evident that FQs are accompanied by a variety of systemic side effects, including common (gastrointestinal disturbances, headaches, skin rash, allergic reactions and others) and uncommon side effects [7]. These include QT prolongation [8], seizures [9], hallucinations [10], depression and anxiety [10], peripheral neuropathy [11], tendon rupture [12][13] and others. While the common side effects tend to disappear shortly after the treatment, the rare side effects seem to affect patients for longer, potentially their entire life time. Due to these side effects, the Federal Drug Agency (FDA) has released a statement in 2016 warning healthcare providers of the possibility of a “Fluoroquinolones associated disability” (FQAD) or “Fluoroquinolones toxicity syndrome” [14], which patients colloquially refer to as “being Floxed”. Despite the FDA as well as the European Medicine Agency (EMA) warnings on FQ use, it was reported in 2018 that 19.9% of all FQ prescriptions were prescribed for conditions outside the suggested administration protocol. Indeed, about 6.3 million FQs prescriptions

were written for urinary tract infections (UTI), and about 1.6 million prescriptions were written for bronchitis and the common cold, for which FQs should not have been selected for treatment [2]. Even more concerning is that in addition to these aforementioned cases, 5.1% of adult ambulatory FQ prescriptions were issued for conditions that did not require antibiotics at all [2]. Even though the Infectious Diseases Society of America (IDSA) advises avoiding FQs for uncomplicated urinary tract infections [15], FQs were still prescribed in 40% of cases compared to other antibiotics including penicillins, urinary anti-infectives, and tetracyclines [2].

Despite the FDA proposing the existence of FQAD, this disease has yet to be formally recognized by healthcare systems worldwide. To date, there is still a degree of dismissal of FQAD-affected patients by healthcare providers and physicians. This is mainly due to the fact that there is variability in the presentation of the symptoms, especially the uncommon ones. Moreover, the lack of compelling evidence of FQAD as a whole, and of an animal model that is capable of recapitulating the characteristics of the disease in a research setting contribute to the lack of legitimization of the syndrome. As a consequence, “floxed” patients go undiagnosed or misdiagnosed. The majority of their symptoms are still being unjustly attributed to anxiety and depression, or other umbrella-diseases including fibromyalgia [16]. While this is currently a problematic aspect of FQAD, plenty of clinical and laboratory evidence indicates that FQs are strongly associated with cellular toxicity causing specific side effects.

3. Effects on the Central Nervous System

CNS effects that are caused by FQs range from mild reactions such as irritability, insomnia and dizziness [10][17], to more concerning and long-lasting side effects including anxiety, depression, hallucinations [17], convulsions [18], seizures [9] and peripheral neuropathy [10][18][19][20][21]. Evidence showed that the peripheral neuropathies that are associated with FQs can even lead to patients developing Guillain-Barré syndrome [22]. Clinical trials have comparatively looked at the adverse effects of FQs on the CNS, and found that trovafloxacin, norfloxacin, and gatifloxacin caused the most severe reactions while, in comparison, ciprofloxacin, ofloxacin, levofloxacin caused the least severe reactions [23][24][25].

FQs act as selective antagonists of $GABA_A$ receptors, and therefore inhibit their function once bound [26]. Notably, the side chain substituent in the R7 position of the FQs nucleus is determining the decreased binding affinity of GABA to its receptor [27]. Physiologically, GABA is one of the major inhibitory neurotransmitters of the CNS. In the presence of FQs, GABA may not properly inhibit its target, potentially leading to overactivation of the CNS [28]. A study conducted in rats suggested that rodents treated with ciprofloxacin had a significant decrease in GABA levels in brain tissue when compared to a control group and showed depression and anxiety-like behaviors [29].

