Local Anesthesia and Pain

Title: Plasma and Cerebrospinal(CSF) Fluid Pharmacokinetics Following Intrathecal, Epidural, and Intravenous Clonidine Administration in Sheep

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Introduction. Epidurally and intrathecally administered clonidine are currently being evaluated for analgesia. However, dural transfer and elimination of clonidine from CSF following these routes of administration have not been examined. This study determines the disposition and elimination of clonidine in sheep CSF and plasma and correlates clonidine concentrations with hemodynamic effects.

Methods. Arterial, venous, and lumbar epidural and intrathecal catheters were inserted in 6 nonpregnant ewes. Three days later, each ewe received, on separate days and in random order, clonidine (250 ± 30 μg) by bolus intrathecal (it), epidural, or intravenous (iv) injection. Plasma and CSF samples were obtained at various times to allow for adequate pharmacokinetic analysis, and assayed for clonidine by radioimmunoassay. Mean arterial pressure (MAP) and heart rate (HR) were measured at each sampling time and blood obtained for arterial blood gas tension analysis at times of peak CSF and plasma concentrations, determined in preliminary studies. Clonidine concentration vs time curves were fit to compartmental pharmacokinetic models using PCNONLIN. Bioavailability was calculated from the ratios of the appropriate areas under the concentration-time plots and adjusted for minor differences in dose administered. Statistical analysis included mean, SEM, 1- and 2-way ANOVA, and Student's t-test.

Results. Following redistribution, plasma clonidine concentrations did not differ among the 3 routes of administration, whereas CSF clonidine concentrations were greater following it and epidural than iv injection throughout the 6-hr study (Figure 1). Plasma and CSF pharmacokinetic parameters were similar (Table 1). Plasma bioavailability for epidural and it routes of administration were 107 ± 15% and 86 ± 12%, respectively, while CSF bioavailability for epidural and iv routes were 17 ± 5% and 0.027 ± 0.007%. Only iv administration decreased arterial Po2 (from 99 ± 7 to 73 ± 6 mm Hg; P<.05), whereas all injections altered MAP (Table 2).

Discussion. The pharmacokinetics of clonidine are similar to those of meperidine (which has a similar lipid solubility) but not to those of morphine (which is much less lipid soluble). For example, epidurally administered meperidine is absorbed quicker into CSF and slower into plasma than morphine,(1) and these absorbance rates for meperidine are similar to those for clonidine. Likewise, intrathecally administered meperidine has a CSF volume of distribution larger than morphine,(2) but similar to clonidine (80 ± 41 ml). These results suggest that epidural clonidine may have a similar time of onset and duration of analgesia to those of meperidine. Clonidine produces hypoxemia and vasoconstriction by actions on peripheral α2-adrenoceptors, and these effects were only seen at high plasma clonidine concentrations(iv bolus). In contrast, clonidine produces hypotension in part by actions in the spinal cord, and this effect was more marked following it than epidural injection. These results corroborate clinical findings that epidural is less likely to produce hypotension than intrathecal clonidine injection.

References.

1. Sjostrom S, Hartvig P, Persson MP, Tamsen A: Pharmacokinetics of epidural morphine and meperidine in humans. Anesthesiology 67:877-888, 1987
2. Sjostrom S, Tamsen A, Persson MP, Hartvig P: Pharmacokinetics of intrathecal morphine and meperidine in humans. Anesthesiology 67:889-895, 1987

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TABLE 1. PHARMACOKINETIC PARAMETERS

	$t_{\frac{1}{2}}\beta$	$t_{\frac{1}{2}}ab$	Cmax	Tmax
Plasma				
IV	95 ± 21	-	19.2 ± 2.3	-
IT	81 ± 12	7.5 ± 2.6	1.23 ± .30	24 ± 6
Epidural	98 ± 15	10 ± 2.8	1.41 ± .23	34 ± 6
CSF				
IV	79 ± 28	9 ± 4.0	0.94 ± .18	25 ± 3
IT	64 ± 14	-	4200 ± 6700	-
Epidural	26 ± 2	18 ± 4.0	1149 ± 272	29 ± 7

Times in min, Concentrations in ng/ml, (n=5-6)

TABLE 2. EFFECT OF CLONIDINE ON BLOOD PRESSURE

	Time Following Injection (min)					
	1	10	40	60	120	240
IV	14* ±1.2	3.3 ±1.8	0.6 ±1.0	-5.3 ±1.4	-18* ±2.6	-7.3 ±2.5
IT	-3.3 ±0.9	-11.7* ±1.1	-11.3* ±2.2	-12.7* ±2.5	-8.7* ±1.5	4.7 ±2.0
Epidural	-2.2 ±1.4	-5.3 ±1.8	-8.7* ±1.2	-7.0* ±1.5	-9.0 ±4.0	-3.0 ±3.

Data expressed in change from baseline. *P<.05

Fig. 1.