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More on Benzocaine and Methemoglobinemia

To the Editor:—Severinghaus and colleagues make a valid point about the relationship between benzocaine and methemoglobinemia.¹ The replies of Beutlich² and Wachman³ are puzzling, because the efficacy or safety of topical benzocaine is not being called into question. There is, however, sufficient evidence to make a strong argument for a dose-dependent relationship between benzocaine and methemoglobinemia. This first came to my attention in 1989 and is exemplified by the case that I reported to the Food and Drug Administration and is referred to by Severinghaus *et al.* in their letter.¹

In reference to the 1979 Food and Drug Administration panel on this subject,* the findings of the panel convened in 1979 may not be valid in 1991 and deserve reassessment. Only 13 of the 50 references provided by Severinghaus *et al.*¹ are from articles appearing in the literature prior to 1979. It is in the best interests of our patients that users of benzocaine be educated so that they can be vigilant to the possibility of methemoglobinemia and be prepared to treat it. This is neither an indictment of benzocaine nor a suggestion that it be condemned or removed from products that contain it, as Wachman's³ letter implies; rather, it is a plea for the dissemination of knowledge

about the drug so that it may be used intelligently and safely and thereby continue to enjoy an admirable record of safety and efficacy.

I wholeheartedly support the recommendations of Severinghaus and colleagues.¹

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Site of Hemodynamic Effects of α_2 -Adrenergic Agonists

To the Editor:—Eisenach *et al.*¹ recently demonstrated the thoracic spinal cord to be the site of hemodynamic effects of intrathecal α_2 -adrenergic agonists.

Our clinical experience with epidural clonidine partially confirms their conclusions.

With institutional approval and informed consent, 20 patients were prospectively studied to establish the intraoperative analgesic potency of epidural clonidine. Before induction of anesthesia, all of the patients had a catheter inserted 4 cm in their epidural space. The site of puncture was in accordance with the surgical procedure (esophagectomy, n = 7;

TABLE 1. Site of Catheter Puncture, Hemodynamic Data, and Duration of Analgesia

Level		n = 15	Mean Arterial Blood Pressure		%	Vasopressor (n)	Heart Rate		%	Duration of Analgesia (h)
			A	B			A	B		
T4-T5	Mean	3	88.6	54.0	-40	3	88	58	-34	4.2
	SD		2.4	1.4			10	2		1.3
T5-T6	Mean	2	78.5	48.0	-39	2	85	65	-24	3.2
	SD		1.5	5.0			5	5		3.0
T6-T7	Mean	2	82.5	50.5	-40	2	85	59	-31	3.0
	SD		7.5	0.5			5	11		
T7-T8		1	93.0	70.0	-25	0	80	60	-25	3.6
T8-T9		1	93.0	80.0	-14	0	60	50	-17	5.0
T9-T10		1	70.0	57.0	-19	0	100	60	-40	4.0
T11-T12	Mean	5	73.0	67.3	-8	0	85	64	-25	3.3
	SD		5.3	4.5			11	6		0.8
L2-L4	Mean	5	77.8	70.0	-9	0	82	62	-24	3.4
	SD		6.3	4.2			7	5		0.6

A = preinjection value; B = lowest value at 30 min; vasopressor = number of patients requiring vasopressive therapy.

gastrectomy, $n = 4$; pancreatectomy, $n = 4$; or lower abdominal procedure, $n = 5$). Catheter tip location was tested with a solution (3 ml) of local anesthetic and epinephrine 1/200,000. General anesthesia was induced with alfentanil, propofol, and pancuronium and maintained with isoflurane.

At least 1 h after test-dose injection and before surgical stimulation, a dose of 8 $\mu\text{g/kg}$ clonidine was injected epidurally.

The site of catheter puncture, allocation of the patients, hemodynamic data, duration of operative analgesia are summarized in table 1.

In this limited clinical study, the hemodynamic data support the hypothesis of increased cardiovascular depression with upper thoracic injection of epidural clonidine. Although no patient suffered undesirable long term consequences from this dosage regimen and despite the excellent quality of surgical analgesia obtained, we elected to interrupt this clinical trial because of the magnitude of the hypotensive episodes encountered.

