Pharmacologix

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Re: Haldol contraindication in Parkinson's disease

Dear Dr[redacted] ,

Please find attached the write-up for the pharmacological mechanisms underlying the contraindication for Haldol use in Parkinson's disease (PD). Please add this documentation toyour expert witness testimonial. The time spent on this write-up totals two hours as requested.

Brief Summary:

The use of haloperidol (Haldol) in PD patients is contraindicated based on the underlying pathology of the disease state. PD is characterized by neuronal death in the substantia nigra andsubsequent depletion of dopamine in the midbrain striatum. Haloperidol is an antipsychotic thatacts as a dopamine antagonist, depleting dopamine tone within the brain. Haloperidol use in PDpatients would further deplete dopaminergic levels within the striatum, exacerbating parkinsonian symptoms. Therefore, the use of haloperidol, and other dopamine antagonists, arestrongly discouraged in this patient population.

Thank you,

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Parkinson's disease (PD) is a prominent neurodegenerative disorder characterized by progressive degeneration of midbrain dopamine (DA) neurons resulting in loss of dopaminergic innervation within the nigrostriatal pathway. Dopamine cell bodies are located in the substantia nigra and neuronal loss in this region results in loss of dopamine innervation to the striatum, a brain area that is critical for motor function. Cardinal symptoms for PD include tremor, rigidity, akinesia and postural instability. The most widely utilized drug treatment regimens in PD are those that induce changes in dopaminergic neurotransmission. Specifically, the gold standards for treatment in this patient population include indirect and direct acting DA agonists that act to increase synaptic dopamine levels. Indirect-acting agonists include levo-dopa, the precurser to DA, which is metabolized into DA thereby increasing synaptic levels and restoring function in the depleted system. Direct-acting agonists, such as pramipexole, bind directly to DA receptors and imitate the effects of endogenous DA in the synapse. These drugs improve the symptoms of PD because they normalize dopaminergic function in a system (nigrostriatal DA pathway) that has suffered a significant depletion of DA. As PD progresses, there is an even greater loss of DA in the system resulting in more severe symptoms of the disease and neural dysfunction.

Haloperidol (marketed under the trade name Haldol) is a typical antipsychotic medication used in the treatment of psychiatric disorders including schizophrenia and bipolar disorder. Historically, hyperdopaminergic activity in the brain has been considered a major contributor to the appearance of these psychiatric disorders. Antipsychotics are largely thought to alleviate psychotic symptoms through their activity at DA receptors, i.e., through blockade of DA receptors and thus, dopaminergic transmission within the brain. Evidence from positron emission tomography indicates that the therapeutic effects of antipsychotics are noted at 60-70% blockade of DA receptors (Hudson et al., Parkinson's disease, 2014).

Haldol, and other DA receptor antagonists, are contraindicated in patients that present with PD. In the naïve disease state, PD patients have significantly depleted dopaminergic tone, particularly in the striatum. The administration of a DA antagonist would compete with the greatly reduced endogenous DA for binding sites at available receptors in the synapse, thereby significantly reducing any DA neural transmission. The additional insult to dopaminergic transmission, particularly in the nigrostriatal pathway, will exacerbate PD symptoms. Indeed, high doses of Haldol alone in a normal dopaminergic state results in many symptoms that mirror those of PD (e.g., tremor, muscle rigidity, and akinesia). Studies suggest that 26-67% of patients treated with antipsychotics develop parkinsonian-like symptoms. Antipsychotic-induced parkinsonian symptoms are observed with 34-80% blockade of D2 receptors (Hudson et al., Parkinson's disease, 2014). Haldol is frequently associated with CNS extrapyramidal symptoms and these are acknowledged and discussed in the package insert. These symptoms include akathisia and dystonia (including opisthotonos and oculogyric crisis). The severity of these symptoms are dose-dependent with greater

severity at higher doses. Overdosage with Haldol results in prominent extrapyramidal reactions, hypotension, and sedation. Extrapyramidal reactions can present as muscular weakness or rigidity with generalized or localized tremor.

The package insert for Haldol lists use in patients with Parkinson's disease as a contraindication. Case report studies with PD patients that were exposed to DA antagonists, such as Haldol, generally demonstrate exacerbated PD symptoms and incapacitation (Hudson et al., Parkinson's disease, 2014). Interestingly, very low doses of haloperidal are reported to supersensitize DA D2 receptor subtypes, allowing for lower doses of antiparkinsonian medications to be administered. This is attributed to increased numbers of D2 receptors that are in the high-affinity state for DA. One clinical trial reports that an add-on dose of 40 micrograms of haloperidol per day enhanced the clinical action of levodopa (Hudson et al., Parkinson's disease, 2014). While extremely low doses may be beneficial for patients with PD, increased dosage will have profound adverse effects.