Comparative study of the effect of Diacerein and Diclofenac sodium and their combination in osteoarthritis model induced by monoiodoacetate in albino rats.

Thesis

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Abstract

Background and aim: Osteoarthritis (OA) is the most common joint disorder in the world. It is one of the most frequent causes of pain, loss of function and disability in adults. The current treatment of osteoarthritis is primarily focused on symptomatic relief by the use of rapidly acting analgesics such as NSAIDs and newer cyclooxygenase-2(COX-2) specific inhibitors that have many adverse effects. Hence, there is continuous search for new and better drugs for OA treatment. Interleukin-1β plays an important role in the pathogenesis of OA. Diacerein, an Interleukin-1β antagonist has been used recently in treatment of OA. Accordingly this work was designed to compare the anti-inflammatory effect of diacerein with one of the NSAIDs namely diclofenac sodium and their combination on animal model of osteoarthritis, and to study the effect of these drugs on systolic blood pressure.

Experimental approach: 90 adult healthy female albino rats were allocated into 5 groups: normal untreated animals (negative control), the disease model group that received a single dose of monoiodoacetate (MIA) intra articularly in their right knees (positive control), and the (MIA) induced osteoarthritis treated either by diacerein, diclofenac sodium, or their combination for 6 weeks. Level of serum cartilage oligomeric matrix protein as a specific biochemical marker for cartilage, histopathologic examination, and radiological assessment were performed to evaluate the effect of the studied drugs. In addition a non-invasive measurement of systolic blood pressure was done to study the effect of these drugs on systolic blood pressure.

Results: Induction of OA by monoiodoacetate (MIA) resulted in development of osteoarthritic changes detected by elevation of the biochemical parameter measured, deterioration of pathological scores and X-rays. Interestingly the administration of diacerein alone or with diclofenac sodium resulted in significant amelioration of all the parameters measured with no effect on systolic blood pressure. However, diacerein intake alone showed the best results.

Conclusion: The results of the present study revealed that diacerein has the potential to ameliorate osteoarthritic changes with no effect on the blood pressure unlike the commonly used NSAIDs.

Key words: Osteoarthritis, Diacerein, Diclofenac sodium, Monoiodoacetate.

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LIST OF ABBREVIATIONS

ACL:	Anterior cruciate ligament.
ACR:	American College of Rheumatology.
ADAMTS:	A disintegrin and metalloproteinase domain with thrombospondin.
ANOVA:	Analysis of variance.
AUC:	Area under the curve.
BIPED:	Burden of disease, Investigative, Prognostic, Efficacy, Diagnostic.
BJD:	Bone and Joint Decade.
BMI:	Body mass index
Cm:	Centimeter.
COMP:	Cartilage Olgomeric Matrix Protein.
COX-1:	Cyclooxygenase-1.
COX-2:	Cyclooxygenase-2.
CTX-II:	C-terminal telopeptide of type II collagen.
e.g:	example.
ECM:	Extra Cellular Matrix.
ELISA:	Enzyme-linked immunoabsorbant assay.
ERK:	Extracellular-signal-regulated kinase.

EULAR: European League against Rheumatism.

F.F.D: Focal Film Distance.

Fig: Figure.

Gm: gram.

H&E: Hematoxylin and Eosin.

hr: hour.

I.M: Intramuscular.

ICE: Interlukin-1 converting enzyme.

IL-1β: Interleukin-1beta.

IL-1R: Interleukin-1 receptor.

IL-1ra: Interleukin-1 receptor antagonist.

IL-6: Interleukin-6.

IL-8: Interleukin-8.

I κ B: nuclear factor kappa B (NF-κ B) inhibitor.

Kg: Kilogram.

KSS: Knee society score

KVP: kilo volt potential.

L: Liter.

LII: Lequesne impairment index

Lt:	Left.
mAs:	mille Ampere.
MEK:	mitogen-activated protein kinase (MAPkinase).
mg:	milligram.
MIA:	Monoiodoacetate.
ml:	milliliter.
Mm:	millimeter
MMP:	Matrix Metalloproteinase.
MRI:	Magnetic Resonance Image.
NF-κB:	Nuclear factor-kappa B.
ng:	nanogram
NO:	Nitric oxide.
NSAIDs:	Non-steroidal anti-inflammatory drugs.
OA:	Osteoarthritis.
PGs:	Prostaglandins
PGE2:	Prostaglandin E2.
Pg/ml:	pictogram per milliliter.
ROS:	Reactive oxygen species.
Rt:	Right.

SBP: systolic blood pressure.

SD: Standard deviation.

SR: Sustained release.

SYSADOA: Symptomatic Slow Acting Drug in OA.

T1/2: half-life.

TGF-β: Transforming growth factor β.

TIMP: Tissue inhibitors of metalloproteinase.

TNF-α: Tumor necrosis factor –alpha

US: United States.

VAS: Visual analogue scale

WHO: World Health Organization

W: week.

µl: micro liter.

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Introduction

Osteoarthritis was considered for many years as a non-inflammatory condition affecting the joint. Later, it was found that some sort of inflammation occurs in the joint which cause the pathological changes that precede the pain, which is the most striking complaint in a patient with OA, making him seek medical advice ***(Brandt et al., 2008).*** Although non steroidal anti inflammatory drugs (NSAIDs) play a major role in relieving the process of inflammation in many disorders in medicine, ***(Colville-Nash and Willoughby, 2002; Boileau et al., 2008)*** stated that their effectiveness in disease control mainly through their analgesic action rather than their anti-inflammatory effect.

OA patients are usually of a senior age, suffering from reduction in the function of various organ systems. Non-steroidal anti-inflammatory drugs (NSAIDs) and COX-2 inhibitors are associated with high rates of adverse events (e.g., gastrointestinal, cardiovascular, renal) especially in older patients. In addition, there is an analgesic ceiling effect of NSAIDs, at which efficacy plateau occurs despite increasing the doses ***(Steinmeyer and Konttinen, 2006).*** All these facts can render increasing the NSAIDs dose inappropriate for the management of painful OA flare ***(Felson et al., 2000).***

The economic costs of OA are high. They include those related to treatment for patients and for their families who must adapt their lives and homes to the requirement of the disease, and those due to loss of work and productivity ***(Altman, 2010).*** At present, there are no therapies proven to arrest or decrease the progress of the disease process, and therefore in some individuals, OA may require hip or knee joint replacement ***(Martel-Pelletier and Pelletier (a), 2010).***