A Comparative Study on the Effect of Vitamin B6 and Cabergoline in Preventing Risperidone-Induced Hyperprolactinemia in Adolescent Female Wistar Rats

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Data Note

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Abstract

Context:
Hyperprolactinemia is a common side effect of antipsychotic medications, including risperidone, resulting from the blockade of dopamine receptors in the hypothalamus. This condition can lead to various complications, emphasizing the need for effective preventive measures.

Objective:
This study aimed to investigate the efficacy of Vitamin B6 supplementation and compare it with Cabergoline administration as a preventive measure for risperidone-induced hyperprolactinemia.

Design, Setting, Patients, and Intervention:
An experimental study was conducted using inbred adolescent female Wistar rats. The rats were divided into four groups: Control, Standard (risperidone only), Test 1 (risperidone + Vitamin B6), and Test 2 (risperidone + Cabergoline). The interventions were administered orally for 14 days.

Outcome Measures:
The primary outcome measure was the serum prolactin level, assessed using the Elisa method and the Elabscience Rat PRL Elisa Kit.

Results:
The results showed that Vitamin B6 and Cabergoline significantly reduced serum prolactin levels compared to the standard group ($p < 0.05$). However, Vitamin B6 supplementation exhibited a slightly greater reduction (60%) than Cabergoline (75%).

Conclusion:
Vitamin B6 supplementation may be an effective preventive measure for risperidone-induced hyperprolactinemia. It demonstrated comparable efficacy to Cabergoline but with the advantage of being more affordable and having fewer side effects. Further research is warranted to validate these findings in human populations and explore the feasibility of Vitamin B6 as a prophylactic measure for antipsychotic-induced hyperprolactinemia.

Introduction:

Hyperprolactinemia is a prevalent endocrinological syndrome that affects both males and females. It can be categorised into two types: organic and functional hyperprolactinemia. Stellar, parasellar lesions, pituitary adenomas which include Prolactinoma, Growth hormone/PRL-secreting adrenocorticotropic hormone/ PRL-secreting adenomas come under Organic hyperprolactinemia with serum prolactin levels over 200 microgram/L. Non pituitary neoplasias and various infiltrative conditions such as craniopharyngioma, sarcoidosis, vascular malformations, pituitary metastases or non-functioning adenomas which may compress the pituitary stalk are amongst many other causes. On the other hand, functional hyperprolactinemia occurs during pregnancy and is frequently observed in conditions such as renal failure, polycystic ovary syndrome (PCOS), hepatic cirrhosis, intake of drugs, hypothyroidism, chest wall lesions, idiopathic causes and renal or lung tumours. In these cases the levels are usually less than 200 microgram/L in which first line treatment with dopaminergic drugs prove to be successful. Surgical management and subsequently radiotherapy are alternative choices when first line treatment fails. (1,2).

The cell bodies of Tuberoinfundibular dopaminergic neurons located in the Arcuate nucleus with their terminals reaching the external layer of Medial eminence increases its activity when exposed to high levels of Prolactin levels for a short period of time, which is shown by increased dopamine secretion and release which is also enhanced by tyrosine hydroxylase activity in the stalk of the Medial eminence (3).

Some of the drug classes that may cause hyperprolactinemia include Antihypertensives (Verapamil, Alpha-Methyldopa), Antidepressants (MAO inhibitors, Tricyclic and tetracyclic agents, SSRI), Opiates (Methadone, Morphine), Antiemetics (Metoclopramide, Domperidone), and other agents such as Estrogens, Cocaine and Cimetidine (1).

One of the significant contributors to hyperprolactinemia is the use of antipsychotic medications (Phenothiazines, Haloperidol, Resperidone, Reserpine). This occurrence is attributed to the ability of antipsychotics, including risperidone, to block D2 receptors on lactotrophs in the anterior pituitary gland (4,5). Dopamine, an essential inhibitory factor for prolactin secreted in the hypothalamus,traverses via the portal venous system, binds to D2 receptors on lactotrophs tonically suppressing the secretion of prolactin. Antipsychotics can replace dopamine by blocking these receptors, resulting in the removal of dopamine's inhibitory effect and subsequent hyperprolactinemia (6,7).

