World Bulletin of Public Health (WBPH)
Available Online at: https://www.scholarexpress.net
Volume-19, February 2023
ISSN: 2749-3644

ETORICOXIB VERSUS PIROXICAM IN ACCENTUATING THE COGNITIVE FUNCTIONS

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Article history:
Received: December 11th 2022
Accepted: January 11th 2023
Published: February 20th 2023

Abstract:

Background: Cognitive functions are processes of knowing. When it is impaired, reviving is needed. Studies to bustle off the psychomotor activities using COX-1 inhibitors revealed variable results. **Aim:** To evaluate the effects of a single oral dose of etoricoxib and piroxicam (COX-2 inhibitors) on cognitive activity in healthy, young volunteers. **Subjects and Methods:** Thirty-two healthy young volunteers were participated, allocated into two groups. After a7-day washed-out period, each participant was randomly given a single oral dose of either etoricoxib (90mg) or piroxicam (10mg) or placebo. Psychomotor tests were performed to record their sensory and motor reactions. **Results:** the placebo-administered subjects had non-significant changes in both choice reaction time and critical flicker fusion. Etoricoxib-administered subjects had a significantly reduced recognition reaction time without a significant effect on motor reaction time. While piroxicam-administered ones had a significant reduction in motor reaction time without a significant effect on recognition reaction time. All drug-given individuals had a non-significant change in choice reaction time when compared with corresponding baseline and placebo values. **Conclusion:** selective cox-2 inhibitors show no place in improving the cognitive functions.

Keywords: Etoricoxib, choice reaction time, critical flicker fusion, piroxicam

INTRODUCTIION

Cognition is a mental action or process of acquiring knowledge and understanding through thought, experience, and the senses which allows the humans to display much of their intelligence (e.g. you may remember your birthday without thinking about it, but memorizing someone else's birthday may take some mental effort). [1] There are many cognitive processes such as attention, perception, reasoning, emoting, learning, synthesizing, rearrangement and manipulation of stored information, memory storage, retrieval, and metacognition. [2] These mental processes should distinguish from experiences of feeling or of willing. [3] All eicosanoids with ring structures e.g. the prostaglandins (PGs), thromboxane A2 (TXA2), and prostacyclins (PGI2) are synthesized via the cyclooxygenase pathway which has two related isoforms of the cyclooxygenase enzymes. [4] Cyclooxygenase-1 (COX-1) is a constitutive enzyme that regulates normal cellular processes (e.g. gastric cytoprotection, platelet aggregation, and vascular homeostasis), whereas cyclooxygenase-2 (COX-2) is constitutively expressed and increased in chronic inflammation of certain tissues such as the bone, brain, and kidney because it generates the 'bad' PGs responsible for pain at the site of inflammation. [5] Therefore, COX-2 inhibitors were developed to inhibit the 'bad' PGs synthesis centrally and then relieve pain such as Etoricoxib (a highly selective COX-2 inhibitor) which attenuates the behavioral responses like anxiety and retention memory that resulted from chronic stress [6] and Piroxicam (a preferential selective Cox-2 inhibitor) which depresses the response to noxious mechanical stimulation of the cutaneous receptive field. [7] A Study showed that Etoricoxib improved the motor performance in patients with rheumatoid Arthritis [8], while Piroxicam improved the cognitive function in elderly patients with osteoarthritis. [9] Accordingly, it is interest to perform a study evaluating the effect of a single oral dose of these drugs on cognitive activities in healthy humans.

SUBJUCTS AND METHODS

Thirty-two medical students, 22 males and 10 females, aged between 20 and 23 years (mean age 21 years) were participated in this randomized, double-blind, placebo-controlled and one-period study. The students were recruited randomly from the college of medicine / Al-Nahrain University in April 2022 and were allocated in two groups of 16 students where 8 of them in each group acted as own control. They should be in good

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ISSN: 2749-3644

health, without any history of physical or mental illness. Exclusion is occurred if they were taking drugs that could influence cognition (e.g.,cholinesterase inhibitors, sedatives, antidepressants, or anxiolytics) or certain supplements that could have such effects (e.g., ginkgo biloba). Students with a history of excessive tobacco use were also excluded from participation. Approval to conduct it was granted by the ethical committee in the college of medicine. The nature of the study was explained to each participant and a written consent was obtained. The students were trained on the battery of psychometric tests [choice reaction time (CRT) and critical flicker fusion (CFF)]. [10] The test began with pre-treatment baseline assessment on the laboratory battery and then the test drugs (etoricoxib 90 mg or piroxicam 10 mg) or placebo were administered as a single oral dose at 9 a.m after a7-day washed-out period during which all beverages were forbidden. 2 hours later, psychomotor tests (CRT and CFF) were performed.

