A successful treatment strategy for clozapine-induced parotid swelling: a clinical case and systematic review

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Abstract: Parotid gland swelling is a less frequently reported side effect of clozapine and has no licensed treatment. A 58-year-old man treated with clozapine for treatment-resistant schizophrenia developed bilateral painful parotid swellings and hypersalivation. Initial trials of dose alteration and antihypersalivatory medication had limited success. A combination of benztropine and terazosin was successful in treating the parotid hyperplasia. Clozapine was the probable cause of parotid swelling in our case, as established using the Naranjo adverse drug reaction probability scale and World Health Organization causality categories. Literature for treatments of clozapine-induced parotid gland swellings was reviewed. None of the published articles suggested a treatment regimen for clozapine-induced parotid hyperplasia. Most reports only highlighted the occurrence of salivary gland swelling with clozapine. Others mentioned management strategies, which included spontaneous resolution, or resolution on discontinuing clozapine. One report, a trial with benztropine and ipratropium, had variable success. In this case the re-emergence of parotid swelling when terazosin and benztropine doses were missed followed by a quick resolution upon recompliance, goes some way in proving that this combination is indeed effective. The combination of terazosin and benztropine appears to have a role in treating parotid gland swellings induced by clozapine.

Keywords: Benztropine, clozapine, parotid, swelling, terazosin

Introduction

Clozapine is an antipsychotic drug that was first manufactured in 1959 and introduced into clinical practice in the 1970s. It has been shown to be more effective in the treatment of schizophrenia than typical antipsychotics [Wahlbeck *et al.* 2000]. It is the drug of choice for treating treatment refractory schizophrenia. It is the most effective antipsychotic for severe, refractory schizophrenia [Barnes, 2011].

Clozapine is a widely used atypical antipsychotic, and it has a complex and not entirely understood mechanism of action. It has a pharmacological profile and side effects that are different to those of other typical and atypical antipsychotic drugs; in fact, it interacts with several subtypes of dopaminergic (D1, D2, D3, D4), serotonergic (5-HT1A, 5-HT2A, 5-HT2C, 5-HT3, 5-HT6,

5-HT7), adrenergic (1, 2), histamine (H1) and muscarinic (M1) receptors [Raggi *et al.* 2004]. It has been hypothesized that this high affinity of clozapine for dopamine D4 receptors, rather than the D2 receptors, is the origin of its superiority.

There is a 2.8% risk of granulocytopenia when taking clozapine and a 0.6% risk of agranulocytosis [Loebel *et al.* 1992]. Other well-known side effects concern sedation in 39% of patients [Safferman *et al.* 1991], and precipitation of seizures.

One of the most common side effects is hypersalivation, with reported incidences ranging from 30% [Davydov and Botts, 2000; Rogers and Shramko, 2000] to 80% [Ben-Aryeh *et al.* 1996; Schmauss *et al.* 1989]. Clozapine-induced hypersalivation can wear off with time; however, it can be severe and persistent and is often particularly

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problematic at night. The consequences of hypersalivation can be embarrassing, and in some cases life threatening. There have been reports of choking and aspiration of excess saliva [Young *et al.* 1998; Syed *et al.* 2008], with the risk of aspiration pneumonia [Hinkes *et al.* 1996]. Hypersalivation has also been associated with cases of parotid gland swelling and inflammation [Brodkin *et al.* 1996; Robinson *et al.* 1995].

Parotid gland swelling is a less reported side effect of clozapine. The UK Medicines and Healthcare Products Regulatory Agency collected 32 reports of parotid gland swellings in comparison to 504 cases of hypersalivation by January 2012.

Various pharmacological approaches have been used to alleviate this problem, mainly issued in the form of case reports. It appears most treatments target the hypersalivation in the hope of treating the swelling.

To the best of our knowledge there are no licensed drug treatments for clozapine-induced hyperplasia. Pharmacological treatments are generally either anticholinergic, with the aim of blocking muscarinic receptors, or alpha 2 agonists to reduce sympathetic stimulation of the salivary glands. A nonrandomized trial found that terazosin (an alpha 1 receptor antagonist) and benztropine (an antimuscarinic agent) in combination were more successful at controlling hypersalivation than either drug alone [Reinstein *et al.* 1999].

We describe below the results of a successful treatment strategy we used, together with a review of available literature on clozapine-induced parotid gland swelling.

