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Role of H2 Histamine Receptor Blockers for Anti-Implantation Activity in Rats.

Abha Upadhyay and Deepak Kumar Mittal
School of Studies in Zoology, Jiwaji University, Gwalior, India

Abstract

To study the anti-implantation activity of H(2) receptor blockers ranitidine and famotidinein combination, considering the role of histamine and prostaglandins in implantation.The drugs were administered orally to female albino Wistar rats at different dose levels for 1 2 and 4 weeks, immediately after confirming copulation by observing sperm in the vaginal smear. A laparotomy was done on the 1-4 weeks of pregnancy, the implants and corpora lutea were counted, and the pre and post implantation losses determined. The mast cell stabilising activity was studied using in vivo methods.Ranitidine and famotidine150 and 300 mg/kgshowed significant anti-fertility activity. No increase in activity was seen at higher doses.Our results indirectly confirm the combined involvement of histamine and prostaglandins in the implantation process. The mast cell stabilising property of H(2) blockers appears to be a possible mechanism for their anti-implantation activity.

Keywords: Antiimplantation, Ranitidine, Famotidine, Female Rats.

Introduction

Histamine plays an important role in implantation and decidualization and its inhibition may result in the insult of blastocyst attachment on 5th day of gestation in rats. It has reported that histamine is released by uterine mast cells. Histamine works via at least three histamine receptor subtypes H_1, H_2 and H_3. It is interesting to note that most of histamine receptor blocking agents like famotidine and ranitidine are useful against gastric ulceration.[1] The role of H_1 and H_2 histamine receptor blockers on the implantation and during various periods of gestation are not fully understood. The use of H_2 antagonists by pregnant women is not frequent as it may induce fetal toxicity. These antagonists frequently used by pregnant and non–pregnant women to cure acidity, however, its use during pregnancy is not recommended.[2]

Implantation is a complex event that is precisely controlled and timed. The process of implantation in mammals is usually cyclic which initiates by interaction between blastocyst and uterine epithelium. The entire process of implantation is controlled by the hormones. The amount of hormones is so specific and kinetic that a little disturbance may imbalance the entire process which may result in the impairment of implantation.[3] In the eutherian mammals blastocysts are capable of effective two way communication to initiate the process of implantation. Uterine environment for implantation is able to support blastocyst growth, attachment and the subsequent events of implantation. The major factors include the ovarian steroids, progesterone and estrogen which play a key role in the beginning, development and termination of gestation.[4] The hormonal

regulation of uterine receptivity has long been established, the underlying mechanism of action however remains largely unknown.

The H_2-receptor antagonists (H_2RA, often shortened to H_2 antagonist) are a class of drugs used to block the action of histamine on parietal cells in the stomach, decreasing the production of acid by these cells.[5] H_2 antagonists are used in the treatment of dyspepsia, although they have largely been surpassed in popularity by the more effective proton pump inhibitors. In the United States, all four FDA-approved members of the group cimetidine, ranitidine, famotidine, and nizatidine are available over the counter in relatively low doses.[6]

Experimental design

Healthy virgin female rats of Wister strain (120 ± 10g) were selected from the animal colony. To evaluate the effect of H_2 receptor blockers on biochemical constituents in reproductive organs, doses were prepared as described under materials and methods. The rats were divided into different experimental and control groups and doses of 150 and 300 mg/kg were administered orally for 1, 2 and 4 weeks to experimental rats. Control animals received vehicle only. Thereafter, the treated and control female rats were caged with male rats of proven fertility in the ratio 2:1 for mating. Next morning, the vaginal smear of the female rats was examined for the presence of the spermatozoa and also for the vaginal plug and the day was designated as day 1 of pregnancy. Treatment was stopped. Animals were sacrificed on the 10^{th} day of pregnancy. Autopsy was performed. Ovary and uterus were excised, freed from adhering tissue, weighed on monopon balance to nearest of mg and processed for biochemical estimation of protein, glycogen and activity of acid and alkaline phosphatases as described under materials and methods. Biochemical results were analyzed statistically using student's 't' test.[7]

