

## Diacerein: A New Disease Modulating Agent in Osteoarthritis

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### Abstract

Diacerein is a new anti-inflammatory analgesics and antipyretic drug, developed specially for the treatment of osteoarthritis which is one of the most prevalent degenerative joint disease. It is highly effective in relieving the symptoms of osteoarthritis and may be able to modify the course of the disease condition. Diacerein acts by inhibiting the production of IL-1 $\alpha$  by human monocytes. It is reported to be safe in comparison to NSAIDs with no documented upper gastrointestinal toxicity like gastric or duodenal ulcer. The most common side effect observed in diacerein use is diarrhea. So, diacerein is emerging as a better and safer alternative for the treatment of the osteoarthritis, which provides not only symptomatic treatment but also modifies the underlining pathological process. But further long term clinical trials are needed to prove its safety and efficacy.

**Key words:** Osteoarthritis, degenerative joint disease, diacerein.

### Introduction

Osteoarthritis is a degenerative joint disease characterized by fibrillation, thinning and erosion of articular cartilage, depletion of proteoglycan, abnormal replication of chondrocytes and formation of osteophytes at joint margin.

There is evidence of inflammatory events which increases the destruction of articular cartilage and determines gradual development of joint pain, stiffness and limitation of motion. The inflammatory process is determined by this intervention of polymorphonuclear leucocytes and mononuclear cells which release lysosomal enzymes and oxygen free radicals.<sup>1</sup>

In osteoarthritis, subchondral osteoblasts have abnormal phenotypes, elevated alkaline phosphatase, increased release of osteocalcin, reduced parathyroid hormone (PTH) and prostaglandin E<sub>2</sub> dependent cAMP formation

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elevated urokinase plasminogen and IGF-1 and altered collagen metabolism<sup>2-4</sup>. These disease cells produce more IL-6 and PGE<sub>2</sub> levels than normal. Osteoarthritis is the commonest disease affecting joints, and it affects about 10% of the world population including an estimated 50% of people over 60 years of age. By the age of 75 years, more than 80% of people actually have symptoms of the disease<sup>5</sup>.

The pharmacological treatment of osteoarthritis includes several different types of drugs that can be classified on basis of their mode of action. A large number are NSAIDs which exert their action through the analgesics properties as well as by inhibiting cyclo-oxygenase. While these agents have provided an important means of controlling the inflammation and pain in osteoarthritis but their application has been limited by the deleterious side effects on cartilage<sup>6-7</sup> and the gastrointestinal tract<sup>8</sup>.

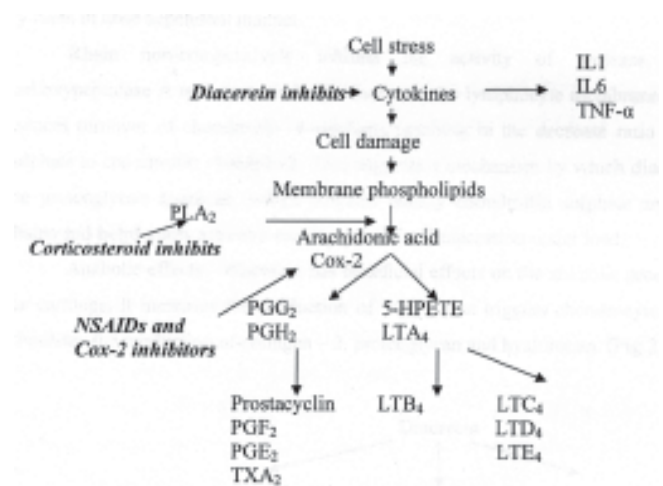
Recently agents have been described that are reported to provide symptomatic relief by targeting the underlying pathology of osteoarthritis particularly in cartilage and subchondral bone, whose structural integrity is essential

for the normal mechanical function of diarthrodial joints. Such agents have been classified as structural modifying osteoarthritis drugs (SMOAD)<sup>9</sup> and expected to retard, stabilize or reverse the pathological changes that occur in osteoarthritis joints, thereby limiting progression of the disease.

Diacerein or diacetylrhien (4, 5- diacetoxy-9, 10-dihydro-9, 10 di-oxo-2 anthracene carboxylic acid)<sup>10</sup> is a new anti-inflammatory, analgesic and antipyretic drug. It is an oral agent that has been developed specifically for the treatment of osteoarthritis. It has a novel mode of action that differentiates it from NSAIDs and other conventional form of drug therapy.

Clinical trials have shown that diacerein is highly effective in relieving the symptoms of osteoarthritis. Moreover results from studies conducted in vitro, in animals and in humans indicate that it may be able to modify the cause of disease. Diacerein is classified as symptomatic slow acting drug whose effects become apparent 2-4 weeks after the start of treatment, reaching significant value after 4-6 weeks but persist for several months after administration ceases.

