Why is ophthalmic follow-up required with prolonged use of haloperidol?

Background

Haloperidol is a first-generation butyrophenone antipsychotic with multiple indications.[1] The drug is available in oral and injectable dosage forms. The injectable formulations, haloperidol decanoate and haloperidol lactate, are approved by the Food and Drug Administration for treatment of schizophrenia.[2,3] The lactate formulation is also approved for management of tics and vocal utterances in patients with Tourette syndrome while the decanoate formulation is also indicated for maintenance therapy of psychoses.

Several ophthalmic adverse effects have been reported with haloperidol.[1-3] These include visual disturbances, retinopathy, cataracts, blurred vision, and oculogyric crises. Effects such as oculogyric crises may be dose- or duration-dependent, and may be related to the pharmacologic activity of the drug (e.g., dopamine blockade).[2,3] In the 2016 label for haloperidol decanoate, the manufacturer reported eye disorders including blurred vision, visual disturbances, and oculogyric crisis occurring in less than 1% of subjects in clinical trials.[2] These data were derived from 13 clinical trials in which a total of 410 patients received the drug. Notably, some ophthalmic abnormalities have been reported with other antipsychotics, as well. For example, Marder et al state that cataracts have been observed with use of phenothiazines (e.g., chlorpromazine, in humans) and quetiapine (in animal subjects).[4] In their 2010 guideline on treatment of schizophrenia, the American Psychiatric Association (APA) also states that cataracts have been observed with quetiapine use in animal subjects, and they further note that pigmentary retinopathies and corneal opacities can occur with chronic administration of thioridazine and chlorpromazine.[5]

Ophthalmologic monitoring has been recommended for patients using haloperidol, specifically by the American Optometric Association (AOA); the AOA recommends an annual comprehensive eye exam and more frequent periodic care depending on ocular signs and symptoms.[6] Other organizations suggest ophthalmologic follow-up in patients with schizophrenia, in general.[4,5] Participants of the 2002 Mount Sinai Conference (Marder et al) developed guidance for mental health care providers in which they state that providers should monitor visual changes in patients with schizophrenia on a yearly basis, and a yearly eye exam should be performed for patients aged >40 years and biannually for younger patients.[4] In their 2010 guideline, the APA makes the same recommendations, citing the guidance developed at the 2002 Mount Sinai Conference.[5] Marder et al also state that patients with schizophrenia usually have other risk factors for lens opacities (e.g., cataracts), such as diabetes and hypertension.[4] Of note, other guidelines on management of schizophrenia were identified, including those of the National Institute for Health and Care Excellence (NICE) and the Schizophrenia Patient Outcomes Research Team (PORT – jointly funded by the Agency for Healthcare Research and Quality [AHRQ] and the National Institute of Mental Health [NIMH]); however, there is no mention of routine visual monitoring in these guidelines.[7,8] Additionally, the manufacturers of Haldol® (decanoate and lactate) do not have recommendations regarding ophthalmic monitoring of patients using these products.[2,3]

Literature Evaluation

A search of PubMed was performed to identify literature describing ophthalmic adverse effects associated with haloperidol. A case report was identified in which oculogyric crisis was observed in a patient using intramuscular (IM) haloperidol.[9] Two Cochrane reviews were identified evaluating oral haloperidol use in patients with schizophrenia; outcomes evaluated included adverse effects, among which ophthalmic effects were noted.[10,11] In addition to these publications, a matched cohort study was identified in which investigators examined the risk of cataracts with use of phenothiazine drugs and haloperidol.[12]

With regard to the case report, Jhee et al observed ophthalmic adverse effects in a 22-year-old Hispanic female after receiving 2 IM injections of haloperidol (7.5 mg at 0 hours and 10 mg at 4 hours).[9] The patient had been diagnosed with paranoid schizophrenia and was receiving haloperidol as part of a clinical trial. No other illnesses were noted, and no other medications were administered in the prior 6 months. Twenty-six hours after the first injection, the patient reported neck stiffness and inability to lower her gaze. Psychiatric evaluation led to a diagnosis of acute oculogyric crisis and acute torticollis. The patient was given benztropine 2 mg and she experienced near-complete resolution of her symptoms within 15 minutes. Using the Naranjo scale, Jhee et al determined that there was a probable association between the observed conditions and haloperidol.

A Cochrane review conducted by Adams et al compared the clinical effects of oral haloperidol to placebo for management of schizophrenia.[10] They included randomized controlled trials that enrolled patients with schizophrenia or similar psychosis. No exclusions were made for sex, age, or race. The primary outcomes were death (due to suicide or natural causes), overall improvement, treatment satisfaction, and specific behaviors. Secondary outcomes included duration of hospital stay, study discontinuation, indicators of mental state (e.g., positive and negative symptoms), general behavior, adverse effects, and cost of care. With regard to adverse effects, the investigators evaluated general and specific effects, movement disorders, other central nervous system effects, and cardiovascular effects.