Choice reaction time evaluates the ability to respond to a critical stimulus. [11] The subject placed the index finger of his preferred hand on a starting button and was instructed to extinguish one of six equidistant red lights, by pressing the response key in front of the light as quickly as possible. After 14 consecutive times, the mean was recorded which indicated the measurement of CRT components; total reaction time (TRT), recognition reaction time (RRT) and motor reaction time (MRT). TRT is the sum of RRT and MRT. CRT is the time between stimulus (light) onset and the subject's finger left from the start button. MRT is the time between the subject's fingers left from the start button and touching the response button.

Critical flicker fusion evaluates the integration capacity via subject's ability 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 fixed at a distance of 1m. The students' thresholds are determined by the limits on five ascending (flicker to fusion) and five descending (fusion to flicker) scales. Any decrease in the CFF threshold is indicated a reduction in the CNS integration. [12]

Statistical analysis

The data were statistically analyzed using SPSS (version 13) expressed as mean ± SD of the observations number. Significance was set at $P<0.05$.

RESULTS

After analyzing the data; RRT, MRT, TRT and CFF frequency thresholds did not show any significant effect in placebo-administered subjects [Table-1, 2].

Etoricoxib-administered participants had a significantly reduced RRT by 16.3% from the baseline value but without a significant effect on MRT. Therefore, their TRT frequency thresholds were slightly reduced without significance [Table-1]. CFF thresholds did not show a significant effect when compared with corresponding baseline and placebo values.

Piroxicam-administered participants had a significantly reduced MRT by 11.6% from the baseline value but without a significant effect on RRT. Therefore, their TRT frequency thresholds were slightly reduced without significance [Table-2].

Both Etoricoxib and Piroxicam showed improvement in CFF threshold in all participants but without significance when compared with placebo values. The mean values of CFF threshold of Etoricoxib and Piroxicam were respectively 30.5 and 29.9Hz *vs* 30.2 and 30.3 Hz of corresponding placebo values [Table-1,2].

Table 1: Etoricoxib efficacy in correspondence to placebo according to psychomotor tests in first group

Psychomotor Test	volunteers ingested Etoricoxib		volunteers ingested Placebo	
	Before (mean ± SD)	After (mean ± SD)	Before (mean ± SD)	After (mean ± SD)
Choice reaction time (ms)	586.3 ±22.1	564.2 ±47.5	589.9 ±32.3	587.2 ±31.9
Recognition reaction time (ms)	371.7 ±35.2	319.4 ±38.1	353.6 ±27.3	357.1±28.2
Motor reaction time (ms)	213.8 ±29.2	216.2 ±41.5	227.3 ±20.1	226.0 ±25.8
Flicker threshold frequency (Hz)	29.4 ±2.2	29.6 ±1.9	28.1 ±3.5	29.3 ±0.7
Fusion threshold frequency (Hz)	30.2 ±1.3	31.4 ±3.5	29.9 ±3.0	31.1 ±1.2

***P* = 0.827 (not significant)**

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Table 2: Piroxicam efficacy in correspondence to placebo according to psychomotor tests in second group

Psychomotor Test	volunteers ingested Piroxicam		volunteers ingested Placebo	
	Before (mean ± SD)	After (mean ± SD)	Before (mean ± SD)	After (mean ± SD)
Choice reaction time (ms)	566.1 ±46.1	539.2 ±21.5	561.0 ±35.3	577.5 ±32.2
Recognition reaction time (ms)	353.8 ±15.8	349.1 ±34.6	344.2 ±23.7	345.1±26.4
Motor reaction time (ms)	214.6 ±23.3	189.7 ±16.2	203.3 ±11.7	210.9 ±22.5
Flicker threshold frequency (Hz)	29.0 ±4.7	28.7 ±3.6	28.7 ±9.4	28.8 ±1.2
Fusion threshold frequency (Hz)	30.7 ±0.4	30.2 ±1.7	31.3 ±5.5	31.8 ±2.6

***P* = 0.091 (not significant)**

DISCUSSION

From analyses the data, there are significant effects of etoricoxib (a highly selective Cox-2 inhibitor) and piroxicam (preferential selective Cox-2 inhibitor) on psychomotor activities differ from placebo where etoricoxib is significantly reduced RRT so improves the sensory component of CRT, because it readily crosses the blood brain barrier (BBB).[14] Piroxicam is significantly reduced MRT so improves the motor component of CRT and this is possibly performed via peripheral mechanisms because it is poorly passed blood brain barrier[13] so that it is relatively free from central adverse reactions. If it enters CNS, it inhibits the production of nitric oxide in cerebellum and attenuates the reduction in dopamine level in nigrostriatum. This study confirms the results of another study which showed some improvement in CNS after use a Cox-2 inhibitor, but not to the level that significantly affects the cognitive function. [14]

CONCLUSIOIN

Although Etoricoxib and Piroxicam enhance some CNS activities in healthy young individuals, but have no real role in improving the cognition.

ACKNOWLEDGMENT

We like to record our appreciation to the manager of Department of Pharmacology and Therapeutics, Al-Nahrain College of Medicine, Baghdad, Iraq for his help and recruit the medial students to participate in this study.

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Volume-19, February 2023
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