American Pain Society
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F14 NSAIDS and Acetaminophen

(384) A phase I, randomized, open-label, cross-over study of the pharmacokinetics, dermal tolerability, and safety of MRX-7EAT Etodolac-Lidocaine Topical Patch in healthy volunteers

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MRX-7EAT Etodolac-Lidocaine Topical Patch (4.4% w/w) is a novel non-steroidal anti-inflammatory drug (NSAID) patch, developed by using a novel transdermal delivery system based on a proprietary ionic liquid technology. Etodolac-lidocaine is a new salt of etodolac with equimolar amounts of lidocaine. In vitro study showed that Etodolac-Lidocaine salt has higher skin permeability than free etodolac. We conducted a Phase I, randomized, open-label, cross-over study of the pharmacokinetics and safety of Etodolac-Lidocaine patch in healthy volunteers to evaluate the systemic exposure of etodolac after administration of Etodolac-Lidocaine patch compared to Etodolac-alone patch. Thirty six total subjects were planned to be enrolled with 18 subjects randomized to a treatment sequence of Etodolac-Lidocaine patch followed by Etodolac-alone patch and the other 18 subjects randomized to a sequence of Etodolac-alone patch followed by Etodolac-Lidocaine patch. At study completion, 33 subjects were enrolled and treated, with 28 subjects completing the study and 5 dropping out. The systemic exposure of etodolac was determined using the pharmacokinetic parameters of etodolac. The study result showed that the Cmax and AUC0-24 of etodolac increased by more than 6-fold after Etodolac-Lidocaine patch applications as compared with Etodolac-alone patch applications. This finding demonstrates that the inclusion of lidocaine in Etodolac-Lidocaine patch to form an ion-pair with etodolac enhanced the skin permeability to etodolac and subsequently increased the absorption of systemic exposure to etodolac through the skin by more than 6 times as compared with Etodolac- alone patch. 33.3% of subjects had at least one adverse event during Etodolac-Lidocaine patch applications and 51.5% of subjects had at least one adverse event during Etodolac-alone patch applications. All adverse events were mild to moderate. No serious adverse event or death occurred.

(385) Macrophage prostaglandin E2 mediates inflammatory pain in peripheral tissues

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Nonsteroidal anti-inflammatory drugs (NSAIDs) alleviate inflammatory pain by inhibiting prostanoid formation, but are associated with serious cardiovascular and gastrointestinal adverse effects. Identification of the dominant tissue sources of prostanoid formation may lead to more targeted therapeutic approaches. We studied the contribution of macrophage derived prostanoid formation to inflammatory pain in mice. Selective deletion of COX-2 in macrophages (Mac-COX-2-KO) by crossing LysMCre mice with COX-2flox/flox mice resulted in complete suppression of lipopolysaccharide-induced prostaglandin (PG) E2, prostacyclin and thromboxane in peritoneal macrophages. Mac-COX-2-KO mice exhibited normal mechanical and heat sensitivity at baseline, as well as normal formalin induced chemical pain, while both mechanical and thermal hyperalgesia were significantly reduced in complete Freund's adjuvant (CFA) evoked hind paw inflammation by 29% (n=6, p< 0.001) and 20% (n=6, p< 0.001), respectively, compared to controls. Inflammatory cell infiltration and concentrations of PGE2, IL-1β and TNFα were significantly reduced in Mac-COX-2-KO paw tissues following CFA induction. This was reflected by a 10% reduction in paw swelling (n=6, p<0.001). Mechanical and thermal pain hypersensitivity were also reduced in the zymosan-evoked monoarticular arthritis and collagen II antibody-induced polyarthritis. We identified PGE2 as the major prostanoid which underlies the effect of macrophage COX-2 on hyperalgesia using macrophage mPGES-1 deficient mice obtained by crossing mPGES-1flox/flox with LysMCre mice (Mac-mPGES-1-KO). These mice fully recapitulated the phenotypes observed with Mac-COX-2-KO. Pretreatment of Mac-mPGES-1-KO mice with celecoxib at a biochemically-validated COX-2 selective concentration (100mg/kg/day) failed to reduce CFA-induced inflammation and hyperalgesia beyond deletion of mPGES-1 in macrophages, further demonstrating the importance of macrophage-derived PGE2. This also indicates that central COX-2 plays only a minor role in this setting. Our results demonstrated that the macrophage COX-2-mPGES-1-PGE2 biosynthetic pathway might be the dominant source of prostanoids in inflammatory pain hypersensitivity in peripheral tissues and may afford a more targeted approach to NSAID therapy.

