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The Permanent Effect of Indomethacin Drug on Body and Some Organs Weight in Male Wister Rats

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Summary

The biology department's animal house in college of sciences at Iraq's AL-Qadisiyah University hosted this study. It's part of Iraq's AL-Qadisiyah University, to demonstrate that the kidneys and Liver were subjected to oxidative stress from reactive oxygen species, which led to harmful consequences of the indomethacin medication on the body and the weight of the organs. 40 male Wister rats, aged (2 - 3) months, weighing between 200 and 300 grams. Four groups of 10 rats. Control, 5 mg/kg, 7 mg/kg, and 10 mg/kg of indomethacin were given for 21 days to the groups.

After the experiment, the animals were killed. The results demonstrated a substantial rise in body weight ($p<0.05$) in all groups following the experiment compared to the initial weight, although a significant reduction in body weight ($p<0.05$) in each of the groups that received the 5 mg/kg, 7 mg/kg, and 10 mg/kg treatments compared to the control group during the course of 21 days.

When compared to the rats in the control group, the relative liver mass of the rats that were administered doses of indomethacin at dosages of 5, 7, and 10 mg/kg rose considerably ($p< 0.05$). The group that received 10 mg/kg saw the greatest percentage rise. The control group and those receiving 5, 7, or 10 mg/kg indomethacin had similar kidney weights ($p< 0.05$).

In conclusion, indomethacin causes an increase in body weight, increase in liver weight, but the kidney weight remained the same.

Key word : Indomethacin, weight, liver, kidney

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التأثير الدائم لعقار الإندوميتاسين على الجسم ووزن بعض الأعضاء في ذكور الجرذان

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الخلاصة

الدراسة الحالية تم تنفيذها في البيت الحيواني في قسم علوم الحياة / كلية العلوم / جامعة القادسية، ليظهر أن الكبد والكلية عرضة لأجهاد التأكسدي من جذور الاوكسجين الحرة، ويؤدي الى عواقب ضارة لعلاج الاندوميثاسين على الجسم ووزن الاعضاء.

تم اختيار اربعين جرذ من الذكورتتراوح اعمارهم (2-3) اشهر والوزن (200-300) غم ، قسمت الحيوانات الى اربع مجاميع (10 جرذان لكل مجموعة) . المجاميع هي السيطرة ، 5ملغم/كغم ، 7ملغم/كغم و 10 ملغم/كغم اندوميثاسين لكل كيلوغرام من جسم الحيوان، واستمرت التجربة لمدة 21 يوم.

بعد انتهاء وقت التجربة ، قتلت الحيوانات . اظهرت النتائج زيادة معنوية ($p<0.05$) في وزن الجسم في كل المجاميع بعد انتهاء التجربة مقارنة مع الوزن البدائي ، وانخفاض معنوي ($p<0.05$) في الجرذان المعاملة بالاندوميثاسين 5 ملغم/كغم ،7ملغم/كغم ، و 10 ملغم/كغم خلال مدة التجربة.

لم يظهر الوزن النسبي للكلية اي اختلافات معنوية ($p<0.05$) في كل المجاميع ، السيطرة ،5 ،7، و 10 ملغم/كغم اندوميثاسين . بينما اظهر الوزن النسبي للكبد زيادة معنوية ($p<0.05$) في الجرذان المعاملة بالاندوميثاسين 5، 7، و 10 ملغم/كغم مقارنة مع مجموعة السيطرة ومجموعة 10 ملغم/كغم اظهرت اعلى نسبة.

في الاستنتاج، الاندوميثاسين يسبب زيادة في وزن الجسم ، زيادة في وزن الكبد ، لكل وزن الكلية لم يتغير.

الكلمات المفتاحية: إندوميثاسين ، الوزن ، الكبد ، الكلى

Introduction

The nonsteroidal anti-inflammatory medicine known as indomethacin is a dimethyl indole derivative. It believed that indomethacin pharmacological impact was mediated by the powerful and nonselective inhibition of the COX enzyme. This is true even if the pharmacological effects of indomethacin are still not fully understood (Katary, 2017).

