Olgularla Antibiyotikler ve Yan Etki Yönetimi

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Enfeksiyon Hastalıkları ve Klin. Mikr. AD

OLGU

- 39 E
- Şikayeti: Bilinç kaybı
- Hikaye: Bu sabah aniden evde epileptik nöbet geçiren hasta yakınları tarafından acile getirilmiş.

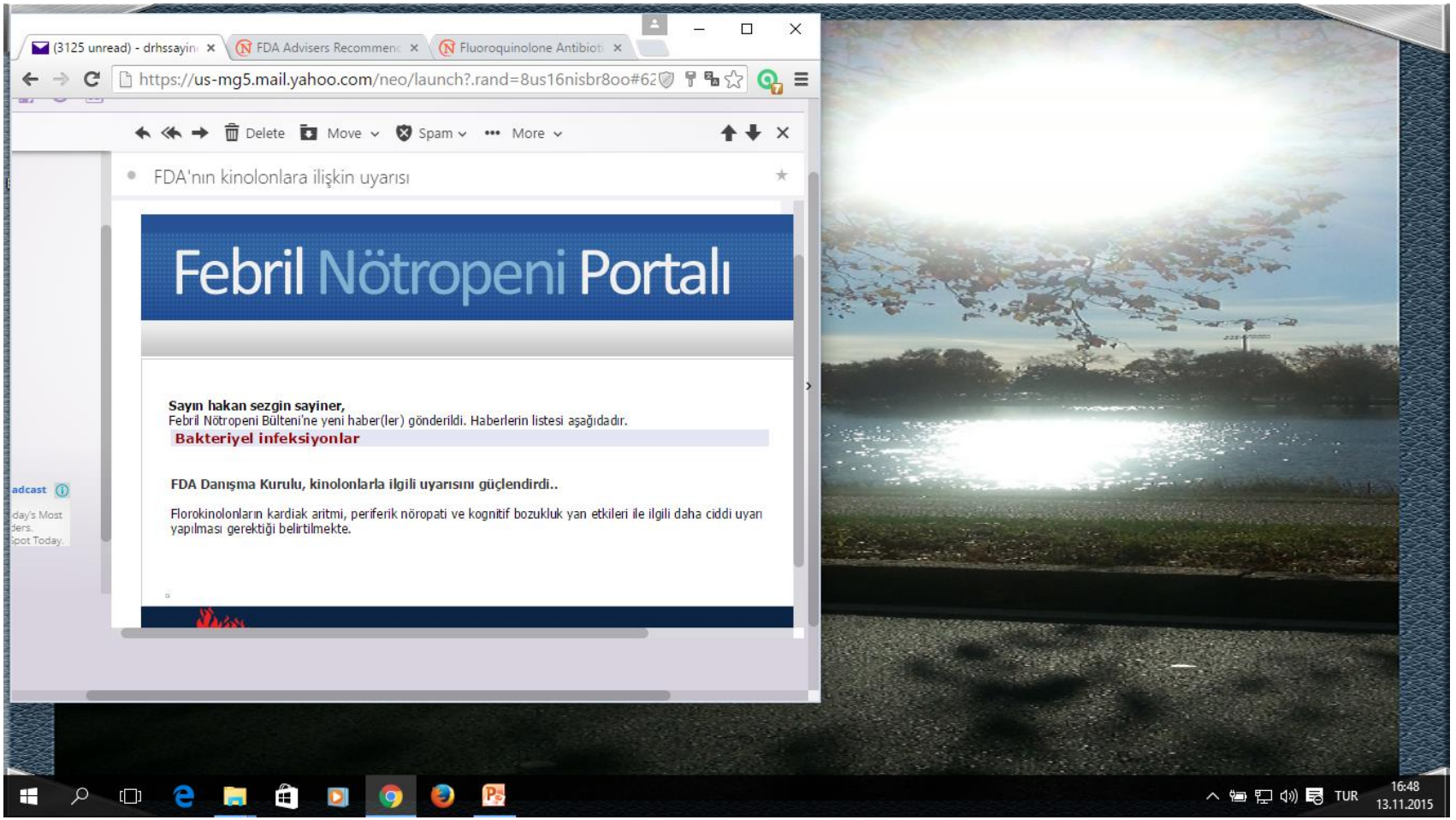
- Vital bulguları normal
- Sistem muayenesi normal
- Laboratuvar değerleri normal
- Radyolojik inceleme normal

