

Original Research Article

Study of analgesic property of diacerein in rat

Rajlaxmi Upadhyay¹, Goutam Siddhartha¹, Manas Ranjan Upadhyay^{2*},
Trupti Rekha Swain³

¹Department of Pharmacology, SCB Medical College, Cuttack, Odisha, India

²Department of Paediatrics, FM Medical College, Balasore, Odisha, India

³SLN Medical College, Koraput, Odisha, India

Received: 07 November 2020

Revised: 14 November 2020

Accepted: 17 November 2020

*Correspondence:

Dr. Manas Ranjan Upadhyay,

E-mail: manl013456@gmail.com

Copyright: © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

Background: Diacerein has been known as an anti-osteoarthritic agent that is usually given along with other analgesic drugs. Still there is no evidence of the analgesic effect of diacerein alone. So this pilot study was undertaken to assess the analgesic property at supra-spinal level by using the tail-flick method.

Methods: Diacerein at doses of 50, 100 and 200 mg/kg was given to *Albino wistar* rats weighing approximately 100-200 grams along with distilled water as placebo. All drugs were given by oral routes and the analgesic effect was evaluated using analgesiometer at baseline, 15 min, 30 min, 60 min and 120 min. Analgesic activity was measured as change in tail flick latency from baseline in animals.

Results: Diacerein showed significant increase in tail flick latency and showed promising analgesic activity compared to placebo starting from 15 mins till 60 mins. However the effect persisted up to one hour only and after which it started decreasing.

Conclusions: Diacerein at all the three doses possess dose dependant analgesic activity that is maximally effective up to 60 minutes.

Keywords: Diacerein, Analgesia, Tail-flick-latency

INTRODUCTION

Pain is an unpleasant sensation that acts as a double edge sword. It has both positive and negative aspect, though we always take it in a deleterious way. Pain can be classified on the basis of types, severity, origin etc. most importantly the origin determines the type of therapy provided. Though pain is often associated with inflammation which might be acute or chronic, treating a single condition per se don't always resolve the other. For this reason we prefer to use dual agent as very few chemical entities have the property to act on both conditions. As the medical science progress to find out the molecular level of the disease, we desperately need

drugs that can act on both pain and inflammation with minimum adverse effect. Chronic pain is often accompanied by depression.¹ Selective serotonin reuptake inhibitors (SSRI) used in the management of depression, by increasing the serotonin level, inhibits the release of transmitters carrying the pain sensation from nerve endings.² There is enough evidence to suggest that descending pain inhibitory pathways involve monoamines such as noradrenaline (NA) and 5-hydroxytryptamine (5-HT, serotonin). Spinal inhibition of pain, brought about by inhibiting NA and 5-HT reuptake, is one of the major mechanisms of action of opioid analgesics.³ The release of transmitters, carrying the pain sensation from nerve endings, is regulated by

intracellular calcium level, which also regulates the synthesis of prostaglandins an important mediator in pain.

Diacerein is an anthraquinone derivative, of which the active metabolite is rhein.⁴ Two mechanisms of action have been validated: in vitro inhibition of interleukin-1 (IL-1) synthesis, the main cytokine involved in cartilage destruction, and activity on the synthesis of proteoglycans, and hyaluronic acid, the principal component of cartilage (mechanisms of action of diacerein, the first inhibitor of interleukin-1 in osteoarthritis).⁵ So a pilot study was conducted to evaluate the anti-nociceptive activity of diacerein.

METHODS

Type, place and duration of study

Present study is an experimental study performed at the post graduate department of pharmacology, SCB medical college, Cuttack, Odisha, India. Study was conducted between October 2019 to November 2019.

Animals

For current study *Albino wistar* rats of either sex weighing 80 to 130 gm were used. Animals were housed at an optimum temperature of 25-27°C on 24 hour dark and light cycles provided with laboratory chow and water ad libitum. Animals were maintained under standard laboratory conditions. All experiments were carried out between 10 am to 5 pm. After the experiments were over the animals were kept separately from other animals in different cages and the cages were also numbered to enable observation for development of any complication.

Selection and screening of animals

Animals were prior tested for one week to find out their basal reaction time. Animals who did not flick their tail within 3 to 5 seconds on exposure to current of 0.5 mA and 20 Hz by analgesiometer were excluded from the study.

