**Case Report**

**Indoxacarb-Related ARDS, Neurotoxicity and Orange Urine**

**İndoksakarb İlişkili ARDS, Nörotoksisite ve Turuncu İdrar**

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**Abstract**

A 17 year old male developed adult respiratory distress syndrome (ARDS), seizures, intravascular hemolysis and peripheral neuropathy following self-poisoning with a pesticide containing 14.5\% indoxacarb. He was managed conservatively with fluid management, antibiotics, mechanical ventilation and physiotherapy. There is limited data concerning the human toxicity of indoxacarb. This case demonstrates that findings from animal studies, such as seizures, respiratory distress, and intravascular hemolysis are possible following self-poisoning in humans. In this patient, partial recovery was achieved following supportive care.

**Key Words:** ARDS, indoxacarbs, neurotoxicity, orange urine

**Özet**

17 yaşındaki bir erkekte % 14.5 indoksakarb içeren bir pestisit ile zehirlenmeyi takiben ARDS, nöbet, intravasküler hemoliz ve periferik nöropati gelişti. Sıvı tedavisi, antibiotikler, mekanik ventilasyon ve fizyoterapi ile konservatif olarak tedavi edildi. İndoksakarbin insanlardaki toksisitesi ile ilgili sınırlı veri bulunmaktadır. Bu vaka hayvan çalışmalardan nöbet, solumun sıkıntısı ve intravasküler hemoliz gibi bulguların zehirlenmeyi takiben insanlarda olabileceğini gösterir. Bu hasta destekleyici bakım sonrasında kısmi iyileşme sağlanmıştır.

**Anahtar Kelimeler:** ARDS, indoksakarb, nörotoksisite, turuncu idrar

**Introduction**

Indoxacarb is an oxadiazine insecticide that is considered a safe substitute for organophosphate pesticides against insects such as the cotton bollworm and native budworm in soybeans, fava beans and chickpeas [1]. Only seven cases of indoxacarb poisoning have been reported to date [2, 3]. All seven cases had methemoglobinemia that was treated with intravenous methylene blue without any mortality. We report the case of a 17-year-old boy with deliberate indoxacarb poisoning who presented with adult respiratory distress syndrome (ARDS) at admission and later developed quadripareisis with ophthalmoplegia and orange urine.

**Case Report**

This boy was brought by his friends to our emergency department three hours after having consumed an unknown quantity of a pesticide containing 14.5\% Indoxacarb and APSA-80™ (alkyl aryl oxalate). His consent is obtained from patient’s father. The type of substance ingested was unknown at that time. On arrival, he was restless, tachypneic, and sweating profusely with a blood pressure of 90/60 mmHg and pulse of 110/min. He had bilateral coarse crackles and was intubated on arrival for suspected cholinergic crisis following organophosphate poisoning. Atropine infusion (20 mg IV stat, 5 mg/hour), pantoprazole 40 mg IV, clonazepam 5 mg BID (for myoclonic jerks) and dopamine 5 µg/kg/min were initiated. Continuous gastric aspiration was initiated following gastric lavage. Post-intubation arterial blood gases (ABG) revealed pH 7.24, PO₂ 61 mmHg, pCO₂ 34 mmHg, HCO₃⁻ 14.6 mmHg and SaO₂ 91%. Plasma cholinesterase levels were 409 U/L (3714-11513), hemoglobin 195 g/L, hematocrit 58%, total counts 23.2×10⁹/L, and platelets 3.3×10⁹/L were observed. Chest radiography (CXR) revealed ARDS (Figure 1a). Electrocardiography and echocardiography were normal. Six hours later, his parents brought the manufacturer’s bottle to the hospital for investigation. Atropine was discontinued after carefully questioning the parents regarding the storage of organophosphates/carbamates in the bottle. On the 2nd to 4th days after admission, his urine was discolored orange (Figure 1c). Further investigations included positive urinary RBCs and hemoglobin and negative myoglobin, potassium
3.1 mmol/L, lactate dehydrogenase (LDH) 852IU/L (114-240), creatine kinase (CK) 96U/L (25-200), creatinine (90 µmol/L) and fibrinogen 220 mg/dL (200-400). Inotropes were tapered and discontinued over the next 48 hours. The chest radiograph findings also resolved within two days (Figure 1b). The patient began obeying commands on the 3rd day after admission, but two days later, he developed ptosis (Figure 1d), extraocular paresis and flaccid quadriparesis (4+/5). Beginning on the eighth day, his paralysis and ptosis were complete and the patient had no response to pain stimuli. Nerve conduction revealed demyelinating polyradiculoneuropathy, while computed tomography (CT) of the head was normal. He developed ventilator-associated pneumonia (*Acinetobacter* spp.) that was treated with gentamycin and polymyxin B for 10 days. He had one episode of generalized tonic convulsions on the 9th day of his admission, after which his GCS decreased to 2T/15 and phenytoin was instituted. Cerebrospinal fluid studies conducted on the same day were normal. MRI could not be performed due to financial constraints. A tracheostomy was performed on day 14. By day 20, he had power of 4/5 and 3/5 in his upper and lower limbs, respectively, and was weaned off the ventilator. He was decannulated on day 22. At the time of discharge (day 27), he was able to eat a soft diet, required a condom catheter for urinary drainage, and could produce harsh sounds after closure of his tracheostoma. He returned at 2 months for a follow-up visit, at which time he had gained weight, had normal muscle power and mild hoarseness of voice.

