The Effects of Alpha-methyldopa, Reserpine, Guanethidine, and Iproniazid on Minimum Alveolar Anesthetic Requirement (MAC)

Ronald D. Miller, M.D.,* Walter L. Way, M.D.,† Edmond I. Eger, II, M.D.‡

The effects of prior administration of alpha-methyldopa, reserpine, and guanethidine on the minimum alveolar concentration (MAC) of halothane were studied in dogs. The effect of iproniazid, a monoamine oxidase inhibitor, on cyclopropane MAC was studied in rats. Prior administration of alpha-methyldopa or reserpine, which reduce both central and peripheral norepinephrine levels, was associated with a reduction in MAC which was dose-related. Conversely, prior administration of iproniazid, which elevates central norepinephrine levels, resulted in an increase in MAC. MAC was not altered by prior administration of guanethidine, which reduces norepinephrine peripherally but not centrally. These results suggest that anesthetic requirement may be related in part to changes in norepinephrine content in the brain.

We observed that patients receiving 1 to 6 gm per day of alpha-methyldopa (Aldomet®) (AMD) required lower concentrations of inhalation anesthetic agents than usual to maintain adequate surgical anesthesia. For instance, two patients who underwent nephrectomy had received 3 gm of AMD per day; they required only 70 per cent nitrous oxide and only 0.0 to 0.2 per cent halothane for adequate surgical anesthesia without muscle relaxants.

AMD presumably produces its antihypertensive effect by formation of a false transmitter which displaces norepinephrine from its binding sites. Subsequently, central and peripheral catecholamine levels are reduced. Thus, we might postulate that a drug which reduces catecholamines (AMD or reserpine) may also decrease the concentration of inhalation anesthetic necessary to produce adequate surgical anesthesia. Conversely, this hypothesis suggests that any agent which elevates catecholamines (iproniazid) may increase anesthetic requirement. If reduction in anesthetic requirement is related to central rather than peripheral catecholamine depletion, an agent which reduces only peripheral catecholamines (guanethidine) should have no effect on anesthetic requirement.

This study quantifies the changes in anesthetic requirement associated with prior administration of AMD, reserpine, iproniazid, and guanethidine. The results suggest that anesthetic requirement is related to central catecholamine levels.

Methods

We used the minimum alveolar concentration (MAC) of anesthetic required to eliminate movement in response to a painful stimulus (tail clamp) to test the effects of prior administration of AMD, reserpine, guanethidine, and iproniazid on anesthetic requirement. Unpremedicated dogs (weighing 8 to 15 kg) were used to test the effects of AMD, reserpine, and guanethidine on halothane re-
requirement. All MAC determinations were done in triplicate.

To define the dose-response relationship of AMD and MAC, the following series of experiments was undertaken. MAC was determined in five dogs once a week for six weeks. Control values (no drugs) were determined in the first, third and sixth weeks. AMD, 200 mg/kg/day, was injected intravenously for three days prior to the second week’s determination; 50 mg/kg/day for three days prior to the fourth week’s determination; 100 mg/kg/day for three days prior to the fifth week’s MAC determination. In five other dogs, MAC was determined once a week for three weeks. The first MAC served as a control. AMD, 400 mg/kg/day for three days, was administered prior to the second MAC determination; 600 mg/kg/day for three days prior to the third MAC determination. In five other dogs, we studied the effect of chronic administration of AMD on MAC. After determination of a control MAC, AMD, 200 mg/kg/day, was injected intravenously for ten days. MAC was redetermined on the third and tenth days.

The effect of reserpine on MAC was studied in five dogs. Each animal served as its own control. MAC was then redetermined after two days of intramuscular injection of 0.1 mg/kg/day reserpine; after 0.4 mg/kg/day; and after 1.0 mg/kg/day. MAC was also determined 24 hours after intramuscular injection of 8 mg/kg reserpine. Dextrose (5 per cent) in Ringer’s lactate solution, 30 ml/kg body weight, was infused intravenously prior to the 8 mg/kg-dose series of experiments. MAC determinations were made at least two weeks apart.

To determine whether concomitant administration of AMD and reserpine might have a greater effect on MAC than either drug alone, MAC was determined after intravenous administration of AMD, 200 mg/kg/day for three days, and intramuscular injection of reserpine, 1.0 mg/kg/day, the last two of the three days, in five dogs. The drugs were administered a week or more after determination of a control MAC.

MAC was also determined before and after intravenous injection of guanethidine, 15 mg/kg/day for three days. In five dogs.

