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Research Article

Histopathological Changes Affected by Oral Administration of Diclofenac Sodium in the Bone Marrow of Male Albino Rats (*Rattus rattus*)

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WHH presented research innovation. AHA helped in logical interpretation. AAI performed final review, sample collection and preparing for examination. All authors wrote and edited the manuscript approved it for final publication.

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NSAID, Diclofenac, Bone marrow, Hypercellularity, Arthritis, Rat

Abstract | Diclofenac is a remedy nonsteroidal anti-inflammatory drug (NSAID); that is used for treating the manifestations of rheumatoid arthritis and is being deliberate for forbidding of some types of skin cancer. It plugs releasing substances that cause inflammation and pain. It may also prevent the outgrowth of new blood vessels that tumors need to get bigger. Diclofenac is most potent, so a little amount of diclofenac is needed to relieve pain. Diclofenac is commonly used for arthritis-related joint pain. Twenty white rats were used, the group was divided into four subgroups, each containing five rats for thirty days of oral directing 50, 100 and150 mg/kg daily, with the control group receiving normal physiological saline, the second group given with 50 mg/kg daily of the cure, the third group given with 100 mg/kg daily of the cure, the fourth group was given 150 mg/kg daily of the cure. The rats were slaughtered after the groups received the treatment for one month. in addition to semithin sections for light microscopic examination, followed by statistical studies. This survy, the xeno-biotic is run on the lab-animals top of a period of 15 to 28 days, and the target mainly to pick out short-term toxic effects or injury that might manifest from refined exposure. Duration: Usually scop from 2 to 5 weeks, during the time blood or tissue specimens are taken up to an eye on any changes in physiology or chemical indicator. This allows for the detection of toxic consequence that may come into view only follow up repeated exposure over a short period. (Bemidinezhad, *et al*. 2023). The study showed that the rat bone marrow was affected adversely via the managing with Diclofenac at 50, 100 and150 mg/kg daily for 30 days in histologic structure and easy to perceive differences were observed after light microscopy was used to examine different sections of bone from control and treated animals. The Diclofenac-treated groups' bones showed more active haemopoietic tissue (hypercellularity) relative to adipocytes (white spaces). Diclofenac can cause significant but long-term harm. so this attempt was to determine the effect of Diclofenac on many physiological criteria and several histological indicators in the bone marrow of male rats

Novelty Statement | This study reveals that long-term diclofenac sodium manifest may cause bone marrow hypocellularity, reducing hematopoietic cells and potentially leading to pancytopenia, anemia, and increased infection risk—a drug-induced effect not widely recognized before.

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Introduction

Arthritis is an immunological upset that due to its the damaging in joints is occur premature. actually the

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places where bones are meeting also, some joints naturally wear in aged. Lots of people developed with arthritis premature, lifelong wear and tear (Trehan, 2022).

Osteoarthritis is a form of advanced stages of joint erosion over time or excessive use of certain drugs that cause provocation of the defense system. Thus, Rheumatoid arthritis overactive and adverse reply of the immune system has been responsibility of lapus and sclero-derma, which occasion that tissue has been considered a foreign body to be attacked. Gout occurs as a result of the accumulation of crystals in the joints. There are reasons related to genes, physiology, and the use of some types of tranquilizers (Ahmad *et al.*, 2021).

Rheumatoid arthritis (Where the rat can be chosen as a model to study rheumatoid arthritis), (Noh *et al.*, 2021). and particularly the synovial tissue that fills the spaces of joints, is culminated in inflammation, and a series of interactive defensive events begins. in the early stages, activated immune cells, especially T/cells, entrance the synuvial fluid and releases pre-flaming substance named cyt-okines such as interleukins (IL/1, IL/6) as well the tumor necrosis factor/alpha (TNF-α) (Poznyak *et al.*, 2024).

