Dicle Üniversitesi Veteriner Fakültesi Dergisi
http://www.dicle.edu.tr/veteriner-fakultesi-dergisi
Araştırma Makalesi/Research Article
ISSN:1307-9972 e-ISSN:1308-0679

Effect of Multiple-Dose Administration of Cefquinome on Hematological and Biochemical Parameters in Horse

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Geliş Tarihi/Received	Kabul Tarihi/Accepted	Yayın Tarihi/Published
27.05.2019	21.06.2019	30.06.2019

Abstract

The negative impact of multiple ascending doses of cefquinome (CFQ) on hematological and serum biochemical profile of horse unknown. The objective of this study was to evaluate the effect of multiple ascending doses of cefquinome (CFQ) in horses on the following hematological (WBCs, LYM, MON, GRA, RBCs, HB, HT, MCV, MCH, MCHC, RDW, and PLT) and biochemical parameters (ALB, ALP, ALT, AST, CH, CR, GGT, LDH, TB, TP, TRIG, and BUN). The study was performed on the sixteen mature horses (4.6 ± 2.1 years, 302 ± 38 kg). Four dosages of CFQ were applied as Group I; 1 mg/kg, Group II; 2 mg/kg, Group III; 4 mg/kg and Group IV; 6 mg/kg, and each animal received intravenously a total of 13 injections, administered every 12 h for 7 days. The hematological and biochemical parameters of horses were monitored on the before 0 day and 1, 3, 7, and 14 days after the administration of the first CFQ. No significant differences in serum biochemical parameters were found amongst the groups ($p>0.05$). Significant differences were found in certain hematological parameters (MONO, GRAN, RBC, HB, HCT, MCH, and PCT) amongst the groups ($p<0.05$) within the reference ranges. These results indicate that the administration of multiple doses of up to 6 mg/kg of CFQ in the horse had no clinically significant impact on the blood parameters measured.

Key Words: Horse, safety, cefquinome

Atlarda Sefkuinomun Çoklu Doz Uygulamalarının Hematolojik ve Biyokimyasal Parametreler Üzerine Etkisi

Öz

Sefkuinomun (CFQ) çoklu doz uygulamalarının, atların hematolojik ve biyokimyasal profilleri üzerinde bir etkisi olup olmadığı bilinmemektedir. Bu çalışmanın amacı, atlarda çoklu artan CFQ dozlarının bazı hematolojik (WBC, LYM, MON, GRA, RBC, HB, HT, MCV, MCH, MCHC, RDW ve PLT) ve biyokimyasal parametreler üzerine (ALB, ALP, ALT, AST, CH, CR, GGT, LDH, TB, TP, TRIG ve BUN) etkisini belirlemektir. Araştırma 16 adet erişkin at (4.6 ± 2.1 yaş, 302 ± 38 kg) üzerinde gerçekleştirildi. Atlara damar içi olarak 7 gün boyunca her 12 saatte dört doz seviyesinde CFQ uygulandı: Grup I; 1 mg/kg, Grup II; 2 mg/kg, Grup III; 4 mg/kg, Grup IV; 6 mg/kg) uygulanan toplam 13 enjeksiyon gerçekleştirildi. Belirlenen hematolojik ve biyokimyasal parametreler ilaç uygulamasından önce (0 gün) ve ilk CFQ dozunun uygulanmasından 1, 3, 7 ve 14 gün sonra izlendi. Tedavi günlerinde gruplar arasında serum biyokimyasal parametrelerinde anlamlı bir fark bulunmadı ($p> 0.05$). Hematolojik parametrelerde (MONO, GRAN, RBC, HB, HCT, MCH ve PCT) doz grupları arasında referans değerler içinde anlamlı farklar bulundu ($p <0.05$). Bu sonuçlar, atlarda CFQ'un 6 mg/kg kadar çoklu doz uygulamalarının, değerlendirilen kan parametreleri üzerinde klinik olarak önemli bir etkisi olmadığını göstermektedir.

