Original Research Article

Adverse effect of Diclofenac sodium on weight and volume of kidneys of adult swiss albino mice

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Abstract

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most common pain relief medicines in the world. Every day lots of people use them for relief from headaches, sprains, arthritis symptoms, and other daily discomforts. In addition to reducing pain, NSAIDs also lower fever and reduce swelling. NSAIDs block the effects of enzymes, specifically Cox-1 and Cox-2 enzymes which play a key role in making prostaglandins leading to less swelling and less pain. But there are risks and side effects with NSAIDs which includes side effects associated with GIT, CVS and Kidney. In this study, adverse effect of Diclofenac sodium, which is one of the most commonly used NSAID, on weight and volume of kidneys of adult Swiss albino mice is demonstrated. It is studied in both, therapeutic as well as more than therapeutic doses, keeping in mind its inappropriate use because of over the counter availability. It is a case control study. In this, adult Swiss albino mice were divided into four groups; one group served as control (Group D) while each of the remaining three groups were given Diclofenac sodium, 1 mg/ Kg(Group A); 2mg/ Kg (Group B) and 4mg/ kg (Group C) body weight of, for 15 days. All animals were kept in proper living conditions necessary for optimal growth. Weight of animals was recorded before giving medicine i.e. day 1 and again on day 15. Then animals were sacrificed and their kidneys were extracted. Weight and volumes of kidneys were recorded and change pattern in four sets was observed. This short term study showed one of the potential side effects of Diclofenac sodium in the form of increase in weight and volume of kidneys due oedematous changes and cellular toxicity.

Key Words: NSAIDs, Side effects, weight and volume, kidney.

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INTRODUCTION

Non steroidal anti inflammatory drugs (NSAIDs) are widely used analgesics, anti inflammatory and anti-pyretic drugs. Diclofenac is unique among the NSAIDs, in that it possesses three possible mechanisms of action i.e. Inhibition of arachidonic acid and COX system, Inhibition of lipo-oxygenase pathway and inhibition of arachidonic acid release and stimulation of its reuptake. It is metabolized in liver and excreted in the urine (65%) and bile (35%). The usual daily dosage is 100 to 200 mg given in several divided doses. It produces side effects in about 20% of patients from which about 2% discontinue the therapy. Most common side effects are gastro intestinal; others include hepatic toxicity, CNS effects, rashes, allergic reaction, fluid retention and oedema. Kidney is an important target site for untoward effect of Diclofenac in humans as well as animals. Toxic effects are usually reported after the drug has been used for a significant period of time[1,2]. In a short term study with therapeutic as well as higher than therapeutic doses of Diclofenac sodium, A. D. Kannamwar *et al* (2017) already studied a potential toxic role of the drug in the form of anorexia and depression which results in changes in behaviour and food habits of animals and lack of weight gain[3]. Farag MM *et al* (1996) studied the effects of two NSAIDs, Ibuprofen and Diclofenac on the Gentamicin induced nephrotoxicity in rats. They noted increase in total renal phospholipids in cortex accompanied by a significant decrease in cortical Na+K+ ATPase activity, reduction of body weight and increase in

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weight of kidney, serum creatinine and urea nitrogen indicating potentiation of Gentamicin induced nephrotoxicity by prolonged treatment with Ibuprofen or Diclofenac sodium.[4] Present study has therefore been done to study the adverse effect on weight and volume of kidneys of adult Swiss albino mice following administration of three different doses of Diclofenac sodium.

MATERIAL AND METHODS

Present study is a case control study.

