**The Effects of Synthetic Cannabinoids on Alveolar-Arterial Oxygen Gradient**

**Sentetik Kannabinoidlerin Alveolo-Arteriyel Oksijen Gradienti Üzerine Etkileri**

**Sentetik Kannabinoidler ve Solunum Fonksiyonları / Synthetic Cannabinoids and Respiratory Functions**

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**Abstract**

**Aim:** Synthetic cannabinoids are chemicals that produce several marijuana-like effects in humans. Aim of this study is to investigate the effects of synthetic cannabinoids on alveolar-arterial oxygen gradient. **Material and Method:** A total of 112 patients, who admitted directly to emergency clinic with synthetic cannabinoid usage, were determined between February 2014 and August 2014. Blood gases of 41 patients were determined as arterial blood gases on room air, and included in this study. Patients were evaluated according to age, sex, decade, partial pressure of arterial oxygen, partial pressure of arterial carbon dioxide, pH, bicarbonate, metabolic status, age consistent expected alveolar-arterial oxygen gradient and calculated alveolar-arterial oxygen gradient. Results: Synthetic cannabinoid usage was higher in males, mean age of patients was 23.32±6.14 years. Number of patients in the third decade were significantly higher than the other decades. The calculated alveolar-arterial oxygen gradient value of patients was significantly higher than age consistent expected alveolar-arterial oxygen gradient value. Respiratory acidosis, was significantly higher than the other types of the metabolic disorders. The best cutoff point for calculated alveolar-arterial oxygen gradient was 12.70, with sensitivity of 90% and specificity of 85%. Area under curve was 0.70 for calculated alveolar-arterial oxygen gradient. Discussion: The value of alveolar-arterial oxygen gradient has been increased due to synthetic cannabinoid usage. This can be used as a supportive parameter in the diagnosis of synthetic cannabinoid usage.

**Keywords**

Synthetic Cannabinoids; Blood Gases; Diagnosis

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**Introduction**

Synthetic cannabinoids (SC) are chemicals that produce several marijuana-like effects in humans. Synthetic cannabinoids are usually known as “Spice” in Europe, “K2’ in United States of America and “Bonzai or Jamaika” in Turkey. These agents are obtained by spraying several different synthetic cannabinoids onto the vegetable ingredient, and herbal cigarettes mixtures that smoking in a similar way to cannabis by users [1]. Recently, SC usage has been increased, and more common seen in young adults and males [2]. Both animal studies and anecdotal clinical evidence suggest that the SC products may lead to more severe and unusual toxic effects than natural marijuana. The euphoric and psychoactive effects of SC are similar to marijuana, but SC have additional sympathomimetic symptoms, including diaphoresis, agitation, and restlessness [3]. The chemical structures of SC are similar to marijuana but there is no correlation between SC and Δ9-tetrahydrocannabinol in terms of toxicological investigations. Recognition of the signs and symptoms of intoxication and a high index of suspicion are necessary to diagnose SC toxicity [4]. In the literature there are several reports of rhabdomyolysis, kidney failure and acute myocardial infarction after SC usage. There have been a number of reports linking cannabis to pulmonary dysfunction. However, to date there are few reports that shows a link between SC and respiratory dysfunction [5-6].

Arterial blood gas analysis is a common investigation in emergency departments for monitoring patients with acute respiratory failure and considered the gold standard to determine oxygenation, patient’s gas exchange, ventilatory control and acid-base status in the acutely injured as well as critically ill patients. The impaired pulmonary function manifests in the form of decreased partial pressure of arterial oxygen (PaO2), an indicator of decreased partial pressure of arterial oxygen (PaO2), an increased alveolar-arterial oxygen gradient (p(A-a)O2) [7]. The depressive respiratory effect of SC inhalation has not been thoroughly investigated in the medical literature. Aim of this study is to investigate the effects of SC usage on alveolar-arterial oxygen gradient.

**Material and Method**

Patients who admitted directly to our emergency clinic for SC using, were determined from forensic records of hospital between February 2014 and August 2014. Due to unknown treatment and application form, patients who referred to our emergency clinic from another hospital were excluded from the study. A total of 41 patients were determined in this time period. Synthetic cannabinoid usage was confirmed by the patient or witnesses. Laboratory and clinical data were obtained from the digital medical records database of the hospital. In this retrospective study, the effects of SC inhalation on alveolar-arterial oxygen gradient were determined by arterial blood gases of patients that not given oxygen therapy. For this purpose, measurements of arterial blood gases were obtained from the patients that room air, and non-incubated arterial blood gas measurements were evaluated. In 18 patients, blood gas samples were not taken during emergency department evaluation, these patients were excluded from study. Blood gas measurements of remaining 94 patients, were evaluated retrospectively with a chest disease specialist to confirm arterial blood gas samples on room air.

