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Case Report

Acute and Intense Urticaria Case due to Donepezıl Treatment

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Abstract

Background: Alzheimer's disease is the most common cause of dementia, a general term for memory loss and other cognitive abilities serious enough to interfere with daily life. The most commonly used treatment for Alzheimer's disease are medicines known as acetylcholinesterase inhibitors (AChEIs). Donepezil is one of the major AChEI drugs used in the treatment of Alzheimer's disease (AD). Most studies agree that donepezil is a safe drug, although important adverse drug reactions (ADRs) have been reported in the literature. Dermatologic side effects can also be seen.

Case Presentation: We present a case of acute and intense urticaria after a single dose of donepezil treatment. A 78-year-oldfemale patient has been admitted to the outpatient clinic for complaints of increasingly slow-growing forgetfulness for one year. Based on the diagnostic criteria, donepezil 5 mg/day was started considering mild cognitive impairment due to Alzheimer's disease. After the first dose, urticaria-like hyperemic, hard, itchy rashes developed in the trunk, arms and legs. Donepezil treatment was discontinued, antihistaminic treatment was started by consulting with the Department of Dermatology. The rash then began to fade and within one week the rash disappeared.

Conclusion: This case report emphasizes that informing patients about acute dermatologic side effects is useful when starting donepezil treatment. It is important that dementia patients are informed and followed up by healthcare professionals about the side effects.

Keywords: Donepezil, Urticaria, Cholinesterase inhibitors, Alzheimer's disease, Adverse drug reactions

Abbreviations: AD: Alzheimer's Disease; ADRs: Adverse Drug Reactions; AChEI: Acetylcholinesterase inhibitors

Background

Alzheimer's is the most common cause of dementia, a general term for memory loss and other cognitive abilities serious enough to interfere with daily life. Alzheimer's disease accounts for 60 percent to 80 percent of dementia cases. Alzheimer's worsens over time. Alzheimer's is a progressive disease, where dementia symptoms gradually worsen over a number of years. In its early stages, memory loss is mild, but with late-stage Alzheimer's, individuals lose the ability to carry on a conversation and respond to their environment. Alzheimer's is the sixth leading cause of death in the United States [1].

Alzheimer's disease is complex, and it is unlikely that any one drug or other intervention will successfully treat it. Several prescription drugs are currently approved by the U.S. Food and Drug Administration (FDA) to treat people who have been diagnosed with Alzheimer's disease. Medications called cholinesterase inhibitors (AChEIs) are prescribed for mild to moderate Alzheimer's disease. These drugs may help reduce some symptoms and help control some behavioral symptoms. The AChEIs are donepezil, rivastigmine and galantamine. A medication known as memantine, an N-methyl D-aspartate (NMDA) antagonist, is prescribed to treat moderate to severe Alzheimer's disease [1,2].

The most commonly used treatment for Alzheimer's disease are medicines known as acetylcholinesterase inhibitors (AChEIs). Also AChEIs have been proposed as feasible candidate drugs for the treatment of MCI [6,7,8] [3-5]. Donepezil is one of the major acetylcholinesterase inhibitor drug used in the treatment of Alzheimer's disease (AD) [3][6]. Donepezil is a reversible acetylcholinesterase inhibitors (AChEI) that enhances cholinergic neurotransmission and may have other non-cholinergic actions with potential benefit for dementia. Compared with other AChEI; donepezil is a selective piperidine derivative which exhibits a good pharmacological profile in terms of cognitive recovery, good response, low drug withdrawal rate and side effects. Many studies on donepezil indicate that this drug has a positive effect on cognition, behaviour and daily life activities in AD and will contribute slowing disease progression [5] [7]. It is clear that an early therapeutic intervention could be of some benefit for these patients precluding the possibility of a premature neuronal death or delaying the onset of the disease for several years.