Immediately following the MAC determinations in each study, we tested (at MAC) the response of systolic blood pressure to ephedrine sulfate, 0.5 mg/kg intravenously. Since ephedrine acts primarily through release of norepinephrine, this provided an indirect index of degree of norepinephrine depletion or antisympathetic activity. Ephedrine was chosen despite a slight direct effect because of its availability. A possible alternative, tyramine, has also been shown to have a slight direct action,

The effects of monoamine oxidase inhibitors on cyclopropane MAC were studied in 11 Sprague-Dawley rats (300 gm) in order to evaluate the effects of elevated central catecholamine levels on MAC. We did not attempt to elevate central norepinephrine levels by peripheral infusion because norepinephrine does not cross the blood-brain barrier. Rats were chosen because administration of the common monoamine oxidase inhibitors elevates norepinephrine and serotonin levels,

while it raises serotonin only centrally in dogs. The cyclopropane MAC was determined using the tail-clamp method described by Hoffman et al. Cyclopropane was used because of its rapid rate of equilibration in animals whose end-tidal concentrations are difficult to measure. After determination of a control MAC, iproniazid phosphate, 125 mg/kg intraperitoneally, was administered. MAC was redetermined in 12 hours, which is within the peak time of central catecholamine elevation.

Each rat was placed in an enclosed clear plastic chamber. Cyclopropane concentrations were measured by infrared analysis at the entrance and within the chamber. MAC determinations were made only after the entrance and chamber cyclopropane concentrations had been equal for a minimum of five minutes. The first MAC measurements were made at least 25 minutes after induction of anesthesia; we assumed that cyclopropane uptake was minimal at this time. Colon temperatures were measured.

Where possible, the t test for paired observations and correlation coefficient were carried out for the results obtained.
Table 1. Effects of Prior Administration of Alpha-methyldopa, Reserpine, Guanethidine, and Alpha-methyldopa + Reserpine on Anesthetic Requirement (Halothane) and Systolic Blood Pressure Response to Ephedrine, 0.5 mg/kg Intravenously

<table>
<thead>
<tr>
<th>Drug</th>
<th>Control MAC</th>
<th>After Drug</th>
<th>Per Cent Decrease in MAC</th>
<th>Systolic Blood Pressure Response to Ephedrine (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha-methyldopa, 50 mg/kg/day × 3 days*</td>
<td>1.01 ± 0.09†</td>
<td>0.85 ± 0.11</td>
<td>16 ± 5</td>
<td>86 ± 14</td>
</tr>
<tr>
<td>Alpha-methyldopa, 100 mg/kg/day × 3 days</td>
<td>1.01 ± 0.09</td>
<td>0.79 ± 0.08</td>
<td>22 ± 4</td>
<td>80 ± 14</td>
</tr>
<tr>
<td>Alpha-methyldopa, 200 mg/kg/day × 3 days</td>
<td>1.01 ± 0.09</td>
<td>0.73 ± 0.08</td>
<td>28 ± 3</td>
<td>80 ± 14</td>
</tr>
<tr>
<td>Alpha-methyldopa, 400 mg/kg/day × 3 days</td>
<td>1.03 ± 0.13</td>
<td>0.71 ± 0.06</td>
<td>31 ± 5</td>
<td>85 ± 15</td>
</tr>
<tr>
<td>Alpha-methyldopa, 600 mg/kg/day × 3 days</td>
<td>1.09 ± 0.07</td>
<td>0.79 ± 0.10</td>
<td>28 ± 4</td>
<td>80 ± 15</td>
</tr>
<tr>
<td>Reserpine, 0.2 mg/kg (total dose)</td>
<td>1.04 ± 0.11</td>
<td>0.90 ± 0.08</td>
<td>14 ± 5</td>
<td>78 ± 20</td>
</tr>
<tr>
<td>Reserpine, 0.8 mg/kg (total dose)</td>
<td>0.98 ± 0.13</td>
<td>0.75 ± 0.09</td>
<td>23 ± 5</td>
<td>74 ± 20</td>
</tr>
<tr>
<td>Reserpine, 2.0 mg/kg (total dose)</td>
<td>1.07 ± 0.12</td>
<td>0.74 ± 0.12</td>
<td>31 ± 2</td>
<td>79 ± 24</td>
</tr>
<tr>
<td>Reserpine, 8.0 mg/kg (total dose)</td>
<td>1.04 ± 0.11</td>
<td>0.70 ± 0.06</td>
<td>33 ± 8</td>
<td>75 ± 14</td>
</tr>
<tr>
<td>Guanethidine, 15 mg/kg/day × 3 days</td>
<td>1.01 ± 0.13</td>
<td>1.00 ± 0.07</td>
<td>10 ± 9</td>
<td>78 ± 21</td>
</tr>
<tr>
<td>Alpha-methyldopa, 200 mg/kg/day × 3 days + reserpine, 2.0 mg/kg (total dose)</td>
<td>1.09 ± 0.07</td>
<td>0.75 ± 0.10</td>
<td>31 ± 6</td>
<td>81 ± 18</td>
</tr>
</tbody>
</table>

* Five experiments with each drug dose level. All MAC's = per cent halothane.
† Standard deviation.

