Medical Journal of the
Islamic Republic of Iran

Volume 3
Number 3,4
Payiz & Zemestan 1368
Fall & Winter 1989

Original Articles

SERUM CONCENTRATIONS OF VARIOUS HORMONES FOLLOWING EXPOSURE TO CHEMICAL WEAPONS CONTAINING SULFUR MUSTARD*

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ABSTRACT

Serum concentration of FSH, LH, testosterone, prolactin, ACTH, cortisol, TSH, T4, T3 and resin T3 uptake were measured in 146 men who were exposed to vesicants used by the Iraqi regime a few days to 4 weeks prior to testing. Clinical and laboratory findings had confirmed the use of mustard gas.

Mean serum concentrations of FSH, LH, TSH and prolactin were not significantly different from normal values. Free T4 index (FT4I) was subnormal in 6 men, and its mean was somewhat decreased (7.4 ± 0.8 vs normal 8.7 ± 1.2; $P < 0.05$). Free T3 index (FT3I) was subnormal in 14 men, and its mean was significantly lower than normal (92 ± 20 vs 130 ± 11; $P < 0.001$).

Serum testosterone concentration was subnormal in 42 men, and its mean was significantly lower than normal (361 ± 254 vs 676 ± 273 ng/dl; $P < 0.001$). Serum cortisol was subnormal in 11 and above normal in 8 men, its mean was not significantly different from normal values. There was an increase in serum ACTH concentration.

We conclude that exposure to chemical weapons containing mustards may cause severe alterations in serum concentrations of various hormones.

MJIRI, Vol.3, No.3 & 4, 105-107, 1989

INTRODUCTION

Chemical weapons had been extensively used during the first world war and their side effects on the eyes, skin, gastrointestinal, respiratory and hematological systems have been reported.[1]

Although the use of chemical weapons was banned by the Geneva protocol in 1925,[2] research on chemical warfare, their modes of delivery, and antidotes to them, continued in the intervening 60 years.[3] Unfortunately these devastating weapons have been repeatedly used by the Iraqi regime against Iranian soldiers and

* This study was partly presented in the First International Medical Congress on Chemical Warfare Agents in Iran, June 13-16, 1988, Mashhad, Iran.

civilians since August 1983. Its use has been reported[4] and condemned[5] by the United Nations Security Council.

Since we were unable to find any report on the effect of chemical weapons on the endocrine system in man, we undertook a study to evaluate the side effects of mustard compounds in Iranian men injured by chemical warfare.

MATERIALS AND METHODS

Men who were injured by chemical war agents were studied. Reported characteristics of chemical warfare where it was used, positive finding by special tests, delayed appearance of symptoms by several hours and characteristic toxic effects on the skin, eyes and respiratory system had confirmed that the chemical weapons used contained mustards.

Fasting blood samples were drawn in 146 subjects who were hospitalized because of side effects of mustards. They were injured a few days to four weeks prior to blood drawing. Their clinical symptoms were of varying degree; however, most of them showed moderate to severe respiratory, ocular and dermatological complications. The injured men were aged 18 to 54 years. 34 normal age-matched men were used as a control group. Serum concentrations of FSH, LH, prolactin, TSH, ACTH, testosterone, cortisol, T4, T3 and T3 resin uptake were determined by commercial kits. Free T4 and T3 indices were then calculated.[6] Statistical analysis was done by using student T test.

RESULTS

The results of various hormone tests in 146 men injured by chemical weapons and 34 normal men are shown in Table I.

Free T4 and T3 indices and serum TSH concentration:

Free T4 index was below normal range in six men (4%). Its mean ± SD was 7.4 ± 0.8, as compared to 8.7 ± 1.2 μg% of normal control ($p < 0.05$). Free T3 index was subnormal in 14 cases (10%). It was significantly decreased as compared to control (92 ± 20 vs 130 ± 11 ng%; $p < 0.001$). Serum TSH concentration was not significantly different in injured and control groups (1.9 ± 1.7 vs 2.0 ± 0.8, μU/ml respectively).

Serum concentration of cortisol and ACTH:

Serum cortisol concentration was below normal range in 11 men (8%) and above normal range in 8 (6%). Mean serum cortisol concentration was not significantly different in injured and control groups (13.8 ± 22.7 vs 15.1 ± 5.2 ng%, respectively). Serum concentration of ACTH was significantly increased as compared to normal controls (54 ± 31 vs35 ± 19 pg/ml; $P < 0.001$).

Serum concentration of testosterone, gonadotropins and prolactin:

Serum testosterone was significantly decreased in men exposed to vesicants as compared to the control group (361 ± 257 vs 676 ± 273 ng/dl, $P < 0.001$). Forty two of 146 men (29%) had serum testosterone concentrations below 300 ng/dl. Serum concentrations of LH, FSH and prolactin were not statistically different from those of control groups (Table I).

