

# Effect of Subanesthetic Concentrations of Halothane and Methoxyflurane on Pain Threshold in Conscious Volunteers

E. S. Siker, M.D.,\* Bernard Wolfson, M.B.,† Harold E. Ciccarelli, M.D.,‡  
Ruben A. Telan, M.D.§

Algesimetric studies were carried out in volunteers during the inhalation of subanesthetic concentrations of methoxyflurane and halothane. Blood levels of agents were measured in venous samples obtained immediately after each determination of pain threshold. Significant increases in threshold were seen with both agents but a linear relationship between pain threshold and blood levels was not seen consistently with either agent. Significant reductions in threshold were seen occasionally with both methoxyflurane and halothane and were most probably related to the onset of drowsiness. The occurrence of analgesia with low blood levels in the majority of subjects lends support to the current practice of reinforcing nitrous oxide oxygen anesthesia with low concentrations of halothane or methoxyflurane.

THE USE of potent inhalational agents to reinforce the analgesia provided by nitrous oxide has become common anesthetic practice. The apparent value of low concentrations of these agents for this purpose has precipitated interest in the degree of analgesia they afford when used alone.

The evidence currently available is limited and conflicting. In an initial study in 1960 carried out in conscious volunteers, Dundee and Moore<sup>1</sup> reported that trichlorethylene (0.5 and 0.35 per cent) and diethyl ether (2.0 and 1.0 per cent) both caused an increase in pain threshold while 0.5 per cent halothane caused a decrease (antanalgesia). Pain

thresholds were estimated with an inverted spring balance pressed on the anterior tibial surface, a method described originally by Clutton-Brock<sup>2</sup> and modified by Dundee and Moore.<sup>3</sup> In a later study, Dundee and his co-workers<sup>4</sup> again reported that 0.5 per cent halothane in oxygen caused a decrease in pain threshold. Further, the administration of a halothane-ether azeotrope produced no alteration in pain threshold despite the markedly analgesic effect of ether alone.

In a recent study using the same method of algesimetry, Robson and his associates<sup>5</sup> reported significant elevations in pain thresholds with 0.5 per cent halothane in oxygen in four of five conscious volunteers. In addition, using a thermal method of algesimetry,<sup>6</sup> these investigators tested the effect of halothane on established nitrous oxide-oxygen analgesia. Five subjects received 25 per cent nitrous oxide in oxygen to which 0.15 to 0.25 per cent halothane was then added for 10 minutes. In all subjects, these concentrations of halothane caused further increases in pain threshold. Thus the results reported by Dundee *et al.*<sup>1,4</sup> are in direct contrast to the work reported by Robson *et al.*<sup>5</sup>

In 1963, Dundee and Love<sup>7</sup> were unable to demonstrate a consistent elevation in pain threshold with 0.25, 0.4 or 0.5 per cent methoxyflurane in oxygen. They noted that the early onset of drowsiness was a limiting factor in their studies. This lack of analgesic effect with subanesthetic concentrations of methoxyflurane is at variance with the clinical impression of analgesia reported in obstetrical practice.<sup>8,9</sup>

The discrepancy between the work of Dun-

\* Director, Department of Anesthesiology.

† Associate Director, Anesthesia Research Laboratory.

‡ Attending Anesthesiologist.

§ Senior Resident in Anesthesiology, Department of Anesthesiology, Mercy Hospital, Pittsburgh, Pennsylvania.

Accepted for publication August 8, 1966.

dee<sup>1,4</sup> and Robson<sup>5</sup> might be explained if there were a significant difference in the blood levels of halothane in the respective sets of subjects. For this reason, we decided to attempt a correlation between blood levels of halothane and methoxyflurane and algesimetric findings.

