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Diffusion of mepivacaine to adjacent synovial structures after intrasynovial analgesia of the digital flexor tendon sheath

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Summary

Reasons for performing study: Controversy exists about the specificity of diagnostic analgesia of the digital flexor tendon sheath (DFTS) in horses.
Objectives: To evaluate the degree of diffusion of mepivacaine from the equine DFTS to adjacent synovial structures.
Study design: Crossover experiment.
Methods: Under general anaesthesia, the DFTS of one front and one hindlimb of 8 horses were injected simultaneously with mepivacaine. Synovial fluid samples of the injected DFTS, the adjacent metacarpo-/metatarsophalangeal (MCP/MTP) joint, proximal interphalangeal joint, distal interphalangeal joint, navicular bursa and contralateral MCP/MTP joint were collected 15 min post injection (T15) from one of the injected limbs and 60 min post injection (T60) from the other limb. Venous blood samples were obtained at T0, T15 and T60 to evaluate systemic distribution of mepivacaine. After a 2-week washout period, the procedure was repeated using the same limbs but reversing the time of sampling (front vs. hindlimbs). The concentration of mepivacaine in samples was measured with a commercial ELISA kit.
Results: Mepivacaine concentrations in the DFTS samples, at both T15 (5077 mg/l) and T60 (3503 mg/l), exceeded those estimated sufficient to produce synovial analgesia (100 mg/l or 300 mg/l). Mepivacaine was found in all synovial structures adjacent to the injected DFTS and in the contralateral MCP/MTP joints, but concentrations were low, with a maximum value of only 3.2 mg/l. With the exception of the navicular bursa samples, the mepivacaine concentrations in the adjacent synovial structures were significantly higher at T60 than at T15 ($P<0.03$). Significantly higher mepivacaine concentrations were found in the ipsilateral than the contralateral MCP/MTP joints at T60 ($P<0.001$). Blood samples had significantly higher mepivacaine concentrations at T15 and T60 than at T0 ($P<0.001$).
Conclusions: Mepivacaine injected into the DFTS of horses diffuses towards adjacent synovial structures without achieving clinically relevant concentrations.

Keywords: horse; diagnostic analgesia; diffusion; digital flexor tendon sheath; local anaesthetic; mepivacaine

Introduction

Analgesia of the digital flexor tendon sheath (DFTS) is performed routinely during orthopaedic examinations in horses to localise the source of pain causing lameness [1–4]. There is some controversy about the specificity of this technique. Harper *et al.* [5] reported a high specificity of DFTS analgesia, whereas other authors have suggested that diffusion of local anaesthetic solution can desensitise structures other than those intended, leading to inaccurate localisation of the lameness [3,6,7]. Moreover, recent studies have shown that backflow of local anaesthetic solution to the subcutaneous tissues through the needle puncture hole could affect the palmar digital nerves, desensitising additional structures in the digit [8,9].

Both mepivacaine hydrochloride 2% and lidocaine hydrochloride 2% are frequently used in horses. However, owing to its longer lasting activity and lower tissue irritation, mepivacaine is often the product of choice for local, regional or intrasynovial analgesia [10,11]. Mepivacaine has a small molecular weight and size, and hence easy diffusion through the tissues or between synovial structures could be expected. There is limited available information on the relative activity of local anaesthetics in the horse and the amount required for successful analgesia [12]. Wintzer *et al.* [13] indicated that concentrations >100 mg/l mepivacaine are sufficient for analgesia of the equine tarsocrural joint, while Keegan *et al.* [14] reported that concentrations >300 mg/kg bwt are sufficient for analgesia of the navicular bone and synovial membrane (equivalent to concentrations >300 mg/l when considering a wet tissue density of 1 mg/ml). Other studies have demonstrated diffusion of mepivacaine between synovial structures in the equine foot [15]. However, no study has evaluated the possible diffusion of mepivacaine from the DFTS to adjacent synovial structures.

Therefore, the goals of this study were to evaluate: (1) whether diffusion of mepivacaine hydrochloride from the DFTS to adjacent synovial structures of the distal limb of the horse occurs; and (2) whether this results in clinically relevant concentrations.

Materials and methods

Subjects

Eight horses belonging to the teaching herd of the Faculty of Veterinary Medicine of Ghent University were included in the study (4 Standardbreds and 4 Warmbloods, 7 females and one gelding). The mean age was 11.5 years (range 4–22 years, s.d. 5.3 years) and the mean bodyweight was 545.6 kg (range 470–650 kg, s.d. 54.8 kg). All horses were clinically sound and free of relevant radiographic abnormalities of their distal limbs.

