Effect of Secobarbital and Morphine on Arterial Blood Gases in Healthy Human Volunteers

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Secobarbital is still widely used as a hypnotic and morphine as an analgesic perioperatively in surgical patients. Their combination is often used as a preanesthetic medication. Although their ventilatory depressant effect is recognized, the resulting blood gas changes have not been studied as yet adequately in a sufficiently large population of healthy volunteers. Therefore this study was undertaken. Thirty healthy volunteers who gave valid written consent were studied. Secorbarbital 2.0 mg/kg intravenously caused a significant (P < .05) decrease in arterial oxygen pressure (Pa_{O_2}), peaking at 10 minutes (n = 10; mean age, 23.4 years). Morphine, 0.2 mg/kg intravenously also caused a significant decrease in Pa_{O_2} at 5 minutes (n = 10; mean age, 26.3 years). The combination of the same doses of morphine and secobarbital caused a significantly (P < .01) greater decrease in Pa_{O_2} at 5 and 10 minutes than the sole administration of either drug (n = 10; mean age, 23.5 years). Arterial oxygen pressure remained significantly (P < .05) reduced for 30 minutes. Although the Pa_{CO_2} increases after secobarbital and morphine did not reach statistical significance, their combination caused a significant (P < .05) increase in Pa_{CO_2}. Both secobarbital and morphine alone caused significant (P < .05) decrease in pH_a at 30 minutes. Their combination caused a significant (P < .01) reduction in pH_a from 5 minutes until 60 minutes. In conclusion, both secobarbital and morphine alone caused ventilatory depression. The duration of ventilatory depression was greater with the intravenous combination than with either drug alone.

Barbiturates cause central nervous system depression resulting in sedation and sleep; therefore, secobarbital is still frequently employed as a hypnotic and preoperative sedative medication. Barbiturates were reported to depress both the respiratory drive and the mechanism responsible for the rhythmic character of respiratory movements.[1,2] Secobarbital was claimed to cause less ventilatory depression as expressed in a lesser shift in the CO_2 response curve in six volunteers than pentobarbital.[3] Because intravenous (IV) secobarbital may be used in patients who have convulsions, even moderate ventilatory depression might be of clinical importance. Arterial hypoxia and respiratory acidosis were observed in

patients who received a combination of meperidine, promethazine, and pentobarbital intramuscularly.[4] Because of this adverse report and the reported shift in the CO_2 response curve after barbiturates in some individuals in a small pilot placebo-controlled study,[3] we set out to study the arterial blood gas changes in a controlled study in a sufficiently large healthy volunteer population.

Morphine is still commonly used for perioperative pain relief, although its ventilatory depressant effect has been well documented in humans.[5-11] Earlier studies employed CO_2 response curves for evaluation of ventilatory depression,[5,6] but no studies have been carried out as yet on the effects of morphine on arterial blood gases that frequently are used in the assessment of ventilation in clinical practice today.

The combination of morphine with secobarbital is still widely practiced. Although adverse reports blamed the combination of these drugs for arterial hypoxia,[4,6] no controlled studies on the effect of this combination on arterial blood gases have been reported as yet. Therefore this study was undertaken.

METHODS

Thirty healthy volunteers who signed a valid written consent and who were not undergoing drug treatment or habituated to any drug were selected for the study. The study was approved by the Institutional Review Board. No minors or pregnant women were accepted. Of these volunteers, 10 (mean age, 23.4 years) received secobarbital 2.0 mg/kg IV over 30 seconds; 10 volunteers (mean age, 26.3 years) received morphine 0.2 mg/kg IV; and 10 volunteers (mean age, 23.5 years) received first secobarbital 2.0 mg/kg IV over 30 seconds followed 2 minutes later by morphine 0.2 mg/kg IV over 30 seconds. In a special research unit, the volunteers were allowed to read or watch television unless they spontaneously fell asleep, which commonly occurred, especially after secobarbital or its combination with morphine. The volunteers usually awakened at 30 minutes. They were maintained in the supine position throughout the study.

After a 20-gauge Riley arterial needle was inserted into the brachial artery of the nondominant arm and an IV infusion of 5% glucose in 0.2% saline solution was started in the dominant arm, a period of rest was allowed. Two baseline arterial blood samples were then drawn at 20-minute intervals. If the two determinations differed less than 5%, the study was begun.

For monitoring respiratory rate, a chest plethysmograph was attached, and a continuous recording was obtained on a Gilson polygraph. The brachial arterial blood pressure through a Statham strain gauge and lead II electrocardiogram also were recorded on a Gilson polygraph, at least up to 1 hour after the last blood gas sample to rule out adverse circulatory changes that might have altered blood gases.

