

HISTOLOGICAL AND HISTOCHEMICAL EFFECTS OF  
ANTIHISTAMINIC DRUGS ON IMPLANTATION IN MOUSE

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ABSTRACT

Four potent antihistaminic drugs were used in this study, Diphenhydramine Hcl (Benadryl), Antazoline (Antistine) and Methdilazine Hcl (Tacaryl) when given systemically do not prevent implantation in mice, while promethazine (Phenergan) caused a failure of implantation in 60% of the used animals when given systemically. This may be due to the effect of this drug on the central nervous system. Almost all the antihistaminic drugs used in this study when given subcutaneously caused a failure of implantation in about 40% to 60% of the total used animals. When implantation of mouse blastocyst succeeds, no histological and histochemical changes of alkaline phosphatase acid phosphatase and glycogen content when compared to control group. On the other hand some changes were found in the distribution and intensity of alkaline phosphatase, acid phosphatase and glycogen content when implantation of mouse fails.

INTRODUCTION

Many agents can cause decidulization, Since histamine was first considered to be the induced of decidulization

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[6] . Shelesnyak [8] found that uterine histamine content and its concentration decreased between day 4 and 5 of pregnancy in rate. This decrease in concentration was correlated with depletion of endometrial mast cells. Sulman [9] showed that antihistaminic drugs instilled into the uterine lumen in pseudopregnant rates, would suppress the decidual response to endometrial trauma. Shelesnyak [7] stated that prothiozine HCL (Pyrrolazote) would prevent implantation in the injected uterine cornua of pregnant rats if applied during the first few days post coitum: However, when given subcutaneously had little effect on implantation. The interference with pregnancy being greatest when the drug was administered on days 8 to 10 after insemination. A few literature are available on the histological and histochemical changes after administration the antihistaminic drugs .

#### MATERIAL AND METHODS

In the present study four potent antihistaminic drugs were used I) Diphenhydramine HCL ( Benadryl) 2)Antazoline (Antistine) 3) Promethazine (Phenergan) 4)Methdilazine HCL (Tacaryl). 50 adult females mice Mus musculus were divided into five groups . They were mated with fertile males and the morning when spermatozoa were found in the vaginal was considered day I of pregnancy. The first group used as a control. Each group of the four groups of the

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animals was divided into two equal subgroup , each of which was treated systemically (Peritoneally) and the other treated subcutaneously. These animals were dosed with 1mg/Kg/day of aqueous solution of the above mentioned drugs, from post coitum until the fifth day of insemination [3]. After that the animals were anaesthetized and dissected, uterine cornua were removed. The specimens were fixed in 10% formaline clearing and embedding in paraffin wax was done as usual. Specimens were cut at 8 microns thickness. Four sections from each specimens were mounted and stained as follows:

- Section 1 stained with HX & E .
- Section 2 & 3 stained with Gomori method for alkaline and acid phosphatase .
- Section 4 stained with PAS .

### RESULTS

#### Control Group:-

The mouse blastocyst was implanted in the wall of the uterus at antimesometrial site (fig.1) .

Alkaline Phosphatase:- Appear as positive area around the blastocyst. The blastocyst, uterine glands and connective tissue corium showed a strong enzymatic reaction. (Fig. 2)

Acid Phosphatase:- The blastocyst, uterine gland showed

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a weak enzymatic reaction, while connective tissue corium showed a moderate one. (Fig. 3) .

Glycogen Content:- The blastocyst was surrounded by positive coat. Uterine gland and connective tissue corium contain a moderate amount (Fig. 4)

Effect of antihistaminic drugs on implanation in mouse:

Drug	Number of mice Injected I.P.		Number of mice Injected S.C	
	Treated	Pregnant	Treated	Pregnant
- Diphenhydramin Hcl (Benadryl )	5	5	5	2
- Antazoline (Antistine)	5	5	5	2
- Promethazine (Phenergan)	5	2	5	3
- Methdilazine Hcl (Tacaryl)	5	5	5	2

From the above table it was shown that Diphenhydramine Hcl (Benadryl), Antazoline (Antistine) and Methdilazine Hcl (Tacaryl) do not influence the implantation of mice when given systemically (Intraperitoneally) i.e on the fifth day of gestation the mouse blastocyst was implanted in the wall of the uterus at its antimesometrial

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region (Fig.5) Promethazine (Pheneragan) when given systemically causes failure of implantation of 60% of the total used animals (Fig.6). All antihistaminic drugs used in this study caused a failure of implantation in about 40% to 60% of the used animals when given subcutaneously.

