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MAGNETIC STIMULATION OF THE NERVOUS SYSTEM IN DOGS AND CATS

Magnetische stimulatie van het zenuwstelsel bij de hond en de kat

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Thesis submitted in fulfillment of the requirements for the degree of Doctor in Veterinary Sciences (PhD), Faculty of Veterinary Medicine, Ghent University

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Heb geduld.
Alle dingen zijn moeilijk, voor dat ze gemakkelijk worden!

(gezegde uit Perzië)

Voor Darko

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AAI	ARX-derived auditory evoked potential index
ALS	amyotrophic lateral sclerosis
AM	acepromazine and methadone
ARX	autoregressive model with exogenous input
BAEP	brainstem auditory evoked potential
BIS	bispectral analysis index
BW	bodyweight
CI	confidence interval
CMAP	compound muscle action potential
CMCT	central motor conduction time
CSM	cervical spondylotic myelopathy
CT	computed tomography
CTM	cranial tibial muscle
DAWS	disc associated wobbler syndrome
DPP	deep pain perception
EEG	electroencephalogram
ECRM	extensor carpi radialis muscle
EMEP	electric motor evoked potential
EMG	electromyography
IV	intravenous
ISI	intraspinal signal intensity
Md	medetomidine
MEP	motor evoked potential
MLAEP	mid-latency auditory evoked potential
MMEP	magnetic motor evoked potential
MRI	magnetic resonance imaging
ms	milliseconds
MS	magnetic stimulation
mV	millivolt
NE	neurological examination
PNP	polyneuropathy
PR	proprioception
TMMEP	transcranial magnetic motor evoked potential
TMS	transcranial magnetic stimulation
TE	echo time
TR	repetition time
µV	microvolt
WR	withdrawal reflex

The central and peripheral motor nervous system controls and initiates every motor action of the body. The nervous system consists of the brain, the spinal cord, spinal nerve roots and peripheral nerves. Motor activities originate in the motor cortex of the brain and descend along different motor pathways in the spinal cord to the peripheral nerves. Injury to one of these different centres will result in clinical symptoms varying from gait abnormalities to paralysis, depending on the severity of the lesion.

Especially in cases of subtle clinical symptoms, an objective and non-invasive clinical diagnostic test to localize the lesion would be extremely helpful. Furthermore, the ability of a diagnostic test to point out clinical significance of abnormal diagnostic findings or to provide additional prognostic information of a lesion would be advantageous.

In man, the development of magnetic stimulation of the nervous system in the 1980's opened new opportunities in studying motor tracts. Since then, several studies have focussed on its application in brain, spinal cord and peripheral nerve disorders. In veterinary medicine, however, clinical studies are still rare. Therefore it was a challenge to test the usefulness of magnetic stimulation as a diagnostic and prognostic tool in small animal medicine.

In the first part of this thesis (**chapter 1**) assessment of motor pathways in human and veterinary medicine is extensively reviewed, describing both techniques of peripheral nerve and motor cortex stimulation. In the second part our own studies on peripheral nerve stimulation in dogs and cats are reported (**chapter 3, 4 and 5**). In the third part of this work, the technique of transcranial magnetic stimulation in healthy dogs (**chapter 6**) and in dogs with cervical spinal cord disease (**chapter 7**) is discussed.

CHAPTER 1

ASSESSMENT OF MOTOR PATHWAYS BY MAGNETIC STIMULATION IN HUMAN AND VETERINARY MEDICINE

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SUMMARY

Magnetic stimulation is a non-invasive and painless technique for studying the motor pathways in medical neurology. A time-varying magnetic field induces an electrical field in conducting objects such as nervous tissue. The technique can be applied to nerve roots and peripheral nerves or to the motor cortex of the brain in human and veterinary medicine. In this review, the basic principles, applications and risk factors of peripheral nerve and motor cortex stimulation in human and veterinary medicine are discussed.

INTRODUCTION

Clinical electrophysiology of the nervous system is an objective extension of the clinical neurological examination and includes, among others, the evaluation of the integrity and the conduction along the motor pathways and of the excitability of the motor cortex and nerves. In medical neurology these techniques have been used for several years and have evolved rapidly (Kimura, 2001a). A good neurological diagnostic tool requires the following benefits: the possibility to establish an early diagnosis or a diagnosis with greater certainty than existing methods, the ability to give a better prediction or a likely course of a disease, supply support for interventions, and aid in the optimal treatment planning or even provide improvement of the clinical outcome as a therapy. Magnetic stimulation of the nervous system may provide promises that are relevant in all these aforementioned ways.

The technique of magnetic stimulation is based on Faraday's law of electromagnetic induction, i.e., a time-varying or moving magnetic field induces an electrical voltage in a circuit. Thus the stimulation of the nervous tissue is electrical but it is induced by the magnetic field. The procedure of magnetic stimulation and capturing the evoked motor responses in the periphery is reported as painless and well tolerated (Barker et al., 1985, Barker et al., 1987), in contrast to electrical stimulation which is uncomfortable and causes distress and pain (Merton et al., 1982). This results primarily from the fact that a magnetic field falls off as the inverse of the distance whereas an electrical field falls off as the inverse square, indicating that substantially higher fields are needed to induce activation of the nervous tissues in electrical stimulation (Levy, 1988).

In this review, we want to discuss the basic principles, applications and risk factors of magnetic peripheral nerve and transcranial magnetic stimulation in human and veterinary medicine.

Magnetic stimulation of the peripheral nervous system

Basic principles

A magnetic field is generated by passing an electric current through a coil of wire, called the magnetic coil, which is placed close to the nerve root or peripheral nerve. This magnetic field induces an electric field which flows perpendicular to the magnetic field and which is

proportional to the magnetic field. The induced electric field can stimulate the nerve root or peripheral nerve and generate a muscle contraction in the periphery which can be measured by a standard EMG machine (figure 1). The mechanism of stimulating at the neural level is the same as for electrical stimulation, namely a current that passes across a nerve membrane and into the axon which results in depolarization and the initiation of an action potential that propagates by the normal method of nerve conduction (Barker et al., 1987). Thus the magnetic motor evoked potential (MMEP) can be used to demonstrate the functional integrity and conduction along the peripheral nerve.

Magnetic peripheral nerve stimulation has three main advantages over conventional electrical stimulation. First, the technique is reported as causing a minimum of discomfort in the patient in contrary to electrical nerve stimulation (Barker et al., 1987; Barker, 1991; Barker, 1999). In veterinary medicine this is extremely important, as the technique can be performed under sedation in contrast to electrical stimulation which has to be performed under general anaesthesia. Second, magnetic fields attenuate very little through various tissues and thus the possibility exists of stimulating deeply situated peripheral nerves (Barker et al., 1985). In human medicine, the ability to stimulate, without discomfort, deeply situated nerves such as the lumbar roots, the brachial plexus and the sciatic, radial and femoral nerve is reported (Krain et al., 1989; Mills et al., 1987). Third, no direct electrical and mechanical contact with the body is needed and hence skin preparation is unnecessary and traumatised regions are easily investigated (Barker, 1991). The magnetic coil can be held some millimetres away for the body which can be advantageous in cases where physical contact with the tissues is contraindicated. Additionally, the coil can easily be moved over the area of interest, which makes positioning for the optimal stimulating site rapid and uncomplicated (Barker et al., 1987).

Since the introduction of magnetic stimulation, however, some objections of the technique have been raised as well. In the first place, the exact site of stimulation on the nerve is not well defined. With electrical stimulation, the site of stimulation is normally taken to be under the cathode. In magnetic stimulation, the site of stimulation is, among others, dependant on the coil and the nerve geometry (Barker, 1991; Barker, 1999). Initially, circular coils were used in which the circumference of the coil acts as the ‘active’ region of the coil (Evans, 1991). The best position to stimulate a nerve is to place the circular coil tangentially to the nerve and parallel to the surface of the limb (Chokroverty, 1989; Jalinous, 1991). Moreover,

the induced current in the tissue decreases rapidly with distance from the coil and hence the coil should be placed close to the area to be stimulated (Ravnborg et al., 1990; Jalinous, 1991). Later on, new coil designs have been proposed to better focus the site of stimulation, including smaller circular coils and 8-shaped or butterfly coils (Cadwell, 1989; Olney et al., 1990); the most successful coil design being the butterfly coil that is far superior in selectively stimulating a peripheral nerve (Cohen et al., 1990; Olney et al., 1990).

A second major problem of magnetic peripheral nerve stimulation is the difficulty in obtaining supramaximal stimulation of the motor nerve (Maccabee et al., 1988; Evans, 1991). In clinical nerve conduction studies this is essential because it reflects the number of functionally intact axons at and distal to the point of stimulation. Several studies have published varying degrees of submaximal stimulation of superficial peripheral nerves after magnetic stimulation (Evans et al., 1988; Maccabee et al., 1988; Amassian et al., 1989; Chokroverty, 1989; Chokroverty et al., 1989a; Hallett et al., 1989; Olney et al., 1990; Evans, 1991). To the contrary, two studies report instances in which compound muscle action potentials (CMAP) with larger amplitudes than that obtained with electrical supramaximal stimulation of the same nerve are observed (Maccabee et al., 1988; Chokroverty et al., 1989a). A possible explanation for this phenomenon may be double stimulation of some axons by the circulating magnetic fields (Benecke, 1996).

In general, magnetic stimulation of peripheral nerves and nerve roots has some major advantages over conventional electrical stimulation and hence its use in clinical practice, especially in veterinary patients, might be promising.

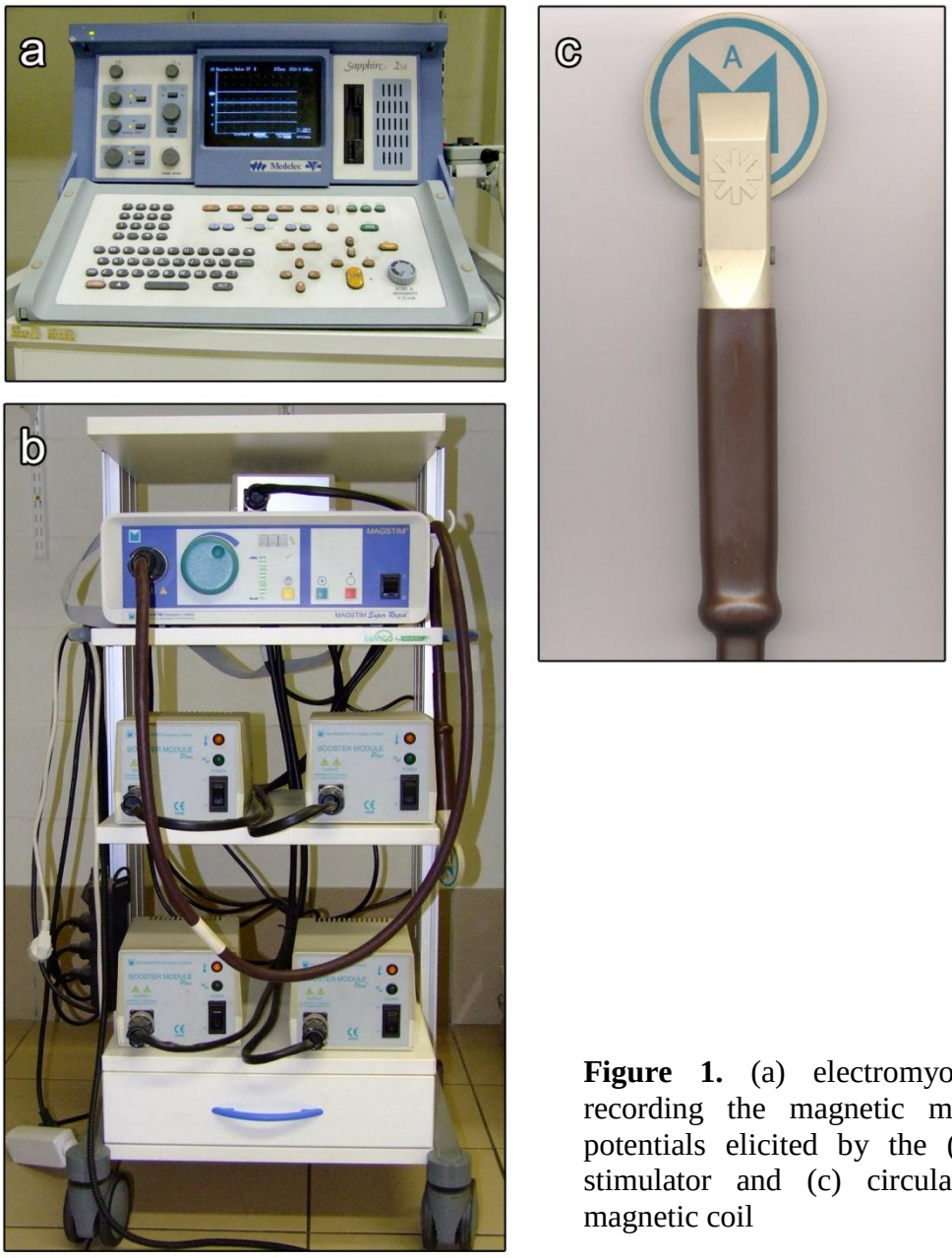

Figure 1. (a) electromyography unit recording the magnetic motor evoked potentials elicited by the (b) magnetic stimulator and (c) circular 45 mm magnetic coil

Procedure and measured parameters

For nerve roots, the magnetic coil is placed in a plane parallel to the axis of the spine and the coil is moved vertically and laterally to obtain consistent and maximal amplitudes of the CMAP. These motor nerve roots appear to be stimulated at their exit from the vertebral canal in the intervertebral foramina (Ugawa et al., 1989; Chokroverty et al., 1991; Epstein, 1991; Tomberg, 1995). For peripheral nerves, the magnetic coil is placed tangentially and as close as possible to the nerve under investigation (Chokroverty et al., 1989a).

Recordings in humans are made from surface electrodes attached to the skin overlying the peripheral muscles using a standard EMG machine (Evans et al., 1988; Maccabee et al., 1988; Amassian et al., 1989; Chokroverty, 1989; Olney et al., 1990; Ravnborg et al., 1990; Binkofski et al., 1999). Surface electrodes are better in nerve conduction studies than needle electrodes because they register electrical activity non selectively from a wider region and thus summate activities from many motor units (Kimura, 2001b). In animal studies, needle electrodes inserted into the muscles are mainly used as surface electrodes might produce inadequate recordings due to the high impedance of the skin (Cuddon, 2002) (Figure 2).

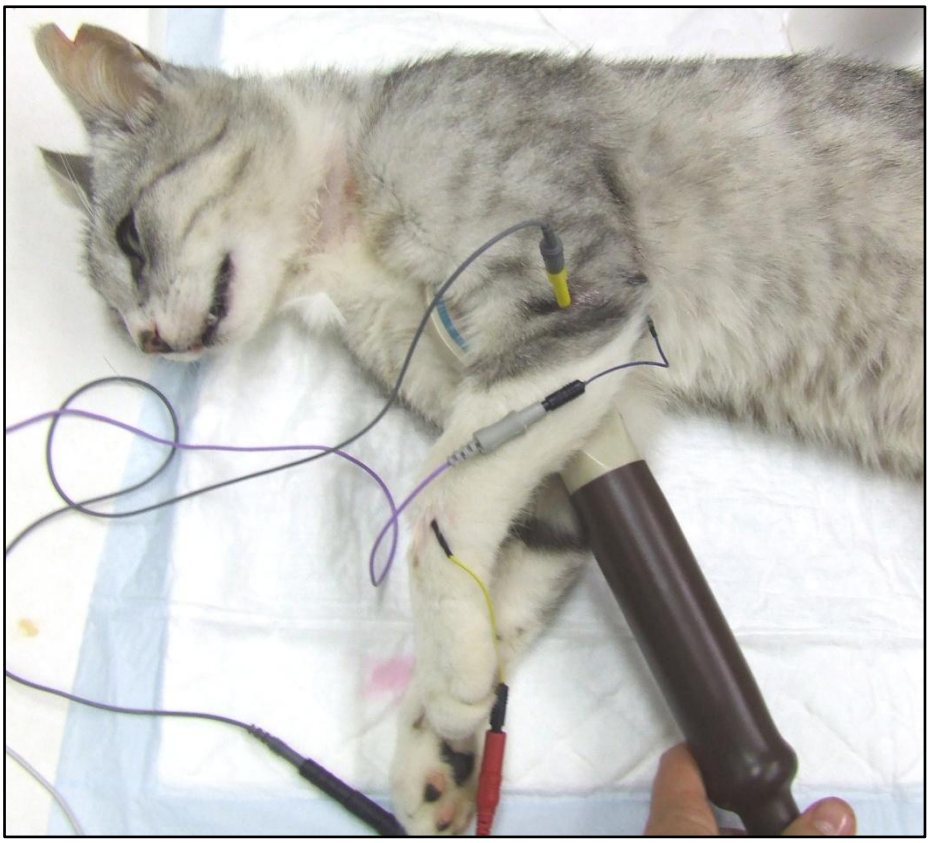

Figure 2. Position of the circular 45mm coil in the axillary region of a cat for stimulation of the proximal radial nerve and position of the recording needle electrodes in the thoracic limb.

MMEP are evaluated by their latency, amplitude and configuration. Latency is the interval between the delivered stimulus and the resulting response and reflects the total conduction from the stimulating point to the target muscle. Latency is expressed in milliseconds (ms). Amplitude refers to the recorded voltage of the response and is measured from the baseline to the initial peak or from the negative to the positive peak (peak-to-peak amplitude). Amplitude

is mostly expressed in absolute terms, as microvolt (µV) or millivolt (mV). The configuration of MMEP after peripheral nerve stimulation is in most instances biphasic as for CMAP recorded after electrical stimulation (Figure 3).

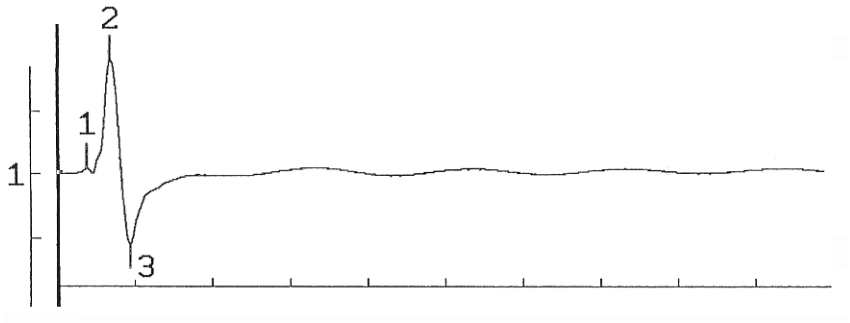

Figure 3. Typical biphasic magnetic motor evoked potential recorded in the extensor carpi radialis muscle of a dog after stimulation of the proximal radial nerve. 1: onset latency (in ms), 2-3: peak-to-peak amplitude

Clinical applications in human medicine

Clinical applications of magnetic stimulation of the peripheral nervous system have been described in different pathologies in humans. In different cases with polyradiculoneuropathy (Maegaki et al., 1994), cervical magnetic nerve root stimulation was useful in evaluating the proximal lesion of the nerve by increasing the latencies, prolonging the durations and changing the shapes of the evoked potentials. In acute and chronic inflammatory demyelinating polyneuropathies, CMAP appeared decreased and conduction prolonged after stimulation of root T1 and the brachial plexus (Benecke, 1996). In brachial plexus injuries (Öge et al., 1997), magnetic nerve root stimulation studies provided information on the site of the lesion and the relative amounts of segmental demyelination and axonal loss. In lumbosacral radiculopathies, however, magnetic stimulation showed less useful than conventional electrical stimulation or needle EMG because of difficulties in obtaining maximal responses in the lower extremities (Chokroverty et al., 1989b; Macdonell et al., 1992; Ertekin et al., 1994).

Clinical applications in veterinary medicine

In comparison to transcranial magnetic stimulation, the clinical use of magnetic stimulation of peripheral nerves in veterinary medicine is rare (Heckmann et al., 1989). For that reason, it was a challenge for us to test the usefulness of peripheral magnetic nerve stimulation in dogs and cats as an index of motor nerve function.

Transcranial magnetic motor evoked response testing

Basic principles

In transcranial magnetic stimulation (TMS) a pulse of current is passed into a coil placed over the patient's head. This current induces changing magnetic pulses that can penetrate the skull and brain and in turn induce ionic current in the brain. Single pulses of stimuli will depolarize neurons, activate motor pathways and evoke measurable effects in the periphery, i.e. an evoked muscle twitch or surface potential response can be recorded in the periphery. TMS can be regarded as the counterpart of somatosensory evoked potential testing where cortical potentials are recorded over the scalp in response to peripheral nerve stimulation (Ghaly et al., 1999).

Since the use of TMS, there has been controversy over which structures in the cerebral cortex are activated. The most recent hypothesis states, that TMS tends to activate corticospinal (pyramidal) neurons indirectly (indirect wave) via synaptic inputs rather than at the axon of the pyramidal tract neurones (Di Lazzaro et al., 2004; Hallett, 2007). This in contrary to transcranial electrical stimulation that produces an early D-wave (direct wave) that reflects direct activation of the descending axons in the corticospinal tracts (Hallet, 2007) . The result of this difference in activation results in EMG responses that are recorded 1-2 ms later than those recorded after transcranial electrical stimulation. Moreover, experimental animal studies concluded that activation of several descending pathways, which converge on common spinal interneurons and motoneurons contribute to MMEP. MMEP evoked by TMS were not only mediated by the corticospinal tract (i.e. pyramidal pathway), but by extrapyramidal pathways as well (Kawai and Nagao, 1992; Nielsen et al., 2007).

Procedure and measured parameters

Stimulation of the motor cortex is achieved via a magnetic coil held tangentially over the scalp (Figure 4) and evokes electromyographic responses in the contralateral appendicular

muscles. In human medicine, MMEP recordings are made with a standard EMG machine using surface electrodes attached to the skin overlying the muscles (Barker et al., 1987). In veterinary medicine, needle electrodes are inserted in the muscles to record MMEP (Nollet et al., 2002; Van Ham et al., 1994, 1995, 1996a, 1996b; Young et al., 1994).

Figure 4. Position of the magnetic circular 45mm coil for transcranial magnetic stimulation in the dog, centrally at the vertex.

Evaluation of TMS is based on specific parameters of the magnetic motor evoked potentials that can be measured on the oscilloscope of the EMG machine. As for peripheral nerve stimulation, onset latency (interval between delivery of the stimulus and the resulting response) and amplitude (refers to the recorded voltage of the response) are the initially measured data of the magnetic evoked potential (Nollet et al., 2005) (Figure 5). Onset-latency and amplitude, however, are influenced by different factors such as voluntary contraction, coil position and age, gender and height of the patient (Nollet et al., 2005) Therefore, in human medicine, additional parameters have been introduced to increase the diagnostic sensitivity. Examples of these parameters are: motor threshold reflecting the lowest TMS intensity capable of eliciting small motor evoked potentials (50-100µV), recruitment curve referring to the increase in amplitude with increasing TMS intensity, central motor conduction time (CMCT) which is an estimation of the conduction time of corticospinal fibers between motor

cortex and spinal or bulbar motor neurons and the triple stimulation technique which is based on the CMCT but suppresses the desynchronization of the magnetic evoked potentials (Magistris et al., 1998; Komissarow et al., 2004; Chen et al., 2008).

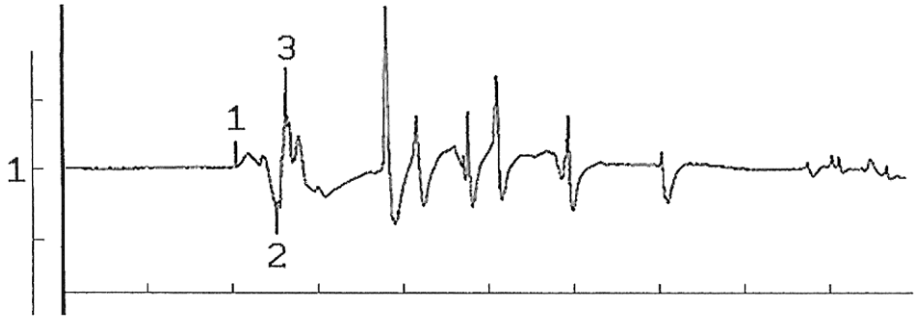

Figure 5. Normal waveform recorded in the cranial tibial muscle in a normal dog after stimulation of the motor cortex with a circular 45mm coil placed centrally at the vertex.
1: onset latency (in ms), 2-3: peak-to-peak amplitude

Clinical application of TMS in human medicine

Transcranial magnetic stimulation in human medicine is applied in several clinical settings: the technique is used for diagnostic, prognostic, therapeutic and monitoring purposes.

Diagnostic applications

The clinical diagnostic utility of TMS has been described in different diseases. First of all, TMS is a sensitive method to detect myelopathy and even in the absence of radiological changes, abnormalities can be detected. Especially in the diagnosis of cervical spondylotic myelopathy (CSM), the use of TMS has been studied and several opportunities of the technique are documented (Maertens de Noordhout et al., 1991; Di Lazzaro et al., 1992; Kaneko et al., 2001; Lo et al., 2004; Kalupahana et al., 2008). For example, TMS of the motor cortex in CSM is useful in the early assessment of corticospinal tract damage and moreover can detect lesions at a preclinical stage (Maertens de Noordhout et al., 1991; Linden and Berlit, 1994; Kaneko et al., 2001). In more recent studies, TMS has shown an excellent correlation with magnetic resonance findings in CSM patients (Lo et al., 2004).

Furthermore, transcranial magnetic motor evoked potentials provide an objective supplement to the neurological examination in recording the level of spinal cord injury (Chan et al., 1998;

Misawa et al., 2001; Taniguchi et al., 2002; Shields et al., 2006). And what is more, during manipulation of the cord, magnetic motor evoked potentials have proven to be sensitive to injury (Levy, 1988) and can therefore be applied as monitoring tool during surgical procedures. In contrast however, TMS cannot determine the nature or cause of the spinal cord lesion (Brunholzl and Claus, 1994) and thus advanced imaging of the spinal cord or histopathology of the lesion remains necessary to find the exact aetiology of the pathology.

In human medicine, a frequent differential diagnosis of myelopathy is amyotrophic lateral sclerosis (ALS), a motor neuron disease. Studies have shown that MMEP can differentiate between ALS and compressive myelopathy (Urban et al., 1998; Truffert et al., 2000). The diagnostic sensitivity of TMS in ALS patients can even be increased by combining different parameters of MMEP or by studying multiple muscles (Schreifer et al., 1989; Eisen et al., 1990; Pouget et al., 2000; Urban et al., 2001; de Carvalho et al., 2003; Attarian et al., 2005; Attarian et al., 2007).

The diagnostic utility of TMS is, however, not restricted to pure spinal cord diseases. Likewise, the different parameters of MMEP after TMS can be changed in multiple sclerosis (Gagliardo et al., 2007; Kalkers et al., 2007), stroke patients (Ferbert et al., 1992; Escudero et al., 1998; Stulin et al., 2003), movement disorders as Parkinson's disease (De Rosa et al., 2006), dystonia (Abbruzzese et al., 2001), cerebellar disorders (Di Lazzaro et al., 1994), epilepsy (Tassinari et al., 2003) and facial palsies (Schreifer et al., 1988).

Prognostic indications

In human medicine, indicators for motor recovery are essential in the course of any underlying disease. Such indicators should be objective, reliable and early detectable in the course of the disease. Therefore, the value of MMEP as prognostic indicator has been assessed in different human studies and although contradictory results have been found, its significance in refining the prognosis has been shown in spinal cord injuries in humans. For example, the inability to evoke MMEP below the level of the spinal cord lesion indicated a worse prognosis in comparison to cases where MMEP could be evoked distal to a lesion (Clarke et al., 1994). Moreover, TMS could be used as an independent predictor of surgical outcome in severe cases of cervical spondylotic myelopathy (Lo, 2007). In contrast, in traumatic cervical spinal cord trauma, TMS did not provide more useful information regarding motor recovery than the physical examination, but may be of benefit in

uncooperative or incomprehensive patients (McKay et al., 1997, Kirshblum and O' Connor, 1998).

Similarly to spinal cord injuries, in acute stroke patients, the presence of MMEP in the paretic limb in response to stimulation of the affected hemisphere, predicted good recovery in those patients (Heald et al., 1993; Escudero et al., 1998; Hendricks et al., 2003). The absence of MMEP within 48 hours predicted absent or very poor functional motor recovery (Pennisi et al., 1999).

Therapeutic applications with repetitive TMS

Recently, repetitive TMS has been introduced. These trains of stimuli can modify the excitability of the cortical neurons or of neurons at remote areas of the stimulating site. The effect can range from inhibition to facilitation depending on the variables of stimulation.

The initial commercially available stimulators could achieve a stimulus frequency of only 0.5Hz because a limitation in recharging time. Currently, however, the magnetic stimulators can achieve frequencies of 100Hz. These stimulators can be used to change the state of the brain for a certain period of time, even after the stimulation has ceased (Terao and Ugawa, 2002). Nowadays, high frequency (> 1Hz) and low frequency (< 1Hz) repetitive TMS are applied to the motor cortex.

It is assumed that the general effect of high frequency repetitive TMS is facilatory and of low frequency repetitive TMS inhibitory (Berardelli et al., 1998; Chen et al., 1997; Pascual-Leone, 1998). With high frequency repetitive TMS, the risk of inducing seizures was issued and specific guidelines for repetitive TMS were drafted (Loo et al., 2008; Wasserman, 1998). Low frequency repetitive TMS decreases cortical excitability and can therefore be useful in suppressing the development or spread of epileptogenic activity in epileptic patients (Wasserman et al., 1996).

Repetitive transcranial magnetic stimulation has been used in human medicine for the treatment of depression (George, 1995, 1997), obsessive compulsive disorders (Greenberg, 1997), spasticity (Nielsen et al., 1995, 1996), Parkinsonism, chronic pain and epilepsy (Kobayashi and Pascual-Leone, 2003; Machii et al., 2006; Bae et al., 2007).

After years of speculations and experiments, however, repetitive TMS has not yet yielded any specific treatment plan that effectively alleviates any of the aforementioned disorders. Most

recent studies indicate that the use of low frequency repetitive TMS might be the most promising approach for future clinical studies (Wasserman and Lisanby, 2001).

Clinical applications of TMS in veterinary medicine

Compared with the growing number of studies in human medicine, there are surprisingly few studies in animals using TMS in clinical settings. Several experimental studies have been performed but basically to explore the possible stimulation parameters and to replicate these findings in human models.

Many experimental studies have been performed in animals to explore the different effects of chemical restraint on the responses elicited by transcranial stimulation of the motor cortex (Ghaly et al., 1990; Strain et al., 1990; Sylvestre et al., 1992; Glassman et al., 1993; Van Ham et al., 1994; Van Ham et al., 1995; 1996a; 1996b; Young et al., 1994; Fishback et al., 1995; Chiba et al., 1998; Ghaly et al., 1999; Nollet et al., 2003). Most of the commonly used anaesthetic regimens severely attenuate or even completely obliterate the magnetic evoked responses. The choice of anaesthetic regimen, therefore, is essential in clinical settings. As the technique of TMS is described as painless and well tolerated (Barker et al., 1985, Barker et al., 1987), sedation in horses and dogs in clinical studies have been shown satisfactory to perform the procedure (Nollet et al., 2003, Van Ham et al., 1994; Van Ham et al., 1995; 1996a; 1996b).