The oxygen tension was directly determined with a Clark oxygen electrode and the carbon dioxide tension by the method of Siggaard-Andersen on a Radiometer Copenhagen pH-blood gas analyzer in the samples taken twice before and at 5, 10, 20, 30, and 60 minutes after drug administration. The pH was directly measured with the glass electrode of the pH-blood gas analyzer at the same time intervals.

The SAS statistical program was used for statistical analysis of the data by Student's t test or paired t test. Differences for $P < .05$ were considered significant. All values are expressed as mean ± standard deviation.

RESULTS

Secobarbital caused a significant ($P < .05$) decrease in arterial oxygen pressure (Pa_{O_2}) at 10 minutes (Table I). Morphine also caused a significant ($P < .05$) decrease in Pa_{O2} at 5 minutes. The combination of secobarbital with morphine caused a significantly greater decrease in Pa_{O2} at 5 and 10 minutes ($P < .01$) and at 20 and 30 minutes ($p < .05$), when the changes were compared with their respective baselines, than either morphine or secobarbital alone (Figure 1). The increases in alveolar carbon dioxide pressure after secobarbital and morphine alone did not reach statistical significance (Table II). The combination, however, resulted in a significant ($P < .05$) increase in arterial carbon dioxid pressure as compared with the baselines or with the values observed at 10, 20, and 30 minutes after morphine alone, indicating greater ventilatory depression with the combination than with either drug alone (Figure 2). Both secobarbital and morphine alone caused a significant ($P < .05$) decrease in pH_a at 30 minutes (Table III). The combination of secobarbital with morphine led to more prolonged ventilatory depression, lasting for about 1 hour, because pH_a was reduced significantly ($P < .01$) at 5 minutes, more significantly ($P < .001$) at 10, 20, and 30 minutes, and remained reduced at 60 minutes ($P < .01$) as compared with the baseline or with

TABLE I

PaO_2 in Healthy Volunteers Given Secobarbital and Morphine Alone and Their Combination (Mean ± SD in mm Hg)

Drugs	N	0 min	5 min	10 min	20 min	30 min	60 min
Morphine 0.2 mg/kg	10	91.3 ± 5.59	84.6 ± 7.27*	87.8 ± 6.94	87.7 ± 6.79	91.2 ± 5.05	91.8 ± 4.21
Secobarbital 2.0 mg/kg	10	91.0 ± 3.41	90.1 ± 6.21	87.5 ± 3.66*	92.4 ± 2.95	93.2 ± 3.73	93.8 ± 4.94
Morphine 0.2 mg/kg & secobarbital 2.0 mg/kg	10	92.4 ± 4.60	80.7 ± 10.64**	82.6 ± 6.60**	85.7 ± 6.22*	87.7 ± 5.40*	89.0 ± 5.81

* P < 0.05 as compared with 0 min value.
** P < 0.01 as compared with 0 min value.
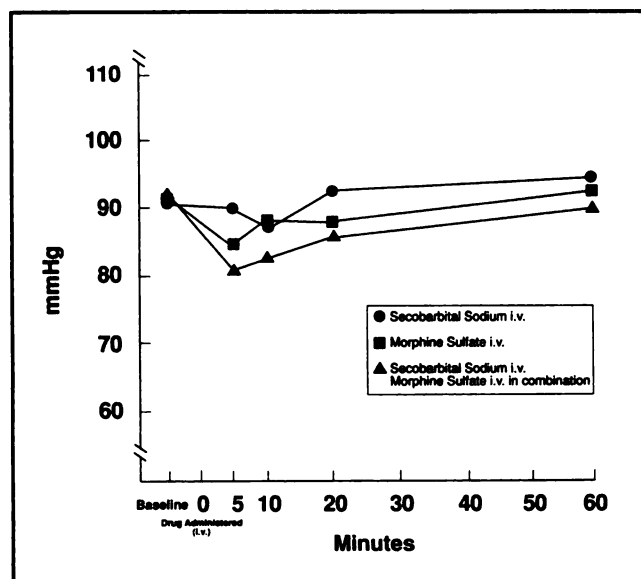*** P < 0.001 as compared with 0 min value.