MATERIAL

- Swiss Albino mice of 12 weeks of age
- Diclofenac sodium: Tablet Voveron-D dispersible form (Novartis India Limited) containing Diclofenac free acid 46.5 mg equivalent to Diclofenac sodium IP 50 mg.
- Normal Saline for perfusion and distilled water for reconstitution of Diclofenac sodium solution.
- Commercial rat food with Ingredients as follows: Wheat: 20 kg; Gram: 5 kg; Soyabean: 5 kg and Corn: 1 kg
- Disposable insulin syringe (1 ml capacity, graduated to 50 segments) and feeding tubes for oral administration of Diclofenac solution in adult mice.
- Weighing machine (electronic single pan type with sensitivity up to 1 mg).
- **Normal Saline** for perfusion and **distilled water** for reconstitution of Diclofenac sodium solution.
- **Injection Thiopentone Sodium** (Neon Lab. Ltd., batch-172151 /Jun 2000 Mfg) for euthanasia.
- **Disposable insulin syringe** (1 ml capacity, graduated to 50 segments) and **feeding tubes** for oral administration of Diclofenac solution in adult mice and **hypodermic needle** (25 – 27 gauges) for giving intraperitoneal injection of Thiopentone for euthanasia.
- **Weighing machine** (electronic single pan type with sensitivity up to 1 mg).

METHODS

- Housing: Adult Swiss Albino mice (males and females separate) were housed in group of five each. The animals were exposed to standard light and dark sequences maintaining proper living conditions necessary for optimal growth with strict regulation of temperature and hygiene. The animals were fed with commercial rat food with cold hygienic drinking water ad libitum.
- Animals were numbered and weighed on the first day before oral administration of calculated dose of Diclofenac sodium. They were segregated in four groups A, B, C and D.
- Procedure of oral administration: With the help of feeding tubes, animals were given solution of Diclofenac sodium for 14 days as per following: Group A was given 1 mg/kg; Group B was given 2 mg/kg; Group C was given 4 mg/kg of body weight and Group D was given equal volume of sterile distilled water
- Weight was again recorded on day 15th. These two parameters (weighing on 1st day and on 15th day) were used in analyzing weight change patterns in four sets of animals.
- Rearing: All mice were kept in properly labelled cages for 14 days.

Sacrifice of animals[5]: On 15th day animals of all the four groups were sacrificed for collection of required tissues. Injection Thiopentone sodium in a dose of 50 mg/kg b.w. was given intraperitoneally for euthanasia. Animals were infused with normal saline and required tissues were dissected out.

Dissection and collection of tissues: Prior to dissection a perfusion set was arranged with 10 ml solution of normal saline. After euthanasia with Thiopentone sodium animal was placed with its back on wax tray. A perfusion was set with normal saline through an intra-cardiac catheter till tissues were blenched (a nick was made in the inferior vena cava for this purpose). It was followed by perfusion with 10% formal saline. After identification, both kidneys were removed for further processing. Volume and weight of kidneys of both sides was recorded..

Qualitative Study: Kidneys were inspected after dissection of animals and their colour and size were reported in all four groups.

Quantitative Study: Records of morpho-metric analysis of weight and volume of each kidney of all animals of all four groups were maintained

Statistical Analysis

The statistical significance was obtained by applying 'ANOVA' and 'Post-hoc tests'. Since we had 4 groups of animals, the result of the weight chart was compared amongst different groups by 'Multiple comparison' after obtaining the 'Descriptive Data'. For 'Multiple comparison' we used 'Variable 1' for the group under consideration and 'Variable 2' for remaining groups with which variable 1 is to be compared and accordingly data were recorded in different tables for statistical analysis.

OBSERVATION AND RESULTS

Findings on Dissection

On dissection of group 'D' (controls), kidneys were seen as reddish bean shaped organs embedded in a layer of para-renal adipose tissue on either side of spinal column. Cut surface of coronal section of kidney showed outer granular reddish-brown cortex and inner pale grayish medulla with radial striations. On dissection, group 'A' (1mg/ kg b.w.) animals did not show much difference in gross appearance of the organs compared to group 'D'. Kidneys of animals of group 'B' (2mg/ kg b.w.) appeared pale externally as compared to group 'D'. Viscera of animals of group 'C' (4mg/ kg b.w.) were looking very unhealthy on dissection. Kidneys were paler and somewhat bigger in size.

