letters to the editor

The following is the abstract of the article discussed in the subsequent letter:

Sysyn, Gregory D., Katherine H. Petersson, Clifford S. Patlak, Grażyna B. Sadowska, and Barbara S. Stonestreet. Effects of postnatal dexamethasone on blood-brain barrier permeability and brain water content in newborn lambs. *Am J Physiol Regulatory Integrative Comp Physiol* 280: R547–R553, 2001.—We showed that antenatal corticosteroids reduced blood-brain barrier permeability in fetuses at 60 and 80%, but not 90% of gestation, and decreased brain water content in fetuses. Our objective was to examine the effects of postnatal corticosteroids on regional blood-brain barrier permeability and brain water content in newborn lambs. Three dexamethasone treatment groups were studied in 3- to 5-day-old lambs. A 0.01 mg/kg dose was selected to estimate the amount of dexamethasone that might have reached fetuses via antenatal treatment of ewes in our previous studies. The other doses (0.25 and 0.5 mg/kg) were chosen to approximate those used clinically to treat infants with bronchopulmonary dysplasia. Lambs were randomly assigned to receive four intramuscular injections of dexamethasone or placebo given 12 h apart on days 3 and 4 of age. Blood-brain barrier function was measured with the blood-to-brain transfer constant \( (K_t) \) to \( \alpha \)-aminoisobutyric acid, brain plasma volume was measured with polyethylene glycol for the calculation of \( K_v \), and brain water was measured by wet-to-dry tissue weights. Postnatal treatment with corticosteroids did not reduce blood barrier permeability in newborn lambs. Brain blood volume was higher in the 0.25 and 0.5 mg/kg dose dexamethasone groups than in the placebo group. Brain water content did not differ among the groups. We conclude that postnatal treatment with corticosteroids did not reduce regional blood-brain barrier permeability or brain water content but increased the brain plasma volume in newborn lambs. These findings are consistent with our previous work indicating that barrier permeability is responsive to corticosteroids at 60 and 80% of gestation and brain water regulation at 60% of gestation, but not in near-term fetuses or newborn lambs.

Effects of Pharmacological Dose of Dexamethasone Given Postnatally on Blood-Brain Barrier Permeability and Brain Water Content

To the Editor: We read with interest the paper from G. D. Sysyn et al. (2), who published their observations regarding the effects of postnatal corticosteroid (intramuscular dexamethasone injections, doses: 0.01, 0.25, and 0.5 mg/kg) on regional blood-brain barrier permeability (transfer constant to \( \alpha \)-aminoisobutyric acid) and brain water content in 3-day-old newborn lambs. They concluded that the blood-brain barrier was not responsive to exogenous corticosteroid, as postnatal treatment with different doses of the drug, which were similar to those used clinically to treat premature infants, did not reduce regional blood-brain barrier permeability or brain water content in newborn lambs. However, the authors could not rule out the possibility that even larger doses of dexamethasone in different species might reduce barrier permeability. Moreover, they claimed in their introduction that the effects of postnatal corticosteroids on blood-brain barrier function had not been studied in newborn subjects of any species.

Indeed, we demonstrated earlier (3, 4) that a pharmacological dose (5 mg/kg sc) of dexamethasone reduced brain water and Evans blue albumin (mol wt 67,000) contents of parietal cortex and cerebellum significantly in 3- to 6-h-old asphyxiated newborn piglets. On the other hand, a therapeutic dose (0.5 mg/kg iv) of the drug had no effect on brain Na\(^+\)-K\(^+\)-ATPase enzyme activity in our animal model (1). Therefore, we suppose that higher doses of dexamethasone might have effects on the blood-brain barrier permeability, especially during different pathological conditions (such as neonatal postasphyctic state), not studied in the cited (2) work.

REFERENCES


REPLY

To the Editor: We appreciate the comments of P. Temesvári et al. and their interest in our work. These authors examined the effects of pharmacologic doses of
dexamethasone on water content and Evans blue albumin extravasation in the brain of newborn piglets exposed to severe bilateral pneumothoraces (7). It is important to point out that their model of bilateral pneumothoraces is associated with severe pH and blood gas and blood pressure abnormalities, all of which may affect brain water content and blood-brain barrier function. They have shown that severe bilateral pneumothoraces are associated with increases in water content and enhanced Evans blue albumin extravasation (mol wt 67,000) in the parietal cortex and cerebellum of newborn piglets. Treatment with 5 mg/kg body wt of dexamethasone subcutaneously 4 h before exposure to the experimental pneumothoraces attenuated the extent of the brain edema and Evans blue albumin extravasation in the parietal cortex and cerebellum of newborn piglets measured 2 h after recovery from the pneumothoraces (7).

In contrast to their findings with experimental pneumothoraces, we did not find increases in blood-brain barrier permeability when the unidirectional transfer constants for influx across the blood-brain barrier (Kᵢ) were quantified with radiolabeled sodium and mannitol or in brain water content in severely asphyxiated and hypotensive newborn piglets (3). In our current study, we examined the effects of postnatal corticosteroids on regional blood-brain barrier permeability and brain water content in 3- to 5-day-old lambs. The 0.01 mg/kg dose was selected as an estimate of the amount of dexamethasone that might have reached the fetus after antenatal treatment of the ewes in our previous studies (4, 5). The other two doses were selected to approximate those used clinically to treat premature infants with bronchopulmonary dysplasia. In this study, we quantified blood-brain barrier permeability with the unidirectional transfer constants for influx across the blood-brain barrier (Kᵢ) with radiolabeled α-aminoisobutyric acid (mol wt 103). We found that postnatal treatment with these doses of dexamethasone did not reduce regional barrier permeability or brain water content in normal newborn lambs.

Differences in our findings compared with those of Temesvári et al. (7) might relate to differences in the methodology used to measure barrier permeability, e.g., leakage of Evans blue albumin across the barrier in their experiments as a measurement of plasma extravasation in contrast with our measurement of the blood-to-brain transfer constant (Kᵢ) as a direct measure of the barrier permeability. Moreover, hypoxia per se has been associated with nonspecific transport of blood-borne proteins across the blood-brain barrier (1, 2). In addition, differences in the dosages of dexamethasone, e.g., doses similar to those used in the clinical setting in our study vs. pharmacological doses in theirs, and/or that our study examined barrier permeability in normal healthy newborn lambs vs. piglets with severe bilateral pneumothoraces in theirs make the comparison of these two sets of experiments somewhat difficult. Nonetheless, we cannot rule out the possibility that pharmacological doses of dexamethasone might have reduced barrier permeability in our newborn lambs or that corticosteroids might have had a different effect on barrier permeability under pathological conditions. Although we cannot rule out this later possibility in newborn lambs, we were unable to demonstrate changes in barrier permeability during 1 h of or 24 h after asphyxia alone or with hypotension in newborn piglets using a similar methodology to measure barrier permeability (3).

REFERENCES

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