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Original article

EFFECTS OF EXHAUSTIVE EXERCISE INVESTIGATION OF RATS IBUPROFEN OF ADVERSE CARDIAC EVENTS

TASGİN Erdal[1], LOK Sefa[1]

Abstract*

Objectives. In determining developing heart damage, Troponin I and cK-MB levels in the blood are measured. It has been determined that both signs of heart damage increase within 2-16 hours after damage occurs. Normal and high dose ibuprofen application's effects on rats' heart, blood counts, resistance to exercise and routine chemistry can be determined with the current research.

Methods. Rats have been divided into four equal groups (control group, ibuprofen group, exhaustive exercise group, ibuprofen + exhaustive exercise group, N=24). 80 mg/kg of ibuprofen has been given with gavage syringe to groups to which drug would be given and exhaustive exercise program has been applied to exercise group. All groups have been euthanized after 6 hours by taking blood from their hearts.

Results. It has been determined in this study that ibuprofen application increases troponin I level ($P<0.05$) and ibuprofen + exercise application increases creatinine and BUN levels ($P<0.05$). It has been determined that troponin I which is the specific sign of heart damage is higher in ibuprafen group compared to exercise group. However, because of the reason that troponini I level of ibuprofen group is same as control group's level ($P>0.05$) and there is no difference in levels of CK-MB mass which is another sign of specific heart damage, this shows that ibuprofenin doesn't have heart damage-inducing effect.

*Conclusions.*Consequently, it can be said that taking ibuprofen during exercise doesn't affect signs of heart damage but, it needs to be careful in terms of kidney damage.

*Keywords:*Exercise, ibuprofen, heartdamage, kidneydamage.

Introduction

Non-steroid anti-inflammatory drugsare commonly used as analgesic and anti-inflammatory (Deniz 2000, O'Malley, 2006).

It is reported that the sportsmen are prescribed with ibuprofen in clinical usage for sports injuries (Zafonte, 2011).

It is stated in humane medicine science that NSAIDs are related with the initiation of edema and congestive heart failure (CHF) (Feenstra et al., 1999).

Ibuprofen is a NSAID which is commonly used in humane medicine science. It is stated that sudden death might occur after the application of ibuprofen.

It is foreseen that ibuprofen might be risky for the people with heart diseases (Ray et al. 2009, Olsen et al., 2011, EMEA, 2013).

It is reported that NSAIDs do not cause congestive heart failure and myocardial depressant directly yet they influence the prostaglandin (PG) synthesis by inhibiting the cyclooxygenase (COX) enzyme function (Feenstra et al., 1999).

For detecting the developed heart damage, it is detected by measuring the Troponin I and ck-MB levels of the blood.

The usage of cardiac troponin as a clinical reagent has become very popular in the pathology of cardiac diseases such as unstable angina, minimal infarcts, left ventricular hypertrophy, congestive heart failure, pulmonary emboli, blunt trauma, sepsis etc. (O'Brien, 2008).

Upper gastrointestinal bleeding, gastric ulcer, prevention of kidney functions and hypersensitivity reactions are connected to the all classes of NSAID (O'Malley, 2006).

The current published researches show that selective NSAIDs are related to the risk of acute myocardial infarcts (AMI) (Singh, 2006). It is stated that NSAIDs can play a role in myocardial infarcts (MI) and sudden cardiac deaths (Marcus et al., 2002, Fitzgerald et al., 2004).

The rate of cardio-toxicity depending on drug usage in the global medicine industry between 1960 and 1999 is reported to be 9% (O'Brien, 2008).

It is reported that the sportsmen are prescribed with ibuprofen in clinical usage for sports injuries (Zafonte, 2011).

Muscles and brain are the tissues where creatine kinase (CK), an enzyme which is found in skeleton muscle, heart muscle and brain, exists in a great volume.

