analysis included paired student- t test. All data were compared with base line values and a $p < 0.05$ was considered significant.
Results: Significant difference ($p < 0.05$) was noted for onset of analgesia between Lidocaine-Distilled water and Lidocaine-MgSO4. Lidocaine-MgSO4 produced analgesia of significantly longer duration than that of Lidocaine–Distilled water produced.
Clinical relevance Utilizing this combination, long duration obstetrical and surgical procedures could commence relatively soon after epidural injection and could be completed without re-administration of anesthetic agent.

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THE EFFECTS OF LORNOXICAM AND KETAMINE ON INFLAMMATION AND MECHANICAL HYPERALGESIA MODELS IN RATS

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Background and Aim: Lornoxicam exerted a more evident anti-hyperalgesic action than piroxicam and meloxicam. We evaluated the additive effects of lornoxicam and ketamine on the hindpaw nociceptive thresholds and anti-inflammatory action, respectively in hyperalgesia and iflammatory experimental models.
Method:122 male Wistar albino rats were included in this double blind, randomized, placebo controlled study. Inflammatory and hyperalgesic steps of the study were held in six different experimental groups. In Group I lornoxicam ($1.3\ mg{\cdot}kg^{-1}$, n = 20), Group II ketamine($10\ mg{\cdot}kg^{-1}$, n = 20), Group III ketamine ($10\ mg{\cdot}kg^{-1}$) and lornoxicam ($1.3\ mg{\cdot}kg^{-1}$, n = 23), Group IV solvent (n = 19), Group V saline (n = 20), and Group VI solvent (n = 20) were given intraperitoneally (i.p.), in equal volumes. All drugs were administered i.p, 15 minutes before carrageenan injection to the hindpaw and 30 minutes before formaline injection to the distal part of the tail, for the inflammatory and hyperalgesic steps respectively. Carrageenan-induced hindpaw oedema was assessed by measuring the paw volume by plethysmometer, 3 hours after intraplantar carrageenan injection. 30, 60, 90, 120 minutes after formalin injection, the time taken for the rat to withdraw its left hindpaw was measured by plantar test aparatus.
Results: Hindpaw oedema measurements (Mean±Standard Deviation) were significantly lower in Group I (7.75±3.23), Group II (10.3±4.14) and Group III(7.29±3.57) with respect to Group IV(17.90±4.79), Group V(17.96±5.73) and Group VI.(14.08±3.79). There were no statistical difference between Group I, II and III in terms of anti-hyperalgesic effect, but these groups are better than Group V($p < 0.02$).
Conclusion: The concominant use of lornoxicam and ketamine had no additive effects on iflammation and hyperalgesia.

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THE MOUSE SKIN TWITCH TEST; A NEW PRECLINICAL METHOD TO EVALUATE THE LOCAL ANTINOCICEPTIVE ACTIVITY OF NSAIDS

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Background and Aims: Some animal models have been used for the evaluation of analgesic effects of NSAIDs. It is known that thermal tests is insensitive to evaluate NSAID-induced antinociception. The skin twich test were used to evaluate the antinociceptive effects of opioids and local anesthesics in big primate. In this study, we aimed to evaluate the local antinociceptive effects of NSAIDs in thermal stimuli-induced skin twich test.
Methods: Balb-C mice were used in accordance with the Ethical guidelines for Investigations of Experimental Pain in Conscious Animals. The dorsal low back region of the mice were shaved. A circle with a diameter of 10 mm was marked with a pen on shaved region of each mouse. NSAIDs and 0.9% saline were injected intradermally via Hamilton injector with a total volume of 50 ml into shaved area. A concentrated light (50 W) was focused on the shaved skin of the mice, and the time it took for the mouse's skin to twitch in response to the light was measured. Diclofenac, lysine acetysalicylate, indomethacin, and 0.9% saline were injected.
Results: Intradermal injection of diclofenac and indomethacin (100, 300 and 400 microgram) and lysine acetysalicylate (100, 300 and 1000 microgram) dose dependently increased skin twich latency of animals.
Conclusions: NSAIDs are sensitive to thermal stimuli-induced skin twich test in mice. Thus, the thermal stimuli induced skin twich test in mice can be used preclinical evaluation of analgesic potency of NSAIDs.

