

Potential of Haloperidol Neurotoxicity in Acute Hyperthyroidism: Report of a Case

Hsin Chu^{1,2}, Jiann-Chyun Lin¹, and Yaw-Dong Hsu¹

Abstract- Haloperidol has been used extensively for the treatment of many psychiatric illnesses as well as for control of agitated patients. Side effects including anticholinergic, extrapyramidal, sedative side effects as well as neuroleptic malignant syndrome are not unusual. Many factors may contribute to these complications including withdrawal or toxicity, concomitant use of other medications or the underlying illness itself. We report a case without previous history of thyroid disorder suffering acute manic episode. Haloperidol was prescribed to control psychotic symptoms. Symptoms and signs of extrapyramidal syndrome, catatonia and hyperthyroidism ensued. Prescription of anti-thyroid agents and discontinuation of haloperidol were essential in the successful treatment of this patient. It is hypothesized that underlying hyperthyroidism might have precipitated haloperidol neurotoxicity. Haloperidol might play a role in the exacerbation of hyperthyroidism.

Key Words: Haloperidol, Hyperthyroidism, Neuroleptic-induced catatonia

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INTRODUCTION

Traditional neuroleptics such as haloperidol had been associated with the development of extrapyramidal side effects as well as neuroleptic malignant syndrome. Dose, prescription interval and duration were believed to determine the occurrence of these side effects. Certain concomitant illness had also been shown to precipitate the development of neuroleptic-induced side effects. For example, several cases of haloperidol neurotoxicity precipitated by hyperthyroidism had been published⁽¹⁻³⁾. However, in those cases, low dose of haloperidol by the

oral route were used for longer than 6 days before the development of neurotoxicity. We describe a patient in whom neuroleptic-induced side effect was greatly exaggerated by the presence of hyperthyroidism. Catatonia developed within 48 hours after intramuscular injection of haloperidol. Possible mutual influences between thyroid state and haloperidol as well as clinical implication were discussed.

CASE REPORT

A 21 year-old male soldier was well before. Two

From the ¹Department of Neurology, Tri-Service General Hospital, ²Institute of Aerospace Medicine, National Defense Medical Center, Taipei, Taiwan.

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Reprint requests and correspondence to: Hsin Chu, MD, PhD. Department of Neurology, Tri-Service General Hospital, No. 325, Sec. 2, Cheng-Kung Road, Taipei, Taiwan.

E-mail: hrchu@mail.ndmctsgh.edu.tw

weeks prior to current hospitalization, he presented with unusual behaviors including absence without permission from work, hypertalkative, negative thinking and increased sexual drive. He was brought to emergency room of a local hospital for help where blood, urine biochemical studies, and brain CT revealed unremarkable findings. Later, as the condition persisted, he was admitted to acute psychiatric ward and treated with low dose benzodiazepine and paroxetine (a selective serotonin reuptake inhibitor). During psychiatric interview, he admitted suffering from failed personal investment, worrying about future career and unstable relationship with girlfriend. He was discharged with the impression of adjustment disorder. Two days later, he was brought to another psychiatric hospital because of unstable mood and agitation. Diaphoresis was noted at arrival but his vital signs were stable and he was afebrile. Results of routine laboratory studies including complete blood count and blood biochemistry were unremarkable. Medications prescribed included clonazepam (6 mg/day in three divided doses), valproic acid (500 mg/day) and clothiapine (800 mg/day). Haloperidol (15 mg in three divided doses on the first day and 10 mg in two doses on the second day) and lorazepam were given intramuscularly to sedate the patient. Extrapyramidal side effects including orobuccal dyskinesia, akathisia and salivation were noted on the 3rd hospital day, 48 hours since the first dose of haloperidol. Tachycardia (PR >120/min) and elevated blood pressure (159/65 mmHg) developed later. He became speechless and lethargic. EKG demonstrated atrial fibrillation with rapid ventricular response. Elevated CPK (392 U/L; N, 55-170 U/L) was noted. He was then referred to this hospital.