Diagnostic applications in clinical practice

The technique of magnetic stimulation of the motor cortex has been described to diagnose spinal cord dysfunction in horses (Nollet et al., 2002; Nollet et al., 2003; Nollet et al., 2005) and dogs (Sylvestre et al., 1993; Poma et al., 2002; da Costa et al., 2006). In horses with cervical spinal cord lesions, significantly different MMEP parameters were found in comparison to reference values of normal horses (Nollet et al., 2002). Moreover, TMS could be used for differentiating thoracic or thoracolumbar spinal cord lesions from mild cervical spinal cord lesions that cause ataxia in the hind limbs only (Nollet et al., 2003). In dogs with intervertebral disc disease, MMEP were very sensitive to spinal cord damage, as indicated by the significant prolongation in the latencies and attenuation in the amplitudes in patients with mild or no neurologic deficits and in the loss of response in dogs that were severely ataxic (Sylvestre et al., 1993). In Doberman Pinschers and other large breed dogs with cervical spinal cord disease, magnetic resonance findings and neurological deficits correlated well with MMEP parameters. Even in dogs with neck pain alone, impairment of the cervical spinal

cord was found with the use of MMEP (Poma et al., 2002; da Costa et al., 2006). Future veterinary studies on the effects of different spinal cord pathologies on MMEP parameters are needed, however, to evaluate its clinical diagnostic relevance. Moreover, an objective parameter to assess the effects of sedatives and anaesthetics on MMEP might be useful.

Prognostic and therapeutic applications in clinical practice

Currently, the prognostic and therapeutic utilities of TMS in veterinary medicine have not been extensively examined.

Risk factors of magnetic stimulation

Risk factors of magnetic stimulation are mainly studied in human reports or experimental animal studies and generally concern transcranial magnetic stimulation. The most important risks and side effects are summarized in this section.

Reported risk factors of single pulse TMS and repetitive TMS include seizures (Loo et al., 2008). These seizures mostly occur during TMS and in epileptic patients, although seizure activity has also been reported in healthy subjects (Loo et al., 2008). Some reports describe delayed seizures after TMS in epileptic patients (Loo et al., 2008).

When a current is discharged in the stimulating magnetic coil, a click sound is produced by the rapid mechanical deformation of the stimulating coil. Counter et al. described in 1990 a threshold increase to auditory stimuli in rabbits after exposure to 50 single TMS stimuli at 50-100% of maximum machine power (Counter et al., 1990). In a follow up study in rabbits, however, no deleterious effects after extensive exposure to long term TMS were observed on the protected ears in rabbits (Counter, 1994). In human patients, a transient increase of the auditory threshold is reported (Pascual-Leone et al., 1992). The routine use of foam earplugs for both patients and operators is, nevertheless, recommended.

Mild headache is reported as the most common side effect of repetitive TMS trails. It is possibly an effect of the induced facial muscles twitch or of a change in cerebral blood flow (Loo et al., 2008).

During single and repetitive stimulations, eddy currents are being induced in any conducting object within the magnetic field. Therefore, metal substances as implants or electrodes might be heated (Pascual-Leone et al., 1990) or moved and malfunctioning of electronic devices

(e.g. pacemakers) can occur. It is therefore recommended to take caution to perform the technique in patients with such implants.
Most human and veterinary studies failed to demonstrate any significant histopathological changes or structural MRI changes after repetitive TMS (Sgro et al., 1991, Okada et al., 2002, Gates et al., 1992, Nahas et al., 2000).

Finally, in human medicine, the possible risk of developing psychiatric complications, as mania or hypomania, after repetitive TMS, has also been reported (Nahas et al., 1999; Nedjat and Folkerts, 1999; Sakkas et al., 2003, Xia et al., 2008).

Overall, the safety profile of magnetic stimulation is good and this supports its further development as clinical tool in both human and veterinary medicine.

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CHAPTER 2

SCIENTIFIC AIMS AND OUTLINE OF THE THESIS

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The central and peripheral motor nervous systems are frequently affected in small animal medicine. Currently available diagnostic tests as radiography, myelography, computed tomography (CT), magnetic resonance imaging (MRI), electromyography and electroneurography can mostly localize the lesion along the motor tracts in dogs and cats. In some cases, however, additional information regarding the clinical significance or the prognosis of the lesion is lacking with the use of the aforementioned diagnostic tools. Moreover, the use of non-invasive diagnostic techniques in small animal medicine is preferential. For this reason, the technique of magnetic stimulation of the nervous system in dogs and cats is studied in this thesis.

The aims of the first part of this research were:

1. to determine whether peripheral nerve stimulation can evoke magnetic motor evoked potentials in normal dogs and cats
2. to standardize the technique of magnetic stimulation of peripheral nerves in dogs and cats
3. to establish reference values for the parameters onset latency and peak-to-peak amplitude
4. to evaluate the usefulness of the technique in different clinical conditions

In the second part of this study, the technique of transcranial magnetic stimulation was investigated. The aims of this second part were:

1. to evaluate a method to monitor transcranial magnetic motor evoked potentials with the use of electroencephalographic parameters during different sedative and hypnotic drug combinations.
2. to assess results of transcranial magnetic motor evoked potentials in Doberman Pincher dogs with and without clinically relevant cervical spinal cord compression due to disc associated wobbler syndrome (DAWS).

CHAPTER 3

MAGNETIC STIMULATION OF PERIPHERAL NERVES IN DOGS

Part I. Standardization of the technique in dogs

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SUMMARY

A model for magnetic stimulation of the radial and sciatic nerves in dogs was evaluated. Onset-latencies and peak-to-peak amplitudes of magnetic and electrical stimulation of the sciatic nerve were compared, and the effect of the direction of the current in the magnetic coil on onset-latencies and peak-to-peak amplitude of the magnetic motor evoked potential was studied in both nerves. The results demonstrate that magnetic stimulation is a feasible method for stimulating the radial and sciatic nerves in dogs. No significant differences were observed in onset-latencies and peak-to-peak amplitudes during magnetic and electrical stimulation, indicating conformity between the techniques. Orthodromic or antidromic magnetic nerve stimulation resulted in no significant differences. This pilot study demonstrates the potential of magnetic stimulation of nerves in dogs.

INTRODUCTION

In veterinary medicine, electrodiagnostic evaluation of peripheral nerve disorders is mostly achieved by electrical stimulation of peripheral nerves (Cuddon, 2002) but little is known about magnetic nerve stimulation in animals (Heckmann et al., 1989). With electrical stimulation, current is passed into the body via needle electrodes, whereas in magnetic stimulation a brief magnetic pulse induces a current in conductive tissues (Barker, 1991). Magnetic stimulation provides a non-invasive and almost painless alternative to electrical nerve stimulation.

MATERIALS AND METHODS

We have evaluated a model for magnetic stimulation of the radial and sciatic nerves in dogs and compared onset-latencies and peak-to-peak amplitudes during magnetic and electrical stimulation of the sciatic nerve. The effect of the direction of the current flow in the magnetic coil on onset-latency and peak-to-peak amplitude of the magnetic motor evoked potential was studied.

Procedures were performed under general anaesthesia on six mongrel dogs of similar height at the withers. The local ethical committee of the Faculty of Veterinary Medicine of the University of Ghent approved the work.

A commercially available magnetic stimulator (Magstim Super Rapid, Acertys Healthcare) was connected to a circular coil (45 mm). For magnetic stimulation of the radial nerve, the magnetic coil was placed in the axillary region, medial to the radial nerve, and the cranial part of the circle on the coil was held tangentially to the radial nerve (Figure 1). For magnetic stimulation of the sciatic nerve, the magnetic coil was placed lateral to the hind limb and the caudal part of the circle on the coil was held tangentially to the sciatic nerve between the greater trochanter and the ischial tuberosity (Figure 2).

For both nerves, the flat surface of the coil was placed parallel to the surface of the skin of the limb. Both nerves were stimulated with the current in the coil flowing in both clockwise and counter clockwise directions by reversing the coil.

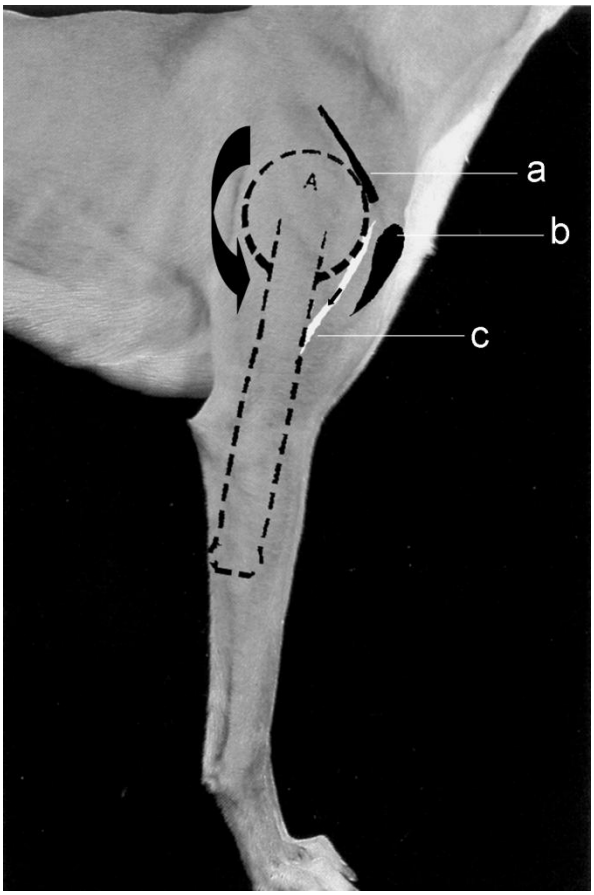

Figure 1

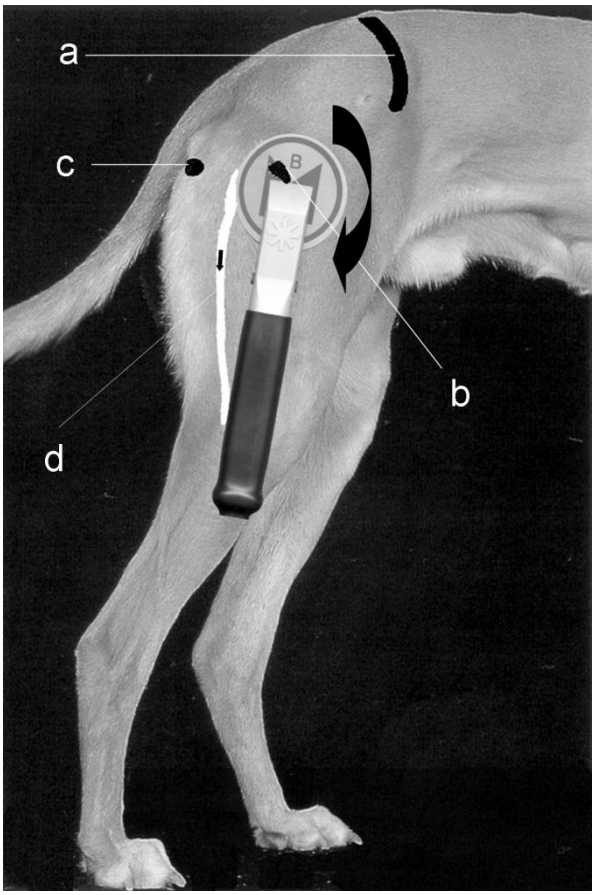

Figure 2

Figure 1. Magnetic stimulation of the radial nerve: Position of the magnetic coil. Schematic view of orthodromic nerve stimulation (current in the coil is counter clockwise). For antidromic nerve stimulation, the magnetic coil is reversed. (a) Spina scapulae. (b) Humerus (greater tubercle). (c) Radial nerve. Small arrow: Direction of induced current in the radial nerve. Large arrow: Direction of the current in the magnetic coil.

Figure 2. Magnetic stimulation of the sciatic nerve: Position of the magnetic coil. Schematic view of orthodromic nerve stimulation (current in the coil is clockwise). For antidromic nerve stimulation, the magnetic coil is reversed. (a) Ilium (crest). (b) Femur (greater trochanter). (c) Ischium (tuber ischiadicum). (d) Sciatic nerve. Small arrow: Direction of induced current in the sciatic nerve. Large arrow: Direction of the current in the magnetic coil.

Electrical stimulation of the sciatic nerve was done using needle electrodes connected to the stimulator of an electromyograph (Sapphire, Acertys Healthcare). The cathodal and anodal stimulating electrodes (monopolar needle electrode, Acertys Healthcare) were placed between the greater trochanter and the ischial tuberosity. Stimulus intensity was increased until supramaximal responses were obtained.

Recording electrodes (monopolar needle electrodes, Acertys Healthcare) were placed in the muscle belly, just in front of the lateral humeral epicondyle for the extensor carpi radialis muscle (ECRM), and slightly lateral to the distal end of the tibial crest for the cranial tibial muscle (CTM). Reference electrodes (subdermal needle electrodes, Acertys Healthcare) were positioned at the carpal and the tarsal joint for the ECRM and CTM, respectively. The ground electrode (subdermal needle electrodes, Acertys Healthcare) was placed over the olecranon of the forelimb or over the patella of the hind limb. All recordings were made using the same electromyograph (Sapphire, Acertys Healthcare). No signal averaging was performed.

Measurements of onset-latency and peak-to-peak amplitude were made using the cursors on the oscilloscope. Onset-latency was measured between stimulus artefact and deflection from the baseline in either a positive or a negative direction. Peak-to-peak amplitude was the amplitude measured from the peak of the negative-going wave and from the nadir of the positive-going wave (Figure 3).

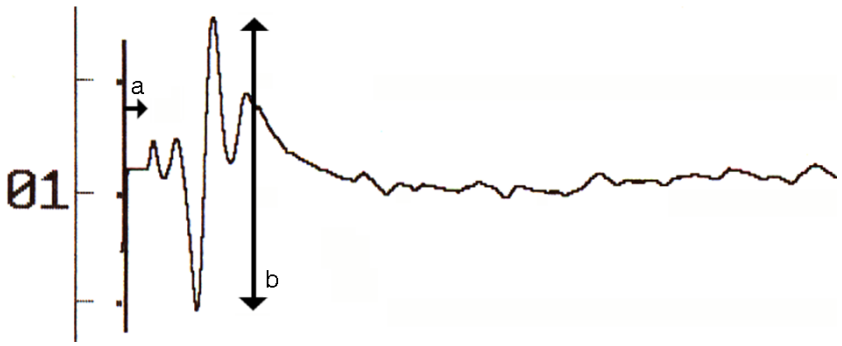

Figure 3. Magnetic motor evoked potential: Onset-latency and peak-to-peak amplitude measurement. (a) Onset-latency. (b) Peak-to-peak amplitude.

One observation per technique and per nerve was used for statistical analyses. Continuous data were analysed for normality using a one sample Kolmogorov Smirov test. The Wilcoxon matched-pairs signed ranks test was used for identification of statistical significances between peak-to-peak amplitudes after magnetic and electrical stimulation of the sciatic nerve and between onset-latencies and peak-to-peak amplitudes after orthodromic and antidromic magnetic stimulation of the radial and sciatic nerve. The Mann-Whitney test was used for comparing the variable onset-latency of magnetic and electrical stimulation (GraphPad Instat, GraphPad Software Inc). Differences with $P<0.05$ were considered to be statistically significant.

RESULTS

Biphasic to polyphasic potentials were easily recorded after magnetic stimulation of the radial and sciatic nerves, respectively. Median onset-latencies and median peak-to-peak amplitudes after stimulation of the sciatic nerve, first using magnetic stimulation (orthodromic nerve stimulation) and then using electrical stimulation are given in Table 1. No significant differences in onset-latencies and peak-to-peak amplitudes were observed for both techniques.

Table 1. Median onset-latencies and median peak-to-peak amplitudes from the cranial tibial muscle (CTM) recordings after magnetic and electrical stimulation of the sciatic nerve

Stimulation	Onset-latency	Peak-to-peak amplitude
Magnetic	3.6 (2.8-4.5) ms	25.16 (0.82-32.41) mV
Electrical	3.2 (3.2-4.1) ms	27.885 (18.36-31.81) mV
P-value	0.6276	0.3125

Significance level $P<0.05$

Median onset-latencies and median peak-to-peak amplitudes for all recordings after magnetic stimulation of both nerves are given in Table 2.

Table 2. Median onset-latencies and median peak-to-peak amplitude from extensor carpi radialis muscle (ECRM) and cranial tibial muscle (CTM) recordings after radial and sciatic magnetic nerve stimulation, respectively

	Onset-latency	Peak-to-peak amplitude
Radial nerve		
Orthodromic nerve stimulation	2.6 (1.6-3.4) ms	23.545 (17.58-33.59) mV
Antidromic nerve stimulation	2.65 (1.6-3.6) ms	23.05 (14.65-36.51) mV
P-value	0.625	0.5625
Sciatic nerve		
Orthodromic nerve stimulation	3.35 (2.8-3.7) ms	22.085 (0.47-35.54) mV
Antidromic nerve stimulation	3.65 (3.2-4.1) ms	12.75 (2.15-25.7) mV
P-value	0.125	0.0625

Significance level $P < 0.05$

No significant differences were found in onset-latencies and peak-to-peak amplitudes when the current in the coil was flowing in either a counter-clockwise direction (antidromic nerve stimulation) or in a clockwise direction (orthodromic nerve stimulation) after magnetic stimulation of both nerves.

DISCUSSION

The results of this study demonstrate that magnetic stimulation provides a feasible, non-invasive method to stimulate the radial and sciatic nerves in dogs. Magnetic nerve stimulation has major advantages over conventional electrical stimulation. These include the ability to stimulate peripheral nerves without discomfort, which make it possible to perform the technique under sedation. Needle electrodes are not necessary to stimulate the nerve and, as such, deep or relatively inaccessible nerves (e.g., radial, sciatic and facial nerve) can be stimulated easily. Similarly, no mechanical contact is needed with the body, which makes it possible to investigate traumatised regions or to stimulate across sterile barriers (Barker, 1991).

The disadvantages of the technique are (1) problems in obtaining a consistent supramaximal response as compared to the response obtained after electrical stimulation and (2) defining the exact site of localisation (Evans, 1988). Although in the present study, data range in peak-to-peak amplitudes after magnetic stimulation seemed larger, no statistically significant differences in onset-latencies and peak-to-peak amplitudes between magnetic and electrical stimulation of the sciatic nerve were observed. Different factors might account for these variations: coil position, position and type of the recording electrodes and angulation of the magnetic coil. However, the limited number of dogs and nerves examined in the present study should be taken into account before the magnetic coil can be recommended for general use.

The current flow in the stimulator head is opposite to the induced current in the tissue (Evans, 1991). Reversing the magnetic coil and thus reversing the direction of the induced current in the tissue had no significant influence on the evoked potential. However, consistent use of one side of the coil is recommended because the configuration and the latency of the response can change as the coil is reversed (Chokroverty, 1989).

In conclusion, this study demonstrates the potential for magnetic stimulation of nerves in dogs. Further studies on magnetic stimulation of different nerves and on the clinical application of magnetic stimulation in peripheral nerve disorders should be evaluated.

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CHAPTER 3

MAGNETIC STIMULATION OF PERIPHERAL NERVES IN DOGS

Part II. Reference values of magnetic motor evoked potentials of the radial and sciatic nerve in normal dogs

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SUMMARY

Magnetic stimulation of the radial and sciatic nerve was performed in 54 healthy dogs with two types of magnetic coils. Reference values for onset latency and peak-to-peak amplitude of magnetic motor evoked potentials (MMEP) recorded from the extensor carpi radialis muscle and cranial tibial muscle were obtained.

No significant differences in onset latencies and peak-to-peak amplitudes of the MMEP were found after stimulation with the circular and the butterfly shaped coil.
No significant influence of age and gender on the MMEP parameters was seen. Height at the withers, bodyweight and side of stimulation, however, had a significant effect on the onset latencies and peak-to-peak amplitudes. Therefore, these parameters were used to predict onset latency and peak-to-peak amplitude reference ranges for dogs.

INTRODUCTION

Stimulation of peripheral nerves can be performed by using a strong and brief external magnetic field, as firstly shown by Barker and colleagues (1987). The produced muscle twitches were reported by the subjects as painless and well tolerated (Barker et al, 1987). In veterinary medicine, the use of magnetic peripheral nerve stimulation is rare (Van Soens et al, 2008; Van Soens et al, 2009) because data acquired from healthy dogs are lacking.

Therefore, in this study the technique was applied to 54 healthy dogs of different height in order to frame reference values of onset latencies and peak-to-peak amplitudes of magnetic motor evoked potentials (MMEP) after stimulation of the radial and sciatic nerve. The radial and the sciatic nerve were magnetically stimulated by two types of magnetic coil: a circular and a butterfly or figure-of-eight shaped coil. Additionally, the possible effect on the neurophysiological measurements of age, gender, height at the withers, weight, position of and side of stimulation was evaluated.

MATERIALS AND METHODS

Dogs

Fifty-four client owned dogs presented at the Small Animal Department of the Ghent University for diagnostic or therapeutic purposes and that had written owner's consent were included in this study. None of the dogs had neurological signs, symptoms or previous diseases related to the motor pathways of the radial and the sciatic nerve.

Breed, age, gender, height at the withers and bodyweight were reported for each animal. Neuronal path length for proximal and distal stimulating sites for the radial and sciatic nerve were measured with a tape-line on the body surface from the stimulating site to the recording needle in the extensor carpi radialis (ECRM) or cranial tibial muscle (CTM), respectively.

Magnetic stimulation of the radial and sciatic nerve

Magnetic stimulation of the radial and sciatic nerve was performed under general inhalation anaesthesia according to reported techniques in dogs (Van Soens et al, 2008). A commercially available magnetic stimulator (Magstim Super Rapid, Acertys Healthcare) was used. Stimulus intensity was 110% of the maximal stimulator output to ensure that the entire group of axons and the fastest conducting fibres of the nerve were stimulated.

Two types of magnetic coils were used: a circular 45 mm coil, capable of producing a peak magnetic field at the coil surface of 4.0 Tesla and a butterfly or figure-of-eight coil (2 coils of each 70 mm), capable of producing a peak magnetic field of 2.2 Tesla (Figure 1). For the circular coil, most of the induced current is concentrated below the circle on the coil and therefore this circle is held tangential to the nerve. For the butterfly coil, the 'active' region is concentrated below the wing junction and therefore this point was held in proximity to the investigated nerve.

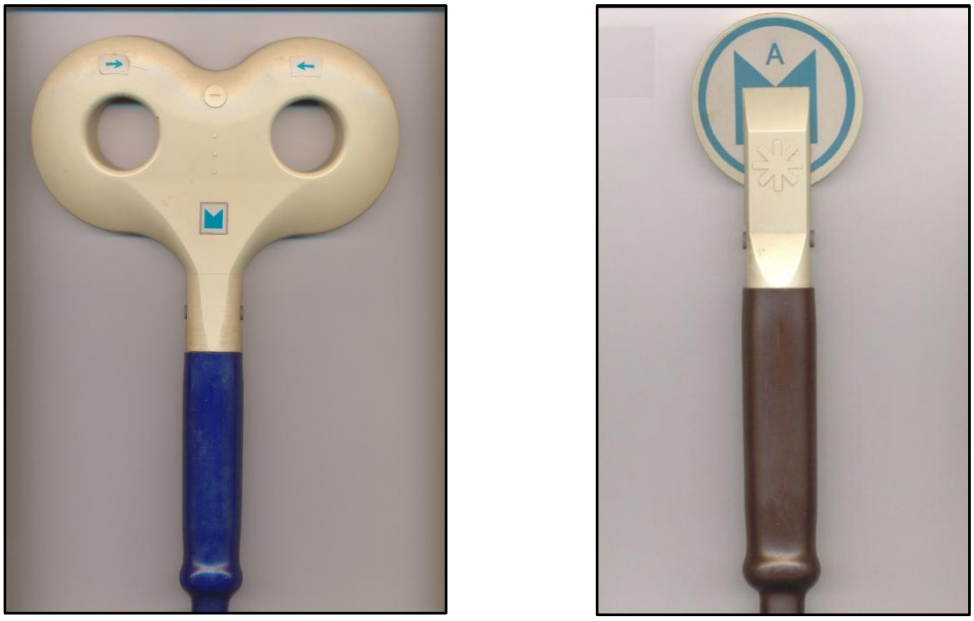

Figure 1. Butterfly or figure-of-eight magnetic coil of 70mm (left) and circular magnetic coil of 45mm (right).

In all animals, magnetic stimulation of the radial and sciatic nerve was performed proximally and distally on the course of the nerve. For the proximal stimulation, the coil was held in the axillary region, medial from the radial nerve for the thoracic limb and, between the greater trochanter and the ischial tuberosity lateral from the sciatic nerve for the hind limb (Van Soens et al, 2008). Distal stimulation of the radial nerve was performed with the coil lateral from the radial nerve at the distal border of the humerus at 2/3 its length. For stimulating the sciatic nerve distally, the coil was held at the height of the stifle joint, between the cranial and caudal portion of the biceps femoris muscle (Figure 2). Both nerves were stimulated in orthodromic direction (Van Soens et al, 2008). For each recording site, four individual stimulations (2 proximal and 2 distal) were recorded to evaluate reproducibility.

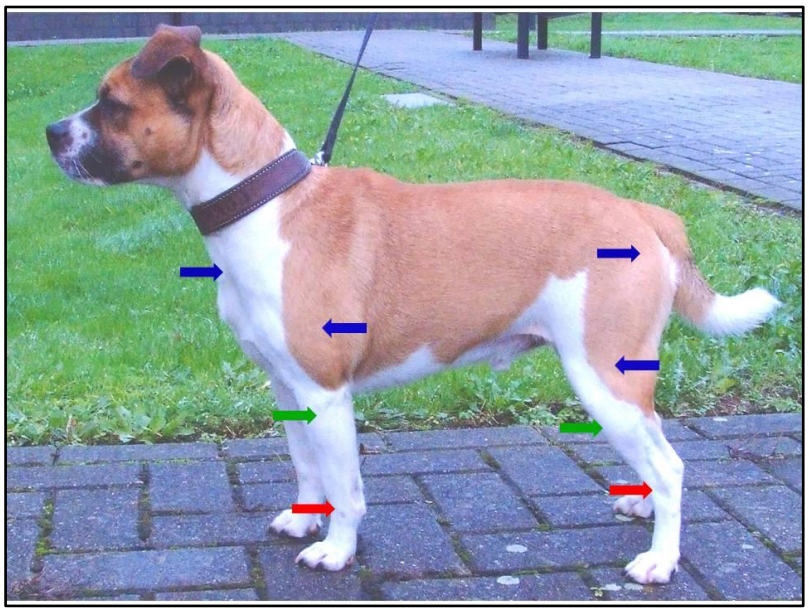

Figure 2. Placement of the magnetic coil (blue arrows), detection electrode (green arrows) and reference electrode (red arrows) on the thoracic and pelvic limb for stimulation of the radial and sciatic nerve, respectively.

Recording of magnetic and electrical motor evoked responses

Electromyographic responses were recorded with a commercially available electromyograph (Sapphire, Acertys Healthcare). The tip of the recording electrode (monopolar needle electrodes, Acertys Healthcare) was inserted in the ECRM, just in front of the lateral humeral epicondyle for the forelimb and in the CTM, slightly lateral to the distal end of the tibial crest for the hind limb. The reference electrode (subdermal needle electrodes, Acertys Healthcare) was positioned at the carpal and the tarsal joint for the ECRM and the CTM, respectively. The ground electrode (subdermal needle electrodes, Acertys Healthcare) was placed over the olecranon of the fore limb or over the patella of the hind limb.

Onset latency and peak-to-peak amplitude were measured from the MMEP with the highest amplitude and shortest onset latency. Furthermore, onset latencies and peak-to-peak amplitudes were measured from proximal and distal recorded MMEP with comparable shapes because this represents nerve fibres with similar conduction characteristics (Cuddon, 2002). Onset latency (in ms) was measured as the shortest distance between the trigger point and the take-off of the initial phase (negative or positive). Peak-to-peak amplitude (in mV) was measured between the two largest peaks of opposite polarity.

Statistical analysis

Frequencies and descriptive statistics were derived for breed, gender, age, height at the withers, bodyweight and neuronal path length.

Initially, the effect of the shape of the coil on onset latency and peak-to-peak amplitude of the MMEP was determined using a linear mixed model analysis which was corrected for stimulating site, nerve, side of the dog and height at the withers. The means were considered significantly different if $P < 0.05$.

For onset latency and peak-to-peak amplitude, the significant effect of different parameters (age, gender, height at the withers, bodyweight, nerve, stimulating site and side of the dog) was determined using a univariate linear mixed model. The means were considered significantly different if $P < 0.05$.

Predicted values and 95% prediction interval of onset latency and peak-to-peak amplitude, based on the parameters that had a significant effect, were calculated using simple linear regression analysis. When highly correlated factors were significant in the univariate analysis, the parameter resulting in the smallest deviance was selected. Predictive values were only calculated for the range of height at the withers of the dogs used in this study (i.e. from 28cm to 89cm).

RESULTS

Fifty-four dogs of 25 different breeds were considered. The group consisted of 22 (41%) female and 32 (59%) male dogs between 11 months and 11 years of age (mean 6.57 years). Height at the withers ranged from 28 cm to 89 cm (mean 59.74 cm) and bodyweight from 11 kg to 65 kg (mean 32.64 kg).

Neuronal path length of the radial nerve varied from 9 cm to 27.5 cm (mean 18.10 cm) and from 4 cm to 13 cm (mean 8.15 cm) for the proximal and distal stimulation point, respectively. For the sciatic nerve, neuronal path length ranged from 13.5 cm to 38.5 cm (mean 25.43 cm) and from 6 cm to 18 cm (mean 11.20 cm) for the proximal and distal stimulation point, respectively.

Motor responses to magnetic peripheral nerve stimulation of the radial and sciatic nerve were clearly identified in the 54 dogs in all four limbs. In most dogs, MMEP recorded from the ECRM and the CTM had a bi- or triphasic shape with an initial positive deflection, followed by a negative deflection.

No significant differences in onset latencies (P= 0.36) and peak-to-peak amplitudes (P= 0.79) were observed after stimulation with the circular and butterfly shaped coil. Further statistical analysis was performed on results with the circular coil. No significant effects of age and gender of the different dogs were observed on onset latency and peak-to-peak amplitude (table 1).

Height at the withers and bodyweight had a significant effect on both onset latency and peak-to-peak amplitude. Increased values of height and bodyweight resulted in longer onset latencies and lower peak-to-peak amplitudes. Height at the withers and bodyweight are, however, strongly correlated (92%) (table 1).

A significant difference was found in onset latencies and peak-to-peak amplitudes between recordings made from the radial nerve and from the sciatic nerve and between recordings made from the proximal and the distal stimulating site on each nerve (table 1).

No left to right difference was seen in peak-to-peak amplitudes in the same dog, however, onset latency differed between the left and right limb responses (table 1). Onset latency of the left limb responses was significantly lower than right limb responses.

Table 1. P values of the univariate linear mixed models analysis showing the significancy of the effect of different parameters on onset latency and peak-to-peak amplitude (significance level $P<0.05$)

	Onset latency	Peak-to-peak amplitude
Age	0.564	0.839
Gender	0.622	0.658
Height at withers	< 0.001*	0.001*
Weight	< 0.001*	< 0.001*
Nerve	< 0.001*	< 0.001*
Proximal versus distal stimulation	< 0.001*	0.007*
Side of the dog	0.007 *	0.452

*Parameter with a significant influence on onset latency or peak-to-peak amplitude

To predict normal values of onset latencies and peak-to-peak amplitudes in the ECRM and CTM in normal dogs, height at the withers was used. The calculated regression equations are given in table 2.

Table 2. Regression equations of predicted onset latency and peak-to-peak amplitude of MMEP recorded from the left extensor carpi radialis (ECRM) and left cranial tibial muscle (CTM) after stimulation of the radial and the sciatic nerve, proximal (p) and distal (d) on its course

	Predicted onset latency (ms)	Predicted peak-to-peak amplitude (mV)
ECRMp	Y = 0.12199 + 0.04879 x height (cm)	Y = 36.39104 – 0.202 x height (cm)
ECRMd	Y = -1.47537 + 0.04879 x height (cm)	Y = 39.14544 – 0.202 x height (cm)
CTMp	Y = 1.26241 + 0.04879 x height (cm)	Y = 32.55714 – 0.202 x height (cm)
CTMd	Y = -0.33495 + 0.04879 x height (cm)	Y = 35.31154 – 0.202 x height (cm)

In figures 3-10, the predicted values and 95% prediction interval of onset latency and peak-to-peak amplitude of the MMEP, based on the height at the withers, are presented per recording and stimulation site**.** As significant differences were observed between left and right responses for onset latency, only the left sided responses are shown in figures 1-4.