[1] Selcuk University Faculty of Sciences Sports, Campus,42075, Konya,TURKEY.
E-mail address: erdaltasgin@gmail.com

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Due to the fact that CK enzyme never go over the blood brain barrier and join in the circulation, it is reported that the CK level measured in the circulation is reported to be related to the skeleton and heart muscle. It is stated that CK-MB level increases its level in the circulation in cases of acute myocardial infarcts, myocarditis, heart surgeries, and congestive heart failure (Dumanand Erden, 2004).

It is detected that the level of Troponin I and CK-MB heart damage reagent increases 4-6 hours after the damage occurs and in some patients this time period prolong up to 12 hours (Harrison and Amundson, 2005).

With the current research, it will be possible to detect the resistance and influence of normal and high dose ibuprofen application on the heart damage reagents, routine biochemistry and exercise of rats.

Methods

In this research, Wistar rats which are supplied from the experimental animals unit of Selcuk University are utilized. In the research carried out in Selcuk University experimental animals unit, the Rats are separated into 4 different groups, 6 subjects in each (control group, ibuprofen group, group with exhaust exercise and group with ibuprofen and exhaust exercise, N=24). The groups to be given drugs are injected ibuprofen with 80 mg/kg gavage (Gola et al., 2013), and the exhaust exercise is applied on the exercise groups. When the subjects come to the point of drowning after 6 hours, all the groups are taken out of the pool. Then, blood is taken from their hearts and they are euthanized.

The serums are separated from the blood samples and the analysis is performed with auto-analyzer and ELISA kits.

Exhaust exercise: The rats in this group make adaptation trials of swimming in the first phase. Then, the rats are placed into the Swimming tank and they practice swimming until they exhaust. The heat of the water in the tank is adjusted to 25 C^o

Statistical analysis: For the statistical analysis of the data, SPSS 22.0 (SPSS 22.0 for Windows/SPSS® Inc, Chicago, USA) package program is utilized. The results are recorded as mean±SD. The intergroup comparison of the data is performed with ANOVA and Duncan tests. The level of $P<0.05$ is accepted as statistically significant.

Results

It is detected that ibuprofen application increases Troponin I level ($P<0.05$) and ibuprofen + exercise application increases the creatine and BUN levels ($P<0.05$).

Table 1. Serum biochemical parameters of rats (mean±SE).

Values	Control	Ibuprofen	exercise	Ibuprofen+ exercise
Troponin I µg/L	122,1±9,8^{ab}	132,8±2,8^{a}	109,1±5,9^{b}	114,8±4,9^{ab}
CKMB, U/L	232,8±39,8^{a}	199,5±13,6^{a}	165,8±15,1^{a}	200,5±14,4^{a}
LDH, U/L	722,1±88,7^{a}	834,1±96,2^{a}	664,6±124,6^{a}	595,3±87,3^{a}
ALP, U/L	183,5±33,1^{a}	138,8±18,4^{a}	179±23,2^{a}	144,8±13,6^{a}
ALT, U/L	544,5±5,2^{a}	72,0±19,8^{a}	64,5±10,3^{a}	48,3±7,6^{a}
AST, U/L	107,6±7,0^{a}	181,1±40,8^{a}	180,6±28,5^{a}	176,8±30,8^{a}
GGT, U/L	0,00±0,0^{a}	0,00±0,0^{a}	0,16±0,1^{a}	0,16±0,1^{a}
Creatinin mg/dl	0,24±0,0^{b}	0,28±0,0^{ab}	0,24±0,0^{b}	0,30±0,0^{a}
BUN mg/dl	15,7±0,8^{c}	19,4±1,3^{bc}	21,4±1,3^{ab}	24,4±2,1^{a}

a,b: Different letters in the line are statistically significant (Duncan test, $p<0.05$)

Discussion

It is reported that the sportsmen are prescribed with ibuprofen in clinical usage for sports injuries (Zafonte, 2011).

It is pointed out that anti-inflammatory drugs are commonly used for sports related tendon injuries or tendinoplasty treatment (Tsai et al., 2010).