Özgeçmiş:

- epilepsi tanısı ile tedavi almaktayken ilaçlarını kesmiş,
- 1 gün önce iş yerinde verilen yemekten çok sayıda kişiyle beraber ateş, karın ağrısı, ishal, bulantı şikayeti ile acile başvurmuş, gayta mikroskopik incelemede bol lökosit görülmüş, kültür alınmış

- Kullandığı ilaçlar
- Epilepsi için ilaçlarını kesmiş
- Gastroenterit tanısı ile CİPROFLOKSASİN tablet 2 adet içmiş

Antibiyotiklerin Nörotoksik Yan Etkileri



En çok bilinenler kinolonlara, karbapenemlere ve tuberkuloz ilaçlarına bağlı nörotoksik etkiler

Antibiyotiklerin Nörotoksik Yan Etkileri

- Diğerlerine göre en az bilinen ve tanı konan yan etki
- Yayınlar genelde olgu sunumları şeklinde, az sayıda çalışma

  JiSheng Zhang Antibiotic-induced neurotoxicity in dialysis patients: a retrospective study 1066 diyaliz hastası (254 peritoneal diyaliz ve 812 hemodiyaliz ;Temmuz 2006 – Nisan 2012.

  Arun Mattappalil Neurotoxicity with Antimicrobials in the Elderly: A Review; 1966-2014. 286 yayın

  Marie F. Grill Neurotoxic effects associated with antibiotic use: management considerations; Ocak1960–Haziran2010 yaklaşık 300 makale taranmış

  Hayvan deneyi;O Atli Evidence for neurotoxicity associated with amoxicillin in juvenile rats

RENAL FAILURE

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CLINICAL STUDIES

Antibiotic-induced neurotoxicity in dialysis patients: a retrospective study

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Abstract

Objective: The study was to evaluate neurotoxicity caused by antibiotics in dialysis patients, including incidence, clinical features, treatments and prognosis. *Methods*: In this retrospective study, we reviewed the medical records of 1066 dialysis patients (254 peritoneal dialysis [PD] cases and 812 hemodialysis [HD] cases) who also received intravenous antibiotics in our hospital during July 2006 – April 2012. Naranjo scale was used for estimating the probability of an adverse drug reaction. *Results*: The incidence of antibiotic-induced neurotoxicity was 5.66% in patients receiving HD, and 7.87% in patients receiving PD. There was no significant difference between the two dialysis modalities about the incidence of antibiotic-induced neurotoxicity ($p > 0.05$). The risk factors included extremely old age, history of central nervous system disorder, low residual renal function, hypoalbuminemia, and the use of multiple antibiotics that share one mechanism. The neurotoxic antibiotics included cephalosporins, penicillins, carbapenems and quinolones in our study. Most patients could be properly diagnosed early according to their medical history, symptoms, signs, electroencephalography (EEG), other related auxiliary examination, and with the help of experienced neurologists. Most neurotoxic patients showed clinical improvement after the discontinuation of antibiotics and active treatment. *Conclusions*: The adverse neurotoxic effects of antibiotics were common in dialysis patients due to wide and incorrect usage. Neurotoxicity could be prevented in high-risk cases with dosage adjustments. Better prognosis can be achieved with early and proper diagnosis, decisive withdrawal, and aggressive treatment including enhanced HD.