Grouping of animals

Animals were divided into four groups with six animals in each group.

Group I animals were given distilled water (0.5 ml); group II animals were given 0.1 ml of diacerein drug solution equivalent to diacerein 50 mg/kg; group III animals were given 0.2 ml of diacerein drug solution equivalent to diacerein 100 mg/kg and group IV animals were given diacerein 0.4 ml of diacerein drug solution equivalent to diacerein 200 mg/kg. Diacerein was obtained from Macleod pharmaceutical as a tablet of strength 100 mg each. Diacerein was dissolved in distilled water and distilled water was taken as control. Drug solution was prepared by dissolving one tab of diacerein (100mg) in 10 ml distilled water making a

solution of 10 mg/ml (w/v). From the above solution 0.1 ml, 0.2 ml and 0.4 ml were given to group II, III and IV respectively. Both the drug and the control were given via oral route with the help of feeding needle.

Experimental procedure

The rats were weighed and numbered and put in different cages and the cages were also numbered for the test of analgesic activity, tail-flick method was followed using analgesiometer. Current of 0.5 mA and 20 Hz cycle AC was used in the experiment. Before starting of the experiment the basal reaction time to radiant heat was taken by placing the tip of the tail of the rat on the heat source. Animals were prior tested for one week. Those animals, who failed to show flickering movement of tail at 3-5 seconds, were excluded from the study. The cut-off time for the experiment was fixed at 10 seconds to prevent any injury to the animals. The time (in seconds) it took for the rats to flick its tail away from the heat of the light was measured as latency of tail flick. After the end of the experiment appropriate care was taken. The drugs were fed orally and the reaction time was noted at 15 minutes, 30 minutes, 1 hour, and 2 hour after the drug administration. Time was measured in seconds.

Statistical analysis

Data were expressed as mean±SD. For within group analysis paired t-test and for in-between group analysis ANOVA with post-hoc analysis was used. For the calculation purpose Microsoft excel and SPSS (version 20) were used.

RESULTS

Baseline values did not show any statistical variation between the groups with respect to tail-flick latency time.

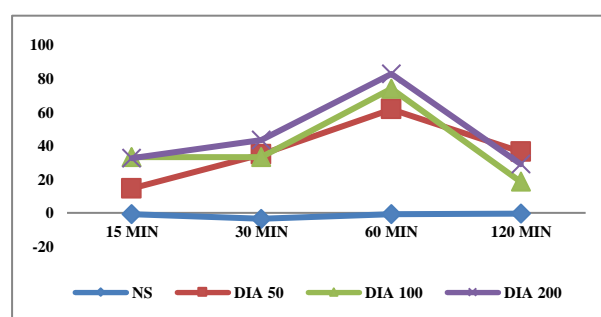


Figure 1: Percentage change in tail flick latency with distilled water and three doses of diacerein.

Animals in the group I did not have any significant variation in tail-flick latency time during the whole study period. Animals in the groups II, III and IV showed dose dependant analgesic property with diacerein. The analgesic effect of diacerein increased upto 60 min in all of its doses and then decreased till the end of the experiment. The increase in TFL time in all the groups of diacerein showed statistically significant.

Table 1: Mean time of TFL in different groups

	Time				
	BL	15 minutes	30 minutes	60 minutes	120 minutes
NS	4.25±0.86	4.21±0.50	4.1±0.5	4.21±0.30	4.23±0.49
DIA 50	4.33±0.65	4.96±0.40*	5.83±0.51*	7±0.62*	5.91±0.52
DIA 100	4.5±0.45	6±0.40*	6±0.36	7.83±0.16*	5.33±0.33*
DIA 200	4.65±0.29	6.16±0.29*	6.67±0.37*	8.5±0.27*	6±0.38

Statistical analysis done from basal by paired 't' test, *p< 0.05 considered significant

Distilled water produced no change in TFL at any time of observation. Diacerein in all the 3 doses produced significant increase in TFL from 30 minutes to 2 hours of observation. Maximum inhibition of pain was observed at 60 minutes with 200 mg/kg of diacerein.

