Dexamethasone Prolongs Local Analgesia after Subcutaneous Infiltration of Bupivacaine Microcapsules in Human Volunteers

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Background: The addition of small amounts of dexamethasone to extended-release formulations of bupivacaine in microcapsules has been found to prolong local analgesia in experimental studies, but no clinical data are available.

Methods: In a double-blinded study, 12 healthy male volunteers were randomized to receive simultaneous subcutaneous injections of bupivacaine microcapsules with dexamethasone and bupivacaine microcapsules without dexamethasone in each calf. Local analgesia was assessed with a validated human pain model; main parameters evaluated were thermal, mechanical, and pain detection thresholds and suprathreshold responses to heat and mechanical stimulation. Measurements were performed every 2 h for the first 8 h and daily for the week after injection. Primary endpoints were evaluation of maximal analgesic effect, time of onset, and duration of analgesia. Summary measures (area under curve [AUC]) were considered best estimate of analgesia. Safety evaluations were performed daily for the first week and at 2 weeks, 6 weeks, and 6 months after injection.

Results: The addition of dexamethasone significantly prolonged local analgesia of bupivacaine microcapsules without influence on maximal analgesic effect. AUC in all thermal measurements and the sensory mechanical threshold were significantly increased between 1–7 days after drug injection in the group given dexamethasone compared with the group not given dexamethasone. No serious side effects were observed.

Conclusions: Addition of small amounts of dexamethasone to bupivacaine incorporated in microcapsules prolonged local analgesia compared with microcapsules with plain bupivacaine after subcutaneous administration in humans.

LOCAL anesthetics are widely used to provide postoperative pain relief, but analgesia is rarely maintained for more than 4–8 h with the longest-acting local anesthetics (bupivacaine, ropivacaine, and levobupivacaine) after incisional administration.1 Attempts to prolong the effect of local anesthetic blockade by increase in dose or by development of new drugs have been unsuccessful, mainly because of toxicity. Long-term catheter infusions of local anesthetics have been useful, particularly when applied in the epidural space or at peripheral nerves, but are inconvenient at most other sites.

A novel approach to achieve an ultra-long local anesthetic effect incorporated an existing local anesthetic into a delivery system that allows a continuous extended release of local anesthetic. One such system incorporates bupivacaine free base into a biodegradable polymer matrix formulated as microcapsules.2 Such a preparation has been found to maintain sciatic nerve blockade in rats between 10 h and 6 days depending on dose, additive, and type of microcapsules.2,3 However, only microcapsules containing small amounts of dexamethasone provided local analgesia for more than 1 day.2 Thus, addition of dexamethasone prolonged sciatic nerve blockade up to 47 h in rats compared with a 7-h duration of sensory blockade obtained with plain bupivacaine microcapsules.3 Further, duration of intercostal nerve blockade in sheep was increased from 4 to 13 days on addition of dexamethasone to bupivacaine microcapsules.4

Thus far, only preliminary clinical data6 are available on the effect of addition of dexamethasone to bupivacaine microcapsules. Therefore, we examined the effect of bupivacaine microcapsules with dexamethasone compared with bupivacaine microcapsules without dexamethasone in a double-blinded, randomized study in a validated human experimental pain model.5

Materials and Methods

We intended to study 12 healthy nonmedicated male volunteers. One subject was excluded from the study at postinjection day 1 (24 h) because of involvement in a traffic accident. This subject was replaced, maintaining the number of studied subjects at 12. The median age of these subjects was 26 yr (range, 23–36 yr); median height, 184 cm (range, 177–202 cm); and median weight, 84.5 kg (range, 70–112 kg). All subjects were interviewed about their health history and underwent a physical examination, including a routine blood and urine analysis, before enrollment in the study. Subjects were excluded on any significant findings in the physical examination or in the medical history. The local Ethics Committee and the Danish National Health Board approved the study, and informed written consent was obtained from all subjects.

The study was performed as a double-blinded, randomized trial with each subject acting as his own

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control, thus receiving microcapsules with and without dexamethasone.

Study medication (supplied by Purdue Pharma L.P., Stamford, CT) consisted of polylactic-coglycolic acid microcapsules, which were approximately 72% loaded with bupivacaine (weight percentage). Microcapsules with dexamethasone contained approximately 72% bupivacaine and 0.04% dexamethasone. When suspended in a special diluent, resulting in a 1.25% concentration of microcapsules, the formulation with and without dexamethasone contained bupivacaine, 9.0 mg/ml. Microcapsules with dexamethasone in addition contained dexamethasone, 5.0 µg/ml.

Immediately before injection, each subject was allocated by computerized randomization to receive bupivacaine microcapsules without dexamethasone in one calf and bupivacaine microcapsules with dexamethasone in the other. Ten milliliters of the 1.25% microcapsule suspension was administered as subcutaneous injections in a 35 × 60 mm area on the medial aspect of both calves containing either microcapsule formulation. The needle size was 0.8 mm × 50 mm (G21 needle). An independent observer provided the syringe for injection, blinded for type of microcapsule preparation. All evaluations were performed by two investigators (K.H. and M.W.) who were blinded to treatment allocation.