Study design

The study was organised in 2 sessions with a 2-week washout period between the sessions. Under general anaesthesia, horses were placed in lateral recumbency (4 left and 4 right lateral recumbency, randomly determined). All 4 limbs were circumferentially clipped from the coronary band to the proximal aspect of the third metacarpus/metatarsus. The hooves were draped and the skin was aseptically prepared. Synoviocentesis of the DFTS of the uppermost front and hindlimbs was performed with a 25 mm 20 gauge hypodermic needle through a palmar/plantar axial sesamoidean approach [16] by 2 of the 3 operators (M.J., A.M. and F.P.; randomly assigned). A maximum of 2 ml of synovial fluid was aspirated (DFTS sample T0) and,

simultaneously, a venous blood sample from the upper jugular vein (approximately 10 ml) was collected by the anaesthetist (blood sample T0). Subsequently, a standard dose of mepivacaine hydrochloride 2% (Scandicaine[a] 1 ml/50 kg bwt) was injected into both DFTS. Criteria used to determine correct injection in the DFTS were successful synovial fluid aspiration, absence of resistance during injection and visible filling of the DFTS outpouchings while injecting the local anaesthetic solution. After removal of the needle, the injection site was protected with a sterile gauze held by hand and the distal limb was flexed and extended 25 times. Synovial fluid samples from the injected DFTS, the ipsilateral metacarpo-/metatarsophalangeal (MCP/MTP) joint, proximal interphalangeal (PIP) joint, distal interphalangeal (DIP) joint, navicular bursa (NB) and the contralateral MCP/MTP joint were obtained from the front limbs 15 min after DFTS analgesia (T15) and from the hindlimbs 60 min after DFTS analgesia (T60) or vice versa, depending on the predetermined random sampling protocol. The synovial structures to be sampled by each operator were also randomly assigned.

In the second session, 2 weeks later, the same ipsilateral limbs were injected but the time at which samples were obtained from front and hindlimbs (T15 and T60) was reversed.

Synoviocentesis was performed with a 40 mm 19 gauge hypodermic needle for all the joints and DFTS (except at T0) and with a 90 mm 19 gauge spinal needle for the NB. Fluoroscopic guidance was used for all NB and for some PIP and DIP joint synoviocentesis. A dorsal or proximo-palmar/plantar approach was used for the MCP/MTP joints, a dorsolateral approach for the PIP and DIP joints and an abaxial distal palmar/plantar approach to the navicular position was used for the NB [10,17]. When no or insufficient (<200 μl) synovial fluid was retrieved by aspiration, sterile 0.9% saline solution was injected into the synovial space and reaspirated immediately to obtain a diluted sample. Additional blood samples from the upper jugular vein were obtained at T15 and T60 to measure mepivacaine and plasma urea concentrations in case diluted synovial samples were obtained. At the end of each session, horses were given sodium benzyl penicillin[b] (20,000 iu/kg bwt i.v.) and limbs were protected with bandages. Horses were monitored daily for signs of local pain or discomfort.

During each session, 14 synovial and 3 blood samples were collected from each horse. Synovial fluid samples were transferred into 3 ml EDTA sprayed tubes to which 50 iu of hyaluronidase[c] had been added. They were centrifuged at 1000 ***g*** for 15 min, aliquoted and stored frozen at −20°C. Blood samples were transferred into 10 ml lithium heparin tubes, centrifuged at 3000 ***g*** for 20 min, aliquoted and stored frozen at −20°C.

Mepivacaine assay

Evaluation of the mepivacaine concentration in the samples was performed using a commercial ELISA kit able to detect mepivacaine concentrations ranging from 5 to 150 μg/l (Racing ELISA for mepivacaine; kit 102710)[d]. A standard curve was included in the plates to obtain semi-quantitative values of the mepivacaine concentrations. Samples were thawed at room temperature and were batch assayed (all samples run in duplicate). The DFTS samples of T15 and T60 were run at 1:100,000 dilution as very high mepivacaine concentrations were expected. The rest of the samples were run undiluted for the first time. Samples falling outside the regression line because of high mepivacaine concentrations were re-analysed at different dilutions (1:2, 1:10, 1:30, 1:50, 1:100 or 1:1000). If the coefficient of variability (CV) between duplicates was >10%, the assay was repeated.

Urea assay

To allow calculation of actual mepivacaine concentrations in diluted synovial samples, the dilution factor of these samples was determined by comparing the plasma and synovial fluid urea concentrations [18], measured with a commercial enzymatic assay kit (Urea assay kit, MAK006)[c]. Urea assays were performed in fresh samples and in duplicate. If the CV between duplicates was >10%, the assay was repeated. The mepivacaine concentrations of the diluted samples obtained with the ELISA test were corrected by the dilution factors.

