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Clinical actions of subarachnoid sevoflurane administration *in vivo*: a study in dogs

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Background. Halogenated ethers produce clinical effects at spinal sites. Nevertheless, *in vitro* and *in vivo* studies have not determined whether the immobilizing effect in the spinal cord is due to inhibition of nociceptive or motor transmission or both. Our goal was to characterize the clinical effects of direct spinal sevoflurane administration.

Methods. Five adult beagle dogs completed the study. In a randomized and blinded manner each animal received placebo (saline 0.1 ml kg^{-1}) and three concentrations of pure sevoflurane administered intrathecally (0.05, 0.075 and 0.1 ml kg^{-1}) by means of a permanent spinal catheter. Sensory and motor block and state of consciousness were determined at baseline and at predetermined regular intervals until at least 2 h after total recovery.

Results. None of the dogs presented a decrease in consciousness with either 0.05 or 0.075 ml kg^{-1} of sevoflurane. Administration of 0.1 ml kg^{-1} produced light sedation (2 on a four-point sedation scale) in three of the five dogs. A comparison of the duration of the sensory and motor blocks among the three sevoflurane dosages shows a significant dose-dependent increase that is greater in all cases than that for the saline solution.

Conclusions. Spinal administration of pure sevoflurane resulted in a dose-related and totally reversible motor and sensory regional block without any signs of clinical neurotoxicity or significant decrease in consciousness. Therefore the model allows us to comment on the analgesic effects at the spinal level in addition to the direct immobilizing effects of sevoflurane.

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The spinal action of halogenated ethers produces several important clinical effects during general anaesthesia. While hypnosis and/or amnesia are caused by the cerebral action of halogenated ethers, immobility despite surgical stimulus and blockade of the adrenergic response to painful stimuli are facilitated by the action of halogenated ethers on spinal motor neurones and the posterior column of the spinal cord.[1–3] Thus halogenated ethers have been recognized (both *in vitro* and in human reports) as immobilizing and analgesic agents through their effects on the spinal cord.[4–6] Consequently, the cerebral action of halogenated ethers may also be enhanced by a spinal action that depresses ascending sensory information.[7]

Existing *in vitro* and *in vivo* studies of the spinal effects of halogenated ethers have not determined whether the immobilizing effect at the spinal cord is due to inhibition of nociceptive transmission acting on dorsal neurones or inhibition of the motor neurones or a combination of both effects.[8–11]

This study presents a novel *in vivo* experimental model in dogs that has not been used before. Sevoflurane is directly administered to the spine instead of through the more traditional route of systemic inhalation. The main objective of our study with this model was to characterize the effects of sevoflurane, administered directly to the spine in pure liquid form for the first time, and to study the clinical effects of increasing concentrations of the drug on consciousness and on superficial and deep sensitivity, as well as on the motor response to a painful stimulus and the possibility of motor block. The study was designed to evaluate sensory effects

separately from motor effects. In addition, we also assessed the reversibility and duration of clinical spinal effects and whether administration produces signs of medullar lesions.

Materials and methods

Eight adult beagles, five males and three females, were used in this study. The age range was 2–6 years and the weight range was 12–18 kg. The animals were acquired, inspected by a veterinarian and underwent an acclimatization period of 1 week before experiments were started. All experimental procedures were performed according to European Union and Spanish Government regulations, and were supervised and approved by the Complutense University Animal Care Facility.

Catheter placement

Catheters were placed under general anaesthesia (premedication with medetomidine, induction with propofol and maintenance with isoflurane and fentanyl) with standard monitoring and mechanical ventilation. A 3 cm vertical incision was made in the medial lumbar region between L5 and L6 creating a tobacco sac to house the catheter connected to an injection site cap with a latex membrane through which the anaesthetic could be administered with a transdermic needle.

