Histamine and Schizophrenia : A Validation Study for Skin Response to Intradermally Injected Histamine in Schizophrenia

By N. Mahallawy, Z.Bishry, A.M. Ashour & A. Okasha

ABSTRACT

The size of the skin wheal that arises 15 minutes after the intradermal injection of 0.05 ml of 1 : 1000 histamine in normal saline is measured by a special template and stencil. This constitutes the histamine skin test.

The test could significantly differentiate between normals (N = 15) and schizophrenics (N = 30) the schizophrenic showing smaller wheals. It failed to differentiate between Schneider positive and negative schizophrenics.

In Schneider positive schizophrenics under phenothiazines and or E.C.T., the clinical improvement was associated with improved histamine skin reactivity after 8 weeks. No similar change was shown by Schneider negative schizophrenics.

The implications of this experiment in the field of diagnosis, theory and treatment of schizophrenia are discussed.

INTRODUCTION

The anterior pituitary and hypothalamus are the brain parts rich in histamine. Various other parts of the brain in the hippocampus and neocortex contain histamine-activated adenylate cyclase. Reserpine reduces histamine concentration of the thalamus and hypothalamus, while chlorpromazine raises it. Brain histamine content is increased by thremorine and mescaline, a tremor producing and a psychotomimetic respectively (William F. Ganong 1977). The brain contains the two known types of histamine receptors H1 and H2.

The triple response is a well known phenomenon following histamine release in the skin and the role of axon reflexes in it is recognized.

Over the last two decades some work was done to describe the schizophrenics' histamine metabolism. Ermala and Autio (1951), Freedman et al. (1956) described the skin response to intradermal histamine injection in schizophrenics. Weckowicz and Hall (1955), Jodery and Smith (1959), and Simpson and Kline (1961) went a step forward by trying to demonstrate significant differences in the skin response to intradermally injected histamine, between different groups of schizophrenics and between them and nodmal controls. Their results were far from conclusive and at the best controversial. Le Blanc (1961) extended the scope of study in this field to include estimation of mast cells in the skin of mental patients before and after tranquilizer therapy, and to look for an index of clinical improvement through increase in skin sensitivity to skin injected histamine.

The aim of our work is to re-examine the question of the value of the skin response to intradermal histamine in the diagnostics of schizophrenias in an Egyptian setting.

MATERIAL AND METHOD

The subjects of the experiment were 30 schizophrenic patients recently admitted to Ain-Shams University Hospital short stay psychiatric wards. They were 18 males and 12 females. Age range 16 - 33 with a mean 24.5 S.D. 7.5. The diagnosis was clinched by the consensus of two clinical judges (A.O. & Z.B. according to the diagnostic criteria of the Egyptian Diagnostic Manual of psychiatric disorders (1976) which is largely a version of the ICD-6. The same judges divided the experimental group into two sub-groups named Schneider +ve and Schneider −ve, according to the ability to demostrate Schneider's first rank symptoms of schizophrenia (Kenneth, Granville — Grossman 1971). Organic Brain involvement was excluded by physical and neurological clinical examination.

A control group of 15 subjects was selected from the relatives coming to visit patients in the surgical deparments. There was a trial to match the control group with the experimental one as regards age, sex, area of residence and social class. Controls were free from psychiatric pathology or a history of psychiatric pathology or a history of psychiatric illness or a family history. History of freedom from allergic disorders was essential for inclusion in the experiment. A three week period of freedom from any drug intake was essential.

The design of the study was to administer intradermal histamine test on admission before any treatment, 4 weeks after being on phenothiazine and/or ECT therapy, then after another 4 weeks of same treatment.

The clinical condition was assessed for improvement by the same judges 4 and 8 weeks after the start of the experiment.

The procedure of intradermal histamine skin testing was the injection of 0.05 ml of air free 1:1000 histamine in normal saline, into the skin of the ventral aspect of the forearm. The size of the wheal is measured 15 minutes after injection using the templates and stencil recommended by Pellegrino and Macedo (1956). To standardize the conditions of the testing and to minimize artefact we prepared the patient by fasting from food and drug for 8 hours before testing and we prepared the forearm skin by allowing a drop of alcohol to evaporate from its surface without any rubbing.

