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Effect of cutaneously applied nonionic surfactants and local anesthetic bases on thermal sensations

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With cutaneously applied local anesthetic bases various effects may be observed, such as a decrease in pricking pain and a change in burning, itch, and thermal sensations. These effects occur after skin penetration and may be attributed to the action of the anesthetics on nociceptors and thermoreceptors, i.e., on C and Aδ nerve fibers, respectively. As little is known about the pharmacodynamic response of nonionic surfactants with a potentially anesthetic action such as polidocanol, this study characterizes nonionic surfactants pharmacodynamically by measuring thermal thresholds with a thermal sensory analyzer after cutaneous application. The results obtained with the nonionic surfactants were compared with data resulting from the cutaneous application of local anesthetic bases such as mepivacaine, bupivacaine, prilocaine, lidocaine, the 1 : 1 mixture of lidocaine and prilocaine contained in EMLA® and a triple mixture consisting of lidocaine, prilocaine and tetracaine (1 : 1 : 1). The results show that none of the investigated surfactants affect thermal thresholds probably due to their high molecular weight. The same was observed with the anesthetics mepivacaine and bupivacaine. In contrast, prilocaine, lidocaine, the 1 : 1 mixture of lidocaine and prilocaine and the triple mixture consisting of lidocaine, prilocaine and tetracaine (1 : 1 : 1) proved to be potent local anesthetics. However, their pharmacodynamic responses do not differ significantly from each other.

1. Introduction

Topical local anesthetic formulations are widely available as over-the-counter remedies. Such products are usually intended for anesthesia of mucosal epithelia and of broken or abraded skin. They are almost without effect on healthy skin where the chemical barrier function of the stratum corneum remains intact; however, if certain anesthetics are applied to healthy skin in their uncharged form, effects may be observed, such as a decrease in pricking pain (McCafferty et al. 1988; Woolfson and McCafferty 1993), a reduction of the flare response to histamine (Pipkorn and Andersson 1987), and a change in burning, itch, and thermal sensations (Adriani and Dalili 1971; Yosipovitch and Maibach 1997). These effects are due to the action of the anesthetics on nociceptors and thermoreceptors, i.e., on C and Aδ nerve fibers, respectively. With the introduction of the eutectic mixture of lidocaine and prilocaine (EMLA®) and the phase change system consisting of tetracaine in a xanthan gum gel (Ametop®) effective percutaneous local anesthesia is feasible.

As the skin is richly provided with sensory nerve fibers, quantitative sensory testing such as the assessment of vibration, light touch, thermal sensations, and pain thresholds is a useful procedure not only for diagnostic purposes but also for the investigation of the effect of topical drugs on sensory perception (Yosipovitch et al. 1997; Yosipovitch and Maibach 1997; Yosipovitch et al. 1996a; b). Thermal sensory testing is becoming an important quantitative sensory testing technique because it allows the investigation of small nerve fiber function, which cannot be evaluated by nerve conduction velocity tests (Yosipovitch and Yarnitsky 1996). Thermal sensory testing allows the measurement of the effect of drugs on both thermal sensations and thermal pain thresholds. If a peltier device such as a thermal sensory analyzer is used as a testing instrument, the effect of topically applied local anesthetics on cold and warmth sensations as well as on thermal pain thresholds may be determined (Leopold and Maibach 1999; Yosipovitch and Yarnitsky 1996). As there is little known about the pharmacodynamic response of cutaneously applied nonionic surfactants with a potential local anesthetic action such as polidocanol, this study was conducted to characterize various nonionic surfactants pharmacodynamically by measuring thermal thresholds over time with a thermal sensory analyzer. Especially in hair care products macrogol ethers are assumed to cause local anesthesia in the cornea and the region around the eyes (Soehring et al. 1952), which could mask irritation caused by these substances (Furrer et al. 2000; Gallo et al. 2001; Heinze et al. 1999; Maurer et al. 1999). To compare the results with conventional local anesthetics, mepivacaine, bupivacaine, prilocaine, lidocaine, the 1 : 1 mixture of prilocaine and lidocaine contained in EMLA® and a triple mixture consisting of lidocaine, prilocaine and tetracaine (1 : 1 : 1) were investigated in the same manner.

