Editorial

Pharmacologists of India: Shiv Prakash 259

Review Article

Therapeutic alternatives from venoms and toxins: Shivaji P. Gawade 260

Research Articles

Genotoxic evaluation of morphine, buprenorphine, pentazocine, and noscapine by micronucleus and comet assay in albino mice: Lakshman Kumar Puli, P. A. Patil 265

Age-related susceptibility to chronic haloperidol-induced orofacial dyskinesia: Biochemical and neurochemical evidence: Mahendra Bishnoi, Kanwaljit Chopra, Shrinivas K. Kulkarni 269

Effect of amlodipine on blood and aortic tissue concentration of endothelin in male rabbits receiving atherogenic diet: M. Mohammadi, F. Mirzaei, Reza Badalzadeh 276


Gastrointestinal permeability studies using combinations of rifampicin and nucleoside analogue reverse transcriptase inhibitors in rats: T.T. Mariappan, Saranjit Singh 284

Effects of meloxicam and rofecoxib on psychomotor performance: A randomized, double-blind, placebo-controlled cross-over study: Marwan S.M. Al-Nimer 291

Non-invasive evaluation of arterial stiffness in patients with increased risk of cardiovascular morbidity: A cross-sectional study: Yashmaina Sridhar, M.U.R. Naidu, P. Usharani, Y.S.N. Raju 294

Serum glucose and triglyceride lowering activity of some novel glitazones against dexamethasone-induced hyperlipidemia and insulin resistance: B.R. Prashantha Kumar, T.K. Praveen, M.J. Nanjan, M.D. Karvekar, B. Suresh 299

Workshop Report

The basic concepts of scientific research and communication: (A Report on Preconference Workshop Held in Conjunction with the 40th Annual Conference of the Indian Pharmacological Society-2007): Pitchai Balakumar, Sreekant Murthy, Gowraganahalli Jagadeesh 303

Author Index, 2007 307

Title Index, 2007 310

The copies of the journal to members of the association are sent by ordinary post. The editorial board, association or publisher will not be responsible for non-receipt of copies. If any of the members wish to receive the copies by registered post or courier, kindly contact the journal’s / publisher’s office. If a copy returns due to incomplete, incorrect or changed address of a member on two consecutive occasions, the names of such members will be deleted from the mailing list of the journal. Providing complete, correct and up-to-date address is the responsibility of the members. Copies are sent to subscribers and members directly from the publisher’s address; it is illegal to acquire copies from any other source. If a copy is received for personal use as a member of the association/society, one cannot resale or give-away the copy for commercial or library use.
Cyclo-oxygenase-2 (Cox-2) enzyme inhibitors relieve pain at the local (peripheral) site of inflammation and also affect the entire central nervous system (CNS).

Meloxicam has spinal antinoceptive actions unrelated to the Cox-2 inhibition in rats.\(^1\) It depresses the response to noxious mechanical stimulation of the cutaneous receptive field.\(^2\) It is known to attenuate the decrease in nigro-striatal dopamine level induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in mice and by virtue of this improves the locomotor activity.\(^3\)

Rofecoxib inhibits Cox-2 without affecting Cox-1.\(^4\) In mice, it attenuated the behavioural responses (hyperlocomotor activity, anxiety and retention memory) that resulted from chronic immobilization stress\(^5\) and it reversed the pentylentetrazole-induced kindling score.\(^6\) Its protective effect extended the ethanol-induced withdrawal symptoms in animals.\(^7\)

There is limited information about the effect of selective Cox-2 inhibitors on psychomotor performance. Nimesulide, a preferential Cox-2 inhibitor, significantly improved the cognitive function in rats,\(^8\) while coxibs improved the spatial and non-spatial motor performance in animals.\(^9,10\)

The aim of this study was to investigate the central effect of single oral dose of meloxicam (a preferential Cox-2 inhibitor related to oxicams) and rofecoxib (a highly selective Cox-2 inhibitor coxib) on psychomotor performance and critical flicker-fusion frequency thresholds in healthy, young volunteers.

### Materials and Methods

This study was conducted in Department of Pharmacology, College of Medicine, Al-Mustansiriya University, Baghdad, Iraq in 2003. Twelve healthy, young males were allocated randomly from college students and participated in a balanced one-period cross-over investigation, with each period separated by a 7-day wash-out period. Participants were asked to perform psychomotor performance (choice reaction time and critical flicker-fusion threshold tests) before and after 2 h of receiving single oral dose of either meloxicam (7.5 mg) or rofecoxib (25 mg).

Results: Meloxicam and rofecoxib were statistically significant, differing from placebo in reducing motor and recognition reaction times, respectively, of the objective test used. Both drugs were not significantly different from placebo in critical flicker-fusion frequency thresholds.

Conclusion: These results allow the conclusion that the effects of preferential (meloxicam) and highly selective (rofecoxib) cyclo-oxygenase-2 inhibitors showed central effect by improving psychomotor performance, but in different directions.

### KEY WORDS: Meloxicam, psychomotor performance, rofecoxib
and placebo. Each single drug dose tablet was taken 2 h before laboratory battery assessment at 9 a.m. Each treatment day was separated by a wash-out of 7 days. All participants who entered the study were familiarized with the study procedures and trained on the battery of psychometric tests in order to preclude learning effects.[11]

The test began with pre-treatment baseline assessment on the test battery and then the treatment dose (placebo or drug) was administered. Performance, using Leeds Battery Psychomotor Instrument [choice reaction time (CRT) and critical flicker fusion (CFF)], was assessed 2 h after the administration of drug or placebo. Caffeine and other beverages were forbidden on study days.

