Letter to the Editor

Fluoroquinolone-associated suicide

ARTICLE INFO

Keywords:
Fluoroquinolones
Suicide
Adverse events
FDA
FAERS

Suicide is a huge global health problem and is the tenth leading cause of death in the United States. Several case reports have raised concerns that exposure to fluoroquinolones (FQs) may increase the risk of suicidal behavior. Though FQs, including levofloxacin, ciprofloxacin, and moxifloxacin, have been available for the last 3 decades, there has been a significant paradigm shift about their safety in the last five years (Supplementary Table 1). Recently, European Medicines Agency has started undertaking a detailed investigation on long-term side effects primarily affecting neurological and musculoskeletal system [1]. In 2013, FQ labeling for levofloxacin, ciprofloxacin, and moxifloxacin, respectively had been revised to indicate that suicide represented “isolated” reports, events that were “reported in < 1% of treated patients,” and “very rarely reported adverse events”. In 2015, a new syndrome termed “FQ associated disability” was described that included serious and disabling side effects that followed even one or two FQ doses. Given their serious and disabling side effects that can occur even with one to two doses, the Food and Drug Administration (FDA) issued a public health announcement that use of FQs should be reserved for patients who have no other alternate options [2]. In February 2017, the levofloxacin manufacturer expanded the suicide-related events in the warnings section of the product label [3]. Similar revisions were not disseminated for ciprofloxacin and moxifloxacin. In this study, we reviewed FDA reports of suicidal behaviors associated with all FDA-approved FQs and evaluated reporting completeness, as many FDA-reported adverse events lack key clinical information.

FDA’s Adverse Event Reporting System (FAERS) database was searched (keywords: “ciprofloxacin, levofloxacin, moxifloxacin, gatifloxacin, and ofloxacin”; suicide; or suicidal attempt) (1994–2015). Included cases had no psychiatric history or stable, controlled, psychiatric illness; had attempted or completed suicide, and were reported to the FDA listing the FQ as the suspected causal drug. FAERS report completeness was analyzed with a 10-point scale evaluating demographics, concomitant drugs, FQ usage, psychiatric history, and suicide details, modified from validated scales developed by us previously (Table 1).

Of the 122 FQ-associated suicide or suicide-attempt events reported to the FDA, 108 met inclusion criteria (Table 1). Half of the events described completed suicides; 61% were male, 18% were < 35 years old, and 40% of the events occurred within two weeks of FQ initiation. Mean completeness scores for attempted versus completed suicides were 5.9 and 6.7 (out of 10-point maximum score), respectively (nominal p = .03). Reporting completeness scores were better if the event occurred ≤ two weeks versus later after FQ initiation (mean score of 7.2 versus 5.7, nominal p = .0003, Fisher-exact). Psychiatric history was rarely present (8 of 39 events reported as occurring ≤ two weeks after FQ initiation and five of 65 events reported as > two weeks after FQ initiation), particularly for levofloxacin-associated attempted or completed suicides (one of 27 reports). Few reports included information on drugs concomitantly taken with the FQ. Characteristics of reported persons who attempted versus completed suicide were similar for age, gender, and event occurrence ≤ two weeks after FQ initiation.

Forty-three of 108 reported FQ-associated suicide events occurred ≤ two weeks of FQ initiation. Since 2013, FQ labeling for neuropsychiatric risks, including suicidal ideation, attempts, or completed suicides has been revised periodically. In 2017, labeling for levofloxacin, but not ciprofloxacin or moxifloxacin, was revised to state that suicide-related events may occur, especially in patients with a medical history of depression, or an underlying risk factor for depression and the descriptor “rare” was no longer included in the labeling information. However, FDA reports rarely included text describing psychiatric histories among FQ-treated persons with reported suicide attempts or completed suicides. Given large numbers of FQ-treated persons, prescribers and patients should be aware of revised use indications and FQ associations with suicides. Our findings suggest that labeling should be revised to be more consistent among levofloxacin, ciprofloxacin, and moxifloxacin with respect to underlying risk factors.

