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Cerebrospinal Fluid and Plasma Concentrations of Clonidine in Pigs after Epidural, Intravenous and Intramuscular Administration

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ABSTRACT

Epidural clonidine is an alternate way to treat severe pain in man. The cerebrospinal fluid (CSF) and plasma concentrations resulting after epidural, intravenous (i.v.) or intramuscular (i.m.) clonidine, 3 ug/kg b.w. have been determined by a sensitive gas chromatographic method. A porcine model was used, where the epidural and intrathecal spaces were cannulated via the atlanto-occipital membrane. After epidural administration of clonidine the CSF concentrations were maximal 20 minutes after the injection, 129±24 ng/ml (mean ± S.D.). Clonidine was eliminated from CSF with an apparent half-life of 26±8.2 minutes (mean ± S.D.). The plasma concentrations stayed below 1 ng/ml. Low plasma and undetectable CSF concentrations resulted after i.v. clonidine. Thus, epidural clonidine readily penetrates the dura mater into the CSF, and there is a marked gradient between CSF and plasma.

INTRODUCTION

Advances in pain physiology have revealed several spinal synaptic systems, capable of modifying nociceptive impulses. The analgesic effect that occurs after stimulation of the spinal opioid receptors with exogenous opiates are now well documented (1,9). In animals the alpha-2-receptor agonist clonidine has been found to produce a powerful, longlasting analgesia, reversible by specific alpha-2-receptor antagonists, but not by naloxone (13,16). This indicates a mode of action different from that of opioids. A combination of low doses of spinally injected morphine and the clonidine analogue ST 91, which both are ineffective when injected on their own, produced in animals a powerful analgesia, to which tolerance did not develop (17). Clinically, antinociceptive action of clonidine has been reported after i.v. administration to patients suffering from postoperative pain (7) and after epidural administration to patients with severe non-malignant pain (15). An analgesic effect of intrathecal administration of clonidine has also been reported in a patient suffering from intractable pain from metastatic carcinoma, already tolerant to the analgesic effect of intrathecal morphine (3).

The mechanism of action for analgesia produced by spinally administered clonidine is considered to be an activation of postsynaptic alpha-2-adrenoceptors (10), located in the dorsal horn of the spinal cord (12) resulting in a decreased transmission of the nociceptive signals. Before widespread clinical use of epidural clonidine can be commenced, its pharmacological properties have to be determined. Investigation of the potential neurotoxic effects from spinal administration of clonidine has not revealed any histopathological changes (5). In pigs epidural clonidine, 3 ug/kg b.w. does not affect spinal cord blood flow, whereas 10 ug/kg b.w. causes a significant decrease (6).

In an investigation of epidural clonidine in sheep marked craniospinal CSF and spinal CSF/plasma concentration gradients were present, but no numerical data were stated (2). Very low plasma concentrations (< 0.05 ng/ml) have recently been reported after 75 ug of clonidine given epidurally to man (11). In the present study the CSF and plasma concentrations resulting from epidural, i.v. or i.m. injection of clonidine in pigs are presented.

METHODS

The investigation was approved by the local Ethical Committee for Animal Experiments.

Pigs of Swedish breed weighing 20-25 kg were used. Anaesthesia was induced 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/kg/h for muscle relaxation. Tracheostomy was performed and the animals received oxygen/nitrous oxide (30/70), 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 use of capnography and blood gas analyses.

Glucose 25 mg/ml in half isotone Ringer's acetate (Rehydrex^{R}) 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 carotid artery. Catheters were introduced in the epidural and intrathecal spaces. Both catheters were passed via the atlanto-occipital membrane according to a method described in detail elsewhere (8). The method permits a reliable simultaneous cannulation of the epidural and intrathecal spaces. The catheter tips were placed at the same spinal level, separated only by the dura mater and the arachnoid membrane. The risk of leakage of a test substance, placed epidurally, into the CSF through the puncture hole in the dura mater, is eliminated using this method.

Clonidine (Catapressan^{R}) 3 ug/kg b.w. dissolved in 5 ml normal saline was injected epidurally in four pigs, i.v. in two pigs and i.m. in one pig. The dose used in this experiment, 3 ug/kg b.w., was chosen after pilot studies in

humans, in which a dose of 2-3 ug/kg b.w. in most cases produces analgesia with tolerable side effects (15).

