on postoperative days 1 and 2 for patients in both groups. This has been demonstrated previously in morbidly obese patients following abdominal incisions.[12,13] In these studies the fall in Pa_{O_2} was greatest on the second postoperative day and began to return towards the preoperative "normal" value on postoperative day 3.[12, 13] After thoracic surgery in morbidly obese patients, a similar depression in respiratory status occurred on the first and second postoperative days (tables 2 and 3). The respiratory variables we studied (PFT and ABGs) were similar for patients in both our groups. However since we did not follow our patients' pulmonary status after postoperative day 2, we do not know if there was a difference between groups thereafter. The average postoperative hospital stay was identical for both groups (8 days). We conclude that morbidly obese patients can tolerate one-lung anesthesia for transthoracic gastric stapling surgery with comparable safety to the abdominal approach.

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Precipitation of Local Anesthetic Drugs in Cerebrospinal Fluid

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Bupivacaine, etidocaine, mepivacaine, and tetracaine solutions have been stated to precipitate in CSF (cerebrospinal fluid).[1] This conclusion was based on an *in vitro* aerobic study, in which human CSF was frozen, reconstituted at a later date, mixed with solutions of the local anesthetic drugs, and titrated to the *p*H of CSF. The authors cautioned that injection of these drugs into the subarachnoid space might cause spinal cord damage.[1] Also, when CSF is added to solutions of tetracaine or its lyophilized (Niphanoid, crystalline) form, turbidity may occur, depending on the *p*H of the CSF, the temperature, the amount of the drugs, the diluent employed, and the duration of its exposure to air.[2] Likewise, when solutions of dibucaine are mixed with CSF in a syringe without the addition of glucose, a precipitate results.[3] Finally, Scott *et al.*[4] believe that precipitation of an etidocaine solution when combined with CSF is not unique to that drug, and that it occurs with solutions of bupivacaine and tetracaine.

In 40 years of performing spinal anesthesia with solutions of all of these drugs except etidocaine, this author has yet to observe precipitation when aspirating CSF into the syringe containing these local anesthetics. Therefore, this investigation was undertaken to determine which formulations of the local anesthetic drugs precipitate when combined with CSF under anaerobic conditions such as exist in the subarachnoid space.

Method

The withdrawal of CSF when performing spinal anesthesia for a surgical procedure received approval of the Human Rights Committee of The Virgina Mason Medical Center, provided that the patient gave verbal consent. A total of 93 patients were studied.

The single-dose ampules or vials of the commonly used

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local anesthetic drugs for epidural and spinal anesthesia, as well as for peripheral nerve block with and without epinephrine, were interfaced with CSF (N = 1 for each ampule or vial, that is, 83 patients, tables 1, 2, and 3). The epinephrine content of the epidural and peripheral nerve block solutions was 1:200,000 (either commercially prepared or added by author, tables 1 and 2), and 0.2 mg of epinephrine was added to the spinal anesthetic drugs (table 3). CSF was withdrawn into either a plastic or a glass syringe and immediately mixed with the local anesthetic drug in a sterile 7.5-ml vacuum test tube containing no additives. In all instances the amount of the local anesthetic solution and the CSF totaled 7.5 ml so that the vacuum tubes were filled completely, thereby hopefully maintaining anaerobic conditions and the *p*H of CSF.

For the solutions used for epidural and peripheral nerve block, 2.5 ml of each was mixed with 5 ml of CSF (table 1). These test tubes were visually inspected immediately after mixing, at three hours, and daily for one week, at which time they were opened and the *p*Hs determined. Then 4 ml of only the strongest concentration of each drug was mixed with 3.5 ml of CSF, because precipitation might be more likely with strong concentrations than with weaker ones (table 2). These test tubes were observed for 15 minutes and their *p*H determined. Another group of identical samples were stored for 24 hours, at which time they were observed and their *p*H determined.