Keywords

Antibiotics, dialysis, encephalopathy, neurotoxicity, renal failure

History

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- Hemodiyaliz hastalarında %5,87,Periton diyalizi olanlarda %5,66 anlamlı fark bulunmamış,
- İleri yaş, Santral sinir sistemi hastalığı öyküsü olanlar, renal fonksiyon bozukluğu olanlar, hipoalbüminemi ve çok sayıda antibiyotik kullanımı risk faktörleri arasında
- Sefalosporinler, penisilinler, karbapenemler ve kinolonlar nörotoksik antibiyotikler arasında
- Bir çok hastaya hikaye, semptomlar EEG ile erken tanı konmuş
- Riskli hastalarda doz ayarlanmalıdır
- Erken ve doğru tanı kararlı olmak ve agresive tedavi

PubMed and OVID (Ocak 1960–Haziran 2010) tarihleri arasında antibiotics, side effects, neurotoxicity and encephalopathy terimleri ile yapılan taramada yaklaşık **300 articles**. case reports, case series, letters and retrospective reviews describing neurotoxic effects and those discussing mechanisms of neurotoxicity içermekte.

Table 1

Neurotoxicity associated with aminoglycosides and all beta-lactams, their mechanisms of neurotoxicity and risk factors

Antibiotic class	Number of publications	Neurotoxic effects	Mechanism of neurotoxicity	Risk factors
Aminoglycosides: **1. Gentamicin** **2. Streptomycin** **3. Amikacin** **4. Tobramycin** **5. Neomicin** **6. Kanamycin**	5: retrospective case reviews; case series; case reports	Ototoxicity-class effect Peripheral neuropathy; encephalopathy (gentamicin) Neuromuscular blockade-class effect	Activation of NMDA receptors Lysosomal abnormality; Axonal loss; Inflammatory response Inhibition of pre-synaptic quantal release of acetylcholine and binding of drug to postsynaptic receptors	Increased CNS permeability Intrathecal administration
Beta lactams-Cephalosporins: ***High risk agents*:** **1. Cefazolin** **2. Cefesolis** **3. Ceftazidime** **4. Cefoperazone** **5. Cefepime** ***Low risk agents*:** **1. Cephalexin** **2. Cefatoxime** **3. Ceftriaxone**	24- Case reports; retrospective reviews; review articles	Encephalopathy with Triphasic waves on EEG Tardive seizures Seizures NCSE Myoclonus Asterexis	Inhibition of GABA-A release; Increased glutamate; Induction of endotoxins; Cytokine release	Renal failure Prior CNS disease Older age Excess dosage
Beta-lactams-Penicillins: **1. Benzylpenicillin** **2. Penicllin G** **3. Pipercillin** **4. Ticarillin** **5. Ampicillim** **6. Amoxacillin** **7. Oxacillin**	4: Case reports; case series	Seizures Tardive seizures Encephalopa Tremors	Inhibition of GABA-A receptors	Renal failure; low birth weight-neonates
Beta-lactams **Carbapenems** **1. Imepenem** **2. Meropenem** **3. Paripenem** **4. Ertapenem** **5. Doripenem** **6. Ceftaroline**	4: Case reports	Encephalopathy Seizures Myoclonus Headache	Inhibition of GABA-A receptors; Possibly binding of glutamate	Renal failure

Table 2

Neurotoxicity associated with all other groups of antibiotics, mechanisms and risk factors

Antibiotic class	Number of publications	Neurotoxic effects	Mechanism of neurotoxicity	Risk factors
Tetracyclines	1: Review article	Cranial nerve toxicity; Neuromuscular blockade; Intracranial hypotension		
Trimethoprim-Sulfametaxazole	8: case reports	Transient psychosis; encephalopathy; aseptic meningitis	CNS penetration	Advancing age; Immunocompromized
Macrolides.azalides: **1. Erythromycin** **2. Clarithromycin** **3. Azithromycin,** **4. Dirithromycin**	6: Case reports; Review articles	Ototoxicity	Damage to Cochlea	
Quinolones: **1. Ciprofloxacin** **2. Norfloxacin** **3. Ofloxacin** **4. Gemifloxacin** **5. Levofloxacin** **6. Gatifloxacin**	5: Case reports; case series	Psychosis Encephalopathy Seizures NCSE Orofacial dyskinesias Action myoclonus Ataxia Dysarthria Chorea	Inhibition of GABA-A receptors; Activation of NMDA receptors	Advancing age; Impaired renal function; Increased permeability of blood-brain barrier
Oxazolidinones **1. Linezolid**	4: case reports; case series	Encephalopathy Bells palsy Optic neuropathy	Not known	
Streptogramins: **1. Dalforpistin-quinupristin**	1: case report	Headache		
Polymixins **1. Polymyxin B** **2. Colistin**	5: case reports; case series; retrospective reviews	Chemical Arachnoiditis Seizures Diplopia Ataxia Paresthsias Polyneuropathy Myasthenia-like syndrome	High affinity binding to CNS Blocking acetylcholine receptors; Prolonged depolarization via calcium depletion	Co-administration of narcotics, anaesthetics, muscle relaxants; Myasthenia gravis Renal failure Cystic fibrosis
Others: **1. Clindamycin** **2. Vancomycin** **3. Nitrofurantoin** **4. Chloramphenicol** **5. Metronidazole**	10: case reports; case series	Tardive dyskinesia; Extrapyramidal syndrome Ventriculitis Polyneuropathy, benign intracranial hypotension Optic neuritis Ataxia Dysphagia Peripheral neuropathy	CSF inflammatory response Cerebellar/brain stem lesions Axonal damage	Impaired renal function

