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RESEARCH PAPER

Effects of transdermal lidocaine or lidocaine with prilocaine or tetracaine on mechanical superficial sensation and nociceptive thermal thresholds in horses

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Abstract

Objective To evaluate the transdermal local anaesthetic effect of lidocaine or lidocaine combined with prilocaine or tetracaine in horses.

Study design Experimental, randomized, complete crossover design.

Animals A total of five healthy adult warmblood horses.

Methods Horses were clipped bilaterally at the withers, cranial saddle area and caudal saddle area. Baseline measurements for mechanical superficial sensation via von Frey filaments and nociceptive thermal thresholds were performed. A 5% lidocaine patch (12 hour exposure, treatment L), a lidocaine/prilocaine cream (each 2.5%, treatment LP) and a lidocaine/tetracaine cream (each 7%, treatment LT) were applied (both 2 hour exposure). The same product was applied at the same location bilaterally, but on the right side an epidermal micro-perforation (dermaroller, 1200 needles) was performed prior to application. A total of five more measurements were performed at each location, immediately at the end of exposure time followed by hourly measurements. Thermal thresholds normalized to thermal excursion were analysed. One- or two-way ANOVA and the Wilcoxon signed-rank test were used for statistical analysis with $p < 0.05$ considered significant.

Results Epidermal micro-perforation had no enhancing effect. Treatments L, LP, and LT resulted in increased thermal excursion (%) immediately (84.7 ± 12.9; 100.0 ± 0.0; 100.0 ± 0.0) and 1 hour (81.7 ± 66; 86.0 ± 17.7; 87.7 ± 14.4) after the removal of the respective product compared to baseline (66.1 ± 9.3; 69.9 ± 8.3; 76.5 ± 7.8). Superficial mechanical sensation was decreased by the lidocaine-and-tetracaine cream at all time points, and by the lidocaine patch and lidocaine-and-prilocaine cream for three measurements.

Conclusions and clinical relevance Eutectic mixtures of lidocaine with either prilocaine or tetracaine led to a reduction in thermal nociception and mechanical sensation for up to 2 hours.

Keywords filament, frey, local, micro-perforation, pretreatment.

Introduction

Transdermal local anaesthesia is a noninvasive technique to induce antinociception and anaesthesia of the skin with a low risk of major systemic cardiovascular or neurological side effects. The local anaesthetics most commonly used for topical anaesthesia of the skin are lidocaine, prilocaine, benzocaine and tetracaine. Different local anaesthetics are often combined as eutectic mixtures, such as lidocaine with either prilocaine or tetracaine. The one-to-one mixture of lidocaine with either of the local anaesthetics results in a decreased melting point, and thus, achieving higher concentrations of the unionized active ingredient in the lipid phase of emulsions that leads to increased percutaneous absorption and higher efficacy (Steward 1993).

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Transdermal local anaesthesia in human medicine is used efficaciously prior to venepuncture for minor surgical procedures or the treatment of neuropathic pain conditions. A few studies have examined the pharmacokinetics and pharmacodynamics of transdermal local anaesthetics used in veterinary medicine with conflicting results. It was shown to have positive effects in cats, dogs, laboratory animals and white rhinoceros prior to venepuncture (Flecknell et al. 1990; Walzer 1998; Gibbon et al. 2003), and, compared to infiltration, it displayed similar effectiveness for episioplasty in mares (Erkert et al. 2005), but inferior anaesthetic properties for disbudding in calves (Fierheller et al. 2012) and for diagnostic skin biopsies in dogs (Henfrey et al. 1991).

Lidocaine patches licensed for the treatment of neuropathic pain caused by Herpes zoster in humans were evaluated in dogs, cats and horses. Lidocaine patches in dogs and cats resulted in no systemic side effects, and plasma concentrations were clearly below toxic levels (Weiland et al. 2006; Ko et al. 2007, 2008; Joudrey et al. 2015). An equine study revealed a lack of systemic absorption of lidocaine after application of two 5% lidocaine patches, each containing 700 mg lidocaine (Bidwell et al. 2007).

Chemical or physical pretreatment of the skin may be performed to enhance drug absorption through the barrier of the epidermal surface. Physical penetration with different microneedle devices has already been shown to augment transdermal drug delivery *in vitro* using equine skin (Stahl et al. 2012; Stahl & Kietzmann 2014) and *in vivo* in humans (Alkilani et al. 2015).

Contact heat thermal nociceptive threshold testing is a validated method for the quantification of thermal thresholds in horses (Love et al. 2008; Poller et al. 2013a). Low heating rates in thermal nociceptive threshold testing activate slowly conducting nociceptive C fibres (Yeomans et al. 1996; Yeomans & Proudfit 1996). It has already been used to test the efficacy of different analgesics in horses (Robertson et al. 2005; Sanchez et al. 2007, 2008; Love et al. 2012; Poller et al. 2013b).

von Frey filaments are nylon monofilaments of different thicknesses used for tactile and nociceptive testing in laboratory animals and humans. These filaments are pressed perpendicularly on the patients' skin and, depending on the applied force of the filament mechanoreceptive Aβ nerve fibres or nociceptive Aδ nerve fibres, are stimulated. von Frey filaments do not stimulate C fibres except in neuropathic conditions, such as hyperalgesia and allodynia when peripheral nociceptors of C fibres are sensitized (Keizer et al. 2008). In horses, von Frey filaments were used to test wound sensitivity at sutured skin incisions (Rédua et al. 2002) and to prove sensory sensitivity (Lansade et al. 2008).

The aim of this study was to determine the percutaneous effect of the local anaesthetics, lidocaine or lidocaine with prilocaine or tetracaine, on mechanical superficial sensation and thermal nociception. In addition, the effect of mechanical pretreatment with a microneedle device was investigated. The hypotheses were, first, that the eutectic mixtures would be more effective than lidocaine alone; second, that the effect on thermal nociception would be greater than the effect on mechanical sensation; and third, that microneedle pretreatment would enhance the effects.

Material and methods

Animals

The study was reviewed and approved by the Ethics Committee for Animal Experimentation of the Federal Office of Consumer Protection and Food Safety of Lower Saxony, Germany (approval number: 33.12-42502-04-15/2023; date of approval 12 January 2016).

This experimental study was performed on five healthy adult warmblood horses (three mares and two geldings) weighing between 473 and 683 kg, with an age range of 8−22 years. The health status of all horses was confirmed by a complete physical examination. All animals were free of acute and chronic pain. The horses were housed in their familiar box stalls during the study period, with free access to fresh hay and fresh water. All horses were accustomed to the surrounding conditions, the examiner and instrumentation devices. The horses were clipped bilaterally at the withers and at the cranial and caudal saddle areas. Areas of 10 cm^2 were marked at each location where the different local anaesthetic products were subsequently applied (Fig. 1).

von Frey stimulation

A commercial set of von Frey filaments (Bioseb, France) was used, which included 20 filaments with sizes from 1.65 to 6.65, representing an applied force of 0.008−300 g, respectively. The filaments were applied perpendicularly on the horse's skin until the nylon thread started to bend (Lansade et al. 2008). Stimulation was started with the smallest filament; in

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