

CONCISE COMMUNICATION

Successful treatment of cholinergic urticaria with methantheliniumbromide

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ABSTRACT

Cholinergic urticaria (CholU) is a frequent and often hard to treat disorder characterized by wheal and flare type reactions that occur in response to exercise and passive warming. Antihistamines are the first-line treatment, but are often not effective. Here, we report a 33-year-old male CholU patient who was able to engage in physical activities without suffering any symptoms for several hours following the intake of methantheliniumbromide, an anticholinergic agent that suppresses sweating. We confirmed this therapeutic response by pulse-controlled ergometry testing, which showed delayed sweating and markedly delayed and reduced whealing after methantheliniumbromide treatment. Our findings suggest that CholU patients may benefit from methantheliniumbromide treatment.

Key words: cholinergic urticaria, methantheliniumbromide, pulse-controlled ergometry.

INTRODUCTION

The established facts of cholinergic urticaria (CholU) are: (i) antihistamines are the first-line treatment, but are often not effective; and (ii) it can be diagnosed by the recently developed pulse-controlled ergometry test. New insights into CholU include: (i) methantheliniumbromide showed to be an effective treatment in an antihistamine refractory patient with CholU; (ii) methantheliniumbromide can be taken three times daily or on demand before trigger situations; and (iii) pulse-controlled ergometry allows for monitoring treatment efficacy and disease control.

BACKGROUND

Patients with CholU develop itchy, pinpoint-sized, relatively short-lived wheals with large flare reactions. This frequent form of inducible urticaria can be induced by exercise, passive warming (e.g. hot bath) and, in some patients, by emotional stress, and hot and spicy food.¹ CholU has a high prevalence in young adults (up to 20%)² and often shows a decrease of signs and symptoms over time until these eventually cease completely.

The underlying pathomechanisms of CholU are not well understood. Japanese studies suggest several distinct CholU subclasses: (i) CholU with poral occlusion; (ii) CholU with hyperhidrosis; (iii) CholU with allergy against sweat; and (iv) idiopathic CholU.^{3,4}

Acetylcholine, a major messenger acting on the sweat glands to induce sweat production, is suspected to play an important role in the pathophysiology of CholU. Previous

reports have demonstrated that subcutaneous injections of cholinergic agents induce sweating and the development of pinpoint-sized hives in patients with CholU.⁵ CholU was, therefore, postulated to be due to elevated local acetylcholine levels.⁴ Also, cholinergic substances were shown to act as mast cell degranulators.^{6,7} Consequently, excess acetylcholine may activate muscarinic CHRM3 on mast cells in the vicinity of sweat glands to cause wheals. Recent studies have demonstrated decreased expression of the muscarinic cholinergic receptor M3^{8,9} and a decreased expression of acetylcholine esterase in the skin of CholU patients,¹⁰ which suggest that cholinergic signaling pathways are relevant in CholU.

The first-line treatment options in CholU are avoidance of eliciting triggers and non-sedating H₁ antihistamines.¹ Most CholU patients, however, are not free of symptoms despite the use of fourfold dosed antihistamines.¹¹ In older case reports, the use of anticholinergic substances like scopolamine butylbromide^{12,13} or clidinium bromide¹⁴ showed symptom relief. Herein, we present a case of a treatment of a severely affected and antihistamine refractory patient with methantheliniumbromide, an anticholinergic drug that is licensed in Germany for the treatment of hyperhidrosis.

CASE PRESENTATION

A 33-year-old man presented to the outpatient clinic of the Department of Dermatology and Allergy, Charité – Universitätsmedizin Berlin. He reported recurrent wheal and flare reactions with severe itching following mild physical exercise, hot showers and emotional stress for the last 2 years. Laboratory

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Received 12 November 2014; accepted 2 December 2014.

examinations exhibited an elevated total immunoglobulin E level of 166 kU/L. The patient was non-atopic according to the Erlanger Atopy Score and had no allergies (allergic rhinitis, asthma, atopic dermatitis or food allergy). Several non-sedating antihistamines in up to a fourfold standard dose had led to minor changes of disease activity. The itch was slightly reduced, but the number or size of wheals were not.

