e-ISSN
2667-8675

Volume: 1 Issue: 2

EJT
Eurasian Journal of Toxicology

www.dergipark.org.tr/ejtox

EPAT
Emergency Physicians Association of Turkey

EJT
Eurasian Journal of Toxicology

Kamara İş Merkezi Abide-i Hürriyet Caddesi
Hasat Sok No: 52 Merkez / Şişli / İstanbul
Telefon: 0212 963 09 46
info@puntodizgi.com
www.puntoajans.com

Editorial

Değerli Meslektaşlarımız,

Akut, kronik, mesleki veya çevresel maruziyetler ve dahası hayatımızın her anında karşılaştığımız zehirlenmelerle mücadelemizin akademik yansıması olan çalışmaların yer aldığı, dergimizin ikinci sayısı ile karşınızdayız. Henüz çok genç bir ilim dalı olan Acil Tıp alanında yayın üretkenliğinin çok üst düzeyde olduğu aşikardır. Türkiye gibi zehirlenmelerle çok sık karşılaşılan ülkemizde, bu alanda yapılan çalışmalar ve olgu sunumları da azımsanmayacak düzeydedir. Bu nedenle yapılmış değerli çalışmaların okuyucuya sunulacağı doğru dergiler önem arz etmektedir. Bu açığı önemli oranda kapatacağını düşündüğümüz dergimizin, sizlerin teveccühü ile ikinci sayısını yayımlıyoruz.

Dergimizin bu sayısında zehirlenmelerde çok önemli bir tedavi seçeneği olan ekstrakorporeal tedavileri ince ayrıntılarıyla sunan ve keyifle okuyacağınız bir derleme bulacaksınız. Ayrıca Ay döngüsün intihar girişimleri ile ilişkisini yansıtarak farklı bir bakış açısı sunan bir klinik araştırma okuyacaksınız. Türkiye'de bölgesel olarak sık karşılaştığımız karbon monoksit ve mantar zehirlenmeleri konusunda yeniliklere ışık tutan klinik araştırmaları da okumaktan keyif alacağınızı düşünüyoruz. Bunlara ek olarak bilgi birikimlerinize önemli farkındalıklar ve yenilikler kazandıracağını düşündüğümüz üç farklı olgu sunumu da bu sayıda yer almaktadır.

Derginin vücut bulması aşamasından itibaren hep yanımızda olan ve destek veren başta ATUDER Yönetim Kurulu Başkanımız Prof. Dr. Başar Cander ve yönetim kurulu üyelerimize, yine ilk andan itibaren ciddi çabalar harcayan editöryal ekip ve danışma kurullarına, bilimsel yazıları ile dergi gelişimine katkı sunan yazarlarımıza şükranlarımızı sunuyoruz.

Eurasian Journal of Toxicology Editörler kurulu adına,

Baş Editörler

Prof. Dr. Yunsur Çevik

Prof. Dr. Zeynep Gökcan Çakır

Contents

Review Article

Original Articles

Case Reports

Review Article

Eurasian Journal of Toxicology

Zehirlenmelerde Ekstrakorporeal Tedaviler

Seda DAĞAR, Yunsur ÇEVİK
Department of Emergency Medicine, University of Health Sciences, Kecioren Training and Research Hospital, Ankara, Turkey

Abstract

Extracorporeal treatments (ECT) include a heterogeneous group of methods for the removal of endogenous or exogenous toxins from the body and/or for the temporary replacement of one of the vital organs.ECT methods may play a key role in preventing mortality and morbidity in appropriate intoxication cases that do not respond to conventional treatments. In general, toxins with low molecular weight, low endogenous clearance, low volume of distribution and low protein binding are suitable for removal by ECT methods. Currently, the most common ECT methods are intermittent hemodialysis, intermittent hemofiltration/hemodiafiltration, continuous renal replacement therapy, hemoperfusion, therapeutic plasma exchange, exchange transfusion, albumin dialysis and extracorporeal membrane oxygenation.ECT methods are invasive procedures that bring some risks of complications. Therefore, in all toxin exposures that may benefit from ECT, the application decision should be made by evaluating the benefit and risk ratio on a case-by-case basis. In determining the most appropriate ECT method for the patient, both the characteristics of the toxin exposed and also the medical history and clinical status of the patient should be taken into consideration.In the near future, presenting a wide range of data about ECT applications beyond the case presentations to the literature will help to determine the optimal use strategies of these methods.

Key words: extracorporeal treatment, intoxication, toxicology, hemodialysis

Özet

Ekstrakorporeal tedaviler (EKT), endojen veya ekzojen toksinlerin vücuttan uzaklaştırılması ve/veya hayati organlardan birinin geçici bir süreliğine replasmanını içeren heterojen bir grup tedavi yöntemini içerir. Konvansiyonel tedavilere cevap vermeyen uygun intoksikasyon vakalarında EKT yöntemleri, mortalite ve morbiditenin önlenmesinde anahtar rol oynayabilir. Genel olarak molekül ağırlığı, endojen klirensi ve dağılım hacmi düşük olan ve proteine az bağlanan toksinler EKT uygulamaları ile uzaklaştırılmaya uygundur. Günümüzde en sık uygulanan EKT yöntemleri aralıklı hemodiyaliz, aralıklı hemofiltrasyon/hemodiafiltrasyon, sürekli renal replasman tedavileri, hemoperfüzyon, terapötik plazma değişimi, exchange transfüzyon, albümin diyalizi ve ekstrakorporeal membran oksijenizasyonudur. EKT yöntemleri, bazı komplikasyon risklerini de beraberinde getiren invaziv işlemlerdir. Bu nedenle, EKT'den olası fayda görebilecek tüm toksin maruziyetlerinde de mutlaka yarar ve risk oranı vaka bazlı değerlendirilerek uygulama kararı verilmelidir. Hasta için en uygun EKT yöntemi belirlenmesi sırasında ise hem maruzkalınantoksinin özellikleri hem de hastanın medikal öykü ve klinik durumu dikkate alınmalıdır. Yakın gelecekte EKT uygulamaları ile ilgili vaka takdiminin ötesinde geniş çapta verilerin literatüre sunulması, bu yöntemlerin optimal kullanım stratejilerini belirmeye yardımcı olacaktır.

Anahtar kelimeler: ekstrakorporeal tedavi, intoksikasyon, hemodiyaliz, toksikoloji

Giriş

Zehirlenmeler, tüm dünyada önemli bir halk sağlığı sorunu olmaya devam etmektedir. Zehirlenme olgularına yaklaşımda çoğunlukla destek tedaviSİ yeterlidir. Ancak 2012'de yayımlanan bir raporda sağlık kuruluşlarına başvuran zehirlenme vakalarının yaklaşık 4'te 1'inde hospitalizasyon gerekliliği bildirilmiştir.[1] Geleneksel destek tedavilerin yeterli olmadığı bu grupta ileri eliminasyon/replasman yöntemlerine geçilmesi söz konusu olabilir.

Ekstrakorporeal tedaviler (EKT), endojen veya ekzojen toksinlerin vücuttan uzaklaştırılması ve/veya hayati organlardan birinin geçici bir süreliğine replasmanını içeren heterojen bir grup tedavi yöntemini içerir.[2] Literatürde bildirilen ilk modern EKT, Abel ve ark. tarafından 1913 yılında hayvanlarda salisilat intoksikasyonunda diyalizin kullanılışıdır.[3] Sonrasındaki 100 yılı aşkın süre boyunca sürekli yenilenen teknolojiler sayesinde EKT, toksikolojinin en hızlı değişen ve gelişen kısmı haline gelmiştir.[4] Günümüzde en sık uygulanan EKT yöntemleri aralıklı hemodiyaliz, aralıklı hemofiltrasyon/hemodiafiltrasyon, sürekli renal replasman tedavileri, hemoperfüzyon, terapötik plazma değişimi, exchange transfüzyon, albümin diyalizi ve ekstrakorporeal membran oksijenizasyonudur (ECMO).[2] Bu uygulamalar "terapötik" (klinik toksisite varlığında) ya da "profilaktik" (tedavisiz kalırsa beklenen toksisite oluşmadan önce) amaçla uygula-

Corresponding Author: Seda Dağar **e-mail:** sedadagar@gmail.com
Received: 09.07.2019 • **Accepted:** 11.07.2019
Cite this article as: Dagar S, Cevik Y. Zehirlenmelerde ekstrakorporeal tedaviler. Eurasian J Tox. 2019;1(2):43-48

nabilir.[5] Ancak olası bir zarardan kaçınmak için hem zehirlenme vakasının EKT' ye uygunluk kararının verilmesi hem de seçilecek EKT yönteminin doğru belirlenmesi gerekmektedir. Bu aşamada klinisyenlerin, maruz kalınan toksin ile hastanın özellikleri doğrultusunda risk/yarar oranını değerlendirmeleri ve EKT yöntemlerinin prensiplerine hâkim olmaları çok önemlidir.

Bu derlemede, EKT uygunluğunun belirlenmesi için değerlendirilen toksikokinetik prensipler ve uygun yönteminin seçilmesi için EKT yöntemlerinin çalışma prensipleri gözden geçirilecektir.

Hastanın EKT ihtiyacının değerlendirilmesi

Zehirlenme hastasında ilk değerlendirme havayolu, solunum ve dolaşım stabilizasyonunu içermektedir. Sonrasında aktif kömür gibi gastrointestinal dekontaminasyon ve üriner alkalinizasyon gibi eliminasyonu arttırma uygulamaları değerlendirilir. Eş zamanlı olarak semptomatik tedavi, volüm replasmanı, aritmi gibi komplikasyonların tedavisi hastanın ihtiyacına göre eklenebilir. Hızlı bir stabilizasyon sonrası tüm zehirlenme hastaları, EKT ihtiyacı ve uygunluğu açısından değerlendirilmelidir. Genel olarak benin klinik seyir izleyeceği öngörülen toksinlerde EKT uygulanmaz. Geniş terapötik aralığa sahip ve tek başına alındığında görece güvenli olan (suda çözünen vitaminler, antibiyotikler, proton pompa inhibitörleri vb.) ksenobiyotikler için çoğunlukla destek tedavisi yeterlidir. Bununla birlikte etkili olduğu bilinen bir antidot varlığında öncelik antidot uygulamasına verilmeli; EKT, antidota ulaşılamayan ya da yanıt alınamayan seçilmiş vakalara saklanmalıdır.[6]

Uygulama olanağına sahip merkez ve uygulayıcı personel sayısındaki olası kısıtlılığın yan ısıra EKT yöntemleri, bazı komplikasyon risklerini de beraberinde getiren invaziv işlemlerdir. Ek olarak zehirlenme hastalarında EKT yöntemlerini değerlendiren randomize kontrollü çalışmalar da mevcut değildir. Bu nedenlerle, EKT'den olası fayda görebilecek tüm toksin maruziyetlerinde de mutlaka yarar ve risk oranı vaka bazlı değerlendirilerek uygulama kararı verilmelidir.[2]

Ekstakorporeal yöntemlerle toksin uzaklaştırılması:

Toksikokinetik prensipler

Ekstrakorporeal yöntemlerin etkinliğini belirleyen 4 kritik parametre mevcuttur; molekül ağırlığı, proteine bağlanma, endojen klirens ve dağılım hacmi.

*Molekül A*ğırlığı (MA)

Yarı-geçirgen membran kullanan EKT yöntemleri için en önemli kısıtlılık parametresidir. Eski tip diyaliz cihazları 500 Da molekül ağırlığına kadar olan maddeleri uzaklaştırabilirken, yeni nesil membranların kullanılması ile günümüzde 45,000 Da molekül ağırlığı yeni sınır olarak bildirilmektedir.[7] Maruz kalınan çoğu toksin 100-1000 Da arasında olduğundan, günümüzde molekül ağırlığı EKT kullanımı için önemli bir engelleyici olmaktan çıkmıştır. İstisnai moleküller (rituksimab:145,000 Da, immunglobulinler-IgM:925,000 Da) için, molekül ağırlığından bağımsız teknikler olan terapötik plazma değişimi ve exchange transfüzyon kullanılabilir.[8]

Proteine bağlanma

Kandaki en önemli bağlayıcı protein albümindir. Albümin-toksin kompleksinin boyutu büyük olduğundan (>67,000 Da), birçok filtreden geçemez.[9] Bu nedenle difüzyon ve konveksiyon prensibi ile çalışan EKT yöntemleri, toksinin sadece proteine bağlanmamış serbest kısmını uzaklaştırabilirler. Genel bir kural olarak, proteine bağlanma oranı %80 ve üzerindeki toksinler için hemodiyaliz ve hemofiltrasyon uygun EKT yöntemi olarak kabul edilmez.[10] Yüksek oranda proteine bağlanan maddeler için absorbsiyon yöntemini kullanan, hemoperfüzyon ve endojen albüminle yarışan albümin diyalizi kullanılabilir.[11,12] Ayrıca terapötik plazma değişimi ve exchange transfüzyon yöntemleri de albümin-toksin komplekslerini uzaklaştırabilir.

Endojen Klirens

Ekstrakorporeal tedavilerin zehirlenme hastasına avantaj sağlayabilmesi için, maruz kalınan toksinin endojen klirensinin seçilen EKT yönteminkine oranla daha düşük olması gerekmektedir. Maksimum EKT klirensi değeri, aralıklı hemodiyalizin ulaştığı 400 ml/dk iken, hızlı enzimatik yıkıma uğrayan bazı ilaçlarda (labetolol, kokain vb.) endojen klirens 2000 ml/dk üzerine çıkabilmektedir. Böyle bir durumda toksin uzaklaştırılmasına EKT katkısından söz etmek güçtür. Bu nedenle genel bir kural olarak EKT'den faydalanabilmek için bir toksinin endojen klirensinin <4 ml/dk/kg altında olması istenmektedir.[10-13] Ek olarak, endojen klirensin baskılandığı renal ya da hepatik hasar gibi eliminasyon organlarının disfonksiyon durumlarında, EKT uygulamaları zehirlenme hastalarına faydalı olabilir.[6]

Dağılım Hacmi (Vd)

Ekstrakorporeal tedavi yöntemleri, sadece vasküler kompartmandaki ksenobiyotiklerin uzaklaştırılmasını sağlayabilir. Buradaki belirleyici parametre Vd'dir. Yüksek lipofilite ve proteine bağlanma ile karakterize yüksek Vd'ye sahip toksinler, vasküler alandan uzaklaşırlar; bu toksinlerde EKT kullanımının yararı düşüktür.[14] Genel bir kural olarak, 1-2 L/kg ve üzerinde Vd'ye sahip olan ksenobiyotikler için EKT yöntemlerin kullanımı uygun kabul edilmemektedir.[13]

EKT Yöntemleri

Ekstrakorporeal tedavi yöntemlerinden sırası ile aralıklı hemodiyaliz, aralıklı hemofiltrasyon/hemodiafiltrasyon, sürekli renal replasman tedavisi, hemoperfüzyon, terapötik plazma değişimi, exchange transfüzyon, albümin diyalizi, periton diyalizi ve ECMO incelenecektir. Ayrıca çalışma prensibi ve toksikokinetik parametrelere göre bazı EKT yöntemleri Tablo-1'de özetlenmiştir.