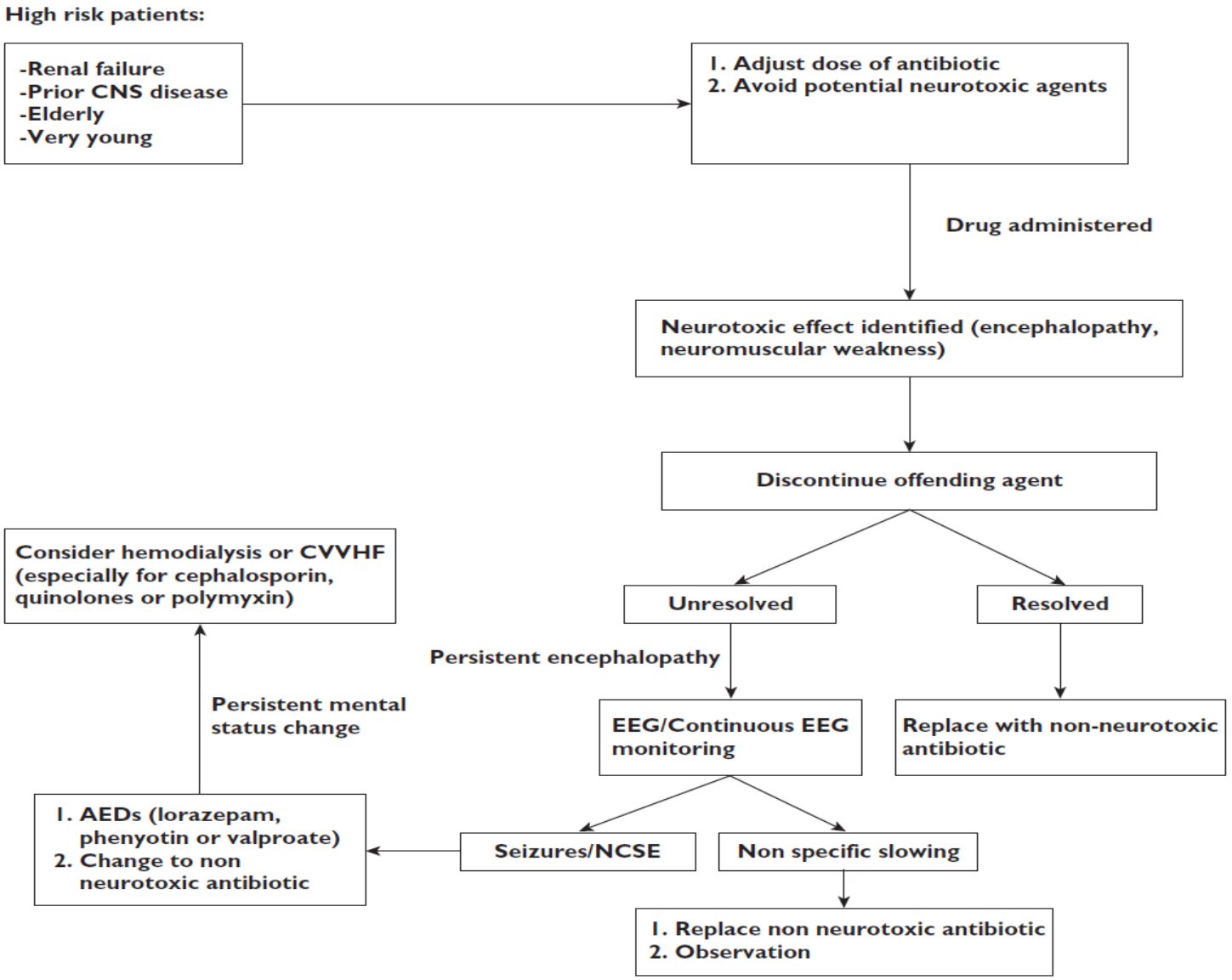