Weight and Volume Of Kidneys

After isolating from the body the kidneys were subjected to morphometric analysis. We recorded their weights and volume in all four groups and tabulated the data as follows

Table 1: Volume and weight of kidneys **(a):** group 'a'

Sr No	Wt of kidney (in mg)			Volume of kidney (in ml)			Sr No	Wt of kidney (in mg)			Volume of kidney (in ml)		
	Rt	Lt	Mean	Rt	Lt	Mean		Rt	Lt	Mean	Rt	Lt	Mean
1	168	165	166.5	0.16	0.17	0.165	9	159	165	162	0.16	0.17	0.165
2	165	168	166.5	0.16	0.16	0.16	10	167	162	164.5	0.16	0.16	0.16
3	169	162	165.5	0.16	0.16	0.16	11	172	165	168.5	0.16	0.15	0.155
4	161	159	160	0.15	0.16	0.155	12	161	162	161.5	0.16	0.16	0.16
5	168	157	162.5	0.16	0.15	0.155	13	163	164	163.5	0.16	0.15	0.155
6	157	162	159.5	0.15	0.15	0.15	14	160	158	159	0.16	0.15	0.155
7	167	167	167	0.15	0.16	0.155	15	162	165	163.5	0.17	0.18	0.175
8	167	159	163	0.15	0.16	0.155							

Mean weight of kidney of experimental mice: 163.53mg. Mean volume of kidney of experimental mice: 0.15220 ml=152.20µl

Table 1 (B): GROUP 'B'

Sr No	Wt of kidney (in mg)			Volume of kidney (in ml)			Sr No	Wt of kidney (in mg)			Volume of kidney (in ml)		
	Rt	Lt	Mean	Rt	Lt	Mean		Rt	Lt	Mean	Rt	Lt	Mean
1	167	180	173.5	0.16	0.17	0.165	9	171	180	175.5	0.15	0.16	0.155
2	170	168	169	0.16	0.17	0.165	10	164	169	166.5	0.17	0.16	0.165
3	174	168	171	0.17	0.16	0.165	11	168	179	173.5	0.15	0.16	0.155
4	158	170	164	0.16	0.16	0.16	12	170	164	167	0.16	0.16	0.16
5	172	165	168.5	0.17	0.15	0.16	13	174	166	170	0.15	0.15	0.15
6	168	166	167	0.15	0.16	0.155	14	179	194	179	0.15	0.16	0.155
7	167	170	168.5	0.16	0.17	0.165	15	172	165	168.5	0.15	0.15	0.15
8	159	172	165.5	0.17	0.16	0.165							

Mean weight of kidney of experimental mice: 169.80 mg. Mean volume of kidney of experimental mice: 0.17313ml=173.13µl

Table 1 (C): GROUP 'C'

Sr No	Wt of kidney (in mg)			Volume of kidney (in ml)			Sr No	Wt of kidney (in mg)			Volume of kidney (in ml)		
	Rt	Lt	Mean	Rt	Lt	Mean		Rt	Lt	Mean	Rt	Lt	Mean
1	181	195	188	0.17	0.17	0.17	9	167	172	176.5	0.17	0.15	0.17
2	172	169	175.5	0.17	0.17	0.16	10	172	167	178	0.17	0.17	0.17
3	171	173	172	0.17	0.15	0.155	11	172	174	173	0.17	0.15	0.16
4	173	167	170	0.16	0.15	0.145	12	167	170	172	0.16	0.17	0.165
5	163	172	174	0.15	0.14	0.155	13	165	181	173	0.17	0.17	0.17
6	159	173	176	0.15	0.16	0.155	14	167	169	172.5	0.15	0.17	0.16
7	169	168	182	0.14	0.17	0.17	15	159	172	165.5	0.15	0.16	0.155
8	166	172	176	0.17	0.17	0.16							

Mean weight of kidney of experimental mice: 174.93mg, Mean volume of kidney of experimental mice: 0.18767ml=187.67µl.