Figure 1. Arterial PO_2 changes after IV administration of 2.0 mg/kg of secobarbital, 0.2 mg/kg of morphine, and their combination.
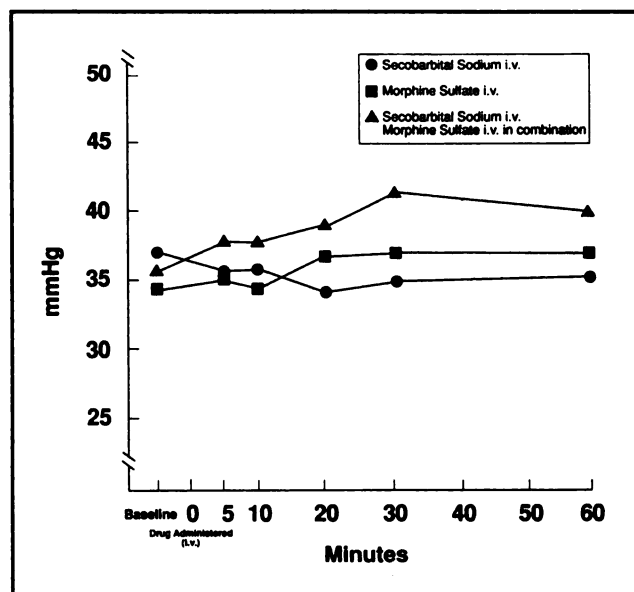

Figure 2. Arterial PCO_2 changes after IV administration of 2.0 mg/kg secobarbital, 0.2 mg/kg of morphine, and their combination.

the values observed after morphine alone (Table III) (Figure 3). The duration of ventilatory depression as evidenced by these blood gases changes was more prolonged with the drug combination than with either drug alone.

DISCUSSION

This is the first objective evaluation of blood gas changes after secobarbital sodium, morphine sulfate, and their combined administration on the arterial blood gases in a sufficiently large healthy population. Our results corroborated the findings of earlier studies that morphine caused a significant ventila-

tory depression evidenced by a shift in the CO_2 response curves.[6-11] Blood gases were not determined in earlier studies, however, because the technology was not readily available as yet. To evaluate the potential ventilatory depressant effect of secobarbital sodium, it was necessary to induce blood gas changes by morphine that are significant but not excessive, because then it should be more difficult to demonstrate additive or synergistic effects. Undoubtedly, the intravenous administration of morphine in a dose of 0.2 mg/kg did cause adequate blood gas changes for the evaluation of potential additive or synergistic ventilatory depressant effect of secobarbital.

TABLE II

PaCO₂ in Healthy Volunteers Given Secobarbital and Morphine Alone and Their Combination
(Mean ± SD in mm Hg)

Drugs	N	0 min	5 min	10 min	20 min	30 min	60 min
Morphine 0.2 mg/kg	10	34.5 ± 2.78	35.5 ± 3.80	34.5 ± 3.87	36.8 ± 2.18	36.9 ± 2.93	37.1 ± 2.85
Secobarbital 2.0 mg/kg	10	37.1 ± 3.30	35.7 ± 2.97	35.8 ± 3.15	34.9 ± 2.32	35.1 ± 3.28	35.2 ± 3.63
Morphine 0.2 mg/kg & secobarbital 2.0 mg/kg	10	35.8 ± 3.87	38.0 ± 5.07	37.9 ± 3.55†	39.0 ± 6.88†	41.5 ± 5.07*†	40.1 ± 5.37

*P < 0.05 as compared with 0 min value.
** P < 0.01 as compared with 0 min value.
*** P < 0.001 as compared with 0 min value.

† P < 0.05 compared with morphine.
†† P < 0.01 compared with morphine.
††† P < 0.001 compared with morphine.

TABLE III

pH$_a$ in Healthy Volunteers Given Secobarbital and Morphine Alone and Their Combination (Mean ± SD)

Drugs	N	0 min	5 min	10 min	20 min	30 min	60 min
Morphine 0.2 mg/kg	10	7.400 ± 0.020	7.395 ± 0.028	7.395 ± 0.023	7.379 ± 0.016*	7.378 ± 0.020*	7.385 ± 0.016
Secobarbital 2.0 mg/kg	10	7.409 ± 0.016	7.395 ± 0.024	7.394 ± 0.023	7.401 ± 0.015*	7.392 ± 0.019*	7.395 ± 0.022
Morphine 0.2 mg/kg & secobarbital 2.0 mg/kg	10	7.408 ± 0.008	7.382 ± 0.021**	7.380 ± 0.012***	7.370 ± 0.019***	7.379 ± 0.016**	7.369 ± 0.018***†

* $P < 0.05$ as compared with 0 min value.
** $P < 0.01$ as compared with 0 min value.
*** $P < 0.001$ as compared with 0 min value.

† $P < 0.05$ compared with morphine.
†† $P < 0.01$ compared with morphine.
††† $P < 0.001$ compared with morphine.