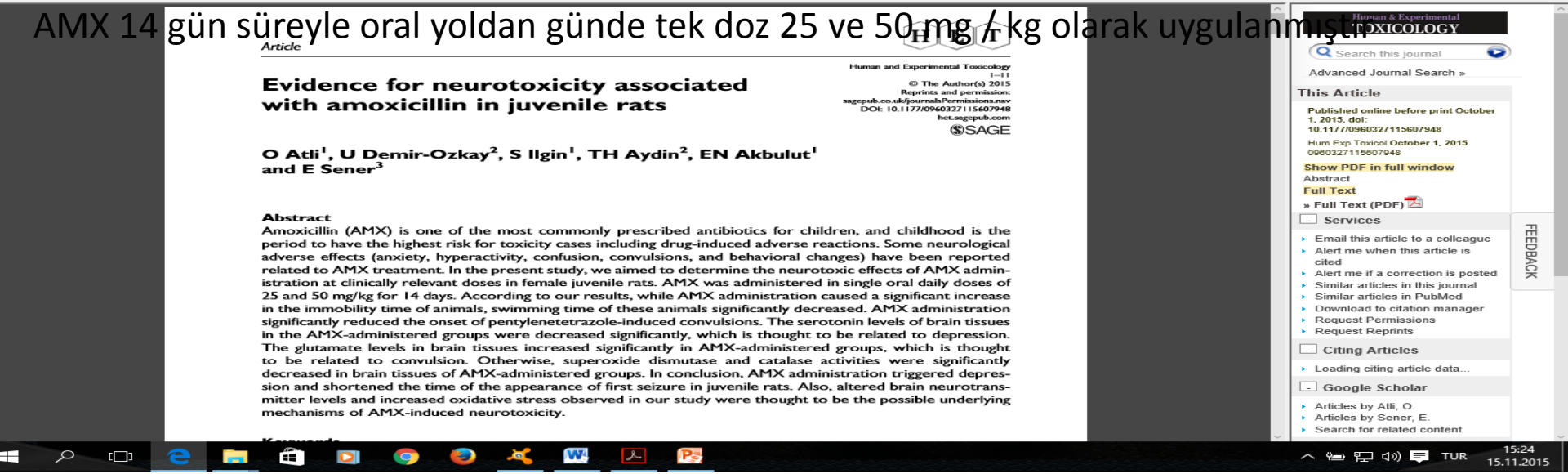