The patient was naive to neuroleptics. His elder sister had been diagnosed with schizophrenia for five years. According to his mother, he had a similar episode of violent behavior, negative thoughts and agitation about two years ago. He had the habit of cigarette smoking and consumption of alcoholic beverages on social occasions but denied of illicit drug abuse.

At the emergency room, the patient appeared comatous (GCS E2V1M1). He was generally rigid and profusely sweating. Mild exophthalmos was suspected. On palpation, no obvious goiter was noted. His skin was

moist and warm. His blood pressure was 167/78 mmHg, with a pulse rate of 140-150/min, and body temperature at 36.7 °C. The neurological examination revealed roving eyes, normoactive tendon reflexes with plantar responses. Although no response to pain stimulation, his limbs, if hold in the air, would be maintained in position and then gradually fall. Intermittently, generalized tremor over limbs was observed. Laboratory studies revealed elevated CPK (392 U/L) and ALT (77 U/L). Urine drug screen showed negative response to amphetamine, opiate and benzodiazepine. Brain CT revealed unremarkable findings. EKG showed atrial fibrillation with rapid ventricular response. The differential diagnoses included thyrotoxicosis, neuroleptic malignant syndrome, neuroleptic withdrawal and non-convulsive status epilepticus. He was admitted to ICU. Intravenous fluid supplement was initiated to prevent dehydration and rhabdomyolysis. After a single dose of bromocriptine and biperiden treatment, rigidity and waxy flexibility gradually subsided. However, signs of autonomic hyperactivity persisted. Initially, he was treated with amiodarone and digoxin without significant response. Thyrotoxicosis with probable thyroid storm was later confirmed by elevated T3 (296.8 ng/dl; N 86-187), free T4 (4.39 ng/dl; N 0.8-2.0) and suppressed TSH level (<0.03 µIU/ml; N 0.3-5). Thyroid sonogram revealed diffuse enlargement of both glands. Elevated titers of anti-microsomal and anti-thyroglobulin antibodies (>1:25,600 and >1:320, respectively) indicated autoimmune-mediated hyperthyroidism. Propranolol and anti-thyroid agents including propylthiouracil 100 mg and Lugol solution were prescribed accordingly. Blood pressure and pulse rate were gradually under control, he returned to euthyroid state clinically and by laboratory examination. On the 6th hospital day, he was transferred to psychiatric service. Several differential diagnoses including mood disorder secondary to hyperthyroid disease and bipolar disorder with most recent manic episode were impressed. Beginning from the third day after hospitalization, olanzapine, valproic acid and clonazepam were prescribed to treat symptoms of increased appetite, irritation, increased sexual drive and insomnia. He also tolerated haloperidol given on p.r.n. basis intramuscularly at a dose of 10 to 15 mg per day (total 60 mg in 9 days)

under euthyroid state without untoward reactions. He was discharged at the day 35.

DISCUSSION

One of the most important adverse effects of haloperidol is the extrapyramidal syndrome (EPS), a group of movement disorders that include akathisia, dystonia, parkinsonism and tardive dyskinesia. Propensity toward the development of these side effects usually depends on the dosage, duration, concurrent medications, underlying medical illness or surgery. Various investigations have shown high percentage of EPS among patients treated with haloperidol. For example, Lane et al demonstrated 63% of EPS reaction in acute Chinese schizophrenic patient treated with haloperidol at 10 mg/day for two weeks⁽⁴⁾. It is not surprising to observe EPS (akathisia and orobuccal dyskinesic reaction) in our patient after 25 mg of haloperidol in total given intramuscularly within 48 hours.

At toxic dose or during withdrawal from neuroleptics, more severe complications such as catatonia or neuroleptic malignant syndrome could occur. In our patient, several hours after the last dose of haloperidol, general weakness, rigidity, and catatonic appearance ensued. We suspect the severe catatonic reaction in our patient was partly due to underlying hyperthyroidism.