1.Aralıklı Hemodiyaliz (HD)

Hemodiyaliz, yarı geçirgen bir membran boyunca solüt moleküllerin, plazma ve diyalizat sıvısı arasındaki konsantrasyon farkı nedeniyle kompartmanlar arasında difüzyon esasına uygun olarak hareket ettikleri bir EKT yöntemidir. Bu sayede HD, diğer EKT yöntemlerine göre daha yüksek kan ve diyalizat akımı sağlamasına bağlI olarak özellikle küçük molekül ağırlığındaki toksinlerin hızla uzaklaştırılmasında oldukça etkindir.[6] Ayrıca asit-baz ve elektrolit bozukluklarının hızlı düzeltilmesi ve ultrafiltrasyon ile volüm yükünün azaltılması gibi ek faydalar da sağlamaktadır.[2] Son dönem böbrek yetmezliğindeki kullanım sıklığı nedeniyle gelişmekte olan ülkelerde hızla yaygınlaşması, zehirlenme hastalarında da en sık kullanılan EKT yönteminin HD olmasını sağlamıştır.[15] Diğer EKT yöntemlerine göre yaygınlık, uygulayıcı sağlık personelinin daha fazla olması, daha düşük maliyet ve komplikasyon oranlarının görece daha az gözlenmesi şeklinde avantajları vardır.[16-17]

Hemodiyaliz ile uzaklaştırılmaya uygun toksinler MA, Vd ve endojen klirensi düşük olan ve proteine daha az bağlanan toksinlerdir. MA için sınır, kullanılacak diyaliz cihazının membranındaki por boyutlarına göre belirlenir.[6] Toksik alkoller, salisilat, benzodiazepin, barbitürat, teofilin, valproik asit ve lityum zehirlenmeleri başta olmak üzere zehirlenmelerin birçoğunda HD, en sık tercih edilen EKT yöntemi olmaya devam etmektedir.[5]

2.Aralıklı Hemofiltrasyon/ Hemodiafiltrasyon (HF/HDF)

Hemofiltrasyon, yarı geçirgen bir membranla ayrılmış iki bölüm arasında basınç gradiyentine bağlı sıvı akışı ve buna eşlik eden solüt geçişi tekniğine dayanır. Ana prensip konveksiyondur. HDF ise hem konveksiyon hem diffüzyon tekniğinin aynı anda uygulanmasıdır. Kaybedilen sıvı, fizyolojik sıvı ile replase edilir.[2]

Toksinler için HF ve HDF yöntemlerine uygunluk özellikleri HD ile benzerdir; düşük Vd, düşük endojen klirens ve düşük proteine bağlanma oranı. Farklı olarak HF ve HDF daha yüksek bir moleküler ağırlık eşik değerine (yaklaşık 25,000 Da) izin verir.[18-20] Ancak artmış teknik gereksinim ve az bulunabilirlik nedeniyle HF ve HDF'nin, zehirlenme hastalarındaki kullanımı kısıtlıdır.[21]

3.Sürekli renal replasman tedavisi (SRRT)

Sürekli renal replasman tedavisi, aralıklı HD-HF-HDF yöntemlerinin daha düşük akımlarda daha uzun periodlarda sürekli uygulanması yöntemidir.[2] Özellikle hemodinamik açıdan stabil olmayan hasta kritik hastalarda renal replasman tedavilerinin uygulanmasına olanak tanırlar. Ancak SRRT'de toksin klirensi, aralıklı uygulamalara göre düşük akım oranlarına bağlı %50-80 oranında daha azdır.[22-24] Zehirlenme hastalarında aralıklı EKT uygulamaları sırasında "rebound fenomeni" olarak adlandırılan seans sonrası plazma toksin konsantrasyonunda ani artışlar gözlenebilmektedir. Bu fenomen toksinlerin ekstravasküler alandan vasküler alana ani geçişi kaynaklıdır. Bazı klinisyenler normal bir HD seansı sonrasında bu olası rebound etkiyi önlemek amaçlı SRRT uygulamasını kullanabilmektedir.[5]

4.Hemoperfüzyon (HP)

Hemoperfüzyon, toksinlerin absorbe edilebileceği aktif kömür ya da non-iyonik reçine kaplı bir kartuş içerisinden tüm kanın geçirilerek toksinlerin uzaklaştırılmaya çalışıldığı bir EKT yöntemidir.[25] Difüzyon tekniği ile kıyaslandığında absorbsiyon yöntemi, daha yüksek MA ve proteine bağlanma oranları olan toksinler için uygundur. Ancak HP, diğer EKT'lere göre daha yüksek sistemik antikoagülasyona ihtiyaç duymaktadır.[26] Üstelik kartuş, non-selektif olarak kan hücrelerini, kalsiyum ve glukozu da absorbe eder. Hemoliz riskinden uzak durmak için kan akım hızının 350 ml/dk'dan daha yüksek sürdürülmesi gereken HP'de, kartuş satüre olduğunda kan akım hızı azalacağından her 2 saatte bir kartuş yenilenmesine ihtiyaç duyulmaktadır. Olası yüksek komplikasyon riski (trombositopeni, lökopeni, kömür embolisi, piyojenik reaksiyonlar, hipokalsemi, hipofosfatemi, hipoglisemi vb.) ve maliyet fazlalığı, 1990'lardan itibaren hemoperfüzyon yerine yeni nesil HD cihazlarının kullanımını arttırmıştır.[5]

5.Terapötik Plazma Değişimi (TPD)

Terapötik plazma değişimi, kanın plazma ve şekilli komponentlerinin santrifüj ya da filtrasyon tekniği ile birbirinden ayrılması esasına dayanır. Ayrılan plazma, steril bir solüsyon (donör plazma, albümin, taze donmuş plazma vb.) ile değiştirilir ve hastaya kan hücreleri ile birlikte geri verilir.[27,28] Amerikan Aferez Cemiyeti kılavuzları, toksin atılımı amacıyla yapılan TPD için klinik semptomlar düzelene kadar her gün iki plazma volümü kadar değişim yapılmasını önermektedir.[27] TPD, çok yüksek molekül boyutuna (>50,000 Da) ve proteine bağlanma oranına (>%95) sahip toksinler için uygun bir EKT yöntemidir.[2] Literatürde özellikle Amanita Phalloides mantarı, tiroksin, vinkristin ve sisplatin maruziyetlerinde başarılı TPD kullanımları bildirilmektedir.[27,29-32] Bununla birlikte düşük klirens kapasitesi

(<50 ml/dk.), TPD'nin intoksikasyonlarda nadiren kullanılmasına neden olmaktadır.[33]

6.Exchange Transfüzyon

Exchange transfüzyon, eritrositlerin diğer kan komponentlerinden ayrıldığı ve normal donör eritositleri ile replase edildiği bir terapötik aferez prosedürüdür. Tek bir volüm değişiminde dolaşımdaki eritrositlerin yaklaşık 3'te 2'si uzaklaştırılır.[2] Toksikolojik literatürde siklosporin, takrolimus gibi eritrositlere bağlanan ksenobiyotikler ve toksik madde (anilin, dapson, sodyum nitrit vb.) maruziyeti sonucu gelişen methemoglobinemi için uygun bir yöntem olarak tariflenmiştir.[34-37] Yeni doğanlarda özellikle uygulama kolaylığı açısından salisilat, teofilin ve barbitüratlar zehirlenmelerinde de exchange transfüzyon denenmiştir.[38-40]

7.Albümin Diyalizi

Aynı zamanda ekstrakorporeal karaciğer destek cihazı olarak da adlandırılan albümin diyalizi, fulminan hepatit ya da ciddi sirozda karaciğer transplantasyonuna köprü olarak kullanılan bir karaciğer replasman tedavi yöntemidir.[2] Ekstrakorporeal destek cihazları, SRRT prensibine benzer şekilde çalışan ancak içerisine albümin eklenmiş bir diyalizat kullanan 'tek geçişli albümin diyalizi (TGAD)' ve içinde diyalizat bulunan ikinci bir devreye sahip olan 'Moleküler absorbe edici resirkülasyon sistemi (MARS)' ile 'Prometheus sistemi'ni içerir.[11,41] Teorik olarak protein bağlı toksinlerin eliminasyonunu sağlaması en büyük avantajıdır.[42] Ancak literatürde değişik derecelerde başarı bildirilmiştir; teofilin, valproik asit ve fenitoin zehirlenmesinde albümin diyalizinin diğer yöntemlere üstünlüğü gösterilememiştir.[42-44] Ulaşılabilirliğin kısıtlı olması, yüksek maliyet ve pek çok ksenobiyotik için öngörülemeyen etki albümin diyalizinin intoksikasyon hastalarındaki rolünü şu an için belirsiz kılmaktadır.[5]

8.Diğer yöntemler

Peritoneal diyaliz, yarı geçirgen membran olarak peritonun kullanıldığı HD yöntemidir. Düşük klirens kapasitesi nedeniyle zehirlenmelerde kullanımı nadir olsa da ekstrakorporeal bir devre gerektirmediği için uygun hastalarda ve kaynak kısıtlılığı bulunan durumlarda periton diyalizi EKT yöntemi olarak tercih edilebilir.[5,15]

Ekstrakorporeal membran oksijenizasyonu (ECMO), solunum ve/veya dolaşım desteğinin ekstrakorporeal bir devre yardımıyla hastaya sağlandığı organ replasman tedavi yöntemidir. ECMO, direkt olarak toksin eliminasyonunun arttırılmasında görev almamaktadır. Ancak konvansiyonel medikal tedavilere yanıtsız kardiyovasküler ve pulmoner yetmezlikli intoksikasyon hastasında iyileşme dönemine kadar bir köprü vazifesi görür.[2] Veno-arteryal ECMO, kalsiyum kanal blokörleri ve beta blokörler gibi kardiyotoksik ksenobiyotikler ile zehirlenmelerde etkinken; veno-venöz ECMO, inhale organik hidrokarbon zehirlenmelerde solunum desteği sağlar.[45-48]

Uygun EKT yöntemi seçimi

Hastaya EKT uygulanmasına karar verildikten sonra hem maruz kalınan toksinin özelliklerine hem de hastanın medikal öykü ve klinik durumuna göre en uygun EKT yöntemi belirlenmelidir. Vd ve endojen klirensi EKT uygulamak için uygun olan toksinler, proteine bağlanma oranı ve MA açısından değerlendirilir. Proteine bağlanma oranı %95 ve üzerinde olan toksinlerde TPD ya da albümin diyalizi, %80-95 arasında olanlarda HP tercih edilebilir. %80 ve altında proteine bağlanan toksinlerde ise uygun EKT yöntemini belirlemede MA dikkate alınır. MA 10,000 ve altındaki toksinlerde HD, 10,000-50,000 arasında olanlarda HF, 50,000 ve üzerinde olanlarda ise TPD uygun olabilecek EKT yöntemleridir.

Hastada eş zamanlı renal disfonksiyonu olması halinde aralıklı HD ya da volüm durumuna göre aralıklı HF uygulanabilir. Şayet toksin ilişkili hipotansiyon mevcutsa, aralıklı uygulamalar yerine SRRT seçilebilir. Karaciğer yetmezliği gelişen hastalarda albümin diyalizi (karaciğer destek tedavisi) geçici bir süreliğine hepatik disfonksiyonu kompanse edebilir. Kanama yatkınlığı bulunan hastalarda diğer EKT yöntemlerine göre sistemik antikoagülasyonun daha az gerektiği HD tercih edilebilir.

Sonuç

Konvansiyonel tedavilere cevap vermeyen uygun intoksikasyon vakalarında, EKT yöntemleri mortalite ve morbiditenin önlenmesinde anahtar rol oynayabilir. EKT uygulama kararı verilirken hasta ve maruz kalınan toksine bağlı özellikler çok iyi gözden geçirilmeli, risk/yarar dengesinde yarar kısmının ağır bastığından emin olunmalıdır. Son yıllardaki teknolojik ilerlemelere bağlı olarak artmış klirens kapasiteli, düşük maliyetli ve düşük komplikasyon oranlarına sahip HD cihazları yaygınlaşma başlamıştır. Buna bağlı olarak günümüzde zehirlenmelerde ilk akla gelen ve en sık kullanılan EKT yöntemi aralıklı HD'dir. Seçilmiş vakalarda diğer yöntemlerin de uygulanması söz konusu olabilir. Ancak bu kararın verilmesinde klinisyenlerin EKT yöntemlerinin avantaj ve dezavantajlarını hesaba katarak, vaka bazlı değerlendirme yapmaları gerekmektedir. Yakın gelecekte EKT uygulamaları ile ilgili vaka takdiminin ötesinde geniş çapta verilerin literatüre sunulması, bu yöntemlerin optimal kullanım stratejilerini belirmeye yardımcı olacaktır.

Tablo 1. Çalışma prensibi ve toksikokinetik parametrelere göre EKT yöntemleri

	HD	HF	HP	Albümin Diyalizi	TPD	Exchange Transfüzyon
Prensip	Difüzyon	Konveksiyon	Absorbsiyon	Difüzyon/ konveksiyon	Sentrifugasyon/ seperasyon	Seperasyon
Molekül ağırlığı	Düşük akım HD: 1000 Da Yüksek akım HD: 10,000 Da	40,000 Da	5,000-10,000 Da	TGAD/MARS: 60,000 Da Prometheus: 100,000 Da	1,300,000 Da	Sınır yok
Proteine bağlanma	<%80	<%80	<%90	Yüksek sınır	Kısıtlama yok	Kısıtlama yok
Dağılım hacmi	Düşük Vd (<1-2 L/kg)					

HD: Hemodiyaliz, HF: Hemofiltrasyon, HP: Hemoperfüzyon, TPD: Terapötik Plazma Değişimi

References

1. Mowry JB, Spyker DA, Cantilena LR Jr, Bailey JE, Ford M. 2012 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 30th Annual Report. Clin Toxicol. 2013; 51: 949-1229.
2. Ouellet G, Bouchard J, Ghannoum M, Decker BS. Available extracorporal treatments for poisoning: overview and limitations. Semin Dial. 2014; 27(4): 342-9.
3. Abel JJ, Roundtree LG, Turner BB. On the removal of diffusible substances from the circulating blood of living animals by dialysis. J Pharmacol. Exp Ther. 1914; 5: 275-316.
4. Patel N, Bayliss GP. Developments in extracorporal therapy fort he poisoned patient. Adv Drug Deliv Rev. 2015; 90: 3-11.
5. Ghannoum M, Hoffman RS, Gosselin S, Nolin TD, Lavergne V, Roberts DM. Use of extracorporal treatments in the management of poisonings. Kidney Int. 2018; 94(4): 682-8.
6. Ghannoum M, Roberts DM, Hoffman RS, Ouellet G, Roy L, Decker BS, et al. A stepwise approach for the management of poisoning with extracorporeal treatments. Semin Dial. 2014; 27: 362-70.
7. Martin-Reyes G, Toledo-Rojas R, Torres-de Rueda A, Sola-Moyano E, Blanca-Martos L, Fuentes-Sanchez L, et al. Haemodialysis using high cut-off dialysers for treating acute renal failure in multiple myeloma. Nefrologia. 2012; 32: 35-43.
8. Ibrahim RB, Liu C, Cronin SM, Murphy BC, Cha R, Swerdlow P, et al. Drug removal by plasmapheresis: an evidence-based review. Pharmacotherapy. 2007; 27: 1529-49.
9. Matzke GR. Status of hemodialysis of drugs in 2002. J Pharm Pract. 2002; 15: 405-18.
10. De Pont AC. Extracorporeal treatment of intoxications. Curr Opin Crit Care. 2007; 13: 668-73.
11. Krisper P, Stauber RE. Technology insight: artificial extracorporeal liver support-how does Prometheus compare with MARS? Nat Clin Pract Nephrol. 2007; 3: 267-76.
12. Kawasaki CI, Nishi R, Uekihara S, Hayano S, Kragh-Hansen U, Otagiri M. How tightly can a drug be bound to a protein and still be removable by charcoal hemoperfusion in overdose cases? Clin Toxicol. 2005; 43: 95-9.
13. Fertel BS, Nelson LS, Goldfarb DS. Extracorporeal removal tech- niques for the poisoned patient: a review for the intensivist. J Inten- sive Care Med. 2010; 25: 139-148.
14. Pond SM. Extracorporeal techniques in the treatment of poisoned patients. Med J Aust. 1991; 154: 617-22.
15. Holubek WJ, Hoffman RS, Goldfarb DS, Nelson LS. Use of hemodialysis and hemoperfusion in poisoned patients. Kidney Int. 2008; 74: 1327-34.
16. Shannon MW. Comparative efficacy of hemodialysis and hemoperfusion in severe theophylline intoxication. Acad Emerg Med. 1997; 4: 674-8.
17. Tyagi PK, Winchester JF, Feinfeld DA. Extracorporeal removal of toxins. Kidney Int. 2008; 74: 1231-3.
18. Ward RA, Schmidt B, Hullin J, Hillebrand GF, Samtleben W. A comparison of on-line hemodiafiltration and high-flux hemodialysis: a prospective clinical study. J Am Soc Nephrol. 2000; 11: 2344-50.
19. Ahrenholz PG, Winkler RE, Michelsen A, Lang DA, Bowry SK. Dialysis membrane-dependent removal of middle molecules during hemodiafiltration: the beta2-microglobulin/albumin relationship. Clin Nephrol. 2004; 62: 21-8.
20. Yamashita AC. Mechanisms of solute and fluid removal in hemodiafiltration. Contrib Nephrol. 2007; 158: 50-6.
21. Bailey AR, Sathianathan VJ, Chiew AL, Paterson AD, Chan BS, Arora S. Comparison of intermittent haemodialysis, prolonged intermittent renal replacement therapy and continuous renal replacement haemofiltration for lithium toxicity: a case report. Crit Care Resusc. 2011; 13: 12-2.
22. Calello DP, Liu KD, Wiegand TJ, Roberts DM, Lavergne V, Gosselin S, et al. Extracorporeal treatment for metformin poisoning: systematic review and recommendations from the

Extracorporeal Treatments in Poisoning Workgroup. Crit Care Med. 2015; 43: 1716-30.

23. Decker BS, Goldfarb DS, Dargan PI, Friesen M, Gosselin S, Hoffman RS, et al. Extracorporeal treatment for lithium poisoning: systematic review and recommendations from the EXTRIP workgroup. Clin J Am Soc Nephrol. 2015; 10: 875-87.

24. Roberts DM, Yates C, Megarbane B, Winchester JF, Maclaren R, Gosselin S, et al. Recommendations for the role of extracorporeal treatments in the management of acute methanol poisoning: a systematic review and consensus statement. Crit Care Med. 2015; 43(2): 461-72.

