EFFECT OF CITALOPRAM AND BUSPIRONE ON THE ANTINOCICEPTIVE ACTION OF ANALGESIC DRUGS

WANDA PAKULSKA and ELŻBIETA CZARNECKA

Department of Pharmacodynamics, Medical University of Łódź, 1 Muszyńskiego Str., 90–151 Łódź, Poland

Abstract: The influence of citalopram (20 mg/kg i.p.) and buspirone (3 mg/kg i.p.) on analgesic effects of morphine (10 mg/kg i.p.), metamizole (500 mg/kg i.p.) and indomethacin (10 mg/kg) was studied with tail-flick and hot-plate tests on mice. The research studies were further conducted with multiple (14 days) drug dosage. The results indicate that citalopram and buspirone decrease analgesic effects of morphine, metamizole and indomethacin. This mode of action is more pronounced in case of a single dose than after multiple doses.

Keywords: citalopram, buspirone, analgesic drugs, interaction.

Pain is one of the most common human symptoms. The pharmacotherapy is an essential method of fighting pain. Regarding the important role of psychological factors in the origins of pain feeling, analgesic drugs were postulated to be applied simultaneously with anxiolytic or antidepressive drugs. Amitriptyline, a tricyclic antidepressant, has an established role in the treatment of neuropathic pain (1,2,3).

Interactions between analgesic and various psychotropic drugs constitute a subject of many research investigations. Literature concerning this issue are often inconsistent. Research results are usually associated with the type of applied pharmaceuticals, their dosage and mode of application.

The current study was aimed to investigate citalopram and buspirone influence on analgesic effects of morphine, metamizole and indomethacin. Citalopram is an antidepressant drug included among selective inhibitors of serotonin re-uptake (SSRIs), (4). Buspirone belongs to anxiolytic drugs and mechanism of its action is associated with 5–HT1A receptors. It seems that buspirone is agonist of 5–HT1A postsynaptic receptors. Stimulation of these receptors result in membrane hyperpolarization. It is believed that buspirone has presynaptic activity also (4). Analgesic drugs as morphine, metamizole and indomethacin were included into research study. Morphine is an opioid analgesic drug and its biological effects depend mainly on agonist action upon µ opioid receptors. Its action is probably related to different levels of CNS (4). Metamizole (pirazolone derivative) displays analgesic and antifibrile activity due to prostaglandin cyclooxygenase inhibition. Analgesic action of metamizol is of central origin (4). Indomethacin is a potent prostaglandin cyclooxygenase inhibitor, it has anti-inflammatory and anti–edematous properties along with the ability of fighting pain of inflammatory origin (4).

EXPERIMENTAL

Materials

The experiments were carried out on Swiss male mice, 18–24 g. The animals were housed in group cages under normal laboratory conditions (temperature of 20–21°C, natural day/night cycle) and day had free access to commercial chow food and water. All experiments were performed between 9.00 a.m. and 3.00 p.m. The drugs were given intraperitoneally (i.p.) and solutions were in 0.9% NaCl.

Citalopram (Cipramil, H. Lumbeck A/S Kobenhavn–Valby) in dose 20 mg/kg, buspirone (Spamilan, ANPHARM S.A.—Warszawa) at the dose of 3 mg/kg were given 30 min before analgesic drugs; morphine (Morphinum hydrochloricum, Polfa–Warszawa) was given at the dose of 10 mg/kg, metamizole (Pyralgin, Polpharma S.A.) 500 mg/kg, indomethacin (Metindol–Polfa Kraków) 10 mg/kg. In prolonged administration experiments citalopram (10 mg/kg/day) and buspirone (3 mg/kg/day) were administered with morphine (10 mg/kg/day), metamizole (500 mg/kg/day) and indomethacin (2 mg/kg/day) for 14 days.

Nociception tests

The hot-plate (HP) test was derived from Eddy and Leimbach (5). A plastic cylinder (he-
ight: 20 cm, diameter: 14 cm) was used to confine a mouse to the heated surface of the plate. The temperature of the plate was maintained at 52±0.4°C. The latencies to paw licking were determined 30, 60 and 90 min after treatment with analgesic. Each group consisted of 8–10 mice. The tail–flick (TF) tests derived from D’Amour and Smith (6), modified for mice were used. Mice were placed in retention boxes. The latency to withdrawal of the tail was determined by focusing a radiant heat source on the tail at about 3 cm from the tip of the tail. The latency was measured at 30, 60 and 90 min after administration of analgesic drugs. Each group consisted of 8–10 mice.