In some studies, relationship between arterial and venous blood gases has been investigated. In these studies, mean PaO2 value has been found between 55-115 mmHg, mean partial pressure of venous oxygen (PvO2) value between 25-48 mmHg, mean partial pressure arterial of carbon dioxide (PaCO2) value between 35-42 mmHg, mean partial pressure of carbon dioxide (PvCO2) value between 41-42 mmHg. Partial pressure of oxygen (PO2) is significantly different between arterial and venous blood gases according to partial pressure of carbon dioxide (PCO2). The saturation of oxygen (SO2) value has been found between 87-89 mmHg, in these studies [8-9-10]. According to these results, blood gases of 40 patients that PaO2 value less than 48 mmHg accepted as venous blood gases, and these patients were excluded from study. In 13 patients, value of SO2 was higher than 89 mmHg, these samples were accepted as arterial blood gases with oxygen treatment, and excluded from study. A total of 41 patients' blood gas samples were determined as arterial blood gases on room air, and included to study. Patients were evaluated according to age, sex, decade, PaCO2, PaCO2, pH, bicarbonate (HCO3), metabolic status, calculated p(A-a)O2 and age consistent expected p(A-a)O2. The p(A-a)O2 of patients was calculated according to formula of p(A-a) O2: [150-(1.25xPaCO2)]-PaO2. Age consistent expected p(A-a) O2 of patients was calculated according to formula of p(A-a) O2: 2.5+[0.25xage(years)] [11].

Data were analyzed using the Statistical Package for Social Sciences version 16.0. (SPSS: An IBM Company, version 16.0, IBM Corporation, and Armonk, New York, USA). All data were expressed as the mean ± standard deviation. The Student’s t test was used to compare the means for the studied variables. For comparing the continued two groups, Pearson Chi-square test was used. The P value smaller than 0.05 was considered statistically significant. The cut-off values of parameters for discrimination of the groups were determined using the Receiver Operating Characteristic (ROC) curve analysis. The areas under the ROC curves were calculated and the specificity, sensitivity and accuracy, for the parameters have been determined.

**Results**

A total of 112 patients were analyzed, 111 patients were male and only 1 patient was female. Synthetic cannabinoid using was significantly higher in males (p < 0.001), and mean age of patients was 23.32 ± 6.14 years (ranged: 15 to 48). Sixty two percent of patients were located between age of 18-24 years. There were 35 patients in the second decade, 60 patients in the third decade,15 patients in the fourth decade and only 2 patients in the fifth decade. Number of patients in third decade were significantly higher than the other decades (p = 0.02). The mean arterial blood gas values of 41 patients that included in the study were shown in Table 1. The value of PaO2 was reduced according to reference range, but not statistically significant (p > 0.05). The value of PaCO2 was adjacent to upper limit of the reference range, but not statistically significant (p > 0.05). The value of calculated p(A-a)O2 was significantly higher than age consistent expected p(A-a)O2 value (p = 0.02). Respiratory acidosis was significantly higher than the other metabolic disorders (p = 0.02).
Table 1. Mean arterial blood gas values of patients.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Determined Value</th>
<th>Reference Range</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO₂</td>
<td>63.95 ± 8.42 mmHg</td>
<td>(83-108 mmHg)</td>
<td>p &gt; 0.05</td>
</tr>
<tr>
<td>PaCO₂</td>
<td>48.00 ± 6.93 mmHg</td>
<td>(35-48 mmHg)</td>
<td>p &gt; 0.05</td>
</tr>
<tr>
<td>HCO₃⁻</td>
<td>25.63 ± 2.59 mmHg</td>
<td>(22-26 mmol/L)</td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.35 ± 0.04</td>
<td>(7.35-7.45)</td>
<td></td>
</tr>
</tbody>
</table>

Age consistent expected p(A-a)O₂: 8.45 ± 1.74

Calculated p(A-a)O₂: 26.02 ± 11.07 p = 0.02

Metabolic Status

Respiratory acidosis: 20 patients p = 0.02
Normal values: 9 patients
Mixed respiratory acidosis + Metabolic alkalosis: 8 patients
Metabolic acidosis: 2 patients
Respiratory alkalosis: 1 patient
Compensated metabolic alkalosis: 1 patient


ROC Curve

Receiver operating characteristic curve for calculated p(A-a)O₂ was shown at Figure 1. Best cutoff point for calculated p(A-a)O₂ was 12.70, with sensitivity of 90% and specificity of 85%. Area under curve was 0.70 for calculated p(A-a)O₂.