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EFFECTS OF AMITRIPTYLINE, GABAPENTIN OR THEIR COMBINATION ON PAIN-RELATED BEHAVIOURS IN TWO RAT MODELS OF CEPHALIC AND EXTRA-CEPHALIC NEUROPATHIC PAIN

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Available neuropathic pain treatments often have incomplete efficacy and dose-limiting adverse effects. We compared for the first time the efficacy of an antidepressant, amitriptyline, and an anticonvulsant, gabapentin, alone or in combination, in two rat models of neuropathic pain, affecting extra-cephalic (somatic) or cephalic territories, respectively.
Adult male Sprague-Dawley rats underwent chronic unilateral constriction injury of the sciatic or the infraorbital (V2 trigeminal branch) nerve. Mechanical hyperalgesia and allodynia were measured (Ugo Basile analgesimeter and von Frey filaments, respectively). Reaction thresholds were markedly reduced 14 days after ligature of the sciatic (paw withdrawal: 121±4 g, vocalization: 236±8 g vs 213±3 g and 453±12 g pre-operatively, respectively) and infraorbital (0.32±0.04 g vs ?12.0 g pre-operatively) nerves. Amitriptyline (10 mg/kg i.p.), gabapentin (30 mg/kg i.p.), or the amitriptyline-gabapentin combination were administered at this time, and reaction thresholds measured for up to 7 hours.
In sciatic nerve-constricted rats, amitriptyline as well as gabapentin significantly reduced mechanical hyperalgesia (~–80% and ~–50% on both tests, respectively, 1h post-administration) but were inactive in infraorbital nerve-constricted rats. The amitriptyline-gabapentin combination completely reversed mechanical hyperalgesia to pre-operative thresholds in sciatic-nerve constricted rats 1–3h post-administration; in infraorbital nerve-constricted rats, this combination significantly attenuated allodynia (~–50%) 3h post-administration. No overt motor dysfunction or behavioural impairment was observed during treatments.
Amitriptyline-gabapentin combination achieved analgesia in two rat models of neuropathic pain much better than either drug administered alone. This drug combination could be a promising treatment of severe forms of neuropathic pain within the trigeminal territory and provide more effective treatment of extra-cephalic neuropathic pain disorders.

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BENFOTIAMINE EFFECT ON ANALGESIC ACTIVITY OF COX-INHIBITORS: EXPERIMRENTAL STUDIES ON RAT MODELS OF NEUROPATHIC ALLODINIA, INFLAMMATORY HYPERALGESIA AND NOCICEPTIVE PAIN

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Benfotiamine is used in the medication of painful diabetic or alcoholic polyneuropathies. The experimental data about analgesic efficacy of benfotiamine in models of neuropathic and inflammatory pain are scarce. Controversial data have been reported about analgesic activity of COX

inhibitors in neuropathic pain. There are no data available so far about the effect of benfotiamine and COX inhibitors co-administration on pain perception.
Aim: To study the effects of benfotiamine on COX inhibitors induced analgesia in different pain models.
Methods: Male rats (Wistar, 180–200 g) were used. Neuropathic pain (chronic constrictive sciatic nerve injury (CCI), inflammatory hyperalgesia (intraplantar Complete Freund's adjuvant) and nociceptive thresholds were measured by incapacitance analgesia meter (2 Biolin), Dynamic plantar aesthesiometer, Hargreaves's apparatus, analgesy-meter and Hot plate (Ugo Basile). Groups (10 rats each) were treated p.o. with benfotiamine (10, 50 and 100 mg/kg), metamizol (50, 100 and 150 mg/kg), ibuprofen (20, 40 mg/kg), indomethacin (2, 5 mg/kg) and parecoxib (5, 10 mg/kg), or combination of benfotiamine plus COX inhibitors. The experiments were approved by the Ethics Committee of the Institute of Physiology.
Results: Benfotiamine (10, 50 and 100 mg/kg) had no analgesic activity per se on nociception and inflammatory hyperalgesia, but 7 days benfotiamine treatment had moderate antiallodynic effect. However Benfotiamine increased significantly the analgesic effect of all COX inhibitors.
Conclusion: The data suggest that benfotiamine can be co-administered as an effective adjuvant in the therapies with selective and nonselective COX inhibitors in neuropathic and inflammatory pain.
Acknowledgements to: Medical University Sofia (Project 14/2005) and Bulgarian Academy of Sciences.

