

Research Paper:

The Lower Levels of Serum and RBC Cholinesterase in Acute Opioid Poisoning



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How to cite this paper Alizadeh A, Lotfinezhad N, Abasian Z, Najari F, Mostafazadeh B. The Lower Levels of Serum and RBC Cholinesterase in Acute Opioid Poisoning. Iranian Journal of Toxicology. 2020; 14(2):111-114.

<http://dx.doi.org/10.32598/ijt.14.2.672>



Article info:

Received: 02 Jan 2020

Accepted: 13 Feb 2020

Online Published: 01 Apr 2020

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ABSTRACT

Background: Cholinesterase is an enzyme that plays a critical role in regulating neural transmission. Many factors may decrease the cholinesterase levels in serum and Red Blood Cells (RBCs). It is suggested that the use of opium may effectively change the levels of Cholinesterase in serum and RBCs. This study aimed to evaluate the serum and RBC levels of cholinesterase in patients who were acutely poisoned with opium.

Methods: This cross-sectional study was conducted in 65 patients suffering from acute opium poisoning. The serum levels of cholinesterase were measured using an automated analyzer. The levels were also measured in RBCs, using a colorimetric method. Simultaneously, 65 patients served as the positive controls from among those poisoned with organophosphates.

Results: The serum cholinesterase levels were lower than the normal range in 16.9% of patients poisoned with opium and in 76.9% of those poisoned with organophosphate agents ($P < 0.001$). Similarly, the levels of RBC cholinesterase were lower than the normal range as found in 64.6% and 15.4% of patients poisoned acutely with opium (Group 1) and organophosphate (Group 2), respectively ($P < 0.001$).

Conclusion: Acute opium poisoning effectively reduced both the levels and activities of cholinesterase in the patients' serum and RBCs significantly different from those noted in patients suffering from organophosphate toxicity.

Keywords: Acute poisoning; Cholinesterase levels; Serum; RBCs; Opium; Organophosphates

Introduction

Cholinesterase is an important enzyme in the human body involved in the metabolism of many biochemical reactions. The function and normal levels of this enzyme are essential for the operation of many systems, including the proper activities of neurotransmitters, and the metabolism of some drugs and chemicals, including succinylcholine and organophosphate agents. Additionally, mus-

cle relaxants, especially succinylcholine, should be used for some treatment plans, such as tracheal intubation. In fact, the normal level and function of cholinesterase is essential for the drug metabolism and restoration of muscle contraction. Also, according to valid sources, health conditions, such as liver, kidney and genetic disorders, trauma, malnutrition, anemia, toxins and chemical agents, consumption of substances, such as morphine and codeine, may reduce the cholinesterase activity or level [1, 2].

Considering that the consumption of opium and its derivatives is relatively common in Iran [3], the aim of this study was to evaluate the serum and red blood cells (RBCs) levels of cholinesterase in patients who were acutely poisoned with opium.

Materials and Methods

Study Participants: This cross-sectional study was conducted on 65 patients suffering from acute toxicity with opium (Group 1) who were referred to and hospitalized in the poisoning ward of Imam Reza Hospital in Mashhad during the winter of 2018. Simultaneously, 65 patients with organophosphate poisoning were selected as positive controls (Group 2). The second group consisted of symptomatic patients who had been poisoned with a variety of organophosphate agents that was expected to decrease the levels of cholinesterase in both the serum and RBCs.

Inclusion Criteria: In the experimental group (Group 1), the definitive diagnosis of opium-related poisoning was confirmed by the urinalysis for each patient. The study method and concept were explained to the patients, and they were included in the study after they agreed to participate and completed the informed consent form.

Exclusion Criteria: Patients with any of the following conditions were excluded from the study, due to the possibility of interference with their cholinesterase response:

History of liver diseases, hemoglobinopathy, drug dependence, anemia (hemoglobin < 10 g/dL), having had a blood transfusion within the past 30 days, prolonged occupational exposure to chemicals, using drugs that inhibit cholinesterase activity, or having a history of Alzheimer or Myasthenia gravis.

Blood Analysis: Within the first 12-24 hours of hospitalization, 5 ml of non-heparinized blood sample was taken from each patient. Approximately 1-1.5 mL of the blood was collected in a tube containing citrated anticoagulant for the purpose of measuring the serum and RBCs cholinesterase levels at the reference laboratory. The serum cholinesterase was measured using an automated analyzer 3000BT (Italy). The level of RBC cholinesterase was also measured colorimetrically, using a Perkin-Elmer spectrophotometer (USA) and Fars Biorex kits. The normal level of cholinesterase in serum was considered within the range of 4000-7000 units/L.

The study's objective was to determine the levels of cholinesterase in patients suffering from acute opium toxicity. The results were summarized by stating the absolute fre-

quencies and percentages of categorical variables, examined through chi-square test. The data were analyzed using SPSS V. 16. A P-value of 0.05 or less was considered a statistically significant difference.

Results

In this study, 65 patients with acute opium toxicity (Group 1) and 65 other patients (Group 2) suffering from organophosphate poisoning were assessed. In both groups, the patients' age ranged from 18 to 65 years old. Regarding patients' gender distribution, 32 patients (49.2%) and 57 patients (87.6%) were male in groups 1 and 2, respectively ($P=0.040$). The remaining individuals in each group were females. The serum cholinesterase levels were lower than the normal range in 16.9% of patients poisoned with opium and 76.9% of those poisoned with organophosphate agents, revealing a significant difference between the two groups ($P<0.001$). Similarly, the levels of RBC cholinesterase were lower than the normal range in 64.6% and 15.4% in groups 1 and 2, respectively, indicating a significant difference between the groups ($P<0.001$).