We had the opportunity to follow serum hormone changes in one man exposed to mustard during the first five weeks. Serum testosterone concentration was 400, 450 and 330 ng/ml in the second, fourth and fifth weeks after exposure. Corresponding serum LH concentrations were 8.4, 13.7 and 15.4 mu/ml and those of FSH were 5.5, 11.2 and 15.0 mu/ml respectively.

We have reported[9] in 53 victims exposed to nerve gas that the concentration of serum testosterone was not significantly different from that of normal controls (918 ± 307 vs 676 ± 273 respectively). Serum concentrations of gonadotropins and prolactin were also within normal range.

DISCUSSION

This study demonstrates the effect of chemical weapons containing sulfur mustard on the serum concentrations of various hormones. Due to special conditions and patients' status we were unable to perform extensive endocrine studies. However, a slight but significant decrease in FT4I and a very significant fall in FT3I and serum testosterone is seen.

Since both FT4I and FT3I are diminshed, one may assume that the secretion of hormones from the thyroid gland may have decreased. It has been shown that even small falls in serum thyroid hormone concentrations are accompanied by increased serum TSH.[7] Lack of increase in serum TSH in the present study may have been due to inadequate senstitivity of the kit to detect small changes in serum TSH. The change in FT3I was disproportionally more than FT4I, suggesting that decreased conversion of T4 to T3 in peripheral tissues might have occurred.[8] If conditions of the study allowed, one should have measured serum T4, T3, rT3 and TSH every 2-3 days for the first few weeks to depict definite changes in thyroid secretion and/or in the peripheral metabolism of the thyroid hormones.

Decreased serum testosterone concentrations to almost half of the normal control values may suggest a profound effect of the mustard on the Leydig cells. A lack of increase in serum gonadotropins, in particular

Table 1. Concentrations and indices of various hormones in 146 subjects exposed to chemical warfare containing mustards

Test	Exposed to mustards (n = 146)	Normal subjects (n = 34)	p
Free T4 index	7.4±1.8	8.7±1.2	< 0.05
Free T3 index	92±20	130±11	< 0.001
TSH (μU/ml)	1.9±1.7	2.0±0.8	NS
cortisol(μg/ml)	13.7±22.7	15.1±5.2	NS
ACTH(pg/ml)	54±31	35±19	< 0.001
Testosterone (ng/ml)	361±254	676±273	< 0.001
LH (μu/ml)	9.7±6.2	8.3±2.1	NS
FSH (μu/ml)	9.5±6.3	10.1±3.2	NS
Prolactin(ng/ml)	10.4±7.1	13.9±5.5	NS

* NS: Statistically not significant.

LH, may suggest that the fall in serum testosterone might have been due to altered binding of total testosterone in the serum and not because of decreases in testicular secretion. Further study measuring serum free testosterone may shed light in this respect. It is also possible that changes in gonadotropins in response to decreased testosterone might have occurred after the first 2-3 weeks and were not depicted by combining the results of 146 patients, whose blood tests were performed in various intervals from exposure to mustard. Indeed, the results of serial determinations in one patient is in favor of this explanation.

The fall in serum testosterone is not due to stress of war or environmental factors in the battle field, since subjects who had similar conditions, but were injured by nerve gas and not the mustards had normal serum testosterone concentrations.[9]

The toxic effect of sulfur mustard was originally attributed to its hydrolysis and the liberation of free hydrochloric acid or to the formation of the highly reactive cyclic onium cation.[9] Sulfur mustard also depresses and inhibits many vital enzymes in various cells. However, it seems likely that the characteristic cytotoxic effect of alkylating agents, including mustard, is due to their ability to cross-link the twin strands of the DNA macromolecule, resulting in prevention of DNA replication.[10]

Our findings suggest that sulfur mustard may have severe effects on thyroid and testicular functions. Althought we did not study the effect of mustard on spermatogenesis, the effects of other alkylating agents on inhibition of spermatogenesis[11] and induction of ovarian failure[12] have been reported by others.

Lack of use of chemical warfare in World War II, although both sides had developed new generations of agents, led to hopes that chemical weapons would never be used. Torald Stollmann in his textbook of pharmacology, published in 1957, writes: "its importance (mustard gas) is now past history, and may perhaps never be revived."[10] However research on chemical war agents was continued by the British and Americans in the 1950's and 1960's, resulting in the discovery of new chemical warfare.[3] The massive use of herbicides and defoliants by the American army in the Vietnam War (1961-75)[13] opened a newera in the use of these devastating agents.[14] The inability of the world to stop the Iraqi goverment in using chemical warfare since 1983, has led to the criminal usage of these agents against civilians residing in Sardasht (Iran) and Halabja (Iraq). Unfortunately, more side effects on various organs, mutagenicity and carcinogenicity of the chemical weapons will be reported in the near future.

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