patients had multiple sclerosis. However, only in 2 of these 19 patients did the complications involve aggrevation of the symptoms of multiple sclerosis.[9]

Although exposure to almost all the anesthetics we use in general anesthesia have been implicated in aggrevating or causing the new onset of symptoms of multiple sclerosis, including such agents as meperidine and fentanyl, these drugs are not neurotoxic, even when given intrathecally.[10] Morphine has not aggravated multiple sclerosis.* It would, therefore, be the agent of choice for intrathecal administration.

We used hyperbaric spinal anesthesia, using a relatively low dose of tetracaine without the addition of epinephrine. The duration of the spinal anesthesia was not prolonged. The addition of general anesthesia in a spontaneously breathing patient did not prolong the duration of the spinal anesthetic. No untoward effects on the patient's condition were noted.

This case also appears to be the first reported use of intrathecal morphine in a patient with multiple sclerosis. The effectiveness of intrathecal morphine for postoperative pain control cannot be evaluated from this case, since postoperative pain in this surgical procedure is not a major therapeutic problem. However, intrathecal morphine did not appear to alter the time course of the spinal or general anesthetic in this patient, nor were any of the known side effects of intrathecal morphine exaggerated in this patient with multiple sclerosis. Only mild pruritis was noted. The bladder was catheterized for the first 24 h, and so urinary retention was not a problem that could be evaluated.

Regardless of the drugs or technique selected for use in anesthesia in patients with multiple sclerosis, postoperative exacerbation of symptoms of this disease remain a significant risk, especially if fever develops. Certainly, the changing neurologic picture in patients with multiple sclerosis must be appreciated when considering the selection of regional anesthesia. The data implicating regional anesthesia in the aggrevation of multiple sclerosis is based on relatively few reported cases. While our case represents only a single case report, it does demonstrate that a combination of spinal and general anesthesia may be appropriate, and can be administered safely to a patient with long-standing but relatively stable multiple sclerosis. In addition, if regional anesthesia is selected, the addition of intrathecal morphine does not increase risk.

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Premedication Abolishes the Increase in Plasma Beta-endorphin Observed in the Immediate Preoperative Period

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Beta-endorphin (B-END) and adrenocorticotropic hormone (ACTH) are released into the circulation from the pituitary gland in response to various stressful stimuli, including surgery, in experimental animals and humans.[1–7] Increased levels of plasma B-END[5,6] and ACTH[7] have been observed in non-premedicated patients before

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and during surgery. These studies demonstrate a direct correlation between stress and B-END and ACTH plasma levels.[1-7] Pharmacological attempts to relieve preoperative stress and anxiety have been shown to be beneficial for patients undergoing surgery.[8-12] The most commonly used drugs to achieve preoperative sedation are narcotics, barbiturates, benzodiazepines, anticholinergics, and antihistamines.[8-12] These studies have used questionnaires and the observers assessments to evaluate the effect of such premedication.[8-12] The present report describes the effects of premedication on the plasma levels of ACTH and B-END during the presurgical period. While untreated and placebo groups showed significantly higher levels of B-END when compared with normal controls, premedication with diazepam, meperidine, or diphenhydramine abolished such an increase.

Materials and Methods

After approval by the New York University Institutional Board of Research Associates, and the Bellevue Hospital Center Human Subjects Review Committee, informed consent was obtained from patients prior to participation. All subjects (n=63) were ASA physical class I or II, taking no medications (other than antibiotics) for at least 2 weeks prior to surgery, and with no history of recent or current pain. Patients were informed that, prior to surgery, they could receive either no premedication, an oral (po) or intramuscular (im) placebo, or a po or im drug. At about 4:00 P.M. of the day prior to surgery, 10 ml of venous blood was drawn into a glass tube containing 0.1 ml of a 15% EDTA solution, then stored at 4° C until centrifugation (within 1 h). Plasma was then removed and stored in siliconized tubes at −30° C until assay. A second blood specimen, handled in an identical manner, was obtained upon the patient's arrival in the OR (8:00 A.M.). Specimens were similarly obtained from ten healthy volunteers (at 4:00 P.M. and 8:00 A.M.) not undergoing surgery, to serve as a control group. Samples were coded to prevent bias during performance of the assays.

Patients were randomly assigned to receive no premedication, a placebo (saline) injection, diazepam 10 mg po, meperidine 1 mg/kg im, or diphenhydramine 1 mg/kg im, 1 h prior to surgery, without knowing which substance had been given. The premedication was revealed to the anesthetist only after the second blood specimen had been obtained.

