Diazepam and Meperidine on Arterial Blood Gases in Healthy Volunteers

ELEMÉR K. ZSIGMOND, M.D., KATHY FLYNN, B.S., and ORESTES A. MARTINEZ, M.D. Ann Arbor, Mich.

ARTERIAL blood gases and pH may reflect the respiratory depression produced by tranquilizing and narcotic-analgesic agents used in premedication before surgical anesthesia. The absence of respiratory depression is one of the desirable qualities of an ideal premedicant or sedative drug. Therefore, it is essential to know if, and to what extent, a particular drug depresses respiration. The respiratory depressant effect of drugs is especially important in patients with pulmonary disease, in whom care must be exercised in selecting an agent that will not be detrimental to ventilation.

Respiratory depression has been reported to occur following the use of phenothiazine tranquilizers and barbiturates.[1,2] Therefore, we wanted to verify the claim[3,4] that diazepam does not induce significant respiratory depression or potentiate the depression caused by meperidine in healthy volunteers.

Materials and Methods

Thirty-six healthy volunteers were adult students and hospital employees between the ages of 19 and 62 years (mean=35). An almost equal number of males and females were present in each study group, as shown in Table I. The volunteers were recumbent during the tests.

After insertion of a 20-gauge Riley arterial needle into the left brachial artery and the start of an intravenous infusion of 5% glucose in 0.2% sodium chloride in the contralateral arm, a period of rest was allowed. Two arterial samples were then drawn at 10-minute intervals as baseline samples. If the two determinations differed less than 5%, the study was begun.

Meperidine 1.5 mg/kg, diazepam 0.15 mg/kg, or meperidine 1.5 mg/kg and diazepam 0.15 mg/kg in combination in alternate sequence were infused intravenously over a 2-minute period. Timing was begun at the end of this period.

The oxygen tension was directly determined with a Clark-Oxygen-Electrode and the carbon dioxide tension by a pCO_2 electrode of IL-113 pH–Blood Gas Analyzer (Instrumentation Laboratories, Inc.) or with Siggard-Andersen's technique on a Radiometer Copenhagen pH–Blood Gas Analyzer, before and at 5-minute intervals after administration of the test medication for 1 hour. The pH was directly measured with the glass electrode of the IL-113 pH–blood gas analyzer or the Radiometer glass electrode at the same time intervals.

From the Department of Anesthesiology, University of Michigan Medical Center, Ann Arbor, Michigan 48104.

TABLE I

Age and Sex Distribution of 36 Healthy Volunteers

Drug study groups	N	Sexes		Age
		Male	Female	Mean and range
Diazepam 0.15 mg/kg	10	5	5	39.7 (20–57)
Meperidine 1.5 mg/kg	19	11	8	32.4 (19–62)
Diazepam 0.15 mg/kg and meperidine 1.5 mg/kg	7	4	3	38.9 (21–53)

Results

In the healthy volunteers, the maximum reduction in PaO_2 after meperidine was 11.5 Torr, after the meperidine and diazepam combination, 5.3 Torr, and after diazepam, 5.3 Torr, as shown in Table II and Fig. 1. The change after diazepam alone was not statistically significant ($P>0.05$). There was, however, a significant decrease in PaO_2 after the intravenous injection of meperidine ($P<0.01$). The combination of diazepam with meperidine caused no more decrease in PaO_2 than meperidine alone ($P>0.05$). As Fig. 1 shows, the reduction in PaO_2 lasted for only 20 minutes following meperidine and meperidine-diazepam combination, and diazepam caused no prolongation of the period of reduced PaO_2 induced by meperidine.

TABLE II

PaO_2 in Healthy Volunteers Given Diazepam and Meperidine Alone and in Combination

Intravenous medications and dose	Control value (means ± S.D.)	Torr values after medication (means ± S.D.)				
		5 min	10 min	20 min	30 min	60 min
Diazepam 0.15 mg/kg	86.5 ±6.06	81.2 ±10.54	85.3 ±8.59	84.8 ±6.76	84.8 ±8.06	87.8 ±6.34
Meperidine 1.5 mg/kg	85.3 ±9.48	73.8 ±9.52	80.6 ±11.12	83.9 ±8.85	82.3 ±9.26	83.8 ±10.86
Diazepam 0.15 mg/kg and meperidine 1.5 mg/kg	80.7 ±3.55	75.4 ±17.73	79.3 ±12.75	80.1 ±8.63	81.3 ±8.85	85.0 ±5.83

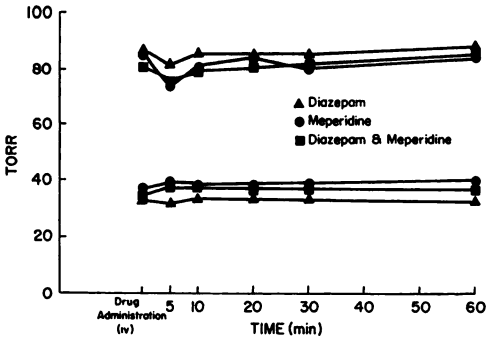

Fig. 1. Changes in PaO_2 and $PaCO_2$ in healthy volunteers given intravenously diazepam, meperidine, and their combinations. The upper lines represent PaO_2, the lower lines $PaCO_2$.