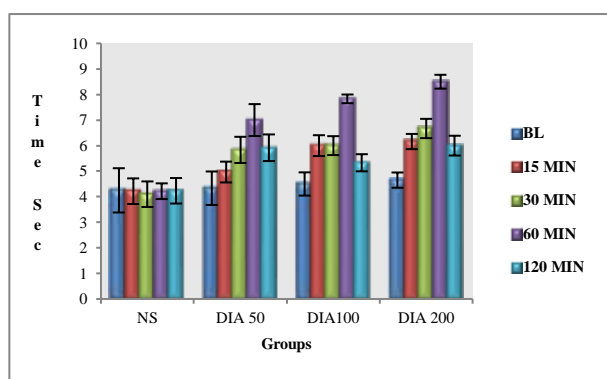


Figure 2: Tail flick latency time in seconds.

DISCUSSION

The effect of diacerein on the anti-inflammatory role has been accepted. Also the action of diacerein as disease modifying osteoarthritic agent is being widely studied in case of joint disorders. But the current study focuses on the analgesic property of diacerein; mainly on the central pathway. Studies by Tamura et al have shown that diacerein is different than NSAIDs with respect to several pharmacological properties.⁶

The tail-flick method is the fastest way to assess the analgesic activity in an animal model with precision. Tail-flick test depicts that diacerein has a potent antinociceptive effect compared to placebo. The increase in the pain thresholding potency in diacerein group was significantly higher than the placebo group. Also the antinociceptive action had increased from the baseline up to one hour but it decreased after that, although it remained higher from the baseline value. The analgesic activity showed a dose dependant increase pattern i.e. with increase in dose of diacerein the analgesic property also increased. In earlier studies diacerein has shown to possess analgesic, anti-inflammatory and antiarthritic property in rats.⁶ From the chochrane data base one study showed pain to be decreasing in people who have used diacerein as a drug for arthritis.

Some study had shown that at the end of the treatment-free follow-up period, diacerein was also found to be significantly better than placebo on pain.⁶ but when compared with standard treatments (mostly NSAIDs), no statistically significant difference regarding pain and physical function was observed at the end of the treatment period.⁶

Limitations of the study

Limitations of current study were; less number of animals was used in current study; analgesic effect was only seen for short term. No active drug was used as control and only one single test was used for analgesic activity measurement.

CONCLUSION

In the current study, diacerein showed a dose dependant analgesic activity. But the effect of this analgesia was of short duration. Thus diacerein is more advantageous to arthritic patients for managing the pain component. Further studies with large sample and diverse method will help to enlighten the above facts.

ACKNOWLEDGEMENTS

Authors would like to thank Mr. Bikash Chandra Naik, and the technical staff of department of pharmacology, SCB medical college, Cuttack.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Colville-Nash PR. Comparison of the pharmacologic effect of diacerein and a selective COX-2 inhibitor in the mouse induced-granuloma model. *Presse Med.* 2002;31(39 Pt 2):4S16-7.
2. Fahmi H, Di Battista JA, Pelletier JP, Mineau F, Ranger P, Martel-Pelletier J. Peroxisome proliferator-activated receptor gamma activators inhibit interleukin-1beta-induced nitric oxide and matrix metalloproteinase 13 production in human chondrocytes. *Arthritis Rheum.* 2001;44(3):595-607.

3. Massicotte F, Lajeunesse D, Benderdour M, Pelletier JP, Hilal G, Duval N, Martel-Pelletier J. Can altered production of interleukin-1beta, interleukin-6, transforming growth factor-beta and prostaglandin E(2) by isolated human subchondral osteoblasts identify two subgroups of osteoarthritic patients. *Osteoarthritis Cartilage.* 2002;10(6):491-500.
4. Yaron M, Shirazi I, Yaron I. Anti-interleukin-1 effects of diacerein and rhein in human osteoarthritic synovial tissue and cartilage cultures. *Osteoarthritis Cartilage.* 1999;7(3):272-80.
5. Sokoloff L. Microcracks in the calcified layer of articular cartilage. *Arch Pathol Lab Med.* 1993;117(2):191-5.
6. Tamura T, Shirai T, Kosaka N, Ohmori K, Takafumi N. Pharmacological studies of diacerein in animal models of inflammation, arthritis and bone resorption. *Eur J Pharmacol.* 2002;448(1):81-7.

Cite this article as: Upadhyay R, Siddhartha G, Upadhyay MR, Swain TR. Study of analgesic property of diacerein in rat. *Int J Res Med Sci* 2020;8:4316-9.