### Methods

Twenty subjects took part in this study; 14 received methoxyflurane, 10 received halothane and 4 received both. An earlobe algesimeter previously described<sup>10</sup> was used to determine pain threshold. Experiments were begun in the morning with the subjects in a fasting state. Each subject reclined in a quiet room for 20 to 30 minutes during which time an antecubital vein was cannulated in order to obtain blood samples. Three determinations of pain threshold were then made at 10 minute intervals with the subject breathing 100 per cent oxygen from a nonbreathing system. The average of these was taken as the control threshold. All the subjects were experienced in the use of the algesimeter having participated in prior studies.<sup>10,11</sup>

Each subject served as his own control and the pretest pain threshold was noted as 100 per cent with subsequent readings taken as per cent of control. Concentrations of methoxyflurane and halothane in blood were deter-

mined by gas chromatography employing techniques previously described.<sup>12,13</sup>

**Methoxyflurane.** At zero time methoxyflurane was added to the inspired oxygen from a "Pentec" vaporizer set at 0.4 per cent and continued for 40 minutes. During this time the setting of the Pentec was altered in a number of subjects to 0.3 per cent in order to prevent unconsciousness. In a few instances administration was temporarily discontinued for the same reason. Pain thresholds were recorded at 10 minute intervals for a period of 60 minutes with additional determinations at 80, and 100 minutes. Blood samples were drawn at the completion of each determination. At 100 minutes blood levels of methoxyflurane were too low for accurate analysis and further sampling was abandoned after the first two studies.

**Halothane.** A different mode of administration was followed with halothane in an effort to determine if the onset of drowsiness had any consistent effect on pain threshold. Halothane was added to the inspired oxygen from a "Fluotec" vaporizer at a constant setting of 0.5 per cent. At the point where marked drowsiness supervened or at 30 minutes administration was discontinued; thus the period of administration varied from 20 to 30 minutes. Determinations of pain threshold were made every 5 minutes for 45 minutes. Blood samples were withdrawn following each determination.

### Results

**Methoxyflurane.** Significant increases in pain threshold during inhalation of methoxyflurane were found in 12 of 14 subjects; blood levels varied from 1.25 to 4.2 mg./100 ml. In one subject minor variations were seen both above and below the control thresholds at blood levels ranging from 2.1 to 3.6 mg./100 ml. and in the other subject there was no change in threshold for the first 20 minutes, followed by a marked fall. The blood level at 20 minutes was 3.4 mg./100 ml. and 3.16 mg./100 ml. when the threshold fell markedly below the control. In four of the 12 subjects who manifested significant analgesia during the inhalation of methoxyflurane, thresholds significantly below control were found in the

TABLE 1. Effect of Methoxyflurane Inhalation in Conscious Volunteers

Time	Pain Threshold (Percentage of Control)	P	Blood Level (mg./100 ml.)
0	100		
10	137 ± 27.7	<0.01	1.89 ± 0.57
20	136 ± 20.2	<0.01	2.45 ± 0.57
30	154 ± 33.1	<0.01	2.77 ± 0.57
40	137 ± 17.8	<0.01	3.18 ± 0.44
Inhalation of methoxyflurane discontinued at 40 minutes			
50	121 ± 16.4	<0.01	1.31 ± 0.10
60	111 ± 20.9	>0.05	1.06 ± 0.43
80	112 ± 13.7	<0.02	0.67 ± 0.14
100	102 ± 9.2	>0.20	—

Average pain thresholds (percentage of control) and venous blood levels (milligrams per 100 ml.).

FIG. 1. Average pain thresholds and corresponding venous blood levels of methoxyflurane in subjects showing analgesic response.

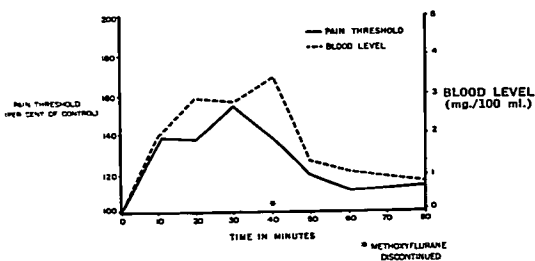


FIG. 2. Linear relation between changes in pain thresholds and venous blood levels of methoxyflurane in one subject.

