Management of Levofloxacin Induced Anaphylaxis and Acute Delirium in a Palliative Care Setting

Arunangshu Ghoshal, Anuja Damani, Naveen Salins, Jayita Deodhar, Mary Ann Muckaden

Department of Palliative Medicine, Tata Memorial Centre, Mumbai, Maharashtra, India

Address for correspondence: *Dr. Arunangshu Ghoshal; E-mail:arun.bata@yahoo.com*

ABSTRACT

Levofloxacin is a commonly prescribed antibiotic for managing chest and urinary tract infections in a palliative care setting. Incidence of Levofloxacin-associated anaphylaxis is rare and delirium secondary to Levofloxacin is a seldom occurrence with only few published case reports. It is an extremely rare occurrence to see this phenomenon in combination. Early identification and prompt intervention reduces both mortality and morbidity. A 17-year-old male with synovial sarcoma of right thigh with chest wall and lung metastasis and with no prior psychiatric morbidity presented to palliative medicine outpatient department with community-acquired pneumonia. He was initiated on intravenous (IV) Ceftriaxone and IV Levofloxacin. Post IV Levofloxacin patient developed anaphylaxis and acute delirium necessitating IV Hydrocortisone, IV Chlorpheneramine, Oxygen and IV Haloperidol. Early detection and prompt intervention helped in complete recovery. Patient was discharged to hospice for respite after 2 days of hospitalization and then discharged home. Acute palliative care approach facilitated management of two life-threatening medical complications in a palliative care setting improving both quality and length of life.

Key words: Delirium, Levofloxacin, Palliative care

INTRODUCTION

The quinolone derivatives (Levofloxacin, Sparfloxacin, Grepafloxacin, Trovafloxacin, Gatifloxacin and Moxifloxacin), are gyrase inhibitors.[1,2] They have been implicated for causing central nervous system adverse effects since Blomer *et al*.[3] who first described this entity in 1979. The development of these effects seems to be related to the specific Fluoroquinolone's affinity for the gamma-amino butyric acid (GABA) and N-methyl D-aspartate receptors.[4] Risk factors for neurotoxicity include renal insufficiency (if no dosage reduction), underlying central nervous system (CNS) disease and increased CNS penetration of drug. Levofloxacin is a third-generation fluorinated quinolone antibiotic, the active levo stereoisomer of Ofloxacin. There are only very few case reports in the literature associating development of delirium with the use of Levofloxacin.[5-10] Association of occasionally fatal hypersensitivity and/or anaphylactic reactions has also been reported in patients receiving therapy with levofloxacin often following the first dose.[11] Here we have described a case report of a 17-year-old child who developed anaphylaxis and delirium following intravenous levofloxacin infusion.

Access this article online

Quick Response Code:

Website:
www.jpalliativecare.com

DOI:
10.4103/0973-1075.150194

Presenting concerns

A 17 years male, known case of synovial sarcoma of right thigh with chest wall and lung metastasis, with no known prior history of psychiatric morbidity/ substance abuse/ dependence presented to palliative care out-patient department (OPD) with 5-days history of high grade fever, pleuritic left sided chest pain and breathlessness. On clinical examination he was sitting upright, not cyanosed and not dyspneic at rest. He had normal vital parameters and was maintaining normal oxygen saturation on room air. Chest examination revealed a dull percussion note and fine crackles in the left inter and infrascapular region. A clinical diagnosis of community-acquired pneumonia was made which was correlated and confirmed with the chest X-ray. Blood work up was requested and he was started on empiric IV Levofloxacin (500 mg) and IV Ceftriaxone (1 gm BD). IV Levofloxacin was started first and after 10 minutes patient developed chest tightness, increase in breathlessness, restlessness and generalized discomfort. On examination BP was 100/70 mm Hg, HR 120/min, SpO2 88% and chest auscultation showed widespread bilateral polyphonic brhonchi. He was initiated on O2 (2 litres/min) and intravenous (IV) Hydrocortisone and IV Chlorpheneramine (20 mg) was administered with Adrenaline (1:1000) (0.5 ml) back-up. His anaphylaxis was well-managed and he was admitted to emergency room (ER) for observation. In next 30 minutes his vital parameters were normalized and was no more requiring O2 for maintaining saturation. Over next 30 minutes he was confused, disoriented and had increased restlessness. The intensity of restlessness increased to agitation and violent behavior and he was trying to get out of the bed and run out of ER. He also had visual hallucinations and was constantly calling out for people. He needed transient mechanical restrain and titrating Haloperidol (2 mg) dose with intermittent boluses of Midazolam (1 mg) was required to attain pharmacological restrain.