25. Ghannoum M, Bouchard J, Nolin TD, Ouellet G, Roberts DM. Hemoperfusion for the treatment of poisoning: technology, determinants of poison clearance, and application in clinical practice. Semin Dial. 2014; 27: 350-61.

26. Rahman MH, Haqqie SS, McGoldrick MD. Acute hemolysis with acute renal failure in a patient with valproic acid poisoning treated with charcoal hemoperfusion. Hemodial Int. 2006; 10: 256-9.

27. Szczepiorkowski ZM, Winters JL, Bandarenko N, Kim HC, Linen- berger ML, Marques MB, et al. Apheresis Applications Committee of the American Society for A. Guidelines on the use of therapeutic apheresis in clinical practice–evidence-based approach from the Apheresis Applications Committee of the American Society for Apheresis. J Clin Apher. 2010; 25: 83-177.

28. Schutt RC, Ronco C, Rosner MH. The role of therapeutic plasma exchange in poisonings and intoxications. Semin Dial. 2012; 25: 201-6.

29. Jander S, Bischoff J, Woodcock BG. Plasmapheresis in the treatment of Amanita phalloides poisoning: II. A review and recommendations. Ther Apher. 2000; 4: 308-12.

30. Jha S, Waghdhare S, Reddi R, Bhattacharya P. Thyroid storm due to inappropriate administration of a compounded thyroid hormone preparation successfully treated with plasmapheresis. Thyroid. 2012; 22: 1283-6.

31. Chu G, Mantin R, Shen YM, Baskett G, Sussman H. Massive cisplatin overdose by accidental substitution for carboplatin. Toxicity and management. Cancer. 1993; 72: 3707-14.

32. Pierga JY, Beuzeboc P, Dorval T, Palangie T, Pouillart P. Favourable outcome after plasmapheresis for vincristine overdose. Lancet. 1992; 340:185.

33. Schonermarck U, Bosch T. Vascular access for apheresis in inten- sive care patients. Ther Apher Dial. 2003; 7: 215-20.

34. Leitner GC, Hiesmayr M, Hoecker P, Jilma B. Therapeutic approaches in the management of oral cyclosporine A intoxication. Transplantation. 2003; 75: 1764-5.

35. McCarthy H, Inward C, Marriage S, Astley P, Tizard EJ. Red cell exchange transfusion as a rescue therapy for tacrolimus toxicity in a paediatric renal transplant. Pediatr Nephrol. 2011; 26: 2245-8.

36. Mier RJ. Treatment of aniline poisoning with exchange transfusion. J Toxicol Clin Toxicol. 1988; 26(5-6): 357-64.

37. Southgate HJ, Masterson R. Lessons to be learned: a case study approach: prolonged methaemoglobinaemia due to inadvertent dap- sone poisoning; Treatment with methylene blue and exchange transfusion. J R Soc Promot Health. 1999; 119(1): 52-5.

38. Manikian A, Stone S, Hamilton R, Foltin G, Howland MA, Hoffman RS. Exchange transfusion in severe infant salicylism. Vet Hum Toxicol. 2002; 44: 224-7.

39. Osborn HH, Henry G, Wax P, Hoffman R, Howland MA. Theophylline toxicity in a premature neonate–elimination kinetics of exchange transfusion. J Toxicol Clin Toxicol. 1993; 31: 639-44.

40. Sancak R, Kucukoduk S, Tasdemir HA, Belet N. Exchange transfu- sion treatment in a newborn with phenobarbital intoxication. Pediatr Emerg Care. 1999; 15: 268-70.

41. Wittebole X, Hantson P. Use of the molecular adsorbent recirculating system (MARS?) for the management of acute poisoning with or without liver failure. Clin Toxicol. 2011; 49: 782-93.

42. Sen S, Ratnaraj N, Davies NA, Mookerjee RP, Cooper CE, Patsalos PN, et al. Treatment of phenytoin toxicity by the molecular adsorbents recirculating system (MARS). Epilepsia. 2003; 44: 265-7.

43. Korsheed S, Selby NM, Fluck RJ. Treatment of severe theophylline poisoning with the molecular adsorbent recirculating system (MARS). Nephrol Dial Transplant. 2007; 22: 969-70.

44. Dichtwald S, Dahan E, Adi N, Moses A, Sorkine P. Molecular adsorbent recycling system therapy in the treatment of acute valproic acid intoxication. Israel Med Assoc J. 2010; 12(5): 307-8.

45. Banner W. Risks of extracorporeal membrane oxygenation: is there a role for use in the management of the acutely poisoned patient? J Toxicol Clin Toxicol. 1996; 34: 365-71.

46. Babatasi G, Massetti M, Verrier V, Lehoux P, Le Page O, Bruno PG, et al. Severe intoxication with cardiotoxic drugs: value of emergency percutaneous cardiocirculatory assistance. Arch Mal Coeur Vaiss. 2001; 94: 1386-92.

47. Scalzo AJ, Weber TR, Jaeger RW, Connors RH, Thompson MW. Extracorporeal membrane oxygenation for hydrocarbon aspiration. Am J Dis Child. 1990; 144: 867-71.

48. Chyka PA. Benefits of extracorporeal membrane oxygenation for hydrocarbon pneumonitis. J Toxicol Clin Toxicol. 1996; 34: 357-63.

Original Article

Eurasian Journal of Toxicology

Demographic and Clinical Characteristics of Applications to the Emergency Service with Mushroom Intoxication

Serdar Özdemir, Kamil Kokulu, Abdullah Algın, Hatice Şeyma Akça

Department of Emergency Medicine, University of Health Sciences Umraniye Training and Research Hospital, Istanbul, Turkey

Abstract

Objective: We aimed to evaluate the demographical and clinical variations and treatment and complications of the patients admitted to emergency department with mushroom intoxication.

Materials and Methods: This is a retrospective study. Patients admitted to the emergency room with symptoms after eating mushrooms, included in the study. Patients with missed data, and patients younger than 18 years were excluded.

Results: 114 patients were included in the study. %58.8 of the cases were female and %41.2 of the cases were male. It was found out that 65 of the patients (%57) had applied to the hospital during the autumn months. 38 patients refused treatment. Hemodialysis was performed in 28 (36.8%) of 76 patients who accepted treatment. Only one patient (0.9%) died during hospitalization.

Conclusion: Mushroom poisoning is an important health problem in our country. Informing the public is essential in preventing poisoning.

Key words: mushroom poisoning, mushroom intoxication, mushroom, emergency service

Özet

Amaç: Acil servise mantar zehirlenmesi ile başvuran hastaların demografik ve klinik özelliklerini, tedavilerini ve komplikasyonlarını değerlendirmeyi amaçladık.

Gereç ve Yöntem: Bu çalışma retrospektif olarak planlanmıştır. Mantar yedikten sonra başlayan semptomları olan ve acil servise başvuran hastalar çalışmaya dahil edilmiştir. 18 yaşından küçük hastalar ve verilerine ulaşılamayanlar çalışma dışı bırakıldı.

Bulgular: Çalışmaya 114 hasta dahil edildi. Olguların% 58,8'i kadın, % 41,2'si erkekti. Hastaların 65'inin (% 57) sonbahar aylarında hastaneye başvurdukları tespit edildi. 38 hasta tedaviyi reddetti. Tedavi alan 76 hastanın 28'ine (% 36.8) hemodiyaliz yapıldı. Sadece bir hasta (% 0.9) hastanede yatış sırasında öldü.

Sonuç: Mantar zehirlenmesi ülkemizde önemli bir sağlık sorunudur. Zehirlenmeyi önlemede halkı bilgilendirmek önemlidir.

Anahtar kelimeler: mantar zehirlenmesi, mantar zehirlenmesi, mantar, acil servis

Introduction

There are about 5,000 mushroom species on earth. However, the number of these mushroom species is not more than hundred[1] . Our country is rich in mushroom flora due to its suitable ecological conditions. The mushrooms consumed as a nutrient are rich in protein and contain essential amino acids. However, they do not contain fat and cholesterol and have low calories. Mushroom poisoning is common, especially in the spring and autumn seasons due to the consumption of nutrients in people living in low socioeconomic conditions[2].

Disease caused by some poisonous compounds in corked mushrooms is called mushroom poisoning or misetusmus. Mushroom poisoning is mostly associated with mild gastrointestinal symptoms. Early onset of vomiting, low toxicity of the mushrooms, suggesting that after six hours of vomiting should be thought of poisoning with fatal mushrooms[2].

Mushrooms shorter period than three hours of onset of signs contain; muscarin, coprin, ibotenic acid, psilocybin toxins. These toxins affect the autonomic and central nervous system. Symptoms of mushrooms with long duration of symptoms appear after 6-24 hours. Gyromytra, Amanita phalloides are from this group[3].

Mushroom poisoning is an important health problem in our country that causes mortality and morbidity. In this study we aimed to evaluate the demographical and clinical variations and treatment and complications of the patients admitted to emergency department (ED) with mushroom intoxication.

Corresponding Author: Abdullah Algın **e-mail:** dralgin@hotmail.com

Received: 19.05.2019 • **Accepted:** 06.07.2019

Cite this article as: Ozdemir S, Kokulu K, Algin A, Akca HS. Demographic and clinical characteristics of applications to the emergency service with mushroom ıntoxication. Eurasian J Tox. 2019;1(2):49-52

Materials and Methods

The population of this retrospective study included all adults who were admitted to the Clinic of Emergency Medicine, Umraniye Training and Research Hospital, Istanbul, Turkey with suspected mushroom intoxication during the date 01.05.2018 and 01.05.2019. The patients who were diagnosed ICD-10 code T62.0 for Toxic effect of ingested mushrooms is a medical classification as listed by WHO under the range -Toxic effects of substances chi, were identified through the computerized medical and laboratory records of the hospital. Patients who is under 18 years of age and have missing data, were excluded from the study.

The data extracted from the patients' files included seasonal variation, age, gender, clinical manifestations, presenting time of clinical manifestations (as hours) and, laboratory records, treatment(hemodialysis), hospitalization and outcome. The application seasons of patients were defined as spring (March, April, and May), summer (June, July, and August), autumn (September, October, and November), and winter (December, January, and February). On admission to the emergency department, blood samples were obtained from patients; Aspartate Aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl trans peptidase (GGT), Total Bilirubin, Direct Bilirubin, sodium and potassium were evaluated. Mortality was evaluated as mortality during hospitalization.

In the statistical evaluation of the data, IBM Statistics 16.0(SPSS) statistical package program was used. The baseline patient characteristics are presented as frequencies for categorical variables and as medians and interquartile ranges for continuous variables.

Results

A total of 121 patents were identified through the computerized medical and laboratory records of the hospital. 7 patients were excluded from the study because of being under 18 years of age or missing data. 114 patients were included in the study. %58.8 of the cases (n=67) are female and %41.2 of the cases (n=47) are male. In addition to the fact that the median age of the people who were the subject of the cases was 37 and, interquartile range (IQR) was 24.

The time interval between exposure and time to onset of symptoms was calculated to be 5.9±0.6 hours in average. It was found out that the patients in the 65 of the cases (%57) had applied to the hospital during the autumn months.(Figure1) The number of cases admitted during the autumn was found to be higher than the number of those admitted in the other season with a significant difference ($p < 0.001$).

The most frequent symptoms were nausea and vomiting (70.2%), diarrhea (14.8%), abdominal pain (7.9%). The laboratory records of the cases are summarized in Table 1.

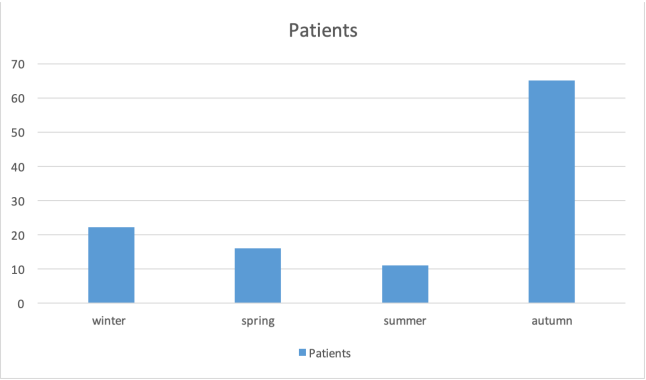

Figure 1. Number of patients approaching emergency department in all years according to seasons

It was found that 38 patients refused treatment. Hemodialysis was performed in 28 (36.8%) of 76 patients, who accepted treatment. The admission clinics of intoxicated patients are shown in Figure 2. The clinics where the patients are admitted are shown in Figure 2. Only one patient (0.9%) died during hospitalization.

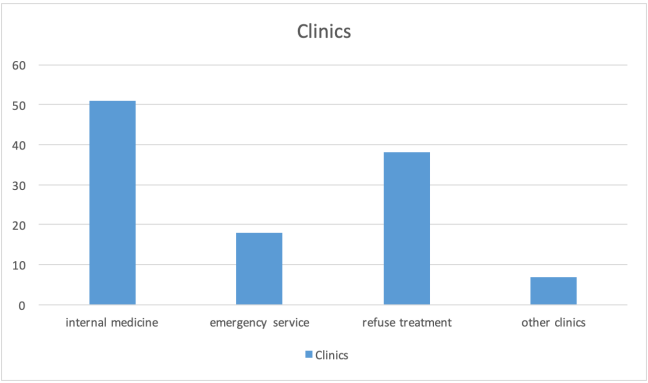

Figure 2. The clinics where the patients are admitted

Discussion

Mushroom poisoning from the genus Amanita is a medical emergency, with Amanita phalloides being the most common species. The typical symptoms of abdominal pain, nausea, vomiting, and diarrhea are nonspecific and can be mistaken for gastroenteritis. If not adequately treated, hepatic and renal failure may ensue within several days of ingestion[3].

Although mushroom poisoning is reported in our country, the mortality rate related to this poisoning is not known exactly. This type of poisoning has been examined by independent regional studies conducted in Turkey. No deaths were reported in 64 cases retrospectively reviewed at Fırat University for 5 years by Durukan et al[4]. In this study, all

Table 1. The laboratory records of the cases

Variables	Median	IQR
AST	24	18
ALT	21,5	18
GGT	18	10
Total Bilirubin	0.62	0.48
Direct Bilirubin	0.22	0.18
Sodium	137	5
Potassium	4.2	0.5

Aspartate Aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl trans peptidase (GGT)

patients were discharged within 2-4 days. In the Göztepe Training and Research Hospital, pediatric patients were examined by Ergüven et al and it was reported that 4 out of 28 patients who presented with mushroom poisoning died[5]. In Osmangazi University, Tayfun et al has examined 143 mushroom poisoning cases between 1996 and 2000, 4 patients died of liver failure[6]. In our study we found that only one patient died because of mushroom poisoning.

Treatment is usually directed by the patient's symptoms. Symptoms can be variable and can easily be confused with gastroenteritis. In our study most common symptoms were nausea, vomiting, abdominal pain, and diarrhea. Eren et al found that most common symptoms were nausea, vomiting, fatigue, abdominal pain, dizziness and diarrhea as our study[7].

In treatment of mushroom poisoning, stomach lavage and activated charcoal administration is recommended for the removal of toxins in early applicants. Severe intoxication may result in coma. In such cases, intensive care treatment is required[8]. Therapy of mushroom poisoning consists of supportive measures, detoxication procedures including extracorporeal blood purification methods, and administration of drugs, namely, benzylpenicillin or other beta-lactam antibiotics, silibinin, and NAC. Methods such as plasma replacement, hemodialysis or hemoperfusion are widely used for the removal of toxin. Hemoperfusion and hemodialysis performed within the first 24 hours following fungal infection were reported to be helpful in eliminating toxin[9]. Toxins cleared from plasma rapidly, extracorporeal decontamination treatment is useful only if started very early, soon after the gastrointestinal symptoms occur[10]. In our study 38 patients refused treatment. We think that patient refused treatment because of, hemodialysis or hemoperfusion are treatment option after symptomatic treatment without any symptoms.

In our study, there are some limitations. One-third of patients refused treatment. We could not reach the mortality information of these patients. Furthermore, the data belongs to one region and clinic. Consequently, regional differences are not included in the study. If a similar, but multicenter, study is conducted, it may represent the data of mushrooms intoxication in our country better.

Conclusion

In conclusion, the basic approach to mushroom poisoning is prevention of the disease, by public education, early recognition of the intoxication, and early initiation of specific therapeutic measures.

Conflicts of Interest

The authors declare that they have no conflicts interests.

