Title : CONTINUOUS EPIDURAL INFUSIONS OF BUPIVACAINE FOR MANAGEMENT OF TERMINAL CANCER PAIN: PHARMACOKINETIC CONSIDERATIONS.

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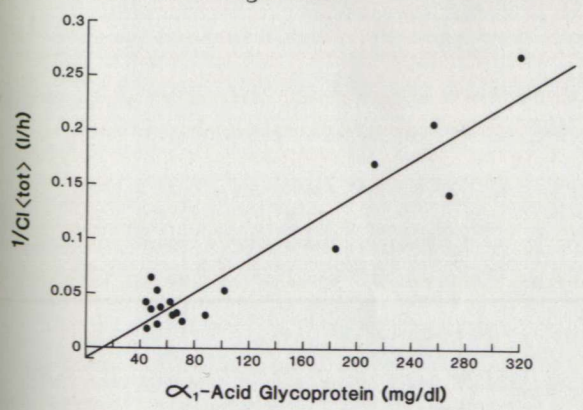
Introduction: Continuous epidural infusions of bupivacaine have been used for the management of refractory chronic pain syndromes (1). The total clearance (Cl(tot)), elimination constant(k), and volume of distribution (Vd) of bupivacaine can be accurately estimated from two blood samples (2). Increased protein binding of lidocaine in cancer patients has been reported (3). This study was designed to evaluate any pharmacokinetic and protein-binding changes associated with terminal cancer patients being treated with continuous epidural infusions of bupivacaine, and to determine the importance of any changes on the safe management of these patients.

Methods: This study was approved by the Committee for Human Research. Informed consent was obtained from each patient. Five patients with intractable pain from terminal cancer, to be treated with continuous epidural infusions of bupivacaine, were studied. Following placement of the epidural catheter, a 2-ml test dose, followed by 15-20 ml of 1.5% lidocaine, was injected to obtain initial pain relief. Patients were then connected in one hour to either an IVAC® or Abbott® pump for continuous infusion. Bupivacaince concentrations were either 0.125 or 0.25%, and the infusion rate varied from 3 to 30 mg per hour. Bupivacaine reservoirs were changed every 24 hours. Blood samples were obtained at t=0, t=3.5h, then every 24 hours until termination. Serum bupivacaine concentrations were determined by gas chromatography. Estimation of the pharmacokinetic parameters for each patient was accomplished as previously described(2). α_1-acid glycoprotein concentrations were determined using M-Partigen radioimmunodiffusion kit (Cal Biochem-Behring). Serum protein binding of bupivacaine was determined by equilibrium dialysis, using a Spectrapor dialysis membrane No. 2(Spectrum Medical Industries, Inc.) in Teflon cells, rotated in a water bath at 37° C for 4 hours. 1.0 ml aliquots of serum were dialyzed against an equal volume of isotonic Sorenson's phosphate buffer at pH 7.40. Correlation between clearance and α_1 acid glycoprotein concentration was determined using the method of least squares. Comparisons of the pharmacokinetic parameters for the cancer patient population and the normal population were accomplished using a t test between two independent means. $p<.05$ were considered significant.



Results: Bupivacaine total clearance decreases with increasing α_1 acid glycoprotein concentration. This correlation is linear with the correlation coefficient of 0.94(see figure). Elimination constants were slightly reduced in the cancer patient population. A statistically significant reduction in total clearance and the volumes of distribution was found in the cancer population. Table 1 compares the pharmacokinetic parameters estimated for the five cancer patients with those estimated for 25 chronic pain patients being treated with continuous epidural bupivacaine infusions. Extent of protein binding at several blood concentrations was examined in four of the five cancer patients, and the % binding was found to be increased over the expected values. (See Table 1.)

Table 1. Highest serum bupivacaine concentration, corresponding percent protein binding, and estimated pharmacokinetic parameters for cancer patients

	Highest Bupivacaine Conc. (μg/ml)	Percent Binding	k (1/h)	CKtot> (l/h)	Vd (l)
Patient No.					
1	4.5	---	0.170	7.0	41.18
2	4.3	95.8	0.075	5.9	79.03
3	4.9	96.3	0.154	3.7	24.02
4	2.8	98.2	0.170	11.1	65.29
5	4.3	96.3	0.155	6.9	44.52
mean	---	---	0.145	6.92[a]	50.80[a]
±sem			0.018	1.20	9.63
Control mean	---	---	0.179	33.18	195.70
±sem			0.010	±2.43	±14.51

a. $p<.001$ when compared to control population.

Discussion: Our results demonstrate a significant decrease in bupivacaine total clearance with increasing α_1-acid glycoprotein concentrations. Accumulation and concomitant increases in total serum bupivacaine concentration for a given infusion rate occur as the result of this decrease in total clearance. Increased plasma protein binding and corresponding decrease in the free fraction appear to prevent toxic reactions even at total serum bupivacaine concentrations above the apparent threshold level of 2.6-3.0 μg/ml. Tinnitus occurred briefly in only one patient. The serum bupivacaine concentration for this patient was 7.1 μg/ml. The results of this study demonstrate the importance of measuring free fraction rather than the total serum bupivacaine concentration, since all five of the cancer patients exceeded the expected toxicity threshold.

References:

1. Raj, PP; Denson, DD; Joyce, TH; et al.: Evaluation of continuous extravascular infusion of bupivacaine for prolonged pain relief. Pain 11: S251(1981).

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3. Jackson,PR, Tucker, GT, Woods HF: Plasma binding of drugs in patients with cancer. British Journal of Clinical Pharmacology, volume 70, 41-42, 1981.