Risperidone, an atypical antipsychotic belonging to the benzisoxazole derivative class, antagonises both dopaminergic and serotonergic receptors, particularly the D2 and 5-HT2 subclasses (8). Clinical studies have shown that risperidone-induced hyperprolactinemia is present in approximately 91% of patients (9). Elevated prolactin levels can lead to decreased secretion of oestrogen and testosterone, potentially causing complications such as osteoporosis and sexual dysfunction (4).

The prevalence of hyperprolactinemia varies among different populations. In individuals without pre-existing psychiatric disorders, the prevalence is around 0.7% in men and 2.5% in women. However, psychiatric patients receiving antipsychotic treatment have a much higher prevalence, ranging from 30% to 70% in Western and Asian countries (10). Moreover, studies have shown a higher prevalence of hyperprolactinemia in women of reproductive age compared to postmenopausal women and men (11). Additionally, recent research suggests that hyperprolactinemia is more common in patients receiving treatment for psychosis and bipolar disorders compared to those receiving treatment for depression and anxiety (4).

Hyperprolactenemia may result in hypogonadism, infertility or galactorrhea. Lactotropic effect of PRL in women and mammotropic action of PRL in men cause Galactorrhea. The clinical presentations are gender specific. Women often present with issues in their cycles, such as anovulatory cycles (due to inhibition of the pulsar isle secretion of LH and FSH), changes from normal bleeding such as oligo and amenorrhea, dyspareunia, hirsutism, premenstrual syndrome and are prone to higher incidences of anxiety and depression. Men, however present with very subtle symptoms and are only diagnosed at an advanced stage. They present with symptoms like impotence, loss of libido, gynecomastia and galactorrhea. Decrease in the bone density occurs secondary to hyperprolactinemia mediated sex steroid attenuation. Approximately 25% of total women with hyperprolactinemia have a decrease in bone density of the Spine. Patients also have altered body composition with decreased lean mass and an increase in fat mass (1,7).

Managing serum prolactin levels often involves reducing the dosage of antipsychotic drugs to prevent or alleviate hyperprolactinemia. If dosage reduction is not feasible, conventional approaches include administering bromocriptine, which can lower prolactin levels. Other agents used in hyperprolactinemia management include amantadine (a dopamine agonist), clozapine, and traditional herbal agents such as Shakuyaku-kanzo-to-to and the Chinese formula Longdan Xiegan Tang, which have shown positive effects in animal studies (8,12).

Among the available options, cabergoline, a long-acting dopamine agonist, has demonstrated superior effectiveness compared to bromocriptine. Cabergoline not only reduces prolactin levels but also offers increased tolerance and restores normal gonadal functions. Its longer half-life allows for once or twice weekly administration, promoting better patient compliance. Conversely, vitamin B6, another alternative, exhibits a slightly lower rate reduction (60%) compared to cabergoline (75%).

However, vitamin B6 is advantageous due to its affordability, accessibility, and minimal side effects, which typically disappear upon discontinuation [9]. The most probable mechanism for use of Vitamin B6 might be due to the action of pyridoxal phosphate, a coenzyme of DOPA decarboxylase, promoting the conversion of intraneuronal preformed DOPA to dopamine. The experimental findings by Kamberi et al. Further cement this theory by proving that an increase in dopamine concentration in the hypothalamus leads to inhibition of prolactin, most probably by stimulating the prolactin inhibiting factor (13,14).
It is worth noting that high doses of cabergoline over a prolonged period can lead to valvular regurgitation, while lower doses are associated with mild to moderate tricuspid regurgitation (15,16). Additionally, rare adverse events, such as erythema nodosum and arthritis, have been reported with cabergoline administration (17,18).
This article aims to explore strategies for improving the management of Risperidone-induced hyperprolactinemia. It will discuss the efficacy of different treatment options, including cabergoline and vitamin B6, in reducing prolactin levels and mitigating associated complications. Additionally, the potential use of dopamine agonists as a prophylactic measure for hyperprolactinemia in specific populations will be examined.

Methodology:

Experimental Procedure:

A total of 24 inbred adolescent (3 weeks old) female Wistar rats, with weights ranging from 50g to 150g, were obtained from the Central Animal House, Madurai Medical College . These rats were housed in a laboratory room under controlled conditions for a two-week acclimatization period. The laboratory room was maintained at a constant temperature of 22°C. During this acclimatization period, the rats were provided unrestricted access to tap water and standard laboratory feed to adapt to their new environment.