Funding Statement: None

References

1. Brent J, Kulig K. Mushrooms. In: Haddad LM, Shannon MW, Winchester JF, eds. Clinical management of poisoning and drug overdoses, 3rd ed. Philadelphia: WB Saunders Company; 1998: 364-5.
2. Yardan T, Eden A, Baydın A, Arslan B, Vural K. Mantar zehirlenmeleri. OMÜ Tıp Dergisi 2008;25: 75-83.
3. Broussard CN, Aggarwal A, Lacey SR, Post AB, Gramlich T, Henderson JM, et al. Mushroom poisoning--from diarrhea to liver transplantation. Am J Gastroenterol. 2001 Nov;96(11):3195-8.
4. Durukan P, Yildiz M, Cevik Y, et al. Poisoning from wild mushrooms in Eastern Anatolia region: analyses of 5 years. Hum Exp Toxicol 2007; 26: 579–82.
5. Ergüven M, Çak S, Deveci M. Mantar zehirlenmesi: 28 vakanın değerlendirilmesi. Çocuk Sağlığı ve Hastalıkları Dergisi 2004; 47: 249–53.
6. Tayfur M, Unluoglu I. Mushroom poisoning: An analysis of the data between 1996 and 2000. Eur J Emerg Med 2003; 46: 1071–8.
7. Eren SH, Demirel Y, Uğurlu S, Korkmaz I, Aktaş C, Güven FM. Mushroom poisoning: retrospective analysis of 294 cases. Clinics (Sao Paulo) 2010; 65: 491-6.
8. Yıldırım C, Celik GK, Haydar GC, Gunaydın GP, Otal Y, Özhasenekler A. Mushroom poisoning with symptoms of pantherina syndrome: a case report. Journal of Emergency Medicine Case Reports 2016,7;67-9.
9. Kieslichova E, Frankova S, Protus M, Merta D, Uchytilova E, Fronek J, et al. Acute Liver Failure due to Amanita phalloides Poisoning: Therapeutic Approach and Outcome. Transplant Proc. 2018;50(1):192-7.
10. Mullins ME, Horowitz BZ. The futility of hemoperfusion and hemodialysis in Amanita phalloides poisoning. Vet Hum Toxicol 2000; 42: 90-1.

Original Article

Eurasian Journal of Toxicology

The Effects of Moon Phases on Suicide Attempts

Avni Uygar Seyhan[1], Nihat Müjdat Hökenek[1], Nurhayat Başkaya[1], Erdal Yilmaz[1], Semih Korkut[2], Hatice Kübra Önder Karagöz[1], Huda Almadhoun[1]

[1]Department of Emergency Medicine, University of Health Sciences Kartal Dr. Lütfi Kırdar Training and Research Hospital, İstanbul, Turkey

[2]General Director of Emergency Health Services, Republic of Turkey Ministry of Health, Ankara, Turkey

Abstract

Objective: The effects of changes in moon phases on human psychology and behavior have been extensively studied. In our study, we aimed to compare the effect of the five different phases of the moon on the frequency of patients suicidal admissions to the hospital.

Materials and Methods: Patients who presented to emergency department between January 2018 and December 2018 due to attempts of suicide were inclueded. Patients data were analyzed in relation to the new moon, full moon, last quarter moon, first quarter moon and lunar eclipses in the moon calendar. Moon cycles were taken from the moon calendar and the dates when the moon was visible and the exact date of the cycle have been evaluated.

Results: 419 patients included in this study, 280 were female and 139 were male. Suicide attempts is most commonly seen in the 18-49 age range, and it is found that the frequency of suicide due to secondary gain is high in female gender. The most frequent suicide attempts have been found to be the in the new moon, lunar eclipse, last quarter moon, first quarter moon and the full moon, respectively (Pearson chi2(5) = 59.2428 Pr = 0.000). When we analyzed the same data with Cramér's V test, we got the result of 0.2751, which confirms our hypothesis that the frequency of suicides increased with the advances of lunar cycles.

Conclusion: It was found that during specific phases of the moon the rate of suicide attempts the present to the emergency department had been increased.

Key words: suicide, moon effects, emergency medicine

Özet

Amaç: İnsan psikolojisi ve davranışı üzerine aydaki değişimlerin etkisi olduğu düşünülerek bir çok araştırma yapılmıştır. Ay, Dünya'ya yakınlığı ve onun synodic (dört fazlı) döngüsünü gözlemlemenin basitliği nedeniyle olağanüstü olaylar veya sapkın davranışlarla ilişkilendirilmiştir. Çalışmamızda, ayın beş farklı evresinin ile yapılan intihar nedenli başvuruların sıklığı üzerindeki etkilerini karşılaştırmayı amaçladık.

Gereç ve Yöntem: İntihar girişimi nedeniyle Ocak 2018 ile Aralık 2018 tarihleri arasında acil servise başvuran hastalar bu çalışmaya dahil edildi. Hasta verileri ayın beş evresine göre analiz edildi.

Bulgular: Çalışmaya 419 hasta dahil edildi. Hastaların 280'i kadın, 139'u erkekti. İntihar girişimleri en sık 18-49 yaş aralığındaydı. Sekondere kazançlı nedenli intihiharlar kadınlarda daha sıktı. Evrelere göre intihar girişim sıklığının sırasıyla, yeni ay, ay tutulması, son çeyrek, ilk çeyrek ve dolunay evrelerinde olduğu tespit edildi (Pearson chi2 (5) = 59.2428 Pr = 0.000). Aynı verileri Cramér'in V testiyle analiz ettiğimizde, 0.2751'in sonucunu aldık, bu, ayin döngüsünün ilerleyişiyle intihar sıklığının arttığı hipotezimizi doğruladı.

Sonuç: Ayın belirli evrelerinde intihar oranlarında artış olduğu tespit edildi.

Anahtar kelimeler: intihar girişimi, ayin etkisi, acil tip

Introduction

The Moon is the world's only natural satellite and it is approximately 385,000 km away from our planet[1]. Even at this distance, it can cause many natural phenomena in our world due to the effect of gravity. The effects of changes in moon phases on human psychology and behavior have been extensively studied[2]. In our study, we aimed to compare the effect of the 5 different phases of the moon on the frequency of patients suicidal admissions to the hospital. Fluctuations in the number of suicides committed during a year are affected by several factors including seasonal changes, seasonal transitions[3] and moon calendar[4].

The hypothesis of the cosmic effect on human behaviors has long been investigated. Tradition and folklore in many cultures have regarded the moon as a perfect destination because it is associated with extraordinary events and deviant behaviors due to its proximity to the earth, and because of

Corresponding Author: Avni Uygar Seyhan **e-mail:** uygarseyhan@gmail.com

Received: 27.06.2019 • **Accepted:** 11.07.2019

Cite this article as: Seyhan AU, Hokenek NM, Baskaya N, Yilmaz E, Korkut S, Onder Karagoz HK, Almadhoun H. The effects of moon phases on suicide attempts. Eurasian J Tox. 2019;1(2):53-56.

to the simplicity of observing its synodic cycle, these correlations have been deceptive in most cases[5]. Although there is no scientific evidence, the hypothesis of the lunar effect on suicide still believed[6]. We conducted a population based study to assess the effects of moon phases on suicides by age, gender, chosen method, cause of suicide and the clinical outcomes.

Material and Methods

Our study included 419 patients who presented to our hospital between January 2018 and December 2018 due to attempts of suicide. Age, gender, history, moon calendar, clinical outcome, suicide mechanism and cause of the patients were retrospectively obtained from hospital records. These data were evaluated statistically. The data obtained in this way were analyzed in relation to the new moon, full moon, last quarter moon, first quarter moon and lunar eclipses in the moon calendar. These cycles were taken from the moon calendar and the dates when the moon was visible and the exact date of the cycle have been evaluated. Cases whose identity information could not be reached and those with suspected criminal offenses where judicial process have been initiated were excluded from the study. Pearson chi-square, Fisher exact and Cramér's V tests were used to analyze the data in our study

Results

Of the 419 patients included in this study, 280 were female and 139 were male. 27 of the patients had organic pathology and 109 had psychiatric disease history. Other patients had no history of disease.236 of the applicants were discharged from the emergency department, 50 were admitted to psychiatry, 24 were transferred to the intensive care unit and 109 left the hospital without permission. The most frequent suicide mechanism was found to be drug intake 93.3% (391), hanging 3.1%[13], only by firearm 1.2%[5], firearm and incision 1.9%[8] and 0.5% by drowning in water[2]. When causes of suicides were examined, 155 patients had sudden anger, 126 patients wanted death and in135 patients causes were due to secondary gains. We concluded that the most frequent suicide attempt among the age groups was between 18-49 years in both sexes. (Table 1)

Table 1. Distribution of patients according to age groups

	N			%		
	Total	**Female**	**Male**	**Total**	**Female**	**Male**
14-17 age	46	41	5	10,98	14,64	3,60
18-49 age	340	222	118	81,15	79,29	84,89
50-65	27	13	14	6,44	4,64	10,07
65+	6	4	2	1,43	1,43	1,44
	419	280	139	100	100	100

When the phases of the moon are compared with the frequency of suicide, the days in which the moon is seen in the lunar calendar differ significantly from the other days when it is not. The most frequent suicide attempts have been found to be the in the new moon, lunar eclipse, last quarter moon, first quarter moon and the full moon, respectively (Pearson chi2[5] = 59.2428 Pr = 0.000). When we analyzed the same data with Cramér's V test, we got the result of 0.2751, which confirms our hypothesis that the frequency of suicides increased with the advances of lunar cycles.

Table 2. Comparison of the frequency of suicides per day and lunar phase

	Number of days	**Number of Suicides**	**Suicide per day**	**FEMALE**	**MALE**
Full moon	11	28	2,55	22	6
Last quarter moon	13	39	3,00	25	14
New moon	12	50	4,17	29	21
First quarter moon	12	35	2,92	27	8
Lunar eclipse	2	7	3,50	6	1
Other	314	260	0,83	171	89

No significant relationship has been found between the patients gender and frequency of suicides per day in lunar phases (p>0.05) (Table 3)

Table 3. Gender evaluation of suicide attempts in the cycles of the moon.

		Female n=280		Male n=139		p
		n	%	n	%	
New moon	Absent	251	89,64	118	84,89	0.158
	Present	29	10,36	21	15,11	
First quarter moon	Absent	253	90,36	131	94,24	0.176
	Present	27	9,64	8	5,76	
Last quarter moon	Absent	255	91,07	125	89,93	0.704
	Present	25	8,93	14	10,07	
Full moon	Absent	258	92,14	133	95,68	0.172
	Present	22	7,86	6	4,32	
Lunar eclipse	Absent	274	97,86	138	99,28	0.284
	Present	6	2,14	1	0,72	

Table 4. Relationship between gender and he causes of suicide attempt

		Female n=280		Male n=139		p
		n	%	n	%	
Anger	Absent	182	65,00	82	58,99	0.230
	Present	98	35,00	57	41,01	
Death	Absent	203	72,50	131	94,24	0.176
	Present	77	27,50	8	5,76	
Secondary gains	Absent	177	63,21	107	76,98	0.005
	Present	103	36,79	32	23,02	

Statistical analysis of the reasons of suicide attempt showed that suicide attempt due to secondary gains was found to be significantly higher in female gender (p<0.05) (Table 4). Suicide attempt due to anger or desire for death can be seen in both sexes and no significant difference was observed.

Discussion

The effects of the Moon's cycles on the world have been investigated for millennia. Although the hypothesis of the lunar effect on suicide is widespread, there is still insufficient scientific evidence[7]. Contrary to our hypothesis, there are many studies and contradictory views[8]. At the same time, many organic pathologies have been studied in relation to the cycles of the moon. Renal colic and stroke has been studied also and no relationship has been found between these medical condition and moon cycle. Our study should be evaluated separately from organic conditions since it includes more psychopathological issues. As a prediction of this study, suicidal admission to hospital was significantly increased in the four stages when the moon was visible and when there was lunar eclipse. Another important finding in our study is that the frequency of suicide due to secondary gain is significantly higher in women than men. In a study, specific biological factors found in women may contribute to suicide and these factors work differently in female and male populations[11]. In fact, this results are correlated with the results of our study. In addition to that understanding this extremely complex phenomenon, social and biological explanations should be considered as complementary work, not as rivals.

Conclusion

It was found that during specific phases of the moon the rate of suicide attempts the present to the emergency department had been increased. Suicide attempts is most commonly

seen in the 18-49 age range, and it is found that the frequency of suicide due to secondary gain is high in female gender. Further studies are still needed in this subject.

Referances

1. Duan W, Huang S, Nie C. Entrance Pupil Irradiance Estimating Model for a Moon- Based Earth Radiation Observatory Instrument. Remote Sensing. 2019;11(5):583.
2. Carroll RT. The skeptic's dictionary: a collection of strange beliefs, amusing deceptions, and dangerous delusions: Wiley Hoboken, NJ; 2003.
3. Partonen T, Haukka J, Nevanlinna H, Lönnqvist J. Analysis of the seasonal pattern in suicide. Journal of affective disorders. 2004;81(2):133-9.
4. Zonda T, Bozsonyi K, Kmetty Z, Veres E, Lester D. The birthday blues: a study of a large Hungarian sample (1970–2002). OMEGA-Journal of Death and Dying. 2016;73(1): 87-94.
5. Gutierrez-Garcia J, Tusell F. Suicides and the lunar cycle. Psychological reports. 1997;80(1):243-50.
6. Chaudhari NK, Mori R, Garg S, Rathwa V, Shah J. Lunar phases and suicide-A prospective study. Available online from 2008 with www indianjournals com. 2018;21(1-2): 28.
7. Biermann T, Estel D, Sperling W, Bleich S, Kornhuber J, Reulbach U. Influence of lunar phases on suicide: the end of a myth? A population-based study. Chronobiology international. 2005;22(6):1137-43.
8. Martin SJ, Kelly IW, Saklofske DH. Suicide and lunar cycles: a critical review over 28 years. Psychological reports. 1992;71(3 Pt 1):787-95.
9. Yang AW, Johnson JD, Fronczak CM, LaGrange CA. Lunar phases and emergency department visits for renal colic due to ureteral calculus. PloS one. 2016;11(6):e0157589.
10. Ruuskanen JO, Sipilä JO, Rautava P, Kytö V. No association of moon phase with stroke occurrence. Chronobiology international. 2018;35(8):1168-74.
11. Kmetty Z, Tomasovszky Á, Bozsonyi K. Moon/sun–suicide. Reviews on environmental health. 2018;33(2):213-7.

Original Article

Eurasian Journal of Toxicology

Plasma Lactate Levels in Carbon Monoxide Intoxication, Can be Used at First Step?

Sinem Doğruyol[1], İlker Akbaş[2], Erdal Tekin[3]

[1]Alaşehir State Hospital, Department of Emergency Medicine, Manisa, Turkey

[2]Bingöl State Hospital, Department of Emergency Medicine, Bingöl, Turkey

[3]Atatürk University Faculty of Medicine, Department of Emergency Medicine, Erzurum, Turkey

Abstract

Objectives: The aim of this study was to determine whether there was a significant relationship between carboxyhemoglobin levels and plasma lactate levels at the time of admission in patients who had been admitted to the emergency department due to carbon monoxide intoxication.

Materials and Methods: In this retrospective-cross-sectional study, patients diagnosed with toxic effects of carbon monoxide were evaluated among the patients admitted to the emergency department between 01.01.2013-01.01.2017. Patients were classified as Group 1 (10% -20%) and Group 2 (20% and above) according to their carboxyhemoglobin levels.

Results: A total of 404 patients were included in the study. The mean carboxyhemoglobin level was 21.2 ± 8% for all cases and 14.6 ± 3% for Group 1 and 27.8 ± 6% for Group 2. The difference between the two groups was statistically significant (mean difference 13.2; 95% CI = 12,198-14,157) (p <0.001). The number of patients with lactate levels above normal in Group 2 was higher than Group 1 (p <0.001). There was a significant difference in lactate levels between two exposure groups (p <0.001). There was a correlation between carboxyhemoglobin levels and lactate levels (r = 0,601, p <0,001). In the ROC analysis to determine the value of lactate levels in the diagnosis of severe exposure (Group 2), AUC was calculated as 0,791 (95% confidence interval, 0.748-0.835; p <0.001; Figure 1).

Conclusion: In the evaluation of cases of carbon monoxide poisoning, the question of whether plasma lactate level can be used as a marker is still being discussed. Based on the significant results that we found in our study, plasma lactate levels ,which is correlated with carboxyhemoglobin levels, may be helpful in the classification and evaluation of patients with carbon monoxide intoxication.

Key words: Carboxyhemoglobin, Carbon monoxide, Lactate, Poisoning

Özet

Amaç: Bu çalışmanın amacı karbonmonoksit zehirlenmesi nedeniyle acil servise başvurmuş olan olguların başvuru anındaki plazma laktat düzeyi ile COHb düzeyleri arasında anlamlı bir ilişki olup olmadığını değerlendirmektir.

