CODEN [USA]: IAJPBB **ISSN: 2349-7750**

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.3234065

Available online at: http://www.iajps.com ***Research Article***

EFFECTS OF ORGANOPHOSPHATE POISONING ON THE ENDOCRINE SYSTEM

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Article Received: March 2019 **Accepted:** April 2019 **Published:** May 2019

Abstract:

Objective: *Organophosphates (OPs) are widely used for pest control worldwide, leading to increased risk for human exposure. The acute hormonal effects of OP include deficiencies in the thyroid-stimulating hormone (TSH), adrenocorticotropic hormone, and insulin-like growth factor 1 hormone correlated with the levels of cholinesterase. Most patients with OP-related hormone deficiency recover at 3 months of follow-up. However, the chronic effects of these chemicals are not clear. The aim of the present study was to determine the chronic influences of OP on pituitary functions in patients who had OP poisoning.*

Materials and Methods: *This prospective study was performed in Civil Hospital Badin. All of the patients who had OP poisoning were followed up in the medical intensive care unit (MICU). They were evaluated after discharge from the MICU after at least 6 months with regard to pituitary functions. In all patients, data were extracted from the MICU records. Baseline hormone levels were assessed, and dynamic tests (insulin tolerance test and glucagon stress test) were performed.*

Results: *Twenty-nine adult patients (13 women and 16 men) with OP poisoning were included in the study. The mean age of the patients was 41.9±16.7 years. The mean time from hospitalization to assessment of pituitary functions was 43.9±15.8 months in patients with OP poisoning. All patients had normal prolactin, TSH, follicle-stimulating hormone, and luteinizing hormone levels. Women had normal estrogen levels, and men had normal total testosterone levels. Cortisol deficiency was detected in only 1 (3.4%) patient, and growth hormone (GH) insufficiency was found in 3 (10.3%) patients.*

Conclusion: *GH and cortisol axis may be affected by OP poisoning in the long term. Thus, pituitary hormone levels should be tested following an acute period in patients with OP.*

Keywords: *Organophosphate poisoning, endocrine effects, pituitary functions.*

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Please cite this article in press Fayaz Hussain Khoso et al., ***Effects of Organophosphate Poisoning on the Endocrine System.,*** *Indo Am. J. P. Sci, 2019; 06(05).*

INTRODUCTION:

Organophosphates (OPs) are widely used for controlling pest worldwide; this leads to increased risk for human exposure (1). As a result of their widespread availability, OPs are often used for suicide attempt with an estimation of 300,000 people per year (2). The acute adverse effects of OP on the central nervous system are related with the accumulation of acetylcholine (ACh). When this occurs, symptoms, such as seizures, respiratory failure, anxiety, headache, ataxia, tremor, and general weakness, and, in the end, death can be seen (3). Poisoning with OP-based insecticides is a serious condition requiring rapid diagnosis and timely treatment (4). The acute hormonal effects of OP are deficiencies in the thyroid-stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), and insulinlike growth factor 1 (IGF-1) hormone correlated with the levels of cholinesterase. Most patients with OP-related hormone deficiency recover at 3 months of follow-up (2). However, knowledge of the chronic effects of these chemicals is limited. Known chronic effects include neurological effects (5), some cancers (6), adverse reproductive effects (7), and endocrine disorders (8, 9).

The well-known chronic endocrine adverse effects of OPs related to the reproductive systems include poor semen and sperm quality, menstrual cycle disturbances, longer pregnancies, spontaneous abortions, stillbirths, and some developmental effects in offspring (10). The aim of the present study was to investigate the chronic effects of OP on pituitary functions in patients with OP poisoning.

MATERIALS and METHODS:

This prospective study was approved by the local ethics committee of civil hospital badin. Informed consent was obtained from each patient. Patients were of badin district comprising different areas i-e matli,tando bagho etc.

The history and data of patients was summarized in patient data collection sheet, 38 patients in total reported to our hospital out of which 29 patients fit into the criteria of inclusion of our study. Inclusion criteria were OP poisoning and have had at least 6 months after this exposure and lack of history of endocrine disorder. Exclusion criteria were age <18 or >70 years, history of poisoning for the previous 6 months, pregnancy, lactation, history of traumatic brain injury and hormonal disorders, chronic renal and hepatic failure, contraindications to insulin tolerance test (ITT), history of epilepsy, and cerebrovascular or cardiovascular diseases.

Assessment of Pituitary Function:

TSH, free thyroxine (fT4), free triiodothyronine (fT3), ACTH, cortisol, follicle-stimulating (FSH), luteinizing hormone (LH), prolactin, total testosterone (in male patients), estradiol (in female patients), and IGF-1 levels were measured as basal hormones in all participants.

