PALLIATIVE CARE
CASE OF THE MONTH

Choosing an Antipsychotic for the Treatment of Delirium

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Case:

Last week's patients:

- *26- year- old male patient with cystic fibrosis in the ICU with agitation. On Ativan, Haloperidol, Risperidone and Olanzapine at the same time*
- *90- year- old male on the medical service with hypoactive delirium on low dose Quetiapine who is just sleeping all the time*
- *45- year- old woman on the surgical service with delirium who has been on all three atypical antipsychotics for the last week*

Delirium is a common problem in hospitalized patients. While non-pharmacological interventions are the gold standard for the prevention of delirium, medications are helpful in treating the symptoms of delirium (and there is some evidence suggesting they improve patients' prognosis). Which medication to use to treat symptoms of delirium, however, is often confusing to non-psychiatrists. In the last week on service, I saw five patients with delirium, and they were on the range of atypical antipsychotics and haloperidol—often in interesting combinations of two and three. Longer, more in-depth reviews of the pharmacologic treatment of delirium are available. (1,2,3) The purpose of this case of the month is to describe the three most commonly used antipsychotics for delirium regarding their mechanism of action, dosage, pharmacokinetics, efficacy, side effects, and cost.
This review focuses on short term use of these drugs for delirium in acutely ill, hospitalized patients.
In the ICU setting, these agents are often included in guidelines and commonly used in the treatment of delirium despite a paucity of good randomized controlled trial data to support this practice.

First, data suggest little long-term benefit and increased mortality in elderly patients with dementia. Second, there is no clear head-to-head data supporting one drug over another in the treatment of delirium, so choices of any particular agent are based on expert opinion rather than clear evidence of superiority. Given this, more emphasis should be placed on using an effective dosage rather than on what drug you should choose.

Third, this report focuses on treating delirium alone. There may be some reasons (although largely theoretical) to choose one drug over another because of co-morbid conditions such as insomnia, depression, nausea, or weight loss. Fourth, all of these drugs have the potential to increase QTc and thus can cause Torsades (but the risks are low enough, that I do not believe it is worthwhile differentiating between the different anti-psychotics. Patient risk factors, concurrent medicine, and underlying QTc are more important.). In addition, QTc prolongation with a single agent does not predict QTc prolongation with another agent. Fifth, the cost differences are likely to change as medications go off patent; regardless, haloperidol is likely to be the least expensive. Sixth, benzodiazepines should not be used in delirium (unless due to alcohol or benzediazapine withdrawal) as they do not improve symptoms and may make them worse.

Seventh, while there are data about adding atypical antipsychotics to as needed haloperidol, there are no data supporting antipsychotic polypharmacy over monotherapy. Finally, because of the discomfort associated with IM dosing and the inconsistent absorption, this should be a method of last resort in giving the medications.

Haloperidol – This is the best studied drug and the drug of choice for most patients. It is a strong and relatively specific D1 and D2 antagonist. Typically, it is given twice a day with extra doses as needed every four to six hours (0.5-1.0 mg) although in severe delirium in the intensive care unit, it is dosed much more aggressively (initial dose 2-10 mg repeat bolus every 30 minutes [with sequential doubling of the initial bolus dose] and then giving 25% of the last bolus dose every 6 hours). It has peak effect in about 30-60 minutes (iv) and 4-6 hrs. (orally) and a half-life of 18 hours. Its metabolism is primarily though CYP2D6-mediated breakdown although glucoridation and CYP3A4 and CYP1A2mediated breakdown play a part. There are clear differences when given orally versus intravenously; the former has the least QTc prolongation while the latter has among the most (in a dose-related manner). Conversely intravenous haloperidol has the least extrapyramidal symptoms while given orally, there are more reactions than with atypical antipsychotics.

Risperidone –This atypical antipsychotic is the most like haloperidol in terms of its potency, although it has more 5HT action. It comes in an oral, an oral dissolving and liquid formulation (the latter can be given through nasogastric tubes). It can be given once or twice a day with a starting dose of 0.5 mg. It has a peak effect in 3 hours (in extensive metabolizers) and a half -life of 20 hours. Its metabolism is largely hepatic through CYP2D6.
It has less drug-drug interactions than olanzapine or quetiapine. Extrapyramidal side effects are less than haloperidol given risperidone's 5HT effects.

Olanzapine – This atypical antipsychotic has less D2 receptor antagonism but more balanced antagonism to a wide range of receptors including 5HT3 (equivalent to ondansetron), 5HT6, muscarinic receptors, alpha 1 and 2 adrenergic receptors, and H1.

It comes both as an oral and oral dissolving formulation. It is given in a starting dose of 2.5-5 mg daily, adjusting by 2-5 mg per day to a maximal dose of 20 mg per day in 1-2 daily doses. It has a peak effect in roughly 6 hours, a half-life of 21-54 hours and is highly metabolized in the liver by direct glucuronidation and P450 metabolism (CYP1A2 and CYP2D6). Because there are multiple pathways of metabolism drug-drug interactions are more common than with resipirone. Extrapyramidal side effects are less than haloperidol, and there are good data for its effectiveness in treating nausea.

Quetiapine – This atypical antipsychotic is felt to be more sedating, particularly at lower doses, due to its affinity for H1 receptors. Quetiapine is available only as an oral pill. It is given as 25 mg once or twice a day with dose escalation of 25-50 mg day to a maximal dose of 400 mg/day. Some authors like the wider dose range as it allows for more effective titration, although this may also be a disadvantage if the clinician does not actively titrate the dose. It peaks in 1.5 hours and is primarily metabolized by the hepatic CYP3A4 system, meaning it does have more drug-drug interactions. Extrapyramidal side effects are less than haloperidol. While quetiapine is often used as a medicine for insomnia, there are not data supporting this use.

References:

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