No changes in the distribution and intensity of alkaline phosphatase acid phosphatase and glycogen content when implantation of mouse blastocyst succeeds on the other hand when implantation fails it was shown that some changes in the distribution and intensity of alkaline and acid phosphatase and glycogen content.

**Alkaline Phosphatase:-** Uterine gland and connective tissue corium showed a weak enzymatic reaction.

**Acid Phosphatase:-** Uterine gland and connective tissue corium showed a moderate enzymatic reaction.

**Glycogen Content:-** Uterine gland, connective tissue corium showed a weak reaction for PAS.

### DISCUSSION

From the data obtained in the present study it was shown that diphenhydramine Hcl (Benadryl), Antazoline (Antistine) and Methdilazine Hcl (Tacaryl) when given

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systemically do not prevent implantation in mice. The relative inefficiency of the drug when given systemically was attributed to its failure to reach the uterus sufficient concentrations [5]. Phenergran when given systemically cause a failure of implantation of about 60% of total used animals. This may be due to the effect of phenergran on C.N.S. Almost all antihistaminic drugs used in the present study cause a failure of implantation of about 40% to 60% of the total animal used when given subcutaneously . Similar results obtained by shelesyak and Davies [5]. When implantation of mouse blastocyst succeeds, alkaline phosphatase activity appear as positive area around the blastocyst , the blastocyst, uterine gland and connective tissue corium contain a moderate amount. This finding agrees with that obtained by Finn & Hinchliffe [1] who concluded that implantation chamber is surrounded by big amount of alkaline phosphatase which adjust permeability and absorption of cell membrane. Finn & McLaren [2] claimed that presence of alkaline phosphatase early mean increase cellular activity. When implantation fails this enzyme decrease in amount in uterine gland and connective tissue corium.

Also from this study it was shown that acid phosphatase present in small amount early in pregnancy, this mean that acid phosphatase has catabolic effect which leads to formation of decidua and implantation bed, early in pregnancy this enzyme gave a weak reaction [4] . When implantation

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fails this enzyme increase in concentration in uterine gland and connective tissue corium which may prevent the implantation of the embryo.

The blastocyst was surrounded by positive coat P A S reaction, also uterine gland and connective tissue corium contain a moderate amount of glycogen , when implantation succeeds . This means that glycogen is an important source of energy during expansion, hatching from the zona pellucida and during implantation in uterine wall. In contrast when implantation fails, this content of glycogen decreases.

#### REFERENCES

- 1- Finn, C.A & Hinchliffe J.R. (1965):- Histological & histachemical analysis of implantation chamber in mouse uterus. J. Rep. Fert. 9 301-309 .
- 2- Finn, C.A & Mc Laren, A (1967) :- Study of early stages of implantation in mice .  
J. Rep. Fert. 13: 259-267 .
- 3- Harper, M.J. (1965): Observations on amount and distribution of prenatal motility in albino rat.  
J. Rep. Fert. 7, 185 .
- 4- Schmidt, N. & Wendlr D. (1975) : Histochem. of placenta in rat. J. Folia Morpl. XII No. 3 ^268-271.
- 5- Shelesnyak, M.C & Davies, E (1955) Disturbance of pregnancy by systemic antihistaminic drugs. Proc. Soc. Exp. Biol. N. Y. 79, 752.