Anahtar Kelimeler: At, güvenilirlik, sefkuinom

INTRODUCTION

Cefquinome (CFQ; 2-amino-5-thiazolyl), which contains C-3' quaternary ammonium moiety at the C-3' position and is a member of the fourth generation of cephalosporins, is used only in veterinary medicine (1, 2). This antimicrobial structure provides its a broader spectrum of effects, resistance to β-lactamases synthesized by many clinically important bacteria and antipseudomonal activity (3-6). It has an extended spectrum of activity including Gram-negative pathogens and some Gram-positive, such as *Streptococcus zooepidemicus*, *Staphylococcus* spp., *Actinobacillus equuli*, *E. coli* and other *Enterobacteriaceae*. CFQ is moderately active against *Rhodococcus* spp. and *Pseudomonas* spp (6). CFQ is approved for the treatment of horse respiratory disease and foal septicemia, additionally, it is recommended at treatment of various diseases caused by susceptible bacteria (2). CFQ has been shown to be effective and well tolerated in the horse when administered at the originally

recommended dosage of 1 mg/kg (7-9). However, previous studies suggested that CFQ is effective within the dosage range of 1-6 mg/kg in the treatment against the major equine pathogenic bacteria (7-10).

Antimicrobial drugs are widely used in the treatment of bacterial infections in horses. This extensive use and inappropriate dosage regimens contributing to emergence of antimicrobial resistance have turn out to be a failure at the treatment of bacterial infections (11). The routine use of CFQ in veterinary medicine is unnecessary and could contribute to the development of antimicrobial resistance. However, the authors recommended that cefquinome be kept as a reserve antibiotic for equine therapeutic use in horses, to minimize the development of resistance (12, 13). Minimum inhibitor concentration (MIC) value is the most important pharmacodynamic parameter which is used for determining the effectiveness of the anti-bacterial drug against the infectious agent (11). The antibacterial activity of CFQ generally exhibits a time-dependent trend as in other β-lactam antibiotics, and it is necessary to maintain plasma and tissue concentrations above the minimum inhibitory concentration (T > MIC) of the pathogen for sufficient bactericidal activity (14). It has been reported that the maximal killing activity of on the pathogen is depend on the plasma concentrations remaining above 4 or 5 x MIC and that this value should be maintained at 100% (15). However, in conventional bolus dose regimens, plasma beta-lactam concentrations may be lower than the MIC levels indicated for the pathogen between doses and dose interval. This situation leads to negative effects such as the emergence of resistant pathogens and delayed clinical recovery. These can be solved by changes to the dosage regimen such as increasing the recommended both dose and dose interval (15-17). For these reasons, CFQ is applied on multiple-dose given as a continuous infusion over 20 minutes to block the emergence of resistant pathogens and delayed clinical recovery in this study.

Refractory cases are usually treated with higher doses of the drug which leads to an increase in the occurrence of adverse drug reactions (18). Adverse drug reactions defined as the harmful and unwanted effects of a drug used for prophylaxis, diagnosis or treatment are affected by a number of pharmacological and clinical factors, including the drug dose, drug route of administration, and duration of treatment (19-20). These reactions may be related to dosing or route of administration (Type A; overdosage, side effects, secondary effects, and drug interactions) and unrelated to dosing or route of administration (Type B; drug intolerance, drug idiosyncrasy, drug allergy, and pseudo-allergic reactions) (21-23).

Penicillin and cephalosporins are categorized within the β-lactam antibiotics because of their antimicrobial structure. One of the most important reasons for the frequent use of antibiotics in the β-lactam group is that they rarely cause adverse drug reactions. The most common adverse drug reaction related to it is hypersensitivity reactions (21). The frequency of these reactions in cephalosporins is rarer than with other β-lactam (24). Other adverse events associated with cephalosporins resulting from changes in dosage and administration route are nephrotoxicity, hepatotoxicity, neurotoxicity, hematological effects and gastrointestinal side effects. These events that can be detected by clinical symptoms or laboratory tests (24, 25). Biochemical and hematological parameters are considered to be indicative of alterations in the pathological state (26, 27). These group antibiotics can be affected the function of blood components (negatively by damaging to erythrocytes, leukocytes and thrombocytes) and organs such as liver, kidney, central nervous system (24, 28). Previous studies have investigated the side effects of following administration of cephalosporin in horses, dogs, turkeys, and calves, both clinically (gastrointestinal discomfort, anorexia, diarrhea) and in the laboratory tests (29-32). However, the effect of multiple ascending doses of CFQ on the blood hematological and biochemical parameters in the horses has not been reported to date.

The basic aim of the current study was to use blood hematological and biochemical parameters to investigate the side effects of CFQ using multiple ascending doses in equine. The hematological parameters measured were as follows: white blood cells (WBCs), lymphocytes (LYM), monocytes (MON), granulocytes (GRA), red blood cells (RBCs), hemoglobin (HB), hematocrit (HT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell dispersion width (RDW), and platelets (PLT). The biochemical parameters measured included the following: albumin (ALB), alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), cholesterol (CH), creatinine (CR), gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), total bilirubin (TB), total protein (TP), triglyceride (TRIG), and blood urea nitrogen (BUN).

