Allergic Reactions to Haloperidol: A Systematic Review

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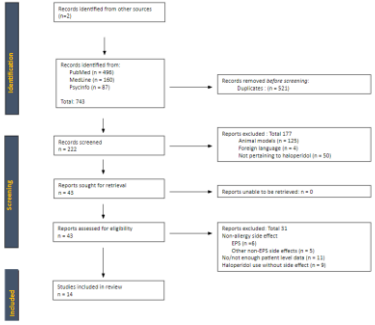
Background

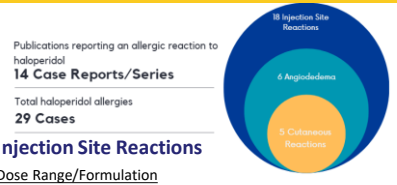
- In clinical practice, us of haloperidol is often hindered by documentation of an *allergy* in the electronic medical record (EMR)
- A *true* drug allergy represents an immunologically mediated reaction with a range of clinical presentations from mild urticaria to severe anaphylaxis.[2]
- EMR documentation of antipsychotic allergies is often incorrect and often includes extrapyramidal symptoms (not traditionally defined as allergy)[3]
- Few case reports detail haloperidol allergies, but there remains limited evidence regarding the prevalence and clinical significance of these events
- This review hopes to guide psychiatrists in weighing the risks of allergic reaction vs clinical benefit of haloperidol based on the full body of evidence available

Methods

A systematic literature review of allergic reactions to haloperidol, including anaphylaxis, hypersensitivity, angioedema, urticaria, and rash was conduced. Side effects including QT prolongation, EPS, or NMS were excluded. Each article was evaluated for clinical context, haloperidol dosing, allergic reaction, and clinical outcomes



Results



Injection Site Reactions

Dose Range/Formulation

- Dose ranged from 62.5 mg - 150 mg, unspecified in majority
- One case with 50mg/mL haloperidol decanoate; otherwise all reactions to 100 mg/mL formulation

Allergic Reaction/ Clinical Context

- Described as pruritic, tender, erythematous nodules
- Onset within 24 hours to a few days of initial injection
- Occurred with concurrent antihistamine/anticholinergic dosing

Management/Outcome

- Subsided overtime with no anti-allergic treatments
- Complete resolution ranged from 1-12 week

Angioedema

Dose Range/Formulation

- Range of formulations (PO, IV, IM)
- Total dose ranged from 1.5 -10 mg (two cases unspecified)

Allergic Reaction/ Clinical Context

- Onset within 4-72 hours of dose
- Occurred with concurrent risperidone, one case with concurrent diphenhydramine and lorazepam
- Five cases reported angioedema of the tongue resulting in tongue protrusion, necessitating acute medical attention

Management/Outcome

- Antihistamines, muscle relaxants, steroids, and epinephrine were employed in emergent treatment, with varying results
- Two cases with an initial resolution with diphenhydramine followed by a resurgence of angioedema of the tongue
- Five cases required the use of an additional agent (secondary antihistamine, steroids, and epinephrine)
- One case refractory to epinephrine, prompting tracheostomy

Literature Review

Other Cutaneous Reactions

Citation	Type of Study	Gender	Age (yrs)	Race	Dose	Route	Indication	Clinical Context/Additional Medications Administered	Allergic Reaction	Management/Outcome
Balai, 2017	Case Report	Female	11	Unspecified	0.5 mg	PO (tablet)	Unspecified	No prior history of drug allergies. No known familial angioedema. Presented to dermatology office with facial edema (primarily effecting eyelids and lips) and diffuse urticaria within three days of haloperidol dosing (1.5 mg total)	Urticaria and Angioedema	Initail urticaria reaction remitted in a day with discontinuation of haloperidol and administration of 2 doses of chlorpheniramine maleate and cetirizine. Upon accidental ingestion of an unknown dose of haldol a few days later, patient developed angioedema and urticaria, and was treated again with PO antihistamines
Kaminer, 1982	Case Report	Male	17	Unspecified	100 mg	PO (oral-liquid)	Agitation	No prior history of drug allergies reported. Patient tolerated haloperidol 100 mg tablets well, but in the setting of poor compliance, he was transitioned to 100 mg po syrup formulation. Within 36 hours of dosing syrup, patient developed an urticarial maculopapular rash over the entirety of his body, sparing his face.	Urticaria	All medications were discontinued. No anti-allergic medications were administered. Blood samples were collected to assess for a macrophage migration inhibition test.
Kaminer, 1982								Kaminer et al re-published the case of this 17-year-old with diffuse urticarial rash following haloperidol administration. They now include the results of a migration inhibition factor testing	Urticaria	Haloperidol was discontinued. Blood samples taken at the time revealed a significant macrophage inhibition with the oral liquid formulation of haloperidol and not tablet. Tests were then performed comparing methylparaben, lactic acid, and the haloperidol solution. Only the haloperidol and methylparaben tests showed evidence of an allergic response. Next haloperidol tablet was re-introduced with both the methylparaben solution and lactic acid. Again, only the methylparaben containing sample elicited response
Lee, 1999	Case Report	Male	59	Asian (Korean)	1.5 mg	not specified	Metabolic Encephalopathy	Hospitalized for the management of a primary neurologic disorder with concurrent administration of nimodipine, indeloxazine HCl, flurazepam HCl. Haloperidol was started on admission for the management of delirium. After 7 days of tolerating haloperidol 1mg, dose was escalated to 1.5mg. Within 4 days of increased dose, patient developed a palpable purpura rash with accompanying edema of legs and feet	Palpabable Purpura	The rash resolved with discontinuation and reappeared with rechallenge. Skin test further confirmed reaction to haloperidol. All other medications (nimodipine, flurazepam, indeloxazine) were re-challenged without symptom relapse.
Roy, 2022	Case Report	Male	35	Asian (Indian)	10 mg	PO (tablet)	Psychosis, unspecified	No prior allergic history, started on 3-day course of unknown psychotropic injection, then switched to Haloperidol 10 mg PO daily. 5 days after initiation, presented with pustular lesions over trunk, upper limbs and associated pruritis	Generalized Exanthematous Pustulosis	Resolved with discontinuing Haldol, starting prednisolone taper starting at 30 mg and fexofenadine 120 mg for 10 days. Subsequently tolerated Abilify up to 20 mg daily.

Discussion

Our systematic review of the literature to date reflects few cases of true allergies to haloperidol

- No significant dose-dependent reactions observed. There is evidence (case report/series) that suggests formulation-specific allergies
- Several cases highlighted resolution of symptoms with initial antihistamine but resurgence soon after requiring emergent 2nd line agents/tracheostomy -- > angioedema should not be minimized and warrants immediate medical attention and monitoring

Extrapyramidal Side Effects or Allergy?

- EPS, especially with facial and oropharyngeal involvement, can be difficult to differentiate from an allergy either during the event or history taking due to the description as well as initial management which normally involves the administration of antihistamines
- Ilchef et al. described a case of a haloperidol-related laryngeal dystonia that mimicked anaphylaxis which was treated aggressively with corticosteroids and angioedema, though later skin testing ruled out a hypersensitivity reaction
- Severe dystonia is a frightening life-threatening experience. When patients have this adverse event, it is not surprising that they or their providers mistakenly document the event as an allergy in hopes of preventing a similar event in the future, but clinically distinguishing remains important

Acknowledgments

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References

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