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Halothane Inhibits Residual Fast Sodium Channels in Human Atrial Muscle

To the Editor:—In isolated human atrial tissue, both isoflurane and halothane may depress electromechanical activity through a reduction of Ca^{2+} influx across the cell membrane.¹ However, halothane also reduces the fast Na^+ current in voltage-clamped rat myocardial cells.² In the present experiments, we used both conventional and ion-selective microelectrode techniques to investigate in human atrial tissue whether halothane reduces intracellular sodium activity (a_{Na}^i), as it would be expected from a decreased Na^+ influx. We studied partially depolarized atrial specimens obtained from two patients (61- and 64-yr-old men) during corrective cardiac surgery for coronary artery disease. Informed consent was obtained before surgery.

Trabeculae from these specimens were perfused in a tissue bath with oxygenated (97% O_2 , 3% CO_2) Tyrode solution at 37° C and driven electrically at 1 Hz, as described in detail previously.¹ Figure 1 shows a recording in normal $[\text{K}]_o$ (4 mM) Tyrode solution. In figure 1A (control), the action potentials show a reduced maximum diastolic potential (MDP; -78 mV) and a plateau beginning near -20 mV. The maximal rate of rise (\dot{V}_{max}) was about 75 V/s, and a_{Na}^i was normal (7.38 mM). In figure 1B, exposure to 0.5 vol% of halothane within 10 min decreased \dot{V}_{max} and the upstroke amplitude by 23 and 10%, respectively. Halothane also slowed phase-3 repolarization, reduced MDP to -73 mV, and reduced a_{Na}^i from 7.38 to 5.56 mM (-24.7%).

In the other atrial preparation, perfused in 8 mM $[\text{K}]_o$ Tyrode solution containing 0.3 μM epinephrine, MDP was -67 mV and \dot{V}_{max} was about 105 V/s. Halothane (0.5 vol%) decreased \dot{V}_{max} and the amplitude of upstroke by -72 and -32% , respectively, and reduced a_{Na}^i from 3.50 to 2.64 mM (-24.6%) within 6 min. Both preparations recovered from halothane effects within 14 min of washout.

In a previous study in six well polarized human atrial preparations (average MDP = -85 mV),¹ halothane at concentrations up to 0.75 vol% did not change significantly the upstroke. In this connection, it should be noted that 1 μM tetrodotoxin (which selectively blocks the fast Na^+ channel) barely affects \dot{V}_{max} (as for halothane in well-polarized tissue), although it depresses the plateau and reduces the action potential

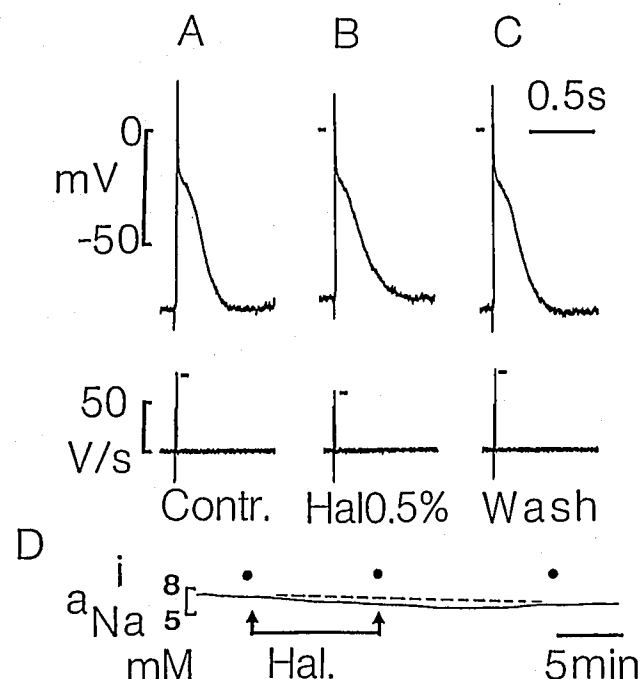


FIG. 1. Halothane decreases intracellular Na^+ activity. (a_{Na}^i) Top: The action potential (upper traces) and first derivatives (lower traces) before (A), during the 10th min of exposure to halothane (B) and after 14 min of recovery (C). In the top panel, the small horizontal bars indicate either the zero potential (upper traces) or the \dot{V}_{max} (lower traces). D: A continuous slow speed chart record of a_{Na}^i . The dots above the trace in D indicate the time at which the fast speed traces shown in A-C were recorded.