Secobarbital sodium is still widely used for overnight and preoperative sedation of patients. Its anticonvulsant effect is often used in the management of epileptic patients and for the prevention of central nervous system toxicity of local anesthetic drugs. In an emergency, secobarbital may be given IV for treatment of convulsions. Hence, its potential ventilatory depressant effect should be known to avoid severe complications, e.g., arterial and cerebral hypoxia, or apnea. Conflicting results of earlier studies[2,3] led to controversy as to the safety of secobarbital: either a moderate ventilatory depression or stimulation was claimed. Brown and associates[3] showed ventilatory depression by both secobarbital and pentobarbital, but the ventilatory depression of secobarbital was only 72% of that caused by pentobarbital based on CO_2-response curves of six healthy volunteers in a randomized study. Because of the small

Figure 3. Arterial pH changes after IV administration of 2.0 mg/kg secobarbital, 0.2 mg/kg of morphine, and their combination.

number of volunteers, only a minimal shift of CO_2-response curve and unpredictable ventilatory stimulation in some volunteers, the results are in some doubt. Certainly, our study definitively showed that reduction in Pa_{O2} is induced by secobarbital. Hence, in the presence of ventilatory depression caused by morphine, secobarbital caused further ventilatory depression. Not only the intensity but also the duration of ventilatory depression was greater with the combination as shown in the Pa_{CO2} increases and pH$_a$ reduction.

Our experimental method was validated in a series of investigations on other drugs and drug combinations earlier published in this Journal.[12-17] To demonstrate an increase in ventilatory depressant effect of morphine by secobarbital (1) we selected the most reliable route of administration to achieve reproducible blood levels: the IV route; (2) we gave a sufficiently large IV dose to induce respiratory depression by either agent when used alone. Using this experimental design, we were able to convincingly show that secobarbital causes ventilatory depression, which further increases the morphine-induced ventilatory depression.

The introduction of phenothiazines provided a new class of drugs for the sedation of patients. These drugs also caused a further increase in the ventilatory depression caused by morphine and meperidine, however, still commonly used as perioperative analgesics.[4,6] In an earlier report in this Journal, we showed that methotrimeprazine further increased the ventilatory depression caused by meperidine in healthy volunteers, although no discernible ventilatory depression was seen after 0.15 mg/kg IV methotrimeprazine alone.[15] In contrast, the ED_{95} of two tranquilizers, hydroxyzine and diazepam IV alone, caused no ventilatory depression in either healthy volunteers or lung disease patients.[13-16,17] Their com-
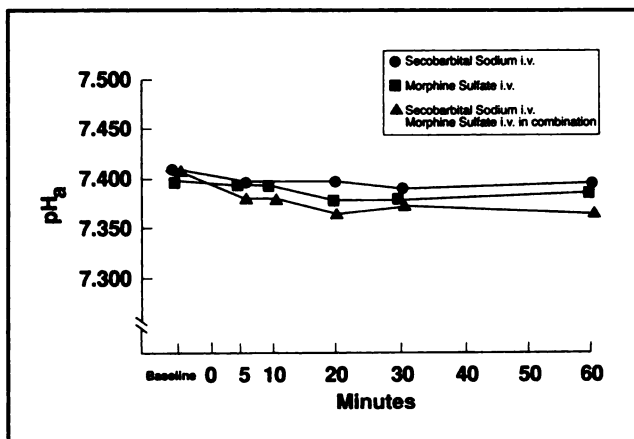
bination with meperidine in ED_{95} dose resulted in no more ventilatory depression. Therefore, either of these tranquilizers can be used for the sedation of surgical patients perioperatively without the hazards of ventilatory depression. Even patients with chronic obstructive pulmonary disease tolerated optimal tranquilizing doses of both diazepam or hydroxyzine and showed no further increase in the ventilatory depression when combined with meperidine,[16,17] as published earlier in this Journal.

Hydroxyzine potentiates the analgesic effect of μ-agonists and reduces bronchospasm and other histamine-release–induced side effects of morphine because of its antihistaminic effect.[18] Hence, hydroxyzine is a popular tranquilizer in clinical practice and may be used in lieu of secobarbital for relief of anxiety and induction of sleep without the hazard of ventilatory depression.[19] Because hydroxyzine possesses analgesics effect of its own,[20] it may be used alone in place of analgesics, especially in patients in whom ventilatory depression should be avoided. In summary, secobarbital sodium in optimal sedative dose, 2.0 mg/kg IV, causes ventilatory depression and further increases and prolongs the morphine-induced ventilatory depression in healthy volunteers. This finding should be taken into account when patient are receiving secobarbital IV, especially when combined with morphine.

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