Gereç ve Yöntem: Retrospektif-kesitsel bu çalışmada, 01.01.2013-01.01.2017 tarihleri arasında acil servise başvurmuş olgular arasından, hastane veri sisteminde 'Karbonmonoksitin toksik etkisi' tanı kodu mevcut olanlar incelendi. Hastalar karboksihemoglobin düzeylerine göre Grup 1 (%10-%20 arası) ve Grup 2 (%20 ve üstü) şeklinde sınıflandırıldı.

Bulgular: Çalışmaya toplam 404 olgu dahil edildi. Tüm olgular için ortalama karboksihemoglobin düzeyi %21,2±8 olup, Grup 1 için ortalama %14,6±3, Grup 2 için ise %27,8±6 olarak hesaplandı. İki grup arasındaki bu fark istatistiksel olarak anlamlıydı (ortalama fark, 13,2; %95 GA= 12,198-14,157) (p<0,001). Grup 2'de normalin üstünde laktat değerleri tespit edilen olgu sayısı, Grup 1'e göre fazlaydı (p<lt;0,001). İki maruziyet grubu arasında laktat değerleri açısından anlamlı fark tespit edildi (p<0,001). Karboksihemoglobin düzeyleri ile laktat seviyeleri arasında korelasyon mevcuttu (r=0,601, p<0,001). Ciddi maruziyet (Grup 2) tanısında laktat düzeylerinin değerliliğini araştırmak için oluşturulan ROC analizinde, AUC 0,791 olarak hesaplandı (95% güven aralığında , 0.748–0.835; p<0,001; Şekil 1).

Sonuç: Karbonmonoksit zehirlenmesi olgularının değerlendirilmesinde, plazma laktat düzeyinin bir belirteç olarak kullanılabileceği konusu hala tartışmalıdır. Çalışmamız, saptamış olduğumuz anlamlı sonuçlara dayanarak, karboksihemoglonin düzeyi ile korele bir yükseliş gösterdiğinden plazma laktat düzeylerinin olguların sınıflandırılmasında kullanılabileceğini göstermiştir.

Anahtar kelimeler: Karboksihemoglobin, Karbonmonoksit, Laktat, Zehirlenme

Introduction

Carbon monoxide (CO) gas poisoning rates in our country vary between 2.1% and 10.2% [1]. Carbon monoxide is a non-irritant, colorless and odorless gas which constitutes approximately half of fatal poisonings[2]. Over the years, CO poisoning remains an important cause of morbidity and mortality in winter, despite increasing public awareness efforts[3]. Carboxyhemoglobin (COHb), formed by CO binding to hemoglobin, blocks the release of oxygen to the tissues

Corresponding Author: Sinem Doğruyol **e-mail:** dogruyolsinem@gmail.com

Received: 28.12.2018 • **Accepted:** 11.01.2019

Cite this article as: Dogruyol S, Akbas I, Tekin E. Plasma lactate levels in carbon monoxide intoxication, can be used at first step?. Eurasian J Tox. 2019;1(2):57-60

and creates hypoxia at the tissue level. Additionally, by disrupting the intracellular oxidative phosphorylation, it causes toxicity at the cellular level 4. When one CO molecule binds to the hem part of hemoglobin, allosteric alteration occurs, the binding affinities of remaining 3 oxygens are increased and the release of oxygen to the tissues is reduced[5]. The diagnosis of CO poisoning is best made by measuring the blood level of COHb[6]. Symptoms in CO poisoning are not specific. This causes an increase in delays and mortality in the diagnosis and treatment process[7]. Blood COHb levels are used to validate clinical suspicion of toxic gas exposure and to assess the severity of intoxication[8].

As an indicator of tissue hypoxia, lactate is a very important indicator of critical patient care. There are studies evaluating the validity of plasma lactate level as a prognostic marker in CO poisoning intoxication[9]. However, there is no clear decision about this topic. The aim of this study was to determine whether there was a significant relationship between COHb levels and plasma lactate levels at the time of admission in patients who had been admitted to the emergency department due to CO intoxication.

Materials and Methods

Study Design

This is a retrospective cross-sectional study. Between 01.01.2013 and 01.01.2017, the patients who were admitted to Atatürk University Faculty of Medicine Emergency Medicine Department and who were diagnosed as 'Toxic effect of carbon monoxide (T58)'in the hospital data system were studied. The study was approved by the ethics committee, by the same institution.

Patient Selection

Patients who had a COHb level of less than 10% and whose laboratory data could not be reached were excluded from the study. Patients aged below 18 years and above 65 years were not included in the study. Patients with chronic kidney and liver disease, atherosclerotic heart disease, diabetes, malignancy, coagulation disorder, hematological disease, antiplatelet and anticoagulant drugs were excluded from the study. Pregnant women were excluded from the study.

Study Protocol

Patients according to COHb level; 10% -20% were classified as 'mild exposure' (Group 1), 20% and above were classified as 'serious exposure' (Group 2)[6, 10]. Blood gas data obtained from the peripheral artery in the first 30 minutes of patients' admission to the emergency department were examined. Carboxyhemoglobin and lactate results were evaluated. For lactate, values below 2 mmol / L were considered normal.

Statistical Analysis

In the statistical evaluation of the data, IBM Statistics 20.0 (SPSS) statistical package program was used. The conformity of continuous variables to normal distribution was measured by Kolmogorov-Smirnov test. Student T test was used to compare the normal distribution of the data. Mann-Whitney U test was used for the comparison of the two groups of data that did not show normal distribution. Chi-square test was used to compare categorical variables. Percentage, frequency, mean and standard deviation values were given as descriptive statistics. Spearman correlation analysis was used to evaluate the relationship between lactate levels and COHb values. Receiver Operator Characteristics (ROC) analysis was used to determine the diagnostic value and cut-off value of lactate level in severe CO exposure. In the obtained ROC curve, the Area under the curve (AUC) value is close to 1, indicating that the value of the test is high. The significance level for the AUC obtained in the same test was also determined. Results were evaluated at 95% confidence interval and $p < 0.05$ at significance level.

Results

A total of 404 patients were included in the study. 172 (42.6%) of the cases were male and 232 (57.4%) were female. The mean age was 35 ± 12 years. There was no significant difference between genders in terms of age distribution ($p > 0.05$). No significant difference was found between the groups in Group 1 (81 males, 122 females, mean age 34 ± 12 years) with respect to age and sex distribution in group 2 (91 males, 110 females, mean age 36 ± 13 years) ($p > 0, 05$).

The mean COHb level was 21.2 ± 8 for all cases and the mean COHb for Group 1 was 14.6 ± 3 and the Group 2 was 27.8 ± 6. The difference between the two groups was statistically significant (mean difference 13.2; 95% CI = 12,198-14,157) ($p < 0.001$).

The median plasma lactate value of all cases was 1.9 (IQR 1.6), and in 201 (49.8%) patients lactate level was found to be above normal. The number of patients with lactate levels above normal in Group 2 was higher than Group 1 ($p < 0.001$). There was a significant difference in lactate levels between two exposure groups ($p < 0.001$). There was also a correlation between COHb levels and lactate levels when all parameters were evaluated ($r = 0.601$, $p < 0.001$).

We developed a ROC curve to investigate the value of plasma lactate levels in the diagnosis of severe exposure

cases categorized as Group 2. AUC for lactate was calculated as 0.791 (95% confidence interval, 0.748-0.835; p <0.001; Figure 1). We also found that a plasma lactate level of 3 mmol /L had a positive predictive value of 88% and a negative predictive value of 63%, which could be used as a cut-off value for Group 2 patients.

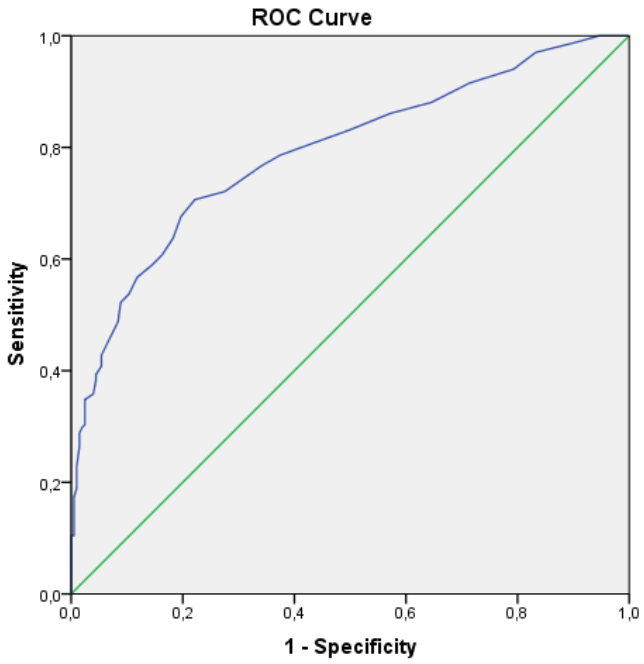

Figure 1. The ROC curve analysis for plasma lactate level.

Discussion

In the evaluation of patients who presented to the emergency department with CO poisoning, there are different opinions that plasma lactate levels can be used in the diagnosis and treatment process, similar to COHb levels. Considering that the poisoning mechanism is tissue hypoxia, it is still controversial that high lactate levels may be an important predictor of the patient clinic. Benaissa et al. in their study with 146 patients in CO poisoning, did not support evidence of lactate measurement is useful[11]. On the other hand, Cervellin et al. stated that high lactate levels are important in patient triage and may be used as a prognostic marker for the follow-up period[9]. Similarly, there are studies in the literature that support plasma lactate levels correlated with COHb levels in cases of CO intoxication[12, 13]. Taken together, the published evidence about the clinical significance of plasma lactate levels in CO-poisoned patients is insufficient and controversial, so the results of our study may have some meaningful clinical implications.

In our study, we found a significant correlation between COHb levels and plasma lactate levels of CO intoxication cases. This was consistent with similar literature[12]. As stated in Doğan et al. we also think that the strong correlation coefficient between these two laboratory parameters may be related to the high COHb levels in our study[13].

In our study, we found that the plasma lactate levels of patients with a COHb level 20% or higher, who were classified as 'serious exposure', were above normal range. In addition, due to the high specificity and high positive predictive value that has been found for plasma lactate level 3 mmol /L in our study, we believe that it can be used as a cut-off value for severe exposure.

There are some limitations in our study. Since the study was conducted at a single center, the characteristics of different patient populations from different regions could not be evaluated. regional differences could not be evaluated in terms of data heterogeneity. However, due to the large patient population in our study, we believed that we have eliminated this limitation by providing a heterogeneous patient distribution. Due to the retrospective nature of the study, there is a lack of data about patient files in 4 years. Therefore, it was not possible to collect the data of patients' clinical symptoms.

Conclusion

It is still controversial that plasma lactate levels can be used as a marker for the evaluation of CO intoxication cases in emergency departments. Based on the significant results that we found in our study, plasma lactate levels ,which is correlated with COHb levels, may be helpful in the classification and evaluation of patients with CO intoxication.

References

1. Satar S, Seydaoglu G, Akpinar A, Sebe A, Karakoc E, Gumusay U, et al. Trends in acute adult poisoning in a ten-year period in Turkey: factors affecting the hazardous outcome. Bratisl Lek Listy. 2009;110(7):404–11.
2. Kao LW, Nañagas KA. Carbon monoxide poisoning. Emerg Med Clin North Am. 2004;22(4):985-1018. doi:10.1016/j.emc.2004.05.003
3. Koylu R, Dundar ZD, Koylu O, Akinci E, Akilli NB, Gonen MO, et al. The experiences in a toxicology unit: a review of 623 cases. J Clin Med Res. 2014;6(1):59-65. doi:10.4021/jocmr1687w
4. Maloney G. Carbon monoxide. In: Tintinalli JE, editor. Tintinalli's Emergency Medicine: A Comprehensive Study Guide. 7th ed. New York: McGraw-Hill; 2011. p. 1410–3.
5. Koruk S, Tuncel I, Mizrak A, Hengirmen Akcali A, Ganidagli S. Cerebrovascular changes and EEG findings in carbon monoxide intoxication: case report. J Emerg Med CASE REPORTS. 2010;1(2):23–6.

6. Smollin C, Olson K. Carbon monoxide poisoning (acute). BMJ Clin Evid. 2010;(June):1–12.

7. Weaver LK. Carbon Monoxide Poisoning. N Engl J Med. 2009;360(12):1217-25. doi:10.1056/NEJMcp0808891

8. Thom SR. Carbon monoxide pathophsyology and treatment. In: Neuman TS, Thom SR, editors. Phsyology and Medicine of Hyperbaric Oxygen Therapy. Philadelphia: Saunders/Elsevier; 2008. p. 321–47.

9. Cervellin G, Comelli I, Rastelli G, Picanza A, Lippi G. Initial blood lactate correlates with carboxyhemoglobin and clinical severity in carbon monoxide poisoned patients. Clin Biochem.2014;47(18):298-301.doi:10.1016/j.clinbiochem.2014.09.016

10. Thom SR, Hampson NB, Mathieu-Nolf M, Raub JA. Carbon monoxide poisoning - a public health perspective. Toxicology. 2000;145(1):1-14. doi:10.1016/s0300-483x(99)00217-6

11. Benaissa ML, Megarbane B, Borron SW, Baud FJ. Is elevated plasma lactate a useful marker in the evaluation of pure carbon monoxide poisoning? Intensive Care Med. 2003;29(8):1372-5. doi:10.1007/s00134-003-1866-0

12. Jeong Mi Moon, Min Ho Shin, Byeong Jo Chun. The value of initial lactate in patients with carbon monoxide intoxication: in the emergency department. Hum Exp Toxicol. 2011;30(8):836-43. doi:10.1177/0960327110384527

13. Doğan N, Savrun A, Levent S, Günaydin GP, Çelik GK, Akküçük H, et al. Can initial lactate levels predict the severity of unintentional carbon monoxide poisoning? Hum Exp Toxicol. 2015;34(3):324-9. doi:10.1177/0960327114538986

Original Article

Eurasian Journal of Toxicology

Evaluation of the Relationship of Serum Digoxin Levels with Demographic Data

Hatice Şeyma Akça, Abdullah Algın, Serdar Özdemir, Kamil Kokulu, İbrahim Altunok
Department of Emergency Medicine, University of Health Sciences Umraniye Training and Research Hospital, Istanbul, Turkey

Abstract

Objective: We aimed to compare serum digoxin levels and demographic data of patients who presenting with digoxin intoxication.

Materials and Methods: This is a retrospective study. Patients admitted to the emergency room with suspected digoxin intoxication included into the study. Patients with missed data, and patients younger than 18 years were excluded.

Results: A total of 118 patients were investigated in our retrospective study. Among these, 38 (%32,2) were men and 80 were female (%67,8). Patients with a digoxin level above 2 ng/mL were evaluated for intoxication. Digoxin intoxication was detected in 31 patients (26.3%). Of 31 patients with digoxin intoxication, 19 (61.2%) were hospitalized. Patients who had digoxin intoxication admission complaints were fatigue in 6 patients (19,35%), nausea in 4 patients (12,9%), bradycardia in 4 patients (12,9%), and general condition disorder in 4 patients (12,9%).

Conclusion: Blood level in digoxin intoxication may not always be decisive. in suspected digoxin intoxication cases, a detailed anamnesis, physical examination, ECG findings routine electrolyte and other blood tests should be examined and cardiology should be consulted.

Key words: Digoxin intoxication, digoxin levels, demographic data, emergency service

Özet

Amaç: Digoksin zehirlenmesi ile başvuran hastaların serum digoksin düzeylerini ve demografik verilerinin karşılaştırılması amaçlanmıştır.

Gereç ve Yöntem: Bu çalışma retrospektif olarak planlanmıştır. Acil servise şüpheli digoksin zehirlenmesi şikayeti ile başvuran hastalar çalışmaya dahil edildi. Verilerine ulaşılamayan veya 18 yaşından küçük hastalar çalışma dışı bırakıldı.

Bulgular: Retrospektif çalışmamızda toplam 118 hasta incelendi. Bunlardan 38'i (% 32,2) erkek, 80'i kadındı (% 67,8). Digoksin seviyesi 2 ng / mL'nin üzerinde olan hastalar zehirlenme açısından değerlendirildi. Digoksin zehirlenmesi 31 hastada (% 26.3) tespit edildi. Digoksin zehirlenmesi olan 31 hastanın 19'u (% 61,2) hastaneye yatırıldı. Digoksin intoksikasyon başvuru şikayeti olan hastalar 6 hastada (% 19,35) yorgunluk, 4 hastada (% 12,9) bulantı, 4 hastada (% 12,9) bradikardi ve 4 hastada (12,9) genel durum bozukluğu mevcuttu.

Sonuç: Digoksin zehirlenmesinde kan seviyesi her zaman belirleyici olmayabilir. Şüpheli digoksin zehirlenmesi vakalarında, ayrıntılı bir anamnez, fizik muayene, EKG bulguları rutin elektrolit ve diğer kan testleri incelenmeli ve kardiyoloji kliniğine konsültasyon planlanmalıdır.

