

COMPARISON OF LIVER FUNCTION IN TERMS OF DIFFERENT PARAMETERS IN PATIENTS RECEIVING IMIPENEM THERAPY IN THE INTENSIVE CARE UNIT; RETROSPECTIVE STUDY

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Abstract: Imipenem is a carbapenem antibiotic agent and, commonly used in intensive care units(ICU), it is known to affect kidney and liver functions. Imipenem may cause transient elevation of liver function test results and eosinophilia. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) enzyme levels are used to monitor liver functions. In addition, international normalization rate (INR) test is among the test parameters in chronic liver failure, Child-Pugh classification. In 'European Association for the Study of the Liver (EASL) Clinical Practical Guidelines on the management of acute (fulminant) liver failure' guideline, acute hepatitis parameters include the use of transaminase enzymes and insufficient liver functions (gallstones, coagulopathy, etc.). In our study, in the period of admission to ICU and imipenem treatment; 1) hemoglobin level, AST, ALT, gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), bilirubin, urea, creatinine, albumin (Alb), calcium (Ca) changes, INR, prothrombin time (PT) and activated partial to detect increases and decreases in thromboplastin time (aPTT) data; and 2) it was aimed to compare the correlation of these changes with AST and ALT changes. The aim of this study was to provide a more rapid and faster follow-up of the adverse effects of treatment during the use of imipenem in the intensive care unit, and to contribute to the acquisition of data in order to detect combinations of alternative laboratory tests. After the approval of TUEK(institutional medical ethics committee) Board of Health Sciences University Konya Training and Research Hospital, the records of patients who were treated in the Anesthesiology and Reanimation Intensive Care Unit between April 2017 and April 2019 were reviewed retrospectively from the hospital database. Data, age, sex, hemoglobin, AST, ALT, GGT, ALP, bilirubin, urea, creatinine, Alb, calcium, PT, INR and aPTT values of patients who received imipenem treatment in ICU were screened and recorded. ALT values were decreased and found statistically significant. However, the decrease in ALT was not clinically significant. AST / ALT \leq 1 suggests acute liver diseases, cholestatic jaundice, hepatitis C, and in case of alcoholic hepatitis, this ratio is expected to be greater than 2. It is an expected result in our study in the group of patients with the possibility of acute liver injury. Although the increases and decreases of these parameters were statistically, there was no correlation with AST and ALT changes. In our study, the strongest correlation was found between AST-adm and creatinine-adm values and AST-dis and creatinine-dis values.

Özet: Imipenem bir karbapenem türü antibiyotik ajandır ve yoğun bakım ünitelerinde (YBÜ) yaygın olarak kullanılır. Böbrek ve karaciğer fonksiyonlarını etkilediği bilinmektedir. Imipenem, karaciğer fonksiyon testi sonuçlarında ve eozinofili üzerinde geçici yükselmeye neden olabilir. Aspartat aminotransferaz (AST) ve alanin aminotransferaz (ALT) enzim seviyeleri karaciğer fonksiyonlarını izlemek için kullanılır. Ek olarak, uluslararası

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normalizasyon oranı (INR) testi kronik karaciğer yetmezliği, Child-Pugh sınıflamasındaki test parametreleri arasındadır. 'Akut (fulminan) karaciğer yetmezliğinin tedavisine ilişkin Avrupa Karaciğer Çalışmaları Birliği (EASL) Klinik Pratik Klavuz' klavuzunda, akut hepatit parametreleri transaminaz enzimlerinin ve yetersiz karaciğer fonksiyonlarının (safra kesesi taşları, koagülopati vb.). Çalışmamızda YBÜ'ne kabul ve imipenem tedavisi döneminde; 1) hemoglobin seviyesi, AST, ALT, gama-glutamil transferaz (GGT), alkalın fosfataz (ALP), bilirubin, üre, kreatin, albümin (Alb), kalsiyum (Ca) değişiklikleri, INR, protrombin zamanı (PT) ve aktif kısmi tromboplastin zmnı (aPTT) verilerindeki artış ve azalmaları tespit etmek; ve2) bu değişikliklerin AST ve ALTdeğişiklikleriyle korelasyonunun karşılaştırılması amaçlanmıştır. Bu çalışmanın amacı, yoğun bakım ünitesinde imipenem kullanımı sırasında tedavinin olumsuz etkilerinin daha hızlı bir şekilde izlenmesini sağlamak ve alternatif laboratuvar testlerinin kombinasyonlarını testip etmek amacıyla veri edinilmesine katkıda bulunmaktadır. TÜEK (Kurumsal Tıp Eğitimi Komitesi) Sağlık Bilimleri Üniversitesi Konya Eğitim ve araştırma Hastanesi'nin onayından sonra, Nisan 2017-Nisan 2019 tarihleri arasında Anesteziyoloji ve Renimasyon Yoğun Bakım Ünitesinde tedavi edilen hastaların kayıtları retrospektif olarak incelendi. Hastane veritabanından, yoğun bakım ünitesinde imipenem tedavisi alan hastaların veri, yaş, cinsiyet, hemoglobin, AST, ALT, GGT, ALP, bilirubin, üre, kreatin, Alb, kalsiyum, PT, INR ve aPTT değerleri tarandı ve kaydedildi. ALT değerleri azaldı ve istatistiksel olarak anlamlı bulundu. Ancak ALT'deki azalma klinik olarak anlamlı değildi. AST/ALT≤1, akut karaciğer hastalıkları, kolestatik sarılık, hepatit C ve alkolik hepatit durumunda, bu oranın 2'den fazla olması beklenir. Çalışmamızda, olasılığı olan hasta grubunda akut karaciğer hasarı beklenen bir sonuçtu. Bu parametrelerin artış ve azalışları istatistiksel olarak olmasına rağmen, AST ve ALT değişiklikleri ile korelasyon yoktu. Çalışmamızda AST-adm ve kreatin-adm değerleri ile AST-dis ve kreatinin-dis değerleri arasında güçlü korelasyon oranları bulundu.