Results and Discussion

Effect on the wet weight

Table-1 shows the effect of famotidine on the wet weight of the ovary and uterus in the pregnant rats prior to mating. The administration of famotidine at 150 mg/kg dose for 1, 2 and 4 weeks prior to mating showed only marginal increase in the ovarian wet weight but all the values were statistically insignificant when compared to respective control.[8] The famotidine administered at 150 mg/kg dose for 1 week did not produce any change in the uterus, however, when administration was continued for 2 and 4 weeks significant reduction in wet weight of the uterus was observed. Similar types of results were observed in the wet weight of the ovary and uterus when famotidine was administered at 300 mg/kg dose for 1, 2 and 4 weeks.[9]

Table-2 summarizes the effect of ranitidine on the wet weight of the ovary and uterus in the pregnant rats. The administration of ranitidine at 150 mg/kg and 300 mg/kg doses for 1, 2 and 4 weeks prior to mating showed no significant change in wet weight of ovary in treated animals compared the respective control.[10] However significant decrease in wet weight of uterus could be observed at 150 mg/kg and 300 mg/kg doses after 2 and 4 weeks of treatment in comparison to unexposed rats.

Table-3 depicts the effect of combination of famotidine and ranitidine on the wet weight of the ovary and uterus in the pregnant rats. The combination of famotidine (75 mg/kg or 150 mg/kg) and ranitidine (75 mg/kg or 150 mg/kg) showed similar effects in the wet weight of the ovary and uterus when compared with the individual treatments of either famotidine (150 mg/kg or 300 mg/kg) or ranitidine (150 mg/kg or 300 mg/kg).

Fig. – 1, 2 and 3 reveals the percent change in the wet weight in ovary and uterus with respect to control. It reveals that percent in the ovary of experimental animal is almost the same. However, in uterus the percent change was same when dose was administered for 1 week. Whereas the percent change was more as compared to the dose administered for 2 and 4 weeks.[11] The percent difference was almost similar in the uterus when 150 and 300 mg/kg doses were administered for 1, 2 and 4 weeks. Highest percent changes were observed at 4 weeks treatment at 300 mg/kg dose.

Table-1- Effect of famotidine on wet weight of the ovary and uterus of rats treated prior to mating.

Treatment	Dose (mg / kg)	Duration of treatment (Weeks)	Ovary	Uterus
Control	-	-	57.6 ± 3.4	288 ± 19.7
Famotidine	150	1	62.4 ± 4.5	262. ± 13.4
		2	63.0 ± 5.8	171 ± 15.0*
		4	65.6 ± 4.3	188 ± 12.8*
	300	1	63.8 ± 4.7	264 ± 1 8.2
		2	64.4 ± 7.2	191 ± 15.4*
		4	66.8 ± 8.8	198 ± 14.1

Values are mean ± SE of 5 animals in each group and expressed as mg/100gm bodyweight. *P Versus control <0.05. Animals were administered daily 150 mg/kg or 300 mg/kg (*per oral*) famotidine for 1 week, 2 or 4weeks.

Table-2 - Effect of ranitidine on wet weight of the ovary and uterus of rats treated prior to mating.

Treatment	Dose (mg / kg)	Duration of treatment (Weeks)	Ovary	Uterus
Control	-	-	57.6 ± 3.4	288 ± 19.7
Ranitidine	150	1	63.8 ± 8.6	276 ± 19.6
		2	64.0 ± 4.5	188 ± 13.4*
		4	68.2 ± 4.6	197± 17.0*
	300	1	62.2 ± 6.9	281 ± 22.6
		2	64.8 ± 6.2	176 ± 15.1*
		4	68.4 ± 5.8	215 ± 17.6*

Values are mean ± SE of 5 animals in each group and expressed as mg/100gm body weight. *P Versus control <0.05. Animals were administered daily 150 mg/kg or 300 mg/kg ((*per oral*) ranitidine for 1 week, 2 or 4weeks.