Case report

Mr G was a 58-year-old married man with an 8-year history of schizophrenia accompanied by significant affective (depressive) symptoms. He had episodes of depression in his late teens, which were treated by various antidepressants, including dothiepin, citalopram and paroxetine. He was a smoker and known to have misused alcohol in the past. He has enjoyed good physical health for most of his life.

Mr G had his first episode of psychosis along with depressive symptoms in late 2003. He was given a diagnosis of schizophrenia in early 2004 after a long hospital admission and through investigations. He

was treated with a combination regimen of an antipsychotic and an antidepressant.

He was initially treated with mirtazapine and olanzapine on which he developed severe extrapyramidal side effects (EPSE). In order to address this, his antipsychotic was switched to aripiprazole. He continued to have intractable EPSEs on aripiprazole with relatively poor control of psychosis. The escalation in risk index due to psychosis led to his third inpatient admission in 2005. His antipsychotic treatment was switched to clozapine in early 2006 for treatment refractoriness. His mental state showed marked improvement on clozapine. He was discharged from hospital on clozapine 300 mg

After starting clozapine he developed hypersalivation and bilateral painful parotid gland swellings; he was initially treated with hyoscine hydrobromide, which resulted in urinary retention. Hence he was given tamsulosin to treat the urinary retention. This strategy resulted in a partial improvement of hypersalivation and some improvement of urinary retention, but little improvement in the swelling and pain, and unfortunately he developed a sexual side effect of retrograde ejaculation.

Mr G was extensively investigated for any parotid pathology with blood tests for infection and inflammatory markers, a computerized tomography scan, magnetic resonance imaging and sialogram, which ruled out all the common conditions such as salivary stones or infections. The reports noted bilateral parotid hypertrophy with no localized lesions.

Various strategies were tried to relieve the parotid swelling. Initially the clozapine dosage was reduced to 250 mg, while rigorously monitoring his serum clozapine levels. This resulted in some improvement in parotid side effects, but a worsening of his psychotic symptoms. In an effort to better treat the psychosis he was augmented with amisulpride, but this had little benefit. Hence the clozapine dose was increased back to 300 mg and the amisulpride discontinued, with a relapse of parotid gland swelling and pain as expected. Options to treat him with another antipsychotic such as quetiapine were explored but not tried, as the risk of relapse and consequent increase in risk to others were deemed high.

We tried a new strategy after an extensive literature review. Hyoscine hydrobromide and tamsulosin

were reduced and stopped; this helped improve urinary and sexual side effects. He was then treated with benzatropine 1 mg initially, titrated up to 2 mg/day over a period of 3 months, resulting in a mild reduction in symptoms. Hence, terazosin was added to this at an initial dose of 1 mg/day, subsequently increased to 2 mg/day. This resulted in a good effect, as the hypersalivation reduced in intensity with a gradual reduction in the parotid gland swelling. At 3 months into the treatment with this combination of benzatropine and terazosin the parotid gland swelling was completely gone.

Mr G has been on clozapine 150 mg twice daily, mirtazapine 45 mg, benzatropine 2 mg at night, terazosin 2 mg at night, and diazepam 5 mg as required for 2.5 years. During this time he has enjoyed a stable mental health. He now reports little hypersalivation. On occasions of noncompliance with medication, a pain-free left parotid swelling reappears, which resolves quickly with treatment. He also reports an increase in confidence and an improved social life. He has been able to maintain himself in the community, with a care plan involving minimal nursing and medical input.

Causality

We assessed the question: 'is clozapine the causative factor for parotid swelling in this case?' We scored our case against the Naranjo adverse drug reaction probability scale where it scored 7, indicating it to be 'probable' [Naranjo *et al.* 1981]. When assessed under the World Health Organization (WHO) causality categories, it qualified for category C2, i.e. 'probable/likely' [WHO, 2000]. This showed that clozapine is the probable or likely cause for parotid swelling in this case.

Systematic review

A systematic review was performed with the aim of finding evidence regarding the treatment of clozapine-induced parotid gland swellings. Five medical databases were searched (i.e. PubMed, PsycINFO, Embase, MEDLINE and NHS Evidence – mental health). Articles in English up to March 2012 were considered.