Table 1(D): GROUP 'D' **[Control group]**

Sr No	Wt of kidney (in mg)			Volume of kidney (in ml)			Sr No	Wt of kidney (in mg)			Volume of kidney (in ml)		
	Rt	Lt	Mean	Rt	Lt	Mean		Rt	Lt	Mean	Rt	Lt	Mean
1	161	159	160	0.17	0.18	0.175	9	160	162	161	0.15	0.16	0.155
2	166	163	164.5	0.16	0.15	0.155	10	163	162	162.5	0.16	0.15	0.155
3	160	161	160.5	0.16	0.16	0.16	11	163	165	164	0.16	0.16	0.16
4	160	165	162.5	0.16	015	0.155	12	164	160	162	0.15	0.16	0.155
5	162	161	161.5	0.15	0.16	0.155	13	163	159	161	0.16	0.17	0.165
6	162	162	162	0.14	0.16	0.15	14	164	160	162	0.15	0.15	0.15
7	160	166	163	0.16	0.15	0.155	15	166	163	164.5	0.14	0.16	0.15
8	161	159	160	0.15	0.16	0.155							

Mean weight of kidney of experimental mice: 162.0667mg, Mean volume of kidney of experimental mice: 0.15113ml=151.13µl The weights of the kidneys were statistically analysed in four groups as follows:

Table 2: (A): Descriptive data weight of kidneys

Group	No. of samples	Mean of Weight of kidney (milligrams)	Standard Deviation
A	15	163.53	2.8814
B	15	169.80	4.0567
C	15	174.93	5.2094
D	15	162.06	1.4744

Table 2B: Multiple comparisons

Variable- 1	Variable- 2	Difference between means of variable -1 and variable- 2	P- Value
Group-A	Group-B	6.27	<0.05
	Group-C	11.4	<0.05
	Group-D	1.47	0.279*
Group- B	Group-C	5.13	<0.05
	Group-D	7.74	<0.05
Group- C	Group-D	12.87	<0.05

P-value <0.05 -Statistically significant. * Value statistically insignificant

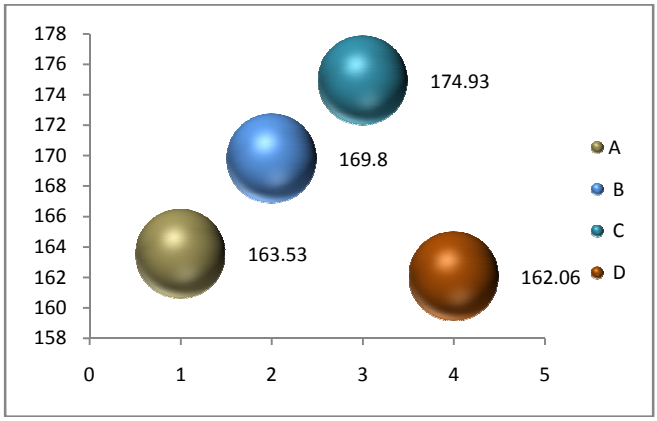

Figure 1: Mean weight (in mg) of kidney in different groups
A: 1mg/kg b.w. B: 2 mg/kg b.w. C: 4mg/kg b.w. D: control

Table 3 A: Descriptive data volume of kidneys

Group	No. of samples	Mean of volume of kidneys (micro litres)	Standard Deviation
A	15	152.20	4.1438
B	15	173.13	6.4903
C	15	187.67	4.3534
D	15	151.13	6.4461

Table 3 B: Multiple comparisons

Variable- 1	Variable- 2	Difference between means of variable -1 and variable- 2	P- Value
Group-A	Group-B	20.93	<0.05
	Group-C	35.47	<0.05
	Group-D	1.07	0.74*
Group- B	Group-C	14.54	<0.05
	Group-D	22	<0.05
Group- C	Group-D	36.54	<0.05