Anahtar kelimeler: Digoksin zehirlenmesi, digoksin seviyeleri, demografik veriler, acil servis

Introduction

Digital glycosides shows the inotropic effect by inactivating Na-K ATPase pump by binding to specific receptors in the cell membrane. Sodium - Calcium exchange increases intracellular calcium ion concentration; calcium increases contractility and occurs a positive inotropic effect. This physiological state increases cardiac output and stroke volume. Ejection fraction increases, ventricular wall tension decreases, heart rate decreases and oxygen consumption decreases. Kidney blood flow and glomerular filtration rate increases, edema decreases. With parasympathetic effect, the ventricular response is suppressed in supraventricular tachycardia[1-4]. Digoxin is absorbed from the gastrointestinal system by passive diffusion, excreted by glomerular filtration from the kidneys, very few are metabolized in the liver and undergoes renal tubular secretion. Safe dosage range are narrow medications[4]. Sinoatrial block, AV block, atrial and ventricular arrhythmias, ectopia, hyperkalemia, confusion, nausea, anorexia and color vision disorders are among the side effects. Tissue levels and blood levels are different, even at the treatment dose of poisoning findings can be observed. Toxicity is associated with tissue level. While the blood levels of digoxin are generally high in acute toxicities, digoxin blood level in chronic toxicities is normal or slightly higher. Factors affecting the occurrence of toxicity findings

Corresponding Author: Abdullah Algın **e-mail:** dralgin@hotmail.com
Received: 25.05.2019 • **Accepted:** 04.07.2019
Cite this article as: Akça HS, Algin A, Ozdemir S, Kokulu K, Altunok I. Evaluation of the relationship of serum digoxin levels with demographic data. Eurasian J Tox. 2019;1(2):61-64

in chronic poisoning; metabolic and electrolyte abnormalities, hypokalemia, hypomagnesemia, hypercalcemia, myocardial ischemia, old age, renal dysfunction, liver disease, hypothyroidism, chronic obstructive pulmonary disease, drug interactions[4-7].

Today, it is used in the treatment of heart failure and atrial fibrillation[8, 9]. Intravenous digoxin or amiodarone with grade IIa (level of evidence B) was recommended to slow the heart rate in a new-onset high-speed AF-Acute or Chronic Heart Failure[10]. Digoxin concentration according to DIG (Digitalis Investigation Group) study data; mortality increased in patients with ≥1,2 ng / mL[11].

According to the ACC (American College of Cardiology); digoxin should be started at doses between 0.125 and 0.25 mg / day. Therapeutic serum concentrations were 0.6-1.2 ng / mL. In older patients, the use of digoxin at low doses (day-by-day or 0.125 mg daily) was suggested in patients with impaired renal function or low body mass index[4, 12].

Digoxin intoxication is an important health problem in our country that causes mortality and morbidity. In this study we aimed to compare serum digoxin levels and demographic data of patients who presenting with digoxin intoxication.

Materials and Methods

This was a retrospective study including patients over 18 years of age who were admitted to the Clinic of Emergency Medicine of University of University of Health Sciences Umraniye Training and Research Hospital, Istanbul, Turkey with suspected digoxin intoxication between 01.01.2017 and 01.01.2019.

On admission to the emergency department, blood samples were evaluated. With digoxin level in the blood, urea, creatinine, potassium, calcium and magnesium levels, hospitalization, ECG findings and mortality status were evaluated.

The data obtained were analyzed using the SPSS v25 (SPSS Inc, Chicago, IL) program package. The Kolmogorov-Smirnov and the Shapiro-Wilk tests were used to analyze the compliance to the normal distribution, and the chi-square and t-tests were used for the remaining analyses. The quantitative data were expressed as mean, standard deviation (SD) and median (minimum – maximum value), and the qualitative data were expressed as case number (n) and percentages (%). The outcomes were evaluated in 95% confidence interval and the significance was accepted at a level of $p<0.05$.

Results

A total of 118 patients were investigated in our retrospective study. Among these, 38 (%32,2) were male and 80 were female (%67,8). The median age was 76,5 (70,0 – 83,0). 53 (44.9%) patients were hospitalized. Of these, 23 (43.3%) were male; 30 (56.6%) were female. 65 (55.1%) patients were discharged. Two patients (1.7%) died during hospitalization. One of them was male and the other was female. (Table.1)

Table 1. Demografic Data-Digoxin Levels-Laboratory Findings

		Normal	High	Total
Age		75,0 (69,0 – 82,0)	80,0 (74,0 – 85,0)	76,5 (70,0 – 83,0)
Gender	Female	55 (%46,6)	25 (%21,2)	80 (%67,8)
	Male	32 (%27,1)	6 (%5,1)	38 (%32,2)
Digoxin Levels		0,73 (0,42 – 1,16)	2,81 (2,42 – 3,74)	1,06 (0,57 – 2,12)
BUN		49,20 (38,50 – 79,15)	72,70 (48,11 – 109,00)	53,50 (38,50 – 85,60)
Creatinin		0,90 (0,80 – 1,30)	1,10 (0,99 – 1,91)	1,04 (0,80 – 1,50)
Potasium		4,3 (3,9 – 4,8)	4,8 (4,2 – 5,3)	4,40 (4,00 – 5,00)
ECG Finding	No	23 (%19,5)	4 (%3,4)	27 (%22,9)
	Yes	64 (%54,2)	27 (%22,9)	91 (%77,1)
Hospitalization	No	53 (%44,9)	12 (%10,2)	65 (%55,1)
	Yes	34 (%28,8)	19 (%16,1)	53 (%44,9)
Mortality	No	85 (%72,0)	31 (%26,3)	116 (%98,3)
	yes	2 (%1,7)	0 (%0)	2 (%1,7)

Table 2. Digoxin Levels and Hospitalization

		Hospitalization		Total
		No	Yes	p=0.033
Digoxin Levels	Normal	53	34	87
	High	12	19	31
Total		65	53	118

Patients with a digoxin level above 2 (ng/ml) were evaluated for intoxication. Digoxin intoxication was detected in 31 patients (26.3%). 25 (%21,2) of them were female; 6 (%5,1) of them were male. Of 31 patients with digoxin intoxication, 19 (61.2%) were hospitalized. Of these, 5 (16.1%) were male; 14 (45.1%) were female. Patients with high digoxin levels had significantly higher hospitalization rates (p=0.033). (Table.2)

The admission complaints of patients, who had digoxin intoxication, were fatigue in 6 patients (19,35%), nausea in 4 patients (12,9%), bradycardia in 4 patients (12,9%), and general condition disorder in 4 patients (12,9%). 4 patient was unconsciousness (12.9%) and 3 patients had shortness of breathness (9.6%) One patient was admitted with seizure, one patient with chest pain, one patient with dizziness, one patient with edema and one patient with aphasia (3.2%).

The most common ECG finding was Atrial fibrillation (AF). 12 patients (38.7%) had AF. 5 patients (16,12 %) had bradycardia. ECG was normal in 4 (12.9%) patients. Comorbidities: coronary artery disease in 6 (19.3%) patients; atrial fibrillation in 5 (16,12%) patients, diabetes mellitus and atrial fibrillation in 3 (9,6%) patients; hypertension, diabetes mellitus and coronary artery disease in 2 (6,4%) patients. There was also diabetes mellitus and congestive heart failure in 2 (6,4%) patients. Patients with abnormal ECG findings had significantly higher hospitalization rates than the others (p=0.007). (Table.3)

Discussion

Since the safety interval of the digitals is narrow, poisoning is divided into acute and chronic toxicity. In a patient presenting with emergency service, vomiting, weakness, bradyarrhythmia, atrioventricular block and supraventricular arrhythmia, digoxin poisoning should be questioned. Routine blood tests of these patients should be evaluated. These patients should be monitored. However, the severity of signs of intoxication and digoxin blood levels are not always proportional. Because the tissue levels of digoxin are different from blood levels, signs of poisoning can be observed even at the treatment dose. Toxicity is associated with tissue level. While the blood levels of digoxin in acute toxicities are generally high, digoxin blood level in chronic toxicities is normal or slightly high.

It is known that the absorption rate of the standard tablet formulations of digoxin can be as high as 50-70% and the absorption rate of the solution in gelatin capsule can be as high as 100%. Digoxin is excreted primarily by glomerular filtration from the kidneys and metabolized in the liver and conjugated to inactive metabolites. The protein binding rate is low and varies between 20-30%. The distribution of adipose tissue is insignificant. Can cross the blood-brain barrier and the placenta. The distribution volume of digoxin is large and the distribution in adults is approximately 5 L / kg. The half-life at the treatment dose is 36-48 hours. This period may be prolonged in patients with low glomerular filtration rate[1, 4, 6, 7, 13].

Table 3. ECG findings and Hospitalization

		Hospitalization		Total
		No	Yes	p=0.007
ECG Finding	No	21	6	27
	Yes	44	47	91
Total		65	53	118

In the last 2 years, drug levels were studied in 118 patients and only 31 patients had high levels of digoxin. Of the 31 patients, only 19 were hospitalized. Of the 87 patients with normal or low digoxin levels, 34 were hospitalized for various reasons. It should be calculated that some patients may have different history due to neurological problems, and that drug intake may not be fully known by their relatives. Tissue distribution, glomerular filtration rate, acute-chronic toxicity symptoms and differences in digoxin levels should be kept in mind in cases where intoxication is considered.

The most important cardiac finding of digital poisoning is rhythm disturbances manifested as tachyarrhythmias and conduction blocks. The cause of death is usually ventricular tachycardia or ventricular fibrillation. Cardiac glycosides generally cause A-V (atrioventricular) block of all degrees up to the full block, but rarely form a sinoatrial node block. In cases where the patient cannot be monitored by ECG (electrocardiography), if the pulse falls below 60, is considered to be the A-V block[2, 4, 7, 14].

In our study, in inpatients the most common ECG finding was Atrial fibrillation (AF). 12 patients (38.7%) had AF and 5 patients (16,12 %) had bradycardia. Patients with abnormal ECG findings had significantly higher hospitalization rates than the others (p=0.007). However, the normal ECG should not mean that there is no intoxication.

High serum potassium levels in acute digoxin poisoning is a good predictor of organ toxicity. In acute digoxin intoxications, the patient may be asymptomatic within the first few hours[4, 6, 7].

While the level of digoxin blood is generally high in acute toxicity, digoxin blood level in chronic toxicities is normal or slightly high[4, 6, 7]. In a study in which digoxin levels were found to be normal but patients with symptoms and clinically intoxication were considered, coronary artery disease was more common in the toxic group. There was no significant difference in other data.[15]

In another study that investigated the effect of digoxin use on hospital admission and prognosis, 3397 patients with heart failure were treated with digoxin. 3403 patients were treated with angiotensin converting enzyme inhibitors and diuretics. It was determined that digoxin did not decrease mortality but prevented hospitalization and clinical deterioration[16].

This study has certain limitations. Firstly, the relatively low number of evaluated cases may be considered as a limitation. It is necessary to undertake a further study with a higher number of cases to obtain more reliable results. If the drugs used by the patients were known, the rate of hospitalization of patients using drugs that changed serum digoxin levels could also be investigated. This situation also can be considered as a limitation.

Conclusion

As a matter of fact, blood level in digoxin intoxication may not always be decisive. After a detailed anamnesis, physical examination, ECG findings should be followed, routine electrolyte and other blood tests should be examined and cardiology should be consulted.

References

1. Ochs HR, Grube E, Greenblatt DJ, Arendt R, Bodem G. Pharmacokinetics and pharmacodynamics of intravenous digoxin and digitoxin. Klinische Wochenschrift, 1981; 59(16):889-97.
2. Kayaalp O. Medical Pharmacology for Rational Therapy (10th edition). Ankara: Hacettepe-Taş Kitapçılık. 2002.
3. Kepez A, Kabakcı G. Treatment of Heart Failure, Hacettepe Medical Journal, 2004; 35 (2):69-81.
4. Çiftçi E, Aydın S. Toxicological Evaluation of Digital Glycosides in Congestive Heart Failure, FABAD J. Pharm. Sci, 2018; 43(3):263-77.
5. Dec G W. Digoxin Remains Useful in the Management of Chronic Heart Failure, The Medical Clinics of North America, 2003; 87 (2):317-37.
6. Satar S, Acilde Klinik Toksikoloji. Akademisyen Kitabevi. Ankara, Türkiye, 2009.
7. Vyas A, Bachani N, Thakur H, Lokhandwala Y. Digitalis toxicity: ECG vignette. Indian Heart Journal, 2016; 68(2):223-5.
8. Boyle JS, Kirk MA. Digitalis Glycosides. In:Tintinalli JE, Tintinalli's Emergency Medicine, A Comprehensive Study Guide, seventh edition, New York, McGraw Hill, 2010:1260-4.
9. Gerede D M, Koboev R, Çağlar N, Kılıçkap M, Erol Ç. Evaluation and Clinical Significance of Factors Affecting the Serum Digoxin Levels in Patients Taking Digoxin. MN Kardiyoloji, 2015; 22:30-6.
10. Sarı I, Çavuşoğlu Y, Temizhan A, Yılmaz MB, Eren M. ESC and ACC/AHA/HFSA Heart Failure Guideline Updates: Changes, Similarities, Differences, and Unresolved Isssues. Turkish Society of Cardiology Ars, 2016;44(8):625-36.
11. Ahmed A, Rich MW, Love TE, Lloyd-Jones DM, Aban IB, Colucci WS, et al. Digoxin and Reduction in Mortality and Hospitalization in Heart Failure: A Comprehensive Post Hoc Analysis of the DIG Trial. Eur Heart J, 2006; 27:178-86.
12. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, et al. ACCF/AHA Guide¬line for the Management of Heart Failure: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation, 2013; 128 (16): 240-327.
13. Francke DE, Bioavailability of Digoxin. The Annals of Pharmacotherapy, 2006; 40(6):1185.
14. Roberts DM, Gallapatthy G, Dunuwille A, Chan BS. Pharmacological Treatment of Cardiac Glycoside Poisoning, British journal of Clinical Pharmacology, 2016; 81(3):488-95.
15. Aslantaş U, Yıldırım S, Bayram MK, Yurtseven A, Çimen T, Doğan M, et al. Digoxin Toxicity in Therapeutic Serum Levels. Mustafa Kemal Üniv Tıp Derg 2015; 6(23): 21-6.
16. Moten M, Anand IS, Sarma RJ, Babb JD. The Effect of Digoxin on Mortality and Morbidity in Patients with Heart Failure. New England Journal of Medicine, 1997; 8(336):525:33.

Case Report

Eurasian Journal of Toxicology

A Rare Cause of Serotonin Syndrome: Chronic Olanzapine Use

Seda Dağar, Emine Emektar, Meral Tandoğan, Şeref Kerem Çorbacıoğlu, Hüseyin Uzunosmanoğlu, Yunsur Çevik
Department of Emergency Medicine, University of Health Sciences, Kecioren Training and Research Hospital, Ankara, Turkey

Abstract

Serotonin syndrome is a life-threatening, undesirable drug reaction. It is a combination of symptoms caused by over activation at central and peripheral serotonin receptors secondary to high serotonin levels. Olanzapine, a second generation antipsychotic agent, is an antagonist of serotonin receptor. Despite the effect of serotonin antagonism, it is reported that olanzapine may paradoxically trigger serotonin syndrome. In this case report, we present a patient with SS due to chronic olanzapine use accompanied by bullous drug reaction.

Key words: serotonin syndrome, olanzapine, atypical antipsychotic

Özet

Serotonin sendromu hayatı tehdit eden, istenmeyen bir ilaç reaksiyonudur. Yüksek serotonin düzeylerine ikincil olarak merkezi ve periferik serotonin reseptörlerinde aşırı aktivasyonun neden olduğu semptomların bir birleşimidir. İkinci kuşak bir antipsikotik ajan olan Olanzapin, serotonin reseptörünün bir antagonistidir. Serotonin antagonizmasının etkisine rağmen, olanzapinin serotonin sendromunu paradoksal olarak tetikleyebileceği bildirilmiştir. Bu olgu sunumunda, büllöz ilaç reaksiyonunun eşlik ettiği kronik olanzapin kullanımı nedeniyle oluşan serotonin sendromlu bir hastayı sunuyoruz.

Anahtar kelimeler: serotonin sendromu, olanzapin, atipik antipsikotik

Introduction

Serotonin syndrome (SS) is a life-threatening, undesirable drug reaction caused by the increase in serotonergic activity in the central and peripheral nervous system. The syndrome which is considered as one of the entities under the heading 'toxic syndromes' or 'toxidromes', is actually an idiosyncratic reaction. The use of serotonin-inducing agents, including selective serotonin reuptake inhibitors (SSRI) and monoamine-oxidase inhibitors (MAOI) are accepted to have the potential for development of SS[1].

Olanzapine is a second generation antipsychotic agent which is an antagonist of serotonin and dopamine receptor (5HT-2A, D2). Despite serotonin antagonism, it has been rarely reported to cause SS in the literature[2].

