

TO STUDY THE EFFECT OF THE PARENTERAL ADMINISTRATION OF CIMETIDINE ON SERUM PROLACTIN LEVEL IN EXPERIMENTAL ANIMALS

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ABSTRACT

BACKGROUND

Among the H₂ receptor antagonists, Cimetidine promotes healing of peptic ulcer and reduces ulcer pain, but produces a few significant side effects- gynaecomastia, galactorrhoea, etc. H₁ antagonists and H₂ agonists suppress prolactin release in suckled mother, while H₁ agonists and H₂ antagonists release prolactin in non-suckled mother.² The relationship between H₂ receptor inhibitory and H₁ receptor stimulant for the raise or decrease of serum prolactin level and also for involvement of third ventricle in hypothalamus area is to be investigated.

MATERIALS AND METHODS

The present study was to ascertain the site of action of Cimetidine for the raised serum prolactin, whether peripheral action or central action. Therefore, the route of administration of the H₂ receptor antagonist Cimetidine was chosen as intravenous and intracerebroventricular respectively. Finally, serum prolactin level was estimated by drawing blood from the ear vein of the experimental animal (Rabbit) every 15 mins, 30 mins and 45 mins respectively. Then, serum prolactin levels were compared and analysed statistically.

RESULTS

The serum prolactin level was found significantly raised at 15 mins ($p < 0.05$) and 30 mins ($p < 0.001$) after the IV Cimetidine. However, there is no significant difference between IV Cimetidine and ICV Cimetidine pre-treated group as Diphenhydramine blocked H₁ receptor.

CONCLUSION

So, it can be concluded that Cimetidine causes raise in serum prolactin level due to its peripheral and central action.

KEYWORDS

Prolactin, Cimetidine, Diphenhydramine, Intracerebroventricular, Radioimmunoassay, Rabbits.

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BACKGROUND

The involvement of histamine in controlling of gastric acid secretion was supported with the discovery of specific inhibitor of H₂ receptor on parietal cells. The role of histamine and its pharmacological importance has increasingly come to light after which the characterisation of H₂ receptor antagonists- Burimamide, Metiamide and Cimetidine.¹ Among the H₂ receptor antagonists, Cimetidine promotes healing of peptic ulcer and reduces ulcer pain, but produces a few significant side effects- gynaecomastia, galactorrhoea, etc. H₁ antagonists and H₂ agonists suppress prolactin release in suckled mother, while H₁ agonists and H₂ antagonists release prolactin in non-suckled mother.² The relationship between H₂ receptor inhibitory and H₁ receptor stimulant for the raise or decrease of serum prolactin level and also for involvement of third ventricle in hypothalamus area is to be investigated.³

There is a report that the parenteral administration of Cimetidine produces many changes in hormone profile.^{4,5} The rise in prolactin secretion after IV Cimetidine is widely agreed, but the mechanism of action is still unclear.⁶ Even though there were many reports of raised prolactin level with many side effects,⁷ only a few case of raised prolactin level is related with Cimetidine administration.⁸ But the effect of the newer H₂ receptor antagonists Ranitidine does not produce the rise in serum prolactin level even after IV Ranitidine.⁹

MATERIALS AND METHODS

This randomised, controlled study was conducted in the Postgraduate Department of Pharmacology, the Nuclear Medicine and RIA unit of the Postgraduate Department of Medicine and Therapeutics, SN Medical College, Agra as part of dissertation of Postgraduate study.

Grouping of Animals

Twenty-four adult albino rabbits (1 - 2 kg) of either sex were fed on chana and green vegetables for two weeks before starting the study. The animals were randomly grouped (six rabbits in each group).

- IV Cimetidine group.
- IV Cimetidine pre-treated with Diphenhydramine group (DH).
- ICV Cimetidine group.
- ICV Cimetidine pre-treated with Diphenhydramine group.

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Selected Time for Collection of Sample

Pre-drug blood samples for estimation of prolactin level were collected between 11 am to 1 pm as the stabilisation of prolactin level for several hours is recorded after 10 am.¹⁰

Chemical Used

- Cimetidine (Pharma, Research Dept., Glaxo Group).
- Diphenhydramine HCL.
- Reagents and radioactive materials for radioimmunoassay of prolactin (Dr. AF Parlow, Los Angeles, USA).
- Sodium Azide 0.1% solution.

Collection and Storage of Samples

5 mL of blood samples were collected from each animal with clean and dry syringes taking all precautions to avoid haemolysis. The samples were transferred to a clean dry test tube of 8 mL. After 10 mins, the serum was separated and transferred to the clean vials (approx. 2.5 mL serum). 1-2 drops of 0.1% sodium azide solution was added to the serum and the resultant sample were stored at 2°C deep freezer.

Implantation of Intracerebroventricular (ICV) Cannula

ICV cannulas were implanted to twelve rabbits (Group C and D) under Urethane anaesthesia (0.5 - 1 gm/kg).¹¹

Administration of Cimetidine

Group A (Intravenous Cimetidine Treated Group)

Six rabbits were injected Cimetidine 50 mg/kg intravenously.¹² Samples of blood were collected at 15 mins, 30 mins and 45 mins respectively from ear vein as the raised prolactin level was repeatedly observed after 10 - 45 minutes of IV Cimetidine therapy.

Group B (IV Cimetidine and Diphenhydramine Treated Group)

Six rabbits were pre-treated intravenously with Diphenhydramine HCL at a dose of 7.5 mg/kg.¹³ After one hour, the same rabbits were again injected Cimetidine (50 mg/kg) intravenously.¹² Samples of blood were drawn at 15 mins, 30 mins and 45 mins respectively as done in Group A.

