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Case Report

Diphenhydramine dependence through deep intramuscular injection resulting in myonecrosis and prolonged QT interval

T.-Y. Chen* MD, Y.-W. Yeh*† MD, S.-C. Kuo*† MD, C.-Y. Chen*† MD, T.-P. Lin‡ MD and C.-C. Chang*† MD

**Department of Psychiatry, Tri-Service General Hospital, School of Medicine, National Defense Medical Center, Taipei, Taiwan, †Graduate Institute of Medical Sciences, National Defense Medical Center, Taipei, Taiwan and ‡Department of Radiology, Kaohsiung Armed Forces General Hospital, Kaohsiung, Taiwan*

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SUMMARY

What is known and objective: **Diphenhydramine (DPH) is a first-generation antihistamine, which is useful in treating allergic reaction, and is usually considered innocuous. We describe a retired nurse with history of depression, who began to develop drug-seeking behaviour after her first receiving of an intramuscular (IM) DPH injection due to urticaria.**
Case summary: **The 49-year-old patient had developed IM DPH dependence within 4 months. She needed to receive psychiatric inpatient treatment because of depressive mood, serious myonecrosis over injected sites, and prolongation of QT interval.**
What is new and conclusion: **This is the first reported case of DPH dependence through the IM route. Second-generation antihistamines might be better choices for patients with psychiatric illness by reason of their lower effects on central nervous system and lower risk of abuse.**

WHAT IS KNOWN AND OBJECTIVE

Many over-the-counter drugs are known to have abuse or dependence potential. Diphenhydramine (DPH) is a first-generation antihistamine that is widely used to relieve allergic reaction, insomnia, extrapyramidal symptoms and motion sickness.[1] The potential for first-generation antihistamine dependence is known and appears to be associated with their euphoric effects including elevated mood and hallucinogenic effects.[1,2] Intramuscular (IM) DPH injection dependence has not been reported in the literature. We present the case of a retired nurse who had developed IM DPH injection dependence complicated with severe myonecrosis and prolonged corrected QT (QTc) interval after her first experience of IM DPH injection due to urticaria.

DETAILS OF THE CASE

Miss C, aged 49, a retired nurse with a history of recurrent major depressive episodes and sustained full remission from alcohol dependence. Miss C mentioned that she had been free from alcohol comsumption for almost 2 years, and her first major depressive episode occurred at age 31. She had twice received psychiatric inpatient treatment for major depressive disorder, and she had been in an even worse depressive mood before visiting our outpatient service. She stated that 6 months ago she had severe urticaria that was relieved by one IM DPH 30 mg injection. After the DPH use, she described feeling 'good, relaxed, calm and slept better'. The patient started to purchase ampoules of DPH (30 mg) and syringes at different local pharmacies. She initially injected 30 mg DPH at night for her insomnia; the frequency and the amount increased every few days. She had her first injection soon after waking up, and the injection frequency then became every 1–2 h. Craving for up to 450 mg of IM DPH per day was noted, and within hours of missed doses, she experienced withdrawal symptoms including anxiety, irritability, poor attention and rebounding insomnia. She had attempted to stop taking DPH injections but in vain. All of the symptoms mentioned above developed within 4 months. The injected sites over both buttocks and thighs showed severe tenderness, swelling and local heat. She could not maintain basic self-care because of bilateral lower limbs oedema with unstable gait. She visited our psychiatric outpatient service, and DPH dependence and recurrent major depressive

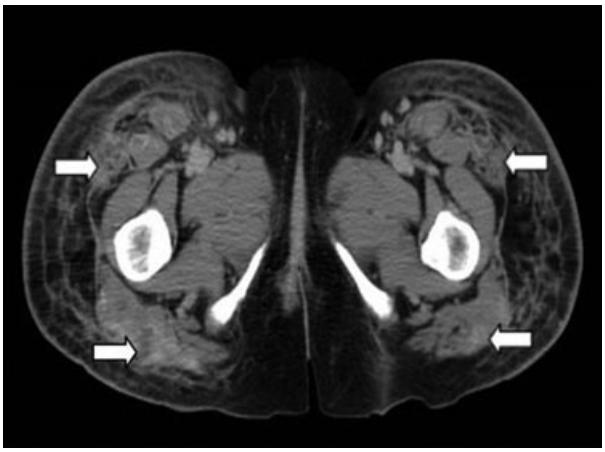

Fig. 1. The computed tomography of the lower extremities showed multiple intramuscular low-attenuated lesions with peripheral enhancing rims in the bilateral gluteus, adductor, and quadriceps muscles (arrows).

Correspondence: Chuan-Chia Chang, MD, Attending Psychiatrist, Department of Psychiatry, Tri-Service General Hospital, National Defense Medical Center, #325, Cheng-Kung Road, Section 2, Nei-Hu District, Taipei, 114, Taiwan. Tel.: 011-886-2-8792-7220; fax: 011-886-2-8792-7221; e-mail: changcc@ndmctsgh.edu.tw

disorder were diagnosed according to the *Diagnostic and Statistical Manual of Mental Disorder*, Fourth Edition, Text Revision criteria.[3] She was then scheduled to enter our inpatient ward for detoxification, physical evaluation and depressive mood management.