Gonadotropin deficiency was detected in male patients when total testosterone level was below the normal range together with low or normal LH and FSH levels (11). Similarly, estradiol levels were under the normal range with low or normal LH and FSH levels in female patients whose gonadotropin deficiency was diagnosed. Secondary hypothyroidism was diagnosed when TSH levels were low or inappropriately normal with low serum fT4 and fT3 levels (12). The somatotrophic and corticotropic functions were evaluated by dynamic tests.

Evaluation of Hypothalamic–Pituitary–Adrenal and GH– IGF-1 Axes by Dynamic Tests:

The ITT and glucagon stress test (GST) were performed to all patients who were euthyroid when dynamic tests occurred. Owing to two main reasons, different tests and cut-off values were used. First, two cut-off values were used worldwide as universal and local. Genetic, race, and lifestyle can affect test results. Second, one dynamic test is weak for demonstrating hormone deficiency. None of the patients had pituitary disorders before dynamic tests. Peak cortisol level 18 µg/dL and growth hormone (GH) level 3 µg/L were obtained as adequate response for ITT. Adequate response for GST was accepted according to both universally (peak GH level 3 µg/L and peak cortisol level 18 µg/dL) and locally determined (peak GH level 1.18 µg/L and peak cortisol level 10.6 µg/dL) cut-off levels.

Statistical Analysis:

The SPSS 22.0 program (SPSS Inc., Chicago, IL, USA) was used for descriptive analysis. Data were expressed as mean±standard deviation and range.

RESULTS:

The study group included 29 patients (16 men and 13 women) with a mean age of 41.9±16.7 (range: 18–69) years who had a history of OP poisoning. The mean body mass index of the study group was 25.7±3.7 kg/m2. In patients with OP poisoning, the mean time from hospitalization to assessment of pituitary functions was 43.9±15.8 months (Table 1). The lowest pseudocholinesterase level was 1509.2±2544.4 (range: 2550–6800) U/mL. The OP components used by

patients were diazinon, monocrotophos, and chlorpyrifos ethyl.

Table 1. *Demographic features of the patients*

Age (year)	*41.9±16.7*
BMI (kg/m^2)	*25.7±3.7*
Waist circumference (cm)	*88.8±10.9*
Length of stay in the MICU (day)	*7.0±5.0*
Intubation time (day)	*6.0±4.9*
Time after poisoning (month)	*43.9±15.8*

BMI: Body mass index; MICU: Medical intensive care unit

Evaluation of Pituitary Hormones:

Prolactin, TSH, FSH, and LH levels were normal in all pa tients. Female patients had normal estrogen levels according to menopausal status and menstrual phase, whereas male patients had normal total testosterone levels. Five patients had low IGF-1 levels according to age, whereas 18 patients had basal cortisol levels between 5 and 15 µg/dL; therefore, ITT and GST were performed in these patients. Two patients had adrenal insufficiency in GST, whereas 11 patients had adrenal insufficiency in ITT. However, when both GST and ITT were evaluated, cortisol deficiency was detected in only 1 (3.4%) patient. It was found that four patients had GH insufficiency according to GST, and three patients had GH insufficiency according to ITT. When both GST and ITT were evaluated, three patients had GH insufficiency (10.3%) (Table 2).

Table 2. Clinical characteristics, study time, basal cortisol, peak cortisol, and GH levels after stimulation tests

Patients	Sex/age	Basal cortisol (µg/dL)	ITT peak cortisol (µg/dL)	ITT peak GH (µg/L)	GST peak cortisol (µg/dL)	GST peak GH (µg/L)
1	M/29	19.21	30.89	5.61	17.58	**0.72**
2	F/36	17.40	13.47	0.78	20.66	**2.92**
3	F/36	6.04	7.88	3.43	14.61	**6.69**
4	M/32	8.19	15.86	4.45	27.83	**5.79**
5	F/52	7.31	9.17	0.30	9.74	**0.89**
6	F/38	9.77	16.34	5.60	11.84	**7.01**
7	M/52	9.59	18.00	0.02	9.29	**0.02**
8	M/28	13.77	14.38	3.30	15.90	**15.59**
9	M/23	21.39	20.88	3.44	13.60	**2.05**
10	F/35	11.40	14.43	4.00	12.79	**4.39**
11	M/52	13.10	32.58	8.26	17.53	**9.96**
12	M/28	16.56	27.95	20.11	34.83	**18.01**
13	M/67	21.58	23.2	15.8	49.70	**4.90**
14	M/69	25.63	19.1	12.7	15.29	**10.51**
15	F/23	15.70	22.16	5.75	13.47	**5.69**
16	M/68	13.09	19.1	4.4	14.61	**2.70**
17	F/25	20.50	38.47	6.90	26.29	**4.11**
18	M/62	13.13	18.8	5.8	22.65	**3.74**
19	M/67	11.01	17.53	3.72	12.46	**1.90**
20	F/18	21.64	16.21	3.05	13.85	**2.02**
21	M/24	14.05	22.42	6.36	12.49	**0.27**
22	F/41	11.14	23.04	7.41	17.94	**1.17**
23	M/53	10.61	22.78	5.46	18.27	**7.66**
24	**M/65**	**11.83**	**19.78**	**7.56**	**11.8**	**1.27**

