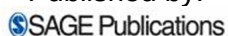


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Urticaria and angio-oedema due to ziprasidone

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Abstract

Antipsychotic medications are commonly associated with adverse cutaneous reactions (ACRs) in approximately 5% of patients. Angio-oedema accompanying urticaria is one of the most serious ACRs. The 36-year-old female patient who was diagnosed with 'Paranoid schizophrenia' 6 years ago, was commenced on ziprasidone 120 mg/day. On day 30 of the treatment, the patient presented urticarial papules and plaques all over the body and angio-oedema in the face. The patient was diagnosed as 'Urticaria+Angio-oedema'. The development of ACRs after the initiation of ziprasidone monotherapy, disappearance of lesions after the

discontinuation of this antipsychotic, and positive intradermal skin test all suggests a possible causal relationship between ACRs and ziprasidone. To our knowledge, this is the first reported case of urticaria and angio-oedema due to ziprasidone monotherapy. Ziprasidone is a valid and effective choice amongst antipsychotic medications, but this case calls for caution regarding ACRs at the time of prescribing.

Key words

ziprasidone, urticaria, angio-oedema

Introduction

Antipsychotic medications are commonly associated with adverse cutaneous reactions (ACRs) in approximately 5% of patients (Srebrnik *et al.*, 1991). The most common ACRs due to antipsychotics are exanthematous eruptions, skin pigmentation changes, photosensitivity, urticaria and pruritus. Urticaria is the second most common adverse cutaneous reaction, and can occur with all types of antipsychotic agents (Warnock and Morris, 2002). Angio-oedema accompanying urticaria is one of the most serious ACRs (Davidson *et al.*, 1992). Urticaria is erythematous pruritic cutaneous elevation that blanch with pressure, whereas angio-oedema is the oedema of the deep dermal and subcutaneous tissues. These reactions are secondary to the release of pro-inflammatory modulators, particularly through an IgE-mediated mechanism (type I hypersensitivity reaction), whereby an antipsychotic or its metabolite combines with IgE on the surface of the cutaneous mast cells. This releases cell vasoactive substances such as histamine, leukotriens and prostaglandin D2 which leads to vascular dilatation and increased vascular permeability resulting in oedema (Warnock and Knesevich, 1988). Urticaria may occur anywhere on the skin, whereas angio-oedema favours the face, tongue, extremities and genitals and may be fatal when involving the

larynx. Large weals appear within minutes to a few hours, or even as late as several days, after the initiation of drug therapy. The lesions generally do not last more than 24 hours, but are constantly being replaced by new eruptions. Lesions may appear within hours after re-administration of the offending agent. Diagnosis is generally based on clinical examination (Kimyai-Asadi *et al.*, 1999).

Although urticarial eruptions have been reported with several typical and atypical antipsychotics (i.e. clozapine, olanzapine, risperidone, ziprasidone and the phenothiazines) (Physician's Desk Reference (PDR), 2005), to our knowledge there is no specific article reporting a relationship between ziprasidone and angio-oedema in medical literature. Here, we report a female patient who developed generalized urticaria and angio-oedema during ziprasidone treatment.

Case report

The 36-year-old female patient who was diagnosed with 'paranoid schizophrenia' according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) (American Psychiatric Association, 2000) 6 years ago, has been followed up by our team since 1 July 2003. At that time,

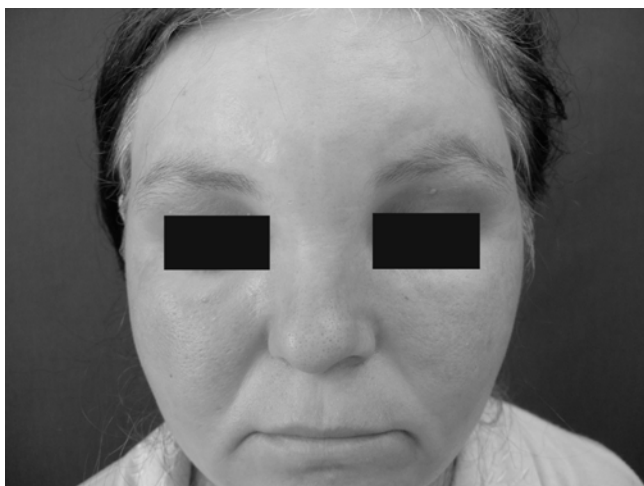


Figure 1a Angio-oedema on the face. Colour figures can be requested from the corresponding author.



Figure 1b Urticarial papules and plaques on forearm. Colour figures can be requested from the corresponding author.

patient was on a combined treatment of zuclopenthixol 50 mg/day and biperiden 4 mg/day. Later on this treatment was changed to haloperidol 2.5 mg/day and biperiden 3 mg/day on 24 December 2003. After the introduction of new treatment, her symptoms alleviated and her daily functioning improved. At one of her follow-up visits, on 28 June 2005, her routine physical examination revealed that she had mild rigidity and cogwheel signs at the elbow and wrist joints and involuntary movements of the mouth, tongue and around the lips. Because of the intolerable side effects, a change in treatment was considered. Electrocardiogram, complete blood count, biochemical blood tests including blood urea nitrogen, creatinine, aminotransferases, alkaline phosphatase, sodium, potassium, fasting glucose, prolactin, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides and blood smear were requested before the initiation of the treatment. With the exception of triglyceride level (310.00 mg/dL, normal range: 50.00–150.00), all other parameters were within normal range. Prior to the onset of the medical treatment, no pathology was observed during the physical examination and patient did not have any medical condition nor reported allergies to a medication or food type. Consequently, the treatment was discontinued on 5 July 2005 and patient was commenced on ziprasidone 80 mg/day due to its safer side-effect profile. On the third day of treatment, ziprasidone dose was increased to 120 mg/day. No pathological changes were observed in the general condition and physical examination during follow-up visits on days 10 and 17, the patient did not complain about any side effects and there was a marked reduction in extrapyramidal system side effects. On day 30 of the treatment, the patient presented ahead of her scheduled control date with urticarial papules and plaques all over the body and angio-oedema in the face. The dermatology consultation revealed that the urticarial symptoms started on day 27 and the lesions gradually intensified in 3 days (Fig. 1a, b). The patient was diagnosed as 'urticaria + angio-oedema'. Since the patient did not use any medication other than ziprasidone and did not have a history of contact with a