**Discussion**

The sodium channel blocker insecticides include dichlorodiphenyltrichloroethane (DDT), pyrethroids, oxadiazines (indoxacarb), semicarbazones (metaflumizone) and pyrazolines. Local anesthetics, antiarrhythmics and antiepileptic drugs block these same sodium channels. Due to increasing resistance to pyrethroids and the high mortality/morbidity associated with organophosphates, indoxacarb is being touted as a safer and effective replacement [4, 5].

Seven case reports and one case series describing indoxacarb poisoning are available. All patients recovered with methylene blue treatment, although two of these
patients were mechanically ventilated and an additional two patients had renal failure. One retrospective study from Korea described 10 indoxacarb poisoning patients, four of whom received methylene blue treatment; the complications observed in these patients included cyanosis, respiratory distress, cardiac arrest, pneumonia, heart failure, hemolytic anemia and generalized seizures [6].

Indoxacarb is an indeno-oxadiazine insecticide whose insecticidal activity is mediated by the S-enantiomer of its active metabolite DCJW (decarbomethoxylated JW062) that blocks the tetrodotoxin-sensitive voltage-dependent sodium channels [7]. Inward sodium currents are blocked, resulting in the hyperpolarization of membrane potential. DCJW acts on the same site as lidocaine. Indoxacarb is a pro-insecticide, and DCJW inhibits compound nerve action potentials in insect nerves. In mammals, indoxacarb itself blocks sodium channels [8]; these sodium channels are less sensitive to the effects of DCJW [7]. Pseudoparalysis, a condition of apparent paralysis accompanied by violent movements when disturbed, occurs in the affected insects. Neurological complications such as ataxia, tremors, hemolysis, and increased RBC turnover have been observed in rats exposed to indoxacarb. In both rats and mice, weakness, head tilting, abnormal gait or ataxia, depression, head shaking and hypersalivation are observed [4]. Neuronal necrosis and pyriform cortex vacuolation are also observed in mice, and weight loss, seizures and hemolytic anemia may occur in dogs.

Our patient had consumed a 14.5% indoxacarb solution containing indoxacarb (14.5% w/w), inactive enantiomers (6% w/w), distilled methyl soylate, amorphous silicon dioxide, polyethoxylated polyaryl phenol and polyethoxylated polyaryl phenol phosphate; APSA 80 is a spray adjuvant concentrate containing butanol [8]. Methyl soylate is a methyl ester (from ethanold and soybean oil), while silicon dioxide is a defoamer and emulsion stabilizer. Polyethoxylated polyaryl phenol phosphate causes only mild abdominal symptoms. Butanol toxicity has been reported in only one instance, causing hypotension, acidosis, respiratory insufficiency, muscle hypotonia and weakness, which were resolved with supportive therapy [9]. Phenolic compounds may cause hemolysis and urinary discoloration, as observed in our patient [10]. Seizures at admission due to indoxacarb have been reported, but our patient exhibited myoclonic jerks initially and seizures only after one week. The low AChE levels observed in our patient could not be explained, although coexisting organophosphate consumption could not be ruled out.

In conclusion, we report the first description of the non-methemoglobinemic effects of indoxacarb poisoning in a human. Its presentation may be similar to that of cholinergic crisis, with low ChE levels, which may cause diagnostic confusion. There are limited data concerning the human toxicity of indoxacarb. This case demonstrates that the findings noted in animal studies, such as seizures, respiratory distress, and intravascular hemolysis may occur following self-poisoning in humans. In this patient, partial recovery was achieved with supportive care.

Conflict of interest statement: The authors declare that they have no conflict of interest to the publication of this article.

References