Figure 1
Management algorithm for antibiotic neurotoxicity: high risk patients

AMX 14 gün süreyle oral yoldan günde tek doz 25 ve 50 mg / kg olarak uygulanmıştır



Article

Evidence for neurotoxicity associated with amoxicillin in juvenile rats

Human and Experimental Toxicology
1–11

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Abstract

Amoxicillin (AMX) is one of the most commonly prescribed antibiotics for children, and childhood is the period to have the highest risk for toxicity cases including drug-induced adverse reactions. Some neurological adverse effects (anxiety, hyperactivity, confusion, convulsions, and behavioral changes) have been reported related to AMX treatment. In the present study, we aimed to determine the neurotoxic effects of AMX administration at clinically relevant doses in female juvenile rats. AMX was administered in single oral daily doses of 25 and 50 mg/kg for 14 days. According to our results, while AMX administration caused a significant increase in the immobility time of animals, swimming time of these animals significantly decreased. AMX administration significantly reduced the onset of pentylenetetrazole-induced convulsions. The serotonin levels of brain tissues in the AMX-administered groups were decreased significantly, which is thought to be related to depression. The glutamate levels in brain tissues increased significantly in AMX-administered groups, which is thought to be related to convulsion. Otherwise, superoxide dismutase and catalase activities were significantly decreased in brain tissues of AMX-administered groups. In conclusion, AMX administration triggered depression and shortened the time of the appearance of first seizure in juvenile rats. Also, altered brain neurotransmitter levels and increased oxidative stress observed in our study were thought to be the possible underlying mechanisms of AMX-induced neurotoxicity.

AMX verilmesi hayvanların immobilite süresi üzerinde önemli bir artışa neden olurken, bu hayvanların yüzme zamanı önemli ölçüde azalmıştır

AMX yönetiminin önemli ölçüde pentilentetrazol kaynaklı konvülziyon başlangıcını azaltılmış

AMX-yönetilen gruplarda beyin dokularının serotonin düzeyleri azaldığı bununda depresyonla ilişkili olduğu düşünülmekte

Beyin dokularında glutamat seviyeleri AMX-yönetilen gruplarda anlamlı artış, bununda konvülziyon ile ilişkili olduğu düşünülmektedir

AMX-yönetilen gruplar da süperoksit dismutaz ve katalaz aktiviteleri anlamlı olarak beyin dokularında azaldı

AMX yönetim juvenil sıçanlarda depresyonu tetikledi ve ilk nöbetin görünüm zamanını kısaltı. değişmiş beyin nörotransmitter düzeyleri ve çalışmada gözlenen artmış oksidatif stresin AMX kaynaklı nörotoksisitenin olası altta yatan mekanizmalar olduğu düşünüldü.

Review Article

Neurotoxicity with Antimicrobials in the Elderly: A Review

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ABSTRACT

Purpose: Mild adverse drug reactions typically associated with antimicrobials are familiar to most clinicians. However, rare phenomena, such as neurotoxicity, are often unpredictable and potentially unexpected. The toxic effects of antimicrobials on the central nervous system are often underreported and the mechanism(s) may be mixed or obscure. Geriatric patients are at increased risk for adverse drug reactions given physiologic alterations affecting pharmacokinetic processes. A dearth of information exists regarding neurotoxic presentations precipitated by antimicrobial use in the geriatric population. The purpose of this review is to present the available Potential mechanisms of neurotoxicity differ between the agents. The etiology of neurotoxicity with some agents is not fully elucidated. Incidence may increase with reported risk factors, renal dysfunction, or drug interactions.

Implications: Awareness of antimicrobials causing or contributing to neurotoxic events may enhance clinical decisions in diagnosis and management when such incidents occur. (*Clin Ther*. 2014;36:1489–1511)

Key word: elderly, neurotoxicity, antimicrobials, central nervous system.

Supplemental Table 1.