ACTH Radioimmunoassay. After thawing, 100 μl of plasma (or standard, supplied by Immuno Nuclear Corp., Stillwater, MN) were combined with rabbit anti-ACTH serum and ^{125}I-ACTH, and incubated for 20 h at 6° C. Goat anti-rabbit precipitating complex (normal rabbit serum, pre-precipitated with goat anti-rabbit serum) was then added to separate bound from free tracer. The mixture was incubated (25° C, 20 min), centrifuged (760 g, 20 min), and the precipitate subjected to gamma-scintillation counting.[13]

B-END Radioimmunoassay. Plasma (1.0 ml) was exposed to Sepharose anti-B-END particles, with rotation for 4 h at 6° C. Plasma was discarded, and the sepharose rinsed three times with 0.9% sodium chloride. B-END was eluted from the Sepharose column with 0.025 N HCL, mixed with buffer and rabbit anti-B-END antibody, and incubated for 20 h at 6° C. Goat anti-rabbit precipitating complex (see above) was then added, incubated (25° C, 20 min), centrifuged (760 g, 20 min), and the precipitate subjected to gamma scintillation counting.[14]

Statistical Analysis

Data were grouped according to the samples taken ("4:00 P.M." or "8:00 A.M."), and each group was further subdivided according to the type of premedication. Analysis of variance (ANOVA) was applied to four categories: ACTH (4:00 P.M.), ACTH (8:00 A.M.), B-END (4:00 P.M.), and B-END (8:00 A.M.). Each category consists of all the premedication groups. Dunnett's test was applied comparing the control group to all the others using the same categories as with ANOVA. In addition, the Dunnett's test was performed on the B-END (8:00 A.M.) category comparing the no-premedication group to the placebo and the three-drug groups. Finally, a paired t test was applied to the 4:00 P.M. and 8:00 A.M. groups of each premedication group to determine differences in sample times. Statistical significance was assumed at the $P = 0.05$ level.

Results

Results are summarized in table 1. All groups were similar in their distributions of sex, age, weight, and surgical procedures.

There was no difference between the ACTH values of the premedication groups for the 4:00 P.M. and 8:00 A.M. samples. B-END levels were the same for all the 4:00 P.M. samples. However, for the 8:00 A.M. samples, the groups receiving no premedication and placebo had significantly higher B-END values than either controls or the groups receiving premedication ($P < 0.05$) (fig. 1).

Discussion

It is well established that a high percentage of patients, ranging from 40–80%,[15,16] show preoperative anxiety. Furthermore, anxiety is significantly reduced by different premedication regimes,[16] as well as by the preoperative visit.[17] Our results demonstrate that presurgical patients which were not premedicated or received placebo have statistically significant higher levels of plasma B-END

TABLE 1. Plasma ACTH and B-END Levels on the Day Before Surgery (4:00 P.M.) and Immediately Pre-induction (8:00 A.M.)

Group	n	ACTH (pg/ml)		B-END (pmol/l)	
		4:00 P.M.	8:00 A.M.	4:00 P.M.	8:00 A.M.
Controls	10	32.5 ± 2.4	34.3 ± 2.3	3.97 ± 0.36	4.29 ± 0.47
No premedication	14	40.6 ± 3.7	40.1 ± 4.1	4.01 ± 0.61	6.01 ± 0.63*‡
Placebo	9	51.8 ± 5.2	49.6 ± 5.5	3.92 ± 0.26	5.98 ± 0.95*‡
Diazepam	12	31.8 ± 30.0	28.4 ± 1.7	3.58 ± 0.13	4.14 ± 0.38†
Diphenhydramine	10	58.7 ± 30.0	46.9 ± 18.0	4.88 ± 1.26	3.85 ± 0.29†
Meperidine	8	35.7 ± 4.3	28.4 ± 3.6	4.35 ± 0.61	3.24 ± 0.20†

Values given are mean ± SE
* Significantly higher than control (8:00 A.M.) $P < 0.05$.
† Significantly lower than No premedication (8:00 A.M.) $P < 0.05$.
‡ Significantly higher than 4:00 P.M. levels $P < 0.05$.

during the immediate preoperative period, before anesthesia induction, than normal controls. Premedication with diazepam, meperidine, or diphenhydramine prevented, in every instance, such an increase in B-END plasma levels. Since ours was a randomized double blind study, we conclude that the abrogation of the B-END increase is due to the effect of the premedication drugs, since no instance of decrease was observed in the placebo group. The fact that premedication abolished the B-END increase during presurgery suggests that the drugs may interfere with synthesis or release of B-END and/or that they decrease the stimuli responsible for the increased B-END levels in the presurgical period.

