Gingival pain: an unusual side effect of ziprasidone

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SUMMARY

The patient is a 52-year-old man with schizophrenia who developed severe, unremitting gingival pain after his ziprasidone dosage was increased from 80 to 120 mg. His physical examination and laboratory findings were unremarkable. He did not have any extra-pyramidal side effects. His pain did not ameliorate after taking acetaminophen and non-steroidal anti-inflammatory drugs. As a last resort, the patient took benztropine and his pain subsided within half an hour. His ziprasidone dosage was decreased and the patient is currently doing well. He has not experienced gingival pain since his medication was adjusted.

BACKGROUND

There have been no previous reports of gingival pain being a side effect of ziprasidone. Since this side effect is extremely rare, the case could provide a valuable teaching point if clinicians are faced with a similar scenario.

CASE PRESENTATION

The patient is a 52-year-old man who was diagnosed with schizophrenia in 1983 at the age of 23. He was admitted to the hospital for the first time in 1986 and presented with catatonic symptoms, including posturing and auditory hallucinations. He was withdrawn and mute. He remained in the hospital for 1 month and was discharged home on dosages of 10 mg twice daily of trifluoperazine, 200 mg of haloperidol long-acting every 4 weeks and 2 mg twice daily of benztropine.

Over time, his trifluoperazine treatment was discontinued and 200 mg intramuscular of haloperidol reduced to 25 mg IM every 4 weeks. In 1997, the patient was switched to nightly oral doses of 2 mg each of haloperidol and benztropine.

In 2000, the patient developed tremors, for which the benztropine dosage was increased from 2 to 4 mg once daily. However, this change caused urinary hesitancy, hence benztropine treatment was discontinued and haloperidol replaced with 10 mg once daily of olanzapine.

The increase in olanzapine resulted in significant weight gain. Between 2000 and 2009, the patient's weight increased from 160 to 212 lbs. Consequently, in June 2009, olanzapine was replaced with 40 mg twice daily of ziprasidone. After 6 months, the ziprasidone dosage was changed to 80 mg once in the morning. From December 2009 to May 2012, the patient did well and remained stable at this dose.

In May 2012, the patient's father died unexpectedly and the patient sought help as he was having difficulty coping with the loss. He could not concentrate and began to withdraw. At this time, his morning ziprasidone dosage was increased from

80 to 120 mg. He was also given benztropine in case of side effects.

When he was seen for a follow-up in July 2012, the patient complained of experiencing excruciating gum pain for 3 weeks. He would take 120 mg of ziprasidone at 8:00 and the pain would start at around noon, continuing until he went to bed at 10:00, but the pain would often also keep him awake at night. It made it extremely difficult for him to eat or drink. The patient described the pain as constant, achy and severe. He had not previously experienced this kind of pain. He denied any radiation, but described the pain as being diffusely severe in his upper and lower gums. Upon physical examination, there was no blood, pus, redness, swelling or warmth. There was no evidence of lymphadenopathy. He did not have any tremors, rigidity, restlessness or other extra-pyramidal side effects.

The patient tried dosages of 500 mg of acetaminophen and 200–400 mg of ibuprofen, but without any decrease in pain. As a last resort, he took 2 mg once daily of benztropine and the pain subsided within half an hour. The pain returned only at noon the following day after his usual 120 mg morning dose of ziprasidone.

INVESTIGATIONS

- ▶ Urine toxicology—negative
- ▶ Complete blood count and electrolytes—within normal limits

TREATMENT

The ziprasidone dosage was reduced from 120 to 80 mg once daily.

OUTCOME AND FOLLOW-UP

The patient has since learned to cope with his father's death through grief counselling and other supportive measures. His ziprasidone dosage was reduced to 80 mg once daily in July and the patient is currently doing well.

DISCUSSION

Ziprasidone is an atypical antipsychotic. The first one, clozapine, was introduced to North America in 1990. Since then, a number of other atypical antipsychotics have been introduced, including risperidone, olanzapine, quetiapine and aripiprazole. Ziprasidone was introduced to the USA in 2001 and to Canada in 2008. It is indicated for use in the treatment of schizophrenia, related psychotic disorders and bipolar disorder for acute manic or mixed episodes.¹ The drug has been used for many off-label conditions as well.² The common side effects of ziprasidone are somnolence, extra-pyramidal side effects, headache, insomnia and respiratory disorders.³

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Conventional antipsychotics are effective in controlling the positive symptoms of schizophrenia, whereas atypical antipsychotics have been beneficial for both positive and negative symptoms. Positive symptoms include delusions, hallucinations and other abnormal behaviour. Negative symptoms include flat affect, poor speech content and an inability to feel pleasure with recreational activities or interests.

Although atypical antipsychotics have been assumed to have a better side-effect profile than conventional ones, lately, doubts have been cast.⁴⁻⁵ For example, the emergence of metabolic syndrome with a few of the atypicals has caused major concern.⁶

In premarketing schizophrenia trials, ziprasidone was found to cause gum haemorrhage in fewer than 1 in 1000 patients. In placebo-controlled bipolar-mania trials, 'tooth disorder' was found in 3.7% of the ziprasidone group versus 2.2% of the placebo group. Gingivitis, gum haemorrhage, mouth ulceration and periodontitis occurred infrequently, between 1 in 100 and 1 in 1000 of the ziprasidone group.

Parkinsonian events were found to occur between 10.7% and 23.6% of the population receiving ziprasidone. Chest pain occurred in 3% of ziprasidone and 2% in placebo group. Pain (Body System and COSTART Preferred Term) was recorded in 3.3% of the ziprasidone group and 5% in the placebo.¹

Pain is an infrequent symptom in Parkinson's disease. The usual sites for pain are the back, legs and shoulders. There have also been reports of unusual presentation such as oral and genital pain syndromes, pain that mimicked angina and upper or lower abdominal pain. The unusual pain symptoms are thought to be from a central source, although peripheral nerves have also been thought to play a part in their aetiology. They may respond to dopamine.⁷⁻⁹ Similarly, neuroleptic-induced extrapyramidal symptoms are associated with painful sensations conforming to sensory symptoms found in Parkinson's.¹⁰

Since benztropine is used to relieve pain in Parkinson's disease and was shown to relieve the gingival pain caused by ziprasidone in this patient, it is likely that gingival pain could be similar to the centrally mediated pain in Parkinson's disease.

It is noteworthy that the patient could tolerate large doses of conventional antipsychotics in the past but had adverse effects from a relatively small dosage of an atypical antipsychotic. It is possible that factors such as past, prolonged exposure to antipsychotic drugs, the passing of years and his individual sensitivity have contributed to the development of adverse effects.¹¹⁻¹²

The general consensus is that newer atypical antipsychotics are superior to the conventional ones because of the better side-effect profile and possible lack of irreversible, long-term,

adverse effects, such as tardive dyskinesia. The patient's gingival pain resulting from a relatively low dose of ziprasidone is suggestive of an extra-pyramidal symptom as it was relieved by benztropine. This is the first report of this unusual side effect.

Learning points

- Novel side effects can occur with all medications, including atypical antipsychotics.
- A patient who can tolerate high doses of a conventional antipsychotic has difficulty tolerating a low dose of an atypical antipsychotic.

Competing interests None.

Patient consent Obtained.

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