At the same time, glutamatergic transmission seems to also be affected by FQs. There is evidence that FQs impair the Mg^{2+} block of N-methyl-D-aspartate (NMDA) receptors, effectively increasing the gating time for this receptor and glutamatergic transmission in the rat hippocampus [30]. If this mechanism holds true in other CNS regions, as well as the increase in intracellular Ca^{2+} concentration resulting from NMDA overactivation, it would result in a higher excitability of the neuron. This, combined with the reduced GABAergic inputs due to $GABA_A$ blockade, strongly suggest that the two main neurotransmitters in the CNS could be imbalanced when FQs are introduced, resulting in unforeseen consequences due to the disruption in the fine balance between GABA and glutamate signaling. It is important to highlight that excessive glutamate transmission due to NMDA receptor dysregulation is associated with excitotoxicity [31][32][33][34][35], a molecular pathophysiological mechanism behind neuronal death in several acute and chronic neurological conditions including stroke, Alzheimer’s Disease, Huntington’s disease, Parkinson’s disease, and Amyotrophic Lateral Sclerosis [36]. Notably, Zn^{2+} is physiologically co-released with glutamate [37] and acts as an inhibitor of both glutamate AMPA and NMDA receptors, a mechanism important to avoid overexcitation of neurons [38][39]; given the cation-chelating properties of FQs, it is possible that synaptic Zn^{2+} might be sequestered by FQs, further contributing to sustained neuronal excitation and, eventually, excitotoxicity. The extent to which Zn^{2+} is chelated in the synaptic cleft is under question; it might be possible that, to some extent, Zn^{2+} might still be available in the extracellular milieu. Whether this unknown amount of FQ-free Zn^{2+} is available to physiologically inhibit AMPA and NMDA receptors is not known yet. However, it is important to point out that Zn^{2+} itself, in addition to Ca^{2+}, is a contributing factor to the molecular cascade that leads to increased radical oxygen species (ROS) formation and cell death in excitotoxicity, hence potentially contributing to the molecular mechanisms of FQs toxicity described earlier (for more information on Zn^{2+} role in excitotoxicity, we direct the readers to Granzotto’s review [40]).

4. Conclusions

Further in vitro and in vivo studies at the CNS as well as the enteric level are necessary to better define the risk factors associated with intake of FQs and to mitigate the onset of FQAD in vulnerable individuals. It is imperative to better

educate and train physicians worldwide about the permanent dangers FQs can induce in vulnerable populations, and to limit the usage of these drugs to life-threatening infections only. With more research available on FQs, there is the potential to better understand the pathophysiological mechanisms behind FQAD, legitimize this condition to physicians and insurance companies alike, and possibly provide preventative measurements or disease modifying approaches that could dramatically improve the quality of life of these patients.