Data analysis

Two samples (one NB and one MCP joint) from different horses were excluded from the statistical analysis because there was suspicion that DFTS penetration occurred during sample collection.

Descriptive statistics were calculated and results are presented as mean and standard deviation (s.d.). Three separate mixed models were fitted using SPSS statistics 21[e] with statistical significance set at P<0.05. The first model was fitted to check for local diffusion of mepivacaine to other adjacent synovial structures. Therefore, mepivacaine concentrations in the different adjacent synovial structures were compared including 'location' (MCP/MTP joint, PIP joint, DIP joint and NB), 'limb' (left front, right front, left hind or right hind), 'session' (first or second testing round), 'time' (T15 or T60) and the interaction between 'location' and 'time' as fixed effects factors, and 'horse' (*Horse 1–8*) as a random effects factor. To evaluate the possible distribution of mepivacaine in the bloodstream, a second model was fitted comparing the mepivacaine concentrations in the venous blood samples at the 3 different time points (T0, T15 or T60) including 'session' (first or second testing round) and 'time' as fixed effects factors, and 'horse' (*Horse 1–8*) as random effects factor. To evaluate a possible distribution of mepivacaine to other synovial structures via systemic circulation, a third model was fitted comparing the mepivacaine concentrations of the ipsilateral MCP/MTP joints with the contralateral MCP/MTP joints including 'limb' (left front, right front, left hind or right hind), 'side' (ipsilateral or contralateral to the injected DFTS), 'session' (first or second testing round) and 'time' (T15 or T60) as fixed effects factors, and 'horse' (*Horse 1–8*) as random effects factor. An interaction between 'side' and 'time' was also taken into account.

Results

A total of 224 synovial fluid and 48 venous blood samples were obtained. Overall, the synovial fluid sampling was straightforward, except for 6 of the 32 NB, where aspiration of a sample was only possible after injection of 3 ml of sterile 0.9% saline solution. The mean dilution factor obtained for these samples was 6.3 (range 5.2–7.6, s.d. 0.9), with a mean urea concentration in the diluted synovial fluid samples of 0.7 mmol/l (range 0.4–0.9 mmol/l, s.d. 0.2 mmol/l), and in the serum samples of 4.5 mmol/l (range 3.02–6.1 mmol/l, s.d. 1.2 mmol/l). Blood contamination occurred in some synovial samples during collection. However, after centrifugation and aliquoting, clear synovial samples were obtained, indicating very limited contamination. No relevant complications were encountered during or after the experiment. However, after the first session, 4 horses had moderate distension of one or both injected DFTS (n = 6) compared to the noninjected limb, but no associated pain or lameness.

Table 1 summarises the mean mepivacaine concentrations measured in the different samples at different time points. The mean T0 values for the blood and DFTS samples were under the detection limit of the ELISA kit (5 μg/l). The ELISA results also showed that all DFTS injections were performed successfully, resulting both at T15 and T60 in synovial fluid mepivacaine concentrations that greatly exceeded those estimated sufficient for synovial analgesia (Fig 1) and that were detectable only at the 1:100, 000 dilution.

Mepivacaine was found in all the samples from the synovial structures adjacent to the injected DFTS, the contralateral MCP/MTP joints and blood. However, these mepivacaine concentrations were very low, with the maximum concentration found (3.2 mg/l) being far below the concentrations considered clinically relevant (Fig 1). In all horses, the mepivacaine concentrations in the different synovial structures adjacent to the injected DFTS were significantly higher at T60 than at T15 (P<0.03), except for the NB samples (P = 0.8). However, no significant differences in mepivacaine concentrations were observed between adjacent synovial structures at T15 (P = 0.4) and at T60 (P = 0.2). There was no significant effect of 'limb' and 'session' on the mepivacaine concentrations in any of the 3 statistical models.

Blood samples had higher mepivacaine concentrations at T15 and T60 than at T0 (P<0.001). No significant differences were found

TABLE 1: Mean values ± s.d. of mepivacaine concentrations in mg/l measured in the different synovial structures and venous blood before (T0) and 15 (T15) and 60 min (T60) following intrasynovial analgesia of the digital flexor tendon sheath

Sample	T0	T15	T60
DFTS (n = 64)	0.001 ± 0.002	5077 ± 1930	3503 ± 973
MCP/MTP (n = 31*)	nm	0.021 ± 0.022	0.209 ± 0.289
PIP (n = 32)	nm	0.063 ± 0.064	0.505 ± 0.766
DIP (n = 32)	nm	0.028 ± 0.033	0.336 ± 0.517
NB (n = 31*)	nm	0.164 ± 0.521	0.191 ± 0.312
JV (n = 48)	0.003 ± 0.003	0.037 ± 0.034	0.042 ± 0.033
Cont MCP/MTP (n = 32)	nm	0.007 ± 0.010	0.015 ± 0.016