Discussion

Synthetic cannabinoids are synthesized to mimic the action of Δ9-tetrahydrocannabinol, that is an active compound in marijuana [12]. Recently, SC usage and toxicity have been increased between young adults and males all across the world. Barratt and colleagues were found, mean age was 27 for SC use in Australia and 77% of users were male [13]. Hoyte and coworkers found, mean age for SC use was 22.5 and 74.3% of users were male [2]. Consistent with the literature, we found SC using was significantly higher in males and mean age of patients was 23.32 years. Most users are young adults, with the desire to experience cannabis-like effects with a substance that cannot be detected on routine drug tests. The relatively low cost is another reason for its popularity in the younger age group [14]. Although there is an extensive literature detailing respiratory effects of conventional cannabis marijuana and non-tobacco additives in cigarettes, pulmonary toxicity in the context of SC abuse is not as well-reported as toxicity in other organs. In some studies researchers indicated that, cannabis using was associated with higher lung volumes and increased large-airways resistance, but there was a little evidence for airflow obstruction or impairment of gas transfer in these studies [15-16]. In a study on conscious monkeys, SC agonists WIN55212-2 decreased tidal and minute volume, whereas respiratory frequency was not changed [17]. Tashkin sad that, Δ9-tetrahydrocannabinol in smoked marijuana initially relaxes airway smooth muscle and causes bronchodilation in both healthy persons and stable asthmatic patients, this bronchodilator effect is relatively short-lived (lasting as long as 60 minutes and six hours) and diminishes with the repeated use of marijuana (tachyphylaxis) [18]. Taylor et al. found a declined lung function in association with the development of chronic obstructive pulmonary disease (COPD) in chronic cannabis smokers [19]. Respiratory depression in rats receiving Δ9-tetrahydrocannabinol was reported in early publications but involvement of specific cannabinoid receptors could not be demonstrated [20]. Schmid and colleagues were showed that, increasing doses of the synthetic cannabinoid agonists WIN55212-2 and CP55940 markedly and dose-dependently lowered mean arterial pressure, heart rate and the plasma noradrenaline concentration in rats. These cardiovascular effects were accompanied by a large decrease in respiratory rate. CP55940, has been caused a decrease in PO2 and pH, whereas an increase in PCO2. The natural cannabinoid agonist, Δ9-tetrahydrocannabinol also decreased mean arterial pressure, heart rate, the plasma noradrenaline concentration and respiratory rate. The first major finding of this study was, cannabinoid agonists – both synthetic and natural – also elicit respiratory depression by acting at CB1 receptors, as shown by a marked decrease in respiratory rate, hypoxia, hypercapnia and arterial blood acidosis. Researchers speculated that cannabinoids could affect the function of different peripheral receptors involved in respiratory regulation. These agents could also influence airway resistance acting directly on the bronchi [21].

Like these studies, we found a higher level of PaCO₂ and lower level of PaO₂ according to reference range, but not statistically significant. And also, respiratory acidosis was the most common type of metabolic disturbance in our study. These findings may be a result of increased large-airways resistance, a large decrease in respiratory rate due to SC using and respiratory suppressor effects of synthetic cannabinoids.

Additionally, we found significantly higher value of calculated p(A-a)O₂ according to expected p(A-a)O₂. The p(A-a)O₂ is a simple way to measure alterations between the alveolus and capillary, and has recently been used in the study of different critical disorders such as COPD and pulmonary thromboembolism. The normal p(A-a)O₂ increases with age. An abnormally
increased p(A-a)O2 suggests a defect in diffusion, ventilation/perfusion (V/Q) mismatch or right-to-left shunt [22].

The principal contributor to hypoxemia in COPD patients is V/Q mismatch resulting from progressive airflow limitation and emphysematous destruction of the pulmonary capillary bed [23]. The widening p(A-a)O2 was determined in some studies about COPD in the literature [24]. Like to COPD, cannabis usage was associated with higher lung volumes, suggesting hyperinflation and increased large-airways resistance [15-16]. Additionally, Taylor and Hall were sad that, a small but significant proportion of chronic cannabis smokers will exhibit decline in lung function in association with the development of COPD [19]. Due to similar nature of COPD and cannabis using, a significant higher level of calculated p(A-a)O2 in SC using can be explained by V/Q mismatch due to higher lung volumes, suggesting hyperinflation and intrapulmonary right-to-left microshunting due to lowered mean arterial pressure and heart rate.

**Limitations**

Synthetic cannabinoid using was not determined by the laboratory measurements in this study. And also we couldn't get simultaneous biochemical values. These are the most important limitations of this study. Due to retrospective nature of study, we do not know co-morbidities and how long the patients were using these agents. Additionally we do not know, if they use another agents such as cigarette.

**Conclusion**

Synthetic cannabinoid usage cannot be detected on routine drug tests, and has been increased between young adults and males. The calculated alveolar-arterial oxygen gradient is increased according to age consistent expected alveolar-arterial oxygen gradient in patients with synthetic cannabinoids usage. Increased alveolar-arterial oxygen gradient can be used as a supportive parameter in the diagnosis of synthetic cannabinoid usage.

**Competing interests**

The authors declare that they have no competing interests.

**References**