DISCUSSION

This study was carried out to assess the efficacy and safety of 4,5-diacetyloxy-9,10-dioxo-anthracene-2-carboxylic acid (diacerein) on osteoarthritic knee pain; and the effect of this agent on IL-1β levels.

In the present study, there was apparent improvement in the pain VAS after drug intake in the three studied groups. However, there was only significant improvement in pain VAS after treatment in group I and group III (P = 0.031, and 0.045; respectively).The lack of significant improvement in pain VAS after therapy in group II (diclofenac group) might have been due to the low number of patients who continued the study in this group (n=10) and/or the low dose given (half the maximal dose of diclofenac).

On the other hand, group comparison revealed no significant difference between the three groups regarding the change in pain VAS. This might suggest that diacerein alone was as effective as diclofenac sodium in relieving osteoarthritic knee pain; and that there was no definite additional benefit on combining both drugs for 1 or 2 months. This would also recommend using diacerein alone in patients with osteoarthritic knee pain, especially when there is contraindication to NSAIDs. The use of adjusted *p* value (for height, occupation and knee effusion by linear regression model) in inter-group comparison, in addition to the lack of any significant difference between groups in the other patients' characteristics would suggest group uniformity. This would render group comparison in this study reliable.

Louthrenoo et al [161] found that diacerein was as effective as piroxicam in the treatment of symptomatic knee OA and concluded that diacerein had a better safety profile and an added advantage of carry-over effect.

Baliga et al [162] reported that there was a statistically significant early reduction in the mean VAS scores in knee OA patients given diacerein Modified-Release (MR) 100 mg and conventional diacerein 50 mg for 8 weeks.

Singh et al [163] concluded that the use of diacerein and diclofenac sodium together decreased pain and improved function significantly more than diclofenac sodium alone in knee OA. The pain relieving effect of diacerein plus diclofenac (group III) of the present study is consistent with the finding of Singh et al.[163] However, diacerein alone appeared as effective as diclofenac plus diacerein in the present study.

Zheng et al [164] concluded that diacerein was as effective as diclofenac sodium in treating patients with knee OA. This agrees with inter-group comparisons in this study. However, intra-group changes following treatment in this study suggest that diacerein alone might be better than diclofenac alone when assessment was done two months after therapy.

In the present study, diacerein alone (but not diclofenac alone or diacerein combined with diclofenac) improved the walking time two months after therapy. The finding that diacerein alone was better than diacerein plus diclofenac sodium in improving the walking time two months after therapy; might suggest that diclofenac sodium might have interfered with the structure modifying effect of diacerein, if they were taken together for two continuous months.

Furthermore, it should be noted that the lack of efficacy of diclofenac sodium in improving the walking time might have been also due to the low dose of diclofenac sodium (75 mg per day, which is half the maximum daily dose) and/or the low number of patients in this group. It should be noted that the effect of diacerein on the walking time was not previously addressed.

The synovial fluid IL-1β decreased 1 and 2 months after treatment in Group I. However, this was insignificant. The absence of a decrease in synovial IL-1β levels in Group III could be due to the addition of diclofenac sodium to diacerein. Group comparisons for synovial fluid IL-1β levels may not be reliable as there was a significant difference in IL-1β levels between groups prior to treatment.

The absence of any significant change in blood IL-1β in all groups may suggest that pain severity is not related to blood IL-1β level.

Moldovan et al demonstrated that IL-1β plays a fundamental role in OA pathophysiology and cartilage destruction and that targeting the activation mechanism of this cytokine appears to be important as a therapeutic approach[165]. The expression and synthesis of the interleukin-1 converting enzyme (ICE) were investigated on human OA cartilage explants using in-situ hybridization and immunohistochemical methods, respectively. Data showed that a statistical significant reduction of ICE production was found at both superficial and deep zones of the cartilage. Both diacerein and rhein demonstrated a statistically significant decrease for IL-1β in the superficial zone. A marked decrease was also noted in the deep zone, but statistical significance was reached only for rhein. These results provide a novel regulatory mechanism by which diacerein and rhein could exert a down-regulation on IL-1β's effect on OA cartilage. Our data showed that diacerein reduced synovial IL-1β level after diacerein intake.