2. Investigations, results and discussion

The thermal thresholds versus time profiles of the investigated compounds are shown in Fig. 1. It is obvious from these curves that none of the investigated surfactants affect thermal thresholds. This is surprising in view of the fact that the experiments were done under occlusion conditions and that at least one of the compounds, polidocanol, is known as a substance with local anesthetic potency (Geimer 1953; Soehring et al. 1952; Soehring et al. 1951; Zipf et al. 1957). This also applies to the castor oil macrogol ester Cremophor® EL (Tabarelli et al. 2003). However, a local anesthetic effect with this substance has been observed only after corneal administration, peridural or paravertebral injection and after application to broken or abraded skin. The local anesthetic bases mepivacaine and bupivacaine did not show any effects either. This observation corresponds to the data obtained with etidocaine in an earlier study (Leopold and Maibach 1999). In that study it could be shown, that the pharmacodynamic response of local anesthetic bases correlates linearly with the drug solubility in medium chain triglycerides and the solubility of mepivacaine, bupivacaine and etidocaine (0.3–0.5 mol/l) is significantly lower than that of lidocaine, prilocaine and tetracaine (1.4–1.8 mol/l).

With lidocaine, prilocaine, the 1 : 1 mixture of lidocaine and prilocaine and the triple mixture consisting of lidocaine, prilocaine and tetracaine (1 : 1 : 1) however, a significant effect on cold sensations (CS) and warmth sensations (WS) was observed. All three substances have amphiphilic properties and may interact with the structure of the lipids in biomembranes as observed with surfactants (Seeman 1972). Tetracaine, lidocaine and prilocaine are able to fluidize the lipid bilayers in the stratum corneum (Römmen et al. 1998; Woolfson et al. 1991), a process that may lead to an increase of drug diffusion and even self-diffusion in the barrier. The reasons for the significant differences in thermal sensations between the nonionic surfactants and the local anesthetic bases lidocaine, prilocaine and tetracaine might either be the high molecular weight of the investigated surfactants or the fact that at least polidocanol has a greater effect on itch than on pain (Freitag and Hoppner 1997; Geimer 1953; Wasik et al. 1996). Passive diffusion is compromised at molecular weights over 500 Dalton. A less pronounced difference between the investigated compounds is expected after application to mucosal tissues. Polidocanol for example has been shown to be more effective on abraded or broken skin, where the stratum corneum as penetration barrier is absent or at least compromised (Geimer 1953).

According to the thermal thresholds versus time profiles of lidocaine and prilocaine as well as the two base mixtures, CS and WS appear to change linearly over time, a relationship also found with argon laser-induced cutaneous pain after application of EMLA® cream (Bjerring and Arendt-Nielsen 1990). The lag times of onset have in the past been shown to be suitable response parameters only if one model drug and different vehicles are looked at (Leopold 2000). However, the lag times found for lidocaine, prilocaine and the two base mixtures in this study correspond to the recommended pretreatment period of 1 h for EMLA® cream.

According to the data shown in Fig. 2 for lidocaine, prilocaine and the two base mixtures, the observed maximum responses do not differ significantly from each other. Apparently, the fact that the two base mixtures represent eutectic mixtures does not necessarily mean that they are more efficient. This observation is surprising in view of the fact that EMLA® has been propagated to be most effective just because of the eutectic mixture of lidocaine and prilocaine contained in this formulation.

The data presented in Figs. 1 and 2 indicate that CS is a more suitable parameter for the pharmacodynamic characterization of local anesthetics than WS, possibly because cold receptors are located in the epidermis (Bazett et al. 1930) and can easily be reached by local anesthetics. Warmth receptors are located deeper in the dermis (Zotterman 1959) and therefore, warmth- and heat-related response parameters do not seem to be useful for the characterization of local anesthetics. The fact that CS is mediated by myelinated Aδ fibers in contrast to WS, which is transmitted by unmyelinated and therefore better accessible C fibers, does not appear to affect the pharmacodynamic response.