RESULTS

I. On admission and before treatment :

1. The test could differentiate between the Schneider positive schizophrenics ($N = 15$) and normal controls ($N = 15$) with a high degree of statistical significance ($P < 0.001$). The schizophrenics having a smaller wheal reaction than the normals.

2. The test could differentiate between the Schneider negative schizophrenics (N = 15) and the normal controls (N = 15) with a high statistical significance (P < 0.001). The schizophrenics having a smaller wheal reaction than the normals.

3. The test failed to differentiate with acceptable significance between the two groups of schizophrenics. Yet, the Schneider negative schizophrenics had smaller wheal reactions than the Schneider positive schizophrenics. (P = 0.05)

Table (1) summarizes the differences in wheal size in the different groups at admission.

	Schneider −ve (N = 15)	Schneider +ve (N = 15)	Normal (N = 15)
Size of wheal : (in c. m.s)			
Range	0.3—1.7	0.2—2.25	2.8—1.45
Mean	1.13	0.996	1.91
S.D.	0.370	0.468	0.365

II. 4 and 8 weeks after treatment :

1. In the Schneider positive group a significant correlation could be demonstrated between clinical improvement and progression of the size of the intradermal wheal 8 weeks after treatment and not before that.

   In the eight cases which showed improvement over 8 weeks the size of the wheal increased from a mean of 1.025 (S.D. 0.4) cms to a mean of 1.118 (S.D. 041) cm. whereas in the non improved seven cases the wheal size failed to move from a mean of 1.25 (S.D. 0.27) cm over 8 weeks.

   Another way of expressing the trends in the size of the wheal

alongside with clinical improvement is to state that with improvement in the 8 cases the wheal size increased in four cases, did not change in two and decreased in two cases. While in the non improved seven cases, four showed an increase and three showed a decrease and three showed a decrease in wheal size after eight weeks of treatment.

2. In the Schneider negative group we failed to show significant correlation between clinical improvement and change in wheal size four and eight weeks after installing treatment.

Ten cases showed clinical improvement but the wheal size moved only from 0.84 (S.D. 3.6) cms to 1.09 (S.D. 0.27), size of wheal increasing in 6, no change in one, and decreasing in 3 cases.

In the five non-improved cases there was increase in the wheal size in one case. The wheal size decreased insignificantly over 8 weeks from 1.3 (S.D. 0.5) to 1.1 (S.D. 0.27) cms.

DISCUSSION

Our results demonstrating the smaller cutaneous response to intradermally injected histamine of the schizophrenics compared to the normals is in agreement with similar results by workers like Ermala and Autio (1951), Freedman **et al** (1958), Wechowicz and Hall (1957) (1958) and Le Blanc and Lemieux (1961) in different cultures.

Our work cannot be compared to Jodry and Smith's (1959) because of gross differences in the technique and way of evaluating the results.

It emphasizes once more that schizophrenics have high tolerence to histamine injected intradermally. This is parallel to the finding of Lucy (1954) that schizophrenics have an abnormally high level of tolerence to the systemic effects of injected histamine.

This result also highlights the diagnostic potentiality of this simple

bedside test in differentiating between schizophrenics and normals in an Egyptian population. The test procedure is highly standardized and the results are rather reliable. The reasonable reliability can be inferred from the high repeatability scores. The mean values of the test remained rather constant over an 8 weeks retest period in most of the subjects. We hope that with application on larger groups a specific reliability index will be obtained.

As to the question of validity of this test to differentiate between normals and schizophrenics taking the clinical judgement as a validation criterion, it seems quite clear that the test showed a reasonable degree of criterion validity. Clinical judgment is up till now the most used diagnostic criterion for schizophrenia, probably for the lack of more objective reliable biological or psychological testing.

Because of the limited number of subjects in this experiment we cannot offer a specific protocol for use of this test in clinical practice.

Because the overlap is wide; only extreme results can be of diagnostic help. For example; a wheal recation of 2.5 cms or more is against diagnosis of schizophrenia. Reactions below 1.4 cms and specially those below 0.5 cms are suggestive of illness.

The failure of the test to differentiate between the two sub-groups of schizophrenics has no simple and straightforward review, The interplay of many factors makes the schizophrenics a grossly heterogenous group.