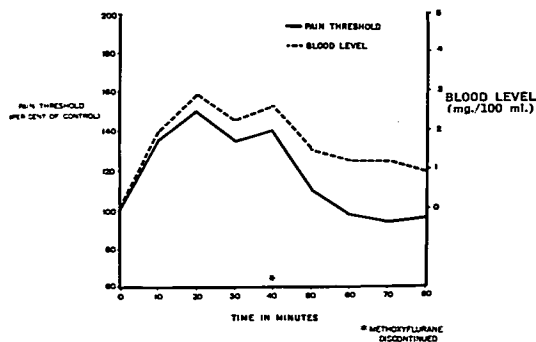


FIG. 3. Reduction in pain thresholds and corresponding venous blood levels of methoxyflurane in one subject.

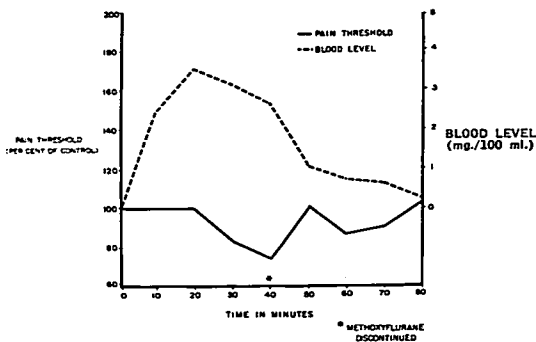


TABLE 2. Effect of Halothane Inhalation in Conscious Volunteers

Time	Pain Threshold (Percentage of Control)	P	Blood Level (mg./100 ml.)
0	100		
5	142 $\pm$ 23.6	<0.01	0.92 $\pm$ 0.28
10	167 $\pm$ 60.1	<0.05	1.87 $\pm$ 0.45
15	145 $\pm$ 39.8	<0.05	2.67 $\pm$ 0.80
20	171 $\pm$ 70.1	<0.05	2.96 $\pm$ 0.60
25	148 $\pm$ 24.5	<0.01	2.45 $\pm$ 0.74
30	157 $\pm$ 31.9	<0.01	2.49 $\pm$ 0.93

Inhalation of halothane discontinued between 20 and 30 minutes			
35	133 $\pm$ 43.9	>0.05	1.64 $\pm$ 0.77
40	103 $\pm$ 22.4	>0.50	1.35 $\pm$ 0.76
45	114 $\pm$ 15.5	>0.20	1.23 $\pm$ 0.57

Average pain thresholds (percentage of control) and venous blood levels (mg./100 ml.).

recovery period. Blood levels during reductions in pain threshold varied between 0.8 and 3.16 mg./100 ml.

Thus with increasing blood levels of methoxyflurane an antanalgesic-analgesic sequence was never seen and the appearance of antanalgesia at higher blood levels was seen only once. An analgesic-antanalgesic sequence was seen with decreasing blood levels in the recovery period on four occasions.

The average pain thresholds and blood levels of methoxyflurane in the 12 subjects exhibiting an analgesic response are shown in table 1 and graphically in figure 1. An increase in the average pain threshold can be seen through 80 minutes. However, this was not statistically significant at 60 minutes. There was no linear correlation between threshold changes and blood levels although individual instances of linearity (fig. 2) occa-

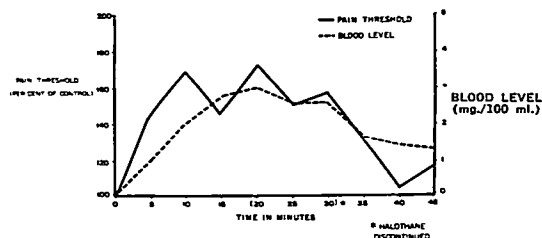


FIG. 4. Average pain thresholds and corresponding venous blood levels of halothane in subjects showing analgesic response.

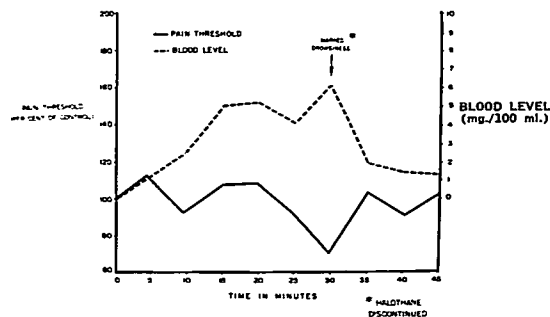


FIG. 5. Pain thresholds and corresponding blood levels of halothane demonstrating effects of drowsiness in subject showing little initial response.

sionally occurred. Figure 3 shows the pain thresholds and blood levels for the individual showing a significant reduction in pain threshold.