(386) A novel formulation of ibuprofen sodium has a faster onset of analgesia than standard ibuprofen tablets in the treatment of postoperative dental pain

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A novel formulation of ibuprofen sodium (IBU_{Na}) is absorbed faster than standard IBU tablets, and as fast as solubilized IBU and IBU lysinate. The objective of this randomized, double-blind, single-center, 8-hour, inpatient study using the third molar extraction model of dental pain was to compare overall efficacy and onset of analgesia of IBU_{Na} with standard IBU tablets. Subjects (N=316) with at least moderate baseline pain were randomized 2:2:2:1 to receive a single-dose of IBU_{Na} (2x256mg; equivalent to 400mg IBU; n=95), Advil® (IBU_{Adv}; 2x200mg; n=86), Motrin® (IBU_{Mot}; 2x200mg; n=87), or placebo (n=48). Primary endpoints were time-weighted sum of pain relief and pain intensity differences over 8 hours (SPRID 0-8) and time to meaningful pain relief (TMPR) as assessed by the double-stopwatch method. The mean SPRID 0-8 score was significantly greater for IBU_{Na} and the other active treatments versus placebo (P<.001). The IBU_{Na} group reported TMPR significantly earlier (median 42.4 minutes) than placebo (>8 hours; P<.001), pooled IBU_{Adv}/IBU_{Mot} (median, 55.3 minutes; P<.001), and IBU_{Mot} (median, 60.7 minutes; P<.001), and marginally faster than IBU_{Adv} (median, 52.0 minutes; P=.075). By study end, 22.9%, 95.8%, 88.4%, 94.2%, and 82.8% of subjects in the placebo, IBU_{Na}, pooled IBU_{Adv}/IBU_{Mot}, IBU_{Adv}, and IBU_{Mot} groups, respectively, achieved meaningful relief. Results for secondary endpoints, including time to first perceptible pain relief; SPRID scores over 2, 3, and 6 hours; time to treatment failure; and global evaluation of study treatment, were similar. Most adverse events reported were mild or moderate gastrointestinal disorders (eg, nausea and vomiting) and were similar across treatment groups. Additionally, there were no serious adverse events or discontinuation because of adverse events. This novel formulation of IBU_{Na} provides more rapid onset of analgesia than standard IBU tablets and represents a new treatment option for rapid relief of acute pain. Funded by Pfizer Consumer Healthcare.

(387) A novel formulation of ibuprofen sodium has a safety profile comparable to standard ibuprofen tablets: a pooled analysis of randomized clinical trials

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A desirable attribute of over-the-counter analgesics/antipyretics such as ibuprofen (IBU) is rapid onset of action; therefore, faster-absorbed formulations have been developed. Pharmacokinetic studies demonstrate that a novel formulation of IBU sodium (IBU_{Na}) is absorbed faster than standard IBU tablets, and as fast as solubilized IBU and IBU lysinate. Clinical studies demonstrate that this formulation of IBU_{Na} provides more rapid pain relief than standard IBU tablets for the treatment of dental pain. The objective of this pooled analysis, which included 5, double-blind, randomized clinical trials evaluating dental pain (2 trials), tension-type headache (2 trials), and fever (1 trial), was to compare the safety profile of a single dose (equivalent to 400 mg) of IBU_{Na} (n=362) with standard IBU tablets (n=342) and placebo (n=187). In total, 5.0%, 6.4%, and 10.2% of subjects in the IBU_{Na}, standard IBU, and placebo groups experienced 25, 41, and 31 treatment-emergent adverse events (TEAEs), respectively. Significantly more placebo-treated subjects had a TEAE than subjects in the IBU_{Na} group (P=.03). The most frequent TEAEs occurring in $\geq$2% of subjects in the IBU_{Na}, standard IBU, and placebo groups, respectively, were in the following MedDRA system organ classes: gastrointestinal disorders (2.8%, 3.2%, and 5.9%), nervous system disorders (1.4%, 3.5%, and 3.7%), and general disorders and administration site conditions (1.1%, 1.5%, and 2.1%). Only 2 AEs were considered treatment-related; pruritus and nausea in the IBU_{Na} and placebo groups, respectively. Of those reporting at least 1 TEAE, 44.4%, 36.4%, and 89.5% of subjects in the IBU_{Na}, standard IBU, and placebo groups, respectively, received rescue medication. These data demonstrate that the safety profile of IBU_{Na} is no worse than placebo and comparable to that of standard IBU tablets in single-dose studies evaluating analgesic or antipyretic efficacy. Therefore, this novel, faster-acting formulation of IBU_{Na} has a favorable safety profile. Funded by Pfizer Consumer Healthcare.