Human dura mater permeability

To the Editor:

I read with interest the paper by McEllistrem *et al.*[1] The authors attempted to determine the effect of molecular weight and lipid solubility on drug diffusion from the epidural space to the spinal cord. They addressed this question by measuring drug flux through human dura mater *in vitro*. Unfortunately, the study has several shortcomings which would seem to render the authors' conclusions invalid:

1 The most important is that the authors measured drug flux through the dura mater only. We have previously shown that the arachnoid mater, which is composed of overlapping cells with frequent tight junctions, is the principal meningeal permeability barrier.[2] Our study also demonstrated that the acellular dura mater is an unimportant meningeal diffusion "[the spinal arachnoid] ... is unlikely to pose an important barrier to diffusion." If the authors believe that the arachnoid is not the principal meningeal permeability barrier, then they need to explain why the water, electrolytes and glucose which make up the CSF are confined within the subarachnoid space. Clearly, it is because the arachnoid mater is highly permeable. If the dura mater were the principal meningeal permeability barrier, then CSF would freely diffuse through the arachnoid and collect beneath the dura mater in the subdural space. That this is not the case is very strong support of our experimental evidence that the arachnoid mater, not the dura mater, is the only important meningeal barrier. Thus the authors' data regarding diffusion through the dura mater would not appear to be applicable to movement of drugs through the intact spinal meninges.

2 The authors froze their tissue at −70°C before study. However, they have not demonstrated that the proteins, glycolipids, proteoglycans, etc. which make up the dura mater and its ground substance behave normally after being frozen at this temperature. Thus, it is unclear if their data reflect the *in vivo* behaviour of the dura mater either.

3 The authors state that neither molecular weight nor lipid solubility are important in determining meningeal permeability. However, using an *in vitro* model which uses intact (dura, arachnoid and pia mater), live primate meningeal tissue, we previously demonstrated that lipid solubility is the only important determinant of meningeal permeability.[3] The reason that lipid solubility is important is that movement through the lipid bilayers of the arachnoid mater cells is the rate-limiting step in meningeal diffusion.

4 The authors report drug flux, not "permeability" as stated in the manuscript. Flux is a measure of the rate of drug transfer (units of mass per unit time) and is therefore dependent on the concentration gradient across the tissue. Permeability takes concentration gradient into account and has units of distance per unit time. Thus, it is not surprising and not very informative that the authors found that drug flux is dependent on the initial concentration gradient across the tissue.

I applaud the authors' interest in this area of research. Clearly more work needs to be done before we fully understand the dynamics of epidural drug delivery. However, our understanding can be advanced only by use of models which are appropriate to the questions being addressed. I believe that the available experimental data indicate that the model employed by Dr. McEllistrem and co-workers is not appropriate to further our understanding of the dynamics of epidural drug delivery.

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REFERENCES

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Negative arterial to end-tidal CO_2 gradients in children

To the Editor:

The paper by Campbell *et al.*[1] is another important contribution to confirm that the recent developments in end-tidal CO_2 monitoring have made capnography in infants and children as reliable as in adults. However, I would like to make some comments.

First, the reliability of end-tidal CO_2 ($PETCO_2$) as sampled from the nasal cavity in awake infants, breathing spontaneously, has been evaluated previously and found to be a reliable estimate of $PaCO_2$.[2-4] Dumpit and Brady designed a nasal catheter to sample end-tidal gas from the nostril in infants.[2] They found an arterial (arterialized capillary sample) to end-tidal gradient, (a-ET) PCO_2, of