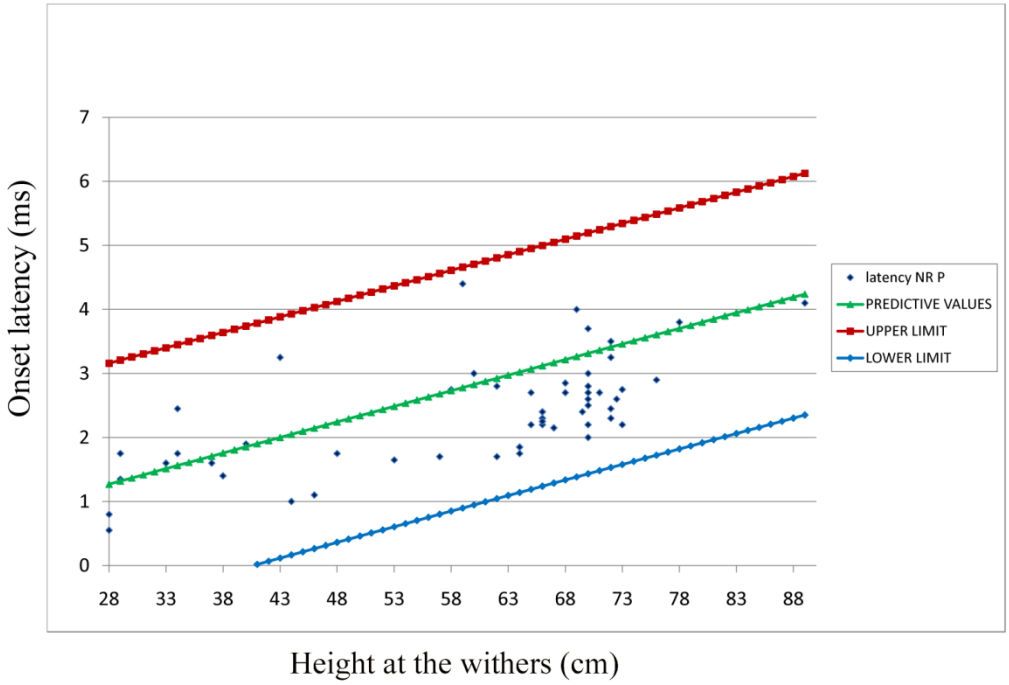

Figure 3. Graph of raw data, predicted values and 95% prediction intervals of onset latency of MMEP recorded from the left extensor carpi radialis muscle after proximal stimulation of the radial nerve (NR P), based on the height at the withers.

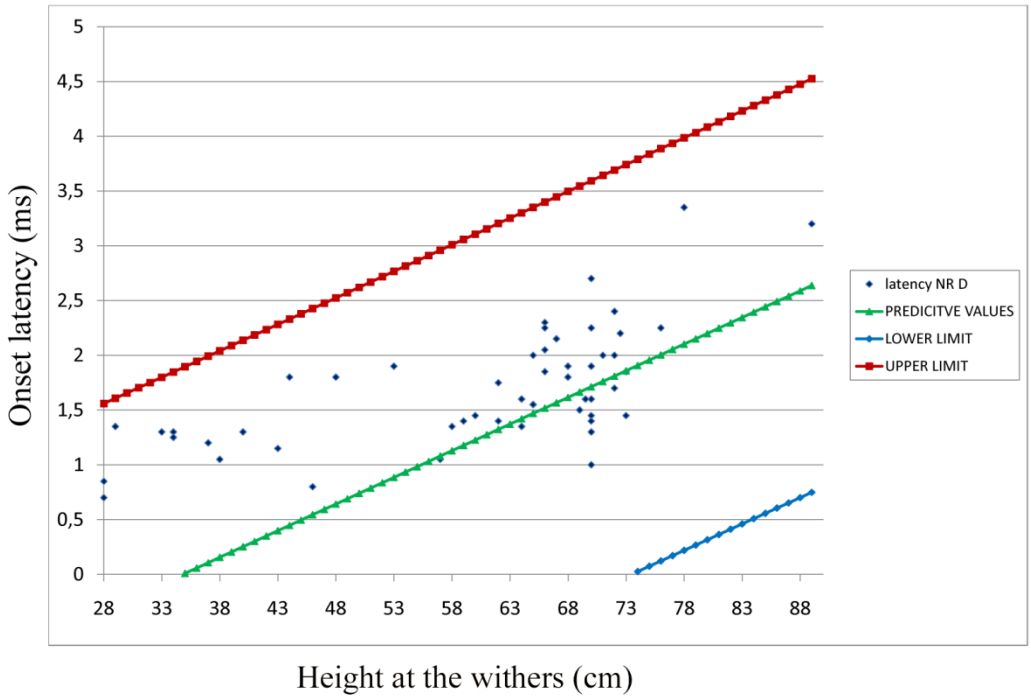

Figure 4. Graph of raw data, predicted values and 95% prediction intervals of onset latency of MMEP recorded from the left extensor carpi radialis muscle after distal stimulation of the radial nerve NR D), based on the height at the withers.

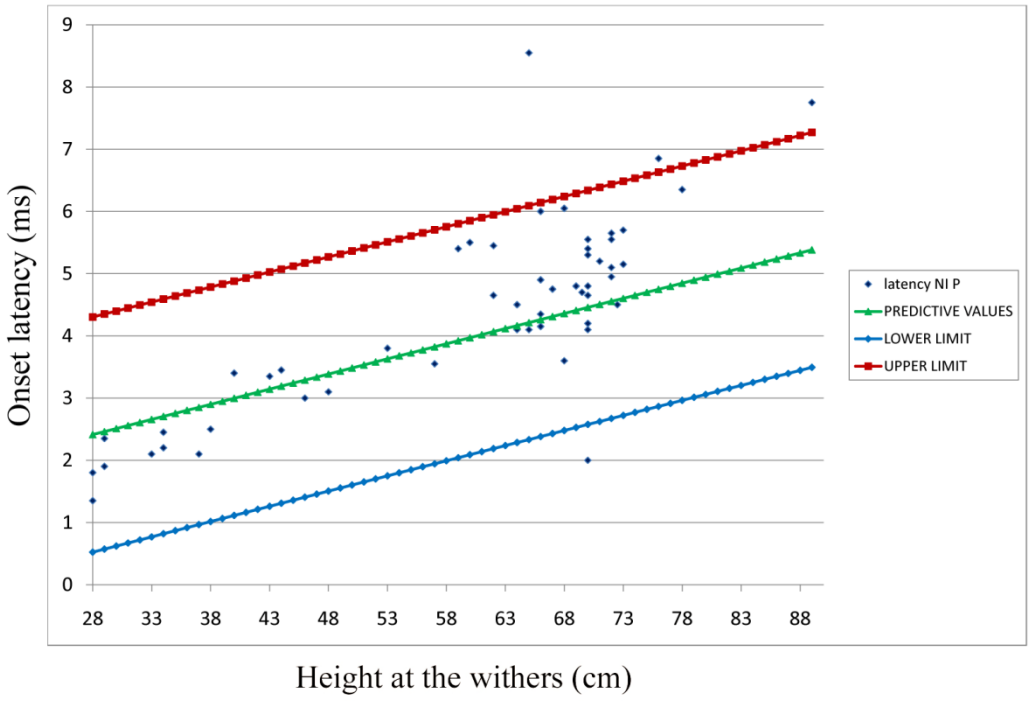

Figure 5. Graph of raw data, predicted values and 95% prediction intervals of onset latency of MMEP recorded from the left cranial tibial muscle after proximal stimulation of the sciatic nerve (NI P), based on the height at the withers.

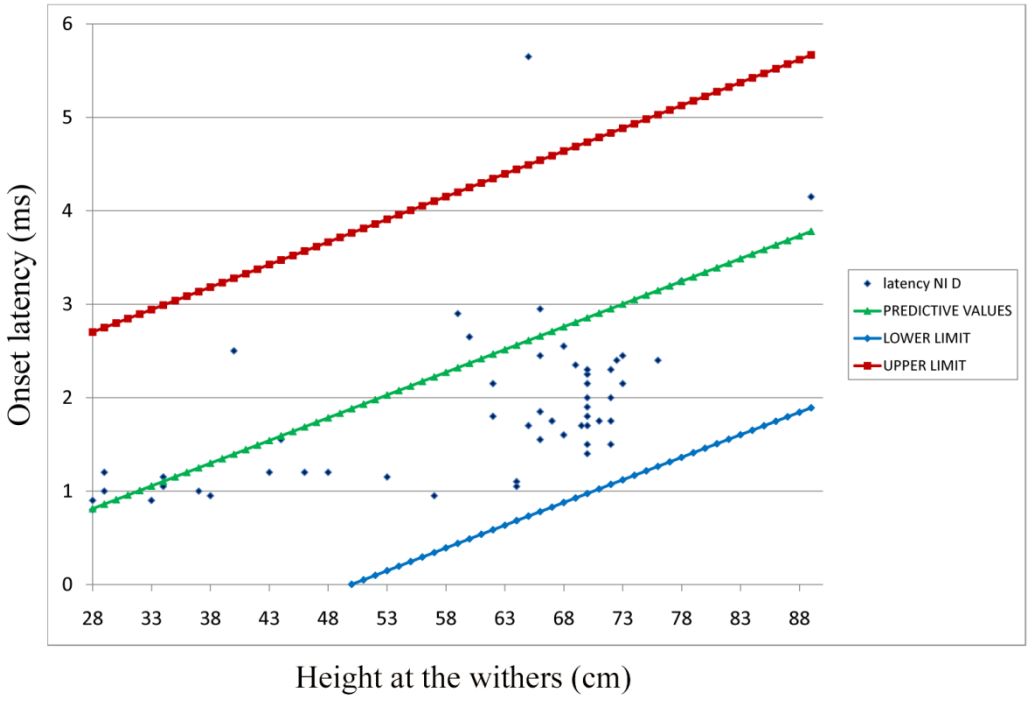

Figure 6. Graph of raw data, predicted values and 95% prediction intervals of onset latency of MMEP recorded from the left cranial tibial muscle after distal stimulation of the sciatic nerve (NI D), based on the height at the withers.

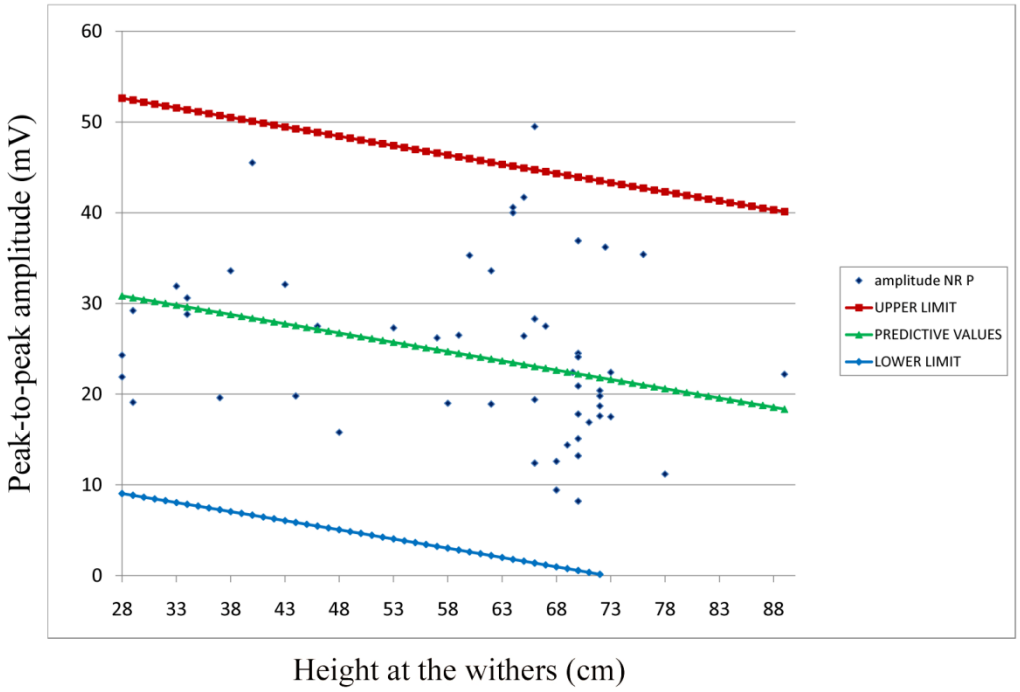

Figure 7. Graph raw data, of predicted values and 95% prediction intervals of peak-to-peak amplitude of MMEP recorded from the extensor carpi radialis muscle after proximal stimulation of the radial nerve (NR P), based on the height at the withers.

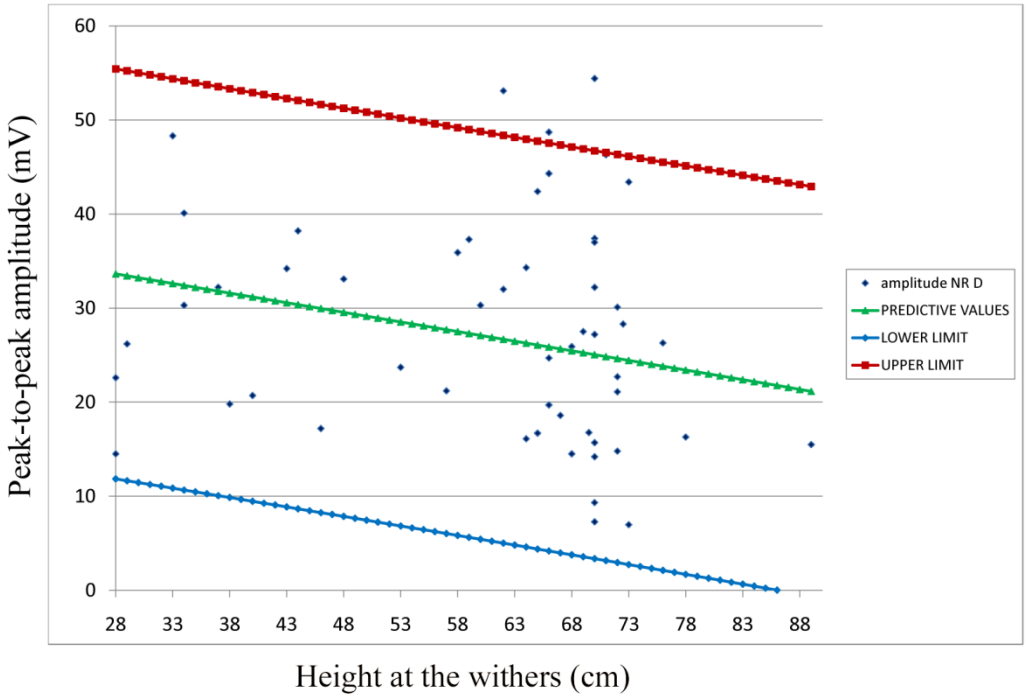

Figure 8. Graph of raw data, predicted values and 95% prediction intervals of peak-to-peak amplitude of MMEP recorded from the extensor carpi radialis muscle after distal stimulation of the radial nerve (NR D), based on the height at the withers.

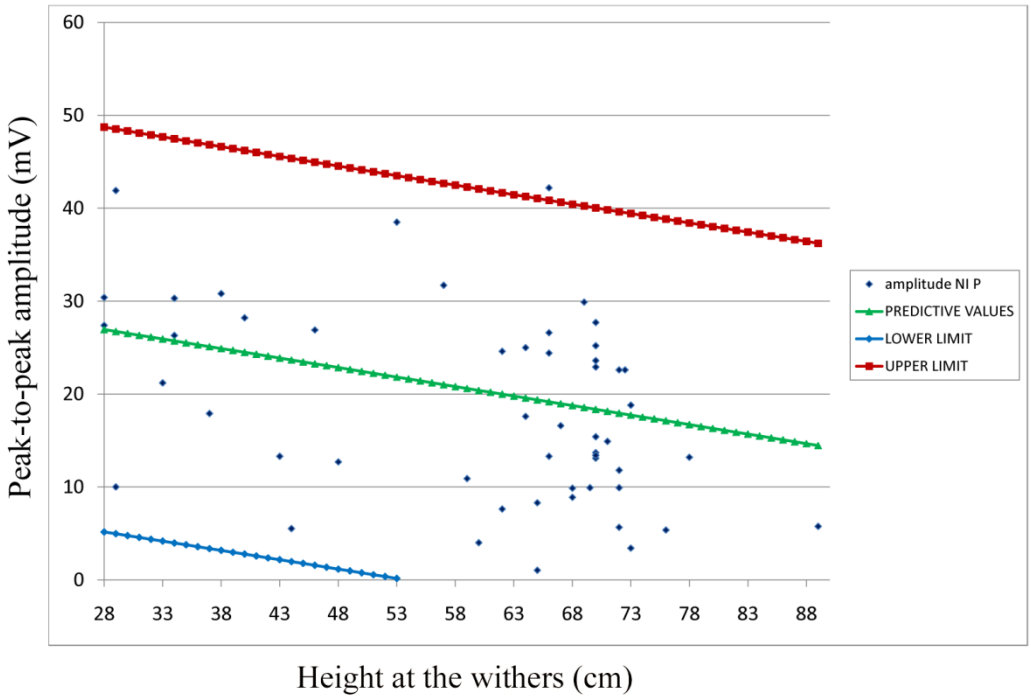

Figure 9. Graph of raw data, predicted values and 95% prediction intervals of peak-to-peak amplitude of MMEP recorded from the cranial tibial muscle after proximal stimulation of the sciatic nerve (NI P), based on the height at the withers.

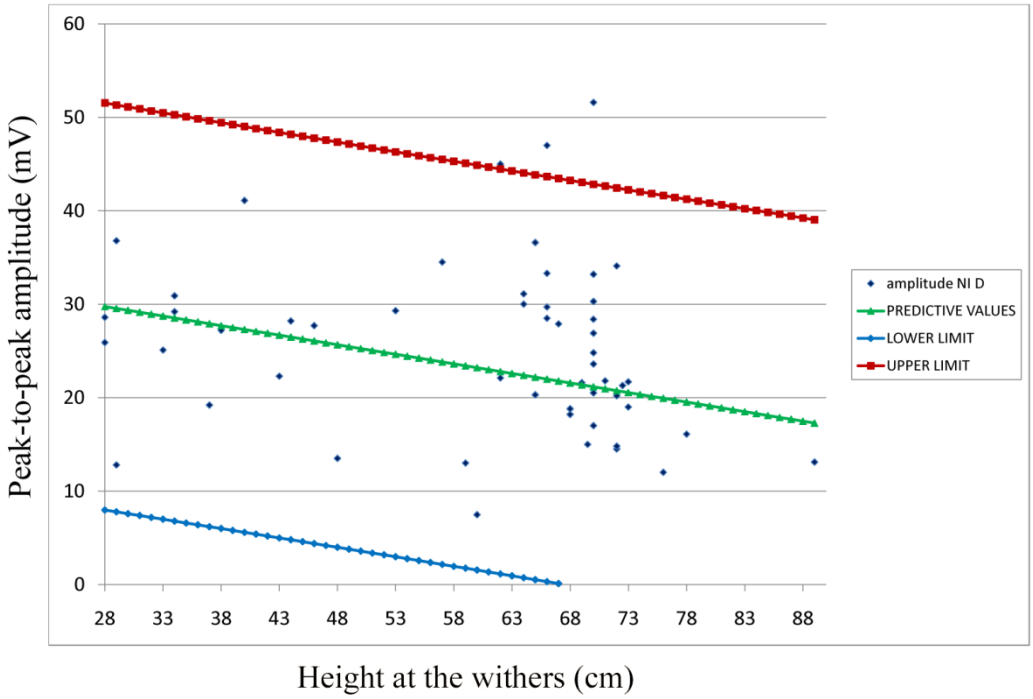

Figure 10. Graph of raw data, predicted values and 95% prediction intervals of peak-to-peak amplitude of MMEP recorded from the cranial tibial muscle after distal stimulation of the sciatic nerve (NI D), based on the height at the withers.

DISCUSSION

Our goal was to determine reference values for onset latencies and peak-to-peak amplitudes of MMEP after proximal and distal stimulation of the radial and sciatic nerve in healthy dogs. The present data set shows that in dogs of different breeds, heights and ages, MMEP were easily obtained from muscles of the thoracic and pelvic limbs. Onset latencies and peak-to-peak amplitudes, however, are dependent on the dog's height at the withers, bodyweight and side of stimulation.

Two types of magnetic coil design were compared in this study. For magnetic stimulation, a brief strong current is passed through a coil of wire, generating a time-varying magnetic field, called the magnetic coil. Several coil designs are currently used for clinical purposes: circular, butterfly shaped, cone shaped, four-leaf and H-coils (Cohen et al., 1990; Barker, 1999; Thielscher and Kammer, 2004; Zangen et al., 2005; Lontis et al., 2006). For stimulation of peripheral nerves, initially the circular coil was proposed because its simplicity for construction and convenience to apply to many parts of the body (Barker, 1991). The difficulty in determining the exact site of stimulation encouraged the development of newer shaped coils that delivered more focal stimulation. The butterfly-shaped or figure-of-eight coil contains two circular coils placed side by side that are wired such that the current from the stimulator passes in opposite direction in each. This construction results in induced currents under the centre of the two coils which are two to three times greater than the circular coil design (Barker, 1991). In this study design, however, no significant effect of the coil design was observed on the parameters onset latency and peak-to-peak amplitude of the MMEP indicating similar activation site and stimulus intensity, respectively. As the 70 mm butterfly shaped coil is rather large and less convenient to use in small dogs or cats, the smaller circular coil seems more suitable for veterinary use.

MMEP parameters were independent of gender and age of the dogs. In the dog, the conduction along motor nerves reaches adult values between 6 months and 1 year of age and remains stable until the age of 7 years. By the age of 10 years, a decline of 10-15% of the adult values is observed (Cuddon, 2002). The dogs' age in the present study ranged from 11 months to 11 years and therefore the age effect was not significantly important. Similarly and expected, gender had no influence on the MMEP parameters.

Height at the withers significantly correlates with onset latency; larger dogs result in longer onset latencies. This can mainly be explained by the fact that onset latency expresses the duration between stimulus and response. Moreover, conduction along nerves decreases more distally due to peripheral tapering of nerves(Cuddon, 2002). Therefore, height is the main contributor to the predictive values of onset latencies.

Peak-to-peak amplitude also correlated with height at the withers; in larger dogs smaller peak-to-peak amplitudes were registered. Different factors may account for this: in longer limbs, a longer tapered segment of nerve is present due to smaller axons and therefore smaller amplitudes are recorded (Cuddon, 2002). Moreover, as the magnetic field attenuates with distance, stimulation of nerves in larger dogs might be at a lower intensity, resulting in lower peak-to-peak amplitudes (Barker, 1991). Furthermore, the use of surface electrodes might have been better as this type of electrodes registers electrical activity of all contributing motor units (Cuddon, 2002) and thus might have produced larger and more stable peak-to-peak amplitudes. The use of surface electrodes as active electrodes in dogs, however, is more difficult as the high impedance of the skin results in less adequate recordings (Cuddon, 2002).

Onset latency and peak-to-peak amplitude of the MMEP correlated with bodyweight as well. This can be explained by the high correlation grade between height and bodyweight (92%). In clinical circumstances, however, it is easier and more practical to consider the former measure and thus predictive values were calculated from height at the withers.

A limitation of the present study is the lack of consideration of the effect of limb temperature on the conduction along the nerves. Onset latencies were significantly shorter on the left side and because all dogs were firstly stimulated on the left side, a difference in body temperature might have caused this discrepancy in results between left and right responses. Randomisation of the sequence of stimulation of the different limbs might have avoided this inconsistency. For this reason, the predictive values presented in this study were established using the left sided responses.

Another limitation of the technique is the fact that both onset latency and peak-to-peak amplitude have a wide 95% prediction interval. Therefore, interpretation of results of MMEP of animals with suspected neuropathic disease might be impeded. Onset latency is a measure for conduction along the nerves and especially for the smaller segments of nerves

investigated, a minimal change in coil position might have resulted in onset latency changes. Similarly, the parameter peak-to-peak amplitude has an even larger inter-individual variability (Van Soens et al, 2008) and different factors might account for these variations: coil position, position and type of the recording electrodes and angulation of the magnetic coil. In a clinical and observational study, therefore, all these factors are difficult to control. Further studies on larger populations are necessary to define more clearly onset latencies and peak-to-peak amplitudes of MMEP in dogs. They should provide evidence as to whether additional evaluation of other variables, e.g. configuration and duration of the responses, could attribute to more precise evaluation of MMEP.

CONCLUSION

In this study we have presented normal values for MMEP parameters of dogs of different breeds. These MMEP are highly reproducible and as it is a simple and non-invasive technique, its future applications might be promising.

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CHAPTER 4

MAGNETIC STIMULATION OF PERIPHERAL NERVES IN CATS

Standardization of the technique in cats

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SUMMARY

Magnetic stimulation of radial and sciatic nerves was performed bilaterally in 40 healthy cats. Reference values for onset latency and peak-to-peak amplitude of magnetic motor evoked potentials (MMEP) were obtained, and compared with values of electric motor evoked potentials (EMEP) in 10/40 cats.

Magnetic motor evoked responses were easily recorded in all normal cats. Significant differences were found in onset latencies between MMEP and EMEP, but peak-to-peak amplitudes were equal.

MMEP from the radial and sciatic nerve are easily obtained and stably reproducible in normal cats. The technique could represent a useful adjunct in the assessment of peripheral nerve disorders.

INTRODUCTION

Magnetic stimulation of the nervous system is a non-invasive, painless and safe technique to evaluate the functional integrity of motor pathways (Barker 1991). The clinical use of magnetic stimulation of peripheral nerves in veterinary medicine is rare (Van Soens et al., 2008; Van Soens et al., 2009).

Data acquired from cats using magnetic peripheral nerve stimulation are lacking. Therefore the technique was applied to 40 healthy cats in order to establish reference values of onset-latency and peak-to-peak amplitude of magnetic motor evoked potentials (MMEP) of the radial and sciatic nerve. Data of 10/40 cats were compared to results of electrical stimulation of the radial and sciatic nerve.

MATERIALS AND METHODS

After local Ethical Committee (EC 2006/112) and national Deontological Committee (149/4.4.2./01/07) agreement, the radial and sciatic nerve were proximally and distally stimulated, with a commercially available magnetic stimulator (Magstim Super Rapid, Acertys Healthcare) in 40 healthy cats (Van Soens et al., 2008). In 10/40 cats, the radial and sciatic nerve were also electrically stimulated with the stimulator of an electromyograph (Sapphire, Acertys Healthcare). For stimulation of the radial nerve, the magnetic coil or the cathodal and anodal stimulating electrodes (monopolar needle electrode, Acertys Healthcare) were placed cranio-medial from the shoulder joint and at the distal border of the humerus at 2/3 its length for the proximal and distal stimulating point, respectively. For the sciatic nerve, the magnetic coil or needle electrodes were placed between the greater trochanter and the ischial tuberosity and at the height of the stifle joint, between the cranial and caudal portion of the biceps femoris muscle for the proximal and distal stimulating point, respectively. Electromyographic responses were recorded from the extensor carpi radialis muscle and the cranial tibial muscle of the thoracic and pelvic limb, respectively (Van Soens et al., 2008) (Figure 1).

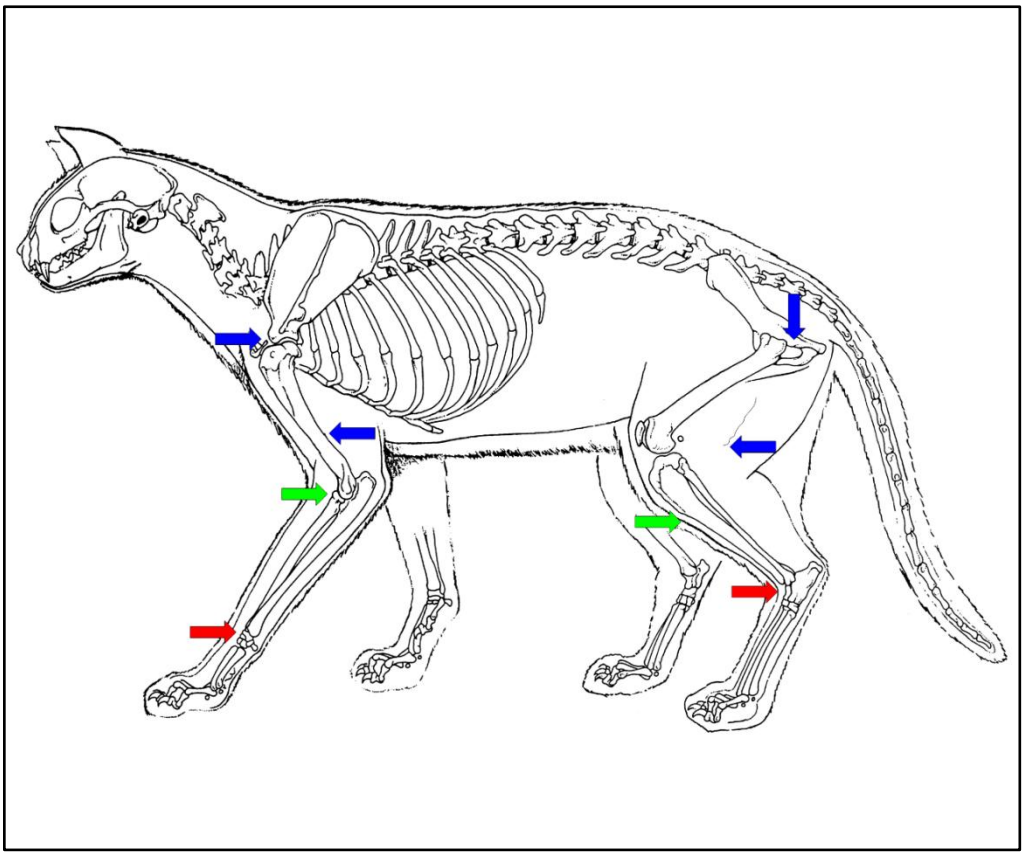

Figure 1. Placement of the magnetic coil or the stimulating electrodes (blue arrows), detection electrode (green arrows) and reference electrode (red arrows) on the thoracic and pelvic limb for stimulation of the radial and sciatic nerve, respectively.

Onset latency (in ms) was measured as the shortest distance between the trigger point and the take-off of the initial phase. Peak-to-peak amplitude (in mV) was measured between the two largest peaks of opposite polarity.

The 95% confidence interval was calculated for onset latency and peak-to-peak amplitude of the MMEP and electric motor evoked potential (EMEP). Intergroup differences were analysed using a paired *t*-test or a Wilcoxon Rank's test. Box plot graphs were designed to show the distribution of the normal MMEP parameters in the 40 healthy cats. Statistical analyses were performed with Graph Pad Instat software (Graph Pad Software). Differences were considered significant at the 5% probability level ($P < 0.05$).

RESULTS

Biphasic to polyphasic potentials were easily recorded after magnetic and electrical stimulation. Results of onset latencies and peak-to-peak amplitudes of EMEP and MMEP and upper and lower limits of the 95% confidence interval of the MMEP are shown in Table 1. Significant differences were observed in the proximal peak-to-peak amplitudes of the MMEP between the right and left pelvic responses (Table 1). In comparing MMEP and EMEP, significant differences in the proximal onset latencies were observed in the thoracic limbs. Box plot graphs of the onset latencies and peak-to-peak amplitudes of the MMEP are shown in Figure 2-5.