For the duration of the 18-day experiment, the rats were individually housed in separate cages based on their assigned groups. Group I (Control) received the normal feed orally. Group II (Test 1) received normal feed, an oral administration of risperidone (5 mg/kg/day) daily, and an oral administration of cabergoline (0.6 mg/kg) on the 12th day. Group III (Test 2) received normal feed, an oral administration of risperidone (5 mg/kg/day), and vitamin B6 (200 micrograms) daily. Group IV (Standard) received normal feed and an oral administration of risperidone (5 mg/kg/day) daily.

The groups received their respective treatment for 17 days (19). Since 17 rat days equals 1.5 human years, this was done to replicate the long-term sustained side effects of risperidone (20). On the 18th day, rats were under general anaesthesia and via a cardiac puncture blood samples were collected . Centrifugation of the blood samples at 3000 rpm were performed to separate serum, and the serum prolactin levels were measured using the Elisa method with the Elabscience Rat PRL Elisa Kit.

The rats in the standard group (Group IV) continued to receive vitamin B6 for an additional two weeks, this was done to rehabilitate the rats from the sustained action of risperidone (20). Serum prolactin levels were measured again on the 40th day. This is to ensure the safety of the rats and allow them to recover their total blood volume (21).

Throughout the entire experimental period and the subsequent two-week follow-up period, all rats were closely monitored for any potential side effects that may arise. The research protocol and experimental procedures have undergone thorough review and approval by the local Institutional Animal Ethics Committee (IAEC) to ensure adherence to ethical guidelines and the welfare of the animals [IAEC- 06/22].

Disclaimer:

All animal experimentation described was conducted in accordance with accepted standards of humane animal care, as outlined in the Ethical Guidelines. All research animals were acquired and used in compliance with federal, state, and local laws and institutional regulations. All animals were maintained in accordance with the Guide for the Care and Use of Laboratory Animals [1996 (7th ed.) Washington, DC: National Research Council, National Academies Press]. All research animals received appropriate tranquilizers, analgesics, anesthetics, and care to minimize pain and discomfort during preoperative, operative, and postoperative procedures. The choice and use of drugs were made in accordance with the NRC Guide.

Chemical Substances:

The following chemical substances will be used in the study:

1. Risperidone (5 mg/kg/day)
2. Vitamin B6 (200 mcg/day)
3. Cabergoline (0.6 mg/kg - single dose) These substances will be dissolved in appropriate vehicles, such as 0.2% acetic acid, distilled water, and sesame oil, for oral administration via a special feeding tube.

Experimental Groups:

GROUP	STUDY	TREATMENT(X 14Treatment (X 14 days) days)
I	CONTROL	Normal feed orally.
II	TEST 1	Normal feed, Tab risperidone(5 mg/kg/day) and Vit B6 (200 micrograms)
III	TEST 2	Normal feed, Tab risperidone(5 mg/kg/day) and Tab Cabergoline (0.6 mg/kg)
IV	STANDARD	Normal feed and Tab risperidone (5 mg/kg/day)

Fig1.

Hormone Assay:

After collecting the blood samples, they will undergo centrifugation to separate the serum. The serum prolactin levels will be quantified using a Sandwich ELISA Kit, specifically the Elabscience Rat PRL Elisa Kit. This assay will be performed following the standardized protocols provided by the manufacturer, ensuring accurate and reliable measurements of prolactin levels in the serum samples.

Statistical Analysis:

The collected data will undergo thorough statistical examination through SPSS 20 software. Summary statistics like calculating averages and standard deviations will be used. To evaluate variable differences, a one-way ANOVA will be conducted, followed by relevant post hoc tests. The chi-square test will be used for categorical data. A significance threshold of $p < 0.05$ will be applied to establish statistical significance, ensuring dependable result interpretation.

Results:

						EXTENDED ARM	
Group	**Study**	**Treatment**	**Test Subject**	**Prolactin Levels (DAY 18) ng/ml**	**Average Prolactin Levels (DAY 18) ng/ml**	**Prolactin Levels (DAY 40) ng/ml**	**Average Prolactin Levels (DAY 40) ng/ml**
I	**Control**	**Normal Feed Only**	1	7.54	8.73	NA	NA
			2	10.08			
			3	8.65			
			4	8.54			
			5	9.68			
			6	7.9			
II	**Test I**	**Normal Feed + Tab. Risperidone (5 mg/kg/day) + Vit. B6 (200 micrograms)**	7	5.46	5.85	NA	NA
			8	7.34			
			9	4.72			
			10	5.98			
			11	4.89			
			12	6.74			
III	**Test II**	**Normal Feed + Tab. Risperidone (5 mg/kg/day) + Tab. Cabergoline (0.6 mg/kg Single Dose)**	13	7.24	6.45	NA	NA
			14	4.59			
			15	7.87			
			16	6.98			
			17	5.43			
			18	6.59			
IV	**Standard**	**Normal Feed + Tab. Risperidone (5 mg/kg/day)**	19	37.15	32.49	5.89	6.04
			20	28.96		5.45	
			21	34.96		6.47	
			22	26.49		-	
			23	35.95		6.35	
			24	31.46		-	

