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Effects of meloxicam and rofecoxib on psychomotor performance: A randomized, double-blind, placebo-controlled cross-over study

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ABSTRACT

Objectives: To investigate the effects of meloxicam and rofecoxib on psychomotor performance in young, healthy 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 washed-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

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 pentylenetetrazole-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 male volunteers (medical students) aged between 20 and 22 years (mean age 21 years) were allocated randomly from college by using randomized tables to participate in a balanced one-period cross-over investigation, with two periods separated by a 7-day wash-out in two groups of 6 each. All participants were in good health, without any significant clinical history of physical or mental illness and not taking any concomitant medication (including non-steroidal anti-inflammatory drugs) that was likely to interfere with the study. Written informed consent was obtained from all participants. The study was approved by Local Scientific Committee of the institution.

This study was a randomized, double-blind, placebo-controlled one-way cross-over study where each subject acted as own control. The treatment sequence was balanced using Latin Square design. The drugs under investigation were meloxicam (7.5 mg tablet, Boehringer Ingelheim, Germany) and rofecoxib (25 mg tablet, Pfizer, United States) scored tablets

and placebos. 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

The effect of single oral dose of 25 mg rofecoxib and its corresponding placebo on choice reaction time, recognition reaction time, motor reaction time and critical flicker-fusion threshold frequency

	Placebo		*Rofecoxib*	
	Before	***After***	***Before***	***After***
Choice reaction time (ms)	588.3 ± 36.5	584.3 ± 36.7	592.6 ± 36.1	543.2 ± 54.5†
Recognition reaction time (ms)	368.7 ± 34.7	370.8 ± 29.4	379.9 ± 32.8	327.4 ± 29.4††*
Motor reaction time (ms)	221.3 ± 35.8	213.3 ± 33.2	213.2 ± 29.9	215.8 ± 50.1
Flicker frequency (Hz)	31.2 ± 3.1	30.8 ± 1.8	31.3 ± 3.3	31.5 ± 0.6
Fusion frequency (Hz)	31.5 ± 1.8	31.7 ± 1.7	31.5 ± 2.2	33.4 ± 1.7

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

Table 2

The effect of single oral dose of 7.5 mg meloxicam and its corresponding placebo on choice reaction time, recognition reaction time, motor reaction time and critical flicker-fusion threshold frequency

	Placebo		*Meloxicam*	
	Before	***After***	***Before***	***After***
Choice reaction time (ms)	555 ± 35.1	560.8 ± 33.5	569.7 ± 37.1	527.3 ± 65.6
Recognition reaction time (ms)	346.7 ± 45.8	344.2 ± 46.6	356.8 ± 26	348.2 ± 51.3
Motor reaction time (ms)	208.3 ± 19.7	216.7 ± 36.3	212.9 ± 40.1	179.1 ± 36.8†*
Flicker frequency (Hz)	30.2 ± 4.2	29.8 ± 3.6	30.3 ± 5.2	31.2 ± 4.9
Fusion frequency (Hz)	30 ± 2.6	30 ± 2.6	29.8 ± 3	30.6 ± 3.6

The results are expressed as mean ± SD; $n = 6$ for each group. †$P < 0.02$ in comparison with baseline value of meloxicam treatment. *$P < 0.05$ 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 CFF 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.

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