MATERIAL AND METHODS

Animals

Sixteen healthy mature horses (4.6 ± 2.1 years, 302 ± 38 kg) were kept in a dry lot for 1 month prior to the start of the study and housed individually in 4 m^2 box stalls for 48 h prior to drug administration and during the study and were maintained on mixed alfa⁄grass hay and water *ad libitum*. The horses were clinically monitored for drug reactions every 12 h during the study and every 24 h for 7 days after completion of the study. The Ethics Committee of the Faculty of Veterinary Medicine (University of Selçuk, Konya, Turkey) approved the use of the animals for this study, and all study protocols.

Experimental Design and Drug Administration

The horses were randomly divided into four dose groups according to the dosage of CFQ administered to each horse: levels of 1, 2, 4, and 6 mg/kg were selected. CFQ sulphate was diluted with 100 mL sterile water to prepare infusion solutions of CFQ at concentrations of 1, 2, 4, and 6 mg/kg, which were administered as a constant-rate intravenous (IV) infusion over 20 min. Each animal received a total of 13

injections, administered every 12 h and at a given dose level.

Blood sampling

Blood samples for measurement of biochemical (3 mL) and hematological (2 mL) parameters were collected from the jugular vein before dosing (day 0) and 1, 3, 7, and 14 days after the initial administration of first CFQ. Blood samples were divided between two tubes, one with heparin as an anticoagulant and one without. The tubes without anticoagulant were centrifuged for 10 min at 3000 *g* for serum collection, which was stored at –70°C until required for analysis. The serum samples were analyzed using commercial kits (bioMérieux Diagnostics, Marcy l'Etoile, France) using an autoanalyzer (ILab-300 plus, Instrumentation Laboratory, Milan, Italy) to determine the respective concentrations.

Serum in the tubes containing anticoagulant was analyzed for measurement of the above-mentioned hematological parameters using an automatic cellular counter (BC-2800 Auto Hematology Analyzer, Mindray Bio-Medical Electronics, Shenzhen, China).

Statistical analysis

Statistical analysis was done using "SPSS 16.0" software (SPSS Inc., Chicago, IL). Differences in hematological and biochemical parameters between the groups were analyzed by one-way analysis of variance (ANOVA) using Duncan's test. The values were expressed as mean ± standard deviation (SD). P-values of < 0.05 were considered significant.

RESULTS

All horses remained clinically healthy during the study period. No general or local adverse reactions were noted after the multiple administrations in any horses; administration of CFQ was well tolerated by all horses. The effects of different doses of CFQ on the hematological and biochemical parameters measured are shown in the Tables 1 and 2, respectively. Statistical analysis indicated that CFQ caused a significant (P<0.05) alteration in MON, GRA, RBC, HB, HT, MCH and MCHC among the four groups ($P< 0.05$, Table 1). The results indicated that varying the dose of CFQ had no significant effect on the biochemical parameters (P>0.05), except for TB levels. The mean TB level in the 4 mg/kg dose group was significantly higher than that in the 6 mg/kg dose group (P<0.05, Table 2).

DISCUSSION AND CONCLUSION

In the equine species, the determination of appropriate antimicrobial therapy is more difficult than in some other animals because of several characteristics such as the susceptibility of the equine intestinal micro flora and the risk of adverse side effects (33, 34). Cephalosporins generally give rise to few side effects such as hypersensitivity reactions or nephrotoxicity (35). Other side effects have been described for ceftiofur and CFQ, including gastrointestinal discomfort, anorexia, and diarrhea. (13, 26). In this study, multiple ascending doses of CFQ up to 6 mg/kg were well tolerated by all horses. At the same time, there were no clinically significant finding indicating side effects.

The hematological and biochemical parameters of blood are considered to be good indicators of the physiological and pathological status of animals exposed to drugs, toxins, and other adverse conditions (37-39). Hematological parameters are related to the blood and blood-forming organs. Many antimicrobial agents, such as the cephalosporins, can affect the hematopoietic system leading to hematopoietic suppression (40), which can cause potentially life-threatening thrombocytopenia, anemia, and neutropenia (40). Hematological parameters such as RBC, MCHC, MCH and WBC are used to assess the physiological status of the animals (41). In this study, statistical analysis indicated that CFQ caused a significant (P<0.05) alteration in MON, GRA, RBC, HB, HT, MCH, and MCHC in all four groups (P<0.05, Table 1). Despite this finding, all values were found to be within the respective reference ranges (42, 43). Hematological parameters in the horse can be affected by many factors such as the breed, gender, age, time of feeding, and reproductive and training status. Any excitement can cause an increase in the number of circulating red blood cells, by stimulating blood-forming organs such as the spleen (44, 45).