Discussion

Cholinesterase plays a critical role in regulating the transmission of neural signals. This enzyme has two main isoenzymes, i.e., *C cholinesterase*, which is mainly present in the nervous system and RBC membrane and *butyryl cholinesterase* that is found in plasma, liver, pancreas, and brain. Normal levels of *acetyl cholinesterase* in human RBC range from 5-10 U/mL or 30-40 U/g of the hemoglobin. In serum, the normal cholinesterase levels range between 8 and 18 U/mL [4].

One of the important roles of cholinesterase is to metabolize drugs used to relax skeletal muscles. This is especially important for the metabolism of a depolarizing relaxant called succinylcholine [5]. Succinylcholine is used in the early stages of anesthesia in preparation to intubate patients, and sometimes in critically ill patients requiring emergency intubation [5]. If for any reason, the amount or activity of cholinesterase is low, muscle relaxation or paralysis caused by succinylcholine will persist for a long time and the anesthetist may have difficulty restoring the patient's muscle strength to normal.

Therefore, it is important to be aware of the patient's cholinesterase level and the responses to the test for the underlying conditions, such as drug usage [5, 6]. Therefore, it is necessary to check both cholinesterase and dibucaine concentrations before using succinylcholine.

At the lower values of these variables, the risk of long-term apnea following the use of succinylcholine may be raised. It is worth noting that the dibucaine concentration is used to differentiate individuals who have substitution mutations of the *butyryl cholinesterase* resulting in lower enzyme activity.

According to valid sources [1, 2], many factors may reduce the cholinesterase levels such as anemia, hemoglobinopathies, anti-malarial drugs, liver diseases, malnutrition, and pregnancy. Also, genetic factors and the use of certain drugs such as morphine, codeine, succinylcholine, and some toxins, such as organophosphates may lower the *butyryl cholinesterase* activity [1, 2]. Some studies have shown that in cases of inflammatory disorders and in critically ill patients admitted to the intensive care units, this enzyme has been reduced and hence its use as a prognostic agent [7, 8]. The levels of cholinesterase in serum and RBCs can be used for monitoring organophosphate poisoning.

However, its level may not be closely related to the severity of the poisoning [9]. For the reasons stated, it is necessary to measure the patient's serum cholinesterase levels and verify the interpretation before deciding to use such drugs, as succinylcholine for emergency intubation or in cases of toxicity analysis. For this purpose, this study selected a group of patients who were poisoned with organophosphate agents as the positive controls (Group 2). The experimental group was chosen from those with acute opium poisoning (Group 1) to determine differences in the levels of cholinesterase in acutely poisoned patients.

Our results showed lower than normal serum levels of cholinesterase in 16.9% of patients poisoned with opium and 76.9% of those poisoned with organophosphate. Particular attention must be paid to this important phenomenon when taking action to induce anesthesia or perform surgery in those who have used some of these agents or when trying to identify potential drugs or organophosphate agent as the cause of poisoning. Of note, the results of this study showed that in 15-16% of people who used any of these drugs may have decreased cholinesterase levels and thus precautions must be taken before using Succinylcholine. Also in people who are tested for a variety of toxicities by assessing cholinesterase levels that the low levels of this enzyme are confirmed, exposure to other toxins, such as organophosphate should also be ruled out.

Numerous studies have investigated the effects of opioids on the level of *acetyl cholinesterase*. Opioids have been considered as modulators of the cholinergic system

since the early 1970's when morphine was found to impair acetylcholine release and to facilitate neurotransmitter activities in the neuromuscular junction [10, 11]. In this study, no association was found between serum *acetyl cholinesterase* and the total period of use or average daily opioid intake. Patients who use opioids chronically may suffer from malnutrition, which in turn can contribute to lower *acetyl cholinesterase* levels.

In 2017, two scientists studied the effects of *morphine* and *tramadol* on the *acetyl cholinesterase* activity [12]. They showed that the enzyme activity in the cerebral cortex increased following the administration of repeated doses of tramadol or morphine. The data showed that the two drugs had a significant effect on the *acetyl cholinesterase* activity [12]. Bailey and Briggs in an *in vitro* study examined the effect of 17 commonly used substances on serum's pseudo-cholinesterase activity [13].

In the present study, morphine, quinidine and thioridazine at therapeutic doses could inhibit pseudo-cholinesterase activity higher than 5%. It was also concluded that the higher concentrations of these substances may have a higher inhibitory effect. Therefore, in this study, the *in vivo* evaluation of the conditions in humans at higher doses was recommended [13]. Our findings indicated that cholinesterase levels may also be lower in acute intoxicated patients. On the other hand, more studies in larger sample sizes are warranted to examine the effect of drug use, the type of drug, and other baseline variables, such as age, sex, nutritional status, and pharmacokinetic differences on the level of cholinesterase.

Conclusion

Serum cholinesterase level was lower than the normal range in 16.9% of patients with acute opium poisoning. Also, the level of this enzyme was reduced significantly in RBCs of 64.6% of these patients. Acute opioid poisoning can be reliably monitored by the measurement of serum and RBC cholinesterase levels. Broader studies are recommended to increase the validity and accuracy of the results, and to investigate the associated factors and differences involved in acute and chronic opioid poisoning.

Ethical Considerations

Compliance with ethical guidelines

All authors met the criteria of authorship based on the recommendations of the international committee of medical journal editors.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author's contributions

All authors contributed in preparing this article.

Conflict of interest

The authors declared no conflict of interest.

Acknowledgments

The authors express appreciation to the Department of Clinical Toxicology, Imam Reza Hospital, Mashhad University of Medical Sciences, Mashhad, Iran.

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