INTRODUCTION

Imipenem is a carbapenem antibiotic agent and, commonly used in intensive care units(ICU), it is known to affect kidney and liver functions [1, 2]. Imipenem may cause transient elevation of liver function test results and eosinophilia. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) enzyme levels are used to monitor liver functions [3]. In addition, international normalization rate (INR) test is among the test parameters in chronic liver failure, Child-Pugh classification [4]. In 'European Association for the Study of the Liver (EASL) Clinical Practical Guidelines on the management of acute (fulminant) liver failure' guideline, acute hepatitis parameters include the use of transaminase enzymes and insufficient liver functions (gallstones, coagulopathy, etc.) [2, 3, 5]. In our study, in the period of admission to ICU and imipenem treatment; 1) hemoglobin level, AST, ALT, gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), bilirubin, urea, creatinine, albumin (Alb), calcium (Ca) changes, INR, prothrombin time (PT) and activated partial to detect increases and decreases in thromboplastin time (aPTT) data; and 2) it was aimed to compare the correlation of these changes with AST and ALT changes. The aim of this study was to provide a more rapid and faster follow-up of the adverse effects of treatment during the use of imipenem in the intensive care unit, and to contribute to the acquisition of data in order to detect combinations of alternative laboratory tests.

MATERIAL and METHODS

After the approval of TUEK (Institutional medical ethics committee) Board of Health Sciences University Konya Training and Research Hospital, the records of patients who were treated in the Anesthesiology and Reanimation Intensive Care Unit between April 2017 and April 2019 were reviewed retrospectively from the hospital database. Data, age, sex, hemoglobin, AST, ALT, GGT, ALP, bilirubin, urea, creatinine, Alb, calcium, PT, INR and aPTT values of patients who received imipenem treatment in ICU were screened and recorded. The values of the scanned values were recorded at admission and at the end of admission to the intensive care unit.

Patients were identified from our hospital electronic database. Patients with 5 days of imipenem therapy were included the study. Patients over the age of 18 and with the specified laboratory values were

included in the study. Patients with missing data, liver cancer, cirrhosis, cardiopulmonary resuscitation history, multi organ failure and liver trauma were excluded from the study.

RESULTS

The data of 428 patients included in the study have been presented. There was no difference in demographic data and hemoglobin values ($p > 0.05$). The recorded values and statistical analyses of the other parameters have been presented in the tables.

Table 1- Comparison of liver parameters admission to ICU and discharge from ICU values. (acronym -adm: value at admission to ICU, -dis: value at discharge from ICU)

Parameter	Value	Parameter	Value	<i>p</i> values
ALT-adm (admission)	131,8775 U/l	ALT-dis (discharge)	84,5679 U/l	$p < 0.001$
AST- adm	31,1514 U/l	AST-dis	199,2392 U/l	$p < 0.001$
ALP- adm	199,3759 U/l	ALP- dis	31,7968 U/l	$p < 0.001$
BIL- adm	2,2758 mg/dL	BIL- dis	13,4944 mg/dL	$p < 0.001$
PT- adm	14,0780 seconds	PT- dis	100,9933 seconds	$p < 0.001$
URE- adm	110,1158 mg/dL	URE- dis	1,6592 mg/dL	$p < 0.001$
KRE- adm	1,8797 mg/dL	KRE- dis	148,8352 mg/dL	$p < 0.001$
GGT- adm	134,4276 U/l	GGT- dis	10,5791 U/l	$p < 0.001$
ALB- adm	11,1604 g/L	ALB- dis	48,2094 g/L	$p < 0.001$
APTT- adm	51,2584 seconds	APTT- dis	8,1269 seconds	$p < 0.001$
Ca- adm	7,9911 mg/dL	Ca- dis	10,8352 mg/dL	$p < 0.001$
INR-adm	1,3363 %	INR- dis	1,3719 %	$p < 0.001$