In this case report, we present a patient with SS due to chronic olanzapine use accompanied by bullous drug reaction.

Case Report

A 27-year-old male presented to the emergency department (ED) with altered mental status. It was learned from his family that previous day, the patient had come home in a dazed state and gone to sleep directly, but he could not be awakened on the day the he was brought to the ED by ambulance. The patient who had been using valproic acid and olanzapine for five years due to bipolar disorder, was also hospitalized for drug abuse a year ago. The vital signs were blood pressure:100/60 mm/hg, pulse:111/min, fever:38.2°C, saturation:92%. The physical examination revealed that the general status was moderate, he was confused, the pupillary myotic, bilateral light reflex was positive and had had no lateralizing deficit. There were also multiple sterile bullous lesions due to drug reaction in lower extremities of the patient (Figure-1). The other system examinations were normal. The laboratory results were glucose:113 mg/dl, urea:51 mg/dl, creatinine:1.74 mg/dl, alanine amino transferase (ALT):958 U/L, aspartate amino transferase (AST):696 U/L, amylase: 449 U/L, lipase: 82 U/L, troponin:8216 pg/ml, creatine kinase-MB (CK-MB):45.5 ng/ml and blood paracetamol level:<4.89 µg/ml. Blood gas parameters were within normal limits. Cocaine, opiate and paracetamol were found positive in urine drug test. Electrocardiography (ECG) and echocardiography were normal except for sinus tachycardia. The patient was monitored and 0.4 mg of naloxane was given intravenously (IV). Appropriate fluid, electrolyte and anti-

Corresponding Author: Seda Dagar **e-mail:** sedadagar@gmail.com
Received: 14.01.2019 • **Accepted:** 23.02.2019
Cite this article as: Dagar S, Emektar E, Tandogan M, Corbacioglu SK, Uzunosmanoglu H, Cevik Y. A rare cause of serotonin syndrome: chronic olanzapine use. Eurasian J Tox. 2019;1(2):65-68

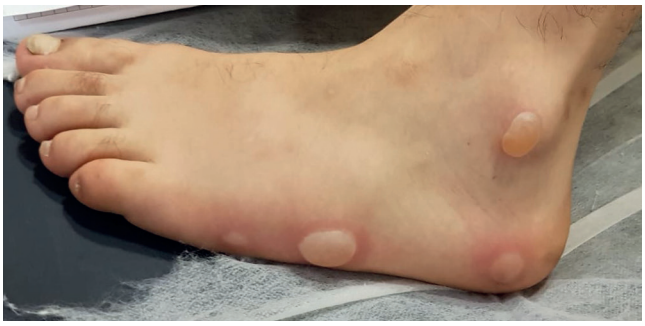

Figure-1. Multiple sterile bullous lesions due to drug reaction

pyretic treatment was initiated. In the follow-up examinations, he had increased fever (39.1°C) and tremor. Muscular rigidity and hyperreflexia were detected in bilateral lower extremities. Serotonin syndrome was considered because of the patient's history and new onset symptoms. All medications were discontinued. The patient was started on external cooling, supportive therapy and cyproheptadine 2 mg/5 mL syrup. After 12 mg loading, 2 mg cyproheptadinewas given every two hours. The patient was admitted to the intensive care unit. On the second day of the follow-up, the fever of the patient decreased, his mental status became normal, also rigidity and hyperreflexia were resolved. He was discharged without any sequelae on the fifth day of hospitalization.

Discussion

Serotonin syndrome is a combination of symptoms caused by over activation at central and peripheral serotonin receptors secondary to high serotonin levels[1]. It is usually easy to skip the diagnosis because of mild symptoms attributed to the general side effects of drugs. The findings may range from mild constitutional symptoms to a life-threatening complex syndrome. In mild cases, tachycardia, tremor, mydriasis, sweating can be seen and usually no fever is observed. In moderate severity syndrome, hyperthermia (>40°C), hyperactive bowel sounds, horizontal ocular clonus, agitation can be seen. In severe cases, hyperthermia (exceeding 41°C), hemodynamic instability, muscle rigidity and delirium are seen. Hyperreflexia, rigidity and clonus are more prominent in the lower extremities[3].

In the literature, SS is reported as a diagnosis of exclusion. There is no diagnostic test to confirm the presence of the syndrome. The most important diagnostic stage is the clinician's suspicion. In the history, the initiation of a serotonergic drug, the dose change or the addition of other drugs should be questioned. Although many diagnostic criteria are described, Hunter Seratonin Toxicity Criteria (HSTC) has the highest sensitivity and specificity rates. According to the HSTC, in addition to the use of a serotoninergic drug, presence of one of the following criteria is efficient for the diagnosis; spontaneous clonus, inducible clonus plus agitation or diaphoresis, ocular clonus plus agitation or diaphoresis, tremor plus hyperreflexia, hypertonia plus temperature above 38ºC plus ocular clonus or inducible clonus[4]. Patients with peripheral hypertonus and trunk rigidity are at great risk for possible respiratory failure. Nonspecific abnormalities may also be observed in the laboratory results[1].

Neuroleptic malignant syndrome (NMS), malign hyperthermia, anticholinergic toxicity, sympathomimetic drug intoxication, encephalitis, heat stroke and central hyperthermia should be considered as the differential diagnosis. SS that is accompanied by hyperreflexia usually develops in 24 hours, however NMS which is accompanied by bradireflexia, has a slower onset that may extend to weeks. Anticholinergic toxicity is associated with hyperthermia, altered mental status and mydriasis, urinary retention and decreased bowel; but increased muscle tone and reflexes are not expected. An increase in end-tidal carbon dioxide level, widespread rigidity and hyporeflexia are observed in malignant hyperthermia, which may develop after exposure to inhalation anesthetics and depolarizing muscle relaxants. In other differential diagnoses, neuromuscular activation findings that was observed in SS are not expected[1, 3].

In a patient who is thought to have SS, all serotonergic agents should be discontinued and supportive treatment should be initiated. In most cases, symptoms are resolved within 24 hours. Affective sedation may be achieved with benzodiazepines if needed. In severe cases, cyproheptadine, which is a 5HT-2A receptor blocker, may be initiated. Although it provides symptomatic relief in mild to moderate cases, it does not shorten the duration of the recovery phase. The recommended starting dose is 12 mg and a 2 mg maintenance dose may be administered every 2 hours as long as the symptoms persist. Antipyretics are not useful because the fever in SS is dependent on increased muscle activity, not central[5].

Antipsychotic drugs, olanzapine and risperidone paradoxically both trigger SS and are reported to be used in the treatment of this syndrome. Since olanzapine is a 5HT-2A receptor antagonist, its use in treatment of SS is reasonable, but it is underlined that it may also cause SS in chronic use. Although the underlying mechanism is not clear in the literature, it has been reported that chronic olanzapine treatment may cause different interactions on the basis of receptors and neurotransmitters in each patient[6, 7].

Conclusion

Because of the widespread use of serotonergic drugs, it is important for clinicians to keep the SS in mind in patients with altered mental status, fever and neuromuscular hyperactivity. However, it should be remembered that early suspicion and early treatment may prevent from mortality and morbidity.

References

1. Volpi-Abadie J, Kaye AM, Kaye AD. Serotonin syndrome. Ochsner J. 2013; 13(4): 533-40.
2. Monte AA, Waksman JC. Chronic olanzapine, serotonin receptors, and subsequent serotonin toxicity. J Clin Psychopharmacol. 2010; 30(5): 628-9.
3. Boyer EW, Shannon M. The serotonin syndrome. N Engl J Med. 2005; 352: 1112-20.
4. Dunkley EJ, Isbister GK, Sibbritt D, Dawson AH, Whyte IM. The Hunter Serotonin Toxicity Criteria: simple and accurate diagnostic decision rules for serotonin toxicity. QJM. 2003; 96(9): 635-42.
5. McDaniel WW. Serotonin syndrome: early management with cyproheptadine. Ann Pharmacother. 2001; 35(7-8): 870-873.
6. Haslett CD, Kumar S. Can olanzapine be implicated in causing serotonin syndrome? Psychiatry Clin Neurosci. 2002; 56(5): 533-5.
7. Isbister GK, Downes F, Whyte IM. Olanzapine and serotonin toxicity. Psychiatry Clin Neurosci. 2003; 57: 244.

Case Report

Eurasian Journal of Toxicology

Ticagrelor Intoxication: Overdose in a Suicidal Attempt

Sertaç Güler, Dilber Üçöz Kocaşaban
Ankara Training and Research Hospital, Department of Emergency Medicine, Ankara, Turkey

Abstract

Ticagrelor is one of the new generation antiplatelet agents, which acts by reversibly binding to P2Y12 platelet receptors. Literature-related data on overdose intake of ticagrelor is quite limited. Here, we report a 23-year old male patient, who presented to our emergency clinic with the complaint of suicidal intake of 15 tablets of 90 mg ticagrelor (Brilinta® 90 mg tablet, Astra Zeneca Pharmaceuticals, Istanbul). Ticagrelor is one of the new generation antiplatelet agents that is currently being used in the treatment of acute coronary syndrome in our country. The overdose use of the drug for suicidal purpose or accidentally, is a relatively new issue for emergency physicians. According to our knowledge, suicidal ticagrelor overdose intake is a case that has not been reported in the literature previously. In this article, we shared the asymptomatic process of a case with 1350 mg ticagrelor toxicity. With the increased use and prevalence of the drug in our country, we think that the emergency physicians may encounter ticagrelor poisoning at higher rates. Therefore, in ticagrelor poisoning, emergency physicians need to be aware and familiar with the drug

Key Words: Emergency medicine, suicide, ticagrelor, intoxication

Özet

Ticagrelor, P2Y12 trombosit reseptörlerine geri dönüşümlü olarak bağlanarak hareket eden yeni nesil antiplatelet ajanlarından biridir. Tikagrelorun aşırı doz alımı ile ilgili literatürle ilgili veriler oldukça sınırlıdır. Bu yazıda acil servise, intihar girişimi amacıyla 15 adet 90 mg ticagrelor içeren tablet(Brilinta® 90 mg tablet, Astra Zeneca Pharmaceuticals, İstanbul) alma şikayeti ile başvuran 23 yaşında bir erkek hasta sunuldu. Ticagrelor, ülkemizde akut koroner sendrom tedavisinde kullanılan yeni nesil antiplatelet ajanlardan biridir. İlacın intihar amaçlı veya kazayla aşırı dozda kullanılması, acil durum doktorları için nispeten yeni bir konudur. Bilgilerimize göre intihar amaçlı ticagrelor doz aşımı alımı, daha önce literatürde bildirilmemiş bir durumdur. Bu yazıda 1350 mg ticagrelor toksisitesi olan bir olgunun asemptomatik sürecini paylaştık. Ülkemizde ilacın kullanımının ve yaygınlığının artması ile acil hekimlerin tikagrelor zehirlenmesiyle daha yüksek oranda karşılaşabileceğini düşünüyoruz. Bu nedenle, tikagrelor zehirlenmesinde acil durum doktorlarının ilacı bilmesi ve tanıması gerekir

Anahtar kelimeler: Acil tıp, intihar, ticagrelor, zehirlenme

Introduction

Ticagrelor is one of the new generation antiplatelet agents, which acts by reversibly binding to P_2Y_{12} platelet receptors. Different from thienopyridines (clopidogrel and prasugrel), binding to receptors is reversible and it is thought to act faster than clopidogrel[1]. Due to its platelet-inhibition effect, it is recommended in the treatment of both non-ST elevation acute coronary syndromes (NSTE-ACS) and myocardial infarction with ST segment elevation (STEMI)[2, 3]. Literature-related data on overdose intake of ticagrelor is quite limited. Here, we report a 23-year old male patient, who presented to our emergency clinic (ER) with the complaint of suicidal intake of 15 tablets of 90 mg ticagrelor (Brilinta® 90 mg tablet, Astra Zeneca Pharmaceuticals, Istanbul), and who was discharged from the clinic uneventfully following a 48-hour surveillance. According to our knowledge, no previous case in the literature is present related to suicidal overdose intake of ticagrelor.

Case Report

A 23-year-old male patient presented to the ER declaring that he had ingested 15 tablets containing 90 mg ticagrelor about 20 minutes previously in a suicide attempt. He noted that he had not taken any other substance or drugs except ticagrelor. In his history, there was no chronic disease and he had a history of 1 pack/day smoking and alcohol intake 2-3 times a month. The patient had no complaints upon presentation to the ER. On his physical examination, the vital signs of the patient were recorded as follows: pulse: 87 beats/min, rhythmic, blood pressure: 140/ 90 mmHg, respiratory rate: 14 breaths/min, room air oxygen saturation: 98% and body temperature: 37.1 °C. The patient's general condition was good, The Glasgow Coma Scale was 15; he was conscious, fully cooperative and orientated. He had no active bleeding. A vascular access was established for the patient he was monitored in the ER; orogastric lavage was planned, but the procedure failed because the patient was unable to tolerate it.

Corresponding Author: Sertaç Güler **e-mail:** drsertacguler@gmail.com
Received: 02.04.2019 • **Accepted:** 08.07.2019
Cite this article as: Guler S, Ucoz Kocasaban D. Ticagrelor intoxication: overdose in a suicidal attempt. Eurasian J Tox. 2019;1(2):69-72

Activated charcoal of approximately 1 gr/kg dose was given orally to the patient. A normal sinus rhythm with 90 beats/min was observed on the electrocardiogram. On the laboratory analyses, the hemoglobin, hematocrit, platelet count values and the blood glucose, renal and liver function tests, uric acid levels and electrolyte levels were within normal ranges. No metabolic acidosis was detected in the venous blood gases. The patient with admission values of PT:12.9 (9.1-12.1) and INR: 1.12 (0.89-1.06) was followed-up at the ER toxicology unit. The patient was asymptomatic on the follow-up, with 24th hour values of PT:13.7 and INR:1.19. The patient's continuously repeated examinations revealed no headache, chest pain, dyspnea, palpitations, nausea, vomiting, any bleeding symptoms and ecchymosis, or any other complaints. His vital signs were stable. On the 2nd day control examinations, the increased PT and INR values were found to be within normal ranges, as 11.8 and 1.03, respectively. This PT and INR elevation, which lasted for about 48 hours, had no clinically significant outcomes. The patient was informed that this condition was the side effect of the drug he had taken. The patient was referred to the psychiatry clinic for his suicidal thoughts, and was discharged from the ER uneventfully and asymptomatic for about 2 days after his application.

Discussion

Today, the recommended treatment dose of ticagrelor for acute coronary syndromes is generally 180 mg loading dose and 180 mg daily maintenance regime[2, 3]. The case we have presented attempted suicide by taking 1350 mg of a total dose at one time. The drug binds reversibly to P_2Y_{12} ADP receptor, has a half-life of about 7 hours, has biliary excretion and binds to plasma proteins at a rate of over 99%[4]. In the DISPERSE-2 study, which has investigated the efficacy and safety of ticagrelor compared to clopidogrel in NSTE-ACS population, the more common side effects seen in ticagrelor group have been listed as nausea, dyspepsia, hypotension and dyspnea. Again, ventricular pauses were observed more frequently in the ticagrelor group (sinoatrial exit block in 7 patients and complete heart block in 4 patients)[5]. In our case, the vital signs were stable throughout the follow-up period at the ER and he had no complaints of dyspnea or palpitation.

Again, in the PLATO study, which is a large, randomized, double-blind, multi-center study that has investigated the efficacy and safety of ticagrelor compared to clopidogrel in both NSTE-ACS and STEMI populations, ticagrelor has been found to be superior in reducing the mortality rates of vascular origin, compared to clopidogrel; however, intracranial hemorrhage and dyspnea were identified at higher rates in the ticagrelor group[6]. No signs of bleeding were observed in our case. In our asymptomatic case, the slightly increased PT and INR values that lasted for about 2 days did not have a clinically significant outcome. It has been stated that ticagrelor-related dyspnea is mostly milder and moderate, mostly occurs in the first days of the treatment, and in a very small percentage of the patients, the drug requires discontinuation[6, 7, 8]. The mechanism of ticagrelor-related dyspnea is still not clear, and the increase in adenosine levels in the pulmonary vagal C fibers due to the inhibition of reuptake of adenosine has been blamed as the cause[4, 8].

Ventricular pauses are one of the side effects that are determined at higher rates, against ticagrelor in PLATO study[6]; however, most patients are stated to be asymptomatic. Drug-related common side effects apart from these have been reported as increased uric acid levels, atrial fibrillation, hypertension, bradychardia, headache, dizziness, hypokalemia, diarrhea, increase in serum creatinine levels and coughing[9]. In our patient, the uric acid and creatinine levels remained normal for 2 days and no electrolyte imbalance was determined.

