

THE EFFECT OF HISTAMINE AND SOME ANTIHISTAMINE IN THE MOTILITY OF HUMAN SEMIN⁺

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Abstract

The Effect of histamine and some Antihistamine in the motility of human semen were studied.

It shows that the histamine increases sperm motility, further more H₂ antihistamine cimetidine had no effect on sperm motility and classical antihistamines decreased sperm motility, where as the inhibition produced by H antihistamine could be overcome with increasing concentration of histamine.

Finally it is postulated that histamine may play a role in regulating sperm motility and acts through specific histaminergic receptors.

المستخلص

دراسة تأثير الهستامين ومضاداته على حركة الحيامن البشرية اظهر أن:

- ١ - الهستامين يزيد من حركة الحيامن.
- ٢ - مضاد الهستامين من نوع H₂ السمتيديني ليس له أي تأثير على الحركة بينما مضادات الهستامين التقليدية تقلل الحركة.
- ٣ - التنشيط الحاصل بواسطة المضاد H يمكن التغلب عليه بزيادة تركيز الهستامين.
- ٤ - يمكن الافتراض ان الهستامين يزيد من تنظيم حركة الحيامن وانه يعمل من خلال مستقبلات متخصصة لفعل الهستامين.

Introduction

It has been reported that sperm motility is affected by some centrally active, drudge, phosphodiesterase Inhibitors and drugs with local anaesthetic or membrane stabilizing activity [1,2,3].

Studies on human sperm motility have been few, largely due to non-availability of simple techniques.

Recently Hang et al., have described a simple method to quantitate drug effect on sperm motility in Vitro[4,5].

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Using beta agonists and antagonists demonstrated a lack beta adrenergic control of human sperm motility.

The present study was undertaken to investigate the effects of histamine and antihistamine H₁ and H₂ on sperm motility.

Material and Methods

Fresh human seminal fluid samples collected from healthy volunteers who are non smokers and non alcoholics and patients attending a seminology clinic were used within 2 hours of collection . Only samples with a sperm count higher than (15×10^6 / ml) and a trans -membrane migration rate (TMMR) which is the % of progressive forward moving sperms higher than 20% were used [5].

All drugs were dissolved in phosphate saline at pH 7.3.

Sperm motility was measured using the ability of forward moving sperms to move across the 5µm pores of a nucleopore membrane during a 2 hour incubation at 37°C [4] .

The motility of sperms in semen buffer mixture was used as a control and those of semen drug mixtures were expressed as percentage of the control.

Aliquots of semen were mixed with buffer or drug in the ratio 2:1 for each of the drugs, 36 samples were tested. The statistical analysis was carried out using paired “t” test.

When histamine effects on promethazine induced changes in sperm motility were °mixture was kept a constant at 2:1 and then incubated at 37°C.

The drugs tested in this experiment included histamine phosphate (BDH) , chlorpheniramine maleate (Glaxo) promethazine hydrochloride (baler)and cimetidine (Skf) . The concentration of drugs that decreased sperm motility to 50% of control (ED₅₀) were obtained from semilogarithmic concentration effect curves.

Results

Table (1) Shows the effect of histamine and histamine antagonists on the motility of sperms .

These results are clearly depicted in fig. (1)

Histamine in concentration between 1mM produced an increase in sperm motility, but when compared with the control this was not significant.

Cimetidine used in similar concentrations did not affect the sperm motility significantly , although , with the higher concentrations there was a tendency for some dose related inhibition of motility

Table (1) Drug effect on the transmembrane migration ratio of human sperms

Drugs conc. In nM	Histamine	Cimetidine	Promethazine	Chlorpheniramine
1.0	101.0 ±4.00	100.6±3.2	91.8±2.71	94.3±3.07
2.5	104.0±6.07	98.4±2.4	*53.2±3.37	*70.0±6.93
5.0	106.5±7.26	98.2±3.1	*38.0±2.45	*58.2±5.94
7.5	101.8±5.31	96.0±2.8	*22.2±4.00	*47.8±3.31
10.0	99.1±4.21	89.8±2.6	*15.2±3.47	*39.8±2.84

Each value depicts mean ± SD of experiment

* Statistically significant (p<0.01) as compared to histamine.

The two classical antihistamines studied, promethazine and chlorpheniramine produced a dose dependent decrease in sperm motility, the former being the more potent

Fig 2(Histogram) illustrates the ED₅₀ i.e. the effective concentration for 50% inhibition of motility, for promethazine to be 2.5mM where as for chlorpheniramine it was 7.5mM.

Because cimetidine could not inhibit sperm motility to 50% of control even with the highest concentration tested in this study, its ED₅₀ was extrapolated from the dose response curve available.

Table(2) shows the effect of histamine on promethazine induced reduction of sperm motility.

This is illustrated in fig(3) Which shows the antagonism of histamine on the promethazine induced inhibition of sperm motility.

The inhibitory effect of promethazine was reduced significantly (p<0.01) as the concentration of histamine was increased.

The results are suggestive of a possible competitive antagonism.

