ANTİBİYOTİK YAN ETKİLERİ HEPATOTOKSİSİTE

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HASEKİ EĞİTİM VE ARAŞTIRMA HASTANESİ
ENFEKSİYON HASTALIKLARI VE KLİNİK MİKROBİYOLOJİ

Hasta bilgileri

- 47 yaşında erkek hasta
- Baş ağrısı, ateş, yan ağrısı, ishal, boğaz ağrısı, halsizlik şikayetleri ile hastaneye başvurdu.
- Pnömoni ön tanısı ile antibiyotik tedavisi başlandı.
- Tedavinin dördüncü gününde laboratuvar tetkiklerinde aminotransferazlarda yükselme saptandı.

	Tedavinin 1. günü	Tedavinin 4. günü
Beyaz küre	13120/mm^3	
	%87.7 PNL	
Hemoglobin	15.8 g/dl	
Trombosit	174000/mm^3	
AST	41 U/L	319 U/L
ALT	19 U/L	162 U/L
GGT	75 U/L	84 U/L
ALP	101 U/L	103 U/L
Total bilirubin	1.5 mg/dl	
D. Bilirubin	0.3 mg/dl	
C-reaktif protein	294 mg/L	
Sedimantasyon	30 mm/saat	
Kreatinin	1.11 mg/dl	

Sizce hasta hangi antibiyotiği kullanıyor?

Hastaya pnömoni tanısıyla

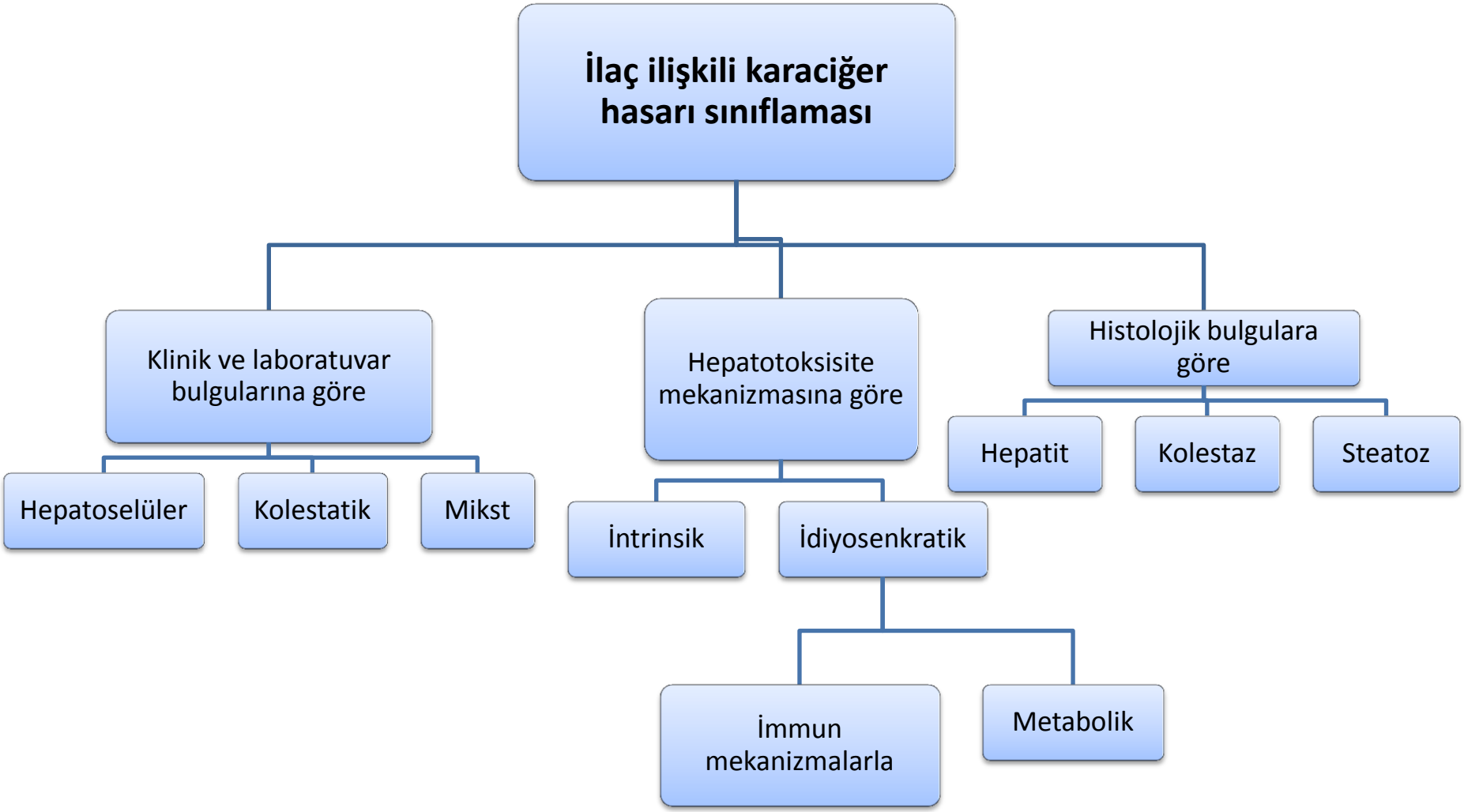
- Seftriakson + klaritromisin başlandı.
- Aminotranferazlarda artış saptandı.
- ALT > 3 kat normal üst sınır