Due to the fact that ticagrelor is metabolized via the CYP3A4 system[4], the use of other drugs that use this enzyme system along with ticagrelor or overdose use as in our presented case, may cause more serious and long-term side effects. Examples of such drugs may include ketoconazole, clarithromycin, ritonavir, rifampicin and carbamazepine[4]. The presented case had a lucky situation of not using any other drug or substance.

There is no specific antidote that can be used in ER treatment of overdose of ticagrelor[9]. We also applied the general toxicology and support measures to our patient and followed the vital signs and possible complications.

Conclusion

As a result, ticagrelor is one of the new generation antiplatelet agents that is currently being used in the treatment of acute coronary syndrome in our country. The overdose use of the drug for suicidal purpose or accidentally, is a relatively new issue for ER physicians. According to our knowledge, suicidal ticagrelor overdose intake is a case that has not been reported in the literature previously. In this article, we shared the asymptomatic process of a case with 1350 mg ticagrelor toxicity. With the increased use and prevalence of the drug in our country, we think that the ER physicians may encounter ticagrelor poisoning at higher rates. Therefore, in ticagrelor poisoning, ER physicians need to be aware and familiar with the drug.

References

1. Schömig A. Ticagrelor--is there need for a new player in the antiplatelet-therapy field? N Engl J Med 2009;361(11):1108-11.

2. Amsterdam EA, Wenger NK, Brindis RG, Casey DE Jr, Ganiats TG, Holmes DR Jr, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;130(25):e344-426.

3. O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2013;127(4):e362-425.

4. Guimarães PO, Tricoci P. Ticagrelor, prasugrel, or clopidogrel in ST-segment elevation myocardial infarction: which one to choose? Expert Opin Pharmacother 2015;16(13):1983-95.

5. Cannon CP, Husted S, Harrington RA, Scirica BM, Emanuelsson H, Peters G, et al. Safety, tolerability, and initial efficacy of AZD6140, the first reversible oral adenosine diphosphate receptor antagonist, compared with clopidogrel, in patients with non-ST-segment elevation acute coronary syndrome: primary results of the DISPERSE-2 trial. J Am Coll Cardiol 2007;50(19):1844-51.

6. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;361(11):1045-57.

7. Storey RF, Becker RC, Harrington RA, Husted S, James SK, Cools F, et al. Characterization of dyspnoea in PLATO study patients treated with ticagrelor or clopidogrel and its association with clinical outcomes. Eur Heart J 2011;32(23):2945-53.

8. Parodi G, Storey RF. Dyspnoea management in acute coronary syndrome patients treated with ticagrelor. Eur Heart J Acute Cardiovasc Care 2015;4(6):555-60.

9. Ticagrelor: Drug information. Available: December 1, 2015. Available at: http://www.uptodate.com/contents/ticagrelor-drug-information?source=search_result&search=ticagrelor&selectedTitle=1%7E50.

Case Report

Eurasian Journal of Toxicology

Acute Myocardial Infarction Following 5-Fluorouracil Use

Muhammed Ekmekyapar, Şükrü Gürbüz, Hakan Oğuztürk, Neslihan Yücel, M. Gökhan Turtay, Serdar Derya
Department of Emergency Medicine, Faculty of Medicine, Inonu University, Malatya, Turkey

Abstract

Fluorouracil (5-FU) is the most common chemotherapeutic agent suggested for colorectal cancers. Cardiogenic side effects such as coroner artery vasospasm, ventricular dysrhythmia, and cardiac ischemia are also rarely stated. 48-year-old male patient applied to the emergency service with conditions of chest pain, nausea and vomiting. ECG was performed and found to be normal sinus rhythm. In the control ECG of the patient, there were ST elevations in inferior and anterior derivations. The control troponin value for the patient was found to be 0,073 µg/L (normal range 0,010-0.023 µg/L). When the patient expressed that his chest pain aggravated even more as he was being prepared for coroner angiography, control ECG was reperformed and seen that lateral derivations were added to ST elevations in inferior and anterior derivations. The patient, who has started to chemotherapy two days ago and still receives 5-FU infusion, is thought to have myocardial infarction with ST elevation based on the cardiotoxic impact of 5-FU, and he was taken to coroner angiography. His CAG is reported as LAD: Plaque CX: Plaque RCA: 40% lesion observed at CB alignment. 5-FU is a partner medical agent used to treat head and neck, gastrointestinal system, bladder, and chest malignancies. Despite cardiac toxicity being a rare and serious complication, the life-threatening toxicity is observed in 0,5% of the patients. In the previous reports, it is underlined that the only mechanism contributing to STEMI development after 5-FU infusion is vasospasm. In our case, the patient came to us with myocardial infarction with ST elevation resulting from the emergence of chest pain after the use of 5-FU. Patients should be closely followed when receiving 5-FU treatment. Due to the cardiac side effects that may seriously show a fatal course, patients should be examined in detail before the treatment.

Key words: 5-FU, chest pain, MI

Özet

Florourasil (5-FU), kolorektal kanserler için önerilen en yaygın kemoterapötik ajandır. Bu ajana bağlı, koroner arter vazospazmı, ventriküler disritmi ve kardiyak iskemi gibi kardiyojenik yan etkiler nadir olsa da bildirilmiştir. 48 yaşında erkek hasta acil servise göğüs ağrısı, bulantı ve kusma şikayeti ile başvurdu. Çekilen ilk EKG'si normal sinus ritmi olarak değerlendirildi. Kontrol EKG'sinde, inferior ve anterior'da ST segment yükselmeleri mevcuttu. Hasta için çalışılan kontrol troponin değeri 0,073 µg/L (normal aralık 0,010-0,023 µg/L) olarak geldi. Hasta, koroner anjiyografi için hazırlanırken göğüs ağrısının daha da şiddetlendiğini ifade etti. Bunun üzerine tekrarlanan EKG'de, anterior ve inferior derivasyonlara, lateral derivasyonda, ST segment yükselmesinin eklendiğini görüldü. İki gün önce kemoterapiye başlayan ve hala 5-FU infüzyonu alan hastanın, 5-FU'nun kardiyotoksik etkisine bağlı ST yükselmeli miyokard enfarktüsü geçirdiği düşünüldü. koroner anjiyografiye alınan hastada. Anjiografi sonucu LAD: Plak CX: Plak RCA: CB hizasında gözlenen% 40 lezyon olduğu bildirildi. 5-FU,baş, boyun, gastrointestinal sistem, mesane ve göğüs malignitelerini tedavi etmek için kullanılan ortak bir tıbbi ajandır. Kardiyak toksisite nadir ve ciddi bir komplikasyondur ve yaşamı tehdit eden toksisite hastaların% 0,5'inde görülür. Önceki çalışmalarda, 5-FU infüzyonundan sonra STEMI gelişimine katkıda bulunan tek mekanizmanın vazospazm olduğu vurgulanmıştır. 5-FU tedavisi alırken hastalar yakından takip edilmelidir. Ciddi ölümcül seyir gösterebilecek kalp yan etkileri nedeniyle, hastalar tedaviden önce ayrıntılı olarak incelenmelidir.

Anahtar kelimeler: 5-FU, göğüs ağrısı, MI

Introduction

Fluorouracil (5-FU) is the most common chemotherapeutic agent suggested for colorectal cancers[1, 2]. Its frequently observed side effects include nausea, vomiting, and diarrhea. 5-FU, which is a medicine from antimetabolite group of chemotherapy medicines, can be given as 5-10 min. or 20-60 min. intravenous infusions, as well as 22-24 hrs., 1-4 days and longer periods of continuous infusions. Cardiogenic side effects such as coroner artery vasospasm, ventricular dysrhythmia, and cardiac ischemia are also rarely stated[3].

Case Report

48-year-old male patient applied to the emergency service with conditions of chest pain existing since yesterday, as well as nausea and vomiting. In the anamnesis of the patient, it is seen that there is metastatic rectum cancer in his history. The patient was operated 2 months ago had a colostomy. The patient is given his first chemotherapy 2 days ago with Bevacizumab + irinotecan + folic acid and 5-FU. The patient did not have a previously known coroner medical history and his echocardiography test before starting chemo-

Corresponding Author: Şükrü Gürbüz **e-mail:** sukrugurbuz@gmail.com
Received: 11.01.2019 • **Accepted:** 09.02.2019
Cite this article as: Ekmekyapar M, Gurbuz S, Oguzturk H, Yucel N, Turtay MG, Derya S. Acute myocardial ınfarction following 5-fluorouracil use. Eurasian J Tox. 2019;1(2):73-76

therapy is considered as normal. There were no characteristics found in the physical examination of the patient. The vital parameters of the patient were 36.5 °C, 77/min pulse, TA: 125/85 mmHg, 20/min respiratory rate. The patient was monitored and ECG was performed (Figure 1) and found to be normal sinus rhythm. Hemogram, biochemistry, troponin, d-dimer and artery blood gas are drawn from the patient. The blood tests of the patient are found to be normal. The patient, whose chest pain vaguely continued, is put on follow-up. During this follow up, the patient expressed that his chest pain has aggravated and had tachycardia. Along with control ECG (Figure 2), control troponin was performed for the patient. In the control ECG of the patient, there were ST elevations in inferior and anterior derivations. The control troponin value for the patient was found to be 0,073 µg/L (normal range 0,010-0.023 µg/L). The patient was consulted for cardiology as myocardial infarction with ST elevation. The patient was planned for coroner angiography. When the patient expressed that his chest pain aggravated even more as he was being prepared for coroner angiography, control ECG was reperformed (Figure 3) and seen that lateral derivations were added to ST elevations in inferior and anterior derivations. The patient, who has started to chemotherapy 2 days ago and still receives 5-FU infusion, is thought to have myocardial infarction with ST elevation based on the cardiotoxic impact of 5-FU, and he was taken to coroner angiography. His CAG is reported as LAD: plaque CX: plaque RCA: 40% lesion observed at CB alignment. 5-FU infusion is stopped along with the advice of medical oncology, the patient was taken into intensive care unit after coroner angiography.

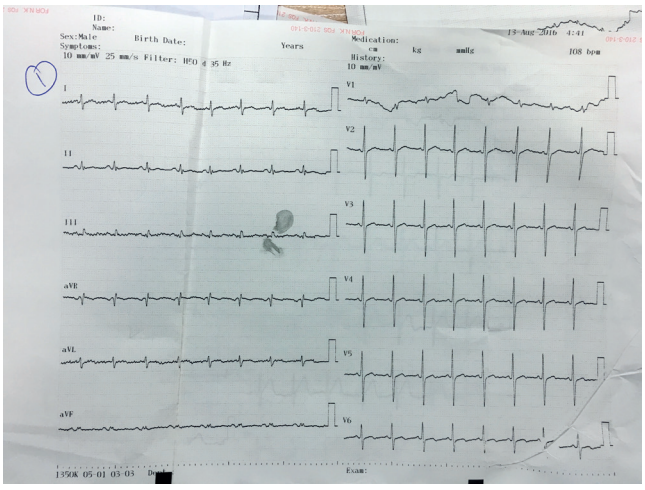

Figure 1. First ECG of the patient

Discussion

5-FU is a partner medical agent used to treat head and neck, gastrointestinal system, bladder, and chest malignancies[4]. Despite cardiac toxicity being a rare and serious complication, the life-threatening toxicity is observed in 0,5% of the patients[5]. Generally speaking, cardiac toxicity is the ischemia emerging with angina, vasospasm, myocarditis, ventricular and supraventricular dysrhythmia, vessel dissection and myocardial infarction; or without myocardial infarction[6]. In experimental research, it is found that cardiotoxic effects cause coroner vasospasm by affecting nitric oxide swing directly from endothelium; and independent from endothelium, by causing vasoconstriction through protein kinase C. In the previous reports, it is underlined that the only mechanism contributing to STEMI development after 5-FU infusion is vasospasm. Existing coronary artery conditions in patients lead to increase in the present risk of cardiac side effects[3, 6]. In a prospective research, angina pectoris attacks, arrhythmia, and LV function decrease incidence are observed for a period of 5 months for 102 patients diagnosed with 5-FU[7]. In our case, the patient came to us with myocardial infarction with ST elevation resulting from the emergence of chest pain after the use of 5-FU. According to another prospective research conducted

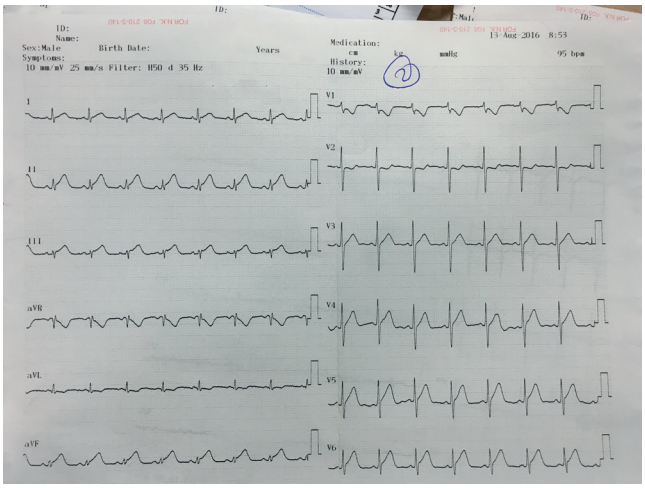

Figure 2. Second ECG of the patient

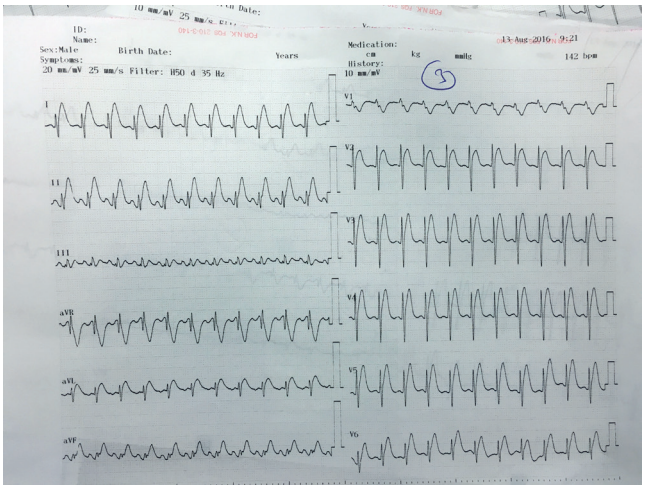

Figure 3. Third ECG of the patient

by Forni et al.[8], 7.6% of the treated patients had cardiotoxicity. Some researchers intended to prevent vasospasm by providing calcium channel blocker or nitrate as prophylactic for patients who have CAD and will receive 5-FU[9]. As the treatment is stopped as soon as possible after cardiotoxicity, it is found beneficial to provide calcium channel blocker and nitrate treatments to remove the vasospastic effect.

Conclusion

Patients should be closely followed when receiving 5-FU treatment. Due to the cardiac side effects that may seriously show a fatal course, patients should be examined in detail before the treatment. Moreover, the cardiac performance of the patient should be analyzed in detail and closely monitored during the infusion treatment.

References

1. de Gramont Ad, Figer A, Seymour M, Homerin M, Hmissi A, Cassidy J, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol 2000;18(16):2938–47.
2. Shimura T, Fuse N, Yoshino T, Minashi K, Tahara M, Doi T, et al. Clinical features of interstitial lung disease induced by standard chemotherapy (FOLFOX or FOLFIRI) for colorectal cancer. Ann Oncol 2010;21(10):2005–10.
3. Alter P, Herzum M, Soufi M, Schaefer JR, Maisch B. Cardiotoxicity of 5-fluorouracil. Cardiovasc Hematol Agents Med Chem 2006;4(1):1–5.
4. Fidan E, Fidan S, Yildiz B, Durmus I, Kavgaci H, Ozdemir F, et al. Bolus fluorouracil induced syncope and pulseless ventricular tachycardia: a case report. Hippokratia 2011;15(1):93–5.
5. Luwaert RJ, Descamps O, Majois F, Chaudron JM, Beauduin M. Coronary-artery spasm induced by 5-fluorouracil. Eur Heart J 1991;12(3):468–70.
6. Sorrentino MF, Kim J, Foderaro AE, Truesdell AG. 5-Fluorouracil induced cardiotoxicity: review of the literature. Cardiol J 2012;19(5): 453–8.http://dx.doi.org/10.5603/CJ.2012.0084
7. Wacker A, Lersch C, Scherpinski U, Reindl L, Seyfarth M. High incidence of angina pectoris in patients treated with 5-fluorouracil. Oncology. 2003;65(2):108-12.
8. de Forni M, Malet-Martino MC, Jaillais P, Shubinski R, Bachaud J, Lemaire L, et al. Cardiotoxicity of high-dose continuous infusion fluorouracil: a prospective clinical study. Journal of Clinical Oncology. 1992;10(11):1795-801.
9. Kleiman NS, Lehane DE, Geyer Jr CE, Pratt CM, Young JB. Prinzmetal's angina during 5-fluorouracil chemotherapy. The American journal of medicine. 1987;82(3):566-8.