Reply to Trezza et al

Trezza et al [1] raise 2 methodological issues regarding our observational study on serious arrhythmia associated with fluoroquinolones [2]. First, Trezza and coworkers point out that our study did not consider exposure to fluoroquinolones during hospitalization, notably...
because the databases we used included only data on outpatient prescriptions, none on inpatient medication use. Indeed, as correctly noted, fluoroquinolones may be administered in hospital (eg, for chronic obstructive pulmonary disease exacerbations) and, given the acute nature of arrhythmias, they can contribute to the development of the event during hospitalization. This is precisely why, within the limits of this study, we considered any hospitalization during the current exposure time window (the 14-day period prior to hospitalization for the arrhythmia event or the corresponding index date for the controls) to be a potential source of missing exposure and immeasurable time bias [3]. A total of 7.3% of the cases vs 1.5% of the controls had been hospitalized during this exposure time window. As Trezza et al suggest, not accounting for missing exposure information during these hospitalizations could bias the findings, leading to an underestimation of the risk. This is precisely what our study found. Indeed, we observed no or attenuated associations when these periods of hospitalization were not taken into consideration, thus assuming that patients were not exposed during their stay. However, when we excluded these individuals hospitalized during the current time window, as a way to adjust for immeasurable exposure, the risk was increased. In other words, in the ideal situation where we could have measured in-hospital exposure to fluoroquinolones, our point estimates would be even greater. This effect can be expected to be higher still from our use of a cohort of users of respiratory medications, for whom the use of in-hospital fluoroquinolones should be higher than in the general population [4, 5].

Second, it is quite unlikely that in-hospital unmeasured confounders can explain the magnitude of risks we found to be associated with the use of fluoroquinolones (the lowest rate ratio was 2.15 for ciprofloxacin). First, our study already adjusted for several confounders, including established risk factors for arrhythmia. Second, while factors such as electrolyte imbalances, ischemia, inflammation, and hypokalemia that often occur during hospitalizations are indeed risk factors for arrhythmia, they must be so above and beyond the already adjusted-for factors. Moreover, it is not evident that they are also associated with the use or choice of fluoroquinolones, an essential second condition for confounding to occur.

In all, Trezza et al bring up important points which, within the realm of our study, would suggest that the risks we found are in fact underestimates of the true risks. Their letter also highlights the need for studies using hospital databases that include inpatient drug exposures.

Notes

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