Table 2 ; Effect of histamine on promethazine induced changes in trans membrane migration ratio of sperms

Conc. Promethazine in mM	Promethazine alone	Promethazine with histamine 2.5mM	Promethazine with histamine 5mM
1.0	91.8±2.71	91.5±2.17	97.2±2.14
2.5	53.2±3.37	*67.0±2.78	80.0±7.62
5.0	38.0±2.45	*58.0±4.96	*62.3±3.51
7.5	22.2±4.60	*39.8±3.90	*52.2±3.66
10.0	15.2±3.47	*24.8±3.60	*38.8±4.22

Each value depicts the mean ± SD of experiments

statistically significant (p<0.01) as compared to promethazine alone.

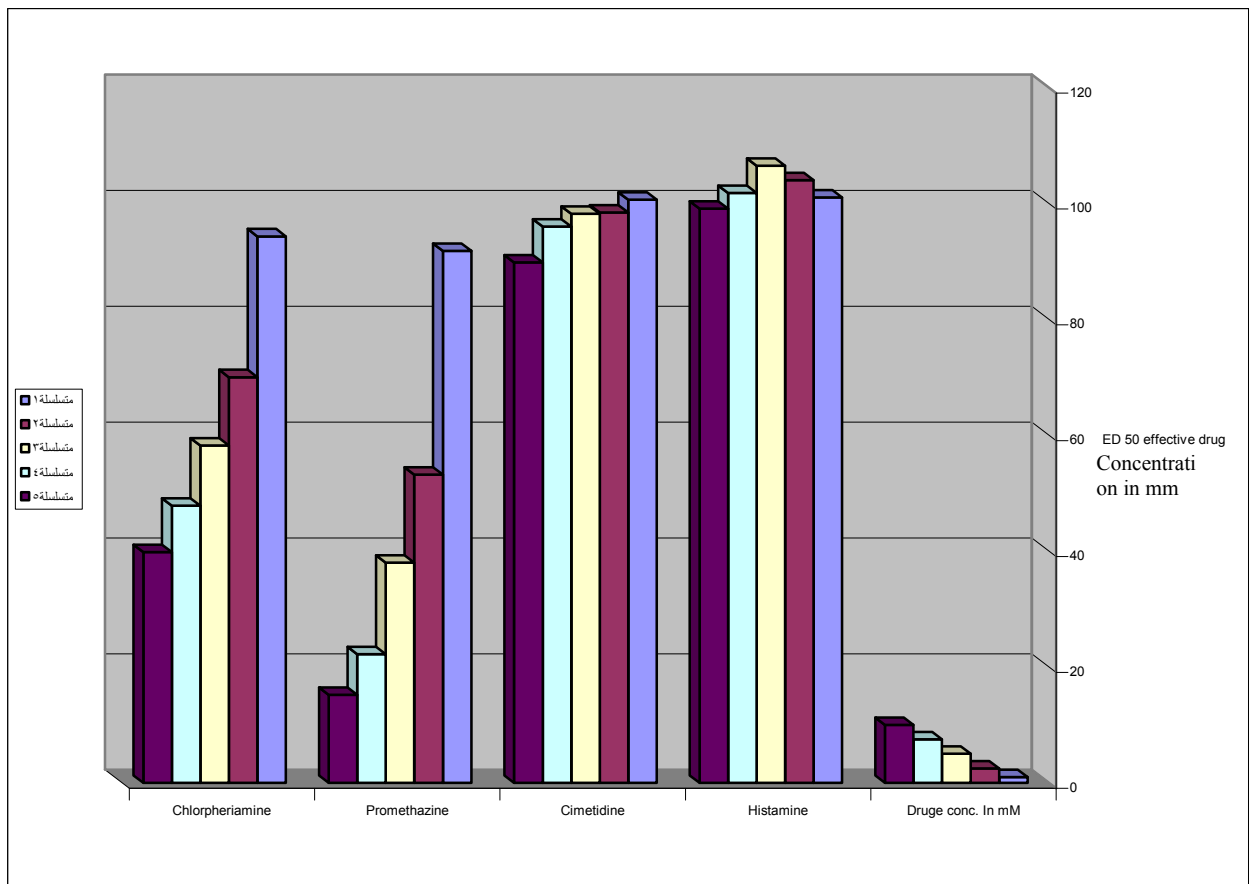
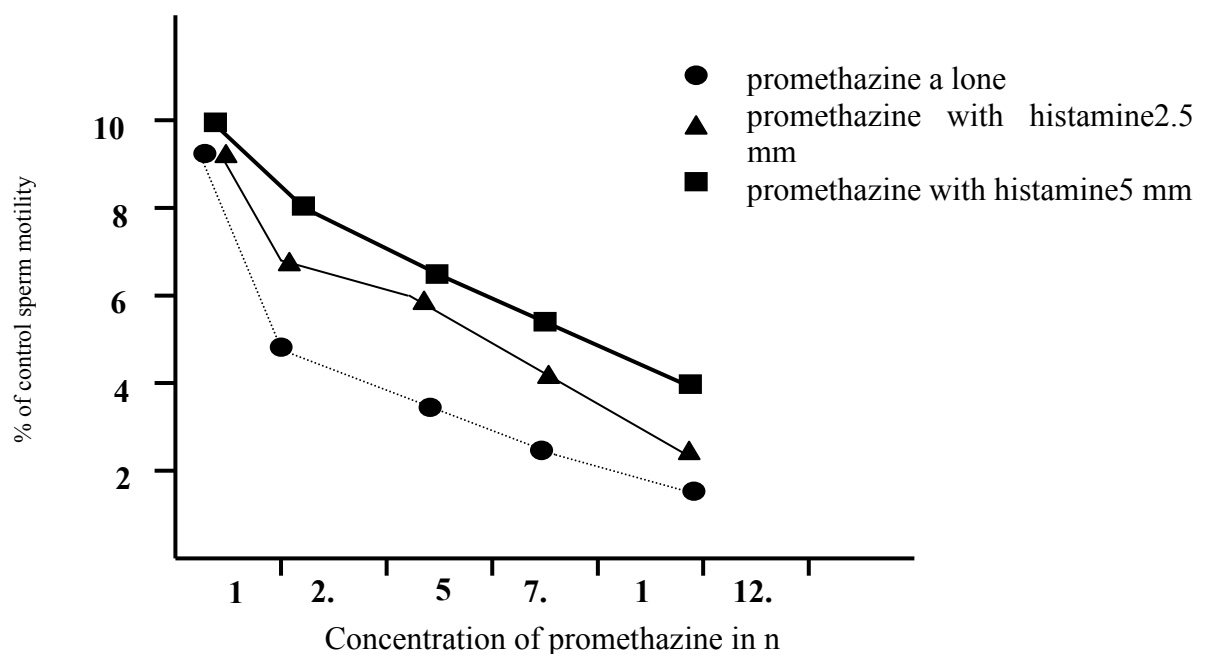