Most studies agree that donepezil is a safe drug, although important adverse drug reactions (ADRs) have been reported in the international literature. The most frequently reported adverse events related to donepezil treatment were; gastrointestinal side effects such as nausea, diarrhea, vomiting [4] [8]. Dermatologic side effects can also be seen. We present a case of acute urticaria after a single dose of donepezil treatment.

Case Presentation

A 78-year-old right-handed, literate, housewife, female patient has been admitted to the outpatient clinic for complaints of increasingly slow-growing forgetfulness for one year. She had a history of hypertension and was used acetylsalicylic acid and valsartan therapy. In the neurocognitive evaluation, amnestic form of mild cognitive impairment was detected. For the uneducated Mini Mental State Examination 22/30, Clinical Dementia Rating: 0.5, Global Deterioration Scale: Stage 3, Lawton & Brody Instrumental Activities of Daily Living Scale: 7. Other neurological examination findings were normal. Routine hemogram and biochemical tests were normal. Brain magnetic resonance images showed bilateral temporoparietal mild cortical atrophy and periventricular ischemic gliotic foci. The patient showed lower FDG (fluorodeoxyglucose) uptake values in the temporoparietal cortex in PET (positron emission tomograhy), that indicates neuronal injury. CSF beta and tau tests could not be performed because the patient did not accept. Based on the diagnostic criteria, donepezil 5 mg/day was started considering mild cognitive impairment (MCI) due to Alzheimer's disease [9,10] [9,10]. After the first dose, acute urticaria-like hyperemic, pruritic light red, hard, itchy rashes developed on the trunk, arms and legs (Figure 1 and 2). She had no associated facial edema or lip or throat involvement. On physical examination, multiple elevated superficial erythematous papules and plaques were noted, with shapes varying from annular to circinate, areas of central clearing, and targetlike lesions on the trunk and extremities. The lesions blanched with pressure. The woman had no mucosal involvement, scars, or change in pigmentation. During this time there was no new drug use and no different food consumption. Donepezil treatment was discontinued, antihistaminic treatment was started by consulting with the Department of Dermatology. The rash then began to fade and within one week the rash disappeared.