Table 1:

Average prolactin levels on day 18 were in the normal range for Group I, Group II and Group III with values 8.73 ng/ml, 5.85 ng/ml and 6.45 ng/ml respectively. For Group IV Average Prolactin level was

32.49 ng/ml corresponding to Hyper prolactinemia. For the extended arm of Group IV on Day 40 Average Prolactin levels returned to Normal i.e 6.04 ng/ml. (During estimated of Prolactin levels on Day 40 there was a technical error that resulted in Error in Prolactin levels for Test subject 22 and 24)

Discussion:

Elevated levels of prolactin are commonly observed in individuals of all genders who experience irregular sexual and reproductive functions or exhibit galactorrhea. If the serum prolactin concentrations measure higher than 200 micrograms/L, it's highly probable that a pituitary adenoma is the root cause. Yet, if the levels are lower, potential alternative factors encompass drug usage, compression of the pituitary stalk, underactive thyroid, kidney impairment, chest wall abnormalities, liver cirrhosis, or unknown origins. In many patients, first-line treatment with dopaminergic drugs proves to be successful. Surgical management and, subsequently, radiotherapy are alternative choices when first-line treatment fails (2).

The cell bodies of Tuberoinfundibular dopaminergic neurons located in the Arcuate nucleus with their terminals reaching the external layer of Medial eminence increases its activity when exposed to high levels of Prolactin levels for a short period of time, which is shown by increased dopamine secretion and release, which is also enhanced by tyrosine hydroxylase activity in the stalk of the Medial eminence. In a study performed by Puliyur S. Mohankumar et al., exposure of the rats (Sprague – Dawley) to Haloperidol induced hyperprolactinemia for a period of 6 months resulted in an increased Tuberoinfundibular dopaminergic neuron activity and 84% increase in dopamine concentration in the Medial eminence as opposed to only 50% increase when exposure was extended to 9 months after which there is no further increase even when the duration is increased. This effect is due to the suppression of Tuberoinfundibular dopaminergic neuronal function by chronic hyperprolactinemia which decreases the gene explores ion and activity of Tyrosine Hydroxylase, which results in lowered dopamine levels at the terminals of these neurons (2) .

The present study aimed to investigate potential preventive measures for Risperidone-induced hyperprolactinemia (AIHP) and compare the effectiveness of Vitamin B6 supplementation and Cabergoline administration. Hyperprolactinemia is a common side effect of Risperidone treatment, affecting approximately 30% of cases. The reason for this adverse reaction is linked to Risperidone's ability to oppose the D1 receptor group. This results in the obstruction of the Mesolithic pathway, the limbic pathway in the prefrontal cortex, and the tuberoinfundibular pathway within the Central Nervous System. This blockade removes the inhibitory effect of dopamine, resulting in increased secretion of prolactin (9).

In an earlier study conducted by Johan Verhelst and Roger Abs concerning the pathophysiology and management of Hyperprolactinemia, findings from comparing plasma half-life indicate that Cabergoline emerges as the most preferable dopamine agonist, with Quinagolide ranking next in line. However, data on the safety of pregnant women is still unavailable (9).

In a significant retrospective analysis, 92% of 244 individuals with macroprolactinomas saw their Prolactin levels return to normal, along with 77% of 181 patients with microprolactinomas. Among 110 patients with macroprolactinomas, tumor sizes reduced by 89%, and a substantial proportion of patients experienced more than 50% reduction. Cabergoline treatment has also proven efficacy in cases of giant prolactinomas, showcasing remarkable tumor shrinkage (22–24).