Table 1. Onset latencies (median, min-max, in ms)) and peak-to-peak amplitudes (median, min-max, in mV) after electrical (ES) and magnetic stimulation (MS) of the radial and sciatic nerve. Lower and upper limit of the 95% confidence interval (CI) of onset latency and peak-to-peak amplitude of the magnetic motor evoked potential.

			Left limb			Right limb		
Nerve			ES	MS	CI	ES	MS	CI
Radial	Onset latency	Proximal	1.32[b]	0.85[b]	0.82 (lower)	1.57[b]	0.95[b]	0.87 (lower)
			(1.00-1.70)	(0.50-1.55)	0.97 (upper)	(1.25-1.90)	(0.55-1.80)	1.02 (upper)
		Distal	0.87	0.80	0.75 (lower)	0.95	0.80	0.78 (lower)
			(0.65-1.20)	(0.45-1.45)	0.88 (upper)	(0.70-1.20)	(0.60-1.55)	0.94 (upper)
	Peak-to-peak amplitude	Proximal	42.60	36.90	33.69 lower)	42.35	34.70	32.06 (lower)
			(32.50-47.50)	(14.80-68.00)	40.44 (upper)	(23.40-65.30)	(19.20-86.60)	40.63 (upper)
		Distal	37.50	36.70	33.35 (lower)	43.05	35.50	34.13 (lower)
			(22.80-51.30)	(15.90-60.70)	40.87 (upper)	(25.70-76.20)	(14.80-62.40)	42.65 (upper)
Sciatic	Onset latency	Proximal	1.60	1.45	1.30 (lower)	1.72	1.47	1.31 (lower)
			(1.35-1.95)	(0.80-2.25)	1.54 (upper)	(1.55-2.05)	(0.75-2.00)	1.53 (upper)
		Distal	0.97	0.85	0.77 (lower)	0.97	0.75	0.74 (lower)
			(0.55-1.25)	(0.50-1.35)	0.90 (upper)	(0.85-1.20)	(0.50-1.75)	0.90 (upper)
	Peak-to-peak amplitude	Proximal	34.90	33.90[a]	31.27 lower)	36.45	36.70[a]	35.29 (lower)
			(30.10-50.80)	(17.40-58.60)	36.78 (upper)	(26.80-54.50)	(24.80-54.00)	40.14 (upper)
		Distal	34.45	37.80	36.21(lower)	36.10	41.55	38.82 (lower)
			(27.40-48.60)	(18.60-86.50)	44.70 (upper)	(30.30-44.80)	(23.60-65.30)	44.65 (upper)

[a] Significantly different from values of the opposite limb
[b] Significantly different from values after magnetic stimulation

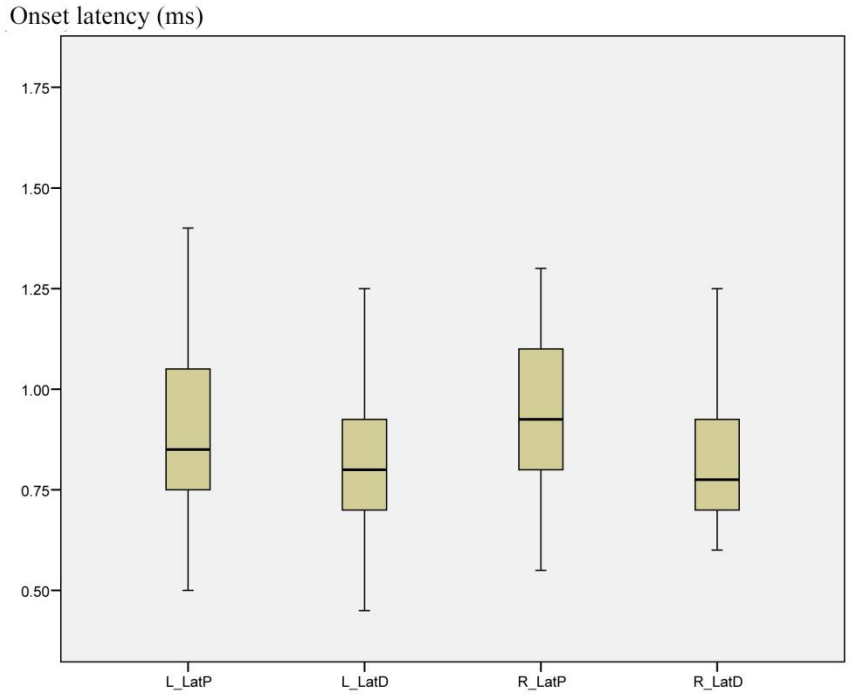

Figure 2. Box plot graphs of onset latencies (Lat) (in ms) of the left (L) and right (R) thoracic limb after stimulation of the radial nerve proximally(P) and distally (D).

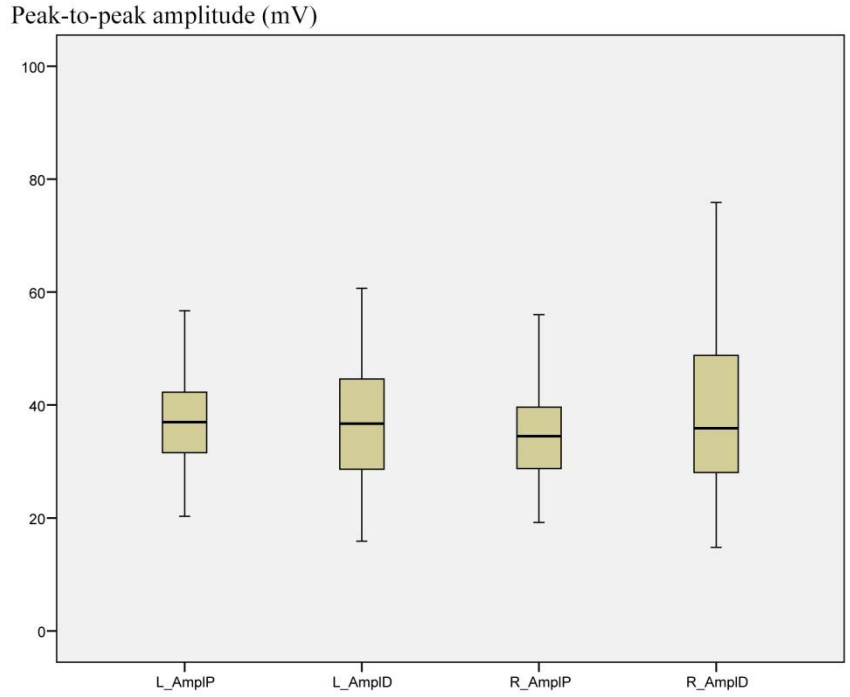

Figure 3. Box plot graphs of peak-to-peak amplitudes (Ampl) (in mV) of the left (L) and right (R) thoracic limb after stimulation of the radial nerve proximally(P) and distally (D).

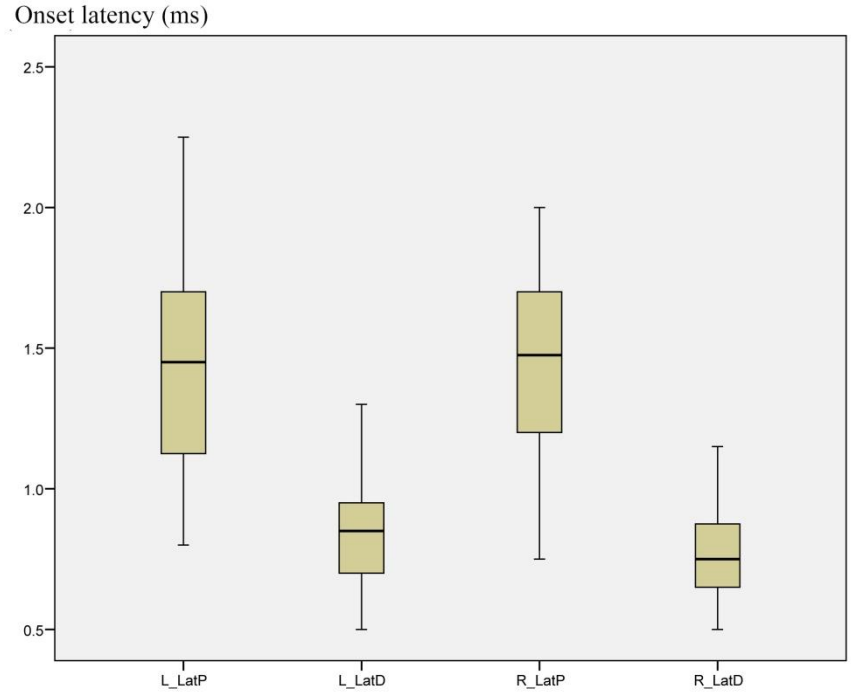

Figure 4. Box plot graphs of onset latencies (Lat) (in ms) of the left (L) and right (R) pelvic limb after stimulation of the sciatic nerve proximally(P) and distally (D).

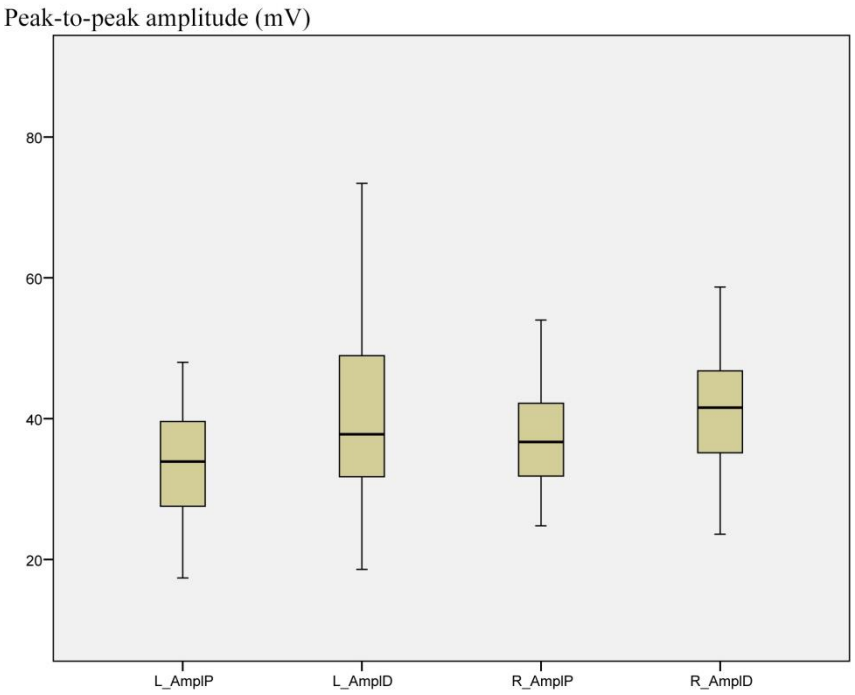

Figure 5. Box plot graphs of peak-to-peak amplitudes (Ampl) (in mV) of the left (L) and right (R) pelvic limb after stimulation of the sciatic nerve proximally(P) and distally (D).

DISCUSSION

Analogous to earlier studies in dogs (Van Soens et al., 2008), MMEP were easily recorded without any exception. Overall variability of onset latency of MMEP in this study was minimal, indicating the reproducibility of this technique in cats. The exact site of excitation on the radial nerve differed, however, between magnetic and electrical stimulation as significantly different onset latencies were obtained. Onset latencies of MMEP at the proximal stimulating points on the radial nerve were significantly shorter than onset latencies of EMEP. Several factors can explain this discrepancy of results. A circular coil stimulates a nerve, which lies tangential to the loop of the coil (Barker, 1999). Placement of the magnetic coil in the axillary region will probably stimulate the radial nerve more distally than the stimulating electrodes of the electrical stimulation, which are placed medial from the shoulder joint. Because of its shape and size it is extremely difficult to place the coil more proximally on the nerve. Determining the exact site of impulse generation on the course of a peripheral nerve, however, has always been a limiting factor of the technique (Evans et al., 1988; Chokroverty, 1989). Moreover, other factors as, ease of access, overlying tissues, bending of the nerve and bony structures have also been suggested to play a role in facilitating magnetic stimulation of nerves (Epstein et al., 1991; Maccabee et al., 1993).

The onset latency of the MMEP is a valuable parameter in magnetic stimulation studies in cats; differences exceeding the 95% confidence interval can be considered as abnormal. Values after magnetic stimulation, however, are dependant on more variables than after traditional electric stimulation (Chokroverty, 1989) and consequently cannot be compared to electrical stimulation results. As a result, reference values for a standardized technique, as presented in this study, are needed.

Peak-to-peak amplitude of the MMEP depends on the number of axons recruited. Therefore, stimulation intensity, orientation of the coil and accessibility of the nerve are important factors influencing the peak-to-peak amplitude (Chokroverty, 1989; Dull et al., 1990; Jalinous, 1991). A high variation in peak-to-peak amplitudes of the MMEP was observed in this study. Different factors account for this variation and are difficult to control in a clinical setting: changing coil position, co-activation of other

nerves and muscles or double stimulation of axons by the circulating magnetic field (Amassian et al., 1989, Barker, 1991). The use of surface electrodes could be advised to overcome this high variation in peak-to-peak amplitudes, although its use in veterinary medicine is less suitable because of the high impedance of the skin (Cuddon, 2002). Analogous to a study in dogs (Van Soens et al., 2008), peak-to-peak amplitude interpretation should therefore be carried out carefully. Peak-to-peak amplitudes of the evoked responses after magnetic and electrical stimulation, however, did not differ, indicating supramaximal magnetic stimulation of the nerve. Therefore, the assumption can be made that a missing or only insufficiently reproducible potential (values lower than the lower limit of the 95% confidence interval) with attenuated peak-to-peak amplitude must be regarded as abnormal.

CONCLUSION

MMEP examination in cats seems to be a valuable diagnostic tool for objective monitoring of motor function of peripheral nerves. Standardization of the technique and of the interpretation of the results is necessary.

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CHAPTER 5

CLINICAL APPLICATIONS OF PERIPHERAL MAGNETIC NERVE STIMULATION IN DOGS AND CATS

Part 1. Magnetic stimulation of the radial nerve in dogs and cats with brachial plexus trauma: 53 cases

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SUMMARY

Brachial plexus trauma is a common clinical entity in small animal practice and prognostic indicators are essential early in the course of the disease. Magnetic stimulation of the radial nerve and consequent recording of the magnetic motor evoked potential (MMEP) was examined in 36 dogs and 17 cats with unilateral brachial plexus trauma.

Absence of deep pain perception (DPP), ipsilateral loss of panniculus reflex, partial Horner's syndrome and a poor response to MMEP were related to the clinical outcome in 29 of the dogs and 13 of the cats. For all animals, a significant difference was found in MMEP between the normal and the affected limb. Absence of DPP and unilateral loss of the panniculus reflex were indicative of an unsuccessful outcome in dogs. Additionally, the inability to evoke a MMEP was associated with an unsuccessful outcome in all animals.

It was concluded that magnetic stimulation of the radial nerve in dogs and cats with brachial plexus trauma may provide an additional diagnostic and prognostic tool.

INTRODUCTION

The brachial plexus is a complex anatomical structure originating from the 5^{th}-8^{th} cervical and the 1^{st} and 2^{nd} thoracic spinal nerves, and providing sensory and motor innervation to the thoracic limbs (Steinberg, 1979; Bailey et al., 1982). Pathological changes to the brachial plexus in small animal medicine include inflammatory, neoplastic and, most frequently, traumatic conditions, such as road traffic accidents (Wheeler et al., 1986). Brachial plexus trauma occurs when there is traction of the thoracic limb or severe abduction of the scapula (Griffiths, 1974; Steinberg, 1988). Typically, the nerve roots are more likely to be damaged than the plexus itself due to a lower capacity to stretch (Griffiths, 1974; Holtzer et al., 2002; Dewey, 2003).

Diagnosis of brachial plexus trauma is most commonly based on history, clinical signs, findings on neurological examination and results of electrodiagnostic testing. As early as 5 days after the initial peripheral nerve injury, spontaneous muscle activity on electromyography (EMG) will be found, although prior to this, muscle activity cannot normally be detected using this diagnostic approach (Griffiths and Duncan, 1974; Bowen, 1987). Since the roots of the radial nerve are commonly injured in brachial plexus trauma (Wheeler et al., 1986), electroneurography of the radial nerve may provide earlier diagnostic and prognostic information in comparison to EMG (Faissler et al., 2002). Electrical stimulation of the radial nerve, however, has some disadvantages, such as technical difficulties in stimulating the deeply situated nerve and unwanted stimulation of pain receptors. Magnetic stimulation of the radial nerve provides a more feasible and less painful method of stimulating peripheral nerves (Barker et al., 1987; Barker, 1991, 1999; Van Soens et al., 2008).

The primary objective of this study was to evaluate the use of magnetic stimulation of the radial nerve as an additional diagnostic tool in 36 dogs and 17 cats with unilateral brachial plexus trauma. Onset latencies and peak-to-peak amplitudes of magnetic motor evoked potentials (MMEP) of the radial nerve of the abnormal limb were compared with the normal limb. A secondary aim was to compare the relationship between MMEP findings and presenting neurological variables (absent deep pain perception (DPP), ipsilateral loss of the panniculus reflex, and presence of partial Horner's syndrome) to the clinical outcomes of the animals examined in this study.

MATERIALS AND METHODS

Animals

Dogs and cats presented with a history or suspicion of trauma and clinical and neurological signs of a brachial plexus lesion were included in this study. All animals were presented at the Small Animal Department of the Ghent University from 1998-2007. Exclusion criteria were brachial plexus lesions with non-traumatic origin. Age, sex, bodyweight (BW), breed, side of the lesion and time elapsed between the original trauma and the magnetic stimulation were reported for each animal.

Neurological assessment

For each animal, a complete neurological examination was performed on presentation and deficits were reported. Neurological status of the affected limb of each animal was graded from 0-4 (Table 1). Grade 0 was characterised by a normal use of the affected limb. Grade 1 animals had paresis but were still weight bearing on the affected limb. Grade 2 animals could not bear weight on the affected limb, although elbow and shoulder flexion were possible. In Grade 3, the animals could not bear weight on the affected limb or flex properly, but DPP remained intact. Grade 4 animals could not bear weight on the affected limb and the DPP was absent.

According to the neurological status of the affected limb, the localisation of the brachial plexus lesion was assigned to the different grades. Grade 1 corresponded to mild damage of the brachial plexus. Grade 2 corresponded to a caudal brachial plexus lesion (C7, C8, T1, T2 nerve roots), Grade 3 with a complete brachial plexus lesion (C5-T2 nerve roots) and Grade 4 with a complete brachial plexus lesion with involvement of the dorsal roots. Any ipsilateral loss of the panniculus reflex and/or presence of partial Horner's syndrome were also recorded.

Electrodiagnostic testing

Electromyography and magnetic stimulation of the radial nerve of both thoracic limbs were performed under general inhalation anaesthesia. Electromyography was performed by standard procedures (Cuddon, 2002) using a commercially available electromyograph (Sapphire, Acertys Healthcare). A concentric 37mm needle electrode (Acertys Healthcare) was used for recording and consecutively placed in the interosseus muscle, carpal flexor muscles, carpal extensor muscles, triceps muscle, biceps muscle, infraspinatus muscle and

supraspinatus muscle of the affected limb. The ground electrode was a subdermal needle electrode (Acertys Healthcare) placed over the olecranon. EMG was only performed if clinical symptoms were present for at least 5 days. The spatial distribution of spontaneous EMG activity was reported for each animal and related to the localisation of the lesion (Tables 2 and 3). In cranial lesions, spontaneous EMG activity was found in the supraspinatus, infraspinatus and sometimes biceps muscles. In caudal lesions, spontaneous activity was expected in all but the supraspinatus and infraspinatus muscles. In complete brachial plexus lesions, EMG activity was present in all muscles examined on the affected limb.

Magnetic stimulation was performed with a commercially available magnetic stimulator (Magstim Super Rapid, Acertys Healthcare), with a circular coil, 4.5 cm in diameter, capable of producing a peak magnetic field of 4.0 Tesla at the coil surface. Maximal stimulator output was used in most of the patients, although the output was reduced to 75% in four of the cats because of a strong stimulus artefact. Magnetic stimulation of the radial nerve was done on both thoracic limbs.

The magnetic coil was placed in the axillary region, medial to the radial nerve and the flat surface of the coil was placed parallel to the skin surface of the limb with the cranial part of the circle on the coil held tangentially to the radial nerve. For both limbs, orthodromic nerve stimulation was performed (Van Soens et al., 2008). All recordings were made using the same commercially available electromyograph. The tip of the recording electrode (monopolar needle electrode, Acertys Healthcare) was placed in the extensor carpi radialis muscle of the forelimb, just in front of the lateral humeral epicondyle. The reference electrode was a subdermal needle electrode (Acertys Healthcare), positioned over the tendons of the extensor carpi radialis muscle, at the level of the carpal joint. The ground electrode was a subdermal needle electrode placed over the olecranon of the forelimb. Sensitivity was set at 10 mV per division. Analysis time was 100 ms following the stimulus. The low and high frequency filters were set at 20 Hz and 10 kHz, respectively. Each recording resulted from a single stimulus and no signal averaging was undertaken. For each recording site, two individual stimulations were delivered and recorded to evaluate reproducibility. Onset latency (in ms) was measured as the shortest distance between the trigger point and the take-off of the initial phase (negative or positive). Peak-to-peak amplitude (in mV) was measured between the two largest peaks of opposite polarity.

Clinical outcome

Follow-up and information regarding the outcome of the patients was collected during follow-up examination at the Small Animal Department of the Ghent University or by contacting the referring veterinarian or owner. The minimal follow-up time was 1 month after the initial neurological examination at the Small Animal Department. For the purposes of this study, the outcome was considered 'unsuccessful' if no improvement in the grade of neurological status of the affected limb was recorded at least 1 month after the initial examination. The outcome was also considered unsuccessful if euthanasia of the animal or amputation of the affected limb was performed as a direct result of the brachial plexus trauma at least 1 month after the initial admission. Outcome was determined 'successful' when the grade of neurological status improved in comparison to the clinical status determined during magnetic stimulation.

Statistical analysis

Frequencies and descriptive statistics were derived for age, gender, weight, side of the lesion, neurological deficits and outcome. A paired Student's *t*-test was used to determine whether there were significant differences in onset latencies and peak-to-peak amplitudes of the MMEP between the affected and the normal limb in both cats and dogs. The relation between outcome and absence of DPP, ipsilateral loss of the panniculus reflex and presence of partial Horner's syndrome was studied using Chi square tests or Fisher's exact tests. The Mann-Whitney test was used to compare onset latencies in animals with a successful and an unsuccessful outcome. This test was also used to compare differences in peak-to-peak amplitudes of dogs with a successful versus an unsuccessful outcome. An unpaired *t*-test with Welch correction was used for the variable peak-to-peak amplitude in the comparison between a successful and an unsuccessful outcome in the cats. Statistical analyses were performed with Graph Pad Instat software. Differences were considered significant at the 5% probability level ($P<0.05$).

RESULTS

Animals

Thirty-six dogs and 17 cats met the criteria for inclusion in the study. The dog group consisted of 23 males (64%) and 13 females (36%) with a mean (± SD) age of 2.7 ± 2.6 years and a mean (± SD) BW of 22.6 ± 13.3 kg. The group comprised different breeds, particularly Rottweilers ($n=4$), Jack Russell terriers ($n=4$) and mixed breed dogs ($n=7$). Twenty-four dogs

(67%) had a left sided lesion and 12 (33%) had a right sided lesion. The median duration of clinical signs at admission was 14 days (range: 0.29-365 days) (Tables 2 and 3).

The cats had a mean age of 2.9 ± 2.7 years and mean BW of 3.7 ± 0.9 kg, with 12 males (70 %) and five females (30 %). All cats were European Shorthairs, with 65% (11/17) that presented with a left brachial plexus lesion and 35% (6/17) with a right brachial plexus lesion. In the cats, the median duration of clinical signs at admission was 6 days (range: 0.5 days-60 days) (Tables 2 and 3).

Neurological assessment

The animals were categorised in four groups according to severity of neurological deficits on the affected limb (Table 1). Most animals (54% of the dogs and 65% of the cats) were presented with symptoms of no weight bearing on the affected limb, but with an intact DPP (complete brachial plexus injury) (Figure 1). None of the animals were presented with clinical signs that corresponded to a cranial brachial plexus trauma.

Figure 1. Typical clinical presentation of a dog with unilateral brachial plexus trauma: no weight bearing on the left thoracic limb.

Table 1. Number of patients per category of neurological deficits.

Grade	Symptoms	Type and localisation of the lesion	Dogs	Cats
0	Normal	Normal	0	0
1	Paresis with weight bearing	Mild injury	1 (3%)	0
2	No weight bearing, elbow and shoulder flexion	Caudal avulsion	6 (17%)	3 (17.5%)
3	No weight bearing, DPP present	Complete avulsion	20 (55%)	11 (65%)
4	No weight bearing, DPP absent	Complete avulsion with involvement of the dorsal roots	9 (25%)	3 (17.5%)

DPP, deep pain perception

In 28 dogs (78%) and 7 cats (41%), unilateral loss of the panniculus reflex was observed, while the presence of a normal panniculus response could not be elicited in three cats. Partial Horner's syndrome (miosis) was seen in 22 dogs (61%) and 8 cats (47%). In two cats, the presence of partial Horner's syndrome could not be evaluated.

Electrodiagnostic testing

An EMG examination was performed in 25 dogs and 10 cats and spontaneous EMG activity (fibrillation potentials and positive sharp waves) was recorded in the muscles of the affected limb of each animal (Tables 2 and 3). In 20 dogs and 5 cats, the spatial distribution of spontaneous EMG activity corresponded with the localisation of the lesion. In 5 dogs and 5 cats, however, the spatial distribution of EMG activity differed from the localisation of the lesion.

In 22 dogs and 12 cats, magnetic stimulation of the radial nerve resulted in biphasic to polyphasic potentials. However, in 14 dogs and 5 cats, no MMEP could be evoked in the affected thoracic limb (Tables 2 and 3) (Figure 2). Statistically significant differences in onset latencies and peak-to-peak amplitudes were found between the normal and the affected thoracic limb in all animals.

Table 2. Neurological grade (Grade), EMG activity (EMG), time elapsed between injury and magnetic stimulation (Time to MS), ability to evoke magnetic motor evoked potential (MMEP) and outcome in dogs with brachial plexus injury (Outcome).

Dog	Grade	EMG	Time to MS	MMEP	Outcome
1	3	C	6	No	U
2	3	P	6	Yes	?
3	3	C	7	Yes	?
4	2	P	83	Yes	?
5	3	C	10	Yes	?
6	3	C	30	No	?
7	2	C	365	Yes	U
8	2	P	66	No	U
9	3	C	121	No	U
10	4	NP	0.5	Yes	U
11	4	C	100	No	U
12	2	NP	3	Yes	U
13	4	NP	2	No	U
14	3	C	47	Yes	?
15	2	P	43	No	U
16	3	C	180	No	U
17	3	NP	1	Yes	S, Grade 0
18	3	NP	0.29	Yes	S, Grade 1
19	3	NP	3	Yes	U
20	3	C	180	Yes	?
21	1	P	17	Yes	S, Grade 0
22	3	C	14	Yes	U
23	3	P	42	Yes	U
24	3	C	16	No	U
25	4	P	15	Yes	U
26	4	C	11	Yes	U
27	3	C	7	No	U
28	4	C	10	No	U
29	2	NP	14	Yes	U
30	4	C	24	No	U
31	4	NP	18	No	U
32	3	NP	2	Yes	U
33	4	C	10	No	U
34	3	P	59	Yes	S, Grade 1
35	3	NP	2	Yes	U
36	3	NP	2	Yes	U

C: Spontaneous EMG activity in all muscles of the affected limb, P: spontaneous EMG activity in all muscles but the supraspinatus and infraspinatus muscle, NP: EMG not performed, U: unsuccessful outcome, ?: unknown outcome, S: successful outcome

Table 3. Neurological grade (Grade), EMG activity (EMG), time elapsed between injury and magnetic stimulation (Time to MS), ability to evoke magnetic motor evoked potential (MMEP) and outcome in cats with brachial plexus injury (Outcome).

Cat	Grade	EMG	Time to MS	MMEP	Outcome
1	3	NP	5	No	U
2	3	NP	2	Yes	S, Grade 0
3	4	P	35	No	U
4	2	P	24	No	U
5	4	C	24	Yes	U
6	2	P	60	Yes	?
7	3	P	11	Yes	S, Grade1
8	2	NP	2	Yes	S, Grade 1
9	4	NP	2	Yes	U
10	3	C	10	Yes	S, Grade 0
11	3	NP	0.5	Yes	S, Grade 0
12	3	C	2	No	?
13	3	P	7	Yes	?
14	3	NP	1	No	U
15	3	NP	4	Yes	S, Grade 2
16	3	P	6	No	?
17	3	P	6	Yes	S, Grade 0

C: Spontaneous EMG activity in all muscles of the affected limb, P: spontaneous EMG activity in all muscles but the supraspinatus and infraspinatus muscle, NP: EMG not performed, U: unsuccessful outcome, ?: unknown outcome, S: successful outcome

Clinical outcome

Twenty-nine dogs were available for follow up (80%; Table 2). Twenty-five of these 29 dogs (86%) showed no improvement at all, with four euthanased (16 %), 11 dogs (44 %) having the affected limb amputated and 10 (40%) showing no improvement. Improvement in the grade of neurological status was reported in 4 dogs (14%), 2 of which regained complete functional activity (Grade 0), while the other 2 showed mild improvement (Grade 1).

The time period between initial admission and follow-up ranged from 1 month to 8 years in dogs that had a successful outcome and from 1 month to 7 years and 9 months in dogs with an unsuccessful outcome.

Thirteen cats were available for follow-up (76%; Table 3), with 6/13 cats (46 %) showing no improvement of the affected limb and 3 of these cats having the limb amputated. Seven of the

13 cats (54%) showed improvement in comparison to the initial presentation. Four of these cats became completely normal (Grade 0), two showed paresis with weight bearing (Grade 1) and one cat regained some motor activity (elbow flexion, Grade 2). The time period between initial admission and follow up ranged from 20 days to 4 years in cats with a successful outcome and from 1 month to 5 years in cats with an unsuccessful outcome.

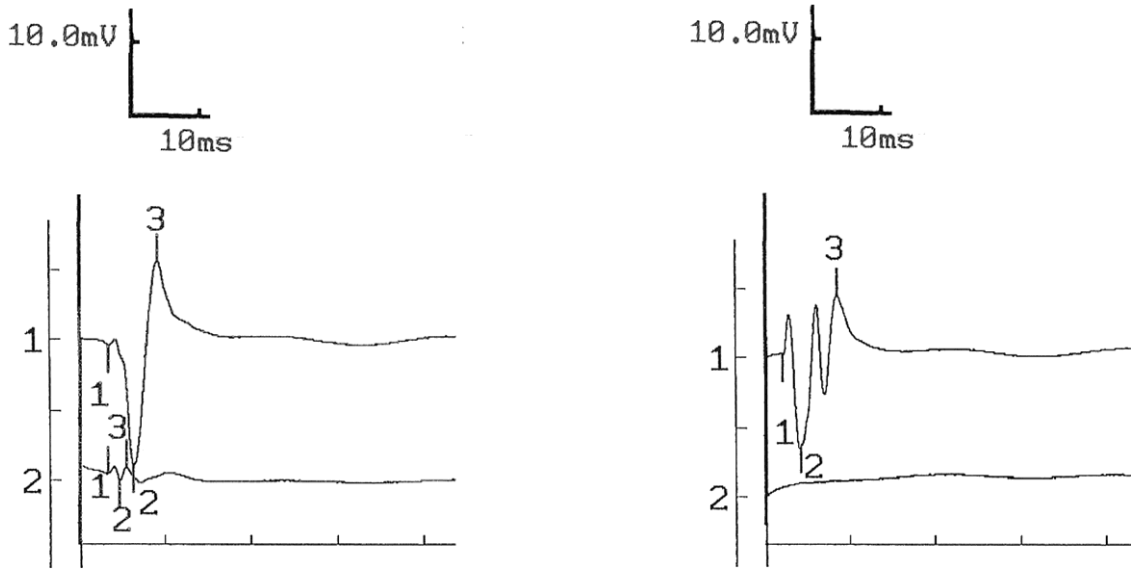

Figure 2. Magnetic motor evoked potential (MMEP) recorded in the extensor carpi radialis muscle after stimulation of the radial nerve of the normal (trace 1) and the affected limb (trace 2) in two dogs with unilateral brachial plexus trauma: (left) in the affected limb a MMEP with decreased peak-to-peak amplitude and prolonged onset latency in comparison to the normal limb was observed. (right) no MEP could be evoked in the affected limb. 1: onset latency; 2 to 3: peak-to-peak amplitude.