A clinical diagnosis of acute delirium was made based on confusion assessment method (CAM) questionnaire. His CAM score was 4/4 and his Richmond Agitation Sedation Scale (RASS) score was +4. With treatment over next 14 hours RASS was 0. Investigations for reversible cause of delirium were negative except for borderline low sodium and potassium needing only dietary correction. His antibiotic regime was changed to Ceftriaxone and Azithromycin (500 mg) and patient recovered well. He was discharged to hospice for further respite care.

Follow-up and outcomes

Patient was discharged from hospice after 4 days in stable condition and went home under supervision of local general practitioner [Appendix I].

DISCUSSION

Serious and occasionally fatal hypersensitivity and/or anaphylactic reactions have been reported in patients receiving therapy with Levofloxacin. These reactions often occur following the first dose. These reactions are often accompanied by cardiovascular collapse, hypotension/shock, seizure, loss of consciousness, tingling, angioedema, bronchospasm, shortness of breath and acute respiratory distress, urticaria, itching, and other serious skin reactions. The drug should be discontinued immediately at the first appearance of a skin rash or any other sign of hypersensitivity. Serious acute hypersensitivity reactions may require treatment with epinephrine and other resuscitative measures, including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines and airway management, as clinically indicated.

The two reports[12,13] of post marketing surveillance of Levofloxacin side effects showed central nervous system (CNS) related events as an infrequent occurrence. The reported incidence of CNS symptoms in these studies were 0.1% for anxiety, 0.3% for insomnia, and 0.1% for "headache"[12] dizziness (0.2%), nervousness (0.1%).[13] Most of these case reports are from adult population. The mechanism underlying Levofloxacin-induced delirium remains to be elucidated. It is possible that quinolone associated non-convulsive status epilepticus (NCSE) is responsible.[14,15] as quinolones are known to lower the seizure threshold by binding competitively to the GABA-A receptor. There have been isolated reports of abnormal electroencephalograms (EEGs) in patients receiving levofloxacin therapy.[16] Unfortunately, an EEG to exclude the existence of drug-induced NCSE was not performed as our patient had improved dramatically within 24 hours of stopping Levofloxacin. Also no neurology or psychiatric referral was made/no brain imaging and cerebrospinal fluid (CSF) studies were done as patient recovered promptly after cessation of the drug.

Delirium is defined as a transient, usually reversible, cause of cerebral dysfunction and manifests clinically with a wide range of neuropsychiatric abnormalities. It can occur at any age, but it occurs more commonly in patients who are elderly and having impaired cognitive function. The clinical hallmarks of delirium are decreased attention span and a waxing and waning type of confusion. The diagnosis of delirium is clinical. *The Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-4)* diagnostic criteria for delirium helps in establishing the diagnosis.[17] Some of the other measures used to assess delirium are Richmond Agitation Sedation Scale.[18,19], The Confusion Assessment Method.[20] The goal of treatment is to determine the cause of the delirium and correct the correctable if possible. Components of delirium management include prevention, supportive therapy (correcting the correctable, reorientation techniques,) and pharmacologic management (antipsychotics).

CONCLUSION

- Drug induced delirium and anaphylaxis is a potentially life-threatening complication and can compromise both length and quality of life
- Early identification and prompt intervention improves both mortality and morbidity associated with these complications
- Impeccable assessment and management of readily reversible complications is an essential component of Acute Palliative Care services.