References

1. National Institute of Diabetes and Digestive and Kidney Diseases. Fluoroquinolones. In LiverTox: Clinical and Research Information on Drug-Induced Liver Injury; National Institute of Diabetes and Digestive and Kidney Diseases: Bethesda, MD, USA, 2012.
2. Kabbani, S.; Hersh, A.L.; Shapiro, D.J.; Fleming-Dutra, K.E.; Pavia, A.T.; Hicks, L.A. Opportunities to Improve Fluoroquinolone Prescribing in the United States for Adult Ambulatory Care Visits. Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am. 2018, 67, 134–136.
3. Baggs, J.; Fridkin, S.K.; Pollack, L.A.; Srinivasan, A.; Jernigan, J.A. Estimating National Trends in Inpatient Antibiotic Use Among US Hospitals from 2006 to 2012. JAMA Intern. Med. 2016, 176, 1639.
4. Aldred, K.J.; Kerns, R.J.; Osheroff, N. Mechanism of Quinolone Action and Resistance. Biochemistry 2014, 53, 1565–1574.
5. King, D.E.; Malone, R.; Lilley, S.H. New Classification and Update on the Quinolone Antibiotics. Am. Fam. Physician 2000, 61, 2741–2748.
6. Stahlmann, R.; Lode, H. Safety Considerations of Fluoroquinolones in the Elderly. Drugs Aging 2010, 27, 193–209.
7. Norrby, S.R. Side-Effects of Quinolones: Comparisons between Quinolones and Other Antibiotics. Eur. J. Clin. Microbiol. Infect. Dis. Off. Publ. Eur. Soc. Clin. Microbiol. 1991, 10, 378–383.
8. Stahlmann, R.; Riecke, K. Well tolerated or risky? Adverse effect of quinolones. Pharm. Unserer Zeit 2001, 30, 412–417.
9. Chui, C.S.L.; Chan, E.W.; Wong, A.Y.S.; Root, A.; Douglas, I.J.; Wong, I.C.K. Association between Oral Fluoroquinolones and Seizures. Neurology 2016, 86, 1708–1715.
10. Li, H.; Jiang, Z.; Zhao, Q.; Ding, Y. Adverse Reactions of Fluoroquinolones to Central Nervous System and Rational Drug Use in Nursing Care. Pak. J. Pharm. Sci. 2019, 32, 427–432.
11. Etminan, M.; Brophy, J.M.; Samii, A. Oral Fluoroquinolone Use and Risk of Peripheral Neuropathy: A Pharmacoepidemiologic Study. Neurology 2014, 83, 1261–1263.
12. Lewis, T.; Cook, J. Fluoroquinolones and Tendinopathy: A Guide for Athletes and Sports Clinicians and a Systematic Review of the Literature. J. Athl. Train. 2014, 49, 422–427.
13. Stephenson, A.L.; Wu, W.; Cortes, D.; Rochon, P.A. Tendon Injury and Fluoroquinolone Use: A Systematic Review. Drug Saf. 2013, 36, 709–721.
14. Yarrington, M.E.; Anderson, D.J.; Dodds Ashley, E.; Jones, T.; Davis, A.; Johnson, M.; Lokhnygina, Y.; Sexton, D.J.; Moehring, R.W. Impact of FDA Black Box Warning on Fluoroquinolone and Alternative Antibiotic Use in Southeastern US Hospitals. Infect. Control Hosp. Epidemiol. 2019, 40, 1297–1300.
15. Gupta, K.; Hooton, T.M.; Naber, K.G.; Wullt, B.; Colgan, R.; Miller, L.G.; Moran, G.J.; Nicolle, L.E.; Raz, R.; Schaeffer, A.J.; et al. International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women: A 2010 Update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin. Infect. Dis. 2011, 52, e103–e120.
16. Ganjizadeh-Zavareh, S.; Sodhi, M.; Spangehl, T.; Carleton, B.; Etminan, M. Oral Fluoroquinolones and Risk of Fibromyalgia. Br. J. Clin. Pharmacol. 2019, 85, 236–239.
17. Holley, A.K.; Bakthavatchalu, V.; Velez-Roman, J.M.; St. Clair, D.K. Manganese Superoxide Dismutase: Guardian of the Powerhouse. Int. J. Mol. Sci. 2011, 12, 7114–7162.
18. Christ, W. Central Nervous System Toxicity of Quinolones: Human and Animal Findings. J. Antimicrob. Chemother. 1990, 26 (Suppl. B), 219–225.
19. Feinberg, S.S. Fluoroquinolone-Induced Depression. Am. J. Psychiatry 1995, 152, 954–955.
20. Kandasamy, A.; Srinath, D. Levofloxacin-Induced Acute Anxiety and Insomnia. J. Neurosci. Rural Pract. 2012, 3, 212–214.

