Effects of Elevated Plasma Magnesium Concentration on Cerebrospinal Fluid Levels of Magnesium in Neonatal Swine (43231)

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Abstract. **To determine whether magnesium (Mg) can cross the blood brain barrier in developing swine, simultaneous measurements of [Mg] in plasma and cerebrospinal fluid (CSF) were made during experimental elevation of plasma [Mg] in 12 swine of differing postnatal age. All were anesthetized with Saffan and maintained at normal arterial blood gas composition. Aortic pressure and heart rate were monitored. Plasma and CSF samples, drawn at the beginning and end of a 60-min intravenous infusion of $MgCl_2$ in all animals and every 10 min during the infusion in three, were analyzed for [Mg] and osmolality. CSF [Mg] increased in all animals as plasma [Mg] increased. There were no changes in CSF osmolality. The differences between plasma and CSF [Mg] was smallest in the youngest animals. These results indicate that Mg crosses the blood brain barrier in neonatal swine and suggest that the blood brain barrier is still maturing within the first postnatal month.** [P.S.E.B.M. 1991, Vol 197]

Hypermagnesia has long been known as a clinical problem in neonates (1, 2). We have recently reported that experimental elevation in plasma magnesium concentration [Mg] in neonatal swine is accompanied by changes in phrenic and sympathetic nerve activity (3) and carotid baroreceptor reflex function (4). These observations suggested that integrative capabilities of the developing central nervous system (CNS) had altered and, by inference, that Mg had crossed the blood brain barrier (BBB) including choroid plexus into the cerebrospinal fluid (CSF). However, it was not known whether or not such a transfer would occur. We therefore tested the hypothesis that Mg can enter the CSF from the plasma of developing swine. Simultaneous determinations of plasma and CSF [Mg] were made before and during intravenous administration of Mg in swine at different ages within the first month of postnatal life (5). Osmolality of plasma and CSF samples was also measured to provide control information on possible osmotic opening of the BBB (6, 7) during the infusion procedure.

Materials and Methods

Twelve piglets ranging in age from 12 hr to 32 days after birth were initially anesthetized with Saffan (Pitman-Moore: 12 mg/kg im). Following placement of a jugular vein catheter, Saffan was then administered by continuous intravenous infusion (10 mg/kg/hr). All piglets were tracheotomized and either breathed spontaneously or were paralyzed with decamethonium bromide and artificially ventilated with 100% O_2 (six animals aged 12 hr to 32 days). Core temperature was maintained at 38–39°C with a servo-regulated heating system and overhead lamp. A femoral venous catheter was inserted for infusion of one half normal saline and $MgCl_2$ (Fisher Scientific, lot 871088) solutions. An aortic catheter was inserted via a femoral artery for registering aortic pressure and sampling arterial blood with heparinized syringes. Heart rate was monitored via the electrocardiogram. End-tidal CO_2 was registered continuously by a Sensormedic CO_2 analyzer; arterial blood gases were determined on 1-ml samples at 45-

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Received October 11, 1990. [P.S.E.B.M. 1991, Vol 197]
Accepted January 19, 1991.

0037-9727/91/1971-0098$3.00/0

min intervals with a Radiometer microsystem. Blood gas composition and recordings of aortic pressure and heart rate on a Sensormedic dynograph were used as evidence of general stability of the animal preparations. A spinal needle was inserted for CSF sampling from the lumbar region or cisterna magna. Further details of methodology were published by Rivera *et al.* (8).

After control samples of plasma and CSF were obtained, $MgCl_2$ solution (0.2 *M*) was infused intravenously for 60 min at rates ranging from 0.2 to 1.9 ml/min, depending upon age and weight of the piglet, as in our previous studies (3, 4, 8). Arterial blood (2 ml) was withdrawn at 10-min intervals thereafter. CSF (0.2–0.5 ml) was withdrawn at 60 min in all animals and at 10-min intervals throughout the infusion in three animals of different ages.