Appendix I: Timeline of events

Time	Event
5.00 pm	Presented to OPD
6.15 pm	Assessed and started on IV Levofloxacin
6.20 pm	Anaphylaxis, given IV steroid, IV antihistamines, O_2, shifted to ER
6.23 pm	Admitted in ER
6.30 pm	Reassessed: Resolution of anaphylaxis
6.50 pm	Developed Delirium: Work up for reversible causes sent, pharmacological treatment initiated
10.00 pm	Delirium improved
6.00 am	Resolution of symptoms
11 am	Shifted to ward
Day 1	Ward
Day 2	Ward
Day 3	Shifted to hospice for respite care

ER: Emergency room, OPD: Out-patient department

REFERENCES

1. Hoshino K, Sato K, Une T, Osada Y. Inhibitory effects of quinolones on DNA gyrase of *Escherichia coli* and topoisomerase II of fetal calf thymus. Antimicrob Agents Chemother 1989;33:1816-8.
2. Hayakawa I, Furuhama K, Takayama S, Osada Y. Levofloxacin, a new quinolone antibacterial agent. An introductory overview. Arzneimittelforschung 1992;43:363-4.
3. Blomer R, Bruch K, Krauss H, Wacheck W. Safety of ofloxacin- adverse drug reactions reported during phase-II studies in Europe and Japan. Infection 1986;14:S332-4.
4. Carbon C. Comparison of side effects of levofloxacin versus other fluoroquinolones. Chemotherapy 2001;47:9-14.
5. Moorthy N, Raghavendra N, Venkatarathnamma PN. Levofloxacin-induced acute psychosis. Indian J Psychiatry 2008;50:57-8.
6. Hakko E, Mete B, Ozaras R, Tabak F, Ozturk R, Mert A. Levofloxacin-induced delirium. Clin Neurol Neurosurg 2005;107:158-9.
7. Kiangkitiwan B, Doppalapudi A, Fonder M, Solberg K, Bohner B. Levofloxacin-induced delirium with psychotic features. Gen Hosp Psychiatry 2008;30:381-3.
8. Raj V, Murthy TV. Levofloxacin induced delirium with psychotic features in a young patient. Med J Armed Forces India 2013;69:404-5.
9. Slobodin G, Elias N, Zaygraikin N, Sheikh-Ahmad M, Sabetay S, Weller B, *et al*. Levofloxacin-induced delirium. Neurol Sci 2009;30:159-61.
10. Singh D, Kapoor A, Singhal MK, Singh V, Kumar HS. Levofloxacin induced psychosis: A rare case report. Int J Basic Clin Pharmacol 2014.
11. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/020634s065,020635s071,021721s032lbl.pdf [Last accessed on 2014 Sep 13].
12. Kahn JB. Latest industry information on the safety profile of levofloxacin in the US. Chemotherapy 2001;47 Suppl 3:32-7.
13. Akpunonu B. Multicenter, postmarketing assessment of levofloxacin in the treatment of adults with community-acquired pneumonia. Clin Infect Dis 2004;38 Suppl 1:S5-15.
14. Isaacson SH, Carr J, Rowan AJ. Ciprofloxacin-induced complex partial status epilepticus manifesting as an acute confusional state. Neurology 1993;43:1619-21.
15. Fernandez-Torre JL. Levofloxacin-induced delirium: Diagnostic considerations. Clin Neurol Neurosurg 2006;108:614.
16. Product Information: Levaquin (R), levofloxacin tablets and injection. Raritan (NJ): Ortho-McNeil Pharmaceutical, Inc; 2004.
17. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. 5th ed. Washington, DC: American Psychiatric Association; 2013.
18. Sessler CN, Gosnell MS, Grap MJ, Brophy GM, O'Neal PV, Keane KA, *et al*. The Richmond Agitation-Sedation Scale: Validity and reliability in adult intensive care patients. Am J Respir Crit Care Med 2002;166:1338-44.
19. Ely EW, Truman B, Shintani A, Thomason JW, Wheeler AP, Gordon S, *et al*. Monitoring sedation status over time in ICU patients: Reliability and validity of the Richmond Agitation Sedation Scale (RASS). JAMA 2003;289:2983-91.
20. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: The confusion assessment method. A new method for detection of delirium. Ann Intern Med 1990;113:941-8. Available from: http://hospitalelderlifeprogram.org/private/cam-disclaimer.php?pageid = 01.08.00 [Last accessed on 2014 Sep 13].

How to cite this article: Ghoshal A, Damani A, Salins N, Deodhar J, Muckaden MA. Management of levofloxacin induced anaphylaxis and acute delirium in a palliative care setting. Indian J Palliat Care 2015;21:76-8.

Source of Support: Nil. **Conflict of Interest:** None declared.