Study limitations exist. Given the strong association of suicide risk with prior psychiatric history in FQ users, our study has a reporting bias inherent to FAERS data. It is possible that persons with FQ-associated suicidal toxicity and underlying psychiatric illness may not have been reported to the FDA as experiencing an FQ-related adverse event, thus leading to underreporting of these events among FQ treated persons with known psychiatric histories [4]. Nonetheless, FAERS have been used in the past to identify rare, important, and serious adverse drug reactions [5].

The study highlights the importance of continued awareness of fluoroquinolone-associated suicide-related events, which can occur even in patients without prior psychiatric illness. FDA should consider
Table 1
Patient characteristics of reviewed patients who had FQ associated completed or attempted suicides.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>≤ 2 weeks</th>
<th>&gt; 2 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug used</td>
<td>Levofoxacin n = 11</td>
<td>Ciprofloxacin n = 15</td>
</tr>
<tr>
<td>Levofoxacin n = 16</td>
<td>Ciprofloxacin n = 33</td>
<td>Other FQ— n = 16</td>
</tr>
<tr>
<td>Median age (years) (range)</td>
<td>45 (23–84)</td>
<td>49 (21–84)</td>
</tr>
<tr>
<td>Male n, (%)</td>
<td>7 (64%)</td>
<td>12 (80%)</td>
</tr>
<tr>
<td>Completed n, (%)</td>
<td>0 (0%)</td>
<td>4 (27%)</td>
</tr>
<tr>
<td>Reports from USA n, (%)</td>
<td>6 (55%)</td>
<td>4 (27%)</td>
</tr>
<tr>
<td>Quality score</td>
<td>9 (82%)</td>
<td>15 (100%)</td>
</tr>
<tr>
<td>Demographics (2 points)</td>
<td>8 (73%)</td>
<td>10 (67%)</td>
</tr>
<tr>
<td>Drug related (3 points)</td>
<td>3 (27%)</td>
<td>2 (13%)</td>
</tr>
<tr>
<td>Prior psych history (1 point)</td>
<td>7 (64%)</td>
<td>12 (80%)</td>
</tr>
<tr>
<td>Concomitant medications (1 point)</td>
<td>8 (73%)</td>
<td>12 (80%)</td>
</tr>
</tbody>
</table>

Quality scoring elements: demographics, drug-related, suicide-related, prior psychiatric history, and concomitant medications. (Maximum score of 10 points for each adverse event report).†

† Demographics: Age (1 point) and gender (1 point).
‡ Drug related: Indication for use (1 point), days on FQ before event (1 point), dates of drug use (1 point);
§ Suicide related: Reported by physician (1 point) or not (0), Suicide modality (1 point), date of event (1 point).
¶ Prior psychiatric history reported (1 point).
§§ Concomitant medications (1 point).
\* Other fluoroquinolones: Ofloxacin (n = 23), Moxifloxacin (n = 11), Gatifloxacin (n = 1).
\*\* Includes cases for which time of event since drug use is not reported.

instituting active-ascertainment procedures for FQ-associated suicide attempts or completed suicides. Going forward, the post-marketing drug labels of FQs should be paralleled for all FQs as per the recent FDA advisory committee recommendations. When reporting FQ-associated suicide behaviors to the FDA or pharmaceutical industry, it is critical to comprehensively report case information.

Acknowledgments of research support for the study
This work was funded partly by the National Institutes of Health (Grant No. R01CA16509), the American Cancer Society (IRG-13-043-01), Supporting Outstanding Academic Research Seed Grants at USC (SOAR-USC), the South Carolina SmartState Program, and unrestricted grants from Doris Levkoff Meddin and Frank P and Josie M Fletcher to the Center for Medication Safety and Efficacy of the Medical University of South Carolina and the University of South Carolina. No funds were accepted from a pharmaceutical manufacturer or a pharmaceutical distributor. The authors wish to acknowledge the contributions of Travis Bailey, Robert C Kane, MD, Andrew C. Bennett, Carolyn Banister, PhD, Linda Martin, Alan Redd, David Melvin, Terry Ashton, John Fratti and Raja Fayad to the manuscript preparation. Andrew C. Bennett received a travel grant from AVAHO to present part of the work.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejim.2018.07.012.

References


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