Pain enzymes (cyclooxygenase-1 and -2) are present at sites of inflammation on cell surfaces. Diclofenac exerts inhibitory activity on cyclooxygenase-1 and -2, the enzymes run up prostaglandin (PG) G2 fabrication, as well as a precursor to other prostaglandins. These molecules have encyclopedic efficiency in action toward of pain and inflammation, and inhibition of their production is the common mechanism that links each of the effects of diclofenac (Yilmaz *et al.*, 2021).

In Rheumatoid arthritis has been get possession of proin-flammatory cytokines from white blood cell specially macrophage that inclusive of TNF-α (tumer necrosis factor/ alpha, IL-1, IL-6, and relative factors. In animating factor/kappa B (NF-κ/B) pathway at nuclea by TNF_α "a major proin-flammatory cytokine in RA" that set up to make louder inflammation and so increases the rate of TNFR II, and exert influence on receptor animator of NF-κ/B bonded (RANKL) discharged in RA-FLS for getting new osteoclast. likewise, the induces of IL_1responses rapid and vigorous and also these employees are chiefly fabricated by phago-cytic cell in RA. IL-1 can further vivifying the proliferation of RA_FLS and the production concerning IL_6, IL_8, GM_CSF, collagenase and prostaglandins (Abbas *et al.*, 2024).

In extension, other inflammatory employees such as IL (8-12-15-18-32), GM_CSF and chemo-kines, monocyte chemo-attractant protein_1 (MCP-1), and C-X-C motif ligand 13 (CXCL13), all of them put up RA partially. but indirectly, the pathogenic inflammatory environment within the synovial membrane is a complex, interconnected, and complex system of factors that perform multiple functions that serve a single mission. Targeting cytokines therapeutically is what provides value in the treatment of arthritis. The successful clinical application of TNF_α and IL_6R antagonists has confirmed the value of cyt-okine_targeted therapy for rheumatoid arthritis (Stievano *et al.*, 2004).

TNF_α inhibitors are the mostly employed as a high society curative for RA. Diclofanec has shown as a TNF-α inhibitors are most effective in treating RA. The pharmacological mechanism is to drop inflaming mediators such as IL_1, IL_6, IL_8, MMPs, to lower the rate of VEGF form endothelial cell-specific angiogenesis, and to reduce the migration of lympho-cytes and macrophages into the joints. as a result, short_term of TNF_α inhibitors uses that can relieve inflammation (Anwar and Laila. 2022).

Diclofenac is metabolized at the liver into most important metabolites, first, -OH--diclofenac, second 5--OH- diclofenac, and the third diclofenac acyl/ glucuronidase (Aboubakr *et al.*, 2021), which are bound up with protein thiol/groups that linked with genesis of reactive oxygen species (ROS) and causally relatives' Covalent modifications protein and ROS due to the cellular injury and different stress signaling pathways to be activated, including c_Jun N_terminal kinase (JNK) (Ahire *et al.*, 2023).

Many disorder conditions in drugs toxicity of bone marrow in varous forms as blood dyscrasias like neutropenia (few neutrophils in the bloodstream, leading to elevated defenselessness to contagion) (Tzankov, 2021). agranulocytosis (a lack of granulocytes in the bloodstream, causing increased allergy to contagion), pancytopenia (deficiency of all three cellular components of the bloodstream (rbc, wbc, and so on platelets) (Minardi *et al.*, 2021).

Any tissue change observed in Stromal cells, because of these are the main target for drug-induced, as scrutinization into the anatomy and physiology of bone marrow has detected. The extra-cellular matrix (ECM) of the stromal layer defines cell structure and promotes the output of lineage-cramped cells in certain regions. certain growth factors (Foucar, 2023).

Experimental animals

The special treatment was carried out on twenty male albino rats (*Rattus rattus*) weighing between 220 and 250 grams, which were obtained from the house of the College of Science at the University of Kufa for animal research. The mice were placed in plastic cages (45*l 25*w 20h*)

cm dimensions, covered with specially made metal covers. The rats were placed in laboratory conditions as ideal as possible in terms of temperature, light and ventilation (Mwangi, 2024; Wachira, 2024).