For the drugs used for spinal anesthesia (with the exception of dibucaine 1:1500 [0.667 mg/ml]), the maximum recommended dose, 2 ml, was mixed with 5.5 ml of CSF (table 3).[2,5] For dibucaine, 4 ml of 1:1500 (2.668 mg) was added to 3.5 ml of CSF so as to approximate as closely as possible its maximum dose, 20 ml (13 mg), being injected into the 20 ml of CSF (approximate) contained in the lower thoracic and lumbar subarachnoid space. These test tubes were observed for 15 minutes,

TABLE 1. *p*H of Solutions of Local Anesthetic Drugs Used for Epidural and Peripheral Nerve Block Alone and Seven Days after Being Mixed with CSF

	Single-dose Ampules or Vials Prior to Mixing with CSF[5]	2.5 ml Local Anesthetic Solution in 5 ml of CSF Seven Days after Mixing
Bupivacaine (0.25, 0.5, and 0.75 per cent)		
Plain	5.37–5.75	6.90–7.23
Epinephrine		
By author*	5.31–5.68	7.06–7.22
Commercial	3.80–3.85	6.52–6.62
Chloroprocaine (2 and 3 per cent, CE)		
Plain	2.83–2.96	5.53–5.89
Epinephrine		
By author*	2.87–2.97	5.82–5.93
Etidocaine (0.5, 1.0, and 2 per cent)		
Plain	4.40–4.51	6.49–6.90
Epinephrine		
By author*	4.40–4.48	6.48–6.65
Commercial	3.58–3.91	6.13–6.23
Lidocaine (1.0, 1.5, and 2 per cent)		
Plain	6.19–6.38	6.80–6.84
Epinephrine		
By author*	6.22–6.41	6.77–6.86
Commercial	3.75–4.17	6.32–6.40
Mepivacaine (1.0, 1.5, and 2 per cent)		
Plain	5.14–5.56	6.74–6.84
Epinephrine		
By author*	5.14–5.56	6.74–6.85
Prilocaine (1.0, 2, and 3 per cent)		
Plain	6.36–6.52	6.71–6.94
Epinephrine		
By author*	6.36–6.54	6.69–6.92

* Epinephrine added by author.

TABLE 2. *p*H of 4 ml of the Strongest Available Concentrations of Local Anesthetic Drugs Used for Epidural Block at 15 Minutes and 24 Hours after Mixing with 3.5 ml of CSF

	15 Minutes	24 Hours
Bupivacaine (0.75 per cent)		
Plain	6.97	6.99
Epinephrine		
By author*	6.80	7.07
Commercial	5.92	6.09
Chloroprocaine (3 per cent CE)		
Plain	6.19	5.96
Epinephrine		
By author*	6.17	5.95
Etidocaine		
Plain (1.0 per cent)	6.39	6.00
Epinephrine		
By author*	6.03	5.98
Commercial (1.5 per cent)†	5.49	5.67
Lidocaine (2 per cent)		
Plain	6.57	6.80
Epinephrine		
By author*	6.56	6.62
Commercial	5.95	5.78
Mepivacaine (2 per cent)		
Plain	6.45	6.32
Epinephrine		
By author*	6.46	6.31
Prilocaine (3 per cent)		
Plain	6.50	6.63
Epinephrine		
By author*	6.47	6.51

* Epinephrine added by author.

† Etidocaine 1.5 per cent is available only with 1:200,000 epinephrine.

TABLE 3. *p*H of Solutions Seven Days after Local Anesthetic Drugs Used for Spinal Anesthesia Were Mixed with CSF

	Mg of Local Anesthetic Drug Added to CSF					
	2.668 in 4 ml of 0.5 Per Cent Sodium Chloride	5 in 2 ml of 5 Per Cent Dextrose	10 in 2 ml of Additives†	20 in 2 ml of 5 Per Cent Dextrose	15 in 2 ml of 8.25 Per Cent Dextrose	100 in 2 ml of 7.25 Per Cent Dextrose
Bupivacaine						
Plain					6.95	
Epinephrine*					6.93	
Dibucaine						
Plain	7.17	7.13	6.64			
Epinephrine*	7.08	7.21	6.60			
Lidocaine						
Plain						6.63
Epinephrine*						6.65
Tetracaine						
Plain				6.73		
Epinephrine*				6.64		

* Amount of epinephrine added to the local anesthetic drug was 0.2 mg.

† Additives/ml: 5 mg sodium chloride, 2 mg sodium phosphate monobasic, 0.45 mg sodium phosphate dibasic and water.

at three hours, and daily for seven days, at which time their *p*Hs were determined.