Findings from in vitro study have demonstrated that in contrast to NSAIDs, diacerein does not inhibit the synthesis of prostaglandins. As a result of this characteristic, diacerein shows no gastrointestinal toxicity in animal models or in humans<sup>19</sup>.



**Fig.1. Mechanism of action of different classes of drugs in inflammatory process of Osteoarthritis ( IL, interleukins; TNF α , tumor necrosis factor alpha; PLA<sub>2</sub> phospholipase A<sub>2</sub> ; COX, cyclooxygenase; PG, prostaglandins; LT, leukotrienes; TX, thromboxane)**

In chronic inflammatory process, as in osteoarthritis the cells are under stress to produce cytokines like IL-1, IL-6, TNF-α which causes damage to the cells and release of membrane phospholipids.

Arachidonic acid, derived from membrane phospholipids by action of phospholipase A<sub>2</sub>, is the precursor of PGs

and leukotrienes, which are the mediators of pain and swelling in case of osteoarthritis.

Diacerein, inhibits the production of IL-1β, corticosteroids inhibits the induction of cyclo-oxygenase and also stimulate production of PLA<sub>2</sub> inhibitors lipocortin, while NSAIDs and COX-2 inhibitors inhibit the action of cyclo-oxygenase. (Fig. 1)

**Mechanism of action**

Rhein, the active metabolite of diacerein, inhibits the production of IL-1β by human monocytes in vitro. IL-1 mediated enhancement of collagenase production by joint chondrocytes was also reduced by diacerein. It also decreases the number of urokinase receptors on chondrocytes to near normal levels and reduced fibrinolytic activity in synovial fluid. Leukocyte migration, lysosomal enzyme release, super oxide production and chemotaxis, are also inhibited by rhein in dose dependent manner.

Rhein non-competitively inhibits the activity of protease, pepsin, trypsin, carboxypeptidase A and elastase. It also increases the lymphocyte membrane fluidity. Diacerein reduces turnover of chondroitin -4-sulphate, resulting in the decrease ratio of chondroitin -6-sulphate to chondroitin -4-sulphate. This suggests a mechanism by which diacerein could protect the proteoglycan aggrecan, which contains mainly chondroitin sulphate and keratin sulphate chains and helps allow articular cartilage to resist compression under load.

Anabolic effects – diacerein has beneficial effects on the anabolic processes that occur in the cartilage. It increases the production of TGF-β that triggers chondrocytes proliferation and stimulates the production of collagen – 2, proteoglycan and hyaluronan. (Fig 2)



**Fig.2: Mechanism of action of diacerein**

Diacerein increases the production of TGF-β collagen2, proteoglycan as well as hyaluronan. This results in stimulation of chondrocyte proliferation, increased synthesis of matrix component as well as restoration of the synovial fluid properties.

**Clinical evaluation**

**SAFETY PROFILE:**

**Upper GI symptoms:** Diacerein differs from other anti-inflammatory drugs by its lack of upper GI effect.

Diacerein has no inhibitory effect on phospholipase A<sub>2</sub>, COX or lipooxygenase<sup>11</sup>. No severe or serious adverse events concerning the upper GI tract such as gastric and duodenal ulcer were reported. These properties are confirmed in a study conducted by M. Petrillo et al<sup>19</sup>, in which diacerein induced gastric mucosal lesion was evaluated endoscopically.

**Diarrhea:** The incidence of diarrhea has been reported as 20 % to 40%<sup>12</sup>. It commonly occurs within the 1<sup>st</sup> two weeks. It may be due to drug class effect and that a laxative effect can be anticipated. Another hypothetical explanation is that because diacerein has been shown to be capable of inducing prostaglandins synthesis, a local increase in PGs may lead to an increase in gut motility and thus causes diarrhea<sup>13</sup>.

In a large randomized double blind placebo controlled multi centric study conducted by Karel Pavelka et al, and presented at annual European Congress of Rheumatology in 2005 evaluating the efficacy and safety of diacerein, involving 168 patients, the incidence of diarrhea and loose stool was slightly higher in diacerein group, but difference with placebo group was not statistically significant.

**Discoloration of urine:** It is expected during treatment with diacerein due to urinary elimination of a metabolite and is without clinical significance.

**Skin reaction:** In the 3 year hip OA trial, rash or purities was observed in 3% patients on placebo and 7% of patients on diacerein 100mg daily.<sup>14</sup>

**Symptomatic efficacy:** the previously reported clinical trials define diacerein as an effective symptomatic treatment of osteoarthritis with following characteristics

- A moderate symptomatic treatment effects
- A 4-6 weeks onset of action
- A 4-8 weeks carry over effects

Considering the variable pain evaluated using a 100 mm VAS scale and considering NSAIDs the usually expected treatment effect is 10-15 mm. Considering diacerein and other specific osteoarthritis drugs (such as chondroitin sulphate, glucosamine and soybean extract), this treatment effect is usually around 6-8mm<sup>15</sup>.