İlaç ilişkili hepatotoksisite

- İlaç ilişkili hepatotoksisite 10/10000 - 15/100000 sıklıkla görülmektedir.
- Amerika Birleşik Devletleri'nde akut karaciğer yetmezliğinin en sık sebebidir.
- Genellikle görülme sıklığı erişkinlerde çocuklardan, kadınlarda erkeklerden daha fazladır.
- Amerika Birleşik Devletleri'nde asetaminofenden sonra en sık antibiyotiklere bağlı gelişmektedir.

Larson MA. Drugs and liver: patterns of drug-induced liver injury. UpToDate, 2014

İlaç ilişkili karaciğer hasarı



- **Hepatosellüler** ALT ≥ 3 kat veya ALT/ALP ≥ 5

- **Kolestatik** ALT ≥ 2 kat veya ALT/ALP ≤2

- **Mikst Tip** ALT ≥ 3 kat, ALP >2 kat ve 2< ALT/ALP < 5

Akut hasarda < 3 ay, kronik hasarda > 3 ay

Council for International Organization of Medical Sciences Classification,Leitner JM , hepatotoxicity of antibacterials, Infection 2010, 38:3-11

Hepatotoksik Kemoterapotikler

Hepatoselüler hasar	Kolestaz	ALT/AST yükselmesi	Yağlanma	Hepatit
Ampisilin	Eritromisin	Amoksisilin	Tetrasiklin	Sülfonamidler
Kloramfenikol	Sefalosporinler	Karbenisilin	Antimon bileşikleri	Nitrofurantoin
Klindamisin	Kotrimoksazol	Sikloserin		
Kotrimoksazol	Amoksisilin-klavunik asit			
Nitrofurantoin	Kloksasilin			
Amfoterisin B	Nitrofurantoin			
Ketokonazol	Klaritromisin			
İNH, PAS, PZA, RİF				
Etionamid				
Zidovudin				

Hepatotoksisiteyi arttıran risk faktörleri

- Genetik
- Alkol kullanımı
- Beslenme
- Eş zamanlı başka ilaç kullanımı
- Yaş
- Cinsiyet
- Altta yatan başka karaciğer hastalığı varlığı
- İlaç kullanım dozu

Larson MA. Drugs and the liver: Metabolism and mechanisms of injury, UpToDate,2014