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STUDY OF NON-OPIOID INDUCED TOLERANCE IN RATS

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Background and Aims: Recent investigations have shown that non-opioid analgesics may induce antinociception of the rat's tail-flick reflex (TFR) with some effects of tolerance. The present study was designed to examine whether administration of analgine (metamizol) and ketorolac contribute to the development of tolerance in rats.
Methods: Two groups of experimental (8 and 6) and control (8 and 6) male rats weighing 250–300 gr. were used in this study. Rats were administered i.p. 250 mg/kg analgine (Metamizol Sodium), and 12 mg/kg Ketorolac Tromethamine for 5 successive days. For the control group the same volume of saline was injected respectively. We measured the latency of TFR for both groups as a parameter of antinociception.
Results: We found that i.p. injection of analgine and ketorolac produced antinociception as revealed by a latency increase in TFR compared to controls with saline. Subsequent testing, however, showed that the antinociceptive effect progressively decreased during the following days as a consequence of repeated injections. Our results indicate to the development of tolerance to non-opioids administration. This is suggested by findings that at the end of the experiment both groups of rats were given morphine and only control animals responded with antinociception, while experimental rats showed cross-tolerance to morphine.
Conclusions: Our data confirm other autors' results that non-opioid analgesics are in close relation with endogenous opioids and the tolerance to analgine and ketorolac probably depends on opioid tolerance.

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REPEATED MORPHINE ADMINISTRATION INDUCED ANALGESIC TOLERANCE TO MORPHINE AND CROSS TOLERANCE TO SYSTEMIC DIPYRONE (METAMIZOL)

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Background and Aims: The development of analgesic tolerance after repeated morphine administration is well documented. Recently we showed that microinjection of nonopioid analgesics like dipyrone into the periaqueductal grey causes naloxone-reversible antinociception and induces tolerance with cross tolerance to morphine. Here we studied if morphine-tolerant rats are cross-tolerant to systemic dipyrone.
Methods: Rats were injected intraperitoneally (i.p.) with either saline (500 μl/kg, SAL group, n = 30) or morphine (5 mg/kg, MOR group, n = 30) in the morning and afternoon for 2.5 days. On Day 3 in the afternoon each group was divided in three subgroups (n = 10 each) which were injected i.p. with either saline, morphine or dipyrone (150 mg/kg). To avoid behavioral tolerance, the hot plate (HP), tail flick (TF) and paw withdrawal (PW) latencies were determined only after this last injection.
Results: In the SAL group both morphine (SAL-MOR) and dipyrone (SAL-DIP) increased the latency ("analgesia") for HP (208 and 191%), TF (183 and 142%) and PW (189 and 143%) vs. the subgroup that received only saline (SAL-SAL, 100%). The MOR group developed analgesic tolerance to morphine (MOR-MOR), as well as cross-tolerance to dipyrone (MOR-DIP), that is, latencies were only 133 and 130% for HP, 107 and 102% for TF, and 108 and 91% for PW vs. the SAL-SAL subgroup (100%).
Conclusions: These results show that repeated morphine administration induces tolerance to morphine and, interestingly, cross-tolerance to the nonopioid analgesic dipyrone. These findings also suggest that both opioids and nonopioids may share mechanisms of action when systemically administered at therapeutic doses.

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THROMBIN RECEPTOR PROTEASE-ACTIVATED RECEPTOR-4 (PAR4) MODULATES NOCICEPTIVE SIGNAL IN VIVO AND IN SENSORY NEURONS

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Background and Aim: Protease-Activated Receptors (PARs) are G-protein-coupled receptors. PAR4, a member of this family considered as pro-inflammatory, is activated by the proteolytic cleavage of its N-terminal domain by thrombin, trypsin or cathepsin G. As other members of the PAR family and serine proteases have been implicated in the transmission of nociceptive messages, we investigated a possible function for PAR4 in sensory neurons and nociceptive pathways.
Methods: PAR4 expression was characterized in sensory neurons isolated from mouse dorsal root ganglia (DRG). The effects of selective PAR4 agonist peptide (AYPGKF-NH2) were investigated in vitro in DRG neurons by following calcium mobilization, and in vivo, by measuring nociceptive responses to thermal or mechanical stimuli (using plantar test apparatus or von Frey filaments respectively) after intraplantar injection of PAR4 agonist. The effects of local injection of PAR4 agonist were also investigated in a model of carrageenan-induced inflammation.
Results: PAR4 was expressed on 70% of DRG neurons where it co-localized with substance P and Calcitonin Gene-Related Peptide. PAR4 agonist did not provoke calcium mobilization in DRG neurons but inhibited KCl- or capsaicin-induced calcium mobilization. Intraplantar injection of selective PAR4-activating peptide dose-dependently increased nociceptive threshold and withdrawal latencies, while control peptide had no effect. Co-injection of PAR4-activating peptide with carrageenan significantly reduced carrageenan-induced mechanical and thermal hyperalgesia in a dose-dependent manner.
Conclusions: Our results identify analgesic properties for selective PAR4 agonists that can modulate nociceptive response to noxious stimuli either in normal or inflammatory conditions. PAR4 could exert a direct inhibitory effect on sensory neurons.