Title: THE RELATIONSHIP BETWEEN FREE BUPIVACAINE CONCENTRATION AND CENTRAL NERVOUS SYSTEM TOXICITY

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Introduction. Toxicity studies with bupivacaine have attempted to relate total serum concentrations with central nervous system (CNS) toxicity (1,2). No data are available which relate the (pharmacologically active) free bupivacaine concentration with toxicity. This study was undertaken to assess the relationship between free bupivacaine concentrations and signs of CNS toxicity.

Methods. Committee on Human Research approval for analysis and comparison of these data was not required since all samples were obtained for therapeutic monitoring over the past 18 months. Venous blood samples were drawn from patients treated with continuous perineural infusion of bupivacaine for pain relief due to trauma, cancer or surgery. If the serum concentration was > 3 μg/ml and the patient was asymptomatic, the patient was put in Group I. If the patient had suspicion of CNS toxicity secondary to bupivacaine administration, the patient was put in Group II. Patients experiencing one or more of the following were classified as demonstrating positive signs of CNS toxicity: tinnitus, metallic taste, circumoral numbness, dizziness, mild tremors, confusion, loss of consciousness.

Serum, obtained by allowing the blood to clot followed by centrifugation, was assayed for both total and free bupivacaine levels. Total bupivacaine concentrations were determined by analyzing the serum prior to ultrafiltration by gas chromatography. Free bupivacaine concentrations were determined using a micro-ultrafiltration apparatus equipped with a YMT ultrafiltration membrane (Amicon). Preliminary studies have demonstrated that nonspecific adsorption of bupivacaine to the YMT membrane does not occur. An adjustment of the serum to pH 7.4 was accomplished just prior to ultrafiltration. Following centrifugation, the ultrafiltrate was removed and assayed for free bupivacaine by gas chromatography. α_1-acid glycoprotein (AAGP) was deterined using radial immunodiffusion. Since data were normally distributed (as determined by a Shapiro-Wilk W statistic), comparisons of free and total bupivacaine concentrations between the asymptomatic and symptomatic groups were accomplished using a t test for independent means. $p < 0.05$ was considered the minimum level of significance.

Results. Table 1 is a summary of total and free bupivacaine concentrations for both groups. Eleven patients formed Group I, whose total serum concentrations were higher than 3 μg/ml. Seven patients fromed Group II, who had some evidence of CNS toxicity, irrespective of total serum concentration.

The total concentrations measured for Group II were not significantly different from those measured for Group I. However, the free bupivacaine concentrations measured for Group II were significantly higher than those for Group I ($p < 0.001$). Elevated AAGP levels were found in all of Group I, as well as in patients 2, 4, 5 and 7 from Group II. Patients 1 and 3 from Group II had low-normal AAGP (50 mg/dl). AAGP levels were not determined for patient 6 of Group II.

Table 1. A comparison of total and free bupivacaine in asymptomatic patients and patients with symptoms of CNS toxicity.

	Group I Asymptomatic		Group II Symptomatic	
Pt. No.	Bupivacaine (μg/ml) Total	Free	Bupivacaine (μg/ml) Total	Free
1	5.30	0.09	2.10	0.25
2	4.50	0.19	6.33	0.34
3	4.30	0.18	1.50	0.20
4	4.90	0.18	10.00	0.54
5	4.30	0.16	7.10	0.33
6	6.60	0.25	1.00	0.40
7	6.15	0.12	5.92	0.40
8	4.50	0.10		
9	4.53	0.15		
10	4.28	0.04		
11	3.64	0.14		
Mean	4.82	0.15	4.85	0.35[a]
SD	±0.88	±0.06	±3.38	±0.11

a. $p < 0.001$ when compared to free concentrations in the asymptomatic group.

Discussion. Based on previous reports (1,2), the total bupivacaine concentrations found in all patients in Group I, as well as patients 2, 4, 5 and 7 from Group II, should have been associated with signs of CNS toxicity. Using similar criteria, patients 1, 3 and 6 from Group II would not have been expected to exhibit CNS toxicity symptoms. The data reported here suggest the free bupivacaine threshold for CNS toxicity is 0.24 μg/ml (X-1SD). This would correspond to a total bupivacaine concentration of 3.1 μg/ml in a patient with normal AAGP and albumin. This value is in agreement with published toxicity values (1,2). However, in patients requiring single or continuous regional anesthetic techniques, abnormal levels of AAGP and/or albumin will often be found. This study demonstrates the protective effect of elevated AAGP, as well as the need for measuring free concentrations for both predicting and verifying CNS toxicity attributable to bupivacaine.

References

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