Adams et al included 25 studies involving a total of 4651 patients.[10] With regard to ophthalmic adverse effects, blurred vision and oculogyric crises were reported. Blurred vision was observed in 2 trials involving a total of 240 participants (durations: 4 weeks and 12 weeks), and it occurred more frequently in patients receiving haloperidol vs. placebo (10.7% [13/121] vs. 2.5% [3/119], respectively; risk ratio [RR] 3.96; 95% confidence interval [CI] 1.21 to 12.93). Oculogyric crises were observed in 2 other trials, involving a total of 83 participants (duration for both: 12 weeks); however, the difference in risk between haloperidol and placebo was not statistically significant (2.4% [1/42] vs. 2.4% [1/41], respectively; RR 0.97; 95% CI 0.14 to 6.57). These effects were not further discussed or addressed in the authors' conclusions. However, Adams et al stated that a large proportion of the data were poor and badly reported.

In another Cochrane review, Tardy et al compared haloperidol to low-potency first-generation antipsychotics in patients with schizophrenia.[11] They included randomized controlled trials involving oral administration of these agents with a minimum follow-up duration of 3 weeks. Low-potency antipsychotic drugs were defined using equivalence tables. The primary outcome was response to treatment. Secondary outcomes included symptoms of schizophrenia, change in global state, relapse, hospitalization, death, and adverse effects. Adverse effects were further categorized as extrapyramidal, cardiac, hypotension, sedation, weight gain, and other side effects.

Tardy et al included 17 trials involving a total of 877 patients.[11] The duration of the studies ranged from 1 to 3 months. Similar to the findings of Adams et al, ophthalmic adverse effects reported by Tardy et al included blurred vision and oculogyric crises. Blurred vision was observed in 2 trials involving a total of 124 participants (durations: 4 weeks and 12 weeks); it occurred less often in patients receiving haloperidol vs. other first-generation antipsychotics (14.8% [9/61] vs. 19.0% [12/63], respectively; RR 0.78; 95% CI 0.35 to 1.70), but the difference was not statistically significant. Oculogyric crises were reported in 1 study involving a total of 86 participants (12 weeks); symptoms were observed more commonly in patients receiving haloperidol vs. other first-generation antipsychotics (2.4% [1/42] vs. 0% [0/44], respectively; RR 3.14; 95% CI 0.13 to 74.98), but the difference was not statistically significant.

These effects were not further discussed or addressed in the authors' conclusions. Tardy et al noted that the overall quality of studies was low.

In a matched cohort study, Isaac et al sought to determine the risk of cataract extraction among patients using phenothiazines and haloperidol.[12] They derived data from the Group Health Cooperative (GHC) of Puget Sound, a consumer-owned health maintenance organization. Patients were matched for sex, year of birth, and year of first use of the GHC pharmacy. Exposures of interest were phenothiazine antipsychotic drugs, other phenothiazine drugs, and haloperidol. Incident cases of cataract extraction were identified and relative incidences were reported comparing exposures to non-exposures. Both antipsychotic and non-antipsychotic phenothiazines were associated with higher incidences of cataract extraction with relative incidences of 3.32 (95% CI 1.17 to 9.45) and 3.79 (95% CI 1.70 to 8.45) after 2-5 years of use; in contrast, the investigators determined that there was no statistically significant association between haloperidol use and risk for cataract extraction, regardless of duration of exposure (examples: year 1: relative incidence 0.80, 95% CI 0.23 to 2.86; years 2-5: relative incidence 0.94; 95% CI 0.15 to 5.69). The route of administration and dosage forms of the drugs evaluated in this study were not specified.

There are several limitations to note regarding all of the aforementioned literature. The case report, though well described, is anecdotal, precluding conclusions regarding a cause-effect relationship between use of haloperidol and development of oculogyric crises.[9] The Cochrane reviews were comprehensive and involved randomized controlled trials; however, they evaluated oral haloperidol, only.[10,11] Additionally, adverse effects were not among the primary outcomes. Importantly, the authors of both publications asserted that the quality of evidence was low. With regard to the matched cohort study, Isaac et al did not specify the dosage forms of the medications they evaluated; also, they did not account for differences in types of cataracts (e.g., age-related vs. drug-related).[12] Additionally, the study was based on administrative data and was observational, precluding conclusions regarding a cause-effect relationship between haloperidol use and development of cataracts.

Conclusion

In conclusion, ophthalmic adverse effects have been reported with use of haloperidol.[2,3] These include visual disturbances, retinopathy, cataracts, blurred vision, and oculogyric crises.[1-3] From a search of the literature, few studies were identified describing these side effects. A case report was identified describing oculogyric crises; oculogyric crises and blurred vision were also mentioned in 2 Cochrane reviews involving randomized controlled trials of oral haloperidol. In addition, a matched cohort study was identified addressing the risk of cataract extraction with haloperidol. Though ophthalmic adverse effects were observed in these publications, not all studies demonstrated a statistically significant association between haloperidol use and the reported adverse effects. Also, as mentioned previously, these studies were not without limitations. Based on these data alone, it is unclear whether ophthalmic follow-up is required for all patients taking haloperidol. The AOA does recommend monitoring patients using haloperidol with an annual (or more frequent) comprehensive eye exam; however, the manufacturers of Haldol® do not address the need for ophthalmic follow-up. Other organizations, including the APA, suggest that patients with schizophrenia receive regular eye exams; however, they do not specify haloperidol as a drug associated with high risks of ophthalmic adverse effects, and they further assert that patients with schizophrenia may have comorbid conditions that could increase their risk for development of ocular abnormalities (namely cataracts). Clinicians may be advised to assess patients taking haloperidol for visual changes with consideration for follow-up with an ophthalmologist based on other factors including medical history and medication use.

References

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