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Title: Effects of Organophosphate Poisoning on Endocrine System in Long-Term: A Pilot Study

Running Title: Organophosphate Poisoning on Endocrine System

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Abstract

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

Patients and methods: This prospective study was performed in Erciyes University Medical School. All of the patients had OP poisoning were followed up in Medical Intensive Care Unit (MICU). They evaluated after discharge from MICU at least after 6 months in terms of pituitary functions. In all patients, data were extracted from MICU records. Baseline hormone levels were assessed and dynamic tests (ITT= insulin tolerance test and GST= glucagon stress test) were performed.

Results: Twenty-nine adult patients (13 women, 16 men) with OP poisoning were included in the study. The mean age 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 (FSH) and luteinising hormone (LH) levels. The women had normal estrogen levels and men had normal total testosterone levels. Cortisol deficiency was detected in only one patient (3.4%) and 3 patients had GH insufficiency (10.3 %).

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

Keywords: Organophosphate poisoning**,** Endocrine effects, Pituitary functions

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Introduction

Organophosphates (OPs) are widely used for controlling pest worldwide, which leads to increased risk for human exposure (1). As a result of widespread availability OP are often used for suicide attempt with estimation of 300.000 people per annum (2). Acute adverse effects of OP on the central nervous system are related with accumulation of the acetylcholine (ACh). When this occurs, symptoms such as seizures, respiratory failure, anxiety, headache, ataxia, tremor, general weakness, in the end death can be seen (3). Poisoning with OP-based insecticidesis a serious condition requiring rapid diagnosis and timely treatment (4). Acute hormonal effects of OP are deficiencies in TSH, ACTH and IGF-1 correlated with levels of cholinesterase. Most patients with OP-related hormone deficiency recover at 3 months of follow up (2). However, knowledge of chronic effects of these chemicals are 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 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 this 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 (Ethics Committee decision 2013/108, Date: 05.02.2013) and informed consent was obtained from each patient.

Patients

Data were extracted from MICU records for all patients admitted between 2007 and 2012. The patients were followed-up in MICU minimum one day, maximum 29 days. Inclusion criterias were OP poisoning and have had at least 6 months after this exposure and lack of history of endocrine disorder. Exclusion criterias were age under 18 or above 70 years, history of the poisoning before previous 6 months, pregnancy, lactation, history of traumatic brain injury and hormonal disorders, chronic renal and hepatic failure, contraindications to ITT such as history of epilepsy, cerebrovascular or cardiovascular diseases.

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Assessment of pituitary function

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

Gonadotropin deficiency was detected in male patients when total testosterone level 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 low or inappropriately normal with low serum fT4 and fT3 levels (12). The somatotrophic and corticotrophic functions were evaluated by dynamic tests.

Evaluation of HPA and GH-IGF-1 axes by dynamic tests

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

Statistical analysis

The SPSS 15 program was used for descriptive analysis. Data were denoted as mean ± standart deviation (SD) and range.

Results

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The study group included 29 patients (16 men, 13 women) with a mean age of 41.9 ± 16.7 years (range 18–69 years) who had previous history of OP poising. In the study group, mean BMI was 25.7 ± 3.7 kg/m^2. 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 pseudo-cholinesterase level was 1509,2 ± 2544,4 u/L (range: 2550-6800 U/l). The organophosphate components used by patients were diazinon, monocrotophos, 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 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 the pituitary hormones

Prolactin, TSH, FSH and LH levels were normal in all patients. The female patients had normal estrogen levels according to menopausal status, menstrual phase while male patients had normal total testosterone levels. Five patients had low IGF-1 levels according to age while basal cortisol levels were between 5-15 µg/dl in 18 patients; therefore, ITT and GST were performed in these patients. According to GST, two patients had adrenal insufficiency while 11 patients had adrenal insufficiency in ITT. However, when GST and ITT were evaluated together, cortisol deficiency was detected in only one patient (3.4%). According to GST, it was found that 4 patients had GH insufficiency and ITT 3 patients had GH insufficiency. When GST and ITT were evaluated together, 3 patients had GH insufficiency (10.3 %) (Table 2).

