The Effect of CNS Catecholamine-depleting Drugs on Dextroamphetamine-induced Elevation of Halothane MAC

Richard R. Johnston, M.D.,* Walter L. Way, M.D.,† Ronald D. Miller, M.D.‡

In a previous study, dextroamphetamine, 1.0 mg/kg, increased halothane MAC 90 per cent. Following intravenous administration of dextroamphetamine, 1.0 mg/kg, in this study, the MAC of halothane increased 50 ± 3.9 (SE) per cent in four dogs pretreated with reserpine, 2.0 mg/kg, and 17 ± 6.4 per cent in four dogs pretreated with alpha-methyl-tyrosine, 100 mg/kg. In six dogs pretreated with a serotonin depleter, paralorphophenylalanine, 350 mg/kg, halothane MAC was unchanged and increased 66 ± 7 per cent following dextroamphetamine, 1.0 mg/kg. These results suggest that increases in MAC after dextroamphetamine are related to CNS catecholamines, and further support the hypothesis that release or depletion of CNS catecholamines may alter the anesthetic dose of halothane. (Key words: Potency, anesthetic: MAC; Analgesics: dextroamphetamine; Anesthetics, volatile: halothane; Serotonin: brain; Brain: catecholamine levels.)

We previously demonstrated that acute intravenous administration of dextroamphetamine, which releases central nervous system (CNS) catecholamines, increased the minimum alveolar anesthetic concentration (MAC) of halothane. Other drug interactions also suggest that CNS catecholamines may influence the dose of anesthetic required. Reserpine and alpha-methyldopa, drugs reported to decrease CNS catecholamines, also decrease MAC, whereas iproniazid increases CNS catecholamines and increases MAC. To test further the postulated relationship between CNS catecholamines and MAC, we determined halothane MAC following acute administration of dextroamphetamine to dogs pretreated with reserpine or alpha-methyl-p-tyrosine (AMT), drugs which reduce brain catecholamine levels. Since reserpine may also reduce 5-hydroxytryptamine (5-HT) in the CNS, we further evaluated the effect of using paralorphophenylalanine, a drug which decreases 5-HT in the CNS of the dog, on halothane MAC.

Methods and Materials

Dogs 9 to 17.5 kg in weight were anesthetized with halothane in oxygen. The tracheas were intubated without use of muscle relaxants and ventilation was controlled with a Harvard pump to maintain $pH_a$ between 7.35 to 7.40.

The minimum alveolar concentration (MAC) of halothane required to eliminate movement in response to a painful stimulus was used as a standard of anesthetic potency. In all studies, esophageal temperatures were controlled at 37.5 ± 0.5 C (SE). Femoral arterial pressure was continuously monitored from a percutaneous indwelling catheter connected to a Statham P23C transducer and recorded on a Grass recorder. $P_{aco_2}$, $P_{ao_2}$, and $pH_a$ were determined with standard electrodes. Ringer’s lactate solution, approximately 5 ml/kg/hr, was infused in a hind limb vein. Arterial blood samples, drawn intermittently, were placed in tubes with ethylenediaminetetraacetic acid and stored at 10 C until they were analyzed for dextroamphetamine by the method of Rowland (Rowland, M., Department of Pharmacy, University of California, San Francisco Medical Center, personal communication).

The dogs were divided into three treatment groups. In a previous study, dextroamphetamine, 1.0 mg/kg, was administered intravenously to five dogs during halothane

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TABLE 1. MAC Changes following Dextroamphetamine in Dogs Pretreated with Reserpine, 1.0 mg/kg, for Two Days

<table>
<thead>
<tr>
<th>Dog</th>
<th>Halothane MAC after Reserpine (Per Cent)</th>
<th>Halothane MAC after Dextroamphetamine (Per Cent)</th>
<th>Per Cent Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>.76</td>
<td>1.12</td>
<td>47</td>
</tr>
<tr>
<td>2</td>
<td>.75</td>
<td>1.19</td>
<td>59</td>
</tr>
<tr>
<td>3</td>
<td>.76</td>
<td>1.07</td>
<td>41</td>
</tr>
<tr>
<td>4</td>
<td>.80</td>
<td>1.22</td>
<td>52</td>
</tr>
<tr>
<td>X ± SE</td>
<td>.77 ± .01</td>
<td>1.15 ± .03*</td>
<td>50 ± 3.9†</td>
</tr>
</tbody>
</table>

* Significant, P < .05 compared with control (after reserpine).
† Significant, P < .05 compared with halothane-dextroamphetamine alone.