The choice reaction time (CRT) task[12,13] is used as an indicator of sensorimotor performance, assessing the ability to attend and respond to a critical stimulus. Participants are required to place the index finger of their preferred hand on a central starting button and are instructed to extinguish one of six equidistant red lights, illuminated at random, by pressing the response key in front of the light as quickly as possible. The mean of 15 consecutive presentations is recorded as a response measure of three components of reaction time: recognition, motor and total reaction time. Recognition reaction time (RRT) is the time between stimulus (light) onset and the subject’s lifting of the finger from the start button. Motor reaction time (MRT) indicates the movement component of this task and is the time between a participant’s lifting of his finger from the start button and touching the response button. Total reaction time (TRT) is the sum of RRT and MRT.

The critical flicker fusion (CFF) task assessed the integrative capacity of the CNS and, more specifically, the ability to discriminate discrete ‘bits’ of sensory information.[14] In this, the participants are required to discriminate flicker from fusion and vice versa, in a set of four light-emitting diodes arranged in a 1-cm square. The diodes are held in foveal fixation at a distance of 1 m. Individual thresholds are determined by the psychophysical method of limits on five ascending (flicker to fusion) and five descending (fusion to flicker) scales.[15] A decrease in the CFF threshold is indicative of a reduction in the overall integrative activity of the CNS.[13]

Statistical analysis

The results are expressed as mean ± SD of the number of observations. The data were statistically analyzed by using one-way ANOVA, taking \( P \leq 0.05 \) as the lowest limit of significance.

Results

Placebo did not show significant effect on TRT, RRT, MRT and CFF frequency thresholds [Table 1].

Single oral dose of 25 mg rofecoxib significantly reduced RRT by 13.8% from the baseline value and it did not show any considerable effect on MRT. Therefore, TRT apparently decreased and it approached the lower limit of significant level in comparison with baseline value [Table 1].

The effect of single oral dose of 7.5 mg meloxicam on the components of CRT differed from that of rofecoxib. It significantly reduced MRT by 15.9% from baseline value [Table 2]. This effect significantly differed from the corresponding placebo effect.

Although both meloxicam and rofecoxib showed improvement in CFF threshold (whether flicker or fusion frequency), their effects did not reach significant level when compared with corresponding baseline and placebo values. The mean values of CFF threshold of rofecoxib and meloxicam treated groups were 32.5 and 30.9 Hz vs 31.3 and 29.9 Hz of corresponding placebo values.

Discussion

Preferential and highly selective Cox-2 inhibitors significantly differ from placebo in their effects on psychomotor performance. The results show difference in the effects of oxicams and coxibs.

Rofecoxib significantly improved the sensory component of CRT, while meloxicam significantly improved the responding component. Although both drugs improved the integrative activity of the CNS, this effect was not significant.

The effect of rofecoxib was similar to indomethacin which improved sensorimotor coordination performance tests in healthy volunteers,[16] while the effect of meloxicam was similar to piroxicam which improved the motivation.[17] It has been demonstrated that meloxicam had no significant effect on motor performance tests that followed middle cerebral artery occlusion.[18]

It is known that meloxicam is free from CNS effects[19] and its analgesic effect is largely mediated via peripheral mechanisms.[20] Therefore, the possible explanation of the central effect of meloxicam in this study seems to be not related to the inhibition of Cox-2.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Rofecoxib</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>Choice reaction time (ms)</td>
<td>588.3 ± 36.5</td>
<td>584.3 ± 36.7</td>
</tr>
<tr>
<td>Recognition reaction time (ms)</td>
<td>368.7 ± 34.7</td>
<td>370.8 ± 29.4</td>
</tr>
<tr>
<td>Motor reaction time (ms)</td>
<td>221.3 ± 35.8</td>
<td>213.3 ± 33.2</td>
</tr>
<tr>
<td>Flicker frequency (Hz)</td>
<td>31.2 ± 3.1</td>
<td>30.8 ± 1.8</td>
</tr>
<tr>
<td>Fusion frequency (Hz)</td>
<td>31.5 ± 1.8</td>
<td>31.7 ± 1.7</td>
</tr>
</tbody>
</table>

The results are expressed as mean ± SD; \( n = 6 \) for each group. \( *P < 0.05 \) and \( **P < 0.01 \) in comparison with baseline value of rofecoxib treatment. \( *P < 0.01 \) in comparison with placebo-treated value.
Meloxicam inhibits the production of nitric oxide in cerebellum[21] and attenuates the reduction in nigro-striatal dopamine level induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in experimental animal model of Parkinson’s disease.[3]

Rofecoxib, unlike meloxicam, improves RRT via its central effects because it readily crosses the CNS.[22] Case reports listed its central adverse reactions in terms of acute psychosis syndrome[23] and amnestic episodes.[24]

In this work, both meloxicam and rofecoxib improved the CF thresholds but did not reach the level of significance. These results are in agreement with those of the others who found that Cox-2 inhibitors did not significantly affect the cognitive function.[25,26]

It is concluded that both meloxicam and rofecoxib improve psychomotor performance in healthy individuals. There is no place for such compounds in improving the overall integration of CNS activity.

References