INVESTIGATIONS

We confirmed CholU by pulse-controlled ergometry test as described recently¹⁵ after the patient had not taken antihistamines for 7 days. When the patient changed his clothes in preparation for the test (in a room with an ambient temperature of 22°C), he already started to develop some mild wheal and flare reactions (Fig. 1a), which continued to develop and

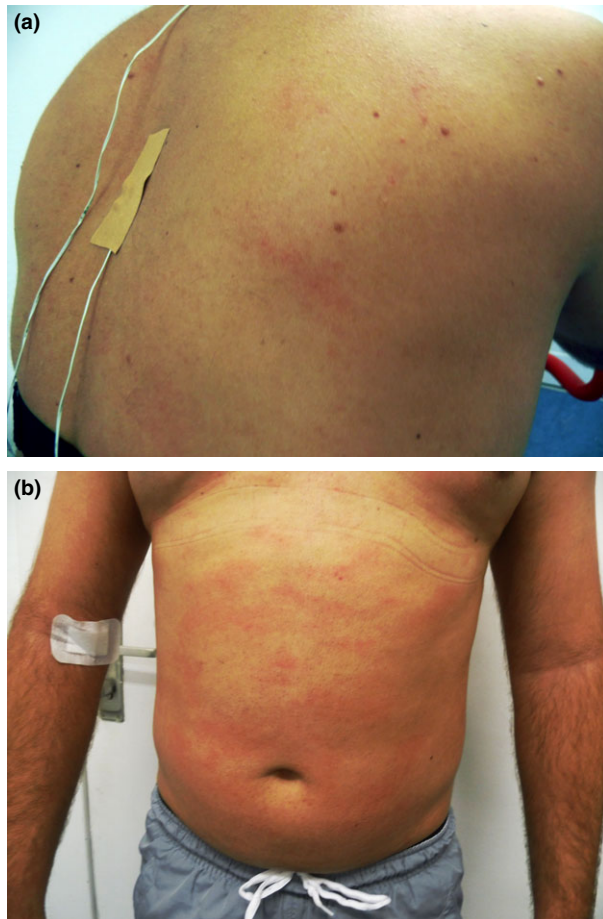


Figure 1. Pulse-controlled ergometry test of cholinergic urticaria patient before methantheliniumbromide treatment. (a) Patient before the start of the test. Single pinpoint-sized wheals due to the minimal physical exercise of changing in a room with ambient temperature before ergometry testing. (b) Patient after the early termination of the test (at 20 min, heart rate at 134 b.p.m.). The whole trunk is covered by pinpoint-sized wheals with large surrounding flare reactions.

increased in number and size after the onset of sweating 12 min after the start of the test at a heart rate of 114 b.p.m. The test had to be stopped due to pronounced wheal and flare skin reactions after 20 min at a heart rate of 134 b.p.m. (Fig. 1b).

TREATMENT

We decided to initiate a trial of methantheliniumbromide treatment and advised our patient to take one 50 mg tablet 2 h before engaging in physical exercise or other activities known to prompt whealing. One week later, we repeated the pulse-controlled ergometry test 2 h after methantheliniumbromide treatment. This time the patient had no symptoms during the change of clothes (room temperature, 23°C). During the test, he started to show the first signs of sweating after 17 min at a heart rate of 130 b.p.m. and developed a mild skin reaction with a few pinpoint-sized wheals and minimal flare after approximately 21 min at a heart rate at 138 b.p.m. (Fig. 2). This time the patient was able to finish the test, and the test was stopped after 30 min at a heart rate at 167 b.p.m.

OUTCOME AND FOLLOW UP

The patient showed no side-effects after the intake of methantheliniumbromide. It was well tolerated. The patient reported to benefit as early as 2 h and as long as 5 h after the intake of the tablet. This allowed him to use the medication on demand prior to physical exercise, which significantly increased his quality of life. The patient has been using methantheliniumbromide treatment for the last 6 months and continues to benefit from it, without significant unwanted effects. Furthermore, three out of four other CholU patients treated with methantheliniumbromide 50 mg reported similar beneficial treatment responses.



Figure 2. Pulse-controlled ergometry test of cholinergic urticaria patient 2 h after methantheliniumbromide 50 mg treatment. Patient after the regular end of the test after 30 min at a heart rate at 167 b.p.m. The patient developed, only single pinpoint-sized wheals with almost no flare reactions.

DISCUSSION

The off-label treatment with methantheliniumbromide was very effective and well tolerated in our antihistamine refractory patient with CholU. Although side-effects were not reported by our patient, a frequent unwanted side-effect is a dry mouth. Other rare problems associated with the use of methantheliniumbromide include problems in the urinary tract, an elevation of the heart frequency, accommodation problems (more frequent in hyperopic patients) and skin reactions. Methantheliniumbromide is licensed for up to threefold daily use. Due to the good effect seen in our patient and in three additional cases with this anticholinergic drug, we believe that this treatment should be considered for antihistamine refractory patients with CholU. Further studies are needed to evaluate the therapeutic potency of this treatment in a larger cohort of patients. These studies could not only improve patient treatment, but also shed light on the pathophysiology of the disease.

CONFLICT OF INTEREST: The authors have no conflicting interests.

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