Clinical biochemical evaluations are useful in assessing the health status or functioning of the animals following repeated administration of antimicrobial drugs (30-32). In the present study, no statistical differences were found regarding serum biochemical parameters (ALT, AST, BUN, CR and TP), except for TB, between the four groups at 1, 3, 7, and 14 days after the initial administration of CFQ (P>0.05, Table 2). Although the TB values in the 4 mg/kg dose group were significantly higher than in the other dose groups, these were within the reference ranges reported for the adult horse (46). In general, the values of the biochemical and hematological parameters measured were consistent with those of previous reports (47-50).

This study showed that following the IV administration in horses of CFQ at dose levels of 1, 2, 4, and 6 mg/kg every 12 h over 7 days, serum biochemical and hematological parameters remained largely unchanged, although a mild effect was noted on some parameters. CFQ at a dosage rate of up to 6 mg/kg can be administered in the treatment of equine bacterial diseases. However, further research is necessary to determine the serum biochemical and hematological parameters of the critically ill horse following the administration of CFQ at dosage rates of up to 6 mg/kg.

ACKNOWLEDGMENTS

This study was supported by the Scientific and Technological Research Council of Turkey (SUBAPK). Presented in abstract form at the 32nd World Veterinary Congress, Istanbul, Turkey, September 2015.

Table 1. Results of hematological parameters for cefquinome in plasma after multiple-dose administrations (mean ± standard deviation) in horses