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- 6- Shelesnyak, M.C (1963): The role of oestrogen in nidation Proc. Nat. Acad. Sci. USA 69: 235-260.
- 7- Shelesnyak, M.C. (1967): Some experimental studies on the mechanism of ava implantation in rat. Recent Progr. Hormone Res. 13, 269.
- 8- Shelesnyak, M.C. (1969): Comparative effectiveness of antihistamines in suppression of the decidual cell reaction in pseudopregnant rat. Endocrin. 54. 396.
- 9- Sulman, F.G. (1965):- Effect of antihistamine drugs on nidation. Res. Coum. Israel, 4, 400.

## REFERENCES



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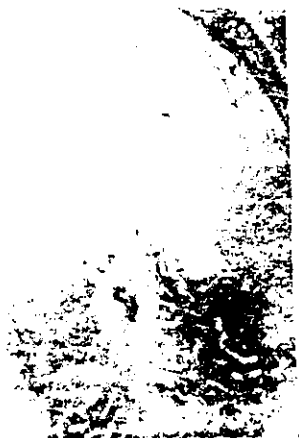
- (Fig. 1) T.S in mouse uterus at fifth day of gestation showing the implanted blastocyst. (X 70)
- (Fig. 2) T.S in mouse uterus at fifth day of gestation showing the distribution of alkaline phosphatase. (X 70)
- (Fig. 3) T.S in mouse uterus at fifth day of gestation showing the distribution of acid phosphatase. (X 70)
- (Fig. 4) T.S in mouse uterus at fifth day of gestation showing PAS positive reaction. (X 70)
- (Fig. 5) T.S in mouse uterus at fifth day of gestation after injection of Antistine (I.P.) (X 70)
- (Fig. 6) T.S in mouse uterus at fifth day of gestation after injection of phenergan (note normal uterus) (X 70)



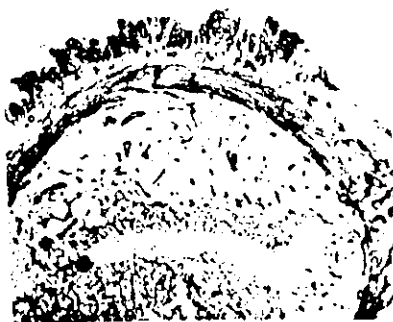
(Fig. 1)



(Fig. 2)



(Fig. 3)



(Fig. 4)



(Fig. 5)



(Fig. 6)

تأثيرات هستولوجية وهستوكيميائية لتأثير العقاقير المضادة  
للهستامين على عملية التصاق الجنين في  
الغار الابيض الصغير

أسامة أحمد شرف الدين - فوزية السعدي - عبد الموجود أنس اسماعيل  
من أقسام علم الحيوان - والهستولوجى بكلية العلوم والطب  
جامعتى الأزهر - وحلوان - مصر

استخدم فى هذا البحث أربع عقاقير مضادة للهستامين • قسمت  
الحيوانات الى خمسة مجموعات • استخدمت المجموعة ضابطة وقسمت  
كل مجموعة من المجموعات التالية الى مجموعتين متساويتين تم حقن الاولى  
داخل البريتونيم والثانية تحت الجلد بكل نوع من العقاقير المستخدمة  
فى هذا البحث • وقد خلصت النتائج الى الاتى :-

١- عقار بنادريل والانتستين وتكريل لا يحدث أى تأثير على عملية  
التصاق الجنين عند حقنه داخل البريتونيم وكذلك لا يحدث أى  
تغيرات هستولوجية أو هستوكيميائية لكل من أنزيمى الفوسفاتيز  
القلوى والحامضى وكذلك محتوى الجليكوجين •

٢- عقار الفنرجان يؤثر على عملية التصاق الجنين بنسبة ٦٠% وقد أرجع  
هذا السبب لكون هذا العقار يؤثر على الجهاز العصبى المركزى •

٣- كل العقاقير المضادة للهستامين المستخدمة فى البحث انا أعطيت  
تحت الجلد فأنها تؤثر على عملية التصاق الجنين بنسب تتراوح  
بين ٤٠ - ٦٠ % •

٤- فى الحالات التى يحدث فيها فشل لعملية التصاق بسبب تعاطى  
العقاقير المضادة للهستامين فإنه يحدث تغيرات هستولوجية  
وهستوكيميائية •