Statistical analysis

The distribution normality was checked by means of the Kolmogorov–Smirnov test with Liliefors correction and then variance equality was tested by Fisher’s test. The statistical evaluation was performed by means of Mann–Whitney U test by use of Statistica for Windows 4.0 programme.

RESULTS

Citalopram (20 mg/kg i.p.) and buspirone (3 mg/kg i.p.) at a single dose prior to morphine application decreased the time period of pain reaction in TF test, but did not influence the reaction time in

Figure 1. The antinociceptive effect on tail–flick and hot–plate tests after i.p. administration of saline (0.9% NaCl), morphine 10 mg/kg (MF 10), citalopram 20 mg/kg + morphine (C 20 + MF 10), buspirone 3 mg/kg + morphine (B 3 + MF 10)

* Significantly different from the saline group, p<0.05

* Significantly different from the morphine group, p<0.05

Figure 2. The antinociceptive effect on tail–flick and hot–plate tests after i.p. administration of saline (0.9% NaCl), metamizole 500 mg/kg (M 500), citalopram 20 mg/kg + metamizole (C 20 + M 500), buspirone 3 mg/kg + metamizole (B 3 + M 500)

* Significantly different from the saline group, p<0.05

* Significantly different from the metamizol group, p<0.05
HP test (Figure 1). Both drugs studied, if administered before metamizole, decreased its analgesic action. This activity was observed principally in HP test and weakly in TF test (Figure 2). Citalopram and buspirone administered before indomethacin also decreased its analgesic effects (Figure 3).

Citalopram alone did not affect pain reaction time in the applied tests, but buspirone decreased the reaction time in HP test (Figure 4).

Citalopram (10 mg/kg daily) and buspirone (3 mg/kg daily) administered daily for 14 days together with morphine decreased analgesic effects of morphine. This effect was noted mainly in TF test and weakly in HP test (Figure 5). Citalopram in daily doses with metamizole did not change metamizole effects in TF test but it decreased analgesic effects of metamizole in HP test (Figure 6).

Buspirone at regular daily doses with metamizole did not change metamizole analgesic effects and it caused transitory increase of the antinociceptive effect of metamizole.

Citalopram, within 14 days along with indomethacin, decreased analgesic effects of the latter drug (Figure 7). This effect was observed mainly in TF test. Buspirone did not influence analgesic effects of indomethacin (Figure 7).

**DISCUSSION**

Neural impulse of pain conducted through
the specific pathways and centers may be both facilitated or inhibited at different levels. Inhibitory and excitatory neurotransmitters may be involved in the processes. The transmission of nociceptive impulses is under constant control of antinociceptive system. The inhibition of nociceptive signaling takes place predominantly within spinal posterior horns, thalamus and non-specific system.

At least three neurotransmitter systems: opioid, serotonine and noradrenaline, are currently known to be involved in essential functions of antinociceptive system (7).

It is also known that serotonin (5-HT) released in spinal posterior horn, blocks nociception by inhibition of substance P release from afferent neural fibers. The discovery of new 5-HT receptors extended as well as complicated the interpretation of serotonin neurotransmitter effects. Serotonin receptor subtypes may influence nociception differently. It was found that receptors 5-HT1A, 5-HT2A, and 5-HT3 may be involved in both nociception and antinociception.

Literature data imply that antidepressants may modulate nociceptive transmission and if, applied with analgesics, may influence the effects of the latter ones. But research data regarding this subject are controversial (8,9,10,11).

The results of this study indicate that citalopram, at a single dose, decreases analgesic effects of morphine in tail-flick test as well as metaraminol and

Figure 5. The antinociceptive effect on tail-flick and hot-plate tests after multiple i.p. administration of saline (0.9% NaCl), morphine 10 mg/kg (MF 10), citalopram 10 mg/kg + morphine (C 10 + MF 10), buspirone 3 mg/kg + morphine (B 3 + MF 10)
* Significantly different from the saline group, p<0.05
* Significantly different from the morphine group, p<0.05

Figure 6. The antinociceptive effect on tail-flick and hot-plate tests after multiple i.p. administration of saline (0.9% NaCl), metamizol 500 mg/kg (M 500), citalopram 10 mg/kg + metamizol (C 10 + M 500), buspirone 3 mg/kg + metamizol (B 3 + M 500)
* Significantly different from the saline group, p<0.05
* Significantly different from the metamizol group, p<0.05
indomethacin effects in both of the applied tests. Experiments on repeated doses of studied drugs revealed that morphine after intraperitoneal dose daily for 14 days exerts decreased analgesic activity if compared with a single dose. These results may be explained with morphine tolerance development.

