LOCAL ANESTHESIA AND PAIN III

A685

TITLE: TRANSFER OF MORPHINE AND FENTANYL ACROSS ARTERIAL WALLS

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Introduction: The mechanism by which opioids move from the epidural space to the spinal cord is poorly understood. Three routes are commonly proposed—diffusion through the meninges, diffusion through the spinal nerve root sleeve and uptake into radicular arteries with subsequent redistribution directly to the spinal cord. Diffusion of opioids across the meninges and through the spinal nerve root sleeve has been demonstrated.[1,2] However, there is no experimental evidence to support the idea that drugs move from the epidural space to the spinal cord by way of the radicular arteries. To determine if such a route was possible, we quantified the rate of morphine and fentanyl transfer across arteries of differing sizes.

Methods: Four New Zealand white rabbits were anesthetized with halothane (1%) and nitrous oxide (60%) in oxygen. Both carotid and both femoral arteries were isolated. In random sequence, a water tight fluid reservoir was placed around one of the isolated arteries so as not to impede blood flow and the artery was reversibly clamped with a bulldog clamp distal to the reservoir. The artery was cannulated between the fluid reservoir and the clamp and the cannula connected to a pump. The fluid reservoir was filled with 1 ml isotonic saline. With this experimental setup, we could control the rate of blood flow through the artery and collect all blood which flowed through the length of vessel within the fluid reservoir. We added either 1 mg morphine and 1 μCi 3H-morphine or 50 μg Fentanyl and 1 μCi 3H-fentanyl to the reservoir at time zero and started the pump at the rate of 1 ml per minute and collected two ml blood fractions for 12 minutes. The amount of drug in the serum from each 2 ml fraction was determined by liquid scintillation counting. In this way we determined the amount of drug crossing the arterial wall to enter arterial blood during each 2 minute period.

Results: Total drug transferred over 12 minutes was calculated as a percentage of the amount of drug available for diffusion across the arterial wall, i.e., the amount of drug present in the reservoir bathing the artery. For the carotid artery this was: Morphine: 1.52 ± 0.65 %; Fentanyl: 0.90 ± 0.3 %. For the femoral artery this was: Morphine: 0.99 ± 0.07 %; Fentanyl: 0.76 ± 0.23%. There was no statistically significant difference between drugs or between arteries with respect to the total amount of drug transferred.

Conclusion: These results indicate that both morphine and fentanyl can cross arterial walls at average rates of approximately 0.1%/ minute and that redistribution by way of radicular arteries could play a role in net transfer of these opioids from the epidural space to the spinal cord.

References

1. Bernards CM, Hill HF: Morphine and alfentanil permeability through the dura, arachnoid, and pia mater of dogs and monkeys. Anesthesiology 73:1214-1219, 1990
2. Bernards CM, Hill HF: The spinal nerve root sleeve is not a preferred route for redistribution of drugs from the epidural space to the spinl cord. In press

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TITLE: PROGLUMIDE POTENTIATES THE ANALGESIC EFFECT OF LOW DOSE EPIDURAL MORPHINE FOR POSTSURGICAL PAIN

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Epidural morphine produces profound analgesia, but also cause much adverse effects in a dose dependent manner. Proglumide, a cholecystokinin antagonist has been shown to potentiate the analgesic effects of parenterally administered morphine in animals and human studies 1-2.

The present study evaluated the analgesic effect and safety profile of the combined administration of intravenous proglumide with low dose Epidural morphine (1 mg) in patients with postsurgical pain.

After giving their informed consent, sixty adult patients scheduled for elective lower abdominal surgeries were enrolled into the study. All the patients received Epidural anesthesia with 2% lidocaine via indwelling catheter inserted at L2-3 or L3-4 lumbar interspace. At the completion of surgery before leaving the operating room the patient were divided equally, with a dabble blind, randomized design, into 3 groups with group A (n=20) receiving epidural morphine 1 mg + normal saline 2 ml IV; group B (n=20) receiving epidural morphine 1 mg + proglumide 0.05 mg IV; and group C (n=20) receiving epidural morphine 1 mg + proglumide 0.5 mg IV.

Pain intensity (assessed by visual analogue scale), vital signs and adverse effects were recorded on all the patients at 1,2,4,8,16 and 24 hour after drug administration.

The initial pain intensity and demographic characteristics were similar for all 3 groups. Starting at the first hour and throughout the 24 hour observation period, both groups B and C showed significantly lower pain score than that of group A ($p<0.05$); however, there is no difference in the pain score between groups B and C as shown in Table 1. Fifty percent (10/20) of the patients in group A required "Rescue" analgesic for their pain whereas only 1 patient each in group B and C required such medication. The incidence of side effects were low among all 3 groups without appreciable difference. No respiratory depression (Resp. rate <10/min) was observed in any of the patients.

Our study demonstrated that intravenous proglumide potentiates the analgesic effect of low dose (1 mg) epidural morphine without potentiating it's adverse effects, and there is no difference in this potentiating effect between the 0.05 mg dose and the 0.5 mg dose. This seems to indicate a narrow dose range or "ceiling effects" on the interaction between proglumide and morphine for analgesia.

The clinical usefulness of the combined use of these two drugs warrants further large scale investigation.

Table 1 pain intensity score (mean value)

Time	0	1	2	4	8	16	24 hr.
Grp A	1.5	4.9	3.85	3.90	4.35	4.55	6.15
Grp B	1.70	1.15	1.20	1.40	1.65	1.95	2.20
Grp C	1.23	0.94	0.86	1.23	1.45	1.65	2.12

Reference:

1. Watkins LR et al, Science 224:395 - 396, 1984

2. Price DD et al, Anesth. Analg. 64:801 - 806, 1985