P-value <0.05- Statistically significant. * Value statistically insignificant

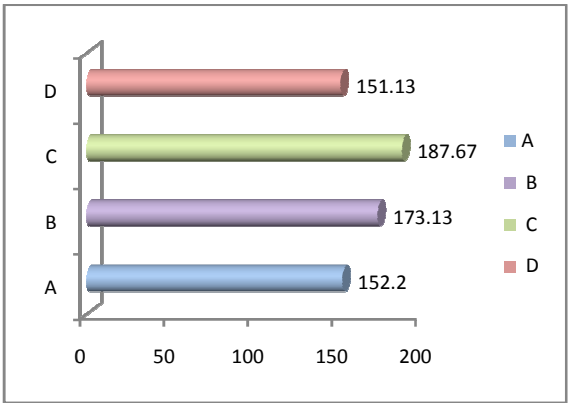

Figure 2: Mean volume (in µl) of kidneys in different groups
A: 1mg/kg b.w. B: 2 mg/kg b.w. C: 4mg/kg b.w. D: Control

DISCUSSION

An attempt of correlation of human tissue damage by NSAIDs was made from the findings in different experimental animal models like mice, rats, ducks, rabbits, guinea pigs, dogs and different species of monkeys. In present study Diclofenac sodium was used, among the NSAIDs, as a study material and Swiss albino mice as animal model. Regarding routes of administration, oral route of administration was used in our study as this route is usually preferred in patients requiring long term analgesic therapy but different routes of administration were used by different researchers. Waggan I A (2004)[7] and Yasmeent T *et al* (2007)[8] used oral route similar to us while Turan C *et al* (1998)[9], Aydin G I *et al* (2003)[10] and Ahmed F A *et al* (2005)[11] used intra-muscular route; Taib NT *et al* (2004)[12], Ragbetli C *et al* (2009)[13] used intraperitonial route and Yapar K *et al* (2008)[14] used subcutaneous route for administration of Diclofenac sodium. In our study Diclofenac sodium was given in three different doses 1 mg/kg b.w. in group 'A', 2 mg/kg b.w. in group 'B' and 4 mg/ kg b.w. in group 'C 'in three experimental sets of animals. Group D comprised control animals in which equal volume of distilled water was used. Different doses of Diclofenac were used by different workers. Turan C *et al* (1998) [9], Waggan I A (2004)[7], Taib NT *et al* (2004)[12], Ahmed F A *et al* (2005)[11], Yasmeent T *et al* (2007)[8] and Ragbetli C *et al* (2007)[13] have used doses ranging from 1 to 2 mg/kg b.w./day. Aydin G I *et al* (2003) [10] used doses of 50, 100 and 150 mg/ kg b.w. /day to study acute toxic effects of higher doses of Diclofenac and Yapar K *et al* (2008)[14] used three different doses of Diclofenac i.e. 2.5 mg, 5 mg and 10 mg per kg b.w. to assess biochemical markers of toxicity. According to these authors and Committee for veterinary medicinal products (2003)[6], 1 to 2 mg/ kg b.w. is the range of therapeutic dose of Diclofenac sodium in animals. They commented doses higher than 2.5 mg/kg b.w. as toxic in mice though lesser doses were also found to cause minor structural changes. In our study the higher dose used (in group C) was to determine the degree of damage, as over the counter and unsupervised use of Diclofenac is a common practice among the general population. Mean weight and volume of kidneys were tabulated for animals of all 4 groups. Weight and volumes of kidney of Group 'A' (Table I-A; mean 163.53 mg and mean 152.20µl) were nearly same as that of control group (Table I-D; mean 162.07 mg and mean 151.13µl). However they were more in group 'B' (Table I-B; mean 169.80 mg and mean 173.13µl) and group 'C' (Tablet I-C; mean 174.93 mg and mean 187.67µl). The difference in weight and volume of kidneys of group 'B' and 'C' with group 'D' was statistically significant (Table II and III; fig 1 and 2). The increased weight and volume of kidney seems to have resulted due to oedema and water logging as suggested by swollen, pale looking kidneys in group 'C', these findings are similar to findings of Cotran R S *et al*, 1999[15]. But they are not in conformity with