**Halothane.** In 2 subjects the studies were abandoned because sleep supervened within five minutes. In 6 subjects, administration of halothane was attended by significant elevations in pain threshold. With the onset of drowsiness the threshold returned to control in one subject and fell significantly below control in another. The remaining two subjects showed little initial effect followed by a reduction in threshold associated with the onset of marked drowsiness and/or disorientation.

The average pain thresholds and blood levels in subjects showing an analgesic response are seen in table 2 and figure 4. The thresholds were significantly raised through the 30 minute reading. No linear relation was observed between either individual or average blood levels of halothane and pain thresholds. Significant increases in pain threshold were seen with blood levels ranging from 1.0 to 3.84 mg./100 ml. In no instance was an antanalgesic-analgesic sequence demonstrated with increasing blood levels of halothane. On two occasions thresholds significantly below control were seen in the recovery period. During inhalation of halothane significant reductions in pain thresholds below pretest levels were seen on three occasions. All were associated with the onset of marked drowsiness combined in one case with disorientation (fig. 5); blood levels of halothane were 2.54, 3.50 and 6.15 mg./100 ml., respectively. In only one of these (3.50 mg./100 ml.) was a significant increase in threshold present prior to the onset of drowsiness. In another case an elevated threshold returned to control level with the onset of drowsiness at a blood level of 3.84 mg./100 ml.

Of the four subjects who participated in both studies, three exhibited qualitatively similar responses with each agent. The fourth showed an excellent analgesic response to methoxyflurane but fell asleep within five minutes with halothane and was excluded from this part of the study.

Acceptance of these studies was excellent. The experience was stated to be pleasant by

all the subjects for both agents. There were no instances of nausea or vomiting and normal activities including eating could be resumed within two hours in all cases.

### Discussion

The characteristic odors of methoxyflurane and halothane made it impossible to make this a "blind" study. Previous experience with this method of algesimetry<sup>10,11</sup> included the double-blind testing of saline placebos and narcotics alone or in combination with phenothiazine derivatives. Intravenous saline produced little change in threshold determined at 10-20 minute intervals for three hours whereas marked analgesic responses followed 1.0 mg./kg. doses of meperidine<sup>10</sup> in the same 16 subjects. As stated previously<sup>10</sup> we believe that algesimetry with any method can at best yield crude quantitative estimates of analgesic potency. This study was planned, therefore, not to compare the analgesic effects of methoxyflurane and halothane but in the hope that measurements of blood levels of these agents during algesimetric studies might explain the discrepancies between the results of Dundee *et al.*<sup>1,4</sup> and Robson *et al.*<sup>5</sup> This has not proved to be the case. The present findings are similar to those of Robson *et al.*<sup>5</sup> Although with methoxyflurane a few determinations in the recovery period suggested the possibility of an antanalgesic phase associated with low blood levels, the majority of the determinations during this phase were not confirmatory of antanalgesia and results during inhalation argued against such a theory. With halothane there was even less evidence of an antanalgesic phase. With both agents the possibility of antanalgesia with high blood levels was suggested by the few studies done. However, it is almost certain that the low pain thresholds obtained in these instances were associated with the onset of drowsiness and disorientation. The influence of drowsiness on reliability of subjects during algesimetric readings has previously been mentioned by Dundee<sup>7</sup> and by the present authors.<sup>11</sup>

Arterial levels during inhalation of methoxyflurane or halothane probably would have been higher than venous levels. This however, would not have altered the algesimetric

patterns and there would still have been no convincing evidence of an antanalgesic effect from either agent.

Because of the wide variations both in pain threshold and in blood levels of the agents concerned, it is not possible to give a meaningful estimate of what constitutes an analgesic blood level of either agent. However, it is worth stressing that the highest levels of methoxyflurane and halothane recorded in venous blood during an increase in pain threshold were 4.2 and 3.84 mg./100 ml., respectively. It would seem reasonable, therefore, to conclude that in individuals who show an analgesic response, a majority with both agents, this would be present with very low blood levels. This would offer experimental support for the anesthetic practice of adding low concentrations of these agents to nitrous oxide and oxygen as a method of reinforcing analgesic effectiveness.