Anesthesia and changes in MAC were determined. Results served as control data for the three groups, pretreated with the following drugs:

Reserpine. Reserpine, 1.0 mg/kg, was administered intramuscularly to each of four dogs for two consecutive days. On the third day the animals were anesthetized and a "reserpine MAC" determined. Dextroamphetamine, 1.0 mg/kg, was then infused and MAC redetermined in a period 60–120 minutes after infusion. MAC values were not determined prior to reserpine treatment in this group since the effect of reserpine alone on anesthetic requirement has been reported.

Alpha-methyl-p-tyrosine (AMT). A control MAC was determined in four dogs. After a one-week recovery, AMT, 100 mg/kg, was infused intravenously and MAC redetermined 96 hours later. Dextroamphetamine, 1.0 mg/kg, was then administered and MAC redetermined one hour later.

Parachlorophenylalanine (PCPA). In six dogs one week after determination of a control MAC, PCPA, 350 mg/kg, was infused intravenously and MAC redetermined 96 hours later. In four of these six dogs, dextroam-

TABLE 2. MAC Changes following Dextroamphetamine in Dogs Pretreated with Alpha-methyl-p-tyrosine

<table>
<thead>
<tr>
<th>Dog</th>
<th>Halothane MAC before AMT (Per Cent)</th>
<th>Halothane MAC after AMT (Per Cent)</th>
<th>Per Cent Change</th>
<th>Halothane MAC after AMT and Dextroamphetamine (Per Cent)</th>
<th>Per Cent Change from Control after Dextroamphetamine and AMT</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>1.16</td>
<td>.95</td>
<td>−27</td>
<td>.98</td>
<td>+15</td>
</tr>
<tr>
<td>7</td>
<td>.98</td>
<td>.75</td>
<td>−24</td>
<td>.98</td>
<td>+30</td>
</tr>
<tr>
<td>8</td>
<td>.96</td>
<td>.72</td>
<td>−24</td>
<td>.72</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>.85</td>
<td>.73</td>
<td>−38</td>
<td>.65</td>
<td>+23</td>
</tr>
<tr>
<td>X ± SE</td>
<td>.99 ± .06</td>
<td>.71 ± .07*</td>
<td>−28 ± 1.0</td>
<td>.83 ± .08</td>
<td>+17 ± 6.4†</td>
</tr>
</tbody>
</table>

* Significant, P < .05 compared with control (pre-drug).
† Significant, P < .05 compared with halothane-dextroamphetamine alone.

TABLE 3. MAC Changes following Dextroamphetamine in Dogs Pretreated with Parachlorophenylalanine (PCPA)

<table>
<thead>
<tr>
<th>Dog</th>
<th>Halothane MAC Control (Per Cent)</th>
<th>Halothane MAC after PCPA (Per Cent)</th>
<th>Per Cent Change</th>
<th>Halothane MAC after PCPA and Dextroamphetamine (Per Cent)</th>
<th>Per Cent Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>.85</td>
<td>.80</td>
<td>−6</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>11</td>
<td>1.03</td>
<td>.96</td>
<td>−7</td>
<td>−</td>
<td>−</td>
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<tr>
<td>12</td>
<td>.82</td>
<td>.90</td>
<td>10</td>
<td>1.56</td>
<td>73</td>
</tr>
<tr>
<td>13</td>
<td>.95</td>
<td>1.01</td>
<td>7</td>
<td>1.64</td>
<td>62</td>
</tr>
<tr>
<td>14</td>
<td>1.02</td>
<td>1.12</td>
<td>10</td>
<td>1.97</td>
<td>75</td>
</tr>
<tr>
<td>15</td>
<td>1.10</td>
<td>1.12</td>
<td>2</td>
<td>1.7</td>
<td>52</td>
</tr>
<tr>
<td>X ± SE</td>
<td>.96 ± .04</td>
<td>.99 ± .05</td>
<td>1.7 ± .08*</td>
<td>66 ± 7</td>
<td></td>
</tr>
</tbody>
</table>

* Significant, P < .05 compared with after PCPA.
amphetamine, 1.0 mg/kg, was then administered and MAC redetermined one hour later.

Drug doses were calculated by weight of their salts. Commercial reserpine (Serpasil, Ciba) was used. Fresh AMT (Regis Laboratories) and PCPA (Pfizer Laboratories) were prepared by solution of the salt in warmed alkaline solution and titrated to a pH of approximately 10. Dextroamphetamine solution was prepared by our hospital pharmacy as a bacteriologically filtered sodium chloride solution of 10 mg/ml.

Data within each drug group were compared using paired t testing. Analysis of variance was utilized to compare per cent changes among the drug groups. Changes in MAC were calculated as the difference between control MAC and posttreatment MAC. Posttreatment MAC values, such as with AMT, were “control” values for subsequent administration of dextroamphetamine. Analysis of variance was used to compare blood dextroamphetamine concentrations among studies of dextroamphetamine alone and the various drug treatments.