During hospitalization, the physical examinations and the computed tomography of her lower limbs (Fig. 1) revealed multifocal myonecrosis of both thighs and buttocks. The initial laboratory findings were as follows: white blood cell count, 7840/μL (reference ranges: 4500–11 000/μL); neutrophil: lymphocyte ratio, 72 : 18 (40–74 : 19–48); sodium, 141 mM (136–145 mM); potassium, 3·8 mM (3·5–5·1 mM); free calcium, 4·6 mg/dL (4·5–5·3 mg/dL); magnesium, 2·0 mg/dL (1·7–2·55 mg/dL); C-reactive protein, 0·51 mg/dL (<0·5 mg/dL); D-dimer, 7887 ng/mL (<500 ng/mL). Electrocardiography (ECG) revealed sinus rhythm with rate of 86/min and prolonged QT interval of 420 ms with corrected QT interval of 503 ms (<470 ms in female) using Bazett's formula.[4] The initial Beck Depression Inventory II (BDI-II) score was 22. We used cephalexin 500 mg four times per day for her myonecrosis, warfarin 1 mg per day for the possibility of deep vein thrombosis, bupropion 150 mg two times per day for her depressive mood, lorazepam 1 mg three times per day for her anxiety and irritability, zolpidem 20 mg, clonazepam 4 mg and flurazepam 60 mg at night for her refractory insomnia.

There is no recorded fever and no obvious leukocytosis during the hospitalization. As a result, we believed that the patient's localized myonecrosis did not lead to systemic infection. We highly suspected that the myonecrosis was the result of muscle injury from repeated injections of DPH solution. The patient's unstable gait, local tenderness and local heat over lower limbs improved after antibiotic treatment. Although the patient had high D-dimer level, deep vein thrombosis was less likely after a negative phleborheograph evaluated by a cardiovascular specialist. We repeated the ECG 5 days later, and her prolonged QTc improved to 492 ms. Possible DPH withdrawal symptoms such as increased irritablility, anxiety, elevated heart rate and refractory insomnia were noted in the early days of admission, and the symptoms resolved after initiating lorazepam. The dosage of lorazepam was tapered gradually to zero 3 weeks later. Throughout the 6-week admission, Miss C's condition was stable after abstinence from DPH, and D-dimer was 625 ng/mL, QTc was 465 ms, and BDI-II was score of 8 before discharge.

Several reports indicate that first-generation antihistamines penetrate the blood–brain barrier easily to occupy up to 50–90% histamine H_1 receptors in the frontal cortex, temporal cortex, hippocampus and pons.[5,6] *In vivo* studies have shown that H_1 receptor blocking induced elevated dopamine levels in the nucleus accumbens,[7] and inhibited dopamine reuptake in the striatum.[8] The dopamine system is known to be related to most drugs of abuse or dependence.[9] This may explain why high-dose DPH injections could produce rewarding effects and related abuse potential because of modulating dopamine activity in both the mesostriatal and mesolimbic systems.[2] Furthermore, this patient had prior alcohol dependence, which might enhance the risk of DPH dependence due to the possibility of a relatively unstable dopaminergic reward system.

Animal studies have shown that first-generation antihistamines have the potential to block serotonin[10] and norepinephrine reuptake,[11] which might provide antidepressant and anxiolytic properties. Miss C initially used DPH for its sedative effect to aid sleep, progressing to its daytime use to help her feel calmer and less depressed. She did not visit a hospital for withdrawal therapy until myonecrosis occurred. This craving and self-medication behaviour resembled her previous dependence on alcohol.

In a previous brief review, six cases of DPH abuse with daily oral DPH dosages ranging from 480 to 3000 mg were described with the subjects taking months to years to ask help.[12] Miss C had been taking a lower dosage and for a shorter period when compared to those cases. There was also one report which reported that several young patients had drug-seeking behaviour after receiving intravenous DPH bolus injections on several occasions.[13]

Prolonged QTc can be related to drug effects, electrolyte imbalance and other metabolic abnormalities. The patient had used IM DPH for several months without taking other regular medications before her admission. Her sodium, potassium, calcium, and magnesium level were in acceptable ranges on admission. The myonecrosis did not appear to lead to any systemic infection that could affect cardiac function. High DPH concentrations may have cardiac toxic effects by inhibiting the cardiac fast sodium and potassium channels. This may present in prolonged QT interval and increase the risk of sudden death.[14,15] The patient's QTc had returned close to the normal range after discontinuing DPH use. Compared with previous reported cases of DPH overdose,[14,15] our patient developed the abuse gradually over a long time. Cardiac adaptation may explain why her prolonged QTc took a longer time to resolve.

WHAT IS NEW AND CONCLUSION

This is the first case of long-term IM DPH injection leading to dependence and complicated with induced concurrent myonecrosis and prolonged QT interval. This patient's previous nursing experience might have predisposed to parenteral use of the drug, and her recurrent major depressive disorder and/or alcohol dependence might have contributed to the development of DPH dependence. Because inexpensive DPH is available over the counter, community pharmacists should be alert to the risk of its abuse potential. Second-generation antihistamines might be better choices for the patients with mood disorder or substance abuse due to their lower effects on central nervous system and lower abuse risks.[1]

CONFLICTS OF INTEREST

None.

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