Case Report

A case of tinnitus induced by chlorpromazine in a pediatric patient

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ABSTRACT

Chlorpromazine is a well-known antipsychotic agent that binds with a variety of receptors in the central nervous system. To date, chlorpromazine has never been associated with onset of hearing disorders and tinnitus. We report on an unexpected suspect adverse reaction to chlorpromazine that occurred in a 12-year-old boy, affected by severe generalized anxiety disorder. After treatment with chlorpromazine, the patient experienced an enhanced sensitivity to sounds accompanied by perception of noises of the buzzing or ringing type. This clinical case is of great clinical interest as chlorpromazine is not currently included among potentially ototoxic drugs.

Key words: Adverse drug reaction, chlorpromazine, tinnitus

INTRODUCTION

Chlorpromazine is a phenothiazine antipsychotic drug. Its effect is mediated via interactions with several receptors in the central nervous system and results from a combination of antidopaminergic, anticholinergic, antihistaminic, and weak antiadrenergic actions. The therapeutic effects of chlorpromazine are frequently accompanied by unwanted side effects that include sedation, autonomic, endocrine, and neurological effects.[1] To date, chlorpromazine has never been associated with onset of hearing disorders and tinnitus.

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Tinnitus is a common adverse reaction (ADR) to several drugs and may occur during long-term therapies or after a single drug administration.[2] Even though not life threatening, tinnitus may be discomforting; it may also be irreversible despite drug withdrawal. To date, over 130 drugs have been described to be potentially ototoxic, among which the most common inducers of tinnitus are aminoglycosides and other antimicrobials.[3]

CASE REPORT

We report on a suspect ADR to chlorpromazine that occurred in a 12-year-old boy, affected by severe generalized anxiety disorder.

He received initially a benzodiazepine therapy, which was switched to chlorpromazine (6.25 mg/day orally) because of the absence of a significant clinical response. The patient received no other concomitant drug or herbal treatment.

Ten days after treatment with chlorpromazine, the patient

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experienced an enhanced sensitivity to sounds accompanied by perception of noises of the buzzing or ringing type.

Information about the patient's medical history did not report conditions that may have predisposed to the onset of the disturbance manifested. Moreover, the patient was in overall good health and had never suffered from hearing disorders.

In view of the medical history, an iatrogenic nature was suspected. No instrumental exams for hearing disorder were performed.

The inability to discontinue therapy with chlorpromazine resulted in an objective worsening of the patient's symptoms, which are still present to date.

The Naranjo ADR probability scale identified the relationship between the patient's development of ADR and the drug as "possible."

DISCUSSION

This is the first report on a case of tinnitus related to the administration of chlorpromazine. Several different mechanisms may explain this clinical development. Chlorpromazine is an antagonist of several dopamine cochlear receptors that play an important role in the sensory process by modulating afferent auditory nerve activity. Dopamine, released from the terminals of lateral olivocochlear efferent fibers, is protective against acoustic trauma, hypoxia, and ototoxicity. In this context, the dopamine antagonist activity of chlorpromazine may result in a higher risk of ototoxicity.[4,5] A second possible mechanism is the antagonist activity of chlorpromazine on histamine receptors. Histamine has physiological roles in the homeostasis of the inner ear and the cochlea.[6] It controls the cochlear blood flow, acting on the precapillary sphincters and increasing the microcirculatory flow. Clinical evidence indicates that H1 histamine agonists are effective in reducing tinnitus via improving vestibular compensation of the microcirculation. Chlorpromazine antagonism on H1-receptors may thus play a role in counteracting the vessel modulatory effect of histamine and by this means have contributed to tinnitus development in our patient.

Chlorpromazine has also anticholinergic effects. Acetylcholine is the major neurotransmitter in the olivocochlear efferent pathway, which is a feedback control system to the inner ear comprising a medial olivocochlear pathway projecting to outer hair cells and a lateral olivocochlear pathway projecting to dendrites of cochlear nerve fibres.[7] In this context, the anticholinergic effects of chlorpromazine may have inhibited efferent signalling via the $\alpha 9/\alpha 10$ nicotinic acetylcholine receptor complex in the outer hair cells which is known to be protective against acoustic injury.[8]

Another action of chlorpromazine that may have contributed to generate tinnitus in our patient is its antagonism of serotonergic receptors. Serotonin is one of the neurotransmitters acting on the auditory pathways; in particular it is involved in sound detection, location, and interpretation. Serotonin is currently believed to be one of the most important neurotransmitter involved in the perception of tinnitus.[9] Indeed, serotonin reuptake inhibitor drugs reduce the intensity of tinnitus acting directly on nerve conduction of the auditory stimulus, particularly in the central auditory pathways.[10] In this scenario, it is thus conceivable that antagonism at serotonin receptor levels caused by chlorpromazine causes auditory disorders leading to tinnitus.

Finally, a role for an action of chlorpromazine on gamma amino butyric acid (GABA) cannot be excluded. GABA inhibits auditory system and systemic administration of a GABA transaminase inhibitor improves tinnitus by suppressing hyperactivity in the auditory system.[11]

The neurotransmitter serotonin, involved in a large variety of physiological functions, behaves as a neuromodulator by strengthening the GABA system.[12] Chlorpromazine, by decreasing the availability of serotonin, may lead to decreased GABAergic activity and this action may have contributed to tinnitus development. We cannot establish which among the actions of chlorpromazine described above has been predominant in the tinnitus-inducing action we observed, and the most likely possibility is that tinnitus resulted from a synergism among these different actions. A predisposition of the patient to develop tinnitus following chlorpromazine cannot also be ruled out. Receptors for serotonin, histamine, dopamine, and GABA are polymorphic and the presence of specific single nucleotide polymorphisms that acted as predisposing factors may be present in this specific patient.[13-15] In addition chlorpromazine is substrate of cytochrome P4502D6 (CYP2D6), a highly polymorphic isoform of cytochrome. Genetically determined functional variations of this cytochrome may be present in the patient and may also have contributed to the onset of tinnitus.[16]

CONCLUSION

To our knowledge, this is the first report on the development of tinnitus following chlorpromazine administration. Although there is no information on dechallenge and rechallenge, the inability to discontinue therapy with chlorpromazine resulted in an objective worsening of the patient's symptoms. This clinical case is of great clinical interest as chlorpromazine is not currently included among potentially ototoxic drugs; paradoxically phenothiazines can be prescribed to alleviate symptoms related to disorders of the vestibular system.

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