suspicious material, the condition was attributed to ziprasidone. Cessation of ziprasidone and treatment with pheniramine hydrochloride 50 mg/day and oral fexofenadine 180 mg/day for 10 days and single dose betamethasone disodium phosphate 3 mg IM were recommended. Electrocardiogram, complete blood count, biochemical blood tests and blood smear were repeated and all were within normal limits. During physical examination, there was no other pathology except for the skin lesions. Ziprasidone treatment was stopped immediately and substituted with haloperidol 2.5 mg/day and biperiden 2 mg/day. ACRs improved within 24 hours of substitution of medication and initiation of dermatological treatment and totally disappeared after 72 hours. Intradermal skin test with ziprasidone was also positive (Fig. 2). Drug re-challenge was not carried out for ethical reasons.

The timing of the drug use and the development of skin eruptions, resolution of the skin lesions after the cessation of ziprasidone and a positive intradermal skin test collectively led us to think of a causal relationship between development of 'urticaria + angio-oedema' and ziprasidone use. The ACRs did not recur after the reintroduction of Haloperidol and Biperiden treatment in the following 14 months.

Discussion

Studies on ACRs secondary to antipsychotics are almost exclusively limited to risperidone (Scuderi and Gift, 1986; Cooney and Nagy, 1995; Baldassano and Ghaemi, 1996; Sanders and Lehrer, 1998; Terao *et al.*, 1998; Kores *et al.*, 2001; Masson *et al.*, 2000; Ravasia, 2001; Tamam *et al.*, 2002; Botey *et al.*, 2004). The mechanisms underlying the association between other atypical antipsychotics and angio-oedema has not been well investigated in medical literature.

Ziprasidone (Geodon[®], Pfizer, Groton and New London, CT, USA) is an atypical antipsychotic with both dopamine (D₂) and

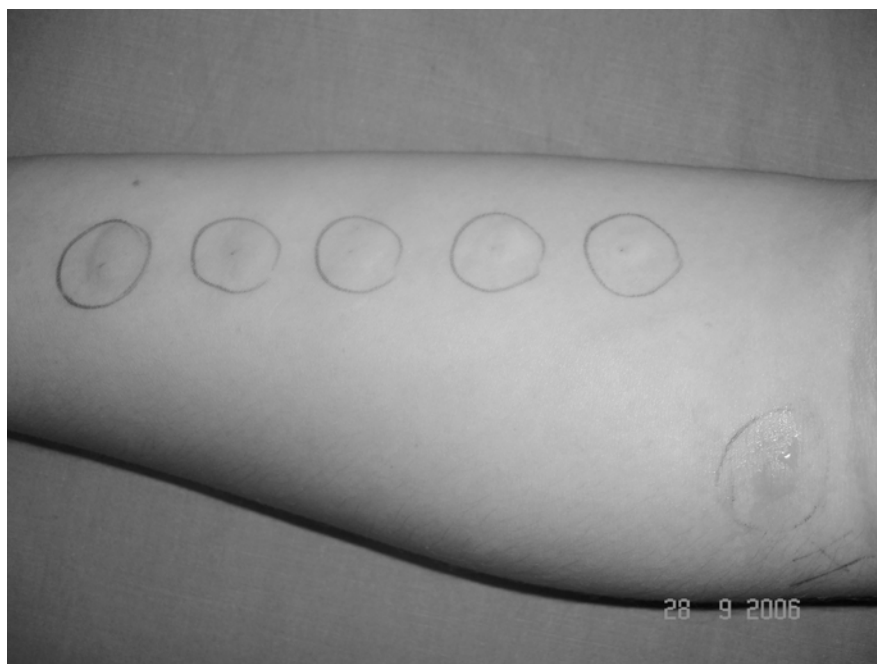


Figure 2 Positive intradermal skin test with Ziprasidone. Colour figure can be requested from the corresponding author.

serotonin (5-HT₂) receptor blocking properties (Schmidt *et al.*, 2001). Possible skin-related side effects associated with ziprasidone are maculopapular rash, urticaria and exacerbation of psoriasis. A Medline search spanning a 40-year period between 1966 and September 2006 did not reveal any reports on the association between urticaria with angio-oedema and ziprasidone. The development of ACRs after the initiation of ziprasidone monotherapy, disappearance of lesions after the discontinuation of drug and positive intradermal skin tests all suggests a possible causal relationship between ACRs and ziprasidone. To our knowledge, this is the first reported case of urticaria and angio-oedema due to ziprasidone monotherapy.

Patients requiring antipsychotic medications for the management of schizophrenia must take these drugs for a long time. Since ACRs to psychotropic medications are common and potentially serious, psychiatrists should be familiar with common and life-threatening ACRs. We reported this ACR to the Committee on Safety of Medicines. Moreover, since ACRs may cause patients distress and lead to non-compliance, psychiatrists should be aware of ACRs. Ziprasidone is a valid and effective choice amongst antipsychotic medications, but this case calls for caution regarding ACRs at the time of prescribing. Even though some side effects such as ACRs are argued as common and mostly not serious, we have to pay attention because it may sometimes be life-threatening.

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