Using positron emission tomography as a tool, Kapur et al. demonstrated that after 2 mg/day of oral haloperidol for two weeks, high levels of striatal dopamine D2 receptor occupancy could be achieved in

schizophrenia patients⁽⁵⁾. The patient we reported was given 25 mg haloperidol in two days. Whether this reflect high degree of D2 receptor occupancy need further study. It had been shown that altered thyroid state might influence the effects of psychotropic drugs. In the literature, only a few cases on possible potentiation of haloperidol neurotoxicity in acute hyperthyroidism had been reported (Table)⁽¹⁻³⁾. The case we presented differs from previous described cases in the duration, dosage, and route of haloperidol given. While in previous reports, haloperidol was given orally in low dose for over one week before the development of catatonic neurotoxicity, 25 mg given intramuscularly within 48 hours was enough to provoke severe neurotoxic effects in our patient. Indeed, different route of administration affects the toxicity of haloperidol. Riker et al. have reported five euthyroid, delirious patients tolerated intravenous haloperidol well at median doses of 250 mg/day but developed EPS reaction after medication was discontinued⁽⁶⁾. It has been suggested that, compared with oral route, parenteral haloperidol use may be associated with less intense EPS, perhaps related to less first-pass metabolism and lower concentrations of reduced haloperidol or other metabolites⁽⁷⁾. If this was the case, the potentiation effect of hyperthyroidism on haloperidol neurotoxicity in our case was obvious.

The severe haloperidol neurotoxic response in our case does not fulfill criteria of neuroleptic malignant syndrome (NMS). Signs of NMS usually appear two weeks after therapy is begun or the dosage of the medication is increased. In our patient, the symptom devel-

Table. Comparison of reported cases of haloperidol neurotoxicity in hyperthyroidism patients

Patient data	Haloperidol dosage & duration	Thyroid state	Clinical symptoms	Ref
54 y/o male	6 mg, p.o. per day 6 days (total 36 mg)	T4: 11.7 (g/dl (2.5-6.5)) I ¹³¹ uptake: 54% (10-30)	Rigidity, clouding of consciousness, tremor, fasciculation, waxy rigidity	1
74 y/o female	1.5 mg p.o. t.i.d 20 days (total 90 mg)	T3 index: 97% Protein-bound iodine: 9.7 µg/dl I ¹³¹ uptake: 30.6	Board-like rigidity Dyspnea, cyanosis	2
23 y/o female	1 mg p.o. q.i.d. 7 days (total 28 mg)	T4: 14 mg/dl	Severe weakness, inability to speak/walk, facial rigidity, diarrhea	3
21 y/o male	5 mg i.m. p.r.n. (total 25 mg in 2 days)	fT4: 4.39 (0.8-2 ng/dl) T3: 296 (86-187 ng/dl) TSH: < 0.03 (0.3-5 µIU/ml)	Mutism, rigidity, fine tremors, diaphoresis, palpitation	Current report

oped only 48 hours after intramuscular haloperidol. Hyperthermia, severe muscular rigidity, autonomic instability, and changing levels of consciousness are the four major hallmarks of NMS. Laboratory studies in NMS patient usually revealed leukocytosis, azotemia and extremely elevated CPK level. But our patient was afebrile and showed normal leukocyte level and only mildly elevated CPK level. Instead, our patient met Woodbury and Woodbury's criteria for neuroleptic-induced catatonia (NIC)⁽⁸⁾. From a case report of a boy with many features of NMS but did not have fever or leukocytotic response, Adrian et al developed a concept of NIC-NMS as a spectrum of disorder⁽⁹⁾. Using their scoring system to evaluate severity of the illness, our patient scored 1 in muscle rigidity (moderate rigidity), 2 in autonomic instability (fulfill 2 of the following: body temperature > 39 °C, pulse rate > 110, blood pressure > 140/100), 1 in mental status (agitation-confusion) and 1 in CPK level (200 < CPK < 1,500 U/L), with total score of 5. This suggests moderate NIC-NMS. Another line of evidence in the potentiation of haloperidol neurotoxicity by hyperthyroidism came from the fact that this patient diagnosed with haloperidol-associated NIC successfully tolerated to haloperidol without reemergence of symptoms, after he reached euthyroid state.