Drug used

The groups treated with diclofenac sodium (tablet 50 mg) 50, 100 and 150 mg/kg daily by using therapeutic doses and calculated for the weight relative of the rats. The drug has been prepared within powdered dissolved in normal saline (N.S) for preparing the different concentrations of the compound and according to the categories mentioned in the design of this study (Barbaud *et al*., 2020). The selection of N.S as diluting liquid depending on. The diclofenac sodium doses that are supposed to be given when doubling the volume of the initially prepared solution (Hadi and Abood, 2022) as follow:

- Group one was administrated 1 ml of normal saline per day as control group.
- Group two was administrated 50 mg/kg taking 1 ml from prepared solution daily
- Group three was administrated 100 mg/kg taking 1ml from prepared solution daily.
- Group four was administrated 150 mg/kg taking 1ml from prepared solution daily.

Methodically cutting up the animals

Finally, the methodically cut up of Animals has been done subsequent to fin of demonstration by mixing of ketamine: Xylazine (90mg/kg:10mg/kg intra peritoneal), using 0.5ml of ketamine and 0.1ml of xylazine per 250g of body weight for impassivity the rats for all groups. kept the femur in containers contain 4% of nitric acid then ten percent of formalin (Imarah *et al*., 2022).

Under total tipping off, for hormonal analysis (FSH, LH and testosterone) from the right ventricle of the rats calming the blood samples also it has been syringed. into gel tubes the blood sample were calmed, also centrifuging the tube at 2_8C and at 1000g for 15 min for obtaining plasma samples (Hadi and Abood, 2023). The hormonal analyses were fulfilled by using the commercially in stock kits and according to the instructions of the manufacturer (Ali *et al*., 2022).

Histological elaboration

Samples have been secure after dissecting from rats in container contains 10% formalin to be ready then processed them in following steps in (Talib Dawod and Hassan, 2022). samples have been fixed after dissected from animals in contain elaboration contains formalin 10% (formalin 38%100 ml in tap water 900 ml) to be ready for processing them in following steps in (Talib Dawod and Hassan, 2022).

Results

Histological study

Histopathological alterations in the bone marrow of male rats in various concentrations of Diclofenac (Figure 1A-D). Figure 1A-D show mild to severe histopathological changes in the bone marrow of male rats given varying doses of Diclofenac.

The histo-morphological devotion of attention of male rats' bone revealed mild to serious changes in bone marrow histo-architecture within concentrations of 50, 100, 150 mg per kg daily for 30 days of Diclofenac (Figure 1A, B, C, D), give away a decreasing ratio of active haemopoietic tissue (hypocellularity: reduction of hematopoietic cells) relative to increasing adipocytes (white spaces).

Bone responsible of blood cells forming from stem cell marrow haemopoietic tissue. The stem cells dividing and maturing to make erythrocytes that boost in the red bone marrow (red blood cells).