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

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Patients	Sex/age	Study time after poisoning (months)	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	48	19.21	30.89	5.61	17.58	0.72
2	F/36	56	17.40	13.47	0.78	20.66	2.92
3	F/36	36	6.04	7.88	3.43	14.61	6.69
4	M/32	25	8.19	15.86	4.45	27.83	5.79
5	F/52	43	7.31	9.17	0.30	9.74	0.89
6	F/38	68	9.77	16.34	5.60	11.84	7.01
7	M/52	44	9.59	18.00	0.02	9.29	0.02
8	M/28	44	13.77	14.38	3.30	15.90	15.59
9	M/23	56	21.39	20.88	3.44	13.60	2.05
10	F/35	46	11.40	14.43	4.00	12.79	4.39
11	M/52	57	13.10	32.58	8.26	17.53	9.96
12	M/28	34	16.56	27.95	20.11	34.83	18.01
13	M/67	51	21.58	23.2	15.8	49.70	4.90
14	M/69	47	25.63	19.1	12.7	15.29	10.51
15	F/23	56	15.70	22.16	5.75	13.47	5.69
16	M/68	60	13.09	19.1	4.4	14.61	2.70
17	F/25	41	20.50	38.47	6.90	26.29	4.11
18	M/62	12	13.13	18.8	5.8	22.65	3.74
19	M/67	12	11.01	17.53	3.72	12.46	1.90
20	F/18	15	21.64	16.21	3.05	13.85	2.02
21	M/24	57	14.05	22.42	6.36	12.49	0.27
22	F/41	11	11.14	23.04	7.41	17.94	1.17
23	M/53	51	10.61	22.78	5.46	18.27	7.66
24	M/65	44	11.83	19.78	7.56	11.84	1.27

25	F/55	44	7.86	8.04	4.94	21.76	1.63
26	F/22	61	15.09	12.89	13.96	20.90	10.39
27	M/24	58	15.00	21.54	3.43	26.25	9.81
28	F/54	58	7.81	19.3	5.54	25.30	2.73
29	F/37	37	12.84	25.7	7.22	18.15	7.03

Discussion

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

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

In acute period, thyroid function tests are altered. Huang et.al revealed that OP poisoning is associated with increased risk for hypothyroidism, within first month (16). Several mechanisms may explain these alterations. One is non-thyroidal illness syndrome which is characterized by

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decreased concentrations of plasma triiodothyronine, normal-to-low thyroxin, and TSH concentration decreased slightly or at normal range. After recovery, thyroid function tests return normal in non-thyroidal illness syndrome (17). Another mechanism proposed is presence of nicotine receptors (cholinergic) in the hypothalamus. After OP poisoning, these receptors are stimulated, which, in turn, stimulates somatostatin secretion, suppressing TRH and TSH secretion (18). In a previous study, serum TSH levels were found to be below the normal range majority patients with OP poisoning in acute period (18). Guven et al. revealed that patients had non-thyroidal illness syndrome which improved after resolution of poisoning (19). Gundogan et al. revealed that there is no statisticaly difference in pituitary hormone levels between untreated patients on admission to the MICU and treated patients before discharged from the hospital in acute period. All of the patients had normal pituitary hormone levels (20). As similar with this result, no patients had abnormal thyroid function tests disorders in chronic period in our study.

Cholinergic mediators may affect LH and FSH levels (2). Manfo et al. revealed that OP didn't alter FSH and LH levels (21). In the present study, the male patients had normal FSH, LH and total testosterone levels, similarly the 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 were detected in acute period. However, prolactin declined to normal limits after resolution of poisoning (19). In our study, all patients had normal prolactin levels in chronic period.

Limitation of the presented study were low number of patients and relatively short following time.

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

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Conflict of interest: None.

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