Results

The control mean MAC's (in per cent halothane) at the first, third, and sixth weeks of the AMD studies were 0.98 ± 0.08 (S.D.), 1.00 ± 0.13, and 1.05 ± 0.08 (mean 1.01 ± 0.09), respectively. These values are within the range of values found by Eger et al., and represent a return to control MAC by one week after AMD administration. Prior administration of AMD resulted in a significant reduction in MAC at a dose of 50 mg/kg/day (P < 0.05) and larger doses (P < 0.01) (table 1). The correlation between dose of AMD and decrease in MAC was significant (r = 0.91, P < 0.05) up to a dose of 200 mg/kg/day. MAC values at three and at ten days of AMD administration were not significantly different from each other. Mean MAC after three days was 0.75 ± 0.07 per cent; after ten days of AMD treatment, 0.73 ± 0.09 per cent halothane. The control mean MAC (no drug) was 0.99 ± 0.07 per cent halothane.

Administration of reserpine produced an effect on MAC similar to that following administration of AMD (table 1, fig. 1). The reductions in MAC were significant at a dose of 0.1 mg/kg/day (P < 0.05) and greater doses (P < 0.01). The correlation between dose of reserpine and decrease in MAC was significant (r = 0.87, P < 0.05) up to a dose of 1.0 mg/kg/day.

Concomitant administration of AMD and reserpine did not reduce MAC more than each drug alone (table 1, fig. 1).

Prior administration of guanethidine did not alter MAC (table 1, fig. 1).

AMD, reserpine, and guanethidine reduced the rise in systolic blood pressure following ephedrine to a comparable degree (table 1, fig. 2). Following AMD, 200 mg/kg/day, reserpine, 2 mg/kg (total dose), or guanethidine, 15 mg/kg/day, administration of ephedrine resulted in increases in systolic blood pressure which were not significantly different from each other.

Administration of iproniazid resulted in a small but consistent and statistically significant (P = 0.01) increase in cyclopropane MAC in ten of 11 rats. The mean control MAC, 18.03 ± 1.22 per cent, rose after iproniazid to 19.51 ± 1.08 per cent. Colon temperatures ranged from 35 to 36.8°C in both control and medicated states.

Discussion

The results of this study support the hypothesis that anesthetic requirement is related to central catecholamine levels (table 2), as evidenced by the equivalent decreases in anes-
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Anesthesiology
Nov.-Dec. 1968

Fig. 1. Per cent decreases in halothane MAC associated with prior administration of alpha-methyl dopa, reserpine, guanethidine, and alpha-methyl dopa + reserpine together.

Thetetic requirement seen with catecholamine depletors, AMD and reserpine. This is supported by the finding that the decrease in MAC paralleled the decrease in systolic blood pressure response to ephedrine with AMD and reserpine. Increases in drug dosages beyond those producing maximum (peripheral) catecholamine depletion produced no further changes in MAC. Guanethidine, which reduces peripheral but not central catecholamines, did not alter MAC. A further decrease in MAC might have been anticipated if the drugs acted directly as depressants. The same reasoning may apply where AMD and reserpine were given together: each dose alone produced a maximum decrease in MAC and blood pressure response to ephedrine, and the combination had no greater effect than the individual drug alone. Last, elevation of central catecholamines by iproniazid was associated with a significant rise in MAC.

Administration of drugs such as monoamine oxidase inhibitors elevates brain catecholamine levels and results in behavioral excitement in many species. In contrast, animals receiving drugs which decrease catecholamine levels (reserpine and AMD) become sedated. Reserpine-induced sedation is antagonized by monoamine oxidase inhibitors. These observations parallel our findings. Spector et al. attributed the excitation seen with monoamine oxidase inhibitors to increases in brain norepinephrine content and not to brain serotonin content. The importance of norepinephrine relative to serotonin is suggested by our results, since others have found that AMD administration produces only a temporary change in brain serotonin. Brain norepinephrine levels, however, remain low for the duration of AMD administration. In contrast, reserpine causes depletion of both norepinephrine and serotonin.