In a specific instance discussed by Yang Guo and colleagues (Case Report: Pyridoxine as a remedy for hyperprolactinemia and amenorrhea induced by quetiapine), the study conveyed that starting with Quetiapine at 0.2 g taken twice daily, combined with pyridoxine at 30 mg taken three times daily, and subsequently adjusting to Quetiapine at 0.2 g twice daily along with pyridoxine at 20 mg twice daily, effectively relieved symptoms of hyperprolactinemia while maintaining stability in schizophrenia status (25).

In the present study, Vitamin B6 was evaluated as a potential preventive measure for AIHP. To compare the efficacy of Vitamin B6 and Cabergoline, a specific D2 dopamine receptor agonist, the experiment incorporated four groups. Group 1 functioned as the reference group, whereas Group 2

was administered solely with Risperidone. In contrast, Group 3 was given Risperidone in combination with Vitamin B6 supplementation, and Group 4 received Risperidone alongside the administration of Cabergoline. The levels of prolactin were measured in each group, and Group 3 exhibited the lowest levels of prolactin, suggesting that Vitamin B6 supplementation may be more useful than Cabergoline in preventing hyperprolactinemia.

Equivalent research has also delved into different strategies for addressing AIHP. Xiaoquin Huang and colleagues examined the potential of Paeoniflorin in mitigating hyperprolactinemia induced by antipsychotics, accomplished by safeguarding the D2 receptor and TGF-B1 signaling pathways from impairment (26). Meanwhile, Liying Ren and co-researchers explored the impacts of Longdan Xiegan Tang, a traditional Chinese formulation, on restoring the TGF-B1 signaling within the hypothalamus and pituitary in rat subjects (12). Furthermore, Wang D et al. conducted an experiment demonstrating that 18B-Glycyrrhetinic acid suppresses prolactin hyperactivity and reduces AIHP in in-vivo and in vitro models (27).

In a study performed by M.T. Yakub and H.T. Fayemo aimed at investigating the impact of a water-based extract from the roots of Uvaria Chaman on hyperprolactinemia in female Wistar rats, the findings indicated that the root extract displayed noteworthy anti-hyperprolactinemia effects. This was evident through the restoration of typical prolactin and dopamine levels, along with the reestablishment of the female tubule-alveolar pattern in the rats. Additionally, the extract mitigated the alterations induced by chlorpromazine in the liver and kidney function indices (7).

The present study's findings suggest that Vitamin B6 may be a more favorable alternative than Cabergoline for reducing AIHP. Vitamin B6 is easily accessible and has fewer side effects compared to Cabergoline, adding to its credibility as a potential preventive measure.

In a study conducted by Chaunjun et al. Vitamin B6 has certain advantages in that patients taking this had lower levels of Triglycerides and cholesterol. Vitamin B6 also had better effects on cognition. The mechanism behind improved Positive and Negative Syndrome Scale scores (PANSS scores) is unknown. However, the probable neuroprotective and anti-inflammatory effects of the Vitamin may increase the scores. However, side effects such as drowsiness, constipation, akathisia, hydro-stomia, transient arrhythmia, and orthostatic hypotension may occur. Therefore, physicians must be vigilant when administering high doses of Pyridoxine (17). However, these side effects are transient and mostly resolve once drug intake is stopped or these effects can be avoided by taking the activated form of B6 (50-200 mg of pyridoxine five phosphate) or 300-1000 mg of pyridoxine hydrochloride in divided doses (28).

However, it is essential to highlight that the research was carried out using Wistar rats in their adolescent stage, specifically female subjects, emphasising the need for further research to determine the accuracy and feasibility of these results in humans, especially in different populations and age groups.

One significant drawback of this research is the limited number of participants, which could restrict the applicability of the results to a broader context. Furthermore, the study did not assess the dopamine levels within the rats, an aspect that could have offered additional understanding about the mechanisms responsible for the preventive outcomes of Vitamin B6. Future studies should consider increasing the sample size and measuring the levels of homovanillic acid, a metabolite of dopamine, using HPLC methods to enhance the comprehensiveness of the analysis.

Conclusion:

In conclusion, this study highlights the potential of Vitamin B6 supplementation as a preventive measure for Risperidone-induced hyperprolactinemia. The results suggest that Vitamin B6 may be more effective than Cabergoline in reducing prolactin levels. However, further research, including studies with larger sample sizes and additional measurements, such as dopamine levels and homovanillic acid levels, is warranted to validate these findings and assess the feasibility of Vitamin B6 as a prophylactic measure for AIHP in individuals taking antipsychotic medications.

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