All of the parameters between -adm and -dis comparisons were found to be $p < 0.001$.

Statistically significant increases and decreases in the recorded parameters were determined. The correlations of the changes in the parameters were evaluated statistically and presented in Table 2.

Table. 2 – Correlation evaluations of all parameters with ALT, AST admission and discharge parameters

Correlation table	Correlation Coefficient			
	ALT-adm	ALT-dis	AST-adm	AST-dis
ALT-adm (admission)	-	-	,692	,056
ALT-dis (discharge)	-	-	,205	,173
AST-adm	,692	,205	-	-
AST-dis	,056	,173	-	-
ALP-adm	,246	,271	,135	,268
ALP-dis	-,091	,326	-,275	-,189
BIL-adm	,150	,035	-,067	,387
BIL-dis	,212	-,074	,101	-,033
ALB-adm	-,125	-,059	-,175	,198
ALB-dis	,119	,001	-,078	-,109
URE-adm	,062	-,035	-,119	,434
URE-dis	-,050	,194	-,020	,397
KRE-adm	,118	-,068	-,096	,435
KRE-dis	,286	,391	,377	,599
GGT-adm	,423	,318	,540	,349
GGT-dis	-,156	-,016	-,196	,177

PT-adm	,305	-,030	,141	,038
PT-dis	-,116	,099	-,177	,435
APTT-adm	,215	-,189	-,100	-,192
APTT-dis	-,065	,087	-,040	,198
INR-adm	,076	-,046	,055	-,081
INR-dis	,217	,006	,032	,154
CA-adm	,136	,026	,161	,170
CA-dis	,124	,150	,191	,215

Statistical analysis

SPSS 22.0 for Windows software was used for statistical analysis. Shapiro Wilks test was used to determine whether the data showed normal distribution. Descriptive statistical analyses were used to evaluate demographic data and data collected from laboratory values. A paired sample T-test was used to compare the data. The Spearman Correlation analysis was used to evaluate the relationship between the data. Data were expressed as mean and confidence intervals. $P < 0.05$ was considered statistically significant. In the Spearman Correlation analysis, confidence intervals and p values showed a statistically significant or non-significant inverse interaction.

DISCUSSION

Imipenem is a carbapenem group antibiotic agent that is frequently used in intensive care units and is known to affect kidney and liver function [1, 2]. While plasma urea and creatinine values are used to evaluate kidney function [6], values above the AST and ALT reference levels indicate one or more causes of inflammation in the liver, that is, to varying degrees of damage [7]. However, the selectivity of these tests is limited due to the multiple treatments used in intensive care units.

ALT is primarily found in the liver and is therefore a more specific marker of hepatocellular damage [8]. In our study, ALT values were decreased and found statistically significant. However, the decrease in ALT was not clinically significant.

$AST / ALT \leq 1$ suggests acute liver diseases, cholestatic jaundice, hepatitis C, and in case of alcoholic hepatitis, this ratio is expected to be greater than 2 [9]. In our study, this ratio was observed as a statistically. It is an expected result in our study in the group of patients with the possibility of acute liver injury.

Alkaline phosphatase and GGT elevations are often associated with cholestasis [10]. In our study group, in which both tests decreased, cholestasis was not expected clinically, however, there was no data in our study based on patient data whether there was a case of cholestasis and this is one of the limitations of our study.

Albumine is the body's main protein produced in the liver. In some liver diseases, Alb production is disrupted and its amount decreases in the blood [11]. In our study where we detected an increase in ALB levels, it is impossible to reconcile this result with liver damage. However, the possibility of blood and blood product transfusion and the possibility of Alb-containing solutions to patients should be considered. In addition, this can be explained by the success of enteral or parenteral nutrition. Ca has very important functions in bone metabolism and coagulation pathways. Up to 90% of the plasma Ca is transported by binding to albumin [12]. An increase in Ca levels can also be explained by the increase in Alb and for the same reasons (treatment and nutrition) as Alb. Increased plasma Ca level (due to

immobilization, transition from bone to plasma Ca) due to long immobility in the intensive care unit can be explained.