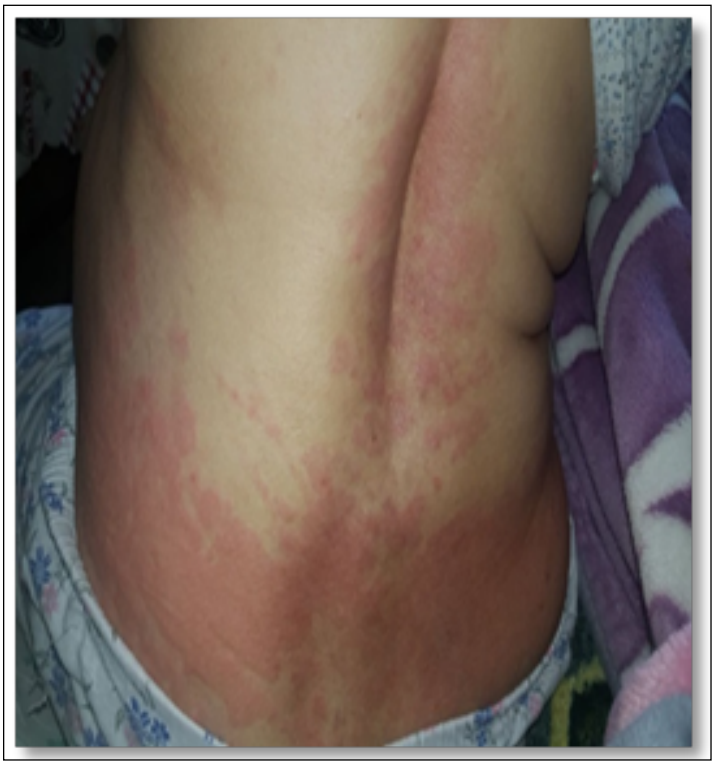

Figure 1: Urticaria rashes on the trunk

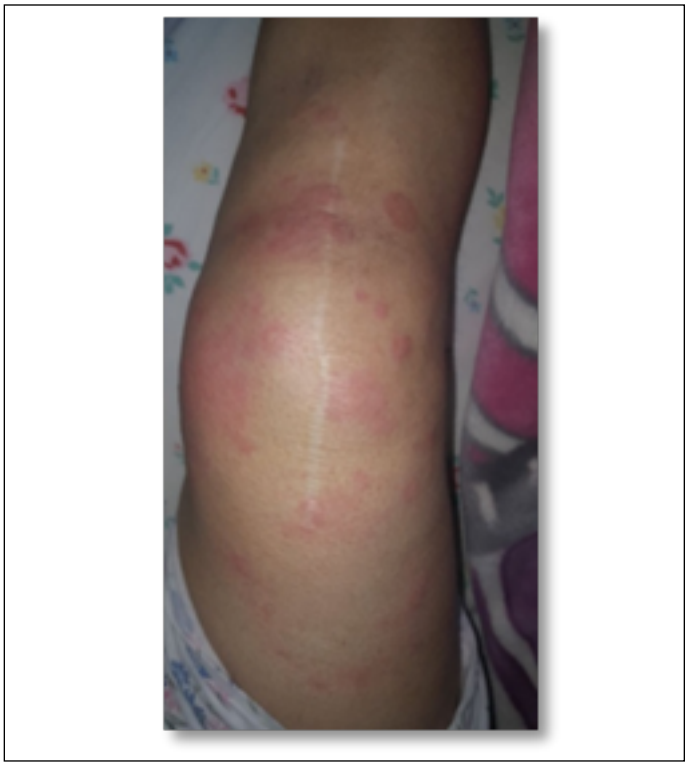

Figure 2: Urticaria rashes on the leg.

Discussion and Conclusions

Alzheimer's disease is the most common cause of dementia in older people. One of the aims of therapy is to inhibit the breakdown of acethycholine by blocking the acetylcholinesterase. Donepezil, an AChEI, is a widely used drug, indicated for the symptomatic treatment of mild to moderate Alzheimer' s disease; the common adverse events are nausea, diarrhea, malaise, dizziness and insomnia [11]. Skin adverse reactions to donepezil are unusual.

Over 770 million days of patient use and an extensive publication database demonstrate that donepezil has a good tolerability and safety profile [12]. The rate of adverse events, dropout for any reason and dropout because of adverse events were also higher among patients receiving AChEIs than among those receiving placebo, with an excess proportion of 7%–8%. The dropout rate was 20%–60% due to adverse events [13].

Industry-sponsored data report discontinuation rates due to adverse events between 5-15%, whereas post-marketing cohort studies have reported discontinuation due to adverse events up to 35% as early as 12 weeks after initiation. Adverse events are common among new users of AChEI within 18 weeks of treatment initiation [14]. According to the prospectus information, the most common dermatological side effects are eczema, pruritis, ecchymosis, diaphoresis, urticaria (1-10%), less than dermatitis, erythema, deep spotting, hyperkeratosis, alopecia, fungal dermatitis, hirsutism, night sweats, skin ulcers (0.1-1%) are reported. In our patient, we had to discontinue treatment due to acute and intense urticaria developing after donepezil treatment.

In AChEIs rivastigmine preferentially inhibits the G1 isoform of cholinesterase, predominantly located in the cortex, hippocampus and in neuritic plaques, while donepezil and galantamine are not selective for any cholinesterase isoforms and have wide cholinergic activity both centrally and peripherally [15]. Due to the wide cholinergic activity of donepezil both centrally and peripherally, acute skin lesions can be seen more frequently in donepezil treatment.