The subjects were asked to rate the pain at injection (not needle insertion) by a visual rating scale (VRS) of 0–10. During the injection and for the next 10 min, subjects were monitored by electrocardiograph (ECG) in the presence of a physician. Measurements were performed in a quiet room, and subjects were instructed to close their eyes during measurements. All subjects were familiar with the assessment technique and were trained in ratings with the VRS before the study. The pain model and the testing paradigm used in the evaluations have been validated previously.5

Testing Paradigm

Sensory testing modalities consisted of painful and nonpainful stimuli. Mechanical thresholds were determined by 8 pinpricks with 11 progressively rigid von Frey hairs numbered 7–17 (Senselab Aesthesiometer, Somedic AB, Höör, Sweden) within the test area. The force of each hair increases logarithmically with the number, covering a range of 3–402 mN. The stimuli were applied every 2 s. Each assessment was repeated three times, and the results were presented as medians because of the nonnormal distribution of data. Thermal detection thresholds were determined using a computerized 25 × 50 mm contact thermode (Thermotest, Somedic AB, Höör, Sweden). Baseline evaluations (thermal and mechanical thresholds and VRS ratings) were performed before injection. Thermal and mechanical thresholds and VRS ratings were evaluated at 2, 4, 6, and 8 h and daily for 7 days after injection of the study drug.

Nonpainful Stimuli

The warm detection threshold (WDT) was determined by instructing subjects to press a button when sensing warmth. The heat stimulus was delivered from a baseline temperature of 32°C and a rate of change at 1°C/s, and the cut-off limit was 52°C. Maximal values were assigned at 53°C. The average of three assessments separated by 9-s intervals was determined.

The cold detection threshold (CDT) was determined by instructing subjects to press a button when perceiving cold. The cut-off was 25°C. Maximal values were assigned at 24°C.

The mechanical touch detection threshold (MTDT) was determined as described previously using the ascending design similar to the WDT and CDT. The subject was asked to indicate when he first perceived touch.

Painful Stimuli

The heat pain detection threshold (HPDT) was determined by instructing the subject to press a button when perceiving heat pain.

The heat pain (HP) response was determined by a stimulation of 45°C with a 15 × 25 mm thermode lasting 5 s. The subjects were asked to rate the pain on a VRS at the end of the stimulation.

The mechanical pain detection threshold (MPDT) was determined in the same ascending design. The von Frey hair number, where four or more of eight stimulations were perceived as painful, was recorded.

The mechanical pain (MP) response was determined by five pinpricks with von Frey hair number 17 (402 mN) within the test area, after which subjects were asked to rate the pain on a VRS.

Safety Assessments

Subjects were considered having completed the study 14 days after injection of the study drug, at which time a repeat physical examination, including a blood and urine analysis, was performed. At every visit, vital signs (temperature, blood pressure, heart rate, and respiratory rate) were obtained, and visual inspection and palpation of the injection area were performed. Six weeks after the injection, the test area of all subjects was reexamined. Additional safety follow-up evaluation at 6 months consisted of a telephone interview. Side effects were evaluated ongoing, and subjects were instructed to contact an investigator at any time on experiencing any sign of illness.

Statistical Analysis

Normality of data was evaluated using the Shapiro-Wilk's W test. Data showing normal distribution were analyzed with Student t test. Data showing nonnormal distribution were analyzed with Wilcoxon signed-rank test. Bonferroni correction was added when multiple comparisons were made. Maximal analgesic effect was
calculated as a summary of the seven measurements (WDT, HPDT, CDT, MTDT, MPDT, HP, and MP). To avoid problems related to multiple comparisons at repeated time points, we considered area under curve (AUC) the best summary of local analgesic effect. \( P < 0.05 \) were considered statistically significant.

**Results**

The results are summarized in figures 1 and 2 and table 1. There was no significant difference between the groups in any of the baseline evaluations. VRS scores to pain on injection were not different between bupivacaine microcapsules with or without dexamethasone (Fig. 1). The maximal analgesic effect based on a summary of the seven assessments (WDT, HPDT, CDT, MTDT, MPDT, HP, and MP) did not differ between the groups (Wilcoxon signed-rank test, \( P = 0.33 \); figs. 1, 2). Time to obtain maximal analgesic effect did not differ between the groups, with median time to maximal analgesic effect in the microcapsules without dexamethasone group being 8 h (quartiles, 2.5–24 h) compared with 8 h in the microcapsules with dexamethasone group (quartiles, 2.5–24 h; \( P = 0.38 \)).