Citalopram applied for 14 days with morphine abolished analgesic properties of its in TF test. Multiple doses of citalopram with metamizole and indomethacin led to the decrease of analgesic action of metamizole and indomethacin in HP test and TF test, respectively.

Metamizole and indomethacin action, after intraperitoneal doses for 14 days is characterized with weak analgesic effects and it is observed only in HP test.

Citalopram alone after multiple doses decreased pain reaction time. Therefore, the observed decrease of pain reaction time after metamizole and indomethacin administered together with citalopram, is probably caused by pronociceptive action of citalopram alone.

The tests on analgesic properties of antidepressive drugs indicated that the potent inhibitors of serotonin re-uptake are the most effective in fighting against chronic pain (12, 13). Other authors prove that better analgesic effects should be attributed to noradrenergic heterocyclic antidepressants (14). Coquoz et al. (15) described analgesic
effects after a single dose of fluvoxamine, desipramine and moclobemide. Testa et al. (13) indicated that citalopram, imipramine and nortriptyline increase stress–induced analgesia after oral dose in rats. Gordon et al. (16) found that fluoxetine does not affect postoperative pain perception at the oral dose of 10 mg/kg for 7 days.

The studies on morphine and fluoxetine interactions, indicated that fluoxetine premedication for 7 days prior to surgery antagonized morphine (6 mg, i.v.) induced analgesia. Analgesia attenuation was defined as decrease of time period of opioid action (16).

Hwang and Wilcox (14) stated that noradrenergic and serotonergic antidepressants possesses different antinoceptive profiles. NA uptake inhibitors applied intraspinally (i.t.) enhanced antinoception elicited by morphine applied systemically or intraspinally in TF test. However, inhibitors of serotonin re-uptake did not exhibit these properties after i.t. dose. Larsen and Christiansen reported on morphine (systemic dose) antinoceptive enhancement by citalopram (i.t.) in rats (17).

Our study indicated that buspirone (i.p.) diminished analgesic effects of morphine in TF test as well as effects of metamizole and indomethacin in HP test. The decrease of pain reaction time after indomethacin administered simultaneously with buspirone in HP test should be attributed to pronociceptive action of buspirone.

Buspirone, after single dose, shortened pain reaction time in HP test. These results are consistent with the studies by Alhaider and Wilcox (18).

Further, the consistent results were reported in case of experiments on effects of simultaneous 5–HT1A agonists with morphine. Buspirone after i.t. dose decreased antinoceptive morphine action after systemic dosage in mice. The similar effect was demonstrated in case of buspirone systemic dose in rats (16,19).

Other research data suggest that excitation of 5–HT1A did not cause antinoception but it was associated with pronociceptive effects (18). Buspirone decreased time of reaction to thermal stimulus in TF test, what was observed in our experiments and other research studies (18,20). The attenuation of morphine analgesic effects by buspirone may be related to the influence on 5–HT1A receptors.

The reports on buspirone effect on analgesic action of 5-HT1A agonists: clonidine and xylazine indicate dose–dependent attenuation of antinoception in TF and in the writhing tests (19,21). Similar observation was made after buspirone metabolite 1–(2–pyridinyl)–piperazine (1–PP). Opposite results were also observed. Galeotti et al. (22) proved that buspirone produce significant antinoception itself after intraperitoneal dose, while Gordon et al. (16) stated that buspirone lacked analgesic properties.

According to data provided by Milan (20) the mechanism of antinoceptive action of 5–HT1A agonists involves adrenergic receptor α2 activation. Also, buspirone has a weak affinity to the receptor α2 (19,21,23,24), but its main metabolite 1–PP is a potent α2 antagonist. Some authors state that antinoceptive effect of morphine in CNS may be weakened by spinal administration of α2 antagonists (25). Because buspirone is rapidly metabolized to 1–PP and one hour after oral dose its concentration in brain is higher than buspirone level itself (24), one may expect that this mechanism plays some role in the inhibition of morphine analgesia.

There are no literature data on interactions between anxiolytic, antidepressive and analgesic drug, as metamizole or indomethacin.

This study indicates that both citalopram and buspirone, after single intraperitoneal doses, decrease analgesic effects of metamizole and indomethacin. These effects are less pronounced or they are absent after multiple doses.

CONCLUSIONS

1. Both single and repeated doses of citalopram and buspirone decrease analgesic effects of morphine.

2. Citalopram and buspirone attenuate analgesic action of metamizol and indomethacin, this effect is pronounced after single dose. After repeated administration, this effect is weak or is not observed at all.

This study was supported by research grant from the Medical University, Łódź, Poland nr 502–13–523 (196).

REFERENCES


Received: 25.04.2000