In the study conducted by Maxime Dougados, involving 507 patients with primary hip osteoarthritis, which is a three year, placebo control trial, showed that diacerein can slow the progressive decrease in joint space in patients with hip osteoarthritis, with a good long term safety profile over the three years periods.

In a 2 months, double blind, 2 X 2 factorial plan study including 288 patients with hip osteoarthritis, 100mg/day diacerein was compared with a placebo, an NSAID (20mg/day tenoxicam), and combination of same dosage of

diacerein and tenoxicam. The improvement of pain on movement showed a significant difference versus placebo for tenoxicam and combination group after 2 weeks of treatment. Similar improvement was observed for the diacerein group, becoming significant after 6 weeks of treatment. No difference was observed among the tenoxicam, combination treatment and diacerein group. The results observed in recent clinical trials in the treatment of osteoarthritis involving NSAIDs showed that magnitude of pain improvement in patients ( versus placebo, assessed with a VAS) was comparable with that observed with 100mg/day diacerein (-7.4 mm to -10.0 mm).

### Structural effect

The chosen structural parameter was the radiologic joint space width evaluated on a pelvic radiograph. The primary outcome variables were the changes in joint space width and the proportion of the patients with radiological progression. The occurrence of radiographic progression (i.e. a change in joint space width of at least 0.5 mm) was significantly lower and occurs later in the diacerein group compared with the placebo group<sup>16</sup>.

### Pharmacokinetic Profile

Oral diacerein undergoes complete deacetylation to its active metabolite rhein. The apparent availability of rhein, as assessed by urinary data, was 35%<sup>17</sup>. The maximum plasma concentration (C<sub>max</sub>) of rhein was 3.2 mm/ lit, 2.2 hrs after administration of a single oral dose of diacerein 50mg. area under the plasma rhein concentration – time curve (AUC<sub>0-∞</sub>) was 21.3mg/lit/ hr, apparent volume of distribution was 13.2 litre, terminal elimination half life (t<sub>1/2</sub>) was 4.3 hrs, apparent total plasma clearance was 1.6lit /hrs and renal clearance (CL<sub>r</sub>) was 0.13 lit/hr. Rhein is metabolized to glucourono- and sulpho- conjugates<sup>18</sup>. Time to C<sub>max</sub> and AUC values were increased by concomitant food, indicating slower absorption and greater bioavailability.

### Current status

NSAIDs are commonly used for symptomatic relief in the patients with osteoarthritis, but they cause decreased prostaglandin synthesis and thereby cause unwanted gastrointestinal side effects. Unlike NSAIDs, diacerein does not affect prostaglandin synthesis. It acts predominantly by inhibiting IL-1 and other cytokines. The most common adverse effect is diarrhea. Diacerein has shown activity in short term trial (≤ 6months). However, because the onset of activity is delayed, additional fast acting analgesic or NSAIDs therapy may be required during the 1<sup>st</sup> month of treatment. Systematic meta-analysis provides evidence for the symptomatic efficacy of diacerein in the treatment of knee and hip osteoarthritis, with reasonable tolerability<sup>20,21</sup>. Thus, if the effects of

**Table 1: Different clinical trials of diacerein in patients of osteoarthritis**

S.No.	Author & year	Total Patients	Study design	Duration of Rx	Drug used	Control	Remarks
1	KayAGLetal	20	Single blind study	14weeks	Diacerein 50mg for 4 weeks & Diacerein 100mg for 8 weeks	Placebo	Efficacious
2	LingettiMetal (1982)	20	CDBCE	14weeks	Diacerein 50mg Diacerein 100mg for 8 weeks	Placebo	Efficacious
3	MorcolongoRetal (1988)	95	RCT	4months	Diacerein 50mg B.I.D.	Naproxen 375mg bid. for 2 months followed by placebo 2 months	Efficacious
4	Petrilloetal (1991)	20	RCT		Diacetylrehin 50mg B.I.D.	Naproxen 250mg B.I.D.	Efficacious
5	Nguyeetal (1994)	288	RCTDB		Diacerein & Tenoxicam	Placebo	Efficacious
6	PelletherJPetal (2000)	484	RCTDB	16weeks	Diacerein 25mg B.I.D. & other gp Diacerein 50mg B.I.D. & Diacerein	Placebo	Efficacious
7	ECHODIAH Trial (2001)	507	RCTDB	36months	Diacerein 50mg B.I.D.	Placebo	Diacerein showed the progressive decrease in patients of OA
8	PavelicaKetal (2005)	168	RCTDB	24weeks	Diacerein 50mg B.I.D. for 3 months	Placebo	Safer and effective in OA and effect persist

diacerein are shown to be maintained in long term clinical trials, this agent has the potential to be a useful, possibly non ulcerogenic alternative to NSAIDs for the treatment of patients with osteoarthritis. (Table 1).

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