The kidneys are responsible for the elimination of the vast majority of drugs, as well as the substances that were produced when these medications were metabolized. The capacity of indomethacin to slow down the glomerular filtration rate and increase the amount of urine that is evacuated may cause a considerable loss in renal function, as reported by de Borst et al. (2012).

On the other hand, the liver is the principal organ that is responsible for the metabolism of several medications .Relatively little is known about the causes and

effects of nonsteroidal anti-inflammatory medicines (NSAIDs) on the enzymes that are located in the liver. It was showed that the majority of NSAIDs, including indomethacin in particular, increased ALT, AST, and ALP activity as well as bilirubin levels (Sriuttha *et al.*, 2018)

Materials and Methods

Animals

Forty adult male Wister rats (Rattus norvegicus) average weight was (200-220 gm.) and aged (2-3 months), these animals were get from the animal house of the Faculty of Sciences/University of Babel / Iraq. Animals placed in plastic cages with wood chip bedding under controlled and standardized conditions of temperature (22-24 ˚C) and light/dark (12/12 h) cycles, feed with standard rodent diet and water.

Chemicals

Indomethacin capsule purchased from pharmaceutical (MEDOCHEMIE / CYPRUS) 25mg/kg concentration, phosphate buffer saline (PBS) (Chem Cruz / China).

Experimental Design

Animals were conducted in the animal house of the Faculty of the Science/ University of Al- Qadisiyah, randomly allocated into Four groups (Each group make of 10 male Wister Rats for 21 days

• Control group gives 3 ml of P.B.S. Orally and daily for 21 days.

• Second group gives suspension of (5 mg/kg of indomethacin powder dissolves in P.B.S solution). Orally and daily for 21 days

• Third group gives suspension of (7 mg/kg indomethacin powder dissolves in P.B.S solution) Orally and daily for 21 days.

• fourth group gives suspension of (10 mg/kg indomethacin powder dissolved in P.B.S solution) .Orally and daily for 21 days .

Measurement of the changes in weight

The animals weight for each group were measured ,and the average calculated before the experiment began and after its end by electronic balance to see the changes that occured in the weight of animals through the experiment , the weight of organ also taken and relative organ weight.

Calculation of the Relative weight of Liver and Kidney

The weight of the organs was calculated for each group after the liver and kidneys taked out of the animals' bodily cavities. Organs' relative weights for kidneys and liver surgically removed after three weeks, and their absolute organ weights calculated using the mass in grams. Patrick-Iwuanyanwu (2014) performed a computation, the relative organ weights of each animal are showed in the below:

Relative organ weight = Absolute organ weight (g)/ Body weight of rat on sacrifice day X 100

Data Analysis

The F-test was used to compare the control group with the treatment group after the results were analyzed using (Mean Standard Error). Using a one-way analysis of variance (ANOVA) and the test (Tukey's multiple comparisons test) at a probability threshold of 0.05. The differences were statistically different from one another. ($p < 0.05$). Statistical analysis were did using Excel program (2010), (Argyrous, 2009)

Results

Effect of Indomethacin on Body Weight

The results in(table 1) showed a significant increase ($P<0.05$) in the body weight of control group which gave P.B.S and treated groups with 5mg/kg ,7mg/kg and 10 mg/kg of indomethacin after experiment compared with the beginning of experiment during 21 day. Also the result for current study showed significant increase ($P<0.05$) in control after experiment than in treated groups with 5mg , 7mg and 10 mg indomethacin during 21 day . Treated group with 5mg indomethacin illustrated significant increase ($P<0.05$) compared to 7mg/kg and 10 mg/kg of indomethacin after experiment, also 7mg indomethacin have significant increase ($P<0.05$) in body weight compared to 10 mg/kg indomethacin during the same period**.**

Table 1: Effect of Indomethacin at dose 5,7,10 mg/kg on total body weight of male Wister rat during 21 day.

Groups	Total body weight	
	Before exp.	After exp.

control	210.9±3.92Aa	282.2±12.8Ab
5mg indomethacin	210.3±3.52Aa	257±10.08Bb
7mg indomethacin	211.8±6.32Aa	249±9.22Cb
10mg indomethacin	211.8±5.02Aa	240±7.8Db
LSD (P<0.05)	7.09	

(Different capital letters denote to the significant difference LSD (P<0.05) vertically, Different small letters denote to the significant difference LSD (P<0.05) horizontally, mean ±SE, No. of animals= 10 for each group)

Effect of Indomethacin on Liver relative weight in treated groups.