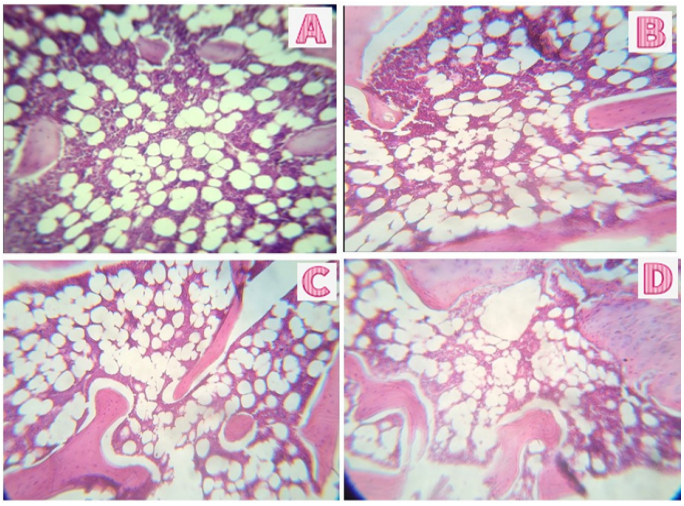

Figure 1: A: control, B: Cross section of the bone marrow treated with 50 mg/kg daily for 30 days showing hypo-cellularity and reducing in hematopoietic cells, C: Cross section of the bone marrow treated with 100 mg/kg daily for 30 days showing hypo-cellularity and more decreasing in hematopoietic cells and D: Cross section of the bone marrow treated with 150 mg/kgdaily for 30 days showing hypo-cellularity and sever reduces of hematopoietic cells. (HandE stain, 100x) (Sameer *et al*., 2023).

Discussion

The outcome of at hand study cause to be visible that commanding of diclofenac at 50, 100 and 150 mg/kg daily for 30 days was dangerous to be damage the histological architecture of rat bone marrow and the light microscopy was saw the visible differences as to be examined a different sections of bone from control and commanded animals.

The Diclofenac-treated groups' bones be obvious more buoyant adipocytes (white spaces) relative haemopoietic tissue (hypocellularity), with a lower ratio of the last (Khan *et al.*, 2023).

Prostaglandins (PGs) are tiny molecule of arachidonic acid derivatives that produced by cyclooxygenases (active COX1 and inducible COX2) and acting on in regulation at variance stages of the immune response ways, as bone marrow as progenitor cell experimented (Xie *et al.*, 2024).

The Diclofenac-treating increased the extracellular proteins expression that associated with macrophages maturation in specific manner as dose-dependent (Pennock *et al.*, 2018). It has been recorded that PGE2 enhances the presence of myeloid derived suppressor cells (MDSCs) (Komura *et al.*, 2020).

Actually, the critical regulators are COXs that influences on angiogenesis factors, inflammation, and carcinogenesis, so as Diclofenac acts on them (Sheng *et al.*, 2020). COXs are attached tightly with the nuclear envelope also they are found on the luminal side of the endoplasmic reticulum (Zhang *et al.*, 2020).

Also, there is evident that the COXs has been enhanced gene expression of the cytokines Interleukin (IL-11) and (IL-12) macrophages (Veenstra *et al.*, 2018). A multi-functional cytokines of the inter-leukins group with capability of anti-inflammatory and hematopoietic proliferative cells, as well as hematopoietic protection, being a censorious regulator of megakaryocyte maturation (Kumar *et al.*, 2018; Lai *et al.*, 2021).

When the mediators is found of an inflammatory, such as during involution, COX-2 inhibition manifest to play a censorious role in encouraging myeloid cellular differentiation. There is evidence that the increasing of white blood cells, platelets, lymphocytes, and neutrophils at all over the body as a sign of inflammation by promoting cell proliferation via this medicine up take (Chen *et al.*, 2020).

Conclusion

To conclude diclofenac sodium is a toxic agent which has deeply physiological and histological changes in bone marrow architecture of male rats when getting it orally permanently. The data proofed that the drug diclofenac has been caused give away a decreasing ratio of active haemopoietic tissue (hypocellularity: reduction of hematopoietic cells) relative to increasing adipocytes (white spaces).

Declarations

Funding

The study received no external funding.

IRB approval and ethical statements

The study was approved by the Institutional Committee for the Ethics of Department of Biology, Faculty of Sciences, University of Kufa, Najaf, Iraq (dated 17 March 2024, Ref. No. 188102).

The mice were placed in plastic cages, covered with specially made metal covers.The rats were placed in laboratory conditions as ideal as possible in terms of temperature, light and ventilation.

Declaration of generative AI and AI-assisted technologies in the writing process

No Generative AI and AI-assisted technologies wer used in the writing process.

Conflict of interest

The authors have declared no conflict of interest.

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