Title: DIFFERENTIAL POTENCIES OF BUPIVACAINE AND ETIDOCAINE ASSESSED BY EQUILIBRIUM AND USE-DEPENDENT BLOCK IN SINGLE AXONS OF VARIOUS TYPES

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Introduction. Previous work with lidocaine on single mammalian axons has revealed a greater sensitivity of myelinated (M) than unmyelinated (U) fibers to equilibrium conduction block, and a greater tendency of U axons to use-dependent (frequency-dependent) conduction block.[1] The present study reveals subtle but potentially clinically significant differences in the corresponding effects of bupivacaine (bup.), and also presents a comparison with etidocaine (etid.).

Methods. The experimental system consisted of a trough with two separately perfused compartments. One contained the desheathed vagus nerve and monopolar stimulating electrodes; the other, either the attached nodose ganglion and extracellular recording microelectrode or a dissected nerve filament on a recording Pt wire. In two additional series of experiments the preparation consisted of the cervical sympathetic or the recurrent laryngeal nerve. The recording compartment was perfused throughout with control Ringer's at 37°C and pH 7.35, buffered with sodium bicarbonate and containing glucose 20 mM (90 mg dl^{-1}; RBG solution) and equilibrated with 5% CO_2-95% O_2; U units were distinguished from M by the control conduction velocity, CV. The distal 20 mm of nerve in the stimulating compartment was perfused for 30-60 minutes with control perfusate, followed by equilibration to constant conduction latency or block, with solution containing added local anesthetic. Only one drug and two concentrations were tested per nerve, using single supramaximal stimuli or shock trains at 10, 20, 40 Hz for U units, and 10, 20, 40, 80, 160 Hz for M.

Results. The anesthetic concentrations tested and the associated incidence of equilibrium block in vagus axons are shown in Table 1. For M axons, the ED_{50} of bup. was between 100 and 150 μM, and the ED_{50} of etid. between 80 and 100 μM; by this criterion etid. was slightly more potent than bup. For comparison, the ED_{50} of lidocaine is about 600 μM. In additional measurements on 26 recurrent laryngeal M axons, the ED_{50} equilibrium blocking concentration of bup. lay between 50 and 100 μM. For vagus U the ED_{50} was smaller than for the M in the case of bup., but larger than for M in the case of etid. (and lidocaine). For sympathetic M axons (N = 10, one per nerve) the ED_{50} of equilibrium block, determined only for bup., was between 25 and 50 μM, i.e. lower than for vagus M.

Use-dependent block (UDB) was tested on nerves in equilibrium with concentrations of bup. and etid. below the equilibrium ED_{50}. With bup. 25 μM, the sympathetic M axons showed UDB at much lower frequencies than vagus M axons (Fig. 1), corresponding to the lower equilibrium ED_{50} of the sympathetics. Vagus M axons showed less UDB with 50 μM etid. than with 50 mM bup. at all stimulation frequencies below 160 Hz, in accordance with the slightly higher equilibrium ED_{50} of etid.; most did not show any UDB at all at frequencies below 80 Hz with etid. At 10 Hz, 75% of bup.-treated U axons (N = 12) but none of the etid. treated U axons (N = 10) exhibited UDB; all U axons showed UDB at 40 Hz.

Discussion. A new and clinically interesting result was that, with bup., ED_{50} for equilibrium block of U axons was lower than for M axons, unlike lidocaine or etid., with which the reverse was true. Sympathetic M axons were more sensitive than other M axons (vagus afferent or recurrent laryngeal efferent) to bup., both as regards equilibrium ED_{50} and UDB; in the clinical setting, where the sympathetic preganglionic myelinated axons carry tonic vasoconstrictor traffic, both factors probably contribute to the higher level of sympathetic than somatic block seen with bup. spinal anesthesia. The equilibrium ED_{50} and UDB data for bup. and etid. confirmed that equilibrium and UDB block of M axons is not a function of conduction velocity (i.e. not a function of axonal diameter),[1] agreeing with previous data for lidocaine.[1] (Supported by USPHS grant GM 31710)

Reference.

1. Fink BR, Cairns AM: Differential use-dependent (frequency-dependent) effects in single mammalian axons: Data and clinical considerations. Anesthesiology 67:477-484, 1987.

Table. Equilibrium block in vagus units

Conc. (μM)	Block incidence M	Block incidence U	% blocked M	% blocked U	No. of nerves
		Bupivacaine			
25	0 /21	0 /19	0	0	8
50	4 /21	2 /19	19	11	11
100	12 /25	13 /19	49	68	4
150	19 /19	16 /17	100	94	2
		Etidocaine			
50	1 /19	1 /16	5	6	10
80	17 /38		45		2
100	13 /16	2 /19	81	11	9
150	26 /30		87		2
200	25 /25	29 /30	100	97	2

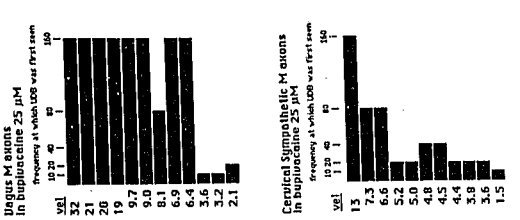

Fig. 1. Lowest stimulation frequency producing UDB in vagus and sympathetic M axons (CV of axon in m/s is shown at foot of bars).