RESEARCH PAPER

Evaluation of Dose-Dependent Toxicity of Different Classes of NSAIDs on Rodents with Special Reference to Chromosomal Aberration

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ABSTRACT

This study aim to evaluate of dose-dependent toxicity of different class of NSAIDs on rodents with special reference to chromosomal aberration. Mice were divided into six groups: group 1 was administration with normal saline and groups 2,3,4,5 and 6 were oral administration using gavages feeding needle and 1 ml syringe with single dose of Aspirin, Diclofenac, Paracetamol, Ibuprofen and Disprin at concentration of 1 and 2 mg/kg BW respectively for 10 days. On day 11 mice were euthanized by cervical dislocation. Cytogenetic changes in mice due to the effect of NSAIDs. The observed chromosomal aberration were the form of fragment, dicentric, double minutes, single minutes, ring, PCD, isochromatide break, acrocentric association and tricentric. The study demonstrated that NSAIDs affects the bone marrow cells where it causes some aberration in the chromosomes. The study concluded that there is a dose dependent detrimental effect of an intake of NSAIDs and also confirmed that by the increase of the concentration of the NSAIDs the toxicity increased in genomic.

Keywords: NSAIDs, Aspirin, Diclofenac, Paracetamol, Ibuprofen, Disprin, Chromosome aberration.

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INTRODUCTION: The Non-steroidal anti-inflammatory drugs are a group of chemically heterogeneous medications widely used to control acute and chronic pain and inflammation. They are medications with analgesic (pain killing) and antipyretic (fever reducing) effects, and in higher doses anti-inflammatory effect that reduces inflammation (swelling) [1]. Most NSAIDs are nonselective and inhibit both Cox-1 and Cox-2 [2]. More than 100 million NSAIDs are prescribed throughout the world [3]. The major effect of all NSAIDs is to decrease the synthesis of prostaglandins by reversibly inhibiting cyclo-oxygenase (COX) enzymes.

The present study aims to evaluate the cytogenetic damage induced in bone marrow cells of mice treated with the different classes of NSAIDs.

MATERIALS AND METHODS

Study conduct

The study was conducted in Jawaharlal Nehru Cancer Hospital and Research Centre, Idgah Hills, Bhopal-462001 (M.P.) India(CPCSEA Registration Number-CPCSEA/a/500/2001)

Experimental design

Total forty four healthy of mice (*Swiss albino* mice, C_{57}BL, Agouties weight 25-30gm) Animals were divided into six groups of four animals each group. **Group1**

(control) was administrated orally water without drugs. **Group 2, 3, 4, 5 and 6** were administrated orally with single doses of Aspirin, Diclofenace, Paracetamol, Ibuprofen and Disprin at different concentration of 1mg & 2mg/kg BW respectively for 10 days on 11 day experimental mice were scarified by cervical dislocation.

Chromosomal Aberration Assay

Before Euthanasia Colchicine to be injected peritoneally to arrest metaphases and after 1.30 hrs cervical dislocation performed and Bone marrow was taken out from Femur. Needle is inserted through cut end of long bone and 1 ml of Normal saline was flushed inside the bone and flushed repeatedly to collect maximum bone marrow cells in the test tube, later on centrifuged at 1200 rpm for 10 min. followed by hypotonic treatment by KCl and fixation by Carnoys. Slides were stained with Giemsa (2%) for 5-7 mins & rinsed in tap water. The slides were dried & mounted in DPX mounted & observed under light microscope. The aberrations were scored for 30 metaphases for each animal at 40X and photographed at 100X [4].

Metaphase scoring

Per animal 30 metaphase spreads were examined microscopically for chromosomal aberrations. Only well spread chromosomes were selected for scoring. All metaphase spreads, were examined for structural chromosome [5].

Statistical Analysis

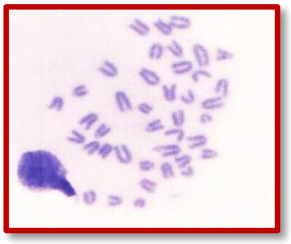
Resulting data were represented as mean ± SD. Statistical data was analyzed between control vs all treated groups. $p<0.05$ was considered statistically significant.

RESULTS

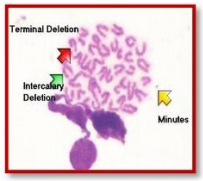
Structural chromosomal Aberration observed in the present study were in the form of terminal deletion, intercalary deletion, minutes, dicentric and Robertsonian translocation (Figure 1 B, C) ring, premature centromere division (Figure 1 D, E) tricentric dicentric, fragment, rebertsonian translocation (Figure 1 F, G) premature centromere division, rebertsonian translocation (Figure 1 H, I) Intercalary deletion, Fragment, minutes (Figure 1 L, K).

Table (1) represented the data obtained after daily treatment with NSAIDs (Aspirin, Diclofenace, Paracetamol, Ibuprofen, Disprin,) 1& 2mg/kg for 10 days. And the total number of structural chromosomal aberration increased in the treate d group when compared with that of the control group other then drugs.

