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A Method for Reliable and Simultaneous Cannulation of the Epidural and Subarachnoid Spaces in Pigs

A tool for the study of cerebrospinal fluid pharmacokinetics and drug penetration of the dura mater

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ABSTRACT

Many drugs are of interest from the point of view of their pharmacokinetical properties in the CSF, as well as their penetration of the dura mater after epidural application. A means of assessment of these properties is therefore of importance. The present report describes a method allowing reliable simultaneous cannulation of the epidural and subarachnoid spaces in the anaesthetized pig, with control of the catheter positions. The catheter tips can be placed at the same spinal level, separated only by the dura mater and arachnoid membrane. Both catheters are introduced via the atlanto-occipital membrane. We found this method a valuable tool in the research of drug disposition and other experimental procedures, where simultaneous and reliable access to the subarachnoid and epidural spaces is mandatory.

INTRODUCTION

Advances in pain physiology and pharmacology has led to the introduction of several endogenous as well as exogenous substances with analgesic effects when administered intrathecally in animals as well as in the clinical situation. The epidural route of administration has often been chosen because of its ability to provide high concentrations of pharmacologically active agent in the vicinity of spinal receptors. Epidurally administered opiates and clonidine are typical examples (1,11). Physostigmine has also been used intrathecally recently (3). The further evaluation of many other drugs concerning their possible spinal neurotoxic actions and circulatory effects in the spinal cord, as well as their CSF pharmacokinetic properties are of interest and essential before clinical trials can be started. When studying the passage of a drug from the epidural space across the dura mater into the subarachnoid space and the pharmacokinetic properties of the drug in the CSF, animal models are useful. Due to its anatomical and economic advantages the pig has been increasingly used in our institution for animal experiments.

Several methods giving access to the epidural (4,12,8,2) and subarachnoid spaces (14,7,5,10) have been described in animals. A catheter can readily be

introduced through a needle placed in the epidural space by percutaneous technique using the loss of resistance method in most large animal species. The use of this technique when the position of the catheter is crucial, however, may lead to difficulties, since the catheter may follow an undesirable direction (9). It is often so that this misplacement is not revealed until autopsy of the animal. Furthermore, the introduction of a subarachnoid catheter by the percutaneous needle insertion technique in the mid or lower spine carries with it the danger of damaging the spinal cord, since this, in e.g. the pig, extends all the way down to the sacral hiatus. We have also found it difficult and unreliable to obtain CSF over longer sampling periods using a percutaneously inserted lumbar catheter.

The present report is a description of an alternative method in the anaesthetized pig which allows reliable simultaneous cannulation of the epidural and subarachnoid spaces with control of the catheter positions. The method enables fixation of the catheter tips at the same spinal level, separated only by the dura mater and arachnoid membrane. The method has proven useful for CSF pharmacokinetic studies and for studies of the drug penetration of the dura mater.

METHODS

Pigs of Swedish breed weighing 20-25 kg were used. Anaesthesia was introduced with ketamine (Ketalar^{R}), 500 mg i.v. followed by a continuous infusion of methomidate (Hypnodil^{R}) 7.5 mg/kg/h and pancuronium bromide (Pavulon^{R}) 2.1 mg/h/kg b.w. Tracheostomy was performed and the animals received oxygen/nitrous oxide (30/70), and were ventilated by means of a volume-controlled ventilator (Servo Ventilator 900B, Siemens Elema). The end-tidal carbon dioxide tension was kept within normal limits by means of capnography and blood gas analysis. Glucose 25 mg/ml in half isotone Ringer's acetate (Rehydrex^{R}, Pharmacia) was infused during the experiment at a rate of 10 ml/kg/h. Catheters for intravascular pressure monitoring and blood sampling were placed in the right atrium via the left jugular vein as well as in the right carotid artery. The animals were placed in the prone position with maximal flexion in the neck. A hard cylindrical pillow below the neck as well as ordinary surgical tape was used to obtain this position. Under aseptic conditions, a midline incision through the skin was made from the external occipital protuberance to about 15 cm caudal of this point. Dissection was continued by dividing the neck muscles strictly in the midline as this approach minimized bleeding. The muscles were divided down to the occipital bone until the dorsal edge of the foramen magnum could be palpated. The spinal processes of the first and second cervical vertebra were located and exposed. A self-holding retractor was used and found to be of invaluable help in visualizing these structures and also served as a haemo-