The second incident in which the test proved its validity as an indicator of schizophrenic pathology is the change in test score parallel with clinical improvement in the small group of Schneider positive schizophrenics who improved under treatment with phenothiazines and of ECT in 8 weeks. Our results are in accordance with Lovett Doust (1953) who found increased reactivity to histamine after shock therapy, and with Le Blanc and Lemieux (1961) who described the same result after tranquilizer therapy.

Why did our Schneider negative schizophrenics fail to show changes in the wheal score over 8 weeks under treatment is open to speculation. If we assume that they scored higher on chronicity than the Schneider positive cases so we can find an explanation to their persistent unresponsiveness ta histamine, Wimpson and Kline (1962), Lucy **et al.** (1954).

It is worthy to notice that most of the phenothiazines used in treating many cases had local antihistamine (H2 recepter block) action and wheal size increased in the improved cases. An explanation can be found in the antipsychotic effect of these drugs on the histamine sensitive adenylate cyclase system or other. That in the non improved cases under the same drugs the wheal size failed to change, implies that there is a failure of the histaminergic systems.

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AUTHORS

N.N. MAHALLAWY, M.B. BCH. Registrar in Psychiatry.

Z. BISHRY, M.D., D.P.M. & N., Assistant Professor in Psychiatry.

A.M. ASHOUR, M.D., M.R.C. Psych., D.P.M. & N., Senior Lecturer in Psychiatry.

A. OKASHA, FRCP., F.R.C. Psych., D.P.M. Professor and Head of Psychiatric Department, Ain Shams University, Cairo.

الملـــوجز

دراسة ـ استجابة الجلد للحقن الجلدى للهستامين فى مرضى الفصام المصريين

يجرى ما يسمى باختبار الهستامين الجلدى بواسطة حقن ٠٫٠٥ سم من الهستامين واحد فى الألف فى محلول ملحى اعتدالى فى جلد الذراع حيث يتكون جبار يجرى قياسه بعد ١٥ دقيقة ٠ وقد أمكن لهذا الاختبار أن يميز بين مجموعة من الفصاميين عددها ثلاثون وبين مجموعة ضابطة من غير المرضى بدرجة عالية من الصدق الاحصائى ٠ وقد كان الجبار فى الفصاميين أصغر منه فى المجموعة الضابطة ٠

ولكن هذا الاختبار فشل فى أن يميز بين مجموعتين كل منهما ١٥ فردا تمثل احداهما مجموعة الفصـــاميين ذوى أعراض (شيندر ايجـــابى) والفصاميين المفتقرين الى مثل هذه الأعراض (شنيدر سلبى) ٠

ولقـــد تغيرت اســـتجابة الفصاميين (شنيدر ايجابى) على الاختبار بطريقة متوازية مع التحسن الاكلينيكى عند اعادة الاختبار والتقويم الاكلينيكى بعد ٨ أسابيع من العلاج بمركبات الفيثوثيازمين والصدمات ٠ ولم يحدث هذا التغير فى الفصاميين (شنيدر سلبى) ٠

وقد ناقش البحث انعكاس هذه النتائج على تشخيص وعلاج ونظريات فهم الفصام ٠

ABSTRAIT

Histamine Et Schizophrenie :
Etude Significative De l'Effet Cutane d'Injection
Intradermique d'Histamine Chez Les Schizophreniques

L'intensité des réactions cutanées qui apparaissent 15 minutes après une injection intradermique he 0.05 ml de 1 : 1000 d'histamine en solution saline normale est mesurée par un "templete special et un stencile". Cette méthode représentant un test de réactions histaminiques cutanées.

Les résultats démontrent une difference significative entre l'état normal (N = 15) et l'état schizophrénique (N = 30). Les schizophréniques demonstrant des réactions cutanées de grosseur moins importante.

La différence rapportée par Schneider entre les schizophréniques positifs et négatifs n'a pu être démontrée par ce test.

Chez les schizophréniques positifs de Schneider sous phenothiazines et/ou E.C.T. l'amélioration clinique était associée à l'amélioration de la réaction cutanée à l'histamine après 8 semaines les schizophréniques négatifs de Schneider ne présenent aucun changement significatif sous des conditions similaires.

Une discussion est également présentée à propos des implications de cette experience dans le domaine du diagnostique, traitement et l'étude de la schizophrenie.