[Mg] in plasma and CSF was determined in duplicate in a Perkin-Elmer 560 atomic absorption spectrophotometer. The samples were diluted by factors of 1:5, 1:10, and 1:20 for accuracy of measurement. Each 100-μl of diluted sample was mixed with 4 ml of 5% EDTA. The spectrophotometer was standardized with three different concentration controls run with each set of samples.

Plasma and CSF osmolality were determined in duplicate on undiluted samples in an Advanced Micro-osmette Osmometer. The precision of this instrument was sensitivity = 0.2% for values < 1000 mOsmol/kg; sensitivity = 0.5% for values >1000 mOsmol/kg.

Individual values of plasma and CSF [Mg] were plotted as a function of time for each of the three animals in which multiple samples were obtained. Control samples in all 12 animals were utilized to examine plasma [Mg], CSF [Mg], plasma-CSF [Mg] differences, and CSF osmolality as a function of age by analysis of variance. The observed difference in [Mg] between plasma and CSF at 60 min after the start of $MgCl_2$ infusion was plotted as a function of age of animal, and the relationship was evaluated by linear regression analysis. All statistical tests were performed on an IBM-AT computer using the CRISP statistical package; the null hypothesis was rejected at $P \leq 0.01$.

Results

Control values of plasma [Mg] ranged from 0.53 to 1.53 m*M*, and CSF [Mg] from 0.45 to 1.48 m*M*, without relationship to age of animals. In all animals, the plasma [Mg] achieved at 60 min after the start of the infusion was greater than plasma [Mg] at 30 min; the 60-min values ranged from 3.3 to 12.34 m*M* depending on the total dose of $MgCl_2$ administered, but not on the control level of plasma [Mg]. Therefore, we decided that 60 min was a suitable time to sample CSF for possible elevations of [Mg]. In the three animals in which CSF was sampled every 10 min, the onset of increase of CSF [Mg] varied between 10 and 20 min and continued until 60 min.

The difference in control [Mg] values between plasma and CSF was ≤0.41 m*M* and was independent of age. At 60 min after the start of $MgCl_2$ infusion, an appreciable age-related [Mg] difference between plasma and CSF was observed, as shown in Figure 1. Linear regression analysis revealed that this difference increased with age of animals. Since control plasma and CSF [Mg] were not age dependent, Figure 1 also indicates that more Mg entered the CSF the younger the animal.

There was no age relationship for control values of plasma osmolality which ranged from 287 to 331 mOsmol/kg, or CSF osmolality which ranged from 282 to 327 mOsmol/kg. At 60 min after the start of $MgCl_2$ infusion, CSF osmolality had not changed nor was there an osmolar gradient between plasma and CSF.

Systolic and diastolic aortic pressures fell significantly ($P < 0.01$) by the time plasma [Mg] reached 2.4 m*M*. The decline in mean aortic pressure averaged 35–45 mm Hg. A significant decrease in heart rate ($P < 0.01$) occurred at plasma [Mg] above 2.47 m*M*. These results are comparable to observations made in another study on other animals and recently reported (8).

Discussion

It has long been thought that either the BBB and/or a transport regulation mechanism protects the CNS by keeping the [Mg] within physiologic limits even in the face of elevation of plasma [Mg]. The results of the present investigation demonstrate for the first time that Mg does pass the BBB in developing swine within the first postnatal month, and to a greater extent in the younger than in the older animals. This is clinically relevant because neonatal hypermagnesia can occur as a consequence of treatment of the mother with Mg; for example, as a tocolytic agent to prevent premature delivery (9, 10). Excess Mg produces a wide variety of effects including skeletal muscle paralysis, respiratory depression, and changes in cardiovascular function. It has been thought that these effects are peripheral at the skeletal neuromuscular junction (11) and vascular smooth muscle (12, 13), but not due to changes in [Mg] in the CNS (14, 15). However, our findings of increased CSF [Mg], hypotension, and bradycardia in the present study support our impression that the changes in neurophysiologic function previously observed during $MgCl_2$ infusion in neonatal swine (3, 4) were at least partly due to CNS actions of Mg.