There is another possible interpretation which requires, however, a specific hypothesis. AMD and reserpine may act directly to interrupt a specific central pathway transmitting some of the response to painful stimuli. Interruption of such a pathway would eliminate responsiveness to pain; dose levels above those causing interruption would produce no additional effect. This explanation is unlikely in

Fig. 2. Effects of prior administration of alpha-methyl dopa reserpine, guanethidine, and alpha-methyl dopa + reserpine together on the increase in systolic blood pressure in response to ephedrine. 0.5 mg/kg intravenously.
the case of reserpine since reserpine is not detectable in significant amounts a few hours after administration, although impairment of storage of norepinephrine persists for days. It may be possible, however, that reserpine is present for longer periods but not detectable.

Since anesthesia per se is not produced by total norepinephrine depletion, other factors must be involved in reducing MAC. Our results indicate the importance of one factor dependent on central norepinephrine levels. Other mechanisms may involve reductions in brain epinephrine or acetylcholine content. Epinephrine, however, is found only in low concentrations centrally. If acetylcholine were involved, one could postulate that its reduction might result in decreased anesthetic requirement. However, prior administration of reserpine results in an increase in acetylcholine content instead of a decrease.

The evidence for the relationship between brain norepinephrine levels and anesthetic requirement is suggestive, but not conclusive. Even the validity of correlating total brain norepinephrine levels with anesthetic requirement is questionable. Recent evidence demonstrates that peripheral adrenergic function may depend on specific, localized catecholamines rather than total tissue content. Although not demonstrated in the brain, one might speculate that brain pharmacologic actions of norepinephrine may depend on localized concentrations rather than total brain norepinephrine content. The quantity released and the effectiveness of that released is of prime importance, and we can only speculate that these parallel the catecholamine stores.

There are several clinical implications of this study. The usual inhalation anesthetic concentrations may be more than would be necessary for adequate surgical anesthesia in patients receiving agents which reduce central norepinephrine levels. However, if a drug reduced only peripheral norepinephrine levels, anesthetic requirement probably would be unchanged. That MAC is decreased to the same degree after three and ten days of administration of AMD suggests that tolerance to AMD does not develop with chronic administration despite the observation that the sedation associated with AMD treatment lasts for only three days. Conversely, patients receiving agents which elevate central norepinephrine levels (monoamine oxidase inhibitors) or those thought to act in the brain in a manner similar to norepinephrine (amphetamine) may have increased anesthetic requirements.

Any attempt to relate to man the doses used in studies of the dog and cat is obviously difficult. We chose the doses of AMD, reserpine, and guanethidine on the basis of peripheral and brain catecholamine-depleting activity demonstrated by others and the reduced increase in systolic blood pressure in response to indirect-acting vasoressors (ephedrine) demonstrated in our study.

Summary

The results of this study suggest that anesthetic requirement may be related in part to central norepinephrine levels. Prior administration of central norepinephrine depleters (alpha-methylidopa and reserpine) was associated with a reduction in halothane anesthetic requirement, while administration of central norepinephrine elevators was associated with an increase in cyclopropane anesthetic requirement. Prior administration of an agent which depletes peripheral, but not central, norepinephrine levels was associated with no change in anesthetic requirement.

The authors acknowledge the technical assistance of Arthur Babad, M.D., and the helpful suggestions of H. F. Morrelli, M.D., K. L. Melmon, M.D., W. K. Hamilton, M.D., and C. P. Larson, Jr., M.D. The following pharmaceutical firms supplied drugs for this study: Hoffmann La Roche; Merck, Sharp, and Dohme; Ayerst; and Ciba.

### Table 2. Relationship between Minimum Alveolar Anesthetic Concentration (MAC) and Central Norepinephrine Levels

<table>
<thead>
<tr>
<th>Drug</th>
<th>MAC</th>
<th>Central Norepinephrine</th>
<th>Peripheral Norepinephrine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha-methylidopa</td>
<td>Decrease</td>
<td>Decrease</td>
<td>Decrease</td>
</tr>
<tr>
<td>Reserpine</td>
<td>Decrease</td>
<td>Decrease</td>
<td>Decrease</td>
</tr>
<tr>
<td>Guanethidine</td>
<td>No change</td>
<td>No change</td>
<td>Decrease</td>
</tr>
<tr>
<td>Iproniazid</td>
<td>Increase</td>
<td>Increase</td>
<td>Increase</td>
</tr>
</tbody>
</table>
References