Hyperemic, pruritic light red, itchy rashes, multiple elevated superficial erythematous papules and plaques developed on the trunk, arms and legs in our patient. These findings were consulted with dermatology, and our patient was diagnosed with acute urticaria. Urticaria is a transient erythematous swelling of the skin, associated with itching, which usually resolves within 24

hours. It is caused by degranulation of histamine containing cells (mast cells) in the superficial dermis. Urticarial lesions itch, have a central white wheal that is elevated, and are surrounded by an erythematous halo. The lesions are typically rounded and circumscribed. Characteristically, hives should blanch with pressure; they generally resolve within 24 hours, and leave no residual scar or changes to the skin. The redness is due to dilated blood vessels in the superficial layers of the skin which have responded to histamine and is then augmented by a local neural reflex (axon reflex) initiated by the same nerve fibers that mediate itch. The wheal is due to leakage of these vessels and as fluid extravasates, compresses the vessels beneath so that the central area appears clear [16].

Urticaria is commonly classified by duration. If hives are present for less than six weeks, the process is considered "acute". If urticaria persists beyond 6 weeks, it is designated "chronic" [16]. In our patient, skin lesions were evaluated as acute urticaria.

Acute urticaria can be divided into two general types, depending on the rate at which hive formation occurs and the length of time it is evident. One type produces lesions that last 1-2 hours and is typically encountered in physically induced hives. The inciting stimulus is present only briefly, and there is prompt mast cell degranulation. Biopsy of such lesions reveals little or no cellular infiltrate. The second type produces a prominent cellular infiltrate, and individual lesions can last as long as 36 hours. This type is encountered with food or drug reactions, delayed pressure urticaria, chronic spontaneous urticaria, and urticarial vasculitis. In our patient, the second type was considered as the type of acute urticaria accompanied by a prominent cellular infiltrate. This type of urticaria occurs when mast cells in the skin are activated, degranulate, and secrete histamine, leukotrienes, platelet activating factor (PAF), enzymes such as tryptase and chymase, cytokines, and chemotactic cytokines (chemokines) [16]. But our patient could not have a skin biopsy.

Acute attacks of urticaria or angioedema can be treated with H1 antihistamines. Patients unresponsive to antihistamines can be treated with a tapering course of corticosteroid. In our patient donepezil treatment was discontinued, H1 antihistaminic treatment was started by consulting with the Department of Dermatology. The rash then began to fade and within one week the rash disappeared.

GA²LEN/EAACI/WAO/EDF guidelines classify urticaria according to clinical manifestations. Urticaria is mediated by mast cells. According to level of mast cell degranulation clinical signs are superficial (Urticaria) or deep swelling (Angioedema). For non-physical urticarias, guidelines suggest a unified scoring system from 0 (no wheals) to 3 (intense, many wheals, longer than 24 h) [17]. In our case, the classification of urticaria according to clinical symptoms score was evaluated as score 3 intense acute urticaria.

Because of the temporal relationship with the onset of treatment and disapperarance of skin rashes after the discontinuation of treatment in our case, it was thought that these skin rashes were due to donepezil treatment. These urticarias were often transient, resolving during discontinued donepezil treatment. People taking donepezil were more likely than those taking placebo to report side effects and to drop out of the studies. Most side effects were described as mild. This case report emphasizes that informing patients about acute intense dermatologic side effects is useful when starting donepezil treatment. We hope that these findings will help healthcare professionals to inform and follow their dementia patients.

Authors' Contributions

OB wrote the manuscript. BSAP collected data and figures and reviewed the manuscript for intellectual content. All authors read and approved the final manuscript.

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Availability of Data and Materials

All data are contained within the manuscript.

Conflict of Interest

The authors declare they have no confict of interest.

Ethical Approval

Ethics approval and consent to participate-not applicable, patient was not part of a study. According to Turkish regulations no ethics approval was required for this case report. This article does not contain any studies with human participants performed by any of the authors.

Informed Consent

Informed consent was obtained from the individual (reported case observation) included in this paper. Written informed consent was obtained from the patient for publication of this Case Report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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