Table-3 -Effect of combination of famotidine and ranitidine on wet weight of the ovary and uterus of rats treated prior to mating

Treatment	Dose (mg / kg)	Duration of treatment (Weeks)	Ovary	Uterus
Control	-	-	57.6 ± 3.4	288 ± 19.7
Famotidine + Ranitidine	75 + 75	1	63.4 ± 3.7	321 ± 10.5
		2	66.0 ± 3.8	186 ± 8.4*
		4	68.4 ± 4.3	229 ± 6.6*
Famotidine + Ranitidine	150 + 150	1	62.4 ± 3.4	315 ± 24.4
		2	61.8 ± 4.3	192 ± 18.1*
		4	61.0 ± 4.2	220 ±16.3*

Values are mean ± SE of 5 animals in each group and expressed as mg/100gm body weight. *P Versus control <0.05. Animals were administered daily 150 mg/kg and 300 mg/kg ((*per oral*) combination of famotidine and ranitidine for 1 week, 2 or 4weeks.

Table-4-Effect of famotidine on protein content of the ovary and uterus of rats treated prior to mating.

Treatment	Dose (mg / kg)	Duration of treatment (Weeks)	Ovary	Uterus
Control	-	-	12.1 ± 1.0	12.4 ± 1.2
Famotidine	150	1	13.0 ± 0.9	15.4 ± 1.0*
		2	13.2 ± 0.7	16.4 ± 0.8*
		4	13.8 ± 0.7	17.0 ± 0.8*
Famotidine	300	1	13.6 ± 1.0	15.6 ± 1.3*
		2	14.0 ± 1.2	16.8± 0.7*
		4	14.3 ± 1.2	17.5 ± 0.9*

Values are mean ± SE of 5 animals in each group and expressed as mg/100gm body weight. *P Versus control <0.05. Animals were administered daily 150 mg/kg and 300 mg/kg (*per oral*) famotidine for 1 week, 2 or 4weeks.

Table-5 - Effect of ranitidine on protein content of the ovary and uterus of rats treated prior to mating

Treatment	Dose (mg / kg)	Duration of treatment (Weeks)	Ovary	Uterus
Control	-	-	12.1 ± 1.0	12.4 ± 1.2
Ranitidine	150	1	12.8 ± 0.9	16.6 ± 0.9*
		2	13.3 ± 0.9	17.3 ± 0.9*
		4	13.6 ± 0.8	18.2 ± 1.3*
Ranitidine	300	1	13.5 ± 1.0	17.0 ± 1.4*
		2	13.9 ± 0.8	17.8 ± 1.1*
		4	14.1± 1.0	18.5 ± 1.2*

Values are mean ± SE of 5 animals in each group and expressed as mg/100gm body weight. *P Versus control <0.05. Animals were administered daily 150 mg/kg or 300 mg/kg (*per oral)* ranitidine for 1 week, 2 or 4weeks.

Table 4 and 5 show the effect of famotidine and ranitidine, respectively, on the protein contents in the ovary and uterus in the pregnant rats prior to mating. No appreciable change was observed in the protein content of the ovary after administration of famotidine or ranitidine at 150 and 300 mg/kg doses for 1, 2 and 4 weeks as compared to control.[12] However, uterus showed remarkable alteration. Its administration for 1, 2 and 4 weeks increased significantly the total protein contents in the uterus with both the drugs and doses evaluated. The combination of famotidine and ranitidine produced similar type of effect in the protein content of the ovary and uterus as observed in alone treatment with either famotidine or ranitidine.[13]

Conclusion

Combined involvement of histamine receptor blockers in the implantation process. The ranitidine and famotidine of H(2) blockers appears to be a possible mechanism for their anti-implantation activity.

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