There has been controversy in the literature concerning the question of whether Mg enters the CSF from plasma in sufficient concentration to alter CNS function when plasma [Mg] is elevated (16, 17). After 3–4 hr of plasma [Mg] as high as 300–400% above normal in adult dogs, Oppelt *et al.* (17) found only a

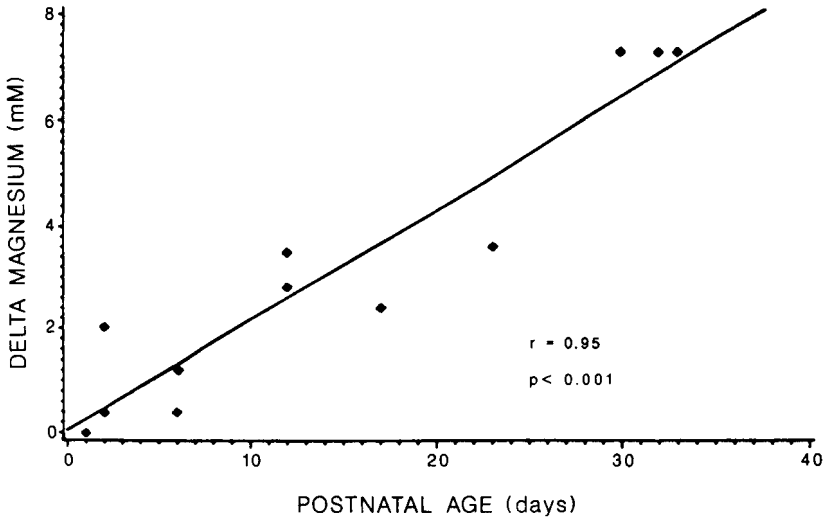

Figure 1. Plasma-CSF difference in [Mg] as a function of postnatal age. Points were obtained from simultaneously sampled plasma and CSF at 60 min after the start of intravenous $MgCl_2$ infusion. Correlation coefficient ($r = 0.95$) was statistically significant ($P < 0.001$).

21% increase in CSF [Mg]. Some investigators have concluded that osmotic opening of the BBB may be required to allow Mg to enter the CSF in sufficient concentrations (6, 7, 18). However, the osmolarity increase reported to be necessary to break down the BBB (18) was significantly large. Our control observations suggest that the entry of Mg into the CSF in the developing swine could not be attributed to osmotic opening of the BBB because no changes in CSF osmolality or plasma-CSF osmolality gradient were detected after 60 min of intravenous infusion with 0.2 *M* $MgCl_2$. The use of artificial ventilation on some of our swine also would not be expected to alter BBB function given the recent report of Temesvari and Kovacs (19) indicating that artificial ventilation in piglets elicited no significant change in the cerebral microcirculation.

Little is known about the development of the mammalian BBB and its permeability to Mg, although piglets 2–9 days of age have a functional BBB that is relatively impermeable to bicarbonate or hydrogen ions (20). Cornford and Cornford (21) reported that it was a misconception to think that the neonatal BBB was immature. However, Johanson (22) recently stated the need for investigations of the response of the developing brain-CSF system to plasma loaded with stable cations. There is one study on Mg homeostasis in the CNS of young rats (23) which demonstrated that 3- to 4-week olds were able to maintain a stable CSF [Mg] in the face of hypercapnia. The results of our study of age-related differences in plasma CSF gradient following Mg loading of plasma in swine suggest postnatal development of a functional barrier to at least one cation, Mg.

We conclude that the increase in CSF [Mg] in our neonatal animal model is probably a reflection of an incomplete BBB and/or a deficient mechanism regulating net movement into the CSF. Thus, it is possible that elevation of CSF [Mg] could be occurring in newborn infants with elevated plasma [Mg], born to mothers treated with Mg.

This work was supported by NIH Grant HL-20864.

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