In the remaining 10 patients 7.5 ml of CSF was withdrawn and immediately placed in the 7.5-ml vacuum test tubes. Five of the tubes, which were placed in the axilla of the author and presumed to be at body temperature, were observed for 15 minutes, and the others were observed daily for one week. At the end of each observation period their *p*Hs were determined.

The *p*Hs of the solutions were determined using the Beckman Model 3560® digital *p*H meter. With the exception of the five test tubes of CSF held in the author's axilla, these determinations were made at room temperature.

RESULTS

Only the test tubes with etidocaine contained a precipitate. A 2.5-ml dose of plain solutions of 0.5 per cent and 1.0 per cent, as well as those to which the author added epinephrine (*p*H range 4.4–4.48, table 1), became turbid immediately on contact with CSF (fig. 1). Similar doses of commercially prepared solution containing epinephrine and 1 mg/ml sodium metabisulfite as a stabilizer (*p*H range 3.58–3.91, table 1) initially did not become cloudy (fig. 1). However, after three hours had elapsed from the time of withdrawal, they started to become turbid (fig. 2). The next day the solutions of etidocaine had cleared, and crystals of it were easily visible either at the bottoms of the test tubes or adhering to their walls (fig. 3). They remained so until discarded. The precipitate was separated by filtration and dissolved in 0.1 M hydrochloric acid; gas chromatography identified it to be etidocaine. When 4 ml of the strongest available concentration of etidocaine (1.5 per cent with 1:200,000 epinephrine) was mixed with 3.5 ml of CSF, no precipitation resulted in 15 minutes, and after 24 hours only a slight precipitate (two to three crystals) could be seen at the bottom of the test tube.

The *p*Hs of the solutions in the test tubes containing the local anesthetic drugs ranged between 5.53 and 7.23 (tables 1, 2, and 3). The *p*H of CSF which was not mixed with a local anesthetic drug ranged from 7.33 to 7.35 after 15 minutes, and after one week from 7.13 to 7.34.

Mixing commercially prepared solutions of local anesthetic drugs containing epinephrine with CSF increased the drug's previously determined *p*H (tables 1 and 2).[5] Conversely, the *p*H of CSF was lowered. Previously this finding was shown to occur *in vivo* with bupivacaine.[6]

DISCUSSION

While tetracaine is available either as a solution or in a lyophilized form, all other commonly used local anesthetic drugs for regional block are available only as solutions. If lyophilized tetracaine is dissolved in CSF, a turbid solution results. Conversely, turbidity is avoided if, prior to mixing with CSF, it is dissolved in 10 per cent dextrose, sterile water, or a combination of these.

Precipitation of a local anesthetic drug from solution when it is mixed with CSF is related to its insolubility at a *p*H of 7.4. All of these drugs will precipitate when their solutions are titrated with sodium hydroxide at or near a *p*H of 7.4. However, this study and others have

shown that the usual pH of human CSF when determined immediately after withdrawal from the subarachnoid space is 7.31 ± 0.027.[7,8] At or below that pH only etidocaine precipitated when mixed with CSF under anaerobic conditions (tables 1, 2, and 3).

The 4-ml dose of the highest concentration of the drugs commonly administered for epidural block mixed with 3.5 ml of CSF did not precipitate with the exception of etidocaine (1.0 per cent). Therefore, precipitation should not result, even when equal parts of CSF and the local anesthetic drug mix as may occur if 20 to 30 ml are unintentionally injected into the subarachnoid space rather than the epidural space. However, when etidocaine contains 1 mg/ml metabisulfite as a stabilizer, as does its commercial preparation with 1:200,000 epinephrine, precipitation is delayed. Perhaps the stabilizer inhibits precipitation. If it does, evidently the higher its ratio to the CSF, the less likely is precipitation, as occurred when 4 ml of etidocaine was mixed with 3.5 ml of CSF, as compared with 2.5 ml of etidocaine mixed with 5 ml of CSF. But, should drugs with additives be used for regional blocks, particularly where unintentional subarachnoid injection is a known possibility? Both methylparaben and sodium bisulfite have been shown to be tissue irritants.[5,9] Finally, the rapid rise in pH of chloroprocaine and other commercially prepared