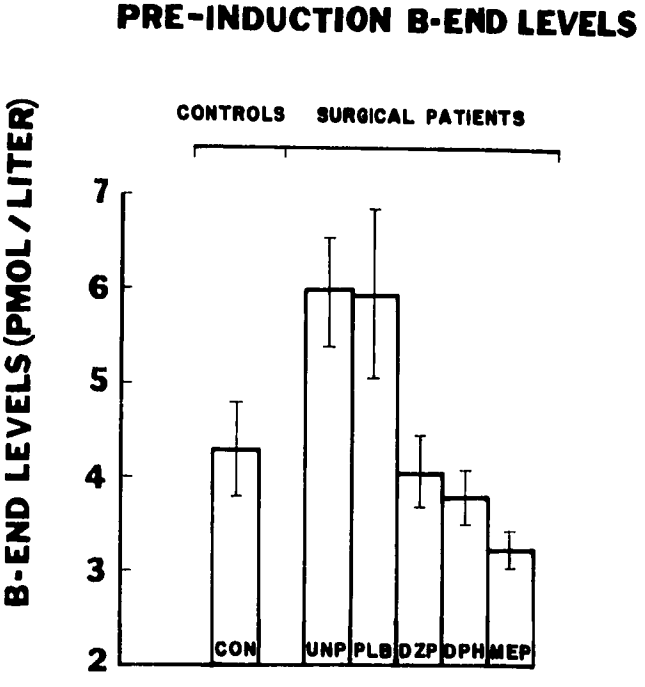

FIG. 1. B-endorphin plasma levels (pmol/l) in control (CON) and pre-surgical patients. Columns indicate mean values and vertical bars SEM. UNP = no premedication; PLB = placebo; DZP = diazepam; DPH = diphenhydramine; MEP = meperidine.

Our study was not designed to differentiate between these possibilities. There is evidence in the literature, however, which indicates that antihistaminics do not interfere with B-END secretion,[18] and that diazepam may encourage endogenous opioid release.[19] Exogenous opioids have been shown to attenuate B-END responses to stress.[20] This may play a role in the effect of meperidine in our study, independent of meperidine-induced relief of anxiety.

The lack of ACTH response in our patients is consistent with other data suggesting that physical stimuli (*e.g.*, incision) are required to produce changes in ACTH.[1,4,21] Our data do suggest that other physiologic changes, as evidenced by B-END activity, begin in the preoperative period. Pharmacologic intervention at this time may be of aid in minimizing undesirable responses in the surgical patient.

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End-tidal P_{CO_2} Monitoring in Infants and Children Ventilated with Either a Partial Rebreathing or a Non-rebreathing Circuit

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End-tidal P_{CO_2} measurements are frequently less accurate in neonates, infants, and small children than in adults.**[1] The difficulty in obtaining accurate measurements in pediatric patients may be attributed to the low ratio of tidal volume to equipment deadspace, rapid ventilatory rates and high fresh gas flows, and high sampling rates required by CO_2 analyzers. We believe that these problems are maximal when pediatric patients (particularly neonates and infants) are ventilated with partial rebreathing circuits, which allow fresh gas to flow past the endotracheal tube during expiration, and are minimal when these patients are ventilated with circuits which have non-rebreathing valves that separate the inspiratory and expiratory phases of respiration. To verify this clinical impression, we compared the arterial P_{CO_2} (Pa_{CO_2}) with the end-tidal P_{CO_2} (Pet_{CO_2}) during ventilation of neonates, infants, and children using a partial rebreathing circuit (Air-Shields Ventimeter® [ASV] and a Mapleson D breathing circuit) or a non-rebreathing circuit (Siemens-Elema "Servo" 900-C® [SES]).

METHODS AND MATERIALS

Fifty children with no known cardiopulmonary disease who were scheduled for general surgery or neurosurgical procedures were studied. The patients varied in age from premature newborn to 9 yr, and in weight from 1.65–23.5 kg. The study was approved by the Institutional Re-

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