Pedal Edema Associated with Clozapine Use

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Clozapine, widely recognized as an efficient agent for treating non-remittent schizophrenic patients, is associated with well-established adverse effects such as sedation, weight gain, sialorrhea, palpitations, seizures, and agranulocytosis. We report a case in which an additional possible negative side effect of clozapine was observed, namely pedal edema.

Case Description

This 24-year-old patient was known to suffer from schizophrenia for 6 years. Previous treatment by a variety of neuroleptics (including mood stabilizers) failed to produce long-term amelioration. In view of her frequent relapses, it was decided to initiate clozapine treatment as a sole anti-psychotic agent while maintaining her long-term valproic acid treatment. Clozapine was gradually increased to 400 mg/day with satisfactory results. However, 6 weeks after the commencement, the patient began to show signs of pedal edema and peri-orbital puffiness. No polydipsia was apparent. Physical examination revealed no other abnormal signs. Albumin blood level, and thyroid and liver function tests indicated normal levels. No proteinuria was detected. Other laboratory tests including electrolytes yielded normal results, except for eosinophilia. Echocardiogram showed normal systolic and diastolic functions.

In view of the apparent association between the development of the edema and the initiation of clozapine, the clozapine dosage was reduced to 200 mg/day over a period of 10 days. Parallel to clozapine diminution, eosinophilia subsided and the pedal edema gradually diminished.

Comment

There have been reports of an association between clozapine and a host of general medical conditions. These include: *de novo* onset or exacerbation of preexisting diabetes mellitus, paradoxical hypertension, lactic acidosis with fatal myocardial failure, acute pancreatitis [1], and pheochromocytoma-like syndrome suggesting

clozapine-induced sympathetic hyperactivity [2]. Eosinophilia has been attributed to clozapine treatment but whether it can serve as a reliable predictor for neutropenia — the main hazardous side effect of clozapine — remains controversial [3].

The attribution of the onset of pedal edema to clozapine treatment in our patient seems to be substantiated by the gradual development of the edema parallel to the initiation of the clozapine treatment, peaking after 6 weeks at 400 mg/day. Diminution of the dosage to 200 mg/day for 10 days led to the gradual disappearance of the edema. Although this may have been purely coincidental, association between the two is indicated. The possibility of water dysregulation — also known as the syndrome of psychosis, intermittent hyponatremia, and polydipsia — is doubtful due to the absence of polydipsia or hyponatremia in the patient. Moreover, clozapine has been shown to be effective for both the polydipsia and sodium dysregulation associated with water dysregulation syndrome [4]. Lack of any other explanation for the edema, as well as its resolution following dosage diminution supports our hypothesis that the edema was drug induced.

Although the possibility of clozapine-induced angio-edema is supported by the eosinophilia, the dose-related effects suggest otherwise. Clozapine affinity is mainly related to dopamine D_1, D_2 (relatively weak) and D_4, $5HT_2$, $\alpha 1$ and $\alpha 2$, muscarine and histamine H_1 receptors. Thus, the edema may reflect an antagonistic effect of clozapine on renal dopamine receptor type 4 (D_4). This receptor, activated by dopamine and the sympathetic system, has natriuretic and diuretic effects. Clozapine has been shown to block this effect in animals [5]. The dose-related edema in this case could be attributed to increased blockage of the D_4 receptor, the reduced natriuresis becoming clinically significant at high dosage levels.

A Medline search through January 2000 did not reveal similar cases of clozapine-associated pedal edema. It may be too early to determine whether the edema in this case is exclusively attributable to the clozapine treatment. However, pending further information regarding this side effect and its underlying mechanism, we feel that it is important that clinicians be alerted to the possibility of such a phenomenon.

References

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Capsule

Chaperone selection

Secretory and plasma membrane proteins begin their life with co-translational translocation into the endoplasmic reticulum (ER). Inside the ER, the correct folding of newly synthesized proteins is assisted by a group of chaperone molecules including binding protein (BiP) and the lectins calnexin and calreticulin. Molinari and Helenius found that chaperone selection occurs co-translationally and describe some of the criteria that select for a particular chaperone. The position of carbohydrate chains in the nascent chain of the protein diverted it from an interaction with BiP to an interaction with calnexin and caireticulin.

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