Table 1: Predisposing factors in children with gallstones

Predisposing factor		Frequency (%)
Pseudolithiasis (due to ceftriaxonee therapy)		18 (27.3)
Hemolytic diseases	Major thalassemia	4 (6.1)
	G6PD deficiency	3 (4.5)
	Fanconi anemia	1 (1.5)
	Eliptocytosis	1 (1.5)
Hepatobiliary disease	Neonatal idiopathic hepatitis	3 (4.5)
	Viral hepatitis	1 (1.5)
	Cryptogenic cirrhosis	1 (1.5)
Cystic fibrosis		5 (1.5)
Renal diseases	Polycystic kidney disease	1 (1.5)
	Nephrotic syndrome	1 (1.5)
	Neurogenic bladder	1 (1.5)
Endocrine diseases	Congenital adrenal hyperplasia	1 (1.5)
	Hyperlipidemia	1 (1.5)
Obesity		2 (3)
Metabolic disease		1 (1.5)
Down syndrome		1 (1.5)
Idiopathic gallstone		20 (30.3)
Total		66 (100)

Esmaeili Dooki M R, et al. Cholelithiasis in Childhood: A Cohort Study in North of Iran .*Iran J Pediatr; Vol 23 (No 5), Oct 2013*


Hepatotoksisite mekanizmasına göre
İntrinsik hepatotoksisite
Hepatositlerde nekroz
Doz bağımlı
Öngörülebilir
Latent peryodu genellikle uzun
Mortalite insidansı insanlarda yüksek
Ör: Asetaminofen
İdiyosenkratik hepatotoksisite
Nekroz veya kolestazla seyreder
Dozdan bağımsız
Öngörülemez
Latent peryodu değişken olmakla birlikte genellikle uzun.
İmmun mekanizmalarla
Hipersensitiviteye bağlı
Ortaya çıkış süresi 1-5 hafta
Test dozuna çabuk cevap
Döküntü, ateş, eklem ağrısı eozinofili gibi klinik bulgular olabilir
Ör: Sülfonamidler, fenitoin, amoksisilin-klavunik asit
Metabolik
Anormal metabolizma sonucu
Ortaya çıkış süresi değişken; 1 hafta->1 yıl
Ör: İzoniazid, ketokonazol, amiodaron, fenitoin

Karaciğer hasarı varlığında dikkatli kullanılması gereken antibiyotikler

- Seftriakson
- Kloramfenikol
- Klindamisin
- Fusidik asit
- İsoniazid
- Metronidazol
- Nafsilin
- Rifabutin
- Rifampin
- Telitromisin
- Tigesiklin
- Tinidazol

Tanıda yaklaşım nasıl olmalı?

- Takip eden doktorun hepatotoksisite olabileceğini düşünmesi
- Kullanılan ilaçların gözden geçirilmesi ve hepatotoksik yan etki yapabileceklerin tespit edilmesi
- Eş zamanlı başka ilaç kullanımının sorgulanması
- Bitkisel ürünler kullanmış mı?
- Detaylı anamnez alınması

- Uyuşturucu ve toksik madde alımının sorulması
- Aile bireylerinin sorgulanması
- Ekstra-hepatik tutulum varlığı
- Başka karaciğer hastalığı veya altta yatan hastalıkların araştırılması
- Klinik bulguların değerlendirilmesi

Naranjo ADR probability scale—items and score

Question	Yes	No	Don't know
Are there previous conclusion reports on this reaction?	+1	0	0
Did the adverse event appear after the suspect drug was administered?	+2	–1	0
Did the AR improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0
Did the AR reappear when drug was re-administered?	+2	–1	0
Are there alternate causes [other than the drug] that could solely have caused the reaction?	–1	+2	0
Did the reaction reappear when a placebo was given?	–1	+1	0
Was the drug detected in the blood [or other fluids] in a concentration known to be toxic?	+1	0	0
Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
Was the adverse event confirmed by objective evidence?	+1	0	0

Scoring for Naranjo algorithm: >9 = definite ADR; 5–8 = probable ADR; 1–4 = possible ADR; 0 = doubtful ADR.