21. Sarro, A.; Sarro, G. Adverse Reactions to Fluroquinolones. An Overview on Mechanistic Aspects. Curr. Med. Chem. 2001, 8, 371–384.
22. Ali, A.K. Peripheral Neuropathy and Guillain-Barré Syndrome Risks Associated with Exposure to Systemic Fluoroquinolones: A Pharmacovigilance Analysis. Ann. Epidemiol. 2014, 24, 279–285.
23. Stahlmann, R. Safety Profile of the Quinolones. J. Antimicrob. Chemother. 1990, 26, 31–44.
24. Lipsky, B.A.; Baker, C.A. Fluoroquinolone Toxicity Profiles: A Review Focusing on Newer Agents. Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am. 1999, 28, 352–364.
25. Hooper, D.C.; Wolfson, J.S. Fluoroquinolone Antimicrobial Agents. N. Engl. J. Med. 1991, 324, 384–394.
26. Green, M.A.; Halliwell, R.F. Selective Antagonism of the GABA(A) Receptor by Ciprofloxacin and Biphenylacetic Acid. Br. J. Pharmacol. 1997, 122, 584–590.
27. Domagala, J.M. Structure-Activity and Structure-Side-Effect Relationships for the Quinolone Antibacterials. J. Antimicrob. Chemother. 1994, 33, 685–706.
28. Halliwell, R.F.; Davey, P.G.; Lambert, J.J. Antagonism of GABAA Receptors by 4-Quinolones. J. Antimicrob. Chemother. 1993, 31, 457–462.
29. Ilgin, S.; Can, O.D.; Atli, O.; Ucel, U.I.; Sener, E.; Guven, I. Ciprofloxacin-Induced Neurotoxicity: Evaluation of Possible Underlying Mechanisms. Toxicol. Mech. Methods 2015, 25, 374–381.
30. Schmuck, G.; Schürmann, A.; Schlüter, G. Determination of the Excitatory Potencies of Fluoroquinolones in the Central Nervous System by an In Vitro Model. Antimicrob. Agents Chemother. 1998, 42, 1831–1836.
31. Bano, D.; Ankarcrona, M. Beyond the Critical Point: An Overview of Excitotoxicity, Calcium Overload and the Downstream Consequences. Neurosci. Lett. 2018, 663, 79–85.
32. Choi, D.W. Excitotoxicity: Still Hammering the Ischemic Brain in 2020. Front. Neurosci. 2020, 14, 579953.
33. Lee, J.-M.M.; Zipfel, G.J.; Choi, D.W. The Changing Landscape of Ischaemic Brain Injury Mechanisms. Nature 1999, 399, A7–A14.
34. Lai, T.W.; Zhang, S.; Wang, Y.T. Excitotoxicity and Stroke: Identifying Novel Targets for Neuroprotection. Prog. Neurobiol. 2014, 115, 157–188.
35. Swanson, R.A.; Wang, J. Superoxide and Non-Ionotropic Signaling in Neuronal Excitotoxicity. Front. Neurosci. 2020, 14.
36. Mehta, A.; Prabhakar, M.; Kumar, P.; Deshmukh, R.; Sharma, P.L. Excitotoxicity: Bridge to Various Triggers in Neurodegenerative Disorders. Eur. J. Pharmacol. 2013, 698, 6–18.
37. Sensi, S.L.; Paoletti, P.; Bush, A.I.; Sekler, I. Zinc in the Physiology and Pathology of the CNS. Nat. Rev. Neurosci. 2009, 10, 780–791.
38. Rachline, J.; Perin-Dureau, F.; Le Goff, A.; Neyton, J.; Paoletti, P. The Micromolar Zinc-Binding Domain on the NMDA Receptor Subunit NR2B. J. Neurosci. 2005, 25, 308–317.
39. Kalappa, B.I.; Anderson, C.T.; Goldberg, J.M.; Lippard, S.J.; Tzounopoulos, T. AMPA Receptor Inhibition by Synaptically Released Zinc. Proc. Natl. Acad. Sci. USA 2015, 112, 15749–15754.
40. Granzotto, A.; Canzoniero, L.M.T.; Sensi, S.L. A Neurotoxic Ménage-à-Trois: Glutamate, Calcium, and Zinc in the Excitotoxic Cascade. Front. Mol. Neurosci. 2020, 13, 225.