	Dose (mg/kg)	0 DAY	1 DAY	3 DAY	7 DAY	14 DAY
WBCs (10^3/µL)	1	5,95±0,64	7,03±1,94	6,50±2,03	6,63±1,76	5,98±0,51
	2	7,03±1,44	8,28±0,78	7,85±1,13	7,38±2,84	6,90±1,85
	4	6,10±0,40	6,30±0,85	5,13±1,91	8,17±1,10	7,87±1,34
	6	6,03±0,75	6,93±2,20	8,23±1,95	7,30±2,72	6,63±1,10
LYM (10^3 /µL)	1	2,13±0,98	1,85±0,99	2,10±1,00	1,55±0,64	2,43±1,10
	2	3,23±0,75	2,80±0,74	3,03±0,90	3,20±1,34	3,60±1,73
	4	3,00±1,13	2,50±1,14	2,03±0,49	3,17±1,25	2,80±0,78
	6	2,13±0,59	1,67±0,51	2,10±0,46	2,07±0,75	1,90±0,46
MON (10^3/µL)	1	0,25±0,06	0,30±0,08^{AB}	0,30±0,08	0,30±0,14	0,23±0,05^{B}
	2	0,28±0,10	0,38±0,05^{A}	0,35±0,06	0,30±0,16	0,28±0,05^{AB}
	4	0,20±0,00	0,27±0,06^{AB}	0,23±0,12	0,37±0,06	0,33±0,06^{A}
	6	0,20±0,00	0,20±0,10^{B}	0,27±0,06	0,23±0,12	0,27±0,06^{AB}
GRA (10^3/µL)	1	3,58±0,95	5,63±1,31	4,10±1,25^{AB}	4,78±1,72	3,33±1,24
	2	3,53±0,67	5,10±0,76	4,48±0,76^{AB}	3,88±1,60	3,03±0,83
	4	2,90±1,48	3,53±1,81	2,87±1,80^{B}	4,63±1,46	4,73±1,29
	6	3,70±1,21	5,07±1,89	5,87±1,65^{A}	5,00±2,43	4,47±1,42
RBCs (10^6/µL)	1	7,28±0,56^{AB}	6,69±1,63	7,15±1,74	7,03±0,44	6,34±1,19^{AB}
	2	8,86±2,54^{A}	7,59±1,07	8,40±1,51	7,00±1,41	7,68±0,54^{A}
	4	7,75±0,43^{AB}	7,64±0,62	8,06±2,67	7,58±0,58	7,26±0,34^{A}
	6	5,82±0,93^{B}	7,28±2,01	6,27±0,53	6,50±1,38	5,57±0,65^{B}
HB (g/dL)	1	110±7,41^{AB}	101±19,86	108±26,52	106±5,44	93,00±12,25
	2	142±44,04^{A}	121±15,29	131±26,63	104±20,71	105±1,29
	4	107±4,04^{AB}	109±5,13	116±30,17	107±9,54	104±10,97
	6	90,33±13,50^{B}	116±28,29	101±5,13	105±19,14	90,00±7,00
HT (%)	1	35,78±2,68	32,53±7,86	34,78±8,26	34,48±2,34	31,08±4,22^{AB}
	2	43,63±14,30	38,05±4,46	41,65±8,10	33,75±5,37	34,20±0,32^{A}
	4	35,50±2,08	34,80±1,85	36,33±9,16	34,43±1,50	32,80±3,30^{AB}
	6	29,23±4,02	37,40±9,54	32,43±1,50	33,10±6,06	28,20±3,03^{B}
MCV (fL)	1	49,40±4,42	48,85±3,80	48,90±3,66	49,25±3,96	42,03±13,60
	2	49,08±4,61	50,53±5,20	49,83±5,02	48,70±4,06	44,75±3,02
	4	46,03±5,25	45,90±5,47	46,07±5,40	45,73±5,20	45,37±5,59
	6	50,43±1,27	51,67±1,02	51,90±1,91	51,23±2,17	50,80±1,87
MCH (pg)	1	15,10±0,35^{AB}	15,18±1,06	15,05±0,64	15,03±0,83	14,68±1,00^{AB}
	2	15,88±1,28^{A}	15,90±1,36	15,58±1,09	14,85±1,56	13,60±0,88^{B}
	4	13,83±1,31^{B}	14,33±1,74	14,67±1,85	14,17±2,20	14,37±2,06^{AB}
	6	15,83±0,47^{A}	16,03±0,50	16,03±0,64	16,13±0,58	16,20±0,89^{A}
MCHC (g/L)	1	308±23,13	313±20,48	310±11,59	307±8,42	297±11,56^{B}
	2	326±19,84	316±10,89	315±11,59	305±16,82	305±2,00^{AB}
	4	269±64,09	314±5,00	319±4,62	310±14,53	318±19,47^{AB}
	6	308±11,50	311±6,08	309±4,73	316±15,14	319±10,21^{A}
RDW (%)	1	18,13±1,20	18,05±0,83	17,83±1,08	18,20±0,68	17,88±0,40
	2	17,93±0,76	18,13±1,11	17,78±0,99	18,03±1,05	18,40±0,74
	4	17,73±0,45	17,97±0,32	18,07±0,15	18,43±0,68	18,43±0,68
	6	18,47±0,75	18,93±0,96	18,70±0,82	18,40±0,82	18,13±0,47
PLT (10^3/µL)	1	181±52,35	158±43,20	160±54,70	163±34,75	187±13,29
	2	213±54,68	212±79,01	199±46,92	169±58,53	157±6,60
	4	162±8,74	150±6,51	138±29,82	189±40,41	173±25,32
	6	187±51,03	135±42,48	149±48,21	177±29,46	180±31,50

WBCs: White blood cells, LYM: lymphocytes, MON: monocyte, GRA: granulocyte, RBCs: red blood cells, HB: hemoglobin, HT: hematocrit, MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration, RDW: red cell dispersion width, PLT: platelets. A, B; different letters in the same column are statistically significant ($p<0.05$).

Table 2. Serum biochemical parameters after multiple-dose cefquinome administrations (mean ± standard deviation) in horses.