The mechanism by which hyperthyroidism might have potentiated neurotoxicity of haloperidol is not clear. Hyperthyroidism might have impeded the metabolism of haloperidol, allowing toxicity to develop. However, this seems unlikely as there was no difference in plasma haloperidol concentration under different thyroid states in human⁽¹⁰⁾. In animal studies, thyroxine has sensitizing effect on the rats' central nervous system to the toxic effects of haloperidol⁽¹¹⁾, and hyperthyroidism increases the receptivity of dopamine receptors in guinea pigs⁽¹²⁾. Whether these mechanisms apply to human need further study.

The case we presented have had no prior history of hyperthyroidism. Thyroid hyperactivity was suggested by mild ophthalmos for unknown period of time and diaphoresis, irritability developed three days before he was sent to this hospital. Full-blown thyrotoxicosis developed later, with typical clinical features of diaphoresis, tachycardia, fine tremor of limbs, muscle

weakness and cloudiness of consciousness. Thyrotoxicosis or thyroid storm occurs in uncontrolled hyperthyroid patients as a result of triggering factors such as surgery, infection or trauma. In our patient, there were no obvious stresses prior to current hospitalization in addition to acute psychiatric illness and haloperidol injection. Prospective study by Spratt and colleagues have shown that 33% of newly admitted psychiatric inpatients have transient elevations in circulating levels of thyroxine (T4)⁽¹³⁾. However, in those with elevated T4 level, only 36% had concomitant elevation in T3 levels. Most important of all, this "transient hyperthyroxinemia" in acute psychotic patient is to be distinguished from true hyperthyroidism by spontaneous resolution over a period of weeks and absence of baseline TSH suppression. We proposed that thyrotoxicosis experienced by this young man was precipitated by haloperidol injection. This is supported by the fact that there was marked deterioration after the drug was started. Also, agitation and diaphoresis decreased, and his coherence improved about 24 hours after last dose of haloperidol, prior to the administration of propylthiouracil and Lugol solution. A direct stimulatory effect of haloperidol on the thyroid is unlikely, in view of the 7-day half-life of T4 and the patient's improvement within 24 hours after haloperidol was discontinued. His initial presentation was the sole result of haloperidol is also unlikely, since diaphoresis, tremor and palpitation are not known to be side effects of haloperidol. Hordiienko et al provided evidence in birds that dopaminergic agents inhibited hypothalamo-hypophyseal-thyroid system⁽¹⁴⁾. It is possible that by blocking dopaminergic transmission in the brain, haloperidol indirectly potentiated thyroid state, causing hyperthyroidism. The synergism between asymptomatic hyperthyroid state and toxic effects of haloperidol presumably resulted in a clinical picture of thyrotoxicosis. Hoffman and his colleagues had reported a patient with similar clinical features⁽¹⁵⁾.

Another possible explanation for clinical presentation was thyrotoxic psychosis. Although the relationship between thyroid disease and psychiatric symptomatology has always been close, thyroid psychosis has been observed and reported rarely in the literature. A prospective study showed only three cases in a total of 3,011

admissions to a large mental hospital⁽¹⁶⁾. In contrary to what happened in our patient, several case reports had pointed to the beneficial effect of haloperidol in alleviating acute psychosis in hyperthyroid patient^(17,18). Interestingly, in those reports, oral form of haloperidol was used, suggesting the possibility that thyroid state might affect haloperidol neurotoxicity in route-specific manner. Persistence of certain symptoms such as irritation, increased sex drive and insomnia after he was treated to euthyroid state suggested mechanisms other than thyrotoxic psychosis are involved.

In conclusion, hyperthyroidism, adverse reaction to haloperidol (and other neuroleptics), and acute manic or psychotic state share some common clinical features such as palpitations, sweating, tremors, irritability and emotional lability. Careful differential diagnosis is essential for proper management of such patients. Thyrotoxicosis should be considered in the differential diagnosis of behavioral changes with hyperactivity. Unusual adverse response to short term use of neuroleptics such as haloperidol should raise the suspicion of underlying provoking events, such as hyperthyroidism in our case. In such cases one would rule out hyperthyroidism before introducing haloperidol into the treatment program.

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