Silver Intoxication Due to Use of Silver Nanocrystals (Acticoat) in a Pediatric Burn Case with High Mortality: Case Report

Yüksek Mortalite ile Seyreden Pediatrik Yanık Olgusunda Nano Kristalin/(Acticoat) Kullanımına Bağlı Gümüş İntoksikasyonu

Hülya ÖZAY YİĞİT,[a]
Tamer KUZUCUOĞLU,[a]
Oğuzhan KILAVUZ,[a]
Hakan Ahmet ACAR[b]

Clinics of
[a]Anesthesiology and Reanimation,
[b]General Surgery,
Dr. Lütfi Kırdar Kartal Training and Research Hospital, İstanbul

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Yazışma Adresi/*Correspondence:*
Tamer KUZUCUOĞLU
Dr.Lütfi Kırdar Kartal Training and Research Hospital,
Clinic of Anesthesiology and Reanimation, İstanbul,
TÜRKİYE/TURKEY
tkuzucuoglu@yahoo.com.tr

ABSTRACT Silver nanocrystals (acticoat) are frequently used in protection of the burn lesions since they have high antibacterial and antimicrobial activity. Depending on size and depth of lesion as well as application duration; use of silver nanocrystals leads to accumulation in the target organs and consequently intoxication. Silver intoxication progresses with findings of fever, gastroenteritis, convulsion, meningismus, leukopenia and increased liver enzymes. It is diagnosed by silver amount in the blood, urine and stool. Cessation of silver intake and symptomatic treatment have primary importance for the treatment. This case presentation aimed to discuss the 2-year-old male patient in the light of literature data with respect to silver intoxication that we have concluded due to high level of silver concentration found in blood and urine because of prolonged use of acticoat for 2nd-3rd degree burn lesions covering 45% of total body surface area in the burn intensive care unit.

Key Words: Silver; burns; acticoat

ÖZET Nano gümüş kristalleri (acticoat), yanık alanlarının korunmasında antibakteriyel ve antimikrobiyal aktivitesinin iyi olmasından dolayı sıklıkla kullanılmaktadır. Yanık alanının büyüklüğü ve derinliği ile uygulama süresi, gümüş kristallerinin vücutta hedef organlarda birikimine ve sonuçta intoksikasyona neden olmaktadır. Gümüş intoksikasyonu; ateş, gastroenterit, konvülziyon, meningismus, lökopeni ve karaciğer enzim yüksekliği bulguları ile seyretmektedir. Tanı kan, idrar ve feçesteki gümüş miktarına bakılarak konulmaktadır. Tedavide gümüş alınımının kesilmesi ve semptomatik tedavi ön plandadır.Bu çalışmada %45 2-3. derece haşlanma yanığı nedeni ile uzun süre yanık yoğun bakım ünitesinde "actiocat" uygulanan ve kanda ve idrarda yüksek düzeyde gümüş bulunması üzerine gümüş intoksikasyonu düşündüğümüz iki yaşındaki erkek olgunun literatür bilgileri eşliğinde tartışılması amaçlanmıştır.

Anahtar Kelimeler: Gümüş; yanıklar; acticoat

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Acticoat (Anka Medikal İşitme Cihazları, Ankara, Turkey) wound dressing including silver nanocrystals, has been used topically in preventing burn wound infections for many years. These nanocrystals are applied by dermal and inhalation use. Their absorption occurs in two forms as ionized silver and nanosilver particles. It is determined that nano silver particles were non-nano silver particles.[1,2] Biological toxic effect of nano silver compound is known as argyria. This phenomenon shows that silver is absorbed in ionized form and faced a long systemic effect period. Silver is especially accumulated in target organs such as liver and kidney.