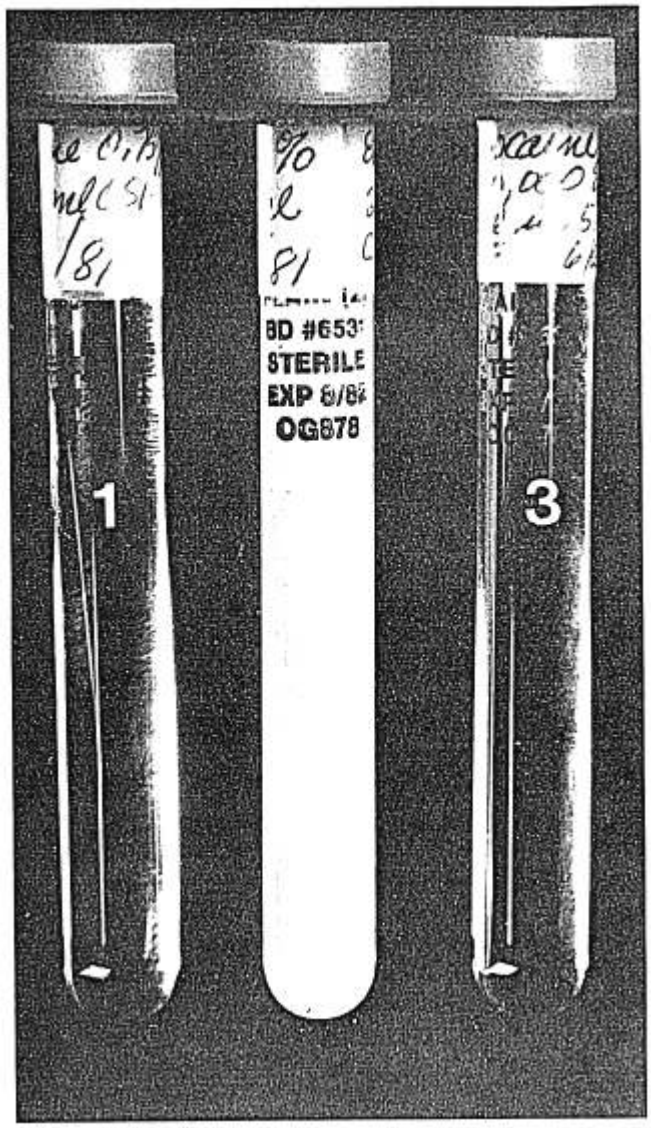

FIG. 1. Solutions on immediate contact with CSF. (Tube 1) 0.75 per cent bupivacaine; (Tube 2) 1.0 per cent etidocaine; and (Tube 3) 1.5 per cent etidocaine with 1:200,000 epinephrine (commercially prepared).