In this research, while there are no alterations detected in liver damage reagents ($p>0.05$, Table 1), it is detected that ibuprofen application increases heart damage reagents and

ibuprofen + exercise application increases kidney damage reagents ($p<0.05$).

In this research, while it is detected that the observed alterations on creatine –one of the kidney damage reagents- are included in the reference range stated for rats (0,2-0,8 mg/dL, Yazar, 2010), the increase observed on the BUN level is a little bit above that range (6-23 mg/dL, Yazar, 2010).

The nephrotoxic influence of NSAID drugs is known (Ribeiro-Ramaet al., 2011, Van Swelmet al., 2013). In this research, it can be stated that the exercise performed with NSAID (Shephard, 2015) might cause the BUN level to increase.

Serum troponins and Creatine Kinase-MB (CK-MB) are the specific and precision reagents which can detect the early myocardial cell damage and cell deaths.

CK-MB is used for determination of acute myocardial infarcts (AMI) which is still common for cardiac tissue (Harrison, 2004).

It is known that lactate dehydrogenase and then CK are related to the heart injury (Howie-Esquivel, 2008).

It is reported that the traditional usage of lactate dehydrogenase (LD) and creatine kinase (CK) and their iso-enzymes are efficiently used as biological reagent of cardio-toxicity.

It is stated that the efficient usage of these enzymes are limited due to the fact that tissue sensitivity is specific (O'Brien, 2008). However, it is reported that Troponin T or I is superior to all other reagents for diagnosing heart specific AMI (Howie-Esquivel, 2008).

Troponin T and I have two different isoforms which are specific to heart and skeleton muscles (O'Brien, 2008).

The recent researches display that COX-2 inhibitors are related to the thrombotic cardiovascular incidents including myocardial infarcts (MI), sudden cardiac death, ischemic stroke and unstable angina (O'Malley, 2006). Cyclooxygenase (COX)is the basic enzyme for prostaglandin formation and COX inhibition is stated to be primer mechanism for the influences of NSAIDs (Deniz, 2000).

In Denmark, between 1997 and 2006, the most commonly used NSAID is ibuprofen, with a rate of 23%. During the traditional 1 week long treatment, an increased risk is detected in diclofenac and ibuprofen.

Due to the fact that the death risk and recurrent myocardial infarcts (MI) are related to the NSAID usage during the short and long term NSAID treatments, it is stated that NSAID usage should be limited for the cardiovascular safety of myocardial infarcts (MI) patients (Olsen et al., 2011). In this research, it is detected that Troponin I – the specific reagent for heart damage – is higher in ibuprofen group than the exercise group (Table 1).

However, the fact that the Troponin I levels of ibuprofen group and control group are the same ($P>0.05$) and there is no alternation observed on CK-MB mass levels – another specific heart damage reagent – shows that ibuprofen does not have a detrimental influence on heart. In a study carried out in Denmark, it is found out that ibuprofen usage is related to coronary death or nonfatal increase in MI risk (Fosbøl et al., 2010).

It is stated that NSAID drugs can cause heart damage (Ray et al., 2009, Olsen et al., 2011, EMEA, 2013). In another study carried out Denmark, it is reported that ibuprofen usage is related to cardiovascular death and coronary death risk dependent on low doses and at the same time naproxen usage is related to abort risk dependent on dose in Cox models.

Therefore, considering the existing results and accumulated proofs in this point, it is reported that naproxen might be a much safer alternative than ibuprofen for the patients requiring NSAID treatment (Olsen et al., 2013).

In the study carried out by Mahmod et al in 2010, it is reported that acute inferior myocardial infarcts develop in the NSAID type drug treatments.

In the research on the treatment of sports injuries, it is reported that ibuprofen inhibits the healing process of tendon in terms of molecular mechanisms(Tsai et al., 2010).

In another research, it is stated that some selective NSAIIs are related to the risks of MI and acute sudden deaths (Cheetham et al., 2008).

Conclusions

Consequently, the ibuprofen intake during exercise does not influence the heart damage reagents however it is necessary to be careful against possible kidney damages.

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