Stoltz et al[166] evaluated the effect of diacerein on IL-1β stimulated articular chondrocytes from human OA cartilage. Intracellular iNOS and COX-2 distribution and synthesis were detected by confocal microscopy and nitric oxide (NO) production by using the Griess method. Results showed that in the absence of stimulation, a weak iNOS and COX-2 expression was detected but there was an increase when IL-1β was added. Diacerein decreased intracellular iNOS expression in stimulated chondrocytes but no effect was observed in COX-2 expression. These results are in concordance with our present study which shows an inhibitory effect of diacerein on IL-1β production. These results suggest an inhibitory effect of diacerein at therapeutic concentrations on NO and iNOS production by articular chondrocytes cultured in vitro.

Burkhard[167] have shown that therapeutic doses of both diacerein and its active metabolite rhein inhibit the production and activity of the pro-inflammatory and pro-catabolic cytokine IL-1β both in the superficial and deep layers of the cartilage and in the synovial membrane from OA patients while stimulating the production of growth factors such as TGF-β and extracellular cartilage matrix components such as proteoglycans, aggrecans, HA and collagen type II even in the presence of IL-1β. Diacerein was also shown to down-regulate IL-1β levels in the synovial fluid of patients with knee OA. This is consistent with the results of the present study.

In the present study, the improvement after treatment in the ROM and the QFM or hamstring power was more in group I. This may be related to the improvement in the walking time in this group

In the present study, there was improvement in the pain VRS after drug intake in the 3 studied groups of patients with statistically significant difference between before, 1 month and 2 months after treatment in group I & III ($P = 0.033$, $P = 0.048$ respectively).

There was no study in the literature that tested the effect of diacerein on quadriceps and hamstring muscle power as well as on pain VRS.

Regarding the observed adverse reactions during the two-month period, it was generally mild. But combined intake of diacerein and diclofenac sodium might increase side effects. Diarrhea was seen in 40% of patients who were taking diacerein (groups I and III). This does not contradict the findings of others.[168] However; the risk of diacerein intake for > 2 months was not investigated in this study.

With respect to adverse effects of diacerein, diarrhoea was the most frequent. Given the recent guidance issued by Europe, the European Medicines Agency (EMA) recommending suspension of diacerein in Europe; and the EMA website should be consulted for further recommendations regarding the use of diacerein. [169]

SUMMARY

This study aimed at assessing the efficacy and safety of 4,5-diacetyloxy-9,10-dioxo-anthracene-2-carboxylic acid (diacerein) on osteoarthritic knee pain; and the effect of this agent on IL-1β levels.

Subjects:

(1) 60 patients with primary knee osteoarthritis (OA).

(2) 6 subjects of matching age and sex with asymptomatic mild knee effusion without having OA or any inflammatory arthritis. (control group).

Methods:

The patients with knee OA were divided randomly into three groups:

Group I: received diacerein (osteocerein) (50 mg capsules twice daily) for 2 months.

Group II: received diclofenac sodium (75 mg capsules once per day) for 2 months.

Group III: received both diclofenac sodium and diacerein in the previous doses for 2 months.

Patient's first assessment:

1. Patients with knee OA were evaluated for pain severity (using both the visual analogue scale and the verbal rating scale) and the 20 meters fast walking time at the start of the study.
2. Determination of the level of IL-1β in the serum of all patients and in the control subjects was performed just before the enrollment in the study.
3. Determination of the level of IL-1β in the synovial fluid (taken from the knees) was performed in 10 patients of Group I and III as well as control subjects.

Patient reassessment:

1. Assessment of pain severity and the walking time was done in all patients with knee OA at 1 and 2 months after the start of treatment, in the same way as before treatment.
2. The levels of IL-1β in the serum (in all OA patients) and synovial fluid (in 10 patients of Group I and group III) were determined 1 month and 2 months after treatment.

Results:

Ten patients in group II did not continue the study until its end. In group I, pain VAS, pain VRS and the fast walking time, improved significantly after 2 months of diacerein intake.

The 20 meters fast walking time was significantly shorter in group I at the second assessment when compared to group III.

There was no statistically significant change in synovial IL-1β level after treatment in group I and group III.

Regarding IL-1β levels in the blood, there was no significant difference between the 3 groups before treatment. After 2 months of treatment, the level of IL-1β decreased significantly in group II compared to group I and group III.

CONCLUSION

Diacerein may be used to control osteoarthritic knee pain, especially in patients with contraindication to NSAIDs and who can tolerate it.