DFTS, digital flexor tendon sheath; MCP/MTP, metacarpo/metatarsophalangeal joint; PIP, proximal interphalangeal joint; DIP, distal interphalangeal joint; NB, navicular bursa; JV, jugular vein blood; Cont MCP/MTP, contralateral MCP/MTP joint; nm: not measured.
*One NB sample and one MCP joint sample were excluded from statistical analysis owing to technical errors during synoviocentesis.

between T15 and T60 plasma concentrations (P>0.9). When comparing the mepivacaine concentrations of the MCP/MTP joints ipsilateral and contralateral to the injected DFTS, a significant effect of 'time', 'side' and their interaction was found (P = 0.01, P = 0.004 and P = 0.02 respectively). *Post hoc* testing revealed no differences in mepivacaine concentrations between the ipsilateral and the contralateral MCP/MTP joints at T15 (P = 0.7). However, at T60, significantly higher concentrations were found in the ipsilateral MCP/MTP joints than in the contralateral MCP/MTP joints (P<0.001). Unlike the ipsilateral MCP/MTP joints, mepivacaine concentrations in the contralateral MCP/MTP joints did not differ significantly between T15 and T60 (P = 0.9).

Discussion

This study shows that diffusion of mepivacaine from the DFTS to adjacent synovial structures does occur, but to a very low degree. Indeed, none of the synovial samples other than the injected DFTS had mepivacaine concentrations sufficient for synovial analgesia [13,14]. This supports the findings of Harper *et al.* [5] that DFTS analgesia had almost no effect on pain originating from the sole, DIP joint or NB. However, we did not include clinical evaluation of pain. Our findings contrast with the results of the diffusion studies looking at other synovial structures in the equine digit, where 32% of NB samples and 44% of DIP joint samples had mepivacaine concentrations >300 mg/l after DIP joint and NB injection, respectively [15]. The different anatomical relationships between the DIPJ and the NB and between the DFTS and the adjacent synovial structures that we tested could explain these differences. Moreover, the differences in volume of local anaesthetic used in these studies could also play a role. Gough *et al.* [15] injected 5 ml of a 2% mepivacaine hydrochloride solution in the NB or DIP joint (which are small synovial cavities) representing a much higher relative volume compared to the approximately 10 ml injected in the DFTS (a much larger synovial cavity) used in our study. Hence, it could be hypothesised that a lower intrasynovial pressure in the DFTS in our study may have influenced the degree of local diffusion. The dose-volume of local anaesthetic used in our study is the same used in clinical situations to provide analgesia during lameness examinations [1,5,9] and did not result in a marked distension of the DFTS outpouchings. However, in the clinical situation the DFTS is often distended when intrasynovial anaesthesia is performed, which may possibly result in a different intrasynovial pressure than occurred in the current study. Further studies comparing different volumes of local anaesthetic solution injected into the DFTS would be necessary to confirm this hypothesis.

Local anaesthetics, once administered into a synovial cavity, are cleared from the synovial fluid by the lymphatic vessels, redistributed to the cardiovascular system and subsequently transported throughout the body [19,20]. Local diffusion through the synovial membrane and soft tissues [14,21] and leakage through the needle entrance point into the subcutaneous tissues [8,9] are other possible ways of redistribution of

