has been moved inadvertently. In intensive care units, the need for x-rays to define tube location can be eliminated. To the neophyte laryngoscopist, this endotracheal tube locator method may serve as a teaching device to pinpoint the location of the tube and the potential problems of intubation, in both manikins and adult patients. It will not yield a false reading in the event of esophageal intubation, as the marker will be beyond the range of the detector.

The commercial cost of adding the marker band to a tube should ultimately be only a few cents, and the cost of one detector, if commercially produced (one is probably sufficient for an entire operating suite or intensive care unit) should be less than $100, since the design has already been refined to contain parts that cost less than $15.

We see no physiologic or physical obstacle to this method. It is simple, inexpensive, non-invasive, and assures proper placement of endotracheal tubes.

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Interaction of the Effects of Hydroxyzine and Pentazocine on Human Respiration

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Hydroxyzine may enhance the effects of analgesics and therefore reduce the requirements for these drugs. Since pentazocine is a commonly prescribed analgesic and is frequently used together with hydroxyzine, information about their effects and interactions is desirable. Pentazocine has been shown to be a potent respiratory depressant.[1] In a recent study[2] we found that the respiratory depressent effect of hydroxyzine is slight but significant; 75 mg hydroxyzine im was equivalent to 7.5 mg diazepam im in respiratory effect. To study this interaction, the following 2 × 2 factorially designed study was done.

Evaluation of the respiratory effects of the interaction of hydroxyzine and pentazocine was carried out in a single-blind study. The five healthy male subjects, aged 20–30 years, had no known respiratory or other disorder. The drugs and dosages employed were: 1) pentazocine, 30 mg; 2) hydroxyzine, 100 mg; 3) pentazocine, 30 mg, and hydroxyzine, 100 mg; 4) placebo (2 ml saline solution). All medications were given im. At least two days elapsed between test sessions to avoid cumulative effects. The test drugs were administered according to a Latin-square order. The research assistant performing the respiratory test, but not the subject, knew which drug had been administered.

The method of measuring respiratory effects has been used by us in previous studies[3,4] and is a modification of the technique of Eckenhoff *et al*.[5] wherein a subject rebreathes in a closed-circle system and endogenous carbon dioxide is used to stimulate respiration. The outputs of an infrared carbon dioxide analyzer sampling from the level of the subject's lips, pneumotachograph strain gauge, and thermistor were fed into a special-purpose analog computer[6] that plotted end-expiratory carbon dioxide versus alveolar ventilation (BTPS) while the subject rebreathed in the closed system. The use of a similar computer has been described by us.[7] Respiratory depression was measured in terms of displacement of the respiratory response curve. A PDP/8 computer stored the results for each breath and a least mean-square line was fit to it. The intercept at 20 l/m and the slope were printed out. The

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TABLE 1. Displacement of Respiratory

	Placebo (Saline Solution)				Hydroxyzine, 100 mg			
	30 Min.	60 Min.	120 Min.	180 Min.	30 Min.	60 Min.	120 Min.	180 Min.
Subject a1	.38	.43	.88	.45	1.87	1.46	1.29	−.55
Subject a3	−.97	−1.42	−1.05	−.78	.29	.09	0.16	−.73
Subject a10	.35	.60	.47	.43	2.12	1.55	2.59	2.47
Subject a2	.80	.27	.55	.35	−.75	−.52	−.28	1.03
Subject a4	−.04	−.25	−.18	−1.93	2.32	1.93	1.87	1.73
MEAN	.10	−.07	.13	0.30	1.18	.90	1.06	.79
GRAND MEAN				0.15				.96

differences between the mean shift in torr P_{CO_2} of the two control runs and the shifts in the 30-, 60-, 120-, and 180-minute runs were calculated (table 1) and the means plotted for each medication (fig. 1). The slope of the response curve was also determined.

RESULTS

The calculated displacement of the response curve expressed in torr P_{CO_2} was entered in a table with four entries for treatment and five entries for subject (table 1). Positive values, a shift of the response curve to the right, indicate respiratory depression, while negative values indicate respiratory stimulation. An analysis of variance was carried out on the crossover data. The subject by medication variance (S × M) was significant and was used as the assay error. The variance due to subject was not significant, but that due to medication was ($P < 0.01$). Orthogonal treatment comparisons showed the respiratory depressant effects of both pentazocine ($P < 0.01$) and hydroxyzine ($P < 0.05$) to be significant. There was nothing to suggest that the interaction was more than additive—the interaction term was not significant.