Antimicrobial Agent	ADR	Predisposing Factors	Predisposition in the Elderly	Time to Resolution	Reference
Quinolortes: Displacement of GABA from receptor site. But exact mechanism is unknown					
Ciprofloxacin	a) CNS toxicity 09%-7.4%:headache, dizziness, ataxia, psychosis, delirium, agitation, depression, hallucinations, nightmares b) Seizures	b) More likely in patients with history of seizures or those taking theophylline or NSAIDs	Possible, but not confirmed	Rapid resolution upon discontinuati on	9, 37, 214–219
Levofloxacin	Insomnia, dizziness, headache (0.2%–11%) Psychosis: 1 in 6 million	Less risk of interaction with theophylline or NSAIDS compared with ciprofloxacin	Possible, but not confirmed	Rapid resolution upon discontinuati on	9, 16
Moxifloxacin	Dizziness (2.8%) Headache (1.1%)	Less risk of interaction with theophylline or NSAIDS compared with ciprofloxacin	Possible, but not confirmed	Rapid resolution upon discontinuati on	9, 220
Macrolides: May inhibit glutamatergic transmission[221]					
Clarithromycin	Headache (2%) Anxiety, confusion, insomnia, psychosis, tremor, dizziness, vertigo, convulsions, disorientation, hallucinations, mania	High dosage and drug interactions	No	Transient; 24 hours until resolution	22, 21, 28, 29, 222–227
Azithromycin	Delirium in case reports	Case reports have been reported in the elderly	Possible, but not confirmed	48-72 hours	28
Sulfamethoxazole-Trimethoprim: Possible hypersensitivity reaction vs. deficiencies in glutathione. Mechanism unknown					
TMP/SMX	Aseptic meningitis Encephalitis Rare seizures Delirium Hallucinations	Symptoms are abrupt	Yes	36 hours- 10 days	34, 45, 46, 228–230
Penicillins: Inhibition of GABA neurotransmission					
Ampicillin	Convulsions	- Large doses: serum levels ≥800 mcg/mL - Predisposition to seizures	No	Within days of discontinuati on	231
Piperacillin/ tazobactam	Seizures, convulsions, myoclonus, hallucinations, drowsiness, confusion	- Reported with large doses - generally occurs in first 7 days	Yes, especially combined with renal failure	Resolved rapidly w HD removal	54–58, 232, 233
Cephalosporins: Antagonism of the GABA receptor					
Cefazolin	Encephalopathy Seizures	- Large doses to patients with renal faifure - Quinolone may increase risk of seizures (mice)	Insufficient data	Upon discontinuation	12, 234

Supplemental Table I. (continued).

Antimicrobial Agent	ADR	Predisposing Factors	Predisposition in the Elderly	Time to Resolution	Reference
Cephalexin	a) Diplopia, headache, tinnitus, ataxia b) Seizures	Very high serum levels. Serum level for a seizure is 120 mcg/mL	Insufficient data	a) Within 2 weeks of discontinuation b) Within 1 week	235–237
Ceftriaxone	Headache and dizziness	<1% of population	Insufficient data	Within days of discontinuation	238
Ceftazidime	Headache, dizziness, paresthesia, seizures, encephalopathy, coma, asterixis, neuromuscular excitation and myoclonus	Large doses to patients with renal failure	Insufficient data	Within 2 after and 2 sessions of HD	239–241
Cefepime	Confusion, hallucinations, agitation, convulsion (0.2%), tremor, delirium and coma	- Onset is 1–10 days - Large doses to patients with renal failure	Insufficient data	Within 2–7 days after discontinuation	65–70, 72, 241–244
Carbapenems: Antagonism of the GABA receptor					
Imipenem-Cilastatin	Seizures (0.4% incidence for seizures in US packaging 1.5%–2% in post market experience)	Risk factors include age, renal failure, pre-existing CNS disease, stroke or history of seizure	Yes, seizures more likely	Upon discontinuation	79–83, 85, 87, 245–248
Meropenem	Seizures, Headache, Delirium (case)	Lower incidence of seizures compares to imipenem. Penetrates the BBB well	Delirium case reported in elderly Seizures in all ages	Upon discontinuation	88, 93, 249, 250
Doripenem	Seizures	Animals studies indicated that doripenem lacked convulsive activity, trial: 1.1%	Yes	Upon discontinuation	84, 85
Ertapenem	Seizures, hallucinations, asterixis, myoclonic jerks and cognitive impairment	0.5% incidence, more likely in patients with pre-existing CNS disease	Yes	Upto 14 days	91, 92, 251, 252
Oxazolidinones: Unknown but may cause mitochondrial injury, contributing to the development of toxic neuropathies [106–108]					
Linezolid	a) Peripheral neuropathy b) Optic neuropathy	Usually after months of treatment. Preexisting neurological disease, alcohol abuse, diabetes, chemotherapy, or antiviral therapy	Possible, but not confirmed	a) can take months to resolve and may be permanent b) Can lead to loss of vision (may be permanent).	94–106, 253

Supplemental Table I. (continued).