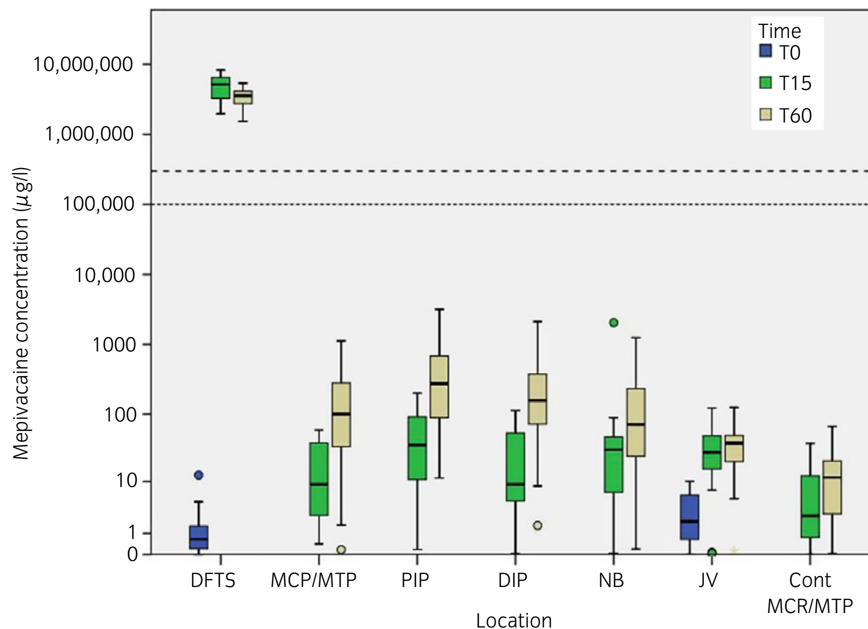

Fig 1: Mepivacaine concentrations in the different synovial structures and blood, at the different time points before (T0) and 15 (T15) and 60 min (T60) following intrasynovial analgesia of the digital flexor tendon sheath. T0: blue; T15: green and T60: yellow, Values are expressed on a logarithmic scale. The box represents the interquartile range, the line represents the median of the values and the whiskers represent the minimal and the maximal values excluding outliers (circles) and extreme values (asterisk). DFTS, digital flexor tendon sheath; MCP/MTP, metacarpo/metatarsophalangeal joint; PIP, proximal interphalangeal joint; DIP, distal interphalangeal joint; NB, navicular bursa; JV, jugular-vein blood; Cont MCP/MTP: contralateral MCP/MTP joint. Clinically relevant mepivacaine concentrations are indicated as ····100 mg/l; ---- 300 mg/l.

local anaesthetic solutions. In our study, mepivacaine concentrations in the synovial fluid of the ipsilateral MCP/MTP joints were significantly higher than in the contralateral MCP/MTP joints 60 min after DFTS analgesia. Mepivacaine concentrations in the venous blood samples were lower than in the ipsilateral MCP/MTP joints but higher than in the contralateral ones. This suggests that absorption of mepivacaine through the synovial membrane to the systemic circulation occurs but the low systemic concentrations achieved are insufficient to result in relevant diffusion of mepivacaine to other synovial structures. Therefore, local diffusion, rather than systemic distribution, seems most likely to be responsible for the mepivacaine concentrations obtained in the ipsilateral synovial structures.

Clearly, the current study only evaluated the presence of mepivacaine in synovial compartments and not in the soft tissues or surrounding nerves. As demonstrated previously, nonspecific desensitisation of the distal limb may occur as a result of leakage of anaesthetic from the puncture hole in the DFTS and/or diffusion of anaesthetic through the wall of the DFTS [8,9]. Further studies measuring mepivacaine concentrations in the synovial lining and in the tissues surrounding the DFTS would be necessary to determine the exact pathway of diffusion of mepivacaine from the DFTS to the nearby structures [14].

The mean mepivacaine concentrations measured in the DFTS samples obtained 15 minutes after intrasynovial analgesia were approximately 17 times higher than those considered clinically relevant and remained very high at 60 min post injection. Local anaesthetics are cytotoxic and the degree of tissue irritation they produce correlates with their anaesthetic potency [12,22]. Four horses in this study had moderate distension of the DFTS after the first synoviocentesis. Hence, it would be tempting to reduce the dose of mepivacaine used for DFTS analgesia during lameness investigations [23]. However, some lameness caused by pathology localised within the DFTS may respond only partially to DFTS analgesia performed with a standard dose of mepivacaine [24]. Therefore, further studies would be necessary before the optimal dose for DFTS analgesia could be established.

Conclusion

In conclusion, the current study shows that diffusion of mepivacaine to adjacent synovial structures at the level of the digit after analgesia of the equine DFTS occurs. However, mepivacaine in the MCP/MTP joint, PIP joint, DIP joint and NB did not reach concentrations sufficient for synovial analgesia. The presence of mepivacaine in those adjacent synovial structures is probably the result of local diffusion rather than of systemic distribution.

Authors' declaration of interests

No competing interests have been declared.

Ethical animal research

The study was approved and overseen by the ethical committee of Ghent University (Belgium) with the approval number: EC 2013/163.

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Authorship

M. Jordana, A. Martens, M. Haspeslagh and F. Pille contributed to the study design, study execution, data analysis and interpretation, and preparation of the manuscript. K. Vanderperren contributed to the study design, study execution, and preparation of the manuscript. L. Duchateau contributed to the study design, data analysis and interpretation, and preparation of the manuscript. M. Oosterlinck contributed to the study design, and preparation of the manuscript. All authors approved the final version of the manuscript.

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