From the presented data it may be concluded that the nonionic surfactants investigated in this study do not affect thermal sensations. Apparently, the molecular weight of these compounds is too high to allow passive diffusion through the stratum corneum. In contrast, various cutaneously applied local anesthetic bases are able to permeate through human skin and significantly affect thermal thresholds. This is true with lidocaine, prilocaine and the two base mixtures consisting of lidocaine/prilocaine (1 : 1) and lidocaine/prilocaine/tetracaine (1 : 1 : 1). Interestingly, these eutectic mixtures do affect thermal sensations not more than the isolated compounds. Mepivacaine and bupivacaine do not affect thermal sensations as was observed with etidocaine in an earlier study. This observation can be explained by the low solubility of these anesthetics in medium chain triglycerides as compared to lidocaine, prilocaine and tetracaine.

CS data appear to be the most suitable response parameters. The investigation of pricking pain thresholds under standardized conditions with the presented compounds is under way. Moreover, the investigation of thermal sensations after mucosal application of the same compounds should give more detailed information on the local anesthetic action of nonionic surfactants.

3. Experimental

3.1. Materials

Four nonionic surfactants, polidocanol (laureth-9, average MW: 583), ceteareth-30 (average MW: 1,578), oleth-5 (average MW: 489) and oleth-10 (average MW: 709), were investigated; all were supplied by Schwarzkopf & Henkel, Hamburg, Germany. In addition, five conventional local anesthetics were included in the study. Mepivacaine-HCl (MW base: 246.35), bupivacaine-HCl (MW base: 288.43) and tetracaine-HCl (MW base: 264.37) were obtained from Aventis Pharma, Bad Soden, Germany. Prilocaine-HCl (MW base: 220.31) and lidocaine-HCl (MW base: 234.34) were kindly donated by AstraZeneca, Wedel, Germany. All local anesthetics were used in their base form. The bases were obtained by dissolving the hydrochlorides in distilled water and adjusting the pH to 10 with 3 M sodium hydroxide. Subsequently, the bases were extracted three times with diethyl ether. The combined fractions were dried with anhydrous sodium sulfate, evaporated to dryness after filtration, and stored in a desiccator under a vacuum for two days.

3.2. Measurement of the pharmacodynamic response

The study was approved by the Ethics Committee of the School of Medicine of the University of California at San Francisco. Eight healthy volunteers (age 25–65 y; i.e. 40.6 y ± 13.7 y) provided written informed consent to participate. They received the four nonionic surfactants and the local anesthetic bases including two base mixtures, one at a time and 7 days apart. The base mixtures consisted of either lidocaine and prilocaine (1 : 1) as contained in EMLA® or lidocaine, prilocaine and tetracaine (1 : 1 : 1).