The subarachnoid space was located with a puncture between the L4 and L5 vertebrae. An epidural Tuohy calibre 20 epidural needle (Perisafe®, Becton Dickison, Bidford-on-Avon, UK) was inserted using the loss of resistance technique and, once the epidural space was located, advanced until a free flow of cerbrospinal fluid (CSF) was obtained. At this point the catheter was introduced into the subarachnoid space. Catheter placement was checked using a myelographic scope, introducing 0.5 ml of a low concentration of iodinated contrast (240 mg ml^{-1}) (Omnipaque®, Amersham Health, Cork, Ireland). The distance between the insertion point and placement in the spinal space was calculated, and another 5 cm was added to place the catheter at L2.

The catheters were left to stabilize for 1 week. Proper catheter placement and function were confirmed 72 h before beginning the studies by administering a test dose of lidocaine 0.1 mg kg^{-1}. If there were doubts as to proper catheter function, myelography was repeated.

Sevoflurane administration

Each animal received three sevoflurane doses (Sevorane®, Abbot Laboratories, Queenborough, Kent, UK): 0.05 ml kg^{-1} (0.076 mg kg^{-1}), 0.075 ml kg^{-1} (0.114 mg kg^{-1}) and 0.1 ml kg^{-1} (0.152 mg kg^{-1}), and saline solution 0.1 ml kg^{-1} (0.9%) as control. The specific gravity of sevoflurane is 1.52 g l^{-1} and its molecular weight is 200.05.[12] The clinically relevant dose of sevoflurane is ~0.4 mM (~1 MAC).[13] We used a priori calculation to design the study based on the theoretical distribution of CSF volume in the dog (2.5–3 ml kg^{-1}).[14] According to this, the maximum dose of 0.1 ml kg^{-1} used in our study corresponds to 0.24 mM, which is <1 MAC, the medium sevoflurane dose of 0.075 ml kg^{-1} corresponds to 0.18 mM, which is ~0.5 MAC and the lowest dose of 0.05 ml kg^{-1} corresponds to 0.12 mM (<0.33 MAC). These doses were assigned randomly and blindly. To ensure blinding, two people randomly chose the doses and administrated each dose in one room, and a third person (the same observer for the entire study) made the evaluations in another room. The animals were dosed at intervals of at least 72 h and after each administration the catheter was flushed with 0.3 ml saline solution. Immediately after administration, the animal was allowed to walk freely.

Data collection

We used four clinical tests following a modification of the method described by Feldman and colleagues[15] (Table 1). The first test evaluated the level of consciousness on a four-point sedation scale, the second test evaluated motor function on a three-point motor block scale, and the third and fourth tests evaluated sensation. The painful stimulus test evaluated the response to a deep nociceptive sensory stimulus (ungueal base pressure with a Halstead clamp) on the dog's four legs on a three-point scale. The other sensory block test was the prick test or pannicular reflex exploration, which evaluated the response to a superficial sensory stimulus (skin pricking by piercing the skin with a needle) on a two-point scale (Table 1). All four tests were performed on all animals at predetermined regular intervals (0, 5, 15, 30, 45, 60, 75, 90, 105 and 120 min, and then every 30 min for as long as necessary until 2 h after the recovery was complete, or for a minimum of 2 h). The maximum degree of blockade of each dose was graded on a three-point scale (1=no effect;

Table 1 Clinical evaluation scales: sedation, motor blockade scale response to pain stimulus and response to prick test. There are two types of possible response to the prick test, one in the sacral and one in the lumbar region

Sedation scale
1 Spontaneous eye-opening without stimulus/unstimulated eye-opening
2 Dog tends to close its eyes spontaneously, but will open them when called or patted on the head
3 Dog tends to close its eyes spontaneously, but will open them if there is a painful stimulus (foreleg)
4 General anaesthesia: eyes do not open even if there is a painful stimulus
Motor blockade scale
1 Normal motor response: dog has normal gait and ability to stand on four legs
2 Ataxia or partial motor block: any alteration of gait
3 Total motor block: dog cannot remain standing on four legs
Painful stimulus test
1 Normal response to stimulus: vigorous/rapid withdrawal of the limb and/or vocalization
2 Attenuated response to stimulus: slower withdrawal of the limb without vocalization
3 Absence of response: no limb movement or vocalization
Response to dermatome sensitivity/pannicular reflex/prick test
1 Normal response to stimulus: pannicular reflex in response to stimulus
2 No pannicular response to prick test