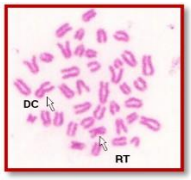
Normal control (A)



Aspirin

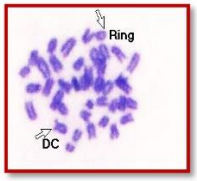


(B) 1Mg

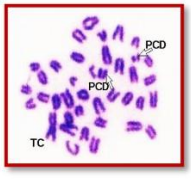


(C) 2Mg

Diclofenace

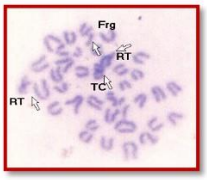


(D) 1Mg

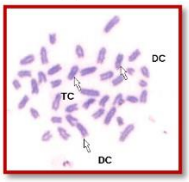


(E) 2Mg

Paracetamol

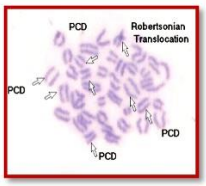


(F) 1Mg



(G) 2Mg

Ibuprofen

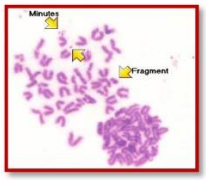


(H) 1Mg

(I) 2Mg

Disprin

(J) 1Mg



(K) 2Mg

Figure: 1. A photomicrograph of metaphase spreading from mice bone marrow. (A) Normal diploid chromosome (B) terminal deletion terminal deletion, intercalary deletion, minutes (C) dicentric and Robertsonian translocation (D) ring and dicentric (E) premature centromere division and tricentric (F) Fragment, rebertsonian translocation and tricentric (G) tricentric, dicentric (H) rebertsonian translocation, premature centromere division (I) rebertsonian translocation (J) intercalary deletion (K) fragment, Minutes

Table 1: Chromosomal Abnormalities in Different Groups of NSAIDs

Treatment	No. of chromosome			Types of chromosomal aberration								% of AM
	TM	NM	AM	PCD	SM	Frg	RT	Ring	DC	TC	TA	
Normal	30	30	0	0	0	0	0	0	0	0	0	0
Aspirin A(1mg)	30	10	20	0	2	0	2	0	0	0	4	66.66
Aspirin B(2mg)	30	20	10	0	1	0	1	0	1	1	4	33.33
Diclofenace A (1mg)	30	15	15	3	3	1	4	1	1	1	14	50
Diclofenace B (2mg)	30	8	22	3	0	1	5	1	0	2	12	73.33
Paracetamol A (1mg)	30	14	16	2	1	1	0	0	2	0	6	53.33
Paracetamol B (2mg)	30	23	7	6	0	1	3	1	3	2	16	23.33
Combiflam A (1mg)	30	16	14	0	2	2	2	2	1	2	11	46.66
Combiflam B (2mg)	30	10	20	0	0	0	4	0	1	0	5	66.66
Disprin A (1mg)	30	17	13	1	0	1	1	1	1	1	6	43.33
Disprin B (2mg)	30	20	10	1	2	1	0	1	4	0	9	33.33

TM: Total Metaphase **AM**: Aberrant Metaphase, **PCD:** Premature Centromeric Divisions, **Frg**: Fragment, **DC:** Dicentric Chromosome, **TC:** Tricentric Chromosome**, RT:** Robertsonian Translocation**, SM**: Single Minutes, **TA**: Total Aberrations, **Ring, NM:** Normal Metaphas

DISCUSSION

Pain killer drugs come under the category of NSAIDs. The present studies were conduct to evaluate the dose dependent toxicity of different class of NSAIDs on rodent. In the present study, it was observed that when these NSAIDs were taken on regularly basis they caused chromosomal aberration.

Chromosomal study was performed, which demonstrated that the number of chromosomal aberration found of Aspirin-treated mice are Fragments, DM, SM, AA, TC, isochromatid break, ring and PCD. According to the study of [6] it was found that Aspirin treated group has more frequency of polychromatic erythrocytes with micronuclei. Diclofenace treated mice are Fragments, TC, SM, AA, isochromatid break, ring, and PCD abnormalities were observed. This study is supported by study of [7] in which chromosomal aberration such as gaps, chromatid, isochromatid break, ring, dicentric were observed in Diclofenac treated mice. Chromosome breaks is also the most frequent other type o1f. chromosomal aberration. In the present study demonstrated that number of aberrations observed in2. animal treated Ibuprofen is Fragments, PCD, DM, SM, AA, isochromatic, ring and PCD. Found decrease in mitotic index (MI) and increase in the frequencies of chromosomal aberrations per cell in the animal treated3. with Ibuprofen [8]. Present study demonstrated that number of aberrations observed in animal treated with paracetamol have shown Fragments, DC, SM, AA4,. isochromatic, ring and PCD. When the number of gaps, break, fragment and polyploidy nuclei are scored and structure aberration was of chromatid type, supported the study [9].

CONCLUSION

Discovery of allopathic medication is the boon fo5r. humankind because of its rapid relieve in pain. NSAIDs are the best-known analgesic on the pain killer ladder6.. The present study was an attempt to find out the toxic effect of NSAIDs in mammalians cells. Vultures population extinction got the high alert on the platform of environmental toxicity because if Diclofenace poisoning7. one of the NSAIDS. The Vultures population diminishing from the world, this was observed from the contaminated carcasses, especially of cattle's like Cow & Buffalos injected with Diclofenace. Present study also focused on the same event of toxicity. The genomic stability was remarked by chromosome assay in which all the NSAIDs have shown its toxicity, Combiflam and Aspirin revealed the highest percentage of chromosome aberration followed by Diclofenace, Paracetamol, and Disprin. Premature centromeric division (PCD) reported highest in Disprin and Paracetamol group; whereas, Robertsonian Translocation (RT) reported highest in Combiflam and Diclofenace. Rest of the aberrations has reported more and less same in all the groups. The present study conclude that there is a dose dependent detrimental effect of an intake of NSAIDs and also confirmed that by the increase of the concentration of the NSAIDs the toxicity increased in genomic and tissue level. The present study warrant more detailed investigation on the toxic effect of different dose of NSAIDs with an aim to decide the safe level of dose if any. The present study also alarm to check an eye on the misuse of NSAIDs for cattles and human in general. This will not only protect the organ system being damage by NSAIDS but also conserve the endangered species like VULTURE and many more Aves.

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