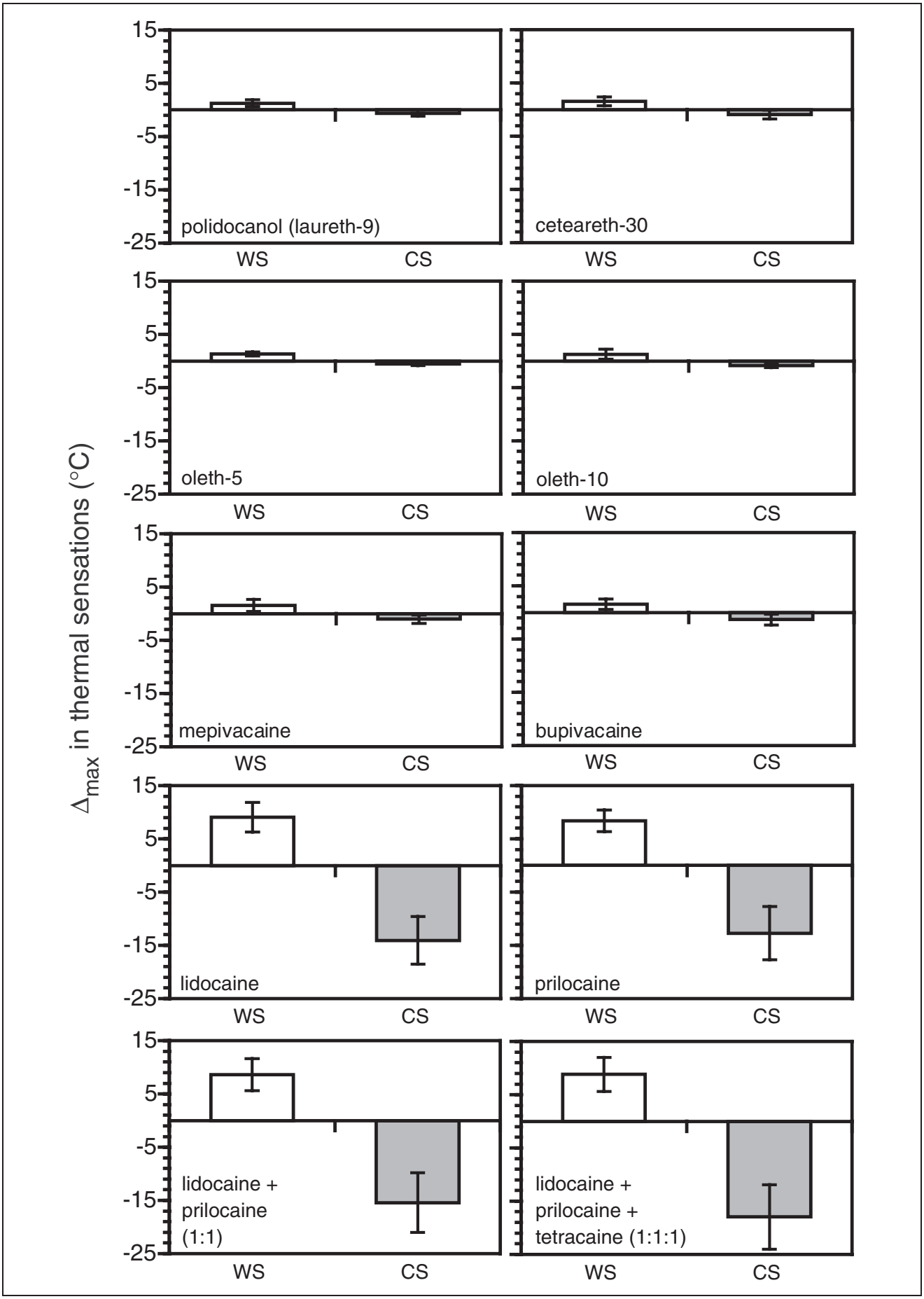

Fig. 1: Typical cold and warmth sensation (CS, WS) versus time profiles after occlusive application of various local anesthetic compounds to forearm skin at maximum thermodynamic activity for 3 h (subject SC). Dashed line: Adaptation temperature