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Several studies have shown that elimination of silver particles occur by urine.[3,4] However, some authors have also detected that silver compounds are found in urine and stool by the equal amounts.[2] Toxic effect of the silver particles acquired by inhalation couldn't have been demonstrated until the present time and some studies also have shown that silver particles leads to argyria and increased liver enzyme levels when acquired by dermal way.[5] It has been determined by several studies that toxic dosages of silver compounds lead to hepatic and renal dysfunction, leukopenia and neurotoxicity in central nervous system.[5-8]

CASE REPORT

After taking written informed consent and approval of intensive care unit by his family, he was accepted to burn intensive care unit (BICU). Topical acticoat has been applied 14 days and after the initial treatment for scald burn fields in several regions of his body patient hospitalized in the healthcare facility. The first examination of the 15 kg two-year-old male patient who was sent to BICU of our hospital in the 14th treatment day for advance investigation and treatment revealed open and cooperative conscious, present pupillary light reflex, pediatric glasgow coma scale (GCS):14, expected mortality rate according to PRISM Score: 92.7%. The patient with burned 40% and more seriously have been accepted high mortality rate according to Prism score. Electrocardiogram (EKG) and peripheric oxygene saturation (SpO_2) was monitorized. Foley catheter (No:8) was introduced for urine output. Tension arterial was evaluated as noninvazive. Tension arterial (TA):70/44 mmHg, heart rate (HR): 139/min, respiratory rate (RR): 43/min, hypothermic (below 36°C), SpO_2: 94% on room air, breathing sounds were bilateral, equal and rough. Laboratory findings were within normal limits except PLT; 24 000/mm^3, aPTT: 47.1sec, PT: 77.6 sec, activity: 9%, INR: 6.78. He required intubation and mechanical ventilation because of increased tachypnea (>45/min), SpO_2 <90% and PaO_2<60 mmHg on room air in the first admission day. Hemogram, arteriel blood gases and laboratory parameters were taken two times in a day. He was administered replacement of fresh frozen plasma and thrombocyte to reach normal limits of coagulometers. He was applied bedside dressing under sedoanalgesia and acticoat to his total 45% of burned fields (Figure 1). In the second day of admission, his measurements were such as following: leukocyte: 6400/mm^3, AST: 523U/L, ALT: 171U/L. He was extubated in the 10th day of admission. Although, the patient was receiving supportive treatment; neurological dysfunction progressing with findings such as fever, gastroenteritis, convulsions, shivering, tendence to sleep and meningismus developed in the 12th day of admission. Silver compounds were administered for twenty six days as a whole. Blood laboratory tests revealed no lekopenia which explains this clinical picture and slightly increased liver enzyme levels (AST, ALT) were noticeable. An urgent cranial magnetic resonance imaging (MRI) was performed and its result was found normal. Silver intoxication was considered according to the literature records and all anticoats were removed. It was monitored that patient's skin showed no argyria. Laboratory tests revealed blood silver levels: 12 mcg/L (N:0.2-1 mcg/L) and urine nanocrystalline silver level: 45.2 mcg/L (N:0.1 mcg/L). The patient underwent bedside dressings once in every 2 days during ICU follow-ups. Daily laboratory levels were followed-up twice in a day. Laboratory test results in the 22nd

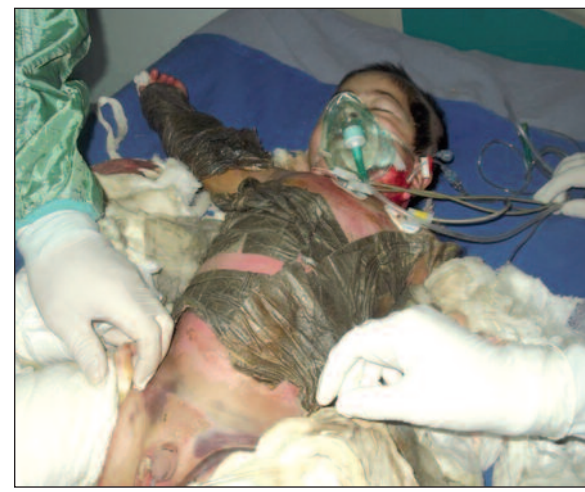

FIGURE 1: Appearance of the patient applied Acticoat.
(That has been taken with written informed consent of his family)

day of admission showed blood nanocrystalline and urine nanocrystalline values respectively: 0.48 mcg/L (N:0.2-1 mcg/L) and 0.40 mcg/L (N:0.1 mcg/L). He was applied debridement+grafting in the 34th day of admission. The patient was discharged from the hospital in the 59th day of admission.