Antimicrobial Agent	ADR	Predisposing Factors	Predisposition in the Elderly	Time to Resolution	Reference
Aminoglycosides: Cochlear and/or vestibular organ damage. Inhibition of neuromuscular and autonomic transmission blockade					
Gentamicin	a) Neuromuscular blockade, myasthenia gravis, psychosis, encephalopathy, acute organic brain syndrome b) Vestibulotoxic,	Renal impairment and low serum calcium	Yes	a) Resolves upon discontinuation b) May be permanent	44, 120, 125, 254-258
Tobramycin	a) Psychosis and delirium in case reports b) Vestibulotoxic	Case report only of psychosis	Yes	a) Resolves upon discontinuation b) May be permanent	122, 126, 257
Amikacin	a) Headache, paresthesia Neuromuscular blockade- rare b) Cochleotoxic	Rare	Yes	a) Resolves upon discontinuation b) May be permanent	121, 259–264
Nitroimidazoles: Possibly by inhibiting protein synthesis and modulation of GABA receptor within the cerebellar and vestibular system					
Metronidazole	a) Peripheral neuropathy b) Ataxia and dysarthria c) Optic neuritis d) Aseptic meningitis e) Psychosis	a) Usually sensorimotor b) MRI: abnormality dentate nucleus of the cerebellum c) Likely due to hypersensitivity May be dose related or due to cumulative drug exposure	No	a) Full recovery when drug is stopped or dose reduced.Occasionally can persist for months/year b) b)MRI changes can persist for months c) 1-14 days	129, 130, 132–134, 137, 138, 140–143, 145, 149, 150, 152, 153, 265–274
Polymyxins: Inhibition of acetylcholine release in the synaptic cleft & interference with lipophilic content of neurons [156, 157].					
Polymyxin	Neurological toxicity: dizziness, vertigo, confusion, muscle weakness, parasthesias, ataxia, headache, partial deafness, visual disturbances, hallucinations, seizures	Generally occurs in the first few days of therapy and may be dose dependent. May also be infusionduration dependent	Insufficient data	Reversible upon discontinuation	123, 154, 155, 159-161, 170, 275-278
Clindamycin: Can inhibit neuromuscular transmission and augment neuromuscular blocking agents[279]					
Clindamycin	Temporary paralysis, increased tremor in a Parkinson's patients, restless leg syndrome	Limited to case reports	Insufficient data	Resolved in 3 days after discontinuation	164, 166–169, 171, 280, 281

Supplemental Table I. (continued).

Antimicrobial Agent	ADR	Predisposing Factors	Predisposition in the Elderly	Time to Resolution	Reference
Nitrofurans: Hypothesized to be due to axon loss					
Nitrofurantoin	Headache, dizziness, drowsiness, depression, confusion, abnormal vision, slurred speech, peripheral neuritis, neuropathy	Peripheral neuritis more common w renal failure Neuritis starts within 45 days of initiation	Yes	Polyneuritis can result in death. Slow recovery	173-175, 177, 282
Tetracycline : Vlechanism unknown					
Tetracycline	Benign intracranial hypertension: headache and blurring of vision Weak neuromuscular blockade	Generally in young adults and children	No	Unknown	170, 255, 283, 284
Minocycline	CNS ADRs (3%-67%): Dizziness, disassociation, vestibular, tinnitus	More likely in elderly and women	Insufficient data	Transient	285, 286
Doxycycline	CNS-related or dizziness (1%-3%)	CNSADRs more common with minocycline	No	Transient	285
Azole Antifungals: Mechanism unknown					
Voriconazole	Visual disturbances, hallucinations and encephalopathy	Unknown risk factors	Insufficient data	Rapid resolution upon discontinuati on	204-207

SONUÇ

- Geriatrik nüfus farmakokinetik değişiklikler nedeniyle advers ilaç reaksiyonları riski artmaktadır
- Özellikle diyaliz hastalarında nörotoksisite riski yüksektir
- merkezi sinir sistemi üzerinde toksik etkileri daha az tanınmakta
- yüksek riskli popülasyonlarda doz ayarlamaları yoluyla azalabilir
- Bu nörotoksik etkileri konusunda daha fazla eğitim ile toksik etkileri tanımak ve genellikle tersinir bir süreç olduğundan gerekli ilaç ayarlamaları yapmak
- Şüphe klinisyenler için çok önemlidir

TEŞEKKÜR EDERİM