Relation outcome-absence of DPP, unilateral loss of the panniculus reflex or presence of partial Horner's syndrome

In dogs, absence of DPP and ipsilateral loss of the panniculus reflex were significantly related with an unsuccessful clinical outcome. No significant relation between clinical outcome and presence of partial Horner's syndrome could be shown.

Clinical outcome of the cats was not statistically related with one of the presenting neurological variables (i.e. absence of DPP, unilateral loss of the panniculus reflex or the presence of partial Horner's syndrome). However, although there was no statistically significant relationship demonstrated, we observed that all cats (3/14) with absence of DPP had an unsuccessful outcome.

Relation outcome-magnetic stimulation

In all animals, the inability to evoke a MMEP after magnetic stimulation in the affected limb resulted in an unsuccessful outcome. Mean peak-to-peak amplitudes (±SD) of the MMEP of the affected limb of dogs and cats with a successful versus an unsuccessful outcome are noted in Table 4. Between affected limbs, a significant difference in peak-to-peak amplitude in dogs with an unsuccessful versus a successful outcome was found; i.e. peak-to-peak amplitude in dogs with an unsuccessful outcome was significantly lower than peak-to-peak amplitude in dogs with a successful outcome.

Table 4. Mean ± SD peak-to-peak amplitude of the affected limb of dogs and cats with a successful (S) or an unsuccessful (U) outcome.

DOGS	S	U
Peak-to-peak amplitude (mean ± SD)	13.71 ± 4.66	2.96 ± 4.98[a]
CATS	S	U
Peak-to-peak amplitude (mean ± SD)	11.57 ± 10.39	3.17 ± 3.47

[a] Significantly different ($P< 0.05$) from values of a successful outcome.

DISCUSSION

A traumatic insult to the brachial plexus usually disrupts the nerve roots rather than the plexus itself (Welch, 1996; Holtzer et al., 2002). Assessing the exact site of rupture in a clinical case setting was, however, extremely difficult and it was assumed that the injury was to the nerve roots, as reported in the literature (Welch, 1996).

Clinical signs of brachial plexus trauma depend on which nerve roots of the plexus are affected and are categorised as cranial (C5-7 roots), caudal (C8-T2 roots) or complete (C5-T2 roots) injuries (Griffiths et al., 1974). In the present study, all animals presented with a caudal or complete lesion. Initial clinical signs and progress of clinical signs of brachial plexus injury, however, depend on the extent of nerve root damage. Nerve root injuries are classified by increased severity in three broad categories: neuropraxia, axonotmesis and

neurotmesis (Seddon, 1943). In this study, a minority of animals was presented with neuropraxia and axonotmesis injury. Most animals, however, were presented with more severe injury and showed only mild or, frequently, no improvement (Welch, 1996; Friedman, 1991; Burnett and Zager, 2004).

Diagnosis of brachial plexus trauma is based on history, clinical signs and electrodiagnostic testing (Steinberg, 1979; van Nes, 1986; Wheeler et al., 1986). Spontaneous EMG activity was found in all animals that underwent EMG examination. In some animals, however, the spatial distribution of spontaneous activity did not corresponded with the clinical presentation. The subjective evaluation of the animals' clinical condition might explain this discrepancy in findings. These findings are similar to those described in other studies (Steinberg, 1979; van Nes, 1986; Wheeler et al., 1986).

Magnetic stimulation of the radial nerves was performed since all dogs and cats were presented with caudal or complete brachial plexus injuries, which indicated radial nerve damage. Similar to electrically evoked activity of a motor nerve, the peak-to-peak amplitude of the MMEP reflected the number and size of motor units innervating the muscle. Onset latency reflected the conduction along the axon and thus reflected the degree of myelination of the nerve fibers (Welch, 1996). Peripheral nerve injuries may therefore decrease peak-to-peak amplitudes and increase the onset latencies. In the present study, statistically significant decreases in peak-to-peak amplitudes and increases in onset latencies of the MMEP in the affected limb were observed in all animals. Interestingly, even in the animals that were presented earlier than 5 days after the traumatic injury, statistically significant differences were found between the affected and the normal limb. These findings may indicate the value of magnetic stimulation as an early electrodiagnostic tool in comparison to electromyography. Electrical stimulation of the radial nerve to evaluate its neural integrity may be difficult because of its relative inaccessibility. In addition, electrical stimulation causes unwanted stimulation of pain receptors so general anaesthesia is required to perform the technique. Conversely, magnetic stimulation provided a less painful method of peripheral nerve stimulation (Barker et al., 1987; Barker, 1991) and could therefore be performed under sedation in veterinary clinical practice.

Prognostic indicators for functional recovery of the affected limb in the early course of the disease would be beneficial. In general, the lack of DPP is an indicator for a poor prognosis.

In a recent study, the presence of pain perception was the best predictor for complete functional recovery (Faissler et al., 2002). In the present study, absence of DPP and unilateral loss of the panniculus reflex were indicative of a negative outcome in the dogs. For the cats, no relation between absence of DPP, unilateral loss of the panniculus reflex or presence of partial Horner's syndrome was detected. However, none of the dogs and cats that presented with symptoms of absent DPP showed further improvement.

An early decreased radial nerve conduction velocity indicates a poor prognosis in brachial plexus injuries (Welch, 1996; Faissler et al., 2002). In this magnetic stimulation study, the inability to evoke a MMEP resulted in all animals of both species in a negative outcome. Even in an early stage of the clinical course of the injury (1 day for the cats and 2 days for the dogs), the inability to evoke a MMEP resulted in an unsuccessful outcome. Interestingly, lower peak-to-peak amplitudes were observed in dogs with an unsuccessful clinical outcome, in comparison to dogs with a successful outcome, which was unexpected and requires further investigation. It can, however, be assumed that the inability to evoke a MMEP indicates a severe nerve root injury and poor prognosis, while a positive MMEP has an uncertain prognostic value.

Some of the limitations in this study relate to the retrospective manner in gathering follow-up information in some animals, the subjective evaluations, and the perception of the owners, which could have influenced the clinical outcome. However, reasons for amputation or euthanasia were primarily based on lack of improvement in the affected limb and not on secondary complications, while all animals that underwent a complete functional recovery were examined at the Small Animal Department. Also, the results of a successful outcome in the animals in this study could have been biased because the animals that only showed a mild degree of improvement were included in the successful groups. Their improvement might have been associated with compensatory signs and therefore not with recovery of the original brachial plexus lesion. In addition, the time that elapsed between the inciting injury and the magnetic stimulation differed between the animals and it might be expected that longer lasting injuries would give more abnormalities. For all animals in this study, however, statistically different results were found between the normal and the affected limb, even though they were presented at different times. The failure to evoke a MMEP resulted in an unsuccessful outcome in all animals, even though they were presented at different times following injury. We consider that this indicates the diagnostic and prognostic value of magnetic stimulation. In

serial stimulation studies, however, time elapsed between the traumatic injury and the performance of magnetic stimulation might be of greater importance; an improvement in the evoked responses in serial stimulations could indicate re-innervation and would provide additional prognostic information. Therefore, serial magnetic stimulation studies would be necessary to obtain more information on the prognostic value of magnetic stimulation of the radial nerve in brachial plexus injuries.

CONCLUSION

Magnetic stimulation of the radial nerve in dogs and cats with brachial plexus trauma may offer an early diagnostic and prognostic tool. To the authors' knowledge, this is the first report on the use of magnetic stimulation of the radial nerve in dogs and cats with traumatic brachial plexus avulsion.

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CHAPTER 5

CLINICAL APPLICATIONS OF PERIPHERAL MAGNETIC NERVE STIMULATION IN DOGS AND CATS

Part 2. Magnetic stimulation of the sciatic nerve in 8 dogs and 3 cats with unilateral sciatic nerve dysfunction

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SUMMARY

Magnetic stimulation of the sciatic nerve and subsequent recording of the motor evoked potential (MEP) was performed in 8 dogs and 3 cats with unilateral sciatic nerve dysfunction. Localisation of the lesion in the sciatic nerve was based on the history, clinical neurological examination and on results of electromyography examination. Aetiology of the sciatic nerve lesion was diverse.

A significant difference was found in MEP between the normal and the affected limbs. Additionally, absence of conscious pain sensation, absence of voluntary motor function and a poor outcome seemed associated with the inability to evoke a MEP in the affected limb.

INTRODUCTION

Sciatic nerve dysfunction can be presented in cases where there is damage to either the L6-S1 spinal cord segments, the intra-pelvine lumbosacral plexus or the sciatic nerve itself. Causes of sciatic nerve dysfunction are diverse and include traumatic, iatrogenic, neoplastic and inflammatory etiologies (Burrows and Harvey, 1973; Rasmussen, 1978; Weaver and Omamegbe, 1981; Fantom et al., 1983; Gilmore, 1984; Chambers and Hardie, 1986; Jacobsen and Schrader, 1987; Van Ham et al., 1989; Abraham et al., 2003; Aňor, 2004; Forterre and other, 2007).

Localisation of the lesion along the sciatic nerve is most commonly based on history, clinical signs, findings on neurological examination and results of electrodiagnostic testing and medical imaging. The technique of magnetic peripheral nerve stimulation has been described in normal dogs (Van Soens et al., 2008) and cats (Van Soens et al., 2009a) and in dogs and cats with brachial plexus trauma (Van Soens et al., 2009b) and can be used as an additional diagnostic and prognostic tool. Magnetic stimulation has several advantages over electrical stimulation: it is minimally invasive, almost painless and a safe technique that requires less time for the investigator (Barker et al., 1987; Evans, 1991; Barker, 1999).

The objective of this study was to evaluate the use of magnetic stimulation of the sciatic nerve as a diagnostic tool in 8 dogs and 3 cats with unilateral sciatic nerve dysfunction. Onset latency and peak-to-peak amplitude of the motor evoked potential (MEP) evoked in the affected limb by magnetic stimulation of the sciatic nerve were compared to values obtained in the intact limb. Furthermore, results of MEP were related to clinical signs, findings on electromyography (EMG) and outcome of the animals.

MATERIALS AND METHODS

Animals and neurological assessment

Between 1999 and 2008, 8 dogs and three cats were presented to the Small Animal Department of the Ghent University with clinical, neurological and electromyographic signs of sciatic nerve dysfunction (Figure 1). For each animal, a complete neurological examination was performed on presentation and deficits reported.

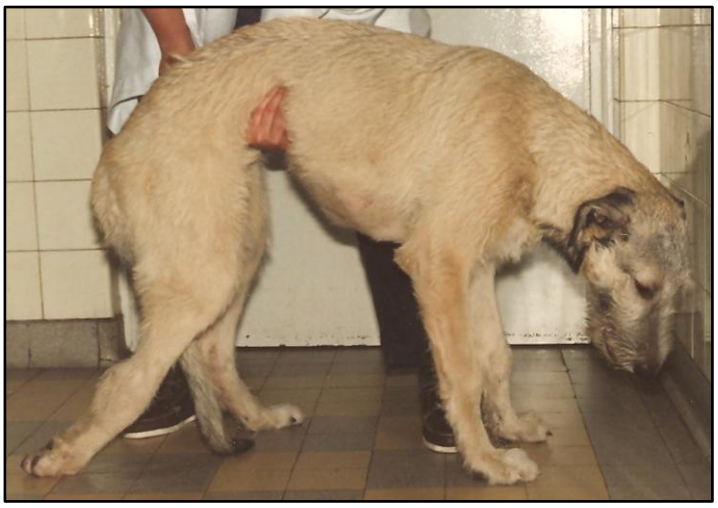

Figure 1. Typical clinical presentation of a dog with unilateral sciatic nerve dysfunction.

Ancillary diagnostic testing

Ancillary diagnostic testing (radiography, myelography, computed tomography, ultrasound, histopathology) was performed to come to an etiological diagnosis. In 1 dog and 1 cat, no ancillary examinations were performed because an iatrogenic trauma of the sciatic nerve after an intramuscular injection was the cause of the lesion.

Clinical outcome

Follow-up and information regarding the outcome of the patients was collected during follow-up examination at the Small Animal Department of the Ghent University or by contacting the referring veterinarian or owner.

Electrodiagnostic testing

For each animal, time elapsed between the original trauma and electrodiagnostic testing was reported (table1). EMG and magnetic stimulation were performed under general inhalation anaesthesia. EMG was performed by standard procedures (Cuddon, 2002) using a commercially available electromyograph (Sapphire, Acertys Healthcare) in 7 dogs and 3 cats. In 1 dog, EMG was not performed because clinical signs were not present for more than 5 days. A concentric needle electrode (Acertys Healthcare) was consecutively placed in the following muscles of the affected limb: gastrocnemius muscle, cranial tibial muscle, quadriceps muscle, semimembranosus muscle, semitendinosus muscle and biceps femoris

muscle. The ground electrode was a subdermal needle electrode (Acertys Healthcare) placed over the patella.

Magnetic stimulation was performed with a commercially available magnetic stimulator (Magstim Super Rapid, Acertys Healthcare), with a circular coil, 45 mm in diameter, capable of producing a peak magnetic field of 4.0 Tesla at the coil surface. Maximal stimulator output was used to obtain supramaximal responses; individual stimulations were delivered until peak-to-peak amplitude of the MEP no longer increased. Magnetic stimulation of the sciatic nerve was done for both pelvic limbs. The magnetic coil was placed lateral from the pelvic limb and the flat surface of the coil was placed parallel to the skin surface of the limb. The caudal part of the circle on the coil was held tangentially to the sciatic nerve between the greater trochanter and the ischial tuberosity. For both limbs, orthodromic nerve stimulation was performed (Van Soens et al., 2008). All recordings were made using the same electromyograph. Recording electrodes were insulated monopolar needle electrodes and reference and ground electrodes were un-insulated subdermal needle electrodes (Acertys Healthcare). The recording, reference and ground electrodes were placed in the cranial tibial muscle, slightly lateral to the distal end of the tibial crest, over the tendons of the cranial tibial muscle, at the level of the tarsal joint and over the patella of the pelvic limb, respectively. Sensitivity was set at 10 mV per division. Analysis time was 100 ms following the stimulus. The low and high frequency filters were set at 20 Hz and 10 kHz, respectively. Onset latency (in ms) was measured as the shortest distance between the trigger point and the take-off of the initial phase (negative or positive). Peak-to-peak amplitude (in mV) was measured between the two largest peaks of opposite polarity. Onset latency and peak-to-peak amplitude were measured from the MMEP with the highest amplitude.

Statistical analysis

The Wilcoxon matched-pairs signed ranks test was used for identification of statistical significance between peak-to-peak amplitudes and onset latencies of the normal and the affected limb. Differences were considered significant at the 5% probability level ($P<0.05$).

RESULTS

Animals and neurological assessment

The dog group consisted of all male dogs with a mean (± SD) age of 6.56 ± 2.91 years and a mean (± SD) bodyweight of 24.85 ± 11.56 kg. The group comprised different breeds, including 1 Rottweiler, 1 Bouvier, 1 Samoyed, 1 Shi Tzu, 1 Golden Retriever,1 Labrador Retriever,1 German Shepherd and 1 mixed breed dog. The cats were male and had a mean (± SD) age of 3 ± 1.73 years and a mean (± SD) bodyweight of 3.43 ± 0.86 kg. Two cats were European shorthairs and 1 cat was a Siamese.

Three dogs and 2 cats still showed voluntary motor function on the affected limb. On neurological examination, all animals had absent or decreased proprioception and absent or decreased withdrawal reflexes on the affected limb. Conscious pain sensation (CPS) was tested by gripping across the nail with a forceps and in three dogs and 1 cat, CPS was absent in the affected limb (table 1).

Table 1. Breed, findings on neurological examination (NE), EMG activity, time to magnetic stimulation (MS), onset latency (L), and peak-to-peak amplitude (A) of the motor evoked potential of the affected limb and the normal limb, results of ancillary diagnostic tests, lesion localisation and outcome in dogs and cats with sciatic nerve dysfunction

Animals	Breed	NE	EMG	Time to MS	Affected limb	Normal limb	Ancillary diagnostic tests and findings	Lesion localisation	Outcome
Dog 1	Bouvier	VMF -, PR-, WR-	C	14d	L: no MEP A: no MEP	L: 5.7 ms A: 10.9 mV	Normal, IM injection or trauma	Sciatic nerve	Poor: amputation
Dog 2	Samoyed	VMF +, PR decreased, WR decreased	C	50d	L: 6.2 ms A: 2.85 mV	L: 3.3 ms A: 33 mV	Computed tomography: mass in the lumbosacral plexus right	Intra-pelvic lumbosacral plexus	Poor: euthanasia after 10 months
Dog 3	Shi Tzu	VMF -, PR-, WR-	C	21d	L: no MEP A: no MEP	L: 1.9 ms A: 24.6 mV	None: after IM injection	Sciatic nerve	Poor
Dog 4	Golden Retriever	VMF +, PR decreased, WR decreased	C	240d	L: 3.7 ms A: 9.63 mV	L: 3.4 ms A: 39.4 mV	Myelography: intramedullary mass at vertebral level L4-5	L6-S1 spinal cord segments	Poor: euthanasia after 3 months
Dog 5	Mongrel dog	VMF-, PR-, WR-, CPS-	C	31d	L: no MEP A: no MEP	L: 3 ms A: 31.5 mV	Radiography: sacroiliac luxation	Intra-pelvic lumbosacral plexus	Poor: amputation
Dog 6	Rottweiler	VMF-, PR-, WR-, CPS-	C	14d	L: no MEP A: no MEP	L: 4 ms A: 18.8 mV	Normal: suspicion of trauma	Sciatic nerve	Fair
Dog 7	German Shepherd	VMF-, PR-, WR-, CPS-	C	101d	L: no MEP A: no MEP	L: 3.3 ms A: 33 mV	Ultrasound: mass lesion in the muscles surrounding and compressing the sciatic nerve; inflammatory on histology	Sciatic nerve	Fair
Dog 8	Labrador	VMF+, PR decreased, WR decreased	NP	1d	L: 5.2 ms A: 9.7 mV	L: 3.8 ms A: 18.9 mV	Radiography: pelvic fracture	Intra-pelvic lumbosacral plexus	Good
Cat 1	European Shorthair	VMF-, PR-, WR-, CPS	C	14d	L: no MEP A: no MEP	L: 2.4 ms A: 41.6 mV	Radiography: arthrotic changes at the femoral head after femoral head excision	Sciatic nerve	Fair
Cat 2	European Shorthair	VMF+, PR-, WR-	P	14d	L: 5.2 ms A: 12.9 mV	L: 1.5 ms A: 21.7 mV	Radiography: severe callus formation after pelvic fracture	EMG findings suggest sciatic nerve	Fair
Cat 3	Siamese	VMF+, PR-, WR-	P	35d	L: 1.7 ms A: 15.9 mV	L: 1.5 ms A: 33.9 mV	None: after IM injection	Sciatic nerve	Good

VMF: voluntary motor function, PR: proprioception, WR: withdrawal reflex, CPS: conscious pain sensation, -: absent, NP: not performed, C: spontaneous EMG activity in all muscles but the quadriceps muscle, P: spontaneous EMG activity present in muscles distal from the stifle (cranial and gastrocnemius muscle), d: days, L: onset latency, A: peak-to-peak amplitude

Ancillary diagnostic testing

Results of the ancillary diagnostic examinations are summarized in table 1. The causes of the sciatic nerve dysfunction were neoplastic, degenerative, traumatic and inflammatory. In 2 of these dogs ancillary diagnostic testing revealed no abnormalities and trauma or an intramuscular injection were assumed to be the origin of the dysfunction.

Clinical outcome

Results of follow-up are summarized in table 1. Follow-up period ranged from 1 month to 9 years after initial admission. In 2 dogs, amputation of the affected limb was performed after 1 month because no improvement was detected. In the 2 dogs that were diagnosed with a neoplastic lesion on the course of the sciatic nerve, euthanasia was performed 3 and 10 months after initial admission because of progressive neurological signs. In 1 dog and 1 cat, complete resolution of clinical signs was reported. In 1 dog no improvement of the clinical signs could be detected. In the other 4 animals, the neurological signs showed some improvement but the animals did not regain normal function of the affected limb.

Electrodiagnostic testing

The spatial distribution of spontaneous EMG activity was reported for each animal in table 1. In 7 dogs and 1 cat, spontaneous activity was found in all muscles except for the quadriceps muscle of the affected pelvic limb. In 2 cats, EMG examination revealed spontaneous activity in the cranial tibial and the gastrocnemius muscle.

Results of onset latencies and peak-to-peak amplitudes of MEP are summarized in table 1. In 3 dogs and 2 cats, magnetic stimulation of the sciatic nerve of the affected limb resulted in biphasic to polyphasic potentials with increased onset latencies and decreased peak-to-peak amplitudes (figure 1a) in comparison to those of the normal limb. In 5 dogs and 1 cat, no MEP could be evoked in the affected pelvic limb (figure 1b). Statistically significant differences in onset latencies and peak-to-peak amplitudes were found between the normal and the affected pelvic limb.

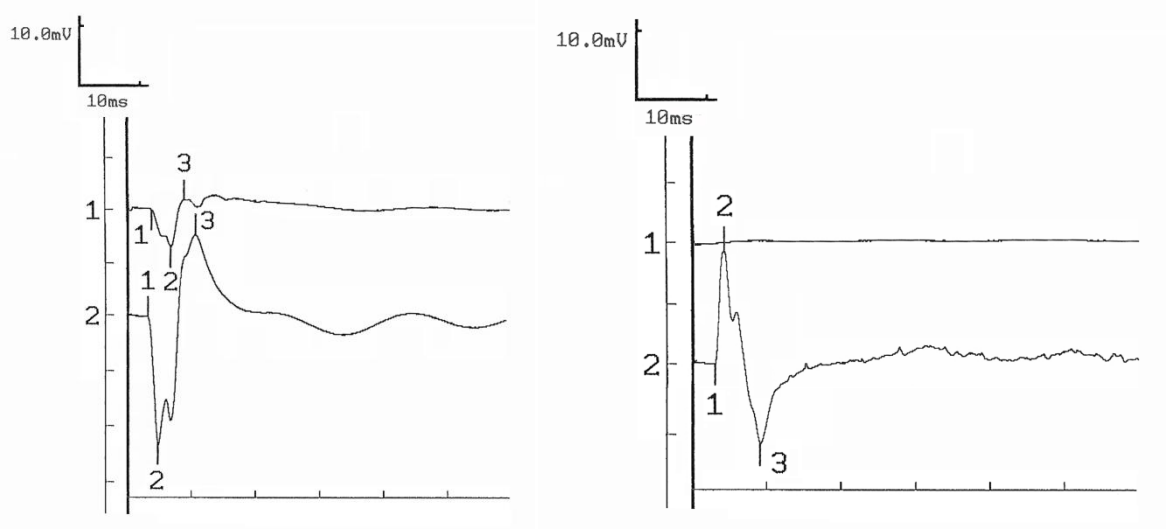

Figure 2. Motor evoked potential recorded in the cranial tibial muscle after stimulation of the sciatic nerve of the affected (trace 1) and the normal limb (trace 2) in two dogs with unilateral sciatic nerve dysfunction: (left) in the affected limb a MEP with decreased peak-to-peak amplitude and prolonged onset latency in comparison to the normal limb was observed. (right) no MEP could be evoked in the affected limb. 1: onset latency; 2 to 3: peak-to-peak amplitude.

DISCUSSION

Magnetic stimulation of the sciatic nerve was performed in dogs and cats with unilateral sciatic nerve dysfunction, to evaluate the integrity and the conduction along the sciatic-peroneal nerve. The technique of magnetic peripheral nerve stimulation has proven useful in veterinary medicine (Van Soens et al., 2008, 2009a,b) as it is an easy, rapid, minimally-invasive and almost painless method that can be performed under sedation or a light plane of anaesthesia (Barker et al., 1987).

The sciatic nerve arises from spinal cord segments L6-S1 and innervates, among others, the biceps femoris, semimembranosus, semitendinosus, cranial tibial and gastrocnemius muscles (De Lahunta and Glass, 2009). Absent or decreased proprioception and absent or decreased withdrawal reflexes on one of the pelvic limbs are indicative of sciatic nerve dysfunction. In this study, EMG findings were consistent with denervation of all probed muscles innervated by the sciatic nerve in 7 dogs and 1 cat. In 2 cats, on the other hand, EMG findings suggested barely peroneal and tibial nerve damage. In 1 of these cats, the cause of the monoparesis was a known intramuscular injection which is a common cause of peroneal and tibial damage (Rasmussen, 1978). In the other cat (cat 2), severe callus formation after a pelvic fracture was considered to be the cause of the monoparesis (Jacobsen and Schrader, 1987) although EMG findings suggested a more distally located lesion on the sciatic nerve. An unobserved sciatic

groove injection can therefore not be excluded as the origin of the nerve injury (Rasmussen, 1978; Aňor, 2004).

Based on the type of nerve injury, the different parameters of the MEP will change. Similar to electrically evoked potentials, peak-to-peak amplitude of the MEP reflects the number and size of motor units innervating the muscle. Amplitude changes can result either from axonal loss, conduction block distal to the stimulation point following acute demyelination or axon severance or both. Onset latency reflects the conduction along the axon and changes either result from loss of fastest axons, conduction blocks of these fastest axons or myelin sheaths changes (Welch, 1996; Cuddon, 2002) Therefore, peripheral nerve injuries may decrease peak-to-peak amplitude and prolong the onset latency (Sims and Redding, 1979). In severe cases, the inability to evoke a MEP can also be seen (Welch, 1996; Van Soens et al., 2009b). With time, a normalisation of the amplitude is possible through collateral re-innervation, re-myelination of acutely demyelinated areas and axon regrowth. Latencies, however, might remain prolonged despite clinical improvement since re-myelination produces shorter internodes (Cuddon, 2002).

In the animals in which still a degree of voluntary motor function was present in the affected limb, MEP with longer onset latencies and smaller peak-to-peak amplitudes were recorded, indicating interrupted conduction and axons along the sciatic nerve. In 5 dogs and 1 cat with absent voluntary motor function, the inability to evoke a response was observed and thus indicated severe damage of the axons and its myelin sheath.

Despite the inability to evoke a MEP in 2 of the dogs, CPS was still present, indicating intact nociceptive pain fibers and severed motor fibers. This finding can be explained by the higher resistance of nociceptive pain fibers compared to motor fibers (Griffiths, 1974).

Although significant differences were found between the normal and the affected limbs, time elapsed between the inciting injury and the magnetic stimulation differed between the animals. In 1 animal, these differences were already observed 1 day after the inciting injury; therefore we consider that this might indicate the early diagnostic value of magnetic peripheral nerve stimulation. These time course differences, however, might have influenced MEP results in this study; improvement in MEP parameters could indicate re-innervation in

traumatic lesions. Consequently, serial stimulation studies could provide additional diagnostic and even prognostic information.

Prognostic indicators for functional recovery of the affected limb in the course of a disease are beneficial. In this study, the different causes of the sciatic nerve dysfunction limited overall interpretation. In general however, the lack of CPS is an indicator for a poor prognosis in traumatic brachial plexus injuries (Faissler et al., 2002). In the present study, four animals with absent CPS had a fair to poor prognosis. Interestingly, the inability to evoke a MEP was also observed in these animals. Moreover, an absent MEP was also observed in 2 more animals with a poor outcome, although CPS was present. However, larger groups of patients are needed to confirm the prognostic utility of magnetic stimulation in sciatic nerve dysfunction.

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CHAPTER 5

CLINICAL APPLICATIONS OF PERIPHERAL MAGNETIC NERVE STIMULATION IN DOGS AND CATS

Part 3. Magnetic stimulation of peripheral nerves in 3 cats with polyneuropathy

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Adapted from Van Soens I., Struys M., Bhatti S., Van Ham L., 2009. Reference values and clinical application of magnetic peripheral nerve stimulation in cats. The Veterinary Journal in press

SUMMARY

Magnetic stimulation of the radial and the sciatic nerve was performed in 3 cats with clinical and electrophysiological signs of polyneuropathy (PNP). Onset latencies and peak-to-peak amplitudes of magnetic motor evoked potentials of these cats were compared to reference values of MMEP parameters of healthy cats.

Onset latencies and peak-to-peak amplitudes of the cats with PNP were different from the reference values.

Additional studies on more animals are necessary to define more clearly the correlation between clinical and electrophysiological findings.

INTRODUCTION

Magnetic stimulation of the nervous system is a non-invasive, painless and safe technique to evaluate the functional integrity of motor pathways (Barker et al., 1985; Barker et al., 1987; Barker 1991). The clinical diagnostic use of magnetic stimulation of peripheral nerves in veterinary medicine is rare. The technique has been reported in dogs and cats with brachial plexus avulsions (Van Soens et al., 2009a) and sciatic neuropathy (Van Soens et al., 2009b).
In this study magnetic stimulation of the radial and sciatic nerve was applied to 3 cats with neuropathic disease. The obtained values of MMEP were compared to previously reported reference values (Van Soens et al., 2009c).

MATERIALS AND METHODS

Cats

Three cats presented to the Small Animal Department of the Faculty of Veterinary Medicine of the University of Ghent with tetraparesis were included in this study. Inclusion criteria for cats in this study were: clinical signs of tetraparesis, absent spinal reflexes, spontaneous activity in all appendicular muscles on routine EMG examination and compound muscle action potentials with low amplitudes, evoked after electrical stimulation of the left sciatic nerve. In these cats, magnetic stimulation of the radial and sciatic nerve was performed proximally on the left side.

Magnetic stimulation of the sciatic nerve and recording of the MMEP

Magnetic stimulation of the radial and sciatic nerve was performed according to reported techniques in cats (Van Soens et al., 2009c; chapter 4) with a commercially available magnetic stimulator (Magstim Super Rapid, Acertys Healthcare). A circular 45 mm coil, capable of producing a peak magnetic field at the coil surface of 4.0 Tesla, was used. Stimulus intensity was 110% of the maximal output.

Onset latency and peak-to-peak amplitude were measured from the MMEP with the highest amplitude. Onset latency (in ms) was measured as the shortest distance between the trigger point and the take-off of the initial phase (negative or positive). Peak-to-peak amplitude (in mV) was measured between the two largest peaks of opposite polarity.

Statistical analysis

Ninety-five % confidence interval was calculated for onset latency and peak-to-peak amplitude of the MMEP in 40 cats in a previous report (Van Soens et al., 2009c). Data of the cats with polyneuropathy (PNP) were compared to the 95% confidence interval of the reference data.

Box plot graphs were designed to show the distribution of the normal MMEP parameters in the 40 healthy cats (Van Soens et al., 2009c). The values of the cats with PNP were plotted manually on these graphs. Points plotted outside the ends of the whiskers are outliers.
Statistical analyses were performed with Graph Pad Instat software (Graph Pad Software). Differences were considered significant at the 5% probability level ($P<0.05$).