WHO–UMC causality categories

Causality term	Assessment criteria (all points should be reasonably complied)
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (ie, an objective and specific medical disorder or a recognized pharmacologic phenomenon) • Rechallenge satisfactory, if necessary
Probable/likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanation
Conditional/unclassified	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable/unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

Seftriakson ve hepatotoksisite

- Safra çamuru (psödolitiasis) oluşumu %3-%46
- Çocuklarda erişkinlerden daha fazladır
- %5 hastada psödolitiasise bağlı kolesistit semptomları görülür
- Genellikle karaciğer enzimleri ve bilirubin değerleri normal seyreder, ancak sarılık ve psödolitiasise bağlı pankreatit gelişmişse cerrahi gerekebilir
- Safra çamuru, seftriaksonun kalsiyuma bağlanma eğilimi sebebiyle safrada çözünmeyen kristallerin oluşması sonucudur.
- Çok nadir görülen idiyosenkratik akut kolestatik karaciğer hasarı seftriakson hipersentivitesine bağlıdır

http://www.livertox.nih.gov/

İmmuno-allerjik kolestatik hepatit

- Seftriaksonun neden olduğu nadir bir formdur
- Sağ üst kadran ağrısı, bulantı, kusma, kaşıntı, sarılık tedavi başlandıktan 1-4 hafta sonra gözlenir ve ilaç kesildikten sonra 1-2 hafta daha devam edebilir.
- Kolestatik enzimlerin yükselmesi, ateş, döküntü, eozinofili gözlenebilir.
- Kendi kendini sınırlar.

http://www.livertox.nih.gov/

TABLE 1
Characteristics of Patients with Positive and Negative Sonographic Findings

	Positive Finding (n = 27)	Negative Finding (n = 129)	*p* Value
Gender (male/female)	14/13	50/79	NS
Mean age ± SD (years)*	6.0 ± 3.4	4.2 ± 3.1	<0.01
Infection			
Pyelonephritis, n (%)	9 (33.3%)	58 (45.0%)	NS
Pneumonia, n (%)	6 (22.2%)	49 (38.0%)	NS
Bacterial meningitis, n (%)	9 (33.3%)	14 (10.9%)	<0.01
Lymphadenitis, n (%)	2 (7.4%)	5 (3.9%)	NS
Sepsis, n (%)	1 (3.7%)	3 (2.3%)	NS
Ceftriaxone dose (mg/kg/d)	80.6 (17.5)	72.8 (15.6)	<0.05
50 mg/kg/day, n (%)	4 (14.8%)	31 (24.0%)	NS
75 mg/kg/day, n (%)	13 (48.1%)	78 (60.5%)	NS
100 mg/kg/day, n (%)	10 (37.0%)	20 (15.5%)	<0.05

No significant difference in gender was observed between the 2 groups.

Biliary pseudolithiasis was more frequent in children with bacterial meningitis ($p < 0.01$) and who were treated with the highest daily drug doses ($p < 0.05$).

* The mean age of children belonging to the biliary pseudolithiasis group was higher than for those with negative sonographic findings ($p < 0.01$).

ORIGINAL ARTICLE

Nephrolithiasis associated with ceftriaxone therapy: a prospective study in 51 children

Z Avci, A Koktener, N Uras, F Catal, A Karadag, O Tekin, H Degirmencioglu, E Baskin