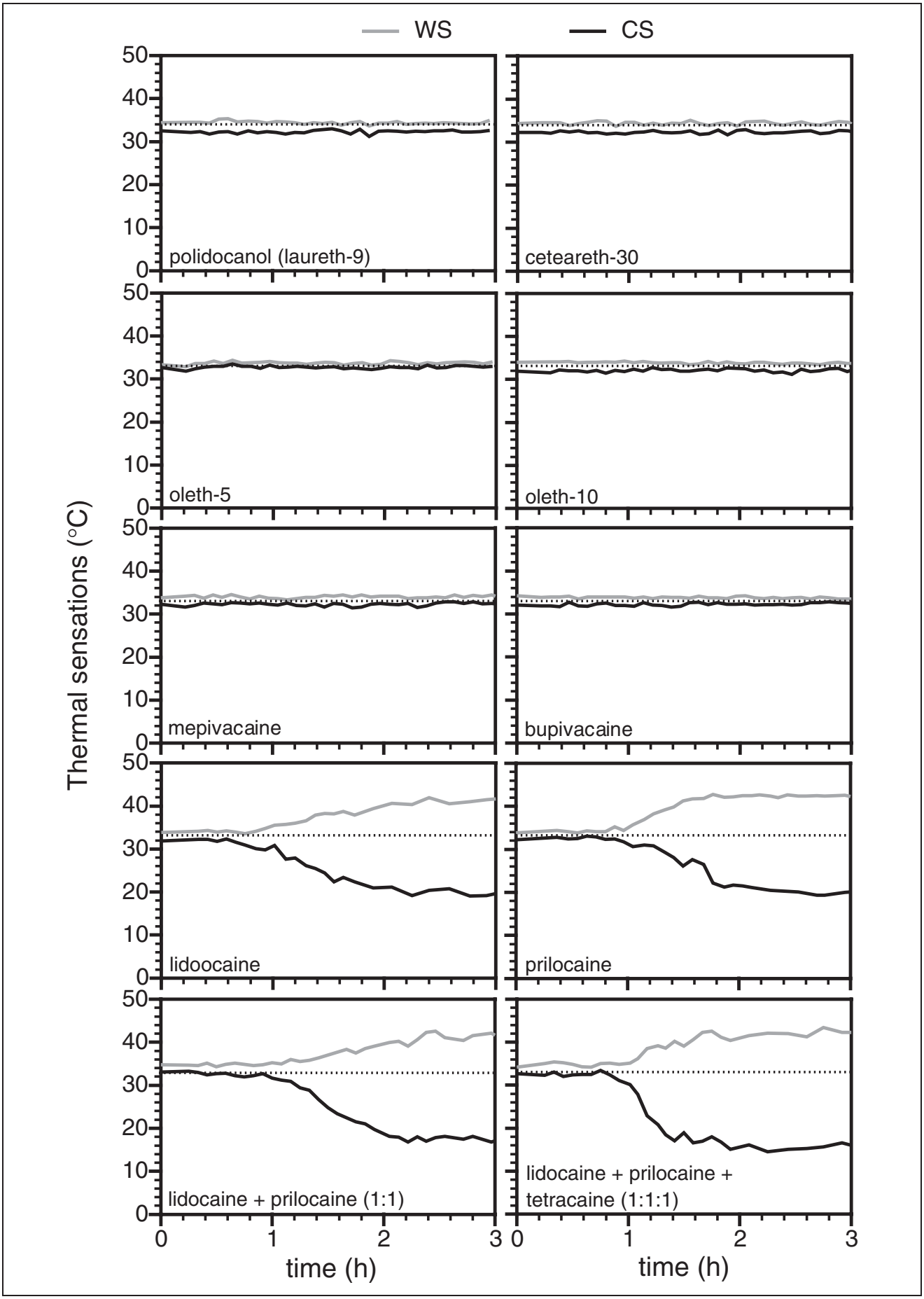

Fig. 2: Maximum change in cold and warmth sensations (CS, WS) after occlusive application of various local anesthetic compounds to forearm skin at maximum thermodynamic activity for 3 h. Means ± SD, n = 8 subjects

100 mg of all surfactants were applied to an area of 3.5×3.5 cm^2 on the volar aspect of the forearm with a spatula, one at a time. The solid local anesthetic bases lidocaine, mepivacaine, bupivacaine were dissolved in ethanol at a concentration of 100 mg per ml and 1 ml of each solution was applied to the skin with an insulin syringe. The liquid bases and base mixtures could be directly applied to the skin with a syringe. To guarantee the maximum thermodynamic drug activity and to avoid a barrier-modifying action of ethanol, the organic solvent was allowed to evaporate using a hair dryer.

Cold sensations (CS) and warmth sensations (WS) were measured after cutaneous application of the compounds with a thermal sensory analyzer (TSA 2001, Medoc U.S., Minneapolis, MN) as described previously (Leopold and Maibach 1999). The instrument was equipped with a thermode (size 3×3 cm^2) adjusted to an adaptation temperature of 33 °C. Control measurements were done immediately before application of the compounds using the method of limits as test algorithm (Yosipovitch and Yarnitsky 1996). With this method, stimuli increase continuously in intensity until the requested sensation is perceived, at which moment the stimulus is halted by the subject and the thermode temperature returns to adaptation temperature. A reaction time artifact is built in this measurement. All subjects were trained in CS and WS perception before starting the experiment to minimize the intersession bias and to achieve acceptable repeatability (Yarnitsky and Sprecher 1994).

Thermal thresholds were obtained in the following manner: WS and CS were measured under occlusion conditions every 5 min over 3 h until constant thresholds were achieved. Six oscillating stimuli starting with WS were given at a constant temperature rate of 0.3 °C and with a time interval of 5 s between stimuli. In preliminary experiments no significant effect of stimulus repetition on thermal thresholds measured over 3 h under the above-mentioned conditions could be detected. Cold pain and heat pain thresholds were not measured, as they were shown to be unsuitable parameters of response (Leopold and Maibach 1999).

Sessions were held in a sound-proof air-conditioned room, with distractions minimized. Subjects did not have visual access to the computer screen; no visual or auditory cues were given to signal stimulus onset. WS and CS means were calculated automatically by the Medoc software for each cluster of stimuli.

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