### Summary

Algesimetric studies using the earlobe algesimeter were carried out in volunteers during and following the administration of sub-anesthetic concentrations of methoxyflurane and halothane. Methoxyflurane in oxygen was administered from a "Pentec" vaporizer for 40 minutes. Settings on the "Pentec" were varied between an initial 0.4 per cent and zero in an attempt to maintain consciousness throughout. Halothane in oxygen was administered from a Fluotec vaporizer at a constant setting of 0.5 per cent for 30 minutes or until unconsciousness supervened. Blood levels of the agents were measured in venous samples by gas chromatography. Significant increases in pain threshold were seen in 12 of 14 subjects receiving methoxyflurane and in 6 of 8 receiving halothane. The two remaining subjects in each group showed little initial effect followed by minimal to marked falls in threshold below control. These instances were usually associated with the onset of drowsiness. In the methoxyflurane group, pain threshold in four subjects fell below control values during the recovery period. No constant relationship between pain threshold and blood levels could be demonstrated although it would appear that significant analgesia may be present with

low levels of methoxyflurane (1.25 to 4.20 mg./100 ml.) or halothane (1.0 to 3.84 mg./100 ml.).

### References

1. Dundee, J. W., and Moore, J.: Alterations in response to somatic pain associated with anaesthesia. IV: The effect of sub-anaesthetic concentrations of inhalation agents, *Brit. J. Anaesth.* 32: 453, 1960.
2. Clutton-Brock, J.: The cerebral effects of over ventilation, *Brit. J. Anaesth.* 29: 111, 1957.
3. Dundee, J. W., and Moore, J.: Alterations in response to somatic pain associated with anaesthesia. I: An evaluation of a method of algesimetry, *Brit. J. Anaesth.* 32: 396, 1960.
4. Dundee, J. W., Nicholl, R. M., and Black, C. W.: Alterations in response to somatic pain associated with anaesthesia. X: Further studies with inhalation agents, *Brit. J. Anaesth.* 34: 158, 1962.
5. Robson, J. B., Davenport, H. T., and Sugiyama, R.: Differentiation of two types of pain by anesthetics, *ANESTHESIOLOGY* 26: 31, 1965.
6. Burns, B. D., Robson, J. G., and Welt, P. J. L.: The Effects of nitrous oxide upon sensory thresholds, *Canad. Anaesth. Soc. J.* 7: 411, 1960.
7. Dundee, J. W., and Love, W. J.: Alterations in response to somatic pain associated with anaesthesia. XIV: Effects of subanesthetic concentrations of methoxyflurane, *Brit. J. Anaesth.* 35: 301, 1963.
8. Boisvert, M., and Hudson, F.: Clinical evaluation of methoxyflurane in obstetrical anaesthesia: a report on 500 cases, *Canad. Anaesth. Soc. J.* 9: 325, 1962.
9. Romagnoli, A., and Kornan, D.: Methoxyflurane in obstetrical anaesthesia and analgesia, *Canad. Anaesth. Soc. J.* 9: 414, 1962.
10. Siker, E. S., Wolfson, B., and Stewart, W. D.: Further experience with the earlobe algesimeter, *ANESTHESIOLOGY* 27: 88, 1966.
11. Siker, E. S., Wolfson, B., Stewart, W. D., and Schaner, P. J.: The earlobe algesimeter. 2. The effect on pain threshold of certain phenothiazine derivatives alone or combined with meperidine, *ANESTHESIOLOGY* 27: 497, 1966.
12. Wolfson, B., Ciccarelli, H. E., and Siker, E. S.: Gas chromatography using an internal standard for the estimation of methoxyflurane levels in blood, *Brit. J. Anaesth.* 38: 29, 1966.
13. Wolfson, B., Ciccarelli, H. E., and Siker, E. S.: Gas chromatography using an internal standard for the estimation of ether and halothane levels in blood, *Brit. J. Anaesth.*, In Press.