	Dose (mg/kg)	0 DAY	1 DAY	3 DAY	7 DAY	14 DAY
ALB (g/dL)	1	3,73±0,62	3,50±0,71	3,60±0,54	3,68±0,73	3,88±0,66
	2	3,65±0,56	3,43±0,29	3,53±0,29	3,25±0,31	3,38±0,56
	4	4,00±0,20	4,03±0,06	4,03±0,23	4,00±0,10	4,10±0,10
	6	3,30±0,40	3,43±0,58	3,50±0,72	3,67±0,76	3,63±0,40
ALP (U/L)	1	194±120	169±93,12	167±69,73	183±20,07	171±146
	2	214±50	192±23,19	203±49,87	198±44,78	202±42,73
	4	206±106	212±108	214±107	176±81,41	206±106
	6	151±24	175±25,12	170±39,51	175±38,16	170±34,53
ALT (U/L)	1	6,25±1,26	5,25±1,71	5,75±0,96	5,25±0,50	6,25±1,50
	2	8,50±2,38	6,50±1,91	5,00±2,31	6,25±0,96	6,00±1,41
	4	6,33±2,08	7,00±2,00	6,33±0,58	6,00±1,00	6,67±3,51
	6	5,33±1,15	5,67±0,58	5,67±0,58	5,33±1,53	5,00±1,00
AST (U/L)	1	237±81,07	210±63,90	207±54,27	192±25,06	214±90,24
	2	222±50,61	211±34,51	212±35,36	196±5,69	205±25,00
	4	244±103,21	244±95,29	237±74,00	189±47,50	242±86,56
	6	193±19,30	199±15,31	203±5,29	204±5,13	184±17,06
CHOL (mg/dL)	1	214±11,56	215±9,88	212±11,39	218±8,61	218±17,84
	2	233±17,44	224±12,96	229±16,38	22010,92	208±35,73
	4	210±15,87	217±15,50	221±15,72	209±5,57	221±11,59
	6	211±15,95	213±15,82	220±9,29	219±9,29	216±9,07
CR (mg/dL)	1	1,22±0,26	1,20±0,35	1,24±0,27	1,38±0,42	1,51±0,11
	2	1,17±0,30	1,00±0,34	1,25±0,25	0,96±0,31	1,08±0,23
	4	0,87±0,23	1,05±0,17	4,31±5,79	0,89±0,28	0,99±0,33
	6	1,33±0,23	1,36±0,25	1,31±0,15	1,38±0,24	1,48±0,20
GGT (U/L)	1	21,00±18,46	19,75±17,21	11,67±6,43	23,00±13,29	18,00±16,79
	2	16,25±8,54	13,75±6,13	11,25±3,95	17,75±6,70	15,50±8,27
	4	20,33±9,07	21,33±9,81	21,00±10,58	19,33±7,23	20,00±8,72
	6	14,67±13,28	15,00±13,86	15,67±13,32	23,33±11,72	17,00±15,62
LDH (UI/l)	1	460±171,36	429±206	454±252	462±170	438±264
	2	380±32,75	355±27,33	351±55,43	408±69,33	373±19,47
	4	394±141,89	369±96,81	374±51,86	362±88,54	378±107
	6	461±227,39	510±207	498±196,73	490±202	409±275
TB (mg/dL)	1	3,38±0,99^{AB}	2,85±0,73	3,78±1,53	3,58±0,93	4,63±2,06
	2	3,73±0,43^{AB}	3,05±1,31	5,57±1,75	4,73±1,25	3,13±0,76
	4	6,03±2,97^{A}	5,00±2,69	4,83±2,48	3,40±0,60	6,30±2,81
	6	3,23±0,85^{B}	2,43±0,38	3,00±0,62	3,30±0,95	3,57±1,02
TP (g/dL)	1	6,85±0,85	6,63±0,60	7,08±0,21	7,03±0,51	7,70±1,39
	2	7,85±0,52	7,48±0,61	7,58±0,26	6,93±0,30	7,53±0,87
	4	7,00±0,20	7,03±0,06	7,23±0,46	6,83±0,25	7,13±0,31
	6	6,83±0,31	7,13±0,25	7,13±0,35	7,33±0,51	7,00±0,36
TRIG (mg/dL)	1	96,50±8,66	95±14,65	91,25±11,87	84,50±4,65	166±110
	2	131±62,91	101±33,11	119±51,70	81,50±10,41	103±28,56
	4	102±14,18	107±22,28	122±52,65	86,67±2,08	114±8,02
	6	83,67±12,66	92,33±25,11	90,67±12,66	89,67±11,59	87±8,72
BUN (mg/dL)	1	45,00±7,44	39,50±7,77	37,75±4,72	45,75±10,31	52,25±12,50
	2	50,00±6,58	41,00±5,35	46,50±11,93	42,75±7,09	45,75±8,22
	4	39,67±8,02	41,00±15,72	42,00±7,00	45,00±2,65	45,00±6,24
	6	38,00±10,44	30,00±3,00	39,67±5,51	45,33±13,80	42,67±10,79

ALB: Albumin, ALP: alkaline phosphatase, ALT: alanine aminotransferase, AST: aspartate aminotransferase, CHOL: cholesterol, CR: creatinine, GGT: gamma glutamyl transferase, LDH: lactate dehydrogenase, TB: total bilirubin, TP: total protein, TRIG: triglyceride BUN: blood urea nitrogen. A, B; different letters in the same column are statistically significant ($p<0.05$).

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