GENERAL PSYCHIATRY
Key Words: Hyperprolactinemia, Antipsychotic, Cabergoline, Bromocriptine, Pharmacovigilance

Antipsychotic Induced Symptomatic Hyperprolactinemia: Are Dopamine Agonists Safe?

By Unax Lertxundi, Saioa Domingo-Echaburu, Javier Peral, Montserrat García

ABSTRACT ~ *Published literature shows that dopamine agonists can reverse antipsychotic-induced hyperprolactinemia without worsening psychotic symptoms in the majority of schizophrenic patients. However, psychiatrists have been reluctant to use drugs with dopaminergic properties for fear of exacerbating psychiatric symptoms. There are reported cases of psychosis worsening published for both cabergoline and bromocriptine. Cabergoline has proven to be more effective and safe when used to treat hyperprolactinemia, but whether cabergoline is also safer than bromocriptine in antipsychotic induced hyperprolactinemia remains unproven.* Psychopharmacology Bulletin. *2011;44(3):66–68.*

Dopamine is the predominant prolactin-inhibiting factor in animals and humans. It is produced by the tuberoinfundibular neurons in the hypothalamus, released from their nerve endings in the median eminence and transported by the portal hypophyseal circulation to the pituitary, where it binds to the dopamine D_2 receptors on the membrane of lactotroph cells.

Antipsychotics block D_2 receptors on lactotroph cells, leading to hyperprolactinaemia by removing the main inhibitory influence on prolactin secretion.

When antipsychotic induced hyperprolactinemia warrants treatment, different approaches can be attempted:[1]

– Dose reduction of the offending antipsychotic. It is the simplest treatment strategy, but its effectiveness is unpredictable and it carries the risk of precipitating an exacerbation or relapse of psychotic symptoms.

Dr. Lertxundi, Pharmacy Service, Red de Salud Mental de Araba, C/alava 43, Vitoria-Gasteiz, Araba, Spain. Dr. Domingo-Echaburu, Pharmacy Service, Hospital Alto Deba, Avda, Nafarroa, 16, Arrasate Gipuzkoa, Spain. Dr. Peral, Pharmacy Service, Hospital de Galdakao-Usánsolo, Barrio labeaga s/n, Galdakao, Vlzcaya, Spain. Dr. García, Basque Country Pharmacovigilance Unit, Galdakao-Usansolo Hospital, Barrio labeaga s/n, Galdakao, Vlzcaya, Spain.

To whom correspondence should be addressed: Dr. Unax Lertxundi, Pharmacy Service, Red de Salud Mental de Araba, C/alava 43, 01006 Vitoria-Gasteiz, Araba, Spain. Phone: 0034 945 00 65 33; Fax: 0034 945 00 65 87; E-mail: Unax.lertxundietxebarria@osakidetza.net

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- Switch to a prolactin-sparing antipsychotic (i.e. aripiprazole, olanzapine, quetiapine or clozapine). This strategy usually proves effective, though there is also a risk of relapse.
- Addition of a prolactin sparing antipsychotic to the current regimen.[2] This practice could promote the use of antipsychotic polypharmacy, a practice that lacks supporting evidence and possesses uncertain consequences for the patients.[3]
- Addition of a dopamine agonist such as bromocriptine or cabergoline.

A meta-analysis comparing bromocriptine and cabergoline in the treatment of prolactinomas and idiopathic hyperprolactinemia showed new evidence favoring the use of cabergoline in comparison with bromocriptine.[4] Clinical and biochemical success rates were significantly higher and adverse events were significantly lower in cabergoline users. The authors concluded that except in particular situations, cabergoline should be the first treatment option for patients with prolactinomas or other hyperprolactinemic conditions.

Nevertheless, the only randomized clinical trial in the treatment of antipsychotic induced hyperprolactinemia has been conducted with bromocriptine,[5] while the only evidence available for cabergoline comes from a pilot study in risperidone induced hyperprolactinemia.[6]

In general, all these results suggest that adding a dopamine agonist can reverse antipsychotic-induced hyperprolactinemia without worsening psychotic symptoms in the majority of schizophrenic patients. However, psychiatrists have been reluctant to use drugs with dopaminergic properties for fear of exacerbating psychiatric symptoms. There are reported cases of psychosis worsening published for both cabergoline and bromocriptine.[7,8] Whether cabergoline is also safer than bromocriptine in antipsychotic induced hyperprolactinemia remains unproven.

We performed a search in the Spanish Pharmacovigilance database (FEDRA) using the Medical Dictionary for Regulatory Activities (MedDRA) version 14.0 "psychosis aggravated" and "schizophrenia aggravated" terms to try to find out if there was any difference in reporting ratios for those adverse reactions between cabergoline and bromocriptine. These MedDRA terms were used to differentiate psychosis worsening in psychiatric patients from psychiatric symptoms in general when these agents (cabergoline and bromocriptine) are used for Parkinson's disease, pituitary adenomas and lactation suppression in healthy puerperals, which is by far their main use.

Unfortunately no spontaneous reports were found from 1984 to July 2011.

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An interesting theoretical approach would be giving a D_2 dopamine agonist which does not cross the blood brain barrier. This hypothetical drug would be able to suppress prolactin secretion by its action on the pituitary gland without worsening psychotic symptoms. It would be more or less like treating nausea/vomiting in Parkinson's disease with domperidone. Dopamine itself would be a valuable option, but evident reasons make its use in this setting impossible.

Carmoxirole is an oral dopamine agonist that does not cross the blood-brain barrier. It was tried with success in the treatment of amisulpride induced hyperprolactinemia in rats. Sadly, it is not commercially available.[9]

In summary, although they appear to be reasonably safe, there is uncertainty about which dopamine agonist, when needed, is the best option in the management of antipsychotic induced hyperprolactinemia. The real incidence of psychosis exacerbation for cabergoline and bromocriptine is simply unknown. We urge clinicians to communicate adverse reactions to the corresponding Pharmacovigilance centre. ✤

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