In comparison to the control group, our results demonstrated a substantial rise ($p< 0.05$) in the indomethacin-treated groups given 5 mg, 7 mg, and 10 mg/kg over the course of 21 days, but neither a significant difference nor a minor change in the group given 7 mg. After 21 days, 10 mg was higher ($p< 0.05$) than 5 mg (table 2).

Effect of Indomethacin on Kidney relative weight in treated groups

The findings presented in (table 2) demonstrated that there was no significant differences ($p< 0.05$) or only a slight difference between the control group and the groups that were given 5 mg and 10 mg of indomethacin. Furthermore, the results demonstrated that there was no significant differences ($p< 0.05$) between the control group and the group that was given 7 mg of indomethacin, however, there was a significant increase ($p <0.05$) in the group that was given 7 mg compared to 5mg, 10mg during 21 days.

Table (2) Effect of Indomethacin at dose 5,7,10 mg/kg on relative organs weight of male Wister rat during 21 day

Groups	liver	kidney
control	3.90±0.16A	0.832±0.04AB
5mg indomethacin	4.33±0.37B	0.770±0.06A
7mg indomethacin	4.70±0.15BC	0.843±0.06B

10mg indomethacin	4.90±0.16C	0.766±0.04A
LSD (P<0.05)	0.38	0.069

(LSD (P< 0.05), mean ±SE, 10 animals per group , different letters denote to the significant difference (p<0.05))

Discussion

This finding was agree with (Almayale, 2019) who showed increase in the body weight after treated rat with indomethacin . Clearance studies in humans and in vitro microperfusion of isolated nephron segments show that PGE2 reduces sodium reabsorption in the thick ascending limb of the loop of Henle (Kaojarern *et al* .,1983).

NSAIDs reduce tubular PGE2, which increases body weight by retaining water, salts, and liquids (Brater *et al*., 2001). Chronic high dose NSAID therapy can cause massive weight gain, these symptoms can be explained by increase in plasma volume and physiological increase in cardiac output due to active sodium and water retention (Mohammed *et al*., 2013). Nies (1988) proved reduce sodium excretion and blunt the diuretic effect of loop diuretics, thus producing or exacerbating edema.

But the decrease in body weight (Khan *et al*., 2019) showed no significant difference in food and water intake between control and treated rats with indomethacin, and the small decrease in the body weights that retained to side effect caused by indomethacin to gastrointestinal tract. It caused morphological change like bubbles and ulceration as we seen during dissection by optical eye, and that agreed with (Al-Maiali, 2009).

Relative liver weight also effected by indomethacin , according to Al-Mayali (2019), substantial intra-hepatic bleeding and blood pooling in the liver caused liver mass index ratio in indomethacin-treated liver rats to slightly rise , that is compatible to our result and with (Al-Jasabi & Abdullah, 2013). As a result, the liver appeared darker than in the other groups as we observed . Hepatocytes' boundaries and their normally shaped nuclei were gone, some nuclei accumulated without borders, whereas blood-filled sinusoids choked them, other examples include portal and central veins that have lost some of their lining epithelium and

are clogged with blood, Koçkaya et al. (2010) this was evidence for increase weight .

On the other side, Al-Mayali et al. (2019) observed no significant difference between the control and treated groups, which matches our results. The 7 mg indomethacin group's relative kidney weight increase may be due to fat and cell debris in invading cells.

Indomethacin has been demonstrated to cause renal atrophy, or kidney shrinkage, via many mechanisms. NSAIDs and indomethacin may break prostaglandin , that renal blood flow depend on it , the narrowing of the kidneys' blood vessels, a decrease in renal blood flow and glomerular filtration rate (Turull *et al.*, 2001), which may lead to acute renal failure (Brater *et al.*,1985), and finally renal atrophy. Second, indomethacin may directly damage kidney cells, causing inflammation and scarring. Toto et al. (1986) referred in a study found that this may shrink the kidney and compromise its function, that was the same as observed in our study.

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