No increase in arterial $PaCO_2$ occurred after diazepam alone, which corroborates the lack of respiratory depressant effect. The maximum increase in $PaCO_2$ in the healthy volunteers was 1.4 Torr after meperidine and 3.1 Torr after the meperidine and diazepam combination, as shown in Table III and Fig. 1. It is of great importance that the increase in $PaCO_2$ was not significantly greater following the diazepam-meperidine combination than following meperidine alone, ($P>0.05$), and the differences in resting $PaCO_2$ values might have partly explained this difference.

Changes in pH of the arterial blood were not statistically significant in any of the groups, as seen in Table IV.

Discussion

Our results corroborate the findings of Sadove et al.[4] and Steen et al.[3] who observed no changes in the respiratory response to carbon dioxide following 0.15 mg/kg diazepam intramuscularly and 0.66 mg/kg intravenously. Furthermore, the combination of diazepam with meperidine caused no greater shift in the CO_2 response curve than meperidine alone in their studies. Huettemann et al.[5] also confirmed the complete lack of respiratory depression by spirometric studies in ten healthy persons who received 10 mg diazepam intravenously. They also observed no alteration in the response of the respiratory center to carbon dioxide. This lack of respiratory depressant effect of diazepam is further confirmed by our blood gas studies with

TABLE III

$PaCO_2$ in Healthy Volunteers Given Diazepam and Meperidine Alone and in Combination

Intravenous medications and dose	Control value (means ± S.D.)	Torr values after medication (means ± S.D.)				
		5 min	10 min	20 min	30 min	60 min
Diazepam 0.15 mg/kg	32.8 ±4.73	31.8 ±3.67	33.0 ±2.82	33.2 ±3.14	33.1 ±2.80	32.1 ±3.52
Meperidine 1.5 mg/kg	37.6 ±3.80	39.0 ±3.22	38.0 ±4.04	38.5 ±3.28	38.9 ±3.75	39.2 ±3.38
Diazepam 0.15 mg/kg and meperidine 1.5 mg/kg	34.1 ±2.65	37.2 ±3.50	37.1 ±5.08	36.5 ±3.76	36.9 ±4.59	36.8 ±4.44

TABLE IV

pH in Healthy Volunteers Given Diazepam and Meperidine Alone and in Combination

Intravenous medications and dose	Control value (mean ± S.D.)	Torr values after medication (means ± S.D.)				
		5 min	10 min	20 min	30 min	60 min
Diazepam 0.15 mg/kg	7.415 ±0.038	7.378 ±0.030	7.386 ±0.031	7.423 ±0.036	7.437 ±0.030	7.432 ±0.033
Meperidine 1.5 mg/kg	7.399 ±0.020	7.382 ±0.031	7.382 ±0.027	7.379 ±0.023	7.381 ±0.020	7.382 ±0.027
Diazepam 0.15 mg/kg and meperidine 1.5 mg/kg	7.406 ±0.032	7.386 ±0.044	7.384 ±0.046	7.391 ±0.039	7.389 ±0.040	7.395 ±0.032

the combined administration of diazepam with a known respiratory depressant dose of meperidine. As noted in Fig. 1, diazepam had no additive effect with meperidine and caused no potentiation of the respiratory depression caused by meperidine, which agrees with the findings of Steen et al.[8]

Although the above findings confirm the lack of respiratory depression with 10 mg diazepam in healthy individuals, cardiac patients may develop respiratory depression following this dose of diazepam according to the report of Dalen et al.[6] They found hypoventilation in all patients scheduled for cardiac catheterization following 5–10 mg/70 kg diazepam intravenously. That respiratory depression may follow the administration of a larger dose, 20 mg diazepam intramuscularly, was reported by Herberg et al.[7] These authors observed a decrease in the respiratory response to carbon dioxide in 74 young test persons. Moreover, Buskop et al.[8] reported respiratory arrest in a patient during epidural anesthesia who received 10 mg diazepam intravenously. In this case, hypersensitivity to diazepam is a more likely cause than is respiratory depression. Our preliminary results, from a pilot study in patients with chronic obstructive lung disease and mitral stenosis with arterial fibrillation, contradict these findings, since 10 mg/70 kg diazepam intravenously caused no alteration in arterial blood gases.[9] Furthermore, clinical experience with several thousand patients who underwent cardioversion[10] or surgery under regional anesthesia supplemented with 0.2 mg/kg intravenous diazepam or sedated with 10 mg/70 kg diazepam further attests to the lack of respiratory depression with this agent in the doses recommended.

Summary

Arterial blood gases were not significantly altered by 0.15 mg/kg I.V. dose of diazepam in healthy volunteers. The PaO_2 was significantly reduced and the $PaCO_2$ increased following the administration of meperidine 1.5 mg/kg intravenously and the combination of meperidine 1.5 mg/kg with diazepam 0.15 mg/kg. Diazepam did not significantly increase the respiratory depression induced

by meperidine. Values for arterial pH were not significantly affected in any of the groups.

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Reprint requests should be sent to: Elemér K. Zsigmond, M.D., Univ. of Michigan Med. Center, Dept. of Anesthesiology, Ann Arbor, Michigan 48104.