Schwarz A *et al* (1988) who had reported functional and histopathological dysfunctions but radiologically no change in sizes of kidneys[16]. In conjunction with our study Walter H. Horl (2010) described effects of Non steroidal anti inflammatory drugs on the kidneys. He described that, NSAIDs exert anti-inflammatory, analgesic and anti-pyretic effects through the suppression of prostaglandin (PG) synthesis, by inhibiting the enzyme cyclooxygenase (COX). PGs regulate a wide variety of renal functions. PGE2 is considered to be mainly a tubular PG and PGI2a vascular PG. However, renal arterioles, tubules, medullary interstitial cells, and mesangial cells are able to produce both PGE2 and PGI2. PGE2 regulates sodium and chloride transport in the loop of Henle and modulates water transport and renal medullary blood flow. PGI2regulates renal vascular tone, GFR and renin release In a person with normal renal hemodynamic parameters, PGs do not play a dominant physiologic role in maintaining renal blood flow and GFR. Selective COX-2 inhibitors were developed to produce the beneficial effects of NSAIDs, but spare the COX-1-mediated adverse events. However, COX-2 appears to be associated with renal vascular tissues and podocytes and has been implicated as the dominant COX at the macula densa and in the medullary interstitium. The identification of constitutive COX-2 in the human kidney and the recognition of the profound effects of PGs on renal homeostasis may indicate that COX-2 inhibitors have the same potential for adverse renal effects as traditional NSAIDs. Therefore, the same precautions in patients at risk for adverse renal effects probably apply to both the nonselective NSAIDs and COX-2 selective inhibition.Sodium retention is a well-described feature of all nonselective NSAIDs due to inhibition of COX-2 by these drugs. Therefore, it is predictable that COX-2 selective inhibitors may have similar effects. In rats, rofecoxib, celecoxib, diclofenac and flurbiprofen but not meloxicam given orally once daily for 4 days caused a significant decrease in urinary sodium and potassium excretion as compared to placebo. NSAIDs administered orally to rats for four days had a transient and time dependent effect on the urinary excretion of electrolytes independent of COX-2-COX-1 selectivity. Both coxibs and traditional NSAIDs can procedure impairment of kidney function, sodium retention with hypertension and peripheral edema, hyperkalemia and papillary necrosis[17]. In concordance with our study, C. M. Modi *et al* (2012) also described how Diclofenac, a NSAID widely used in human and veterinary medicine, causes deposition of urates crystals in kidneys, liver, heart and spleen. Additionally it causes cytotoxicity more extensively in drug metabolizing cells than to non metabolizing cells in in-vitro study using rat and human primary culture hepatocyte. They said that apart from these facts, the exact pathophysiology of cytotoxicity remains unexplained. They also mentioned histopathologic changes in the form of Cloudy swelling and hydropic degeneration in the tubular epithelial cells of the kidney tissue. Necrosis, peritubular lymphocyte infiltration, stromal fibrous tissue proliferation and hyperemia were observed in rats. In the liver and kidney tissue of the high dose group, these changes were rather widespread and intensive, as compared to the group given a low dose[18].

CONCLUSION

Thus our short term study with therapeutic as well as higher than therapeutic doses of Diclofenac sodium reflects a potential toxic role of the drug. Gross examination of kidneys revealed Increased weight and volumes of the kidney which appears to be reactionary due to vascular congestion, oedema and possibly by mild hydronephrotic changes caused by partial blockage of tubules by necrotic debri and inflammatory reaction.

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