RESULTS

Results of MMEP of the three cats with PNP are shown in table 1. In cat 2, no MMEP could be evoked in the pelvic limbs and in cat 3 no MMEP could be evoked in the thoracic and pelvic limbs. Onset latencies and peak-to-peak amplitudes of MMEP of these cats, except for 1 value of onset latency of the sciatic nerve, exceed the 95% confidence interval of the data of the normal subjects. In this case, however, the peak-to-peak amplitude is significantly low. Box plot graphs of the onset latencies and peak-to-peak amplitudes of the normal cats and of the cats with PNP are shown in figure 1. All data, except for onset latency of the pelvic limb of cat 1, lie outside the whiskers and can be seen as outliers.

Table 1. Onset latencies and peak-to-peak amplitudes of MMEP of three cats with polyneuropathy.

	Radial nerve left		Sciatic nerve left	
Cat	Onset latency proximal (in ms)	Peak-to-peak amplitude proximal (in mV)	Onset latency proximal (in ms)	Peak-to-peak amplitude proximal (in mV)
1	2.60*	2.00*	1.10	7.72*
2	2.30*	4.98*	No MMEP*	No MMEP*
3	No MMEP*	No MMEP*	No MMEP*	No MMEP*

* Data that exceed the 95% confidence interval of the reference values of MMEP (Van Soens et al., 2009c)

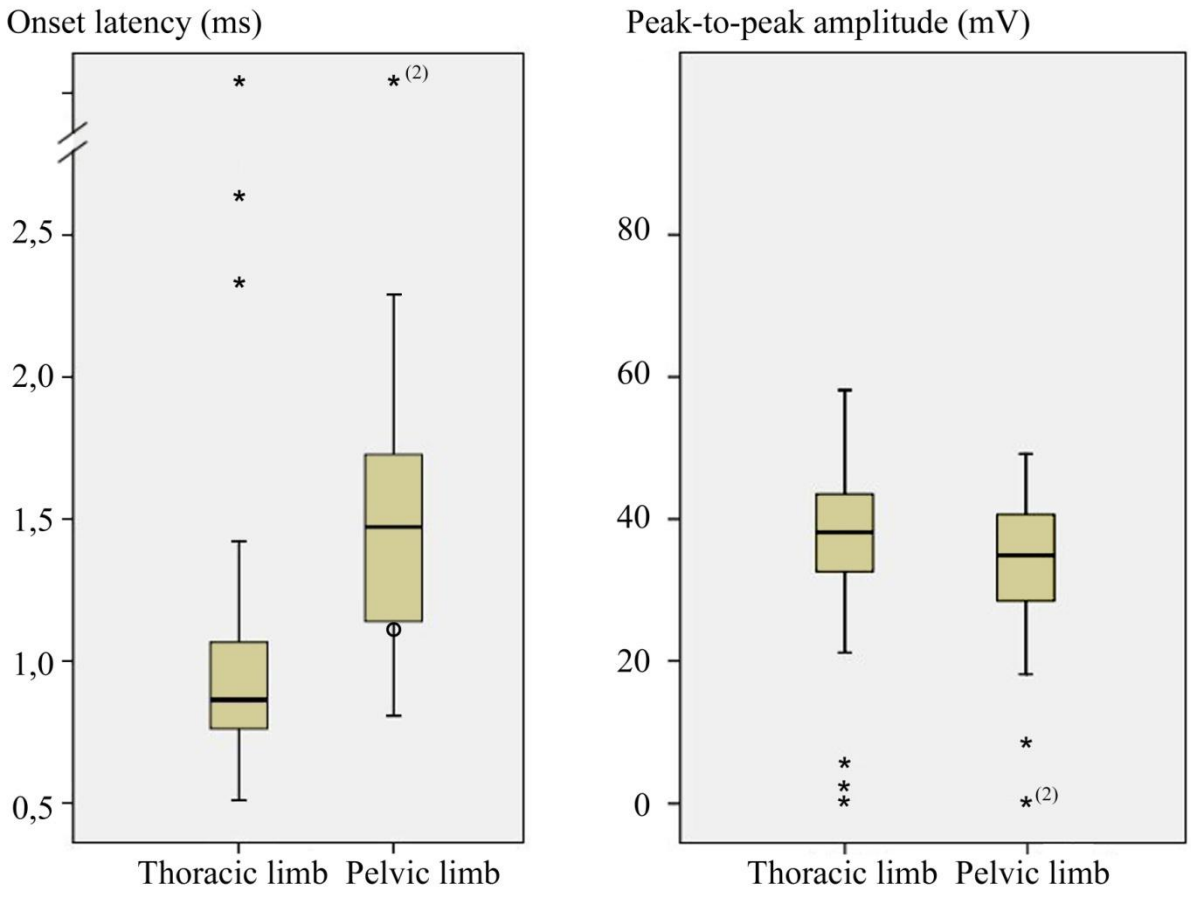

Figure 1. Box plots of proximal onset latencies (left figure) and peak-to-peak amplitudes (right figure) of the left radial and sciatic nerve of MMEP. Observations of cats with neuropathy are added to the box plots: outliers are indicated by an asterisk, other values by an open dot. (2) Point that includes observations of two cats.

DISCUSSION

Magnetic stimulation has several advantages over electrical stimulation: it is a non-invasive, almost painless and safe technique that requires less time for the investigator (Barker et al., 1987; Evans, 1991; Barker, 1999). In veterinary medicine, general anesthesia is required to perform electrical stimulation of peripheral nerves. By using magnetic stimulation, sedation of the animal will be sufficient to perform the examination.

In the present study, results of magnetic peripheral motor nerve stimulation in 3 cats with neuropathic disease were retrospectively compared to the distribution of data of normal cats in a box plot graph. All results except for one did not fall within the range of the reference values of the MMEP recorded in the normal cats. In 3 of the 6 recording sites, even no MMEP could be evoked. In accordance with a study in dogs and cats with brachial plexus avulsion, a missing MMEP or a MMEP with a delayed onset latency and reduced peak-to-peak amplitude can be suggestive for a pathologic condition (Van Soens et al., 2009a). Additional studies on more animals are necessary to define more clearly the correlation between clinical and electrophysiological findings.

A major limitation of this study is the low number of cats with PNP included. This makes it impossible to interpret the results statistically. In veterinary medicine, however, cats with PNP are presented infrequently. For that reason, we tried to visualize and interpret the results by box plot graphs. Furthermore, results of these cats were retrospectively analysed and these cats were only stimulated unilaterally and proximally on the course of the nerve. Stimulation of the contralateral side was not performed because these nerves are preserved for biopsy specimens. Consequently, use of the technique in more animals and in animals with other neuropathic conditions in the future is needed.

CONCLUSION

MMEP examination in cats seems to be a valuable diagnostic tool for objective monitoring of motor function of peripheral nerves. Additional studies in pathological conditions are necessary to provide evidence of a correlation between clinical findings and results of magnetic motor evoked potentials.

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TRANSCRANIAL MAGNETIC STIMULATION IN DOGS

Transcranial magnetic stimulation (TMS) provides a non-invasive and painless technique to objectively monitor the functional integrity of the descending motor tracts in the spinal cord, the ventral nerve roots and the peripheral nerve pathways to the muscle (Chiappa, 1994). The technique of TMS has been described previously in veterinary medicine, and although TMS is described as causing minimal discomfort, the clicking sound and the evoked muscle twitches can produce adverse reactions of the animal. Therefore, often sedation or anaesthesia is required to perform TMS in veterinary medicine. Monitoring motor pathways with transcranial magnetic motor evoked potentials (TMMEP) in the veterinary species, however, is particularly challenging, since sedative and anesthetic agents can suppress or even abolish the elicited potentials.

Therefore, in the second part of this thesis (**chapter 6)**, a workable tool to monitor TMMEP during sedation and anaesthesia in dogs was studied. Such a tool would make it possible to objectively interpret results of TMMEP during sedation and anesthesia in order that effects of sedative and anaesthetic drugs could be taken into account.

In **chapter 7** a clinical application of the technique of transcranial magnetic stimulation during sedation in dogs with and without clinically relevant cervical spinal cord compressions was studied.

CHAPTER 6

TRANSCRANIAL MAGNETIC STIMULATION IN DOGS

Effects of sedative and hypnotic drug combinations on transcranial magnetic motor evoked potential, bispectral index and ARX-derived auditory evoked potential index in dogs

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SUMMARY

Relationships between onset latency and peak-to-peak amplitude of magnetic motor evoked potentials (MMEP) after transcranial magnetic stimulation (TMS), together with the electroencephalographic parameters bispectral analysis index (BIS) and the autoregressive model with exogenous input (ARX)-derived auditory evoked potential index (AAI) were explored during different sedative and hypnotic drug combinations in six dogs.

TMS was performed under sedation with acepromazine/methadone or medetomidine and after a single bolus injection of propofol or etomidate. Data for BIS and AAI were continuously collected during the periods of treatment with the sedatives and with the hypnotic drugs.

Changes in BIS and AAI during both periods were not statistically correlated with changes in onset latencies and peak-to-peak amplitudes of MMEP after TMS.

Therefore, both electroencephalographic techniques are of limited use in titrating sedation and anaesthesia during TMS in the dog.

INTRODUCTION

Transcranial magnetic stimulation (TMS) can be used to evaluate the functional integrity of the motor pathways from motor cortex to muscles in dogs (Sylvestre et al., 1992; Glassman et al., 1993; Sylvestre et al., 1993; Van Ham et al., 1994; Young et al., 1994; Van Ham et al., 1995; Poma et al., 2002). The technical principle of stimulating the motor cortex by a brief and strong magnetic field and recording the potential responses in the periphery (i.e., in the muscle) was established by the work of Barker et al. (1985). Based on Faraday's law, a brief time-varying magnetic field will induce an electrical current in surrounding conductive tissues, which excites cortical neurones, inducing efferent volleys in fast conducting descending pathways along the corticospinal pathways (Amassian et al., 1987). These pathways synapse with the alpha motor neurones, which induce the muscles to contract (Amassian et al., 1987; Chiappa, 1994).

TMS can be used to provide information on the excitability of the motor cortex and on the integrity of the descending motor pathways, the ventral nerve roots and the peripheral nerve pathways to the muscle. Unlike medical imaging techniques, such as computed tomography (CT) and magnetic resonance imaging (MRI), which provide information on anatomical changes, TMS provides information on the functional integrity of the motor pathways (Chiappa, 1994). Therefore, TMS is used extensively in human medicine in diagnosing injury to the motor system, in providing prognostic information on injuries, in intraoperative neurophysiological monitoring during spinal surgery, in brain mapping studies and in treatment of psychiatric diseases (Chiappa, 1994; Hallett, 2000; Hallett, 2007; Rossini and Rossi, 2007). Application of TMS in veterinary clinical studies is described in dogs and horses with spinal cord disease (Sylvestre et al., 1993; Nollet et al., 2002; Poma et al., 2002; Nollet et al., 2003b; Nollet et al., 2005; da Costa, 2006).

In veterinary medicine, often sedation or anaesthesia is required to perform TMS. Although the technique is described as painless and well tolerated (Barker et al., 1985), animals often show adverse effects because of the discomfort induced by the evoked muscle contraction and the noise of stimulation. Therefore, monitoring motor pathways with magnetic motor evoked potentials (MMEP) in veterinary medicine is particularly challenging, since sedative and anaesthetic agents can easily abolish the potentials elicited (Ghaly, 1990; Sylvestre et al.,

1992; Glassman et al., 1993; Van Ham et al., 1994; Young et al., 1994; Van Ham et al., 1995, 1996a, 1996b).

Since 1939, anaesthetists have been aware of changes in the electroencephalogram (EEG) produced by anaesthetic agents (Rampil, 1998). Multiple EEG variables and spontaneous and evoked electroencephalographic derived parameters have been used to evaluate their relationship with the depth of anaesthesia. The EEG bispectrum is a high-order statistical computation derived from the EEG that measures relationships between the sinusoidal components (frequency, amplitude and phase angle) of the EEG (Rampil, 1998). The bispectral analysis index (BIS) was developed as a dimensionless number between 0 (isoelectric EEG) and 100 (awake) (Bard, 2001).

Peaks and troughs of the mid-latency component of the auditory evoked potential also show characteristic changes during anaesthesia; increasing concentrations of anaesthetic agents cause increased latencies and decreased amplitudes of the mid-latency auditory evoked potential (MLAEP) (Pypendop et al., 1999; Murrell et al., 2004, 2005). An objective automated method for analysis of MLAEP resulted in the ARX-derived auditory evoked potential index (AAI) (Jensen et al., 1996; Litvan et al., 2002; Struys et al., 2002; Vereecke et al., 2005). As for BIS, AAI is a dimensionless number scaled from 0 (isoelectric EEG) to 100 (awake). Both indices have the ability to measure differences in degree of central nervous system depression in dogs during sedative and hypnotic drug administration (Greene et al., 2002; Greene et al., 2003; Muir et al., 2003; Carrasco-Jimenez et al., 2004; Joubert, 2004).

The purpose of the present study was to study the effects of different sedative and hypnotic drugs on onset latency and peak-to-peak amplitude of the MMEP and on BIS and AAI in dogs and to assay the hypothesis that changes in BIS and AAI would be related to changes in onset latency and peak-to-peak amplitude of the MMEP during administration of sedative and hypnotic drugs.

MATERIALS AND METHODS

Dogs

After local ethical committee approval (approval number EC 2005/07), three male and three female purpose bred Beagle dogs weighing 11.51 ± 0.89 (mean ± SD) kg and 12.08 ± 2.70 (mean ± SD) months of age were entered in this study. Before each procedure, all dogs were subjected to a thorough clinical and routine neurological examination and appeared normal and were free of any obvious neurological deficits. Complete blood cell counts, serum biochemistry and brainstem auditory evoked potentials (BAEP) tests were normal in all six dogs. Food was withheld on the day of the study.

Procedure

Four sedative/anaesthetic protocols were tested in each dog in a random order, 4 x 6 cross over design, with at least a 1 week interval between the different protocols. The protocols were: 1) acepromazine (0.01 mg/kg) (Placivet, Codifar), methadone (0.1 mg/kg) (Mephenon, Denolin) (AM) and propofol (2 mg/kg) (Rapinovet, Schering-Plough); 2) AM and etomidate (1.5 mg/kg) (Hypnomidate, Janssen-Cilag); 3) medetomidine (4 µg/kg) (Domitor, Pfizer Animal Health) (Md) and propofol (2 mg/kg); and 4) Md and etomidate (1.5 mg/kg).

An intravenous (IV) catheter was placed in the cephalic vein of a forelimb. The sedative was injected at time 0 (T_s). As soon as the sedative state of the dogs permitted, they were placed in sternal recumbency. After appropriate skin preparation, the patch BIS and AAI needle electrodes were placed and measurement of BIS and AAI commenced. Twenty-five minutes after injection of the sedative, two single TMS recordings of the motor cortex and MMEP recordings from the extensor carpi radialis muscle of the right forelimb were performed. Thirty minutes after injection of the sedative, the hypnotic drug was injected IV (T_h). Two minutes after injection of the hypnotic drug, two single TMS and MMEP recordings were performed again. This procedure of two single TMS recordings and simultaneous recording of the MMEP was repeated every three minutes until the dog was too awake to continue (voluntary movements) (Figure 1). Each dog was monitored by a veterinarian throughout its recovery period.

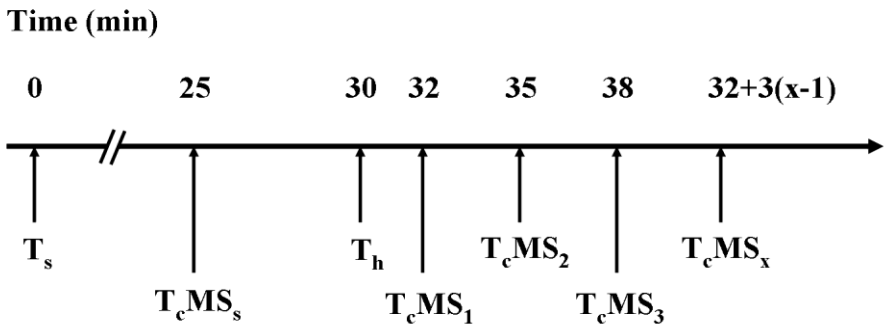

Figure 1. Time chart of procedure. T_s = Time of injection of the sedative drug (0 min); T_h = Time of injection of the hypnotic drug (30 min); TMS_s = Transcranial magnetic stimulation during the sedative drug period (25 min); $TMS_{1\ to\ x}$ = Transcranial magnetic stimulation during the hypnotic drug period (every 3 min, starting 2 min after injection of the anaesthetic).

Transcranial magnetic stimulation of the motor cortex

Magnetic stimulation was performed according to Van Ham et al. (1994, 1995). A commercially available magnetic stimulator (Magstim Super Rapid, Acertys Healthcare) with a circular coil, 4.5 cm in diameter, capable of producing a peak magnetic field of 4.0 Tesla at the coil surface was used. Maximal (i.e., 110%) stimulator output was used to ensure identifiable MMEP. The magnetic coil was placed tangentially to the skull, with the centre of the coil placed over the vertex. The coil was held in contact with the skin and the current flow within the coil ran in a clockwise direction (Van Ham et al., 1994).

Magnetic motor evoked potentials recording

Recordings were obtained by use of an electromyograph (Sapphire, Acertys Healthcare). The recording electrode (25 mm monopolar needle electrode, Acertys Healthcare) was placed in the extensor carpi radialis muscle of the right forelimb. The tip of the recording electrode was positioned percutaneously in the muscle belly of the extensor carpi radialis muscle, just in front of the lateral humeral epicondyle. The recording electrode was connected to the negative input of the preamplifier. The reference electrode was a subdermal needle electrode (Acertys Healthcare), positioned over the tendons of the extensor carpi radialis at the level of the carpal joint. The ground electrode (subdermal needle electrode, Acertys Healthcare) was placed over the olecranon of the forelimb. Sensitivity was set at 10 mV per division. Analysis time was 100 ms following the stimulus. The low and high frequency filters were set at 20 Hz and 10 kHz, respectively. The MMEP were recorded from the right forelimb while stimulating the

contralateral motor cortex. Two distinct waveforms were recorded for each time point during the sedative drug period and the hypnotic drug period.

Measurements of the MMEP onset latency and peak-to-peak amplitude were made manually using the cursors on the oscilloscope. Onset latency (ms) was measured as the shortest distance between the trigger point and the take-off of the initial phase (negative or positive); peak-to-peak amplitude (mV) was measured between the two largest peaks of opposite polarity.

Neuronal path length of each dog, determined by use of a tape measure from the vertex to the active electrode located in the extensor carpi radialis muscle of the right forelimb, was 46.8 ± 2.95 (mean ± SD) cm.

Measurement of bispectral analysis index

BIS was measured with an A-2000 BIS monitor (Aspect Medical Systems) (Figure 2). Data were continuously collected and stored on a computer using Rugloop II software (Demed). The BIS number was automatically calculated and displayed every 5 s and represented the EEG activity during the previous 60 s. The BIS was reported as a dimensionless whole number between 0 and 100. The proprietary patch electrode (BIS sensor 'Quatro', Aspect Medical Systems) was used as recommended by the manufacturer for use with humans. The hair on each dog's head was shaved to promote electrode contact. Conductive gels or degreasing solutions were not applied. The primary lead was placed on the midline approximately one third of the distance from a line connecting the zygomatic processes of the frontal bone and the most caudal part of the external frontal crest that was palpable (Figure 2). The one-piece design of the patch electrode automatically positioned the ground and secondary leads near the rostral bone of the right ear and over the temporal bone, respectively.

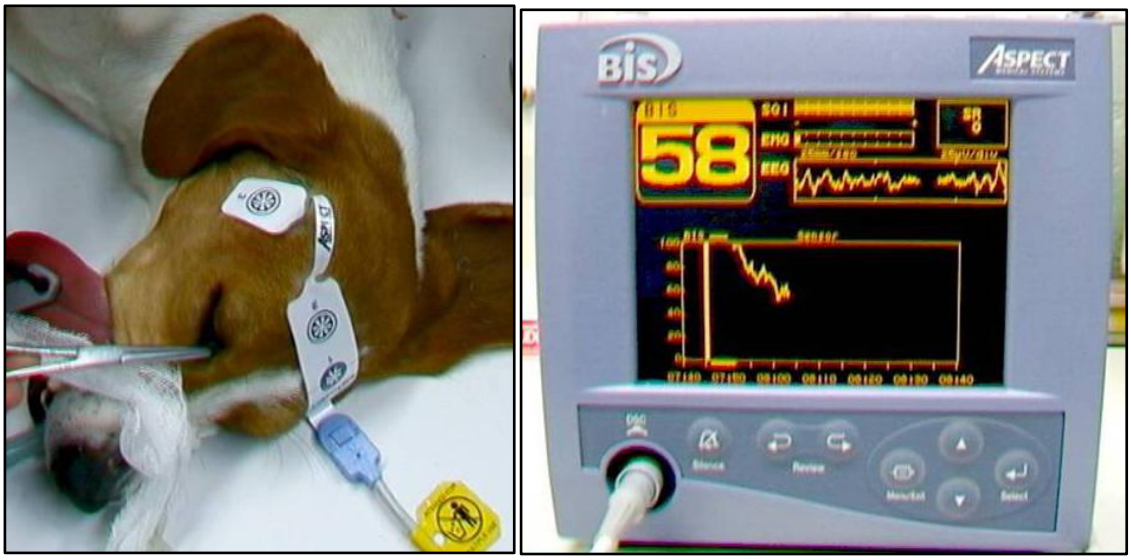

Figure 2. Placement of the BIS sensor 'Quatro' on a Beagle dog's head (left) and an A-2000 BIS monitor (right)

Measurement of the ARX-derived auditory evoked potential index

Measurement of the AAI from the mid-latency auditory evoked potentials was performed using the A-line monitor/2 (Danmeter A/S) (Figure 3). Data were continuously collected and stored on a computer using Rugloop II software. AAI was reported as a dimensionless whole number between 0 and 100. Subdermal needle electrodes (Acertys Healthcare) were inserted subcutaneously and attached to the original patient cable of the monitor (patient cable ALC001, Danmeter A/S). The black (negative) electrode was placed at the mastoid on the left side, the white (positive) electrode at the vertex and the green (reference) electrode at the auditive cortex (5 mm cranial to the interaural line and 5 mm to the right of the midline). Ear phones (monitor earphones ALH003, Danmeter A/S) were placed in both ears of the dogs. The volume for the acoustic stimuli was set in the "Auto" mode; the automatic volume control system automatically adjusts the click volume (45-75 dB) in order to elicit an MLAEP with comparable quality under different situations (noise, stress).

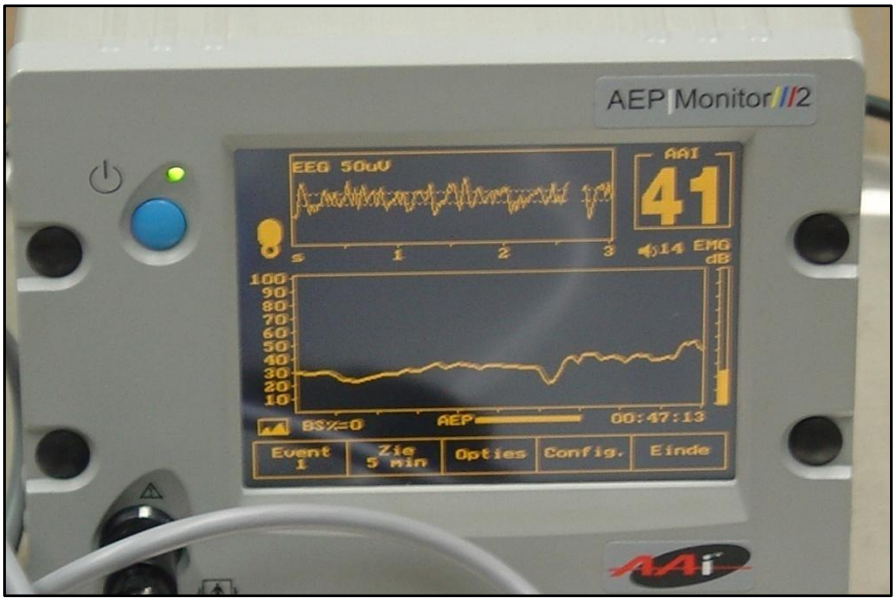

Figure 3. An A-line monitor/2.

Statistical analysis

It was considered that a BIS change of 20 units (SD = 10) caused by a drug effect (Struys et al., 2002; Vereecke et al., 2005) would be significant in terms of revealing a cerebral drug effect. Six dogs were used in the study in order to identify significant differences with a Type I error of 5% and a Type II error of 10%. The significance level was set at 0.05.

Continuous data were analysed for normality using a one sample Kolmogorov test. The significance between the first and second measurement of BIS, AAI and latency and amplitude of the MMEP was tested using a paired *t*-test. The relation between BIS and AAI behaviour was tested by linear regression analysis. As a baseline, the mean and standard deviation of BIS, AAI and onset latency and peak-to-peak amplitude of the MMEP of all dogs was calculated for the two sedative protocols. A *t*-test for equality of means was performed to evaluate significant differences between these variables.

During the sedative and hypnotic drug period, the consecutive data points of BIS, AAI, onset latency and peak-to-peak amplitude of the MMEP were compared with the baseline values measured during the sedative drug period. Within group data (versus time) were analysed using ANOVA statistics with post-hoc test if required. A Spearman Rank correlation was calculated between BIS or AAI versus onset latency or peak-to-peak amplitude.

RESULTS

Data for all variables (BIS, AAI, onset latency and peak-to-peak amplitude) were normally distributed. No significant changes were found between the first and second value of each variable in the same time period; mean values for the different variables were used. BIS and AAI were significantly ($P<0.05$) related to each other during the entire study period, with a goodness of fit of 0.57 for protocol 1, 0.61 for protocol 2, 0.64 for protocol 3 and 0.65 for protocol 4.

Sedative drug period

The effects of the two sedatives on the MMEP were equal. No significant statistical differences were found between onset latency and peak-to-peak amplitude for the two sedatives (Table 1). The sedative effect in each group, as measured by BIS and AAI at the moment of TMS_s is summarised in Table 2. A significant difference was seen in BIS during AM and Md. AAI showed no significant difference during AM and Md.

Table 1. Onset latency and peak-to-peak amplitude (mean ± SD) during AM and Md sedation

Variable	AM	Md	*P*
Onset latency (ms)	10.38 ± 1.01	10.85 ± 1.45	0.38
Peak-to-peak amplitude (mV)	6.84 ± 4.04	6.29 ± 3.68	0.74

Significance level $P<0.05$

Table 2. BIS and AAI (Mean ± SD) during AM and Md sedation

Variable	AM	Md	*P*
BIS	91.65 ± 8.29	73.64 ± 21.64	0.02
AAI	72.05 ± 23.94	55.71 ± 27.59	0.15

Significance level $P<0.05$

Sedative and hypnotic drug period

The behaviour of onset latency and peak-to-peak amplitude of MMEP is shown in Figure 4. Time-dependent significant differences were found for the effects of the four anaesthetic regimens on the MMEP; administration of propofol and etomidate increased onset latencies and decreased peak-to-peak amplitudes of the MMEP or completely suppressed the MMEP. Significant differences in onset latency and peak-to-peak amplitude of the MMEP with the baseline values were observed until 2 min after injection of the hypnotic drug in protocols 1 and 2. In protocol 3, all data were significantly different from baseline values. In protocol 4, the differences were significant up to 8 min after injection of etomidate.

Figure 5 shows the behaviour of BIS and AAI after injection of the anaesthetic. For both BIS and AAI, a significant decrease of the index is observed after administration of the hypnotic drug in protocols 2 ($P = 0.0003$) and 4 ($P<0.0001$) in comparison with baseline values. In protocols 1 and 3, the decrease in BIS and AAI was not significant ($P<0.05$) in comparison with baseline values.

The significant differences in the onset latency and peak-to-peak amplitude of the MMEP between baseline values and values after administration of the hypnotic drug were not correlated with significant changes in BIS or AAI.

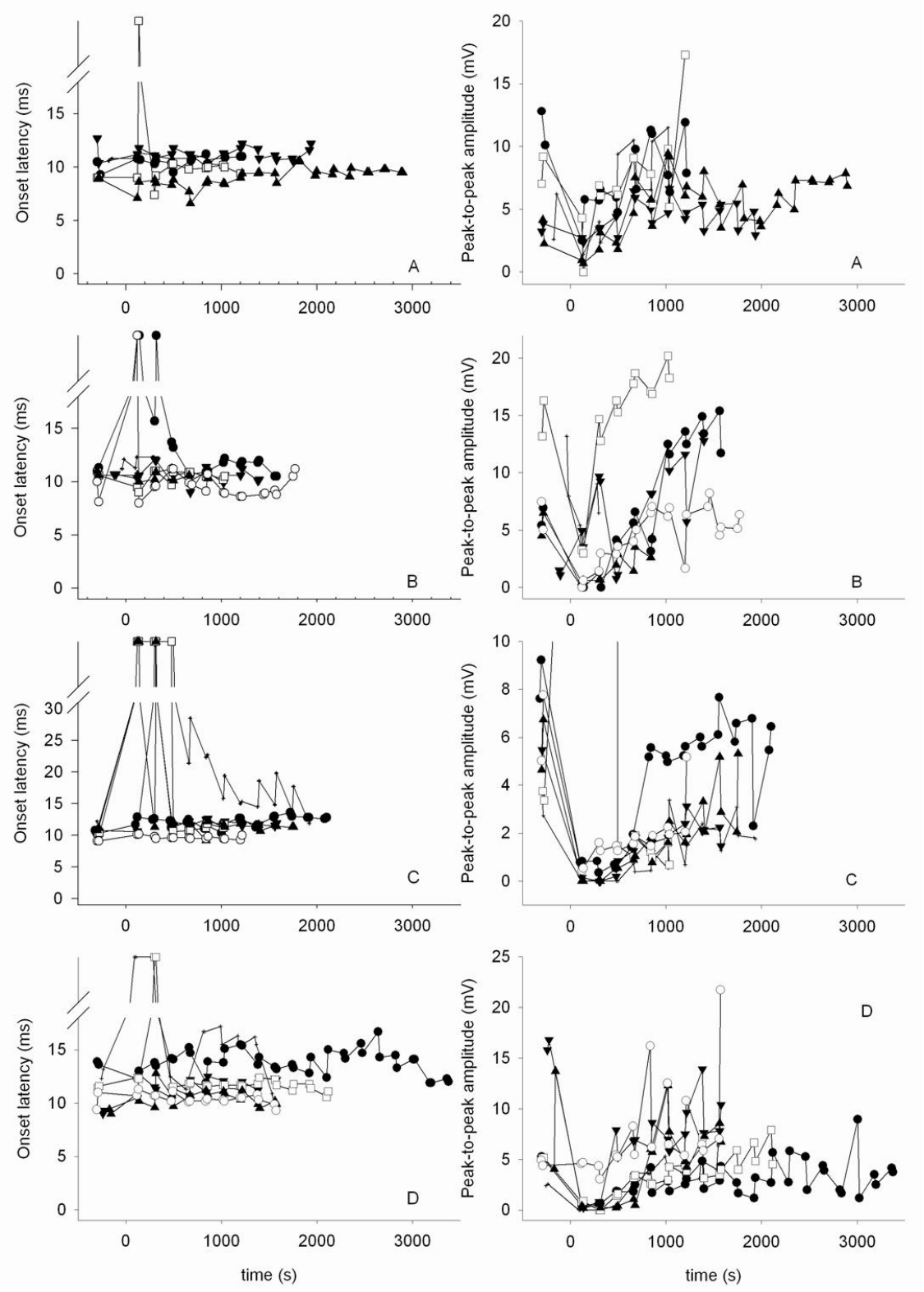

Figure 4. Raw data of the behaviour of onset latency and peak-to-peak amplitude versus time during the sedative drug and the hypnotic drug period of each dog per protocol. Six dogs were in this study. At time 0 s, a bolus of the hypnotic drug was administered. Latency = Onset latency; Amplitude = Peak-to-peak amplitude. A) Protocol 1 (acepromazine-methadone and propofol); B) Protocol 2 (acepromazine-methadone and etomidate); C) Protocol 3 (medetomidine and propofol); D) Protocol 4 (medetomidine and etomidate).