Analysis of clonidine

Samples of 2 ml of CSF and 10 ml of whole blood were drawn 20, 40, 60 and 80 min after the administration of clonidine. The plasma was separated and all samples were stored at -20°C until analysis. The CSF and plasma samples were analysed by a method described previously (4) with determination of clonidine using gas chromatography with electron capture detection. Analysis was done using a 1500 x 2 mm i.d. glass column packed with 3 % OV 17 on Gas Chrom Q (Supelco Inc. Bellefonte, PA, USA) in a PYE Unicam PU 4500 gas chromatograph. Internal standard in the assays was 2-(2.4-dichloro-phenyl-imino) imidazoline. The limit of determination was 1 ng of clonidine in a 3 ml sample. The apparent disappearance half-lives in the CSF were calculated from the slope of the concentration: time curves plotted on lin-log scale.

RESULTS

Epidural administration of clonidine yields high concentrations of clonidine in the CSF after 20 min, 129±24 ng/ml (mean ± S.D.). Thereafter, the CSF concentrations decreased with an apparent elimination half-life of 26±8.2 (mean ± S.D.). The plasma concentrations after epidural clonidine were at all points of measurement below 1 ng/ml, i.e. below the limit of detection of the analytical procedure. Thus, the concentration ratio CSF/plasma of clonidine was > 100:1 after 20 and 40 min following epidural administration (Table 1).

Table 1

CSF AND PLASMA CONCENTRATIONS OF CLONIDINE (ng/ml)
after epidural, intravenous and intramuscular administration to pigs.

Dose and administration route	Pig No.	CSF concentrations ng/ml				Apparent half-life (min) in CSF	Plasma concentrations ng/ml			
		20	40	60	80 min		20	40	60	80 min
Epidural clonidine	1	100	97	66	45	35	not detectable			
3 g/kg b.w.	2	139	133	83	52	30	"	"		
	3	156	85	38	19	17	"	"		
	4	124	-	40	21	21	"	"		
I.v. clonidine	5	not detectable				-	1	2	1	2
3 g/kg b.w.	6	"	"			-	not detectable			
I.m. clonidine	7	not detectable				-	2	2	1	1
3 g/kg b.w.										

After intravenous and intramuscular administration of the same dose of clonidine, the CSF levels were below 1 ng/ml at all times. The plasma concentrations after i.v. or i.m. clonidine were also very low, only slightly above the detection limit. The maximum plasma concentrations were 2 ng/ml (Table 1).

DISCUSSION

These findings support the possibility that the analgesic effect of epidural clonidine results from its penetration of the dura mater into the CSF and the spinal cord. Although the number of animals in each group was small, the results are conclusive concerning the dura mater passage of clonidine, and showed that much higher clonidine concentrations were reached in the CSF compared to plasma after epidural administration.

However, the availability of epidural pethidine and morphine to the CSF in man is only 1-2 % of a total epidural dose (9,14). The concentration ratios CSF/plasma in man 15 and 30 min after epidural administration of morphine or pethidine were 28/1 and 80/1, and 85/1 and 150/1 respectively (14). Analogously, in spite of the pronounced clonidine concentration gradient CSF/plasma, the major part of the epidural dose of clonidine does probably not penetrate the dura mater. Instead, due to its lipophilic character the major fraction can be assumed to reach the systemic blood circulation at a high rate.

A CSF transport of clonidine to supraspinal centers might also contribute to its analgesic effect, but obviously this rate and the fraction of the epidural dose remaining for transport is low (9,14).

Also, the theoretical possibility that epidural clonidine is transported by the systemic blood circulation to supraspinal parts of the CNS to produce analgesia, is not supported by the results of this experiment as the plasma concentrations were at all times low.

It should also be pointed out that the apparent half-lives of disappearance do not reflect a true elimination from the CSF but rather a distribution with the CSF bulk flow in early distribution phase.

In conclusion, epidural clonidine readily penetrates the dura mater, giving rise to a marked concentration difference between CSF and plasma of more than 100/1 within the first hour. The same dose given intravenously produces very low concentrations in both CSF and plasma.

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