

Levofloxacin-induced acute anxiety and insomnia

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ABSTRACT

Fluoroquinolones can cause adverse neuropsychiatric side effects, which are more common in older age. We present three cases of levofloxacin-induced acute anxiety and insomnia in young adults. In all the cases, discontinuation of levofloxacin immediately lead to remission.

Key words: Anxiety, γ -amino butyric acid, insomnia, levofloxacin, quinolones

Introduction

Fluoro-quinolones are one of the most common antibiotics used by clinicians all over the world. They are generally well tolerated.^[1] The most common adverse reactions of fluoro-quinolones involve the GI tract, with 3% to 17% of patients reporting mild nausea, vomiting, and/or abdominal discomfort. Neuropsychiatric adverse effects are not uncommon. Among them, mild headache and dizziness are the common adverse effects. Rarely hallucinations and seizures have been reported.^[1] We report three cases with interesting and clinically significant presentation of acute anxiety and insomnia while treated with levofloxacin.

Case Reports

Case 1

Mr. A, a 30-year-old male developed lower respiratory tract illness. He was prescribed levofloxacin 500 mg for 5 days, once daily in night. The first day he could not sleep throughout the night. He started getting worries throughout the night about the next day routine. This continued onto the next day also. He was able to

sense the qualitative difference in the level of comfort in carrying out his daily routine. He also had severe anxiety and irritable mood the whole day. Again the sleep was disturbed in the night. Next day morning after consultation with his physician, he was prescribed a different class of antibiotic. The same day night his sleep was adequate and satisfactory. His anxiety was less on the next day and then it remitted.

Case 2

Mrs. S, a 30-year-old woman, developed lower respiratory tract illness. She took levofloxacin 500 mg per day as per her physician's advice. She was not able to sleep throughout the night. She was also feeling anxious without any clear reasons. She contacted her physician the next day. He stopped levofloxacin, after which her neuropsychiatric symptoms remitted completely on the next day.

Case 3

Mr. S, a 32-year-old doctor, medicated himself with levofloxacin 750 mg for his acute lower respiratory tract infection. He had taken complete courses of levofloxacin 500 mg for the same complaints in the past. This time he had samples of 750 mg tablets only and so he took it. Within 4 to 6 h, he started feeling restless and had insomnia throughout the night. He was worrying about various day to day things in the night. He was irritable towards his child and wife. The next day he consulted at psychiatry OPD and was diagnosed to have acute nonspecific anxiety. The same day levofloxacin was stopped and his sleep and anxiety symptoms normalized from the next day. There was no relapse of anxiety symptoms in the next 6 months of follow up.

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All the three patients didn't take any other medications along with levofloxacin. They were evaluated by psychiatrist to rule out any primary psychiatric disorder. But no significant psychiatric illness was found in the past and family history. All were followed up for a minimum period of 6 months without any relapse. None of them were willing to restart levofloxacin at any point of time due to their past dreadful experiences.

Discussion

Effects within the central nervous system (CNS) are generally some of the more frequent adverse consequences of quinolones therapy.^[2] One of the recent review on this subject had reported that mania, insomnia, acute psychosis and delirium were the most frequently reported psychiatric adverse events; grand mal convulsion, confusional state and myoclonus were the most frequently reported neurological adverse events. Ciprofloxacin, Ofloxacin, and pefloxacin were the quinolones with more neurological and psychiatric adverse drug reactions reported in the literature.^[3] CNS effects of quinolones correlate with its binding to the receptors for γ -amino butyric acid (GABA) in the brain. GABA is an inhibitory neurotransmitter of brain. Quinolones prevent normal binding of GABA with their receptors. So it increases CNS stimulation.^[4] There are reports on quinolones directly activating *N*-methyl-D-aspartate (NMDA) and adenosine receptors. Thus, under specific conditions of sufficient CNS penetration, associated with antagonism of inhibitory pathways (GABA) and stimulation of excitatory pathways (NMDA, adenosine), observable CNS symptoms are manifested. This mechanism explains the pathogenesis of the acute anxiety and insomnia in the above cases with levofloxacin therapy.^[5,6] These mechanisms are even correlating with non-dopaminergic pathways of psychosis. It is even possible that the above-said cases might have progressed on to psychosis, if the full course of levofloxacin therapy was completed.^[7] In multi-drug-resistant tuberculosis (MDR-TB), higher doses of levofloxacin are prescribed. In this scenario, the third case indicates a strong need for surveillance of neuropsychiatric symptoms in these patients. In the treatment of MDR-TB patients, the other agents like cycloserine are already an established risk factor for neuropsychiatric side effects.^[8] When levofloxacin is combined with them, it might have an additive effect on the above unpleasant symptoms. The other interesting thing to be noted from above 3 cases is that, they all were young adults and none of them had any CNS-related disorders. This is important because the previous literature available on fluoroquinolones suggest that

neuropsychiatric adverse effects are frequently noted in elderly and people with CNS lesions.^[7,9,10]

Conclusion

Levofloxacin is prone to cause neuropsychiatric side effects. Some of the side effects like insomnia and anxiety go unnoticed many a times. So by presenting the above three cases, we like to emphasize on the following points.

1. Physicians and psychiatrists should be aware of neuropsychiatric side effects of levofloxacin. Although neuropsychiatric side effects of fluoroquinolones are more common in the elderly, they can also affect younger patients.
2. Stopping the drug in time may prevent the progress of nonspecific anxiety and insomnia to major psychiatric disorders like psychosis.
3. Although there are neuropsychiatric side effects mentioned as rare in the drug leaflet provided by the pharmaceutical companies, this case series and other reports from the literature indicate that neuropsychiatric side effects are relevant and require more systematic research on their prevalence.
4. The research should also look whether there is a dose relation between levofloxacin and side-effects. This is specifically important in MDRTB where higher doses of levofloxacin are prescribed.
5. There should also be a surveillance of the effect of combined prescriptions like NSAIDs, anti-histaminics, anti-tubercular drugs, etc with levofloxacin.
6. Cooperation of psychiatrists, pulmonologists, and general practitioners is required in further interdisciplinary research on neuropsychiatric side effects of levofloxacin and other fluoroquinolones.

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