Bilirubin is conjugated by adding glucose in the liver. Increased unconjugated bilirubin occurs as a result of excessive destruction of blood cells or inability of bilirubin to be conjugated in the liver [11]. In our study, no significant correlation was found between the changes in AST and ALT values and bilirubin change.

Coagulation factors are largely produced in the liver. In liver diseases, the production of clotting factors is disrupted and clotting problems arise. Therefore, coagulation tests are one of the important tests showing the functioning of the liver [11]. INR, aPTT and PT parameters are the tests we scan in our study. Although the increases and decreases of these parameters were statistically, there was no correlation with AST and ALT changes.

In our study, the moderate correlation was found between AST-adm and creatinine-adm values and AST-dis and creatinine-dis values. Hepatorenal sendrom (HRS) is a reversible functional renal impairment that occurs in patients with advanced liver cirrhosis or those with fulminant hepatic failure (13). It is characterized by marked reduction in GFR and renal plasma flow (RPF) in the absence of other cause of renal failure. The hallmark of HRS is intense renal vasoconstriction with predominant peripheral arterial vasodilation. Tubular function is preserved with the absence of proteinuria or histologic changes in the kidney. If the creatinine level is used in the definition of HPS, it is thought that it can be used as an early stage finding that liver functions are affected. That moderate correlation between AST and kreatinin levels support this suggestion.

Limitations

Causative pathogens, other antibiotics applied, other drugs not recorded, not all of the patient's previous existing diseases were screened, differences in daily imipenem doses were not screened are the limitations of our study.

REFERENCES

1. Zhanel, G.G., et al., *Imipenem and meropenem: Comparison of in vitro activity, pharmacokinetics, clinical trials and adverse effects*. Canadian Journal of Infectious Diseases and Medical Microbiology, 1998. 9(4): p. 215-228.
2. Buckley, M.M., et al., *Imipenem/Cilastatin*. Drugs, 1992. 44(3): p. 408-444.
3. Wendon, J., et al., *EASL clinical practical guidelines on the management of acute (fulminant) liver failure*. Journal of Hepatology, 2017. 66(5): p. 1047-1081.
4. Pugh, R., et al., *Transection of the oesophagus for bleeding oesophageal varices*. British Journal of Surgery, 1973. 60(8): p. 646-649.
5. Basoli, A., et al., *Imipenem/cilastatin (1.5 g daily) versus meropenem (3.0 g daily) in patients with intra-abdominal infections: results of a prospective, randomized, multicentre trial*. Scandinavian journal of infectious diseases, 1997. 29(5): p. 503-508.
6. Beyazpınar, D.S., et al., *İki koroner arter baypas greft ameliyatı tekniğinin akut böbrek hasarı yönünden karşılaştırılması*. Turk Gogus Kalp Dama, 2015. 23: p. 643-50.
7. Kwo, P.Y., S.M. Cohen, and J.K. Lim, *ACG clinical guideline: evaluation of abnormal liver chemistries*. The American journal of gastroenterology, 2017. 112(1): p. 18.
8. Friedman, L.S., S. Chopra, and A. Travis, *Approach to the patient with abnormal liver biochemical and function tests*. UpToDate. Waltham, MA. Accessed March, 2017. 8.

9. Sheth, S.G., et al., *AST/ALT ratio predicts cirrhosis in patients with chronic hepatitis C virus infection*. The American journal of gastroenterology, 1998. 93(1): p. 44.
10. Şentürk, H., B. Canbakan, and İ. Hatemi, *Karaciğer enzim yüksekliklerine klinik yaklaşım*. İstanbul Üniversitesi Cerrahpaşa Tıp Fakültesi Sürekli Tıp Eğitimi Etkinlikleri, Gastroenteroloji Klinik Yaklaşım Sempozyum Dizisi, İstanbul, 2004. 38: p. 9-13.
11. Akarca, Ulus Salih. Karaciğer Fonksiyon Testi Yüksekliğine Tanısal Yaklaşım. 9. İç Hastalıkları Kongresi, 2007.
12. Gençosman, Sevgi; Sayiner, Serkan. Total kalsiyum (tCa), İyonize kalsiyum (iCa), Düzeltilmiş total kalsiyum (ctCa): Hangisi?.
13. Hani M. Wadei, Martin L. Mai, Nasimul Ahsan and Thomas A. Gonwa, Hepatorenal Syndrome: Pathophysiology and Management, CJASN September 2006, 1 (5) 1066-1079; DOI: <https://doi.org/10.2215/CJN.01340406>