Arch Dis Child 2004;**89**:1069–1072. doi: 10.1136/adc.2003.044156

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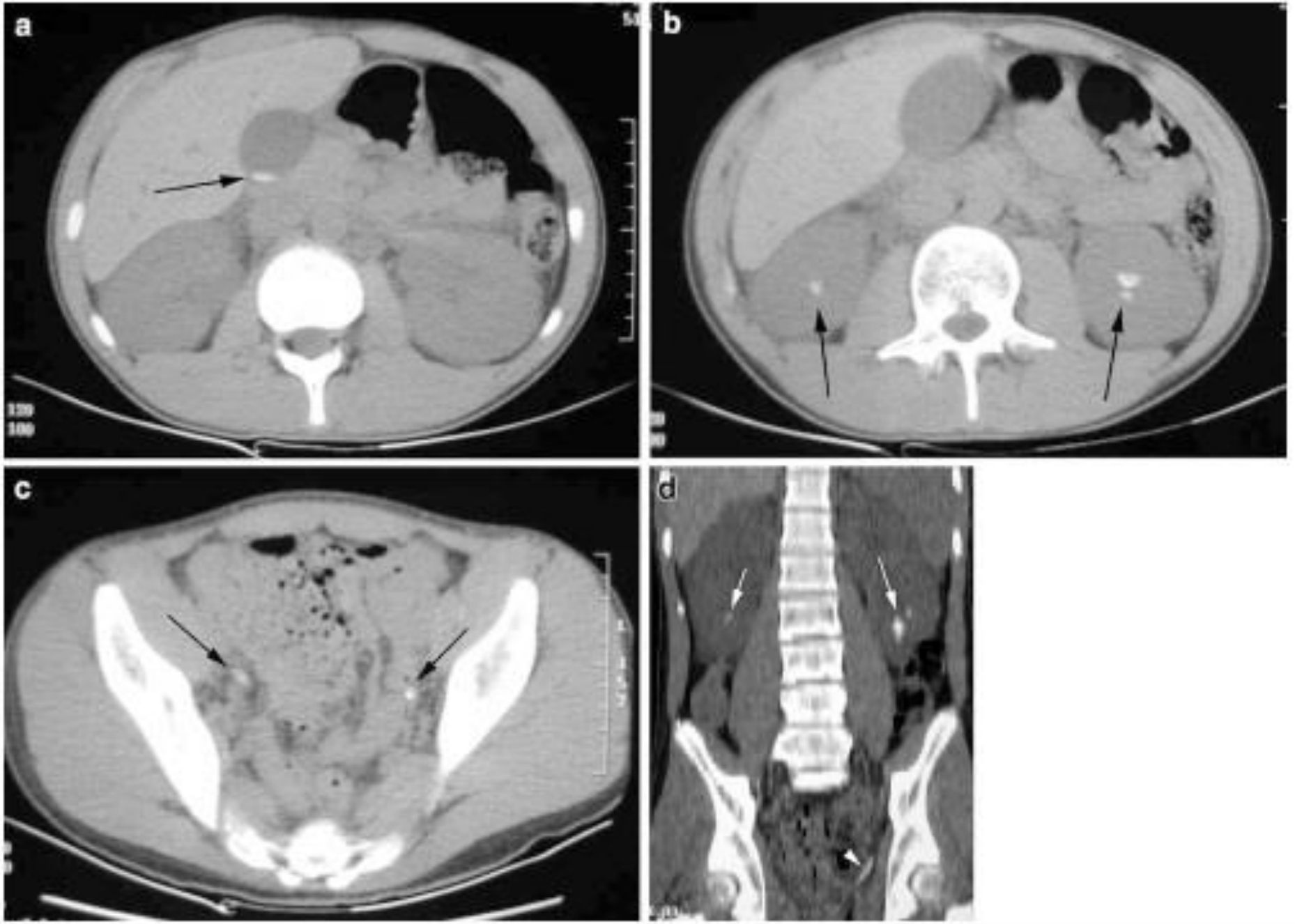
Background: Background: Ceftriaxone, a third generation cephalosporin, is widely used for treating infection during childhood. The kidneys eliminate approximately 33–67% of this agent, and the remainder is eliminated via the biliary system. Ceftriaxone may bind with calcium ions and form insoluble precipitate leading to biliary pseudolithiasis. The aim of this study was to assess whether ceftriaxone associated nephrolithiasis develops by the same mechanism, and whether this condition is dose related.

Methods: The study involved 51 children with various infections. Of these, 24 were hospitalized with severe infection and received 100 mg/kg/day ceftriaxone divided into two equal intravenous doses. The other 27 patients received a single daily intramuscular injection of 50 mg/kg/day. Serum and urine parameters were evaluated before and after treatment, and abdominal ultrasonographic examinations were also carried out before and after treatment.