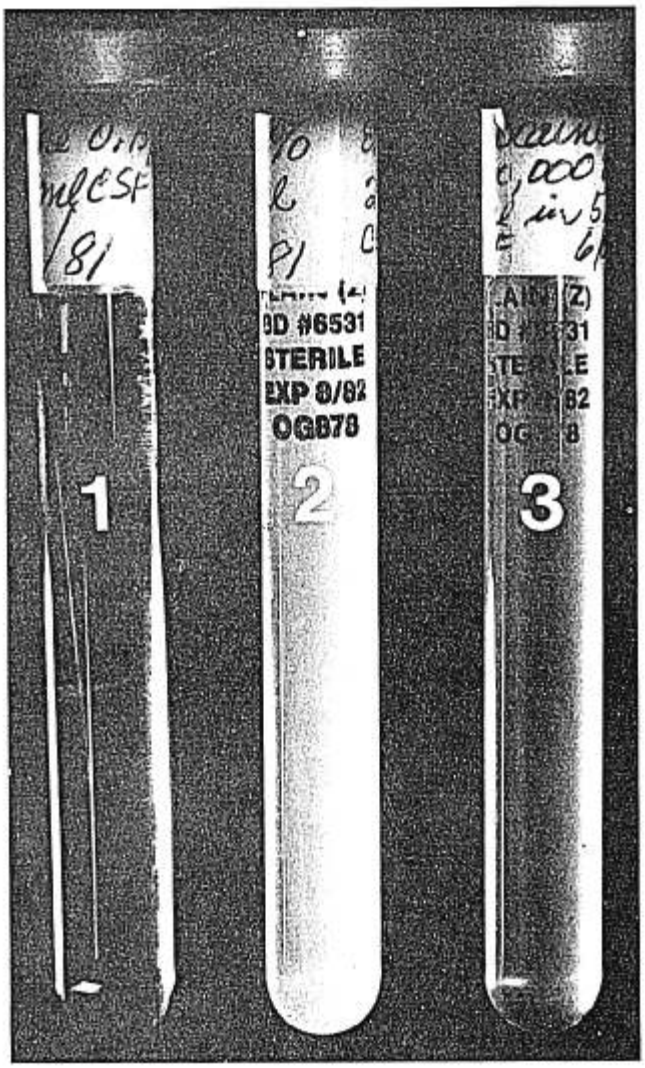

FIG. 2. Same test tubes as in figure 1, but three hours later. No change has occurred in bupivacaine. The etidocaine suspension in test tube 2 is starting to settle, and the etidocaine in test tube 3 is starting to precipitate.

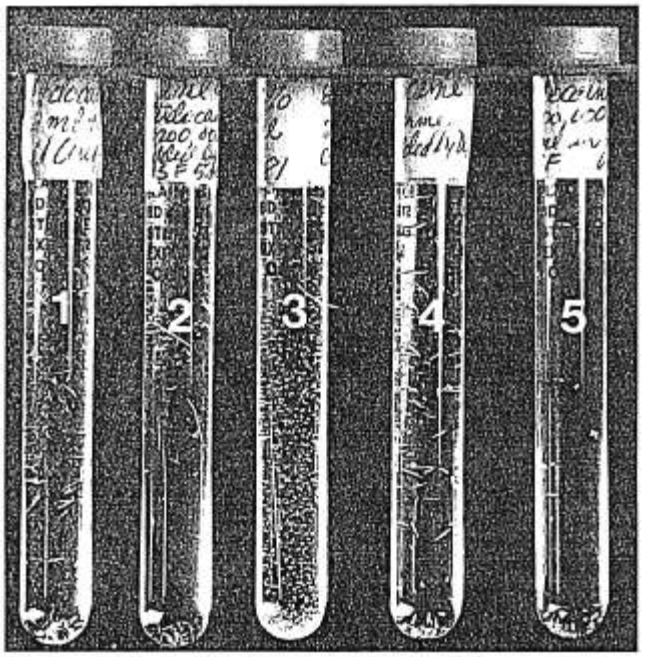

FIG. 3. All five test tubes contain etidocaine 24 hours after withdrawal of CSF. Test tubes contain the following: (Tube 1) 0.5 per cent; (Tube 2) 0.5 per cent with 1:200,000 epinephrine added by author; (Tube 3) 1.0 per cent; (Tube 4) 1.0 per cent with 1:200,000 epinephrine added by author; (Tube 5) 1.5 per cent with epinephrine 1:200,000 commercially prepared.

solutions with epinephrine when mixed with CSF would seem to indicate that low *p*H of the local anesthetic solutions is not, as previously proposed for chloroprocaine, primarily responsible for neuropathy following unintentional subarachnoid injection of a local anesthetic drug.[10–12]

Whether the precipitation of etidocaine in CSF is of significance should unintentional subarachnoid injection occur during an attempted regional block, is unknown. Rabbits injected subarachnoidally with solutions of etidocaine and tetracaine, and sheep injected subarachnoidally with etidocaine showed no morphologic changes in the spinal cord or its roots in gross and microscopic examination.[13,14] Conversely, two unexpectedly prolonged durations of analgesia (26 and 30 h) without sequelae have occurred following epidural block with 1.0 per cent etidocaine.[15]

To conclude, under anaerobic conditions of this study, which simulated closely the interfacing of local anesthetic solutions with human CSF, the following resulted: (1) only etidocaine precipitated; (2) solutions of etidocaine containing a stabilizer did not immediately precipitate; (3) the *p*H of CSF was lowered by the addition of local anesthetic drugs; (4) conversely, the *p*H of the local anesthetic drug was raised by the CSF; and (5) the significance, it any, of etidocaine precipitating in human CSF is not known.

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