Fig (2): The relative ED₅₀ of histamine and its antagonists in inhibiting human sperm motility



Fig(3): The effect of promethazine alone and in presence of varying concentration of histamine on human sperm motility

Discussion

Though it is clinically documented that classical antihistamines can produce sedation, drowsiness and ejaculatory malfunction it is not known whether they have any effect on sperm motility.

Studies using local anaesthetics such as lignocaine [5], have clearly demonstrated an inhibitory effect on sperm motility and this was attributed to its membrane stabilizing effect.

It was also shown by [3], that lipid solubility determines that local anaesthetic effect of certain beta blockers and the sperm immobilizing effect of these beta blockers could be a manifestation of their local anaesthetic effect it is also well established that antihistamine drugs also exert varying degrees of local anaesthetic effect which could lead to cell membrane stabilization [6], even though the local anaesthetic effect of promethazine and chlorpheniramine classical model is negligible. While participation of local anaesthetic activity in the actions of promethazine and chlorpheniramine on sperm motility cannot be excluded, the antagonistic effect of histamine upon the action of promethazine would appear to make this unlikely.

Cimetidine in the close range used produced very little inhibition of sperm motility, whereas the classical H_1 antagonists inhibited motility suggesting involvement of H_1 rather than H_2 receptors.

The drug concentrations used in this study are higher than those achieved with the therapeutic dosage and hence the results are unlikely to have relevance in patients receiving the drugs therapeutically. Very little is known about the factors regulating sperm motility in man.

Even though prostaglandins (PGE) and (PCF) are reported to promote longevity and motility of sperm [7], their exact physiological role in sperm motility is yet to be defined.

The [7] have also shown that mammalian spermatozoa contain the mechanisms for synthesis, release and hydrolysis of cholinergic transmitter and also demonstrated presence of acetylcholine esterase, choline acetyltransferase and cholinergic receptors of the nicotinic type in the tails of the spermatozoa. The studies of [8,9] have demonstrated the involvement of cyclic (AMP) as the intracellular mediator for the initiation of sperm motility.

So histamine receptor promotes nitric oxide which plays an active factor to increase bioactive processes of sperm motility, and that is possible.

Mechanism to get sperm the life behaviour and capacitation.

Further evidence by [4] has shown that caffeine a phosphodiesterase inhibitor, increases sperm motility probably by decreasing breakdown of cAMP.

Histamine is also known to increase the intracellular levels of cyclic AMP [10,11], have shown that human spermatozoa contain N-methyl transferase which is needed for the metabolism of histamine to N-methyl histamine, its major metabolite.

The aforementioned observations of different investigators do not permit postulation of a unified concept of neurochemical transmitter role in sperm motility. However the observations that the classical antihistamines decreased sperm motility which could to a certain extent be overcome by histamine, the relative ineffectiveness of H_2 antagonists on sperm motility, and the presence of histamine N-methyl transferase in the sperm as reported by [12].

All point to the possibility that in the initiation of sperm motility histamine may play a role and that there may be specific histamine receptor on the human sperm.

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