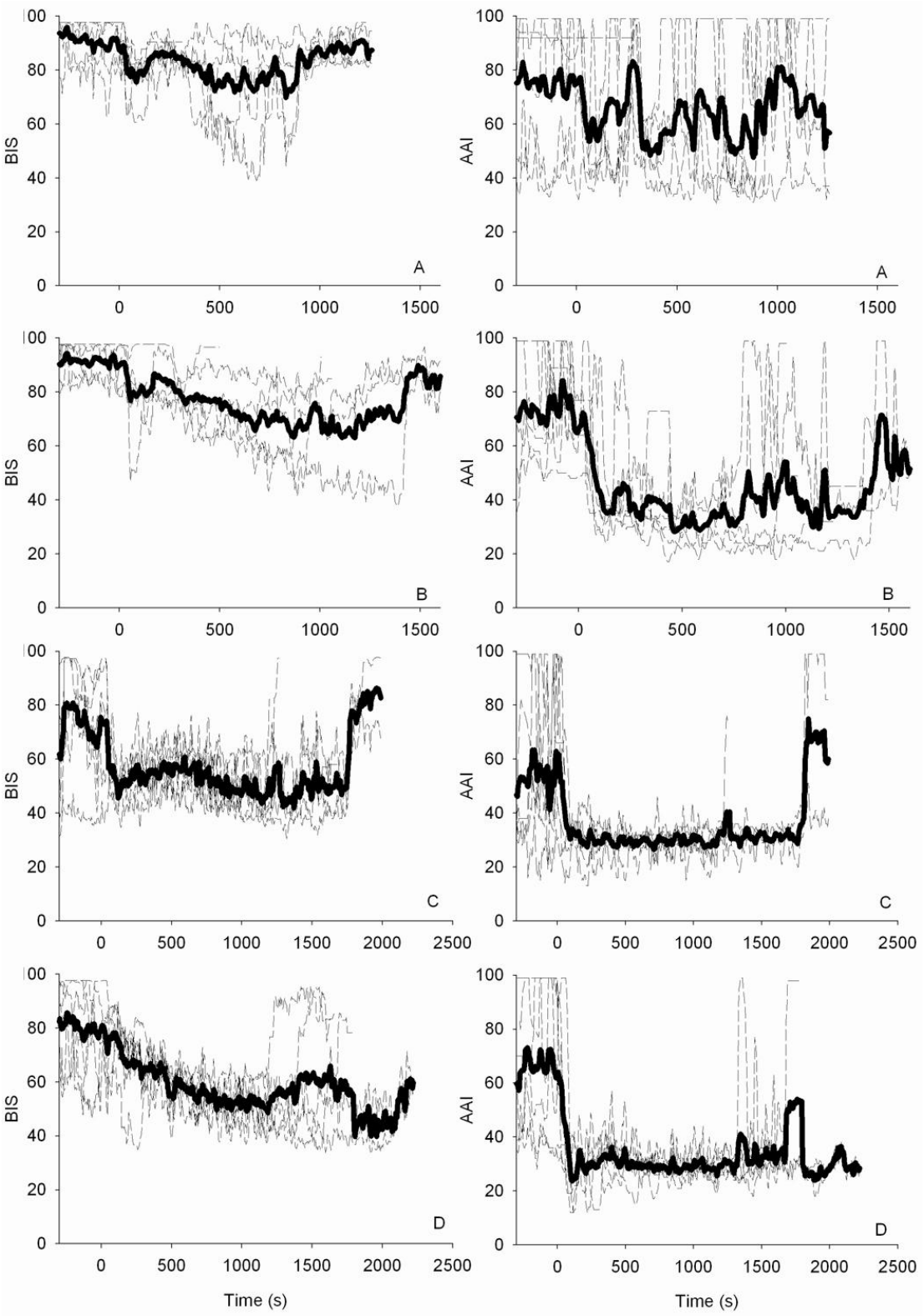

Figure 5. Bispectral analysis index (BIS) and ARX-derived auditory evoked potential index (AAI) versus time, per protocol. The black line represents the mean BIS or AAI of all six dogs per protocol. The grey lines represent the raw data of the six individual profiles of BIS and AAI versus time per protocol. At time 0 s, a bolus of the hypnotic drug was administered. A) Protocol 1 (acepromazine-methadone and propofol); B) Protocol 2 (acepromazine-methadone and etomidate); C) Protocol 3 (medetomidine and propofol); D) Protocol 4 (medetomidine and etomidate).

DISCUSSION

In this study, relationships between onset latency and peak-to-peak amplitude of the MMEP after TMS and the electroencephalographic parameters BIS and AAI were explored during sedative and hypnotic drug combinations.

In humans, TMS during diagnostic procedures is assumed to be an almost painless technique that only produces a mild discomfort induced by the evoked muscle contraction (Barker et al., 1987) and therefore the technique can be performed in conscious, awake and relaxed people. In dogs, drug induced immobility is needed to perform the stimulation to avoid adverse reactions of fear or excitation that will produce undesirable muscle contractions. A balance between immobility and maintenance of MMEP conditions and unwanted side effects, such as bradycardia, hypnotic hang-over effects, respiratory depression or hypotension, should guide the titration of sedative and anaesthetic drugs (Muir and Mason, 1989; Cullen, 1996; Mutoh et al., 2002; Sinclair, 2003; Sano et al., 2003a).

The present study demonstrates that TMS in dogs can be performed during sedation with AM or Md. AM and Md were chosen because of their routine use in clinical practice and their beneficial properties in MMEP recording (Sylvestre et al., 1992; Van Ham et al., 1994, Poma et al., 2002; da Costa et al., 2006). Ideally, the effect of the sedatives on the MMEP should have been investigated. However, the method for recording MMEP in non-sedated dogs is only possible in relaxed and trained animals. In addition, the aim of the study was to explore a relationship between drug-induced cerebral depression and the effects of sedatives and hypnotics on MMEP. As such, the data obtained during sedation with AM or Md for onset latency and peak-to-peak amplitude of the MMEP and for BIS and AAI were used as baseline values.

Previous studies of the effects of sedatives on MMEP have produced conflicting results. Some authors suggest that sedatives have no significant influence on MMEP (Sylvestre et al., 1992; Poma et al., 2002; da Costa et al., 2006). In contrast, Van Ham et al. (1994) found a significant difference in onset latency and peak-to-peak amplitude between TMS during AM and medetomidine-methadone. These differences could be explained by the higher doses of Md used in the study and because Md was combined with methadone (Van Ham et al., 1994). We hypothesise that MMEP are influenced by the physiological properties and the dose of the

applied sedative. Further studies on the effect of increasing doses of sedatives should be undertaken.

On the basis of BIS, a more profound cerebral depression with Md was found, without significantly suppressing the evoked potentials. This result agrees with previous studies, in which Md produces a more profound degree of sedation, with greater drowsiness, in comparison with acepromazine (Nishimura et al., 1993; Kojima et al., 1999; Sano et al., 2003a). Mean AAI values showed no significant differences between the two sedatives. The high variability of AAI, which makes interpretation more difficult, might explain the different findings.

Previous studies report a significant dose-dependent suppressive effect of different anaesthetics/hypnotics on MMEP. At surgical planes of anaesthesia, no potentials could be recorded with propofol, thiopental, diazepam and ketamine, sufentanil and midazolam and halothane (Van Ham et al., 1995, 1996a, 1996b). Other authors reported consistent responses after TMS with ketamine, etomidate and methohexital anaesthesia (Glassman et al., 1993; Young et al., 1994). In this study, propofol was selected due to its beneficial short acting pharmacological profile (Sano et al., 2003b). Etomidate was also included in the study, since previous reports demonstrated a minimal effect of this drug on MMEP (Ghaly et al., 1990; Glassman et al., 1993).

After injection of the hypnotic drug, a significant change in the MMEP was seen in all protocols compared with MMEP at baseline. However, a significant faster return to the baseline levels of MMEP was observed when using AM, in combination with etomidate or propofol. In addition, the combination of Md and propofol suppressed the MMEP for a longer period than the combination of Md and etomidate. As such, a time- and product-dependent effect of the hypnotics on onset latency and peak-to-peak amplitude of the MMEP was demonstrated. Surprisingly, significant cerebral depression, as determined by BIS and AAI, was only present after etomidate administration. For the Md and propofol group, this might be explained by the low baseline values or the higher degree of inter-individual variability (Figure 5).

The hypothesised relationship between the electroencephalographic parameters BIS and AAI and the effects of sedatives and hypnotics on MMEP could not be established. No significant

statistical correlation was found between BIS or AAI and onset latency and peak-to-peak amplitude of the MMEP. This might be explained by the differences between the neurophysiological pathways of MMEP after TMS and the limited cerebral measures performed by BIS and AAI. As such, BIS and AAI are of limited use for predicting values of onset latencies and peak-to-peak amplitudes of MMEP after TMS in dogs.

CONCLUSION

Since no correlation was found between BIS or AAI and onset latency and peak-to-peak amplitude, these electroencephalographic techniques are of limited use in titrating sedation and anaesthesia during TMS. However, different drugs have dose-, time- and product-dependent effects on MMEP and therefore MMEP after TMS in sedated or anaesthetised dogs should be interpreted carefully.

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CHAPTER 7

CLINICAL APPLICATION OF TRANSCRANIAL MAGNETIC STIMULATION IN DOGS

Transcranial magnetic stimulation in Doberman Pinschers with and without clinically relevant spinal cord compression

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Adapted from De Decker S., Van Soens I., Duchateau L., Gielen I., van Bree H., Binst D., Waelbers T., Van Ham L. Transcranial magnetic stimulation in Doberman Pinschers with and without clinically relevant spinal cord compression due to disk associated wobbler syndrome. Journal of the American Veterinary Medical Association in press

SUMMARY

This study evaluates the use of transcranial magnetic stimulation (TMS) for differentiation between clinical relevant and irrelevant spinal cord compressions in Doberman Pinschers.
After sedation with acepromazine and morphine, transcranial magnetic motor evoked potentials (TMMEP) were recorded from the extensor carpi radialis (ECRM) and cranial tibial (CTM) muscles in clinically normal Doberman Pinschers with and without spinal cord compression and in 16 Doberman Pinschers with disk associated wobbler syndrome (DAWS). Onset latencies and peak-to-peak-amplitudes were measured. Magnetic resonance imaging (MRI) was performed to evaluate the presence and severity of spinal cord compression.

There was a significant difference in ECRM and CTM onset latencies between the 3 different groups overall and between the clinically affected Doberman Pinschers and the 2 groups of clinically normal dogs separately. There was no significant difference in ECRM and CTM onset latencies between the 2 groups of clinically normal dogs. There was a significant difference in CTM peak-to-peak amplitudes between the 3 different groups overall and between the clinically affected Doberman Pinschers and the 2 groups of clinically normal dogs separately. There was no significant difference in ECRM peak-to-peak amplitudes for all the different combinations and for CTM amplitudes between the 2 groups of clinically normal dogs. There was a significant correlation between severity of spinal cord compression and ECRM onset latencies, CTM onset latencies, and CTM peak-to-peak amplitudes.

TMS can be used as a diagnostic tool to differentiate between clinical relevant and irrelevant spinal cord compressions

INTRODUCTION

In disk associated wobbler syndrome (DAWS), caudal cervical spinal cord compression is typically caused by protrusion of the intervertebral disks between the sixth and seventh cervical vertebrae (C6-C7) and/or between the fifth and sixth cervical vertebrae (C5-C6), sometimes in combination with dorsal compression resulting from hypertrophy of the ligamentum flavum and generally mild vertebral malformations. This wobbler syndrome occurs in several adult to older large breed dogs and the Doberman Pinscher is overrepresented.

The disorder can be diagnosed by a variety of imaging modalities, such as myelography, computed tomography-myelography, and magnetic resonance imaging (MRI) (Wheeler and Sharp, 2005). MRI allows direct, non-invasive, multiplanar imaging and an excellent soft tissue characterization with an absence of ionizing radiation (Thomson et al., 1993; Lipsitz et al., 2001). A disadvantage of MRI in the evaluation of the spine is the possibility of over-interpretation. Several human and veterinary studies have demonstrated the occurrence of cervical spinal cord compressions in clinically normal subjects (Teresi et al., 1987; Boden et al., 1990; Lehto et al., 1994; Matsumato et al., 1998; da Costa et al., 2006a; De Decker et al., 2009a).

Transcranial magnetic stimulation (TMS) is a non-invasive, painless and sensitive technique for stimulating the cerebral cortex in order to evaluate the functional integrity of the fastest conducting descending motor pathways in the brain and spinal cord (Barker et al., 1985).
The purpose of the present study was to investigate the clinical usefulness of transcranial magnetic motor evoked potentials (TMMEP) in Doberman Pinschers with and without clinical signs of DAWS. It was hypothesized that TMMEP could be used to differentiate between clinically relevant and irrelevant spinal cord compressions seen on MRI. Further, it was evaluated if we could confirm the occurrence of a correlation between the TMMEP findings and an earlier established MRI compression scale (da Costa et al., 2006b; Lo et al., 2004).

MATERIALS AND METHODS

Animals

Thirty-three client-owned Doberman Pinschers were prospectively studied. The experiment was conducted in accordance with the guidelines of the Animal Care Committee of the University of Ghent. Written owner consent was obtained prior to study enrollment. Three groups of dogs were studied. The first group (group 1) consisted of 11 clinically normal Doberman Pinschers without spinal cord compression seen on MRI. This group consisted of 6 males and 5 females, between 1.5 and 8 years old (mean 4.3 years, median 4.5 years). The second group (group 2) consisted of 6 clinically normal Doberman Pinschers with spinal cord compression seen on MRI. This group consisted of 3 males and 3 females, between 1.6 and 7.1 years old (mean 4.0 years, median 3.9 years). The third group (group 3) consisted of 16 Doberman Pinschers with spinal cord compression seen on MRI and who had well defined clinical signs that were associated with the MRI findings. This group consisted of 6 males and 10 females, between 4.6 and 10 years old (mean 8.6 years, median 8.7 years). These dogs demonstrated clinical signs varying from cervical hyperesthesia (n = 2) to ambulatory paraparesis/ataxia with or without cervical hyperesthesia (n = 5), ambulatory tetraparesis/ataxia with or without cervical hyperesthesia (n = 7), and non-ambulatory tetraparesis with or without cervical hyperesthesia (n = 2).

Transcranial magnetic stimulation

Magnetic stimulation was performed using a commercially available magnetic stimulator (Magstim Super Rapid, Acertys Healthcare) using a circular coil 45 mm in external diameter, which generated a peak magnetic field of approximately 4 Tesla. Maximal (i.e., 110%) stimulator output was used to ensure identifiable TMMEP. The magnetic coil was placed tangentially to the skull and in contact with the skin, with the centre of the coil placed over the vertex (Van Ham et al., 1994). To activate each hemisphere preferentially, a clockwise inducing current flow was used to stimulate the right motor cortex and an anticlockwise flow to stimulate the left motor cortex (Nollet et al., 2003a). Although the stimulation is painless, the mild discomfort induced by the evoked muscle contraction and the noise of stimulation can agitate some dogs. Therefore, the dogs were sedated with acepromazine (0.03 mg/kg, IV) and morphine (0.2 mg/kg, IV).

Recording of TMMEP

Recordings were obtained by use of an electromyograph (Sapphire, Acertys Healthcare). Magnetic motor evoked responses were recorded bilaterally from monopolar needle electrodes (monopolar needle electrode, Acertys Healthcare) in the extensor carpi radialis muscle (ECRM) of the thoracic limb and the cranial tibial muscle (CTM) of the pelvic limb. The tip of the recording electrode was positioned percutaneously in the muscle belly, just in front of the lateral humeral epicondyle for the ECRM and slightly lateral to the distal end of the tibial crest for the CTM. The reference electrode was a subdermal needle electrode (subdermal needle electrode, Acertys Healthcare), positioned over the tendons at the level of the carpal and the tarsal joint for the ECRM and the CTM, respectively. The ground electrode (subdermal needle electrode, Acertys Healthcare) was placed over the olecranon of the thoracic limb or over the patella of the pelvic limb. Sensitivity was set at 10 mV per division. Analysis time was 100 ms following the stimulus. The low and high frequency filters were set at 20 Hz and 10 kHz, respectively.

Measurements of the MMEP onset latency and peak-to-peak amplitude were made manually using the cursors on the oscilloscope. Onset latency (ms) was measured as the shortest distance between the trigger point and the take-off of the initial phase (negative or positive); peak-to-peak amplitude (mV) was measured between the two largest peaks of opposite polarity. Individual stimulations were delivered until 2 reproducible TMMEP were recorded. Motor evoked potential responses were considered absent if 4 consecutive stimulations at 110% stimulator output consistently failed to elicit a reproducible TMMEP. In dogs with absent TMMEP, onset latency was regarded as infinite and absent peak-to-peak amplitude was entered as 0 mV. The neuronal path length of each dog was measured with a tape measure from the vertex to the active electrode located within the contralateral ECRM or CTM.

MR imaging

A permanent, 0.2 T magnet (Airis Mate, Hitachi) was used to perform MRI in all dogs. Dogs were positioned in dorsal recumbency with head and neck extended. The thoracic limbs were fixed parallel to the thoracic wall. The cervical spine was positioned in a joint coil (circular transmit-receive coil) with an inner diameter 19 cm. T1- and T2-, spin echo-weighted studies were performed in all dogs in a sagittal, dorsal and transverse plane. The images of this last plane were aligned perpendicular to the cervical spine. The spine was imaged from the second

cervical vertebra (C2) to the seventh cervical vertebra (C7) in the sagittal and dorsal plane and from C4 to C7 in the transverse plane. In all spines, the field of view was 29 cm in the sagittal images, 24 cm in the dorsal plane and 20 cm in the transverse plane.

T1 weighted sagittal images were obtained with a repetition time (TR) of 700 milliseconds (ms) and an echo time (TE) of 25 ms. The T2 weighted sagittal studies were made using a TR of 2700 ms and a TE of 125 ms. Dorsal images were performed in T1 weighted sequence with TR = 600ms and TE = 25 ms and in T2 weighted sequence the settings were TR = 3900 and TE = 120 ms. Transverse T1 weighted images were performed with TR=1100 ms and TE = 25 ms, and in the T2 weighted transverse images the settings were TR = 5000 ms and TE = 120 ms. Slice thickness was 4mm in the sagittal and dorsal images and was 3 mm in the transverse sequences with no interslice gap in all studies.

Occurrence and severity of spinal cord compression was assessed at the most affected level of the spinal cord. Spinal cord compression was defined as complete subarachnoid space compression with deviation or distortion of the spinal cord. It was classified according to the degree of spinal cord deformation, displacement, and intraspinal signal intensity (ISI) changes into 4 grades (Lo et al., 2004): grade 0, no evidence of cord compression; grade 1, mild indentation of the spinal cord with a dorsoventral cord diameter that is not less than two thirds of the expected cord diameter; grade 2, notable spinal cord indentation with a dorsoventral cord diameter that is less than two thirds of the expected cord diameter, but not associated with ISI changes within the cord; grade 3, notable spinal cord indentation associated with ISI changes. Evaluation of ISI changes were based on the relative increase in signal on T2-weighted images and/or decrease in signal on T1-weighted images when compared with the surrounding spinal cord parenchyma.

Statistical analysis

Evaluation between the left and right recorded onset latencies and peak-to-peak amplitudes was based on the signed rank test.

The statistical analysis for the overall comparison of the 3 clinical groups was based on the Kruskall-Wallis test. Significance was claimed when $P < 0.05$. Pair wise comparisons were based on the two-sided Wilcoxon rank sum test using Bonferroni's procedure for multiple comparisons. Significance for pair wise comparisons was claimed when $P < 0.05/3$. Kendall

correlation coefficients were calculated between the spinal compression score and onset latency and peak-to-peak amplitude of the TMMEP. Significance was claimed when $P < 0.05$.

RESULTS

The waveform of the TMMEP recorded from the ECRM and TCM were mainly biphasic or triphasic in the clinically normal dogs (group 1 and 2) and mainly polyphasic in the clinically affected dogs. In none of the groups of dogs, significant differences between right and left onset latencies and peak-to-peak amplitudes for the thoracic and pelvic limbs were recorded.
In 11 of the 16 affected Doberman Pinschers, no TMMEP could be recorded in both pelvic limbs. In 3 of them, TMMEP could be recorded in 1 pelvic limb and in the 2 remaining dogs, TMMEP were recorded in both pelvic limbs.

There was a significant difference in both ECRM and CTM onset latencies for the overall comparison of the 3 clinical groups ($P = 0.00063$ and $P = <0.0001$, respectively). There was no significant difference in ECRM or CTM onset latencies between the 2 clinically normal groups of dogs ($P = 0.80$ and $P = 0.40$, respectively). There was a significant difference in both ECRM and CTM onset latencies between the clinically affected Doberman Pinschers and the 2 groups of clinically normal dogs, separately ($P = 0.0029$ and $P = 0.0090$ for the ECRM onset latencies, respectively; $P = 0.00016$ and $P = 0.0012$ for the CTM onset latencies, respectively). There was no significant difference for ECRM peak-to-peak amplitudes for both the overall comparison of the 3 clinical groups ($P = 0.22$) and between any of the 3 groups separately (group 1 and 2: $P = 0.66$; group 1 and 3: $P = 0.1$; group 2 and 3: $P = 0.37$). There was a significant difference in CTM peak-to-peak amplitudes for the overall comparison of the 3 clinical groups ($P = 0.00003$). There was no significant difference in CTM peak-to-peak amplitudes between the 2 clinically normal groups of dogs ($P = 0.96$). There was a significant difference in CTM peak-to-peak amplitudes between the clinically affected Doberman Pinschers and the 2 groups of clinically normal dogs, separately ($P = 0.00027$ and $P = 0.0037$, respectively).

A grade 0 spinal cord compression was seen in 11 clinically normal Doberman Pinschers (group 1), grade 1 spinal cord compression was seen in 5 clinically normal (group 2) and 5 clinically affected Doberman Pinschers (group 3), grade 2 spinal cord compression was seen in 1 clinically normal (group 2) and 2 clinically affected Doberman Pinschers (group 3), grade

3 spinal cord compression was seen in 9 clinically affected Doberman Pinschers (group 3). There was a significant correlation between grade of spinal cord compression seen on MRI and onset latency for both ECRM and CTM and peak-to-peak amplitude for CTM (ECRM onset latency: $P = 0.0021$, r = 0.42; CTM onset latency: $P = 0.0033$, r = 0.41; CTM peak-to-peak amplitude: $P = 0.0033$, r = -0.41, respectively).

DISCUSSION

It has been reported that the use of TMS in Doberman Pinschers with cervical spondylomyelopathy and dogs with other spinal cord disorders can be used as a valuable diagnostic tool (Sylvestre et al., 1993; Poma et al., 2002; da Costa et al., 2006b). However, data on TMMEP findings in dogs with clinically irrelevant spinal cord compression are lacking. The primary goal of this study was to investigate the usefulness of TMS to differentiate between clinically relevant and irrelevant cervical spinal cord compressions seen on MRI.

Magnetic resonance images of the cervical spine show anatomic detail and degenerative changes unlike any other imaging modality, but does not reveal their clinical significance. Recent veterinary studies have shown that degenerative disease of the cervical spine may be unrelated to patient symptoms (da Costa et al., 2006a; De Decker et al., 2009). The results of our study demonstrated an obvious difference between clinically affected and clinically normal Doberman Pinschers; TMMEP parameters of clinically normal dogs with spinal cord compression seen on MRI were similar to those of the Doberman Pinschers without spinal cord compression and were significant different from clinically affected dogs. This is in agreement with a human study that demonstrated no significant different TMMEP between people with asymptomatic cervical spinal cord compression and a clinically normal control group (Tavy et al., 1999).

In particular CTM onset latencies were useful to differentiate between clinically relevant and irrelevant spinal cord compressions seen on MRI. Peak-to-peak amplitude was less valuable in comparison to onset latency to differentiate between the different groups of dogs. Peak-to-peak amplitude is influenced by the number of fibers recruited by the stimulus, the characteristics of the target muscle, and alterations in the position of the magnetic stimulating coil over the surface of the cranium and is associated with a high degree of inter-trial as well

as intra-individual variability (Levy et al., 1987; Amassian et al., 1989; Chu, 1989; Strain et al., 1990; Sylvestre, 1993; Nollet et al., 2003b). This variability appears to be spontaneous and might, in part, be explained by differences in state of relaxation of the muscles (Dimitrijevic et al., 1992). Therefore, peak-to-peak amplitude can be assumed of limited clinical value, as reported earlier in human and veterinary studies (Brunholzl and Claus, 1994; Nollet et al., 2003b, 2005).

The fact that TMMEP abnormalities were more pronounced in the pelvic limbs in contrast to the findings in the thoracic limbs is in agreement with veterinary and human studies evaluating the use of TMS in cervical spinal cord disease (Poma et al., 2002; Lo et al., 2004; da Costa et al., 2006b). TMMEP abnormalities provide direct evidence of corticospinal tract dysfunction (Barker et al., 1985; Nollet et al., 2003b) and pathological studies have shown that the corticospinal tracts are affected early in human cervical spondylotic myelopathy. Moreover, the lateral corticospinal tracts are affected first in minor compressions (Ogino, 1983) and corticospinal fibers to the pelvic limbs are located more laterally in the somatotopic arrangement of the cervical spinal cord (de Lahunta and Glass, 2009). All these factors explain that TMMEP abnormalities in progressive cervical spinal cord compression are more pronounced in the pelvic limbs.

In several dogs, no TMMEP could be elicited from the pelvic limbs. Sylvestre and co-workers (1993) evaluated TMS for assessing spinal cord integrity in dogs with thoracolumbar intervertebral disk disease. Recordable TMMEP were found only in dogs with mild or no neurologic deficits and in 50% of ambulatory dogs that were severely ataxic. It was impossible to elicit TMMEP from non-ambulatory dogs. Nollet and co-workers (2002) could not elicit TMMEP in some severely ataxic horses with cervical spinal cord disease. The exact reason for this phenomenon is unknown. A possible explanation could be found in animal studies where TMMEP were recorded simultaneously from the epidural space and the peripheral nerves. In these studies, the recorded TMMEP were abnormal or absent at the peripheral nerve level before changes were noticed in the epidural space (Konrad et al., 1987; Owen et al., 1989, Kraus et al., 1990). The propagating impulse, although present in the spinal cord distal to the lesion, may not be strong enough to increase the postsynaptic membrane potential of the motor neuron to its threshold. Therefore, the impulse will not be present in the peripheral nerve.

There was a significant correlation between the MRI compression scale and the onset latencies for ECRM and CTM and the peak-to-peak amplitudes for CTM. This can be explained by the fact that a grade 3 spinal cord compression was only seen in clinically affected dogs. This finding suggests that clinically affected dogs generally have a more pronounced spinal cord compression when compared with clinically normal dogs and that the possibility exists that a certain threshold for amount of spinal cord compression should be reached to result in electrophysiological abnormalities and clinical signs. Further studies are warranted to confirm this hypothesis.

CONCLUSION

The results of this study suggest that TMS can be considered as a useful diagnostic tool to differentiate between clinically relevant and irrelevant cervical spinal cord compressions seen on MRI. The addition of TMS to the diagnostic workup of cervical spinal cord disorders carries the potential to increase the sensitivity and specificity of more routinely used imaging modalities, such as MRI. These findings should encourage further exploration of this technique in veterinary medicine to assess different aspects of spinal cord disorders in different breeds of dogs.

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MAGNETIC STIMULATION OF THE NERVOUS SYSTEM IN DOGS AND CATS: GENERAL DISCUSSION

GENERAL DISCUSSION

The scope of this thesis was to gain insights into the use of magnetic stimulation of the nervous system in dogs and cats. Magnetic stimulation is widely used in human medicine for diagnostic, prognostic and therapeutic purposes but in small animal medicine, its application is still rare. However, this non-invasive, sensitive and painless technique appears promising as a test of motor tract function in dogs and cats.

Magnetic stimulation of peripheral nerves

Magnetic stimulation of the nervous system was firstly described in human medicine (Barker et al., 1985, 1987) and in man the technique is described as causing minimal discomfort, especially in contrast to electrical stimulation. This is mainly achieved by the lower field strength needed to evoke reproducible responses after magnetic stimulation (Levy, 1988). The possibility to stimulate peripheral nerves without the need for general anaesthesia is a major advantage of the technique in veterinary medicine; especially in cases were serial stimulation for follow-up of the condition is required. Moreover, to stimulate the nerve roots or peripheral nerves magnetically, stimulating needle electrodes are no longer needed as the needle electrodes are replaced by the magnetic coil of the stimulator. Likewise, nerves can be stimulated without the need for mechanical contact with the body. A final advantage of the technique exists in the possibility to stimulate deep peripheral nerves, such as the femoral nerve, the facial nerve or the nerve roots.

Although the technique of magnetic stimulation has been introduced in veterinary medicine 20 years ago (Heckmann et al., 1989; Sylvestre et al., 1992), little work has been done to develop its use in stimulation of peripheral nerves. Consequently, it seemed interesting to evaluate its usefulness in cats and dogs as a diagnostic and perhaps as a prognostic tool.

The initial objectives of this thesis were 1/ to find out whether magnetic stimulation of the radial and the sciatic nerve could evoke recordable magnetic motor evoked potentials (MMEP) in dogs and cats, 2/ to standardize the technique in both species and 3/ to establish reference values for onset latency and peak-to-peak amplitude of the MMEP.

In **chapter 3 and 4** of this study, radial and sciatic peripheral nerves were magnetically stimulated in clinically normal dogs and cats and reference values were obtained. In all dogs and cats, MMEP were easily obtained after stimulation of the radial and sciatic nerve, proximally and distally on the course of the nerve. The parameters of the MMEP evaluated are onset latency and peak-to-peak amplitude. Onset latency reflects the conduction along the fastest conducting axons and peak-to-peak amplitude is proportional to the number of available axons (Cuddon, 2002). In human medicine, the problem of determining the exact site of stimulation on the course of the nerve, which is expressed by onset latency, has been raised (Evans, 1988). In the dog studies of this thesis (**chapter 3**), onset latencies after electrical and magnetic stimulation were equal, indicating the same site of stimulation on the course of the nerve. In the cats (**chapter 4**), significant differences in onset latencies were observed between electrical and magnetic stimulation of the radial nerves. This discrepancy in results, however, could be explained by the difficulties in accessibility of the radial nerve by the rather large magnetic coil in cats.

A second shortcoming of the technique described in human medicine, is the problem in obtaining a consistent supramaximal response as compared to the response obtained after electrical stimulation (Evans, 1988), which is expressed by peak-to-peak amplitude. In both dog (**chapter 3**) and cat (**chapter 4**) studies, this problem of submaximal stimulation was not encountered, although a high variation in peak-to-peak amplitude was observed. This variation is caused by different factors (Amassian et al., 1989; Barker, 1991) and therefore peak-to-peak amplitude interpretation should be carried out carefully.