stat during the dissection. Thereafter the atlanto-occipital membrane could be palpated between the occipital bone and the first cervical vertebra. In the pig this structure is situated about 12 cm below the skin. The ligament was exposed by careful dissection until it appeared naked with its shiny greyish-yellow appearance. The epidural space ends at the foramen magnum where a fusion occurs between the ligamentum flavum and the superficial layer of the dura mater. Between the foramen magnum and the first cervical vertebra, however, the epidural space still exists. When penetrating the exposed atlanto-occipital membrane with a blunt needle, in this case a Thouy needle 18 G was used, an audible pop combined with a distinct fell of "give" was experienced, the epidural space had then been reached by the needle tip. The direction of the needle should be caudal and its insertion close to the cranial edge of the first cervical vertebra. The position of the needle tip was verified by lack of CSF in the needle. and no resistance should be felt when injecting a few ml of air. A soft plastic guide wire made of nylon (1.05 mm British Viggo, U.K.) was introduced about 15 cm into the epidural space in the caudal direction after which the needle was withdrawn. A polyethylene catheter (1.25 mm o.d., length 30 cm), (British Viggo, U.K.) was then threaded over the guide wire into the epidural space.

So as to introduce an intrathecal cannula in the same animal, a needle was again passed through the atlanto-occipital membrane, about 1 cm above the point of entry of the epidural catheter. When entering the epidural space, the same signs as mentioned above were expereienced. The needle was then advanced slowly until penetration of the arachnoid membrane occurred which was immediately followed by the appearance of CSF at the needle hub. A 1.05 nylon guide wire was introduced into the subarachnoid space. Care should be taken to use the finest possible needle that allows passage of the guide wire so as to prevent leakage of CSF once the needle is withdrawn. A catheter of the same type as in the epidural space was then introduced in the caudal direction as with the epidural catheter. The tips of the catheters could easily be placed adjactant to each other, separated only by the dura mater and the arachnoid membrane. Of course, the subarachnoid catheters may also be directed cranially. In order to minimize the leakage of CSF around the subarachnoid catheter we have utilized an autologous blood patch technique by pooring 10 ml of the pigs blood onto the bottom of the surgically exposed area and allowed the blood to coagulate before sewing up the wound.

RESULTS AND DISCUSSION

After developing the technique in a number of pilot experiments the method was used in 20 pig experiments. The locations of the epidural and subarachnoid

catheters were controlled and found correct in all cases when checked at autopsy after the experiments. CSF was easily obtained and we were able to sample 0.5-1 ml of CSF as much as three times at five minute intervals and considerably more when the interval between the sampling periods was longer. Over a 4 hour period 2 ml of CSF could be sampled every 20 minutes. No gross lesions of the spinal cord were seen at autopsy.

The method described above has been used successfully by us in experiments where drug passage from the epidural space across the dura mater into the subarachnoidal space was studied. In this situation we found it important to have the tip of the epidural catheter, where the test drug was delivered, as close as possible to the tip of the intrathecal catheter, where the CSF was sampled. Using the present model this was always acieved. Furthermore, the risk of dural lesions in the vicinity of the epidural puncture, which could allow intrathecal leakage of the test drug and thus disturb ghe pharmacokinetic analysis, seems low using this method compared to the method using blind percuatneous puncture. We have used the method for studies of penetration of the dura mater by clonidine administered epidurally (6).

We have also used the method to obtain CSF samples from the posterior cisternal sac during studies of the kinetics of CO_2 and bicarbonate during cardiopulmonary arrest (13). It is probable that this technique could also be used in awake animals allowed to recover after catheterization, although this has not been tried by the authors.

CONCLUSION

Our method of cannulating the epidural and subarachnoid spaces in the pig seems to be a valuable tool in the research of drug distribution and other experimental procedures where simultaneous and reliable access to the subarachnoid and epidural spaces is mandatory.

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