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Complete Resolution of Clozapine-Induced Sialorrhea with Low Dose Trihexyphenidyl

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ABSTRACT *~ Clozapine-induced sialorrhea (CIS) is a frequently occurring debilitating adverse effect. Although various treatment options exist, none has been proved to be distinctly superior to others. We report a case of CIS that responded to low dose of trihexyphenidyl (2 mg/day).* Psychopharmacology Bulletin. *2010;43(4):73–75.*

INTRODUCTION

Clozapine, an atypical antipsychotic agent useful in treatment resistant schizophrenia, causes sialorrhea in approximately one-third of patients leading to treatment noncompliance.[1] Proposed mechanisms for clozapine-induced sialorrhea (CIS) include α_2-adrenoreceptor antagonism, M_4-receptor agonism and inhibition of swallowing reflex.[1] Although frequently sleep-related, occasionally it also appears during waking hours causing significant distress.[1,2] Pharmacological treatment options for CIS include centrally acting α_2-adrenoreceptor antagonists like clonidine, lofexidene and guanfacine, and antimuscarinic drugs such as pirenzepine, amitryptiline, trihexyphenidyl, benztropine, biperiden, scopolamine, glycopyrrolate, ipatropium bromide and atropine.[1,3] Pharmacotherapy often leads to partial response, certain drugs showing greater efficacy in particular subgroup of patients and no single agent can be considered distinctly superior to others. We report complete resolution of CIS with low dose of trihexyphenidyl.

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CASE STUDY

Mr. A, 28-year-old male, a diagnosed case of bipolar disorder with dissocial personality disorder, presented with complaints of overtalkativeness, hyperactivity, decreased sleep and irritability for five months. He had five similar episodes in the past ten years. His elder brother also had bipolar disorder. On mental status, he had increased psychomotor activity and grandiose delusions. The current manic episode occurred as a breakthrough while on sodium valproate. Considering past nonresponse to adequate trials of lithium and carbamazepine, clozapine was added to sodium valproate 1 gm/day, and gradually built up to 300 mg/day over two weeks. Three weeks after starting clozapine, he had excessive, distressing sialorrhea occurring during daytime as well as at night. In night time, an estimated area of 10 centimeters diameter of wet surface[1] was spotted regularly over the pillow. Objective assessment of daytime sialorrhea revealed a score of 4 (constantly drools) on Drooling Frequency Scale (DFS)[4] and 3 (moderate, wet on lips and chin) on Drooling Severity Scale (DSS).[5] To treat the incapacitating salivation, tablet trihexyphenidyl 2 mg at nighttime was added. Within four days, the patient reported dramatic improvement in hypersalivation (score 1 on DSS and DFS suggestive of no drooling) with completely dry pillows indicating resolution of nocturnal sialorrhea. As there was remission of manic symptoms on this combination without reemergence of sialorrhea, he was maintained on the same dosage of these drugs. Constipation, another adverse effect, was managed with laxatives while tachycardia required no intervention.

DISCUSSION

Anticholinergic agents inhibit secretion of the nose, mouth, pharynx and bronchi, which manifests clinically as dry mouth; this property is utilized in treatment of CIS.[6] Trihexiphenidyl, an "M1-selective" muscarinic antagonist, has high affinities for M1 and M4 receptors,[7] and is used as an antiparkinsonian agent. M4 agonism by clozapine, one of the major mechanism of CIS, is probably targeted by trihexiphenidyl. Spivak et al.[8,9] found 44% improvement in hypersalivation on a 5-point subjective scale in 14 schizophrenia patients having CIS when treated with 5–15 mg trihexiphenidyl at night for 15 days. In another case study,[10] trihexyphenidyl 6 mg/day was effective for nocturnal enuresis with marked reduction in nocturnal and complete disappearance of daytime sialorrhea. Interestingly, in our case there was complete resolution of both daytime as well as nighttime sialorrhea after adding lower dose of trihexyphenidyl. Though serum levels of anticholinergic medications are

not routinely measured, evidence suggests that inter-individual variation can be up to 100-fold,[6] which explains effectiveness of low dose trihexyphenidyl in our case. Trihexiphenidyl, when used in combination with clozapine, may aggravate its anticholonergic and cognitive adverse effects. Therefore, a trial of low dose of trihexiphenidyl is warranted before increasing it further. Also, controlled trials of trihexiphenidyl are needed to study its efficacy and tolerability in the treatment of CIS. ✤

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