Other limitations of interpretation of onset latency and peak-to-peak amplitude of MMEP after peripheral nerve stimulation, however, need to be taken into account. First, onset latency and peak-to-peak amplitude are highly dependent on the height at the withers of the examined animal. In studies comparing left to right limbs, this influence is of no importance. Future studies, however, comparing results of for example dogs with polyneuropathy with the predictive values obtained in **chapter 3**, should take account of the height of the animal. Secondly, a standardized technique of magnetic peripheral nerve stimulation is needed to obtain robust results. Stimulus intensity, coil shape and orientation, placement of recording electrodes but also parameters inherent to the patient as age and body temperature can easily change the results after peripheral nerve stimulation (Cuddon, 2002). In this thesis, a standardized technique of stimulation was consistently used. Therefore, the influence of the

body temperature was highly indicative for explaining the left to right difference in the healthy dog group (**chapter 3**). Future studies, eliminating this factor by randomization of the sequence of stimulating the different limb or by controlling the body temperature might be useful

The following objective of this thesis was to determine the usefulness of magnetic peripheral nerve stimulation in different clinical conditions (**chapter 5**). The technique was applied to dogs and cats with unilateral brachial plexus avulsions (**part 1**) and unilateral sciatic nerve lesions (**part 2**). In all these cases, statistically significant differences were observed between the normal limb and the affected limb. In some instances no MMEP could be evoked and in other cases increased onset latencies and decreased peak-to-peak amplitudes were measured in comparison to the measurements of the normal limb. A small study on cats with polyneuropathy (PNP) (**part 3**), showed differences in MMEP parameters between the PNP cats and the reference values of the normal cats. These differences, however, were not statistically sustained because of the low number of cats in this study.

Furthermore, in **part 1 of chapter 5**, the additional prognostic value of magnetic radial nerve stimulation in brachial plexus avulsion was mentioned. The inability to evoke a MMEP in the affected limb was statistically linked with a poor outcome. Also, in animals with a poor outcome, lower peak-to-peak amplitudes were found in comparison to animals with a good outcome. The inability to evoke a MMEP indicates severe injury to the nerve and therefore a bad prognosis. The lower amplitude found in animals with a poor outcome was a rather surprising finding and future experiments on the follow up of nerve injuries with magnetic stimulation could be interesting.

A new diagnostic test that is non-invasive, painless, causes little stress for the animal and gives contingent additional information on the prognosis is welcome, provided it is sufficiently specific and sensitive. Specificity expresses the prevalence of false positive findings, sensitivity the prevalence of false negative findings. In all dogs and cats, MMEP were easily obtained after stimulation of the radial and sciatic nerve, proximally and distally on the course of the nerve. In comparing healthy animals or normal limbs to affected animals or limbs, respectively, the inability to evoke a MMEP was never observed in the former group. Moreover, in every case with brachial plexus avulsion and sciatic neuropathy where a MMEP could be evoked in the affected limb, a statistically significant difference in onset

latency and peak-to-peak amplitude was found with the normal limb. In the cats with polyneuropathy, in some instances no MMEP could be evoked and in other cases increased onset latencies and/or decreased peak-to-peak amplitudes were measured in comparison to the reference values. These results allowed us to conclude that false positive and false negative results were unlikely to occur and demonstrate a high specificity and sensitivity of the test protocol.

A future challenge would be to evaluate the prognostic and diagnostic value of magnetic peripheral nerve stimulation in other neuropathic syndromes. In our experience (unpublished data), MMEP with increased onset latencies and decreased peak-to-peak amplitudes were observed in dogs with polyneuropathy or femoral nerve injury.

Another possible field of interest for magnetic peripheral nerve stimulation may be the follow up of neuropathic diseases with the technique. Serial stimulations to monitor nerve degeneration and regeneration can provide additional prognostic information. In a clinical point of view, however, such follow up studies might be difficult to achieve.

Additionally, it would be interesting to investigate the usefulness of stimulating nerves such as the cranial nerves (Rösler et al, 1989) or the cervical and lumbosacral nerve roots (Britton et al, 1990; Chokroverty et al, 1993; Öge et al, 1997).

Finally, another potential role for peripheral nerve magnetic stimulation may be intra-operative monitoring during for example orthopaedic surgery (e.g. sciatic nerve function during hip replacement surgery) (Schoenfeldt et al, 1987).

Magnetic stimulation of the motor cortex

In the second part of this doctoral thesis (**chapters 6 and 7**), the technique of transcranial magnetic stimulation (TMS) is described. With TMS it is possible to monitor the integrity of the descending motor tracts from the motor cortex, over the spinal cord to the peripheral nerves. In veterinary medicine, the technique appears to be an attractive method to diagnose dysfunction within the motor tracts, for example in cases of subtle or subclinical lesions (Sylvestre et al, 1993; Nollet et al, 2002, 2003; Poma et al, 2002) and, to correlate imaging findings and clinical symptoms (da Costa, 2006a). Furthermore, in human medicine, the technique has proven valuable in prognostic (Heald et al., 1993; Clarke et al., 1994; Escudero et al., 1998; Hendricks et al., 2003; Lo, 2007) and therapeutic applications (George, 1995, 1997; Nielsen et al., 1995, 1996; Greenberg, 1997; Kobayashi and Pascual-Leone, 2003; Machii et al., 2006; Bae et al., 2007).

Although the technique of TMS is described as causing minimal discomfort (Barker et al, 1985), the clicking sound and the evoked muscle twitches can produce adverse reactions of the animals in veterinary medicine. Therefore, often sedation or anaesthesia is required to perform TMS in veterinary medicine. Sedative and anaesthetic agents, however, can easily attenuate the potentials elicited by prolonging onset latencies and decreasing peak-to-peak amplitudes (Ghaly, 1990; Sylvestre et al., 1992; Glassman et al., 1993; Van Ham et al., 1994; Young et al., 1994; Van Ham et al., 1995, 1996a, 1996b). Therefore, monitoring motor pathways with transcranial magnetic motor evoked potentials (TMMEP) in veterinary medicine is particularly challenging. In the past, various studies have reported the depressive influence of sedatives and anesthetics on TMMEP in dogs and horses (Ghaly, 1990; Sylvestre et al., 1992; Glassman et al., 1993; Van Ham et al., 1994; Young et al., 1994; Van Ham et al., 1995, 1996a, 1996b; Nollet et al, 2003).

Therefore, in **chapter 6** the development of a possible workable tool to monitor TMMEP during sedation and anaesthesia was investigated. In this study, two brain monitors that have proven efficiency in monitoring depth of anaesthesia were used (Jensen et al., 1996; Rampil, 1998, Pypendop et al., 1999; Litvan et al., 2002; Struys et al., 2002; Murrell et al., 2004, 2005; Vereecke et al., 2005) and its relationship to TMMEP investigated. BIS and AAI, however, were not related to the changes in onset latencies and peak-to-peak amplitudes of the TMMEP during different sedative and anesthetic drug combinations. Probably the

differences between the neurophysiological pathways of MMEP after TMS and the limited cerebral measures performed by BIS and AAI explain these findings. However, it remains a challenge for future scientific work, to explore workable tools to objectively monitor TMMEP parameters during sedation and anaesthesia.

Nevertheless, this study showed that the combination of acepromazine and methadone or medetomidine alone can be used to facilitate obtaining TMMEP in dogs. Both sedatives produced sufficient sedation and eliminated severe defensive reactions of the dogs. For diagnostic procedures in clinical practice, sedation of the animal has proven adequate to perform TMS (Van Ham et al, 1994; Nollet et al, 2003; da Costa et al, 2006a; Van Soens et al, 2009). The use of hypnotic drugs as propofol and etomidate during TMS, however, was contraindicated as they demonstrated a significant time- and product-dependent effect on the onset latency and peak-to-peak amplitude of the TMMEP. A future challenge for TMS in small animal medicine might be its ability to objectively monitor motor tract function during vertebral surgery. The need for general anaesthesia during this procedure in veterinary medicine remains however a limiting factor. Therefore the requirement of a general anaesthesia protocol compatible with adequate TMMEP recording remains necessary.

In **chapter 7** of this thesis, a clinical application of TMS during sedation was described. Previously it has been reported that TMMEP provide a valuable diagnostic tool in spinal cord disorders in veterinary medicine (Sylvestre, 1993; Nollet, 2002, 2003; Poma et al, 2002; da Costa, 2006a). Significant depressant effects on the TMMEP parameters onset latency and peak-to-peak amplitude were noticed in spinal cord disorders. In a study in horses, TMS even enabled to differentiate between cervical and thoracolumbar spinal cord disease (Nollet et al, 2002, 2003). The use of TMS in dogs, however, as a useful tool to differentiate between relevant and irrelevant spinal cord compressions seen on MRI was not described previously. Different human and veterinary reports demonstrated the issue of over-interpretation of spinal cord compressions seen on MRI (Teresi et al, 1987; Boden et al, 1990; Lehto et al, 1994; Matsumato et al, 1998; da Costa et al., 2006b). In our study, TMMEP were similar in clinically normal dogs with and without cervical spinal cord compression seen on MRI but significantly different between clinically normal dogs and affected dogs. Additionally, a statistical correlation was found between TMMEP parameters and the degree of spinal cord compression. This is in correspondence to human studies; for example, TMS of the motor cortex in cervical spondylotic myelopathy has proven useful in the early assessment of

corticospinal tract damage and moreover in the detection of lesions at a preclinical stage (Maertens de Noordhout et al., 1991; Linden and Berlit, 1994; Kaneko et al., 2001). Lo and coworkers (2004) studied a large population of human patients with myelopathy and TMS findings correlated well with the severity of spinal cord compression; sensitivity of TMS in this study was 100% and specificity 84.8%. These matters open a new perspective for the use of TMS in veterinary medicine.

A possible field of interest for TMS in veterinary medicine may be to evaluate the informative value of TMMEP in other neurological syndromes with motor deficits, for example disc herniation, degenerative myelopathy or degenerative lumbosacral stenosis. TMS might especially be promising in cases where localisation of the lesion along the spinal cord or where the clinical relevance of imaging findings is uncertain. Recording TMMEP from various levels of paravertebral muscles has proven valuable in human patients with restricted cord lesions to allow more precise localisation (Ertekin et al, 1998).

Whether TMS will also help to predict development of clinical symptoms or outcome of neurological disorders, as described in human disorders remains the question (Clarke et al, 1994; Bednarik, 1998; Lo, 2007; Bednarik, 2008). Recent studies of Lo (2007) and Takahashi and co-workers (2008) suggested that TMS parameters were an independent predictor of good surgical outcome in patients with cervical myelopathy. Therefore, a further study investigating the relationship between TMMEP findings and post-surgical outcome in our Doberman Pinschers with cervical myelopathy might be interesting.

A final interesting field of TMS in veterinary medicine to explore is its use as an intra-operative monitoring tool during spine and spinal cord surgery. Approximately 30 years have passed since somatosensory evoked potentials (SSEP) were first used to monitor the spinal cord during surgery (Nash et al, 1977; Engler et al, 1978). However, the enthusiasm for this technique was stemmed by the presence of serious motor deficits in some patients despite preserved SSEP (Lesser et al, 1986). Consequently, the last years, the development of specific methods for monitoring the functional integrity of the motor tracts during spine and spinal cord surgery has opened new fields of interest (Deletis and Sala, 2008). Motor tract monitoring during surgery has not only proven a prognostic value but has also proven the ability to recognize a hazard to the motor system and therefore protects patients from permanent neurological deficits (Deletis and Sala, 2008).

In our study designs, the waveform of the TMMEP was evaluated and onset latency and peak-to-peak amplitude of the TMMEP were measured and statistically analysed. In reported human studies the diagnostic sensitivity of the technique has been increased by using numerous other parameters or by combining different parameters such as for example the motor threshold or central motor conduction time (CMCT). Motor threshold reflects the lowest TMS intensity capable of eliciting TMMEP and has demonstrated utility in the diagnosis of motor neuron diseases (e.g. amyotrophic sclerosis) (Schreifer et al., 1989; Eisen et al., 1990; Pouget et al., 2000; Urban et al., 2001; de Carvalho et al., 2003; Attarian et al., 2005; Attarian et al., 2007). In veterinary medicine, the use of CMCT interpretation in TMS studies might also show potential. CMCT is an estimation of the conduction time of the corticospinal fibers between the motor cortex and the spinal motor neurons (Chen et al, 2008) and can be estimated by subtracting the spinal motor neuron to muscle latency from the cortex to muscle latency. The spinal motor neuron to muscle latency can be estimated by eliciting F waves from the peripheral nerve or by stimulating motor nerve roots at their exit foramina after stimulation of the spinal cord (Mills and Murray, 1986). In human patients with cervical spondylotic myelopathy (CSM), CMCT correlated well with the severity of spinal cord compression based on MRI (Lo et al, 2004). Additionally, CMCT detected incipient cord compression prior to the development of clinical or radiological signs (Maertens de Noordhout et al, 1991; Travlos et al, 1992). Moreover, the sensitivity and specificity of TMS may be improved by the choice of the target muscle. In CSM for example, recordings made in the trapezius muscles might give information on the possible effects of cervical spondylosis (Truffert et al, 2000). In veterinary medicine, all aforementioned techniques need to be extensively explored before clinical use is advised.

Finally, a major limitation of TMS in dogs and in veterinary medicine overall remains the fact that the nature or cause of the spinal cord lesion cannot be determined (Brunholzl and Claus, 1994) and thus advanced imaging of the spinal cord and/or histopathology of the lesion remains necessary to find the exact aetiology of the pathology.

Conclusions

In conclusion, the present thesis allowed obtaining several insights into the use of magnetic stimulation of the nervous system in dogs and cats.

Magnetic stimulation of the peripheral radial and sciatic nerve has proven value as a good complementary diagnostic tool in neuropathic syndromes in small animal neurology. Furthermore, an additional prognostic value of the technique has also shown but further research on this topic is necessary. As noticed, there are still some limitations that need to be adjusted by more detailed standardization of the technique.

Likewise, the technique of transcranial magnetic stimulation has proven value in evaluation of the integrity of the descending motor pathways from the motor cortex to the muscles. The depressant effects of sedatives and anesthetics on the evoked potentials, however, remain a major problem and the search for an objective monitoring tool is still necessary.

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SUMMARY

In man, the development of magnetic stimulation of the nervous system in the 1980's opened new opportunities in studying motor tracts. Since then, several studies have focussed on its application in brain, spinal cord and peripheral nerve disorders. In veterinary medicine, however, clinical studies are still rare. Therefore it was a challenge for us to test the usefulness of magnetic stimulation as a diagnostic and prognostic tool in small animal medicine.
In this thesis several aspects of magnetic stimulation in veterinary medicine were evaluated. It can be divided in the following parts.

As a general introduction (chapter 1) a brief review is given on the basic principles and procedure of magnetic peripheral nerve and motor cortex stimulation in human and veterinary medicine. Furthermore, clinical application of both techniques in man and animal medicine are presented. Finally, the risk factors of magnetic stimulation are reviewed.

The scientific aims (chapter 2) of this thesis were firstly to evaluate the technique of peripheral nerve stimulation in dogs and cats. Can magnetic motor evoked potentials be recorded in dogs and cats? If yes, a standardized technique should be described and reference ranges be established. Furthermore, the use of magnetic peripheral nerve stimulation in clinical patients had to be evaluated.
Secondly, the technique of transcranial magnetic stimulation (TMS) was studied. In the past, influence of sedatives and anesthetics on transcranial magnetic motor evoked potentials (TMMEP) has been reported. In this study we wanted to assess the possibility to objectively monitor these effects of sedatives and anesthetics on TMMEP with electroencephalogram derived parameters. Finally, the usefulness of TMS in dogs with and without clinically relevant spinal cord lesions was evaluated.

Chapter 3 describes the standardization of the method of magnetic peripheral nerve stimulation in dogs. In the first part of chapter 3, the technique is compared with electrical stimulation. No significant differences were observed, indicating conformity of both techniques in dogs. Additionally, the influence of the direction of the current in the magnetic coil was studied. No significant differences, however, were observed between orthodromic and antidromic stimulation.
In the second part of chapter 3, 54 dogs of different breed, age and gender were stimulated proximally and distally on the course of the radial and sciatic nerve. Additionally, two types

of magnetic coils were compared. As such, normal values for onset latency and peak-to-peak amplitude of magnetic motor evoked potentials (MMEP) were set up in order to formulate a 95% prediction interval by which values obtained in clinical patients can be judged as normal or abnormal.
No significant effect of the coil design was observed on the MMEP parameters. Height at the withers and bodyweight had a significant effect on onset latency and peak-to-peak amplitude. Breed, age and gender had no significant effect on the MMEP parameters. Therefore the height at the withers was used to predict onset latency and peak-to-peak amplitude in normal dogs and to calculate the 95% prediction interval.
Onset latency differed between the left and right evoked responses but might be explained by a difference in body temperature because all stimulations were performed in a same sequence.

In chapter 4 the standardized technique of magnetic stimulation of the radial and sciatic nerve is described in cats. Reference values for onset latency and peak-to-peak amplitude of MMEP were obtained and compared to values of electrical motor evoked potentials (EMEP). Significant differences were observed in onset latencies of MMEP and EMEP after stimulation of the radial nerve. This different site of stimulation on the course of the radial nerve is explained by the difficulties in accessing this nerve by the magnetic coil. MMEP, however, were easily obtained and stably reproducible in normal cats.

By using a standardized technique, the usefulness of magnetic stimulation of peripheral nerves was evaluated in clinical patients with neuropathic lesions (chapter 5). In part 1 of chapter 5, magnetic stimulation of the radial nerve was performed in dogs and cats with unilateral brachial plexus trauma. Absence of deep pain perception (DPP), ipsilateral loss of panniculus reflex, partial Horner's syndrome and a poor response to MMEP were related to the clinical outcome. For all animals, a significant difference was found in MMEP between the normal and the affected limb. Absence of DPP and unilateral loss of the panniculus reflex were indicative of an unsuccessful outcome in dogs. Additionally, the inability to evoke a MMEP was associated with an unsuccessful outcome in all animals. It was concluded that magnetic stimulation of the radial nerve in dogs and cats with brachial plexus trauma may provide an additional diagnostic and prognostic tool.
Part 2 of chapter 5 describes the use of magnetic stimulation of the sciatic nerve in dogs and cats with sciatic neuropathy. In all animals, a statistically significant difference was found between the normal and the affected limb. Moreover, the inability to evoke a MMEP, absence

of voluntary motor function and a poor outcome seemed associated with the inability to evoke a MMEP in the affected limb.

In part 3 of chapter 5, magnetic stimulation of the radial and the sciatic nerve was performed in 3 cats with polyneuropathy. Onset latencies and peak-to-peak amplitudes of MMEP of these cats were compared to the reference values of the normal cats of chapter 4. MMEP parameters were different from the reference values but additional studies on more animals are necessary to define more clearly the correlation between the clinical and the electrophysiological findings.

Chapter 6 describes the relationship between transcranial magnetic motor evoked potentials (TMMEP) and the electroencephalographic parameters bispectral analysis index (BIS) and the autoregressive model with exogenous input (ARX)-derived auditory evoked potential index (AAI) during different sedative and hypnotic drug combinations in dogs. TMS was performed under sedation with acepromazine/methadone or medetomidine and after a single bolus injection of propofol or etomidate. Data for BIS and AAI were continuously collected during the periods of treatment with the sedatives and with the hypnotic drugs. Changes in BIS and AAI during both periods were not statistically correlated with changes in onset latencies and peak-to-peak amplitudes of MMEP after TMS. Therefore, both electroencephalographic techniques are of limited use in titrating sedation and anaesthesia during TMS in the dog.

In the final chapter (chapter 7), the usefulness of TMS was evaluated in Doberman Pinschers with clinically relevant and irrelevant spinal cord compressions. Transcranial magnetic motor evoked potentials (TMMEP) were recorded from the extensor carpi radialis (ECRM) and cranial tibial (CTM) muscles in clinically normal Doberman Pinschers with and without spinal cord compression and in 16 Doberman Pinschers with disk associated wobbler syndrome. MRI was performed to evaluate the presence and severity of spinal cord compression. Significant differences were observed between the ECRM onset latencies, CTM onset latencies and CTM peak-to-peak amplitudes between the clinically affected Doberman Pinschers and the 2 groups of clinically normal dogs separately. There was a significant correlation between severity of spinal cord compression and ECRM onset latencies, CTM onset latencies, and CTM peak-to-peak amplitudes. We concluded that TMS could be used as a diagnostic tool to differentiate between clinical relevant and irrelevant spinal cord compressions.

In conclusion, magnetic stimulation of the peripheral radial and sciatic nerve has proven value as a good complementary diagnostic tool in neuropathic syndromes in small animal neurology. Furthermore, an additional prognostic value of the technique has also shown but further research on this topic is necessary. As noticed, there are still some limitations that need to be adjusted by more detailed standardization of the technique.

Likewise, the technique of transcranial magnetic stimulation has proven value in evaluation of the integrity of the descending motor pathways from the motor cortex to the muscles. The depressant effects of sedatives and anesthetics on the evoked potentials, however, remain a major problem and the search for an objective monitoring tool is still necessary.

SAMENVATTING

Midden de jaren ‘80 zorgde de techniek van magnetische stimulatie van het zenuwstelsel voor een interessante ontwikkeling in het onderzoek van de motorische zenuwbanen bij de mens. Verschillende studies hebben de techniek van magnetische stimulatie van de hersenen, het ruggenmerg en de perifere zenuwen al beschreven. In de diergeneeskunde is het aantal studies echter nog beperkt. De verschillende mogelijkheden en voordelen van magnetische stimulatie, zetten ons aan om de bruikbaarheid ervan te testen bij de kleine huisdieren.

De thesis kan onderverdeeld worden in de volgende hoofdstukken.

In hoofdstuk 1 werd er een kort overzicht gegeven over de basisprincipes en de procedure van magnetische stimulatie van perifere zenuwen en van transcraniële magnetische stimulatie. Verder werden de klinische toepassingen in de humane en de diergeneeskunde beknopt beschreven. Tenslotte werden de verschillende risicofactoren van de techniek samengevat.

In hoofdstuk 2 werden de wetenschappelijke doelstellingen weergegeven. Kan magnetische stimulatie van perifere zenuwen motorische magnetisch geëvokeerde potentialen (MMEP) opwekken bij de hond en de kat? Zo ja, dan is er nood aan een gestandaardiseerde techniek en aan referentiewaarden. Aansluitend werd getracht om de bruikbaarheid van deze techniek na te gaan bij klinische patiënten.
Vervolgens werd de techniek van transcraniële magnetische stimulatie (TMS) bekeken. De invloed van sedativa en anesthetica op transcranieel motorische magnetisch geëvokeerde potentialen (TMMEP) werd in het verleden al beschreven. In deze thesis wilden we nagaan of we met behulp van elektro-encefalogram (EEG) afgeleide parameters, de invloed van sedativa en anesthetica op TMMEP objectief konden opvolgen. Aansluitend aan deze studie werd de bruikbaarheid van TMMEP beoordeeld om een onderscheid te maken tussen klinisch relevante en irrelevante ruggenmergcompressie bij de hond.

Hoofdstuk 3 beschrijft een gestandaardiseerde methode van magnetische stimulatie van perifere zenuwen bij de hond. In het eerste deel van dit hoofdstuk, werden de resultaten na magnetische stimulatie vergeleken met de resultaten na elektrische stimulatie van de radialis en ischiadicus zenuw. Er werden geen significante verschillen waargenomen tussen beide technieken wat wijst op conformiteit. De richting van de stroom in de magnetische spoel had geen invloed op de MMEP.

Na standaardisatie van de techniek, werd bij 54 honden van verschillend ras, leeftijd en geslacht, de radialis en de ischiadicus zenuw magnetisch gestimuleerd. Er werden twee verschillende types van magnetische spoel in deze studie aangewend. Zo konden normaalwaarden voor latentietijd en amplitude van de MMEP en een 95% betrouwbaarheidsinterval opgesteld worden.
Er werden geen significante verschillen opgemeten tussen de beide types van spoel. Schofthoogte en lichaamsgewicht hadden een significante invloed op de MMEP parameters latentietijd en amplitude maar ras, leeftijd en geslacht hadden geen invloed. Schofthoogte werd bijgevolg gebruikt om de MMEP parameters te voorspellen bij normale honden. Aansluitend kon het 95% betrouwbaarheidsinterval berekend worden, wat gebruikt kan worden om eventuele pathologie aan te tonen bij patiënten. Latentietijd vertoonde een significant verschil tussen de links en rechts opgenomen potentialen; dit verschil kon slechts verklaard worden door een verschil in lichaamstemperatuur tussen beide lidmaten. Dit zou kunnen vermeden worden door de verschillende metingen niet steeds uit te voeren in dezelfde sequentie.

Hoofdstuk 4 beschrijft de procedure van magnetische stimulatie van perifere zenuwen bij de normale kat. Er werden referentiewaarden opgesteld en deze werden vergeleken met de waarden na elektrische stimulatie van dezelfde zenuwen. Er werden significante verschillen waargenomen tussen beide technieken voor de parameter latentietijd van de radialis zenuw. Dit verschil wees op een verschil in stimulatie op het verloop van de zenuw en kon verklaard worden door moeilijkheden in bereikbaarheid van deze zenuw door de magnetische spoel. MMEP werden echter, ook bij de katten, zonder problemen en reproduceerbaar uitgelokt.

In het volgende hoofdstuk (hoofdstuk 5) werd de bruikbaarheid van magnetische stimulatie van perifere zenuwen geëvalueerd aan de hand van neurologische patiënten met zenuwaandoeningen. In het eerste deel van hoofdstuk 5, werd magnetische stimulatie van de radialis zenuw uitgevoerd op honden en katten met een unilateraal plexus brachialis letsel. Afwezigheid van diep pijngevoel, ipsilateraal verlies van de panniculus reflex, partieel Horner syndroom en de resultaten van de MMEP werden gecorreleerd aan de klinische uitkomst van de dieren.
Bij alle honden en katten werd er een significant verschil van de MMEP parameters waargenomen tussen de normale en de aangetaste poot. Daarenboven was de onmogelijk om MMEP te registreren bij bepaalde dieren geassocieerd met een slechte uitkomst. Hieruit werd

besloten dat magnetische stimulatie bij dieren met plexus brachialis avulsie een aanvullende diagnostische en prognostische test was.
In het tweede deel van hoofdstuk 5 werd magnetische stimulatie van de ischiadicus zenuw beschreven bij dieren met een letsel van deze zenuw. Net als in het voorgaande deel van dit hoofdstuk, werden er significante verschillen gevonden tussen de MMEP parameters van de normale en de aangetaste achterpoot. Daarenboven werd er ook een relatie tussen enerzijds de afwezigheid van het diep pijngevoel, de afwezigheid van willekeurige bewegingen in de aangetaste poot en een slechte uitkomst en anderzijds de onmogelijkheid om een MMEP op te wekken aangetoond.
Deel 3 van hoofdstuk 5 onderzocht 3 katten met symptomen van polyneuropathie waarbij zowel de radialis als de ischiadicus zenuw werden gestimuleerd. De resultaten van deze 3 katten werden vergeleken met de resultaten van de normale katten uit hoofdstuk 4. MMEP resultaten vertoonden duidelijke verschillen met de referentiewaarden maar onderzoek op grotere groepen dieren is nodig om statistische verschillen aan te tonen.

Hoofdstuk 6 onderzocht de relatie tussen TMMEP parameters en de EEG parameters BIS (bispectral analysis index) en AAI (autoregressive model with exogenous input (ARX)-derived auditory evoked potential index) tijdens het gebruik van verschillende sedativa en hypnotica. TMS werd uitgevoerd op 6 honden na sedatie met acepromazine/methadon of medetomidine en na een enkelvoudige bolus injectie van propofol of etomidaat. Veranderingen in de EEG parameters ten gevolge van de sedativa en hypnotica waren echter niet statistisch gecorreleerd aan de veranderingen in de TMMEP parameters. Bijgevolg hadden deze EEG parameters slechts een beperkte bruikbaarheid tijdens het opvolgen van TMMEP parameters gedurende sedatie en anesthesie.

In het laatste hoofdstuk (hoofdstuk 7) werd de bruikbaarheid van TMS geëvalueerd bij Doberman Pinchers met klinisch relevante en irrelevante ruggenmergcompressie. TMMEP werden geregistreerd van de extensor carpi radialis spier (ECRS) en de tibialis cranialis spier (TCS) bij klinisch gezonde Doberman Pinchers met en zonder ruggenmergcompressie op MRI en bij Doberman Pinchers met klinische symptomen van discus geassocieerd wobbler syndroom. MRI werd uitgevoerd om de aanwezigheid en graad van ruggenmergcompressie te beoordelen. Er werden significante verschillen waargenomen in de ECRS en TCS latentietijden en TCS amplitudes tussen de klinisch gezonde en aangetaste honden. Aansluitend werd ook een significante correlatie aangetoond tussen de graad van

ruggenmergcompressie en de ECRS en TCS latentietijden en TCS amplitudes. Hieruit konden we besluiten dat TMS een bruikbare diagnostische test is om te differentiëren tussen relevante en irrelevante ruggenmergcompressie.

Uit deze studie konden we besluiten dat magnetische stimulatie van perifere zenuwen een bruikbare test is gebleken in zenuwaandoeningen bij kleine huisdieren. Bovendien werd een aanvullende prognostische waarde aan de techniek toegeschreven. Een gestandaardiseerde techniek is echter noodzakelijk.

Eveneens werd aangetoond dat transcraniële magnetische stimulatie een waardevolle aanvullende technologie is om de integriteit van het ruggenmerg na te gaan. De onderdrukkende invloed van sedativa en anesthetica op de geëvokeerde potentialen blijft echter een probleem in de diergeneeskunde en het onderzoek naar een objectieve manier om dit effect te beoordelen blijft noodzakelijk.

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Eindelijk is het zover! Als dit dankwoord gelezen wordt, dan weet ik dat ik mijn doel bereikt heb, het is achter de rug, ik ben gedoctoreerd! Ik denk dat ik mijn magnetische stimulator het liefst een tijdje in een donker hoekje zou plaatsen… Alhoewel, de afgelopen jaren is hij toch ook een beetje mijn maatje geworden en niettegenstaande ik er af en toe eens flink op gevloekt heb, meen ik hem beter te kennen dan wie dan ook! De eerste keren dat ik zelf moest stimuleren was het altijd een beetje spannend maar tijdens het verloop van de verschillende studies wist ik beter en beter wat ik van hem kon verwachten. Bovendien ben ik hem erg dankbaar dat hij nooit "technische ziektes" heeft vertoond tijdens mijn onderzoek.

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Iris

CURRICULUM VITAE

Iris Van Soens werd geboren op 16 november 1974 te Borgerhout. Na het behalen van het diploma hoger secundair onderwijs aan de Europese School te Mol, startte ze in 1993 aan de studies Diergeneeskunde, initieel aan de Universiteit Antwerpen, later aan de Universiteit Gent. In 1999 studeerde ze af als dierenarts in de optie kleine huisdieren met grote onderscheiding.

In 2000 trad zij in dienst bij de vakgroep Geneeskunde en Klinische Biologie van de kleine huisdieren van de Faculteit Diergeneeskunde te Merelbeke. Gedurende twee jaar werkte ze als assistent op de afdeling anesthesie.

Van april 2002 tot oktober 2002 werd ze tewerk gesteld door de farmaceutische firma Merial als Junior Product Group Manager.

In het najaar van 2001 werd het diploma van gerechtelijk expert behaald aan de Faculteit Rechtsgeleerdheid van de Universiteit Gent.

Op 15 oktober 2002 startte ze een specialisatie opleiding in de neurologie aan de Faculteit Diergeneeskunde te Merelbeke die werd beëindigd in oktober 2008 en wat haar toelaat het examen voor de European College of Veterinary Neurology af te leggen.

Sinds 1 april 2004 is ze werkzaam als voltijds assistent op de afdeling neurologie bij de vakgroep Geneeskunde en Klinische Biologie van de kleine huisdieren van de Faculteit Diergeneeskunde te Merelbeke en startte ze een doctoraatsstudie over magnetische stimulatie van het zenuwstelsel bij kleine huisdieren. Tijdens deze periode was ze ook actief werkzaam in de kliniek neurologie.

Op 1 mei 2008 werd ze eveneens aangesteld als coördinator voor de kleine huisdieren en bijzondere diersoorten voor het Instituut voor Permanente Vorming van de Faculteit Diergeneeskunde.

Iris Van Soens is auteur en medeauteur van verschillende wetenschappelijke publicaties in internationale en nationale tijdschriften. Zij nam eveneens actief deel aan nationale en internationale congressen.

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