Results: Serum urea, creatinine, and calcium levels were normal in all patients before and after treatment. Post-treatment ultrasound identified nephrolithiasis in four (7.8%) of the 51 subjects. The stones were all of small size (2 mm). Comparison of the groups with and without nephrolithiasis revealed no significant differences with respect to age, sex distribution, duration of treatment, or dose/route of administration of ceftriaxone. The renal stones disappeared spontaneously in three of the four cases, but were still present in one patient 7 months after ceftriaxone treatment.

Conclusions: Conclusions: The study showed that children taking a 7 day course of normal or high dose ceftriaxone may develop small sized asymptomatic renal stones. The overall incidence of nephrolithiasis in this study was 7.8%


a
b
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d

Table 1. Infections in children treated with ceftriaxone.

Infections	Negative sonogram	Positive	*p*
Bacterial pneumonia	9	3	0.65
Bacterial pyelonephritis	8	3	0.57
Acute appendicitis and appendiceal abscess	5	2	0.58
Bacterial meningitis	3	1	0.74
Osteomyelitis	1	–	0.75
Empyema	4	1	0.64
Suspected bacterial infection	3	1	0.74
Total	33	11	

F Papadopoulou et al. Incidence of ceftriaxone-associated gallbladder pseudolithiasis. Acta Pediatr 88: 1352-5. 1999

Table 3. Pseudolithiasis group.

Patient no.	Sex	Age	Infection	Day lithiasis developed	Day lithiasis resolved	Duration of treatment
1	M	5.5 y	Meningitis	2	14	10
2	F	4.5 y	UTI	3	8	3
3	F	13 y	UTI	3	15	3
4	M	8 y	Pneumonia	3	10	7
5	F	3 y	UTI	5	9	5
6	F	6 y	Suspected bacterial infection	2	11	2
7	M	7 mo	Pneumonia	5	18	12
8	M	8 y	Periappendiceal abscess	4	21	7
9	F	10 y	Empyema	9	21	14
10	M	10 y	Appendiceal abscess	4	23	8
11	M	14 y	Pneumonia	2	17	6
Mean		7.5 y		3.8	15.2	7
Median		8 y		3	15	7

F Papadopoulou et al. Incidence of ceftriaxone-associated gallbladder pseudolithiasis. Acta Pediatr 88: 1352-5. 1999

Klaritromisin hepatotoksisitesi

- 2 tip hasara neden olur

1) **Akut, geçici, sıklıkla asemptomatik serum aminotransferazlarında yükselme:**

- Kısa süreli klaritromisin kullananlarda %1-2 oranında izlenir. Bu oran uzun süre kullananlarda daha fazladır.
- Asemptomatik yükselme daha çok yüksek doz kullananlarda görülür.

http://livertox.nlm.nih.gov/Clarithromycin

2) Sarılıkla seyreden akut karaciğer hasarı:

- 3.8/100000 oranında görülür
- Kolestatik tipte bir hasardır
- Sıklıkla tedavi başlangıcından 1-3 hafta sonra karaciğer hasarı görülür ve klaritromisin kesildikten sonra bir süre daha devam eder
- Daha nadir olarak hepatoselüler hasara sebep olur
- İlaç kesildikten sonra 4-8 hafta içinde karaciğer hasarında düzelme gözlenir

http://livertox.nlm.nih.gov/Clarithromycin

- Mikrozomal sitokrom p450 sistemi tarafından metabolize edilen klaritromisinin diğer ilaçlarla etkileşimi sonucu kan değeri yükselir

- Klaritromisinin neden olduğu idiyosenkratik karaciğer hasarının sebebi bilinmemekle birlikte hipersensitiviteye bağlı olduğu düşünülmektedir

Table 3: Crude incidence of admission to hospital for acute liver injury within 30 days of exposure to an antibiotic agent