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DISCUSSION:

ACh as a neurotransmitter has been detected in the human body including the brain, vascular system, urogenital system, and endocrine system. OPs can affect the endocrine system by hormone receptors, hormone synthesis, and transcription factors (13, 14). OPs exert their effects on pituitary hormones in the acute and chronic periods by decreasing cholinesterase levels (15). In the literature, most studies have investigated acute effects, but there are a limited number of studies on the chronic effects of OPs. Thus, we investigated the chronic effects of OPs. The present study showed GH insufficiency in 3 (10.3%) patients and cortisol deficiency in 1 (3.4%) patient according to ITT and GST as evaluated together.

Dutta et al. revealed that in the acute period of OP poisoning, ACTH and cortisol levels are assayed higher than normal range. After 3 months, ACTH and cortisol levels were normal (2). On the contrary, in the present study, one patient had adrenal insufficiency according to ITT and GST in the chronic period. In a previous study, GH and IGF-1 levels were obtained in the acute period of OP poisoning, whereas GH levels were normal in all patients, and one patient had low IGF-1 level. After following up this patient for 3 months, IGF-1 deficiency persisted (2). In the current study, five patients had low IGF-1 level. ITT and GST were administered to confirm GH deficiency. As a result, GH deficiency was detected in three patients in the chronic period, and none of these patients had a history of traumatic brain injury, cerebrovascular event, pituitary adenoma, or another cause of GH deficiency.

In the acute period, thyroid function tests are altered. Huang et al. revealed that OP poisoning is associated with an increased risk for hypothyroidism within the first month (16). Several mechanisms may explain these alterations. One mechanism is non-thyroidal illness syndrome that is characterized by a decreased concentration of plasma T3, normal-to-low thyroxin, and a slight decrease or normal range of TSH concentration. After recovery, thyroid function tests return to normal in nonthyroidal illness syndrome (17). Another mechanism proposed is the presence of nicotine receptors (cholinergic) in the hypothalamus. After OP poisoning, these receptors are stimulated, which, in turn, stimulates somatostatin secretion, suppressing thyrotropin-releasing hormone and TSH secretion (18). In a previous study, serum TSH levels were found to be below the normal range in the majority of patients with OP poisoning in the acute period (18). Guven et al. revealed that patients who had non-thyroidal illness syndrome improve after resolution of poisoning (19). Gundogan et al. revealed that there is no statistical difference in pituitary hormone levels between untreated patients on admission to the MICU and treated patients before discharge from the hospital in the acute period. All of the patients had normal pituitary hormone levels (20). Similar with this result, no patients had abnormal thyroid function test disorders in the chronic period in our study

Cholinergic mediators may affect LH and FSH levels (2). Manfo et al. revealed that OP does not alter FSH and LH levels (21). In the present study, male patients had normal FSH, LH, and total testosterone levels; similarly, female patients had normal FSH, LH, and estrogen levels according to their menstrual or menopausal status. Guven et al. showed that increased serum prolactin, decreased FSH, and normal LH levels are detected in the acute period. However, prolactin declined to normal limits after resolution of poisoning (19). In our study, all patients had normal prolactin levels in the chronic period.

The limitations of the present study were low number of patients and relatively short follow-up time.

In conclusion, OP poisoning may affect pituitary functions in the acute and chronic periods. Most of the hormones improve after recovery in the acute period. In the literature, there is a paucity about pituitary functions at long term after OP poisoning. The present study revealed that GH and cortisol axis may affect OP poisoning. Further clinical and experimental studies are required to understand the mechanisms of hypopituitarism in the chronic phase after OP poisoning and whether routine screening of pituitary functions in this patient group is clinically relevant.

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