The slope of the response curve was measured before and after medication. An analysis of variance was done on these data and it was found that there was no significant effect of the medication on slope of the response curve.

In figure 1 the time effect curves for all four medications are shown. The shift in the respiratory response curve is plotted versus time. Note that hydroxyzine alone and pentazocine alone reach their peak effects on the first measurement at 30 minutes. This graph also confirms the conclusions of the statistical analysis and shows that the combination of hydroxyzine, 100 mg, and pentazocine, 30 mg, produced more respiratory depression at each observation than either drug alone.

DISCUSSION

Interest in injectable hydroxyzine as an analgesic has been stimulated by the work of Momose* and more recently by the work of Sunshine† and Beaver.‡ Momose studied hydroxyzine alone and in combination with 15 mg pentazocine. He found that the com-

‡ Personal communication.

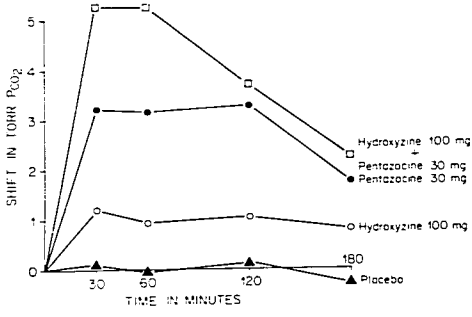

FIG. 1. The mean shift in the respiratory response curve (measured at 20 l/min) is plotted versus time for each of the four medications studied. Note that the effect of hydroxyzine plus pentazocine is greater than the effect of either drug alone.

Response Curve in Torr P_{CO_2}

Pentazocine, 30 mg				Pentazocine, 30 mg, and Hydroxyzine, 100 mg			
30 Min.	60 Min.	120 Min.	180 Min.	30 Min.	60 Min.	120 Min.	180 Min.
2.47	2.42	2.35	.66	2.30	3.45	2.15	1.28
3.52	5.88	4.55	3.85	5.59	5.59	3.22	.74
1.51	3.38	3.94	2.94	5.96	6.41	5.85	2.54
1.90	1.28	2.12	1.10	4.69	3.97	2.93	2.81
6.65	2.73	3.51	.07	7.65	6.74	4.31	3.76
3.21	3.14	3.29	1.72	5.24	5.23	3.69	2.22
			2.73				3.72

bination provided more pain relief than pentazocine alone. The observation that hydroxyzine alone will produce pain relief has been confirmed by Beaver. Thus, hydroxyzine differs from the barbiturate-type sedative in that the analgesic effect of pentazocine is augmented and hydroxyzine by itself appears to have an analgesic effect. Care was taken to differentiate between increased sedative effect accompanying the combination versus increased analgesic effect, in that the patients were awakened to interview them about their pain relief and pain intensity in the study by Beaver.

If these drugs are to be used in combination for analgesia, a question that naturally follows is whether the respiratory and sedative effects are enhanced. Our study has shown that the respiratory depression caused by the combination is no more than additive. While it appears that these effects are additive, a more complex study must be carried out to define the interaction precisely. The simplest design would be a 2×3 factorially designed study so that one could analyze whether adding hydroxyzine to pentazocine displaced the dose–effect curve of pentazocine in a parallel fashion. If the dose–effect curve were not displaced in a parallel fashion, then one would suspect that the interaction was taking place at more than one receptor site.

The present study has shown that the respiratory effects of these two drugs in combination are greater than the effect of either drug alone. Momose has shown that there is less nausea and vomiting with the combination than with pentazocine alone.[8] Thus, there could be an advantage, as this combination provides more analgesia than that afforded by the narcotic alone.

We found no significant change in the slope of the respiratory response curve. Our inability to detect any significant difference in the slopes of the response curves with the four different medications is probably related to the variability in the slope determinations and the limited number of subjects studied. In the past we have noticed that with potent respiratory depressants such as 10 mg morphine[4] significant changes in respiratory response curve slope can be shown. Thus, from this study, it is impossible to make statements about the central versus the possible peripheral effects of these respiratory depressants.

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