Group C (ICV Cimetidine Treated Group)

Six rabbits were administered Cimetidine (50 mg/kg) through ICV cannulas after withdrawing the same amount of ventricular fluid.¹⁴ Blood samples were collected at 15 mins, 30 mins and 45 mins after the infusion of Cimetidine as done in Group A.

Group D (ICV Cimetidine and Diphenhydramine Treated Group)

Six rabbits were pre-treated with Diphenhydramine HCL (7.5 mg/kg) through the ICV cannula, after withdrawal the same amount of ventricular fluid¹⁵ prior to the ICV infusion of Cimetidine. After one hour, Cimetidine (50 mg/kg) was infused through the ICV cannula as in case of Group C.¹⁴ Then blood samples were collected at 15 mins, 30 mins and 45 mins as done in Group A.

RIA of Prolactin

The estimation of serum prolactin level was done by using the protocol of WHO Radioimmunoassay (3rd edition January

1981).¹⁶ The level of prolactin was measured by using the EGL ZRS-23 Scintillation Gamma Counter. The observations of the Prolactin levels were expressed as mIU/L.

Statistical Analysis

The data were expressed as Mean \pm SD. Comparison between two means was carried out by one-way analysis of variance (ANOVA) supplemented with Dunnett's 't' test by using SPSS software version 10, where $p < 0.05$ was considered significant.

RESULTS

The serum prolactin levels in normal rabbits treated with IV Cimetidine (Group A) was 1873.16 \pm 543.04, 2147.33 \pm 393.77 and 1550.5 \pm 398.59 at 15, 30 and 45 mins respectively. The rise in prolactin level was maximum at 30 mins and was statistically significant ($p < 0.01$) when compared with the prolactin level of the own control (1165.33 \pm 95.3).

The serum prolactin level in pre-treated rabbits treated with IV Cimetidine (Group B) were 1231.16 \pm 628.31, 1399.66 \pm 484.77 and 1117.16 \pm 158.49 at 15, 30 and 45 mins respectively. The level of the prolactin is slightly increased when compared with the own control 1040 \pm 135.36, but not significant.

The serum prolactin level in normal rabbits treated with ICV Cimetidine (Group C) were 1446.50 \pm 274.48, 1449.30 \pm 583.82 and 984.5 \pm 78.09 at 15, 30 and 45 mins respectively. There was raise in prolactin level at 15 and 30 mins when compared with own control 1204.16 \pm 247.48, but the raised level was not significant.

The serum prolactin level in pre-treated rabbits treated with ICV Cimetidine (Group D) was 1200.16 \pm 231.12, 1570.5 \pm 746.46 and 1183 \pm 348.83 at 15, 30 and 45 mins respectively. There is considerable raise of prolactin level at 30 mins when compared with own control (1187.33 \pm 296.78), but this raise in prolactin level is insignificant.

Group	Time Interval in Minutes			
	0 (Before any Drug)	15 mins	30 mins	45 mins
IV Cimetidine	1165.33 \pm 95.3	1873.16 \pm 543.04*	2147.33 \pm 393.77**	1550.5 \pm 398.59 ^a
IV Cimetidine + DP	1040 \pm 135.36	1231.16 \pm 628.31	1399.66 \pm 484.77	1117.16 \pm 158.49 ^b
ICV Cimetidine	1204.16 \pm 247.48	1446.5 \pm 274.48	1449.33 \pm 583.82	984.5 \pm 78.09 ^b
ICV Cimetidine + DP	1187.33 \pm 296.78	1200.16 \pm 231.12	1570.5 \pm 746.46	1183 \pm 348.83 ^b

Table 1. Mean Serum Prolactin Level (mIU/L) of Control Intravenous, Intracerebroventricular Therapies of Cimetidine

*DP- Diphenhydramine.

Each value is expressed as mean \pm SD of six observations. * $p < 0.05$, ** $p < 0.01$ when compared with corresponding values of its control group.

Within a column means marked with different superscript letters are significantly different (* $p < 0.05$) as analysed by Tukey-Kramer multiple comparisons test.

DISCUSSION

Measurement of serum prolactin level was done with the method of RIA.¹⁵ The technique is very sensitive, precision, specificity and accuracy.¹⁷ Daily and Diurnal variation in prolactin level could not document as only single blood sample was collected between 10 am – 1 pm as stabilisation of prolactin level for several hours occurs after 10 am.¹¹

The estimated serum prolactin level in normal rabbits ranged from 650 mIU/L to 2142 mIU/L and the mean level was respectively 1356.03 ± 532.09 mIU/L.

The serum prolactin levels estimated in rabbits after parenteral therapy of cimetidine were significantly raised on 30 mins (IV). These findings supported the observations of Bateson et al,¹⁸ Burland et al,⁴ Carlson et al,¹⁹ Winter et al,²⁰ Penden et al²¹ and Nelis et al.⁶ The prolactin levels in pre-treated rabbits were found insignificantly raised on statistical analysis (Diagram).

The observation may show a clue for finding the mechanism of action of Hyperprolactin due to IV Cimetidine administration, i.e. peripheral and central action as Cimetidine crosses the Blood Brain Barrier (Asseis et al,²² Majumdar et al,²³ Spiegel et al,²⁴ Schentag et al²⁵) and that of ICV Cimetidine was only to central action. Lastly, Cimetidine produces Hyperprolactinaemia whether IV or ICV, but the hyperprolactinaemia through ICV is less significant because the role of H1 receptor which is blocked by DP is involved.

CONCLUSION

The study was an effort for finding the mechanism of Hyperprolactinaemia with the synthetic H2 receptor antagonist Cimetidine during the parenteral administration. The present observations may support the action of Cimetidine, which can cross Blood Brain Barrier for producing hyperprolactinaemia through peripheral and central actions.

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