DISCUSSION

In vitro studies suggested that essential mechanism of nanosilver intoxication resulted from increased production of cellular reactive oxygen species (ROS). Increased ROS activates oxidative mechanisms and especially high doses of nanosilver crystallines lead to secondary genetic toxicity, cell death and apoptosis. Christensen et al. have shown that nanocrystalline (acticoat) particles have less toxicity and higher antimicrobial activity than silver sulfadiazine.[9] Nanocrystals with smaller particles are more effective with respect to damage mechanism and they cause highest damage in lung and liver.

It has been shown associated with pulmonary toxicity that silver caused increased production of ROS in the mitochondrial chain system and cessated ATP synthesis and deteriorated DNA synthesis.[10] It is stated associated with liver as the main target organ that nanosilver toxicity initiates oxidative stress by increasing production of ROS in the hepatic epithelial cells and leads to apoptosis and also necrosis due to high dosages. It is suggested that it caused no irritation, corrosion and sensitization in any organ. It has been also demonstrated that it has no mutagenic and carcinogenic properties.[11] Trop et al. have applied acticoat for 1 week in the 17-year-old patient with burned areas covering 30% of total body surface area (TBSA) and they have found findings such as hepatotoxicity and argyria on face and some body regions. They have found plasma silver level and urine silver level in the laboratory tests as 107 mcg/L and 28 mcg/L, respectively. Laboratory values and clinical picture turned to normal levels after removal of acticoat.[10] Vlachou et al. have applied acticoat for averagely 9 days in the 30 patients with burned areas covering averagely 12% of TBSA and measured mean serum silver level 56.8 mcg/L. They have detected serum silver level 0.8 mcg/L at the 6th month following removal of acticoat however no finding of hematological and biochemical toxicity in all patients.[11]

Moiemen et al. have applied acticoat for averagely 9.5 days in the grafted, non-grafted and skin grafted donor sites of the 6 patients with burned areas covering 20% or larger portion of TBSA and have found mean serum silver level 200.3 mcg/L. They have encountered serum silver level 8.2 mcg/L at the final 9th month of the study. They detected no anomaly or argyria by the hematological or biochemical markers in the patients. This study has drawn attention to the point that treatment with acticoat is accompanied with high serum silver levels however this treatment caused no toxic symptoms and that treatment with acticoat is a safe and effective application.[12,13] Even though, diagnosis of silver toxicity is ruled out from absence of leukopenia despite high liver enzyme levels of the patient in our study; silver toxication was taken into account after exclusion of all other factors. We evaluated reduction of silver levels to normal limits in the 22nd day of admission associated with large size of burned surface in the patient. Wang et al. have applied acticoat in the 36 patients with burned areas covering averagely 13.4% of TBSA in their study involving 46 pediatric cases and found serum silver level 114 mcg/L. Serum silver levels of the resting 10 patients with average burned surface covering 1.85% of TBSA were found <5.4 mcg/L. They have stated according to this result that silver products constitute an important part in the burn treatment and that high amounts of silver which is involved for a long duration in the target organs of the patients with burned areas covering high percentile of TBSA should be taken into consideration.[14] As a result, it should be kept in mind that silver products can be used safely in burn treatment, however, neurological dysfunction may develop due to silver intoxication in the prolonged use of nanocrystallines and close monitorization and follow-up is required during treatment.

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