Search terms included: parotid, parotitis, salivary, swelling, ptyalism, hypersalivation, psychosis, schizophrenia, anticholinergic, antihistaminic, alpha 1 antagonist, treatment and other relevant terms. A total of 51 articles were identified by web-based searching in the first phase. After further

manual scrutiny only 12 reports fulfilled the review criteria. All reports were evaluated according to the Oxford Centre of Evidence-based Medicine levels of evidence criteria. Two were classified as level B (retrospective cohort studies), five were case-series-based reports hence fulfilled level C, while five were case reports based on one case.

The aim of most reports was to highlight the occurrence of salivary gland swelling in clozapine and reported spontaneous resolution or resolution by discontinuing clozapine. Three reports tried pharmacological options such as benzatropine and ipratropium with variable success. None of the reports identified a clear treatment regimen for clozapine-induced parotid gland swelling.

Terazosin

Terazosin, classified as a quinazoline, is similar to doxazosin and prazosin (see Figure 1). As an alpha-adrenergic blocking agent, terazosin is used to treat hypertension and benign prostatic hypertrophy (BPH) [Lieber, 1998]. It selectively and competitively inhibits vascular postsynaptic alpha (1)-adrenergic receptors, resulting in peripheral vasodilatation and a reduction of vascular resistance and blood pressure. It is metabolized in the liver and one of the four metabolites (piperazine) has antihypertensive activity. It is completely absorbed in man (90% bioavailability) and has a half-life of 12 h; toxicity $LD_{50} = 259.3$ mg/kg (intravenous in mice)

Benzatropine

Benzatropine possesses both anticholinergic and antihistaminic effects. It is used as an adjunct in the therapy of all forms of Parkinsonism and also for use in the control of extrapyramidal disorders due to neuroleptic drugs [Lieber, 1998]. Benzatropine is a selective M1 muscarinic

Figure 1. Terazosin ($C_{19}H_{25}N_5O_4$).

Figure 2. Benzatropine (C₂₁H₂₅NO).

acetylcholine receptor antagonist acting selectively on central nervous system (CNS) receptors (see Figure 2). It partially blocks cholinergic activity in the CNS, which is responsible for the symptoms of Parkinson's disease. It is also thought to increase the availability of dopamine, a brain chemical that is critical in the initiation and smooth control of voluntary muscle movement. Signs of overdose include confusion, listlessness, hallucinations, dizziness, muscle weakness, ataxia, dry mouth, mydriasis, blurred vision, palpitations, tachycardia, elevated blood pressure, nausea, vomiting, dysuria, coma, shock, convulsions, respiratory arrest, anhidrosis and hyperthermia.

Implications for clinical care

Parotid gland swellings as a side effect of clozapine treatment are a less frequently reported problem than hypersalivation. There could be a multifactor explanation for this: (a) lack of awareness of parotid gland swellings as a side effect of clozapine; parotid gland swellings when present are seen in the domains of other branches of medicine/surgery; low reporting about this condition as it is easy to miss; low incidence of the condition itself.

The few reports that have been published have reported limited success with the treatment approaches they have tried.

However, the combination of terazosin and benzatropine was successful in treating the parotid gland swelling as well as hypersalivation in our patient, and may be a useful strategy in treating other such patients. This strategy may be used especially in treating cases of parotid swelling, when treating a patient with treatment resistance psychosis and high risk of relapse.

In an ideal scenario one could address the academic question 'did the combination of terazosin and benzatropine indeed effect the reduction of the parotid swelling' by either discontinuing the combination, or trying a rechallenge on the emergence of parotid swelling. In our case we felt it would not be ethical to do so. Also the patient had been exercising his choice in continuing the combination. The re-emergence of parotid swelling with noncompliance of terazosin and benzatropine, and resolution of symptoms on recompliance, goes some way toward proving that the combination of terazosin and benzatropine are indeed effective.

In addition, the anticholinergic properties of benzatropine can be useful in treating extrapyramidal reactions. The antihypertensive properties of terazosin can be exploited to treat any comorbid hypertension.

It has been noted that benzatropine could decrease the gut absorption of clozapine, however there was no evidence of change in clozapine levels in our patient.

Conclusion

The combination of terazosin and benzatropine is an effective strategy for the treatment of parotid gland swellings and hypersalivation induced by clozapine. However, further research is needed to elucidate the mechanisms of actions of terazosin and benzatropine, particularly actions on the parotid glands, and their relationship with the observed therapeutic effects.

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Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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