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Low Dose Antipsychotics for the Treatment of Delirium in Hospitalized Elderly Patients and Their Effects on QTc Interval

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Dear Editor

We read the article entitled "Effect of low dose haloperidol and quetiapine on QTc interval in hospitalized elderly patients with delirium" by Pinkhasov et al[1] with considerable interest.

The authors investigated the QTc interval prolongation due to antipsychotic administration for delirium in geriatric inpatients. They found that haloperidol was more significantly associated with QTc interval prolongation compared with quetiapine.

Delirium is a common condition in hospitalized elderly patients, associated with an increased risk of complications, poor outcomes, and death. The challenges of using antipsychotics for delirium in these patients are the potential risk for QTc interval prolongation and Torsade de Pointes (TdP). Therefore, the study by Pinkhasov et al is precious because of comparing the cardiac risks associated with haloperidol and quetiapine. Based on the value of the study, we believe that it is worth mentioning a few points regarding the article.

The first point is that the presence of some underlying conditions which can lead to QT prolongation needs mentioning. For example, sepsis is a risk factor for prolonged QTc interval.[2] Also, in acute infection, increased inflammatory cytokines are associated with QT prolongation.[3]

Moreover, specific concomitant QT-prolonging medications were not reported in the study. Since different drugs can be associated with various risks for developing QT prolongation,[4] it was informative for the audience to know these agents. Additionally, for the assessment of drug interactions leading to QT prolongation; not only the concomitant QT-prolonging agents; but also inhibitors of hepatic cytochrome P450 enzymes and medicines such as diuretics -due to consequent electrolyte disturbance- are worth considering.[4,5]

The percentage of patients who received concomitant QT-prolonging agents at baseline and post-treatment with antipsychotics were different considerably by 18% vs 40%, respectively. It could substantially affect the results due to the confounding effect of initiating QT-prolonging agents in patients whose baseline QTc intervals were measured without the interacting medications. However, this substantial heterogeneity was not among the limitations of the study.

Based on the results, the percentage of patients with baseline prolonged QTc interval was higher in the haloperidol group. It was valuable if the authors mentioned whether the difference among the groups was significant or not.

Additionally, 20 patients had prolonged QTc at baseline before initiation of haloperidol, which raises the question regarding the justification for initiating the medication due to the higher risk for QTc prolongation/TdP.

Another point that needed description in the method section was the measurement of the QTc interval. As previously shown, QT interval is influenced by several factors such as ECG lead and time of the day.[6,7]

Moreover, antipsychotics block the IKr channel in a concentration-dependent manner[6] emphasizes the importance of timing ECG monitoring following the administration of antipsychotics.

Due to the impact of heart rate (HR) on QT interval, QT is generally corrected with HR by different formulas. The sensitivity of these formulas varies in extremes of HR and sometimes causes under-correcting at low HRs and over-correcting at high HRs.[8] Therefore, using the appropriate formula consistently for all patients is important.

The antipsychotics were administered as scheduled, as-needed, or a combination of both. In addition, the route of administration was either orally or parentally while not

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mentioning whether intravenous or intramuscular. It shows a wide variation among patients. As mentioned in the discussion section by Pinkhasov et al, intravenous infusion of haloperidol is more likely to be associated with QT prolongation. However, no more data were provided in the article.

In Table 2 in the result section of the article, the QT intervals were classified as "normal", "borderline", and "prolonged". Based on the differences in the literature regarding the lower and upper limit of normal for QT intervals,[3,4,6,9,10] it was more valuable to determine the basis for this categorization.

There is some inconsistency regarding the numbers in the tables and the result section. For example, the study population in the result section and tables were 68 vs 66, respectively.

In Table 1 in the results of the article, in the section on antipsychotic dosing, the total number of patients who received antipsychotics "as-needed only" and "both scheduled and as-needed" were 44 and 17, respectively. These numbers do not match the summation of the number of patients listed for these dosing regimens in the haloperidol and quetiapine columns.

The inconsistency in the numbers is also seen in the section of QTc in Table 2. The total number of patients with baseline "normal" and "borderline" QTc intervals were mentioned as 22 and 17 instead of 21 and 16, respectively. This issue was repeated in Table 2 in the post-treatment QTc section where patients with borderline and prolonged QTc intervals were written as 12 and 39, instead of 11 and 38, respectively.

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