Antibiotic agent	No. of exposures	Admission to hospital for acute liver injury within 30 d of dispensing	Rate per 100 000 exposures
Clarithromycin (reference)	910 817	36	3.95
Cefuroxime axetil	248 458	16	6.44
Ciprofloxacin	1 051 959	67	6.37
Levofloxacin	324 660	28	8.62
Moxifloxacin	325 920	26	7.98

J. Michael Paterson et al. Fluoroquinolone therapy and idiosyncratic acute liver injury: a population-based study. CMAJ, October , 2012

Progressive Cholestatic Liver Disease Associated with Clarithromycin Treatment

Jean C. Fox, MD, Ronald S. Szyjkowski, MD, Schuyler O. Sanderson, MD, and Robert A. Levine, MD

The authors report a case of an acute toxic cholestatic reaction to clarithromycin, proven by liver biopsy, in a patient with comorbid diseases, prior exposure to erythromycin and ultimate death. No autopsy was performed. A 59-year-old woman with diabetes mellitus and chronic renal insufficiency received clarithromycin 500 mg twice daily for 3 days for acute maxillary sinusitis and then developed a rash and jaundice. She was hospitalized 11 days after stopping clarithromycin. Progressive cholestatic jaundice accompanied by oligo-anuric renal failure requiring hemodialysis ensued. Liver biopsy showed pure bilirubinostasis without parenchymal inflammation. On the 22nd hospital day, after clinical deterioration, she died from an apparent cardiopulmonary death. This is the first report in the literature of a fatality associated with a short-term, low (1 g) daily dose of drug-induced pure cholestasis, an entity not previously identified with severe drug-induced hepatotoxicity.

