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Use of antipsychotics for the treatment of intensive care unit delirium

Uso de antipsicóticos para tratamento do delírio na unidade de terapia intensiva

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Intensivists are faced on a daily basis with patients suffering from delirium, which causes them and their loved ones considerable distress and predicts for those patients worse outcomes, including dementia and death. With the use of routine screening tools delirium is now identified in patients previously thought to be still under the effects of sedation, depressed, simply difficult or overly compliant. World-wide studies document the prevalence of intensive care unit (ICU) delirium as ranging from 30% to 80%.⁽¹⁾ Studies using patients' computerised tomography and magnetic resonance brain scans hypothesize a link between duration of delirium and brain atrophy.⁽²⁾ While the pathophysiology of delirium is still not entirely understood, there is certainly evidence to support the hypothesis of a final common pathway of an ongoing hyperdopaminergic and hypocholinergic state perhaps triggered by oxidative stress and associated with excitotoxicity.⁽³⁾

Put together the diagnosis of a syndrome known to be associated with harm and a basis for ongoing neurotransmitter imbalance it is inevitable that clinicians would use an antipsychotic intervention with the aim of rapid resolution. An educational workshop on attitudes towards pharmacotherapy for delirium resulted in a more positive general attitude to pharmacological interventions, especially in hypoactive presentations and prophylactically in high-risk patients.⁽⁴⁾

The evidence to date to support the use of antipsychotics in critical care delirium remains elusive, other than when needed to control the symptoms of agitation. As a previous editorial pointed out, if we accept the premise that our therapeutic intervention is targeted at the final stage of a complex multifactorial syndrome it is surely unlikely that it would be effective. That editorial was linked to a study that concluded short-term prophylactic administration of low-dose intravenous haloperidol significantly decreased the incidence of postoperative delirium.⁽⁵⁾ Dr Caplan in fact went so far as to speculate whether the antagonistic activity of haloperidol at the sigma-1 receptor conferred a neuroprotective effect in the conditions of oxidative stress. Endoplasmic reticulum protein sigma-1 receptors are unique binding sites in the brain that exert a potent effect on multiple neurotransmitter systems: neurosteroids, glutamate NMDA receptor and dopamine. Other theories would include a sedative

Conflicts of interest: None.

Submitted on March 27, 2014
Accepted on April 6, 2014

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DOI: 10.5935/0103-507X.20140016

sparing effect, an immunomodulatory effect or simply to note the results of observational or cohort trials.

The first published use of an antipsychotic to treat delirium in a critically ill patient was a description of the use of haloperidol in 1977.⁽⁶⁾ Traditional antipsychotic drugs act mainly by interfering with dopaminergic transmission in the brain by blocking dopamine D₂ receptors, which may also result in extrapyramidal side effects and the hyperprolactinaemia. However they may also affect cholinergic, alpha-adrenergic, histaminergic and serotonergic receptors. For the past 10 years doctors have referred to two different groups of antipsychotics: 'typical' the older drugs with dominant action on dopamine release (chlorpromazine, haloperidol, primazide, trifluoperazine and sulpiride) and 'atypical' the newer drugs that interfere with the serotonergic pathways (clozapine, olanzapine, quetiapine and risperidone among others), some with very little dopamine antagonism. Recent large independent research studies suggest that the new drugs are not really different, but in some situations easier to use. Efficacy rates in treating delirium symptoms between typical and atypical antipsychotic agents are similar and optimum doses of low-potency conventional one might not induce more extrapyramidal side effects than new generation drugs.^(7,8) Haloperidol, as the only antipsychotic that can be administered intravenously, is the most used and studied antipsychotic drug for delirium treatment. It has a relatively short time of peak plasma concentration (iv: 5-15 minutes), and it is useful for its sedative effects rather than the specific anti-delirium one.⁽⁴⁾ The dosage and the frequency vary largely among studies, depending on administration route mainly.⁽⁹⁾ More recently studies highlight the increasing use of olanzapine, risperidone and quetiapine as atypical neuroleptic agents for treating delirium. The recent UK NICE guidelines indeed support the use of olanzapine for the short-term use of distress,⁽¹⁰⁾ but the experience of haloperidol administration in everyday practice underpin its continued use for short term symptom control.⁽¹¹⁾

The Hope-ICU trial, a placebo-controlled randomised trial demonstrated that routine administration of haloperidol does not shorten the duration of delirium, as diagnosed by the CAM-ICU, in critically ill patients. It did show haloperidol

reduces agitation, therefore we concluded that, pending further studies, haloperidol should be reserved only for management of acute agitation.⁽¹²⁾ The Pain, Agitation, and Delirium practice guidelines published in 2013 by the American College of Critical Care Medicine concluded:

- I. there is no published evidence that treatment with haloperidol reduces the duration of delirium in adult ICU patients (no evidence).
- II. atypical antipsychotics may reduce the duration of delirium in adult ICU patients (low/very low recommendation).⁽¹³⁾

Are clinicians justified to use antipsychotics when faced with delirium in a non-agitated patient? The negative Hope-ICU trial was inevitably subject to concerns regarding power although there was no signal in either direction for benefit or harm. At the time the question was asked whether clinicians were administering sedation or antipsychotics to treat patients or our own discomfort.⁽¹⁴⁾ One reason that clinicians reach for quetiapine when their patient is failing to make clinical progress after several days of delirium is because they want to give every chance that patient's outcome will be the best possible, to do something active to relieve suffering.

Three clinical trials on prophylactic and treatment use of haloperidol are ongoing and recruiting in the US. Hopefully their results will finally answer the question to clinicians satisfaction, does haloperidol treat delirium? If antipsychotics do not work to treat delirium, what are the alternatives? While we wait to establish the place of antipsychotics in critical care we need to continue looking beyond antipsychotics and explore how and why we sedate patients the way we do, how we medicate patients with deliriogenic drugs and working to "actively mobilize" them 7 days a week. Delirium research has already established anti-cholinesterase drugs are likely to be dangerous in the critical care population,⁽¹⁵⁾ but anti-inflammatory interventions are another option and there is an ongoing trial to determine if simvastatin decreases delirium in mechanically ventilated patients.⁽¹⁶⁾ The answer does not stop at antipsychotics as long as there are clinicians committed to finding solutions however complex the problem.

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