During postinjection day 1 (0–24 h), we found no significant difference in the AUC between the two groups in any of the assessed thresholds (table 1). From day 1 to day 7 (24–168 h), the AUC (HPDT, CDT, and MTDT) was significantly increased in the leg receiving microcapsules with dexamethasone compared with microcapsules without dexamethasone (table 1). Although no significant difference was found in the AUC (WDT, HPDT, CDT, HP, and MP).
Table 1. Comparisons of Analgesia Effect between Microcapsules with and without Dexamethasone

<table>
<thead>
<tr>
<th></th>
<th>AUC (0–24 h)</th>
<th>AUC (24–168 h)</th>
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<tbody>
<tr>
<td>Nonpainful</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warm detection threshold (WDT)</td>
<td>0.398</td>
<td>0.050</td>
</tr>
<tr>
<td>Cold detection threshold (CDT)</td>
<td>0.196</td>
<td>0.015*</td>
</tr>
<tr>
<td>Mechanical touch detection threshold (MTDT)</td>
<td>0.328</td>
<td>0.006*</td>
</tr>
<tr>
<td>Painful</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heat pain detection threshold (HPDT)</td>
<td>0.796</td>
<td>0.019*</td>
</tr>
<tr>
<td>Heat pain (HP)</td>
<td>0.106</td>
<td>0.136</td>
</tr>
<tr>
<td>Mechanical pain detection threshold (MPDT)</td>
<td>0.110</td>
<td>0.182</td>
</tr>
<tr>
<td>Mechanical pain (MP)</td>
<td>0.209</td>
<td>0.090</td>
</tr>
</tbody>
</table>

Level of significance for comparison of differences in area under the curve (AUC) between bupivacaine microcapsules with dexamethasone and bupivacaine microcapsules without dexamethasone. The AUCs for all parameters of analgesia were greater with bupivacaine microcapsules with dexamethasone. Comparisons were made with paired t test or Wilcoxon signed-rank test as appropriate. Significant values marked* ($P < 0.05$).

Microcapsules with and without Dexamethasone

MPDT, or HP) between groups, a longer duration of effect was consistently found in the legs receiving microcapsules with dexamethasone. The time to return to baseline levels was longer in the microcapsules with dexamethasone group in all thermal and mechanical pain detection assessments (figs. 1 and 2).

There was no significant difference between the groups in any of the evaluations 1 week after injection or when baseline evaluations were compared with evaluations 1 week after injection, except for the HP, which differed between baseline and 1-week measurements in the microcapsules with dexamethasone group, baseline median 2 (quartiles, 1.25–3.75) and 168 h median 1 (0–1; $P = 0.04$, Wilcoxon signed-rank test + Bonferroni correction).

In one subject, a slight hematoma was present for 2 days at the injection site after injection of microcapsules without dexamethasone. At the 6-week follow-up examination, one subject had a slight induration in test area where microcapsules with dexamethasone had been injected. At 6-month follow-up evaluation in 11 subjects, no side effects at the injection sites were noted, including the subject with slight induration at 6 weeks. One subject could not be located for the 6-month follow-up evaluation. No other side effects were found or reported.

Discussion

We found a significant increase in the AUC for several painful and nonpainful sensory modalities when small amounts of dexamethasone were incorporated into bupivacaine microcapsules compared with microcapsules containing bupivacaine alone, and injected subcutaneously. No difference in local analgesia (AUC) in the first 24 h after injection, the maximal analgesic effect or the time to reach maximal analgesia, was seen between the groups.

Our results are in accordance with experimental studies$^{2,4}$ and a preliminary study in humans with intercostal nerve blockade.$^{6}$

The mechanisms behind the blockade-prolonging effect of glucocorticoids are mostly unknown, but they possibly involve the inhibition of the synthesis, release, or both, of various inflammatory mediators. Dexamethasone alone does not exhibit analgesic effects when incorporated into microcapsules.$^{3}$ Interestingly, the blockade-prolonging effect of glucocorticoids has been reported to be related to the rank-order of their antiinflammatory effect and is completely reversed by administration of a specific glucocorticoid receptor antagonist.$^{5}$ In experimental studies, the absence of granulomatous tissue reaction around the microcapsules when dexamethasone is present$^{1}$ suggests that dexamethasone suppresses the inflammatory and foreign body response to the microcapsules. Consequently, local blood flow or the interaction between bupivacaine and the peripheral nerves may be altered. Other steroid hormones or nonhormonal sterols, such as cholesterol or nonsteroidal antiinflammatory drugs, do not exert blockade-prolonging effects.$^{3}$ Incorporation of dexamethasone has not been shown to alter the kinetics of bupivacaine release from the microcapsules.$^{2}$ Finally, it may be postulated that with inflammatory cell migration and local blood flow reduction local acidosis may occur in the nerve cell. This event may result in a more highly ionized bupivacaine molecule and subsequent trapping of the bupivacaine in the neuronal cell, thereby extending activity.

A slight induration was present in one subject receiving microcapsules with dexamethasone, and a large-scale study of the potential cosmetic effects of the slow-release, local anesthetic dexamethasone preparations is obviously required.

In summary, incorporation of dexamethasone into bupivacaine microcapsules provided extended local analgesia after subcutaneous administration in humans compared with microcapsules containing bupivacaine alone. Because commonly used preparations of local anesthetics only provide sensory blockade for 4–8 h when administered subcutaneously, the prolonged local analgesia obtained from the addition of dexamethasone to the extended-release bupivacaine microcapsules may be of major clinical relevance, particularly for incisional use in operations where pain is a major factor limiting postoperative recovery and convalescence.$^{7,8}$

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References