Journal of Clinical Pharmacology, 2002;42:676-680

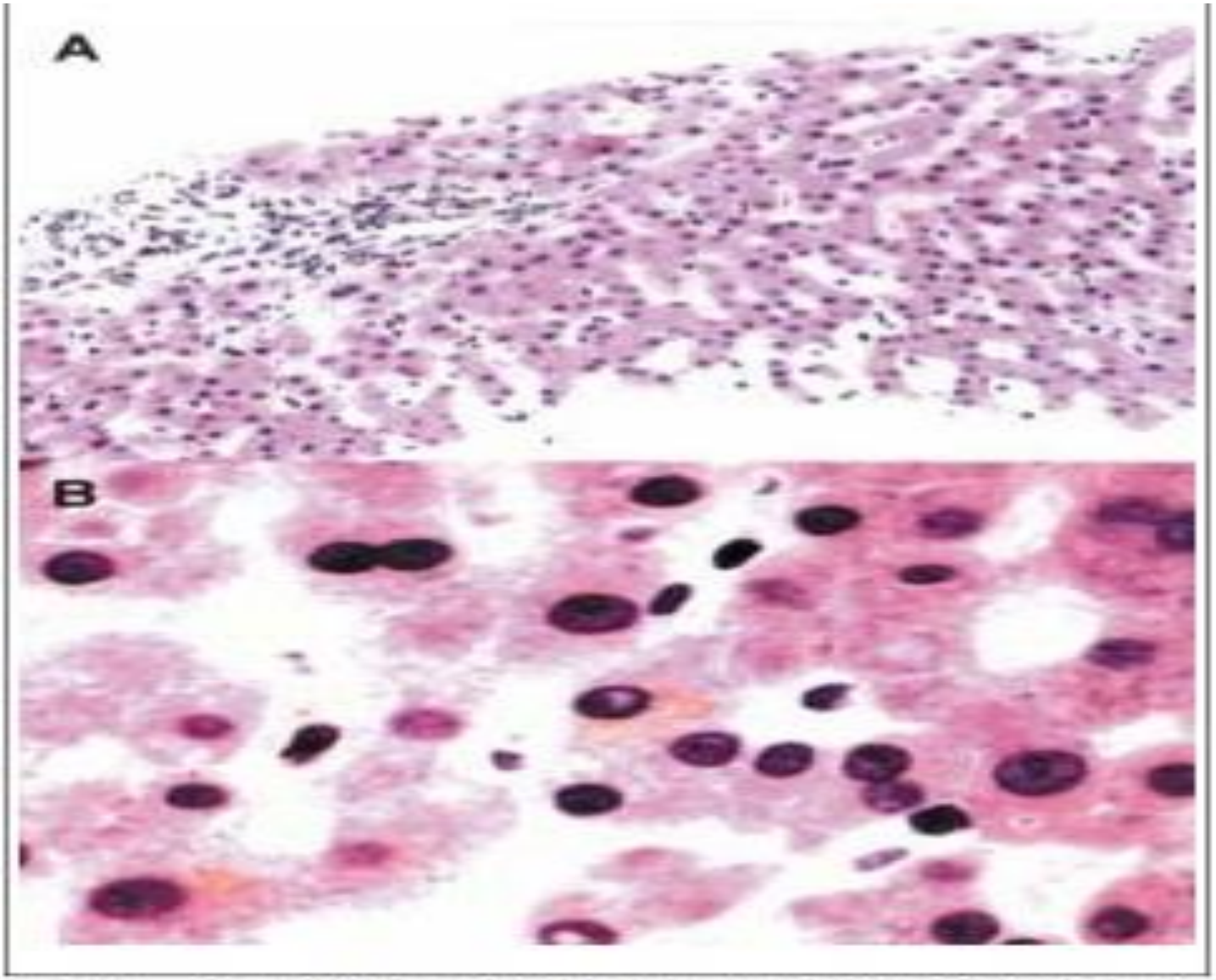

Figure 1. Liver biopsy findings (day 3 of hospitalization). (A) Low-power view of parenchyma, including portal area. Note the absence of inflammation and bile plugging (hematoxylin and eosin—magnification: 200×). (B) Hepatocytes with cytoplasmic bilirubin accumulation. Adjacent Kupffer cell also shows cytoplasmic bilirubinostasis (hematoxylin and eosin—magnification: 1000×).

Fulminant Hepatitis and Fatal Toxic Epidermal Necrolysis (Lyell Disease) Coincident With Clarithromycin Administration in an Alcoholic Patient Receiving Disulfiram Therapy

Mar Masiá, MD; Félix Gutiérrez, MD; Araceli Jimeno, MD; Andrés Navarro, MD; Joaquín Borrás, MD; Jaime Matarredona, MD; Alberto Martín-Hidalgo, MD

Disulfiram is widely used in the treatment of chronic alcoholism. Adverse drug reactions with fatal outcome following disulfiram therapy are infrequent, and hepatic failure accounts for most of them. Since disulfiram is a cytochrome P450 (CYP450) enzyme system inhibitor, numerous interactions with several drugs metabolized in the liver have been reported. Like disulfiram, clarithromycin inhibits a CYP450 isoenzyme, but, despite its widespread use for the treatment of respiratory tract infections, no interactions with disulfiram have been described as yet. We report a case of fatal toxic epidermal necrolysis (Lyell disease) and fulminant hepatitis shortly after starting treatment with clarithromycin in a patient who was receiving disulfiram. This is the first case of such a severe dermatosis in a patient receiving either disulfiram or clarithromycin therapy. The temporal relationship between drug administration and clinical symptoms in this case suggests a probable interaction between the 2 drugs.

Arch Intern Med. 2002;162:474-476

TEDAVİ VE ÖNLEME

- Hepatotoksik olduğu düşünülen ilaç kesilir. Bazı semptomsuz ve karaciğer enzimlerinde hafif yükselme görülen hastalarda ilaç kesilmeden yakın takip yapılabilir
- İlaç kesilen hastalar semptomlar ve karaciğer enzimleri açısından yakın takip edilir
- Antidot kullanımı (N-asetil-sistein)
- Sitoprotektif ajanlar
- Anti-oksidan kullanımı
- Transplantasyon

TEŞEKKÜR EDERİM