Results

Our previous investigation revealed a significant increase (90 per cent) in halothane MAC following 1.0 mg/kg of dextroamphetamine. In the present study, two days of reserpine treatment (1 mg/kg/24 hr) reduced the dextroamphetamine-induced increase in halothane MAC to 50 ± 3.9 per cent (SE) (table 1).

Pretreatment with AMT resulted in a significant 28 ± 1.0 per cent decrease in MAC (table 2). Dextroamphetamine administration after AMT increased MAC by only 17 ± 6 per cent, which was not significantly different from values after AMT alone.

No significant change in MAC followed PCPA treatment, alone or in combination with dextroamphetamine (table 3). The changes in MAC following dextroamphetamine in the PCPA-treated dogs were not different significantly from those in dogs given dextroamphetamine alone. There was no significant difference among blood dextroamphetamine concentrations in dogs given dextroamphetamine alone or dogs pretreated with reserpine or AMT. However, blood dextroamphetamine in dogs pretreated with PCPA was significantly lower than that in dogs pretreated with dextroamphetamine alone.

Discussion

Our study represents an indirect attempt to demonstrate a relationship between CNS catecholamines and MAC. Our results suggest that increases in MAC observed after acute administration of dextroamphetamine were related to release of CNS catecholamines and further support the hypothesis that CNS catecholamines may be important in modulation of anesthetic dose.

Our study design, using each dog as its own control, precluded simultaneous MAC and brain catecholamine determinations. The lack of measurements of brain catecholamine changes after treatment limits interpretation of our data. However, measurement of total brain catecholamine levels might not have
allowed any broader interpretation, since catecholamine content does not define dynamics of release or turnover or concentrations in specific functional areas or availability to a "receptor."

Nevertheless, the drugs utilized in our study are known to alter "availability" to "receptors" of putative brain neurotransmitters, and changes in the availability of brain catecholamines have been associated with altered behavioral patterns. For example, the increased alertness and locomotion following administration of dextroamphetamine have been attributed to increased release of catecholamines. Reserpine and AMT result in lethargy, attributed to decrease in availability of catecholamines in the CNS. Reserpine prevents synthesis,17 while AMT prevents synthesis,18 of catecholamines in the CNS. If CNS catecholamines cannot be released because of inadequate quantities or synthesis, then CNS sympathetic stimulation by dextroamphetamine might not occur. Using reserpine and AMT, we were able to decrease significantly the dextroamphetamine-induced increase in halothane MAC. This lends support to the hypothesis that increases of MAC by dextroamphetamine are related to CNS catecholamine release.

Since reserpine may also alter 5-HT, we evaluated the effect of depletion of 5-HT on MAC. In dogs, PCPA is claimed to depress brain 5-HT by more than 80 per cent 96 hours after intravenous administration, without altering norepinephrine or epinephrine levels (Fuller, R.W., Eli Lilly Company, personal communication). This dose of PCPA resulted in little effect on MAC. That MAC values with dextroamphetamine after PCPA treatment were lower than those with dextroamphetamine alone might relate to the lower blood dextroamphetamine concentrations in the PCPA-treated animals. We have no explanation for the difference between these blood levels. The results with PCPA pretreatment suggest that the changes in MAC with reserpine or AMT pretreatment are not related to 5-HT depletion.

Although we did not establish a dose-response curve with AMT or reserpine, we administered doses of both drugs which probably resulted in maximal effects on brain catecholamine storage or synthesis. A 2 mg/kg dose of reserpine resulted in death in two of three dogs in an earlier pilot study. Diarrhea and dehydration with renal damage14 are produced by larger doses of AMT, and probably occurred in one dog which died 48 hours after the study. We previously found in five dogs no further increase in MAC with 2.0 mg/kg of dextroamphetamine (unpublished observations).

Assuming that reserpine and AMT decrease availability of catecholamines to a "receptor," we postulate that dextroamphetamine increases halothane MAC through release of CNS catecholamines. If this conclusion is correct, increased CNS catecholamine release is excitatory and antagonizes "anesthesia" or "analgesia" produced by halothane.

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References

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Finances

COST OF MEDICAL CARE AND SURVIVAL The author has collected and correlated information on the 702 patients admitted to the Surgical Intensive Care Unit (SICU) at Massachusetts General Hospital during 1970, the first complete year of its operation. Approximately three-fourths of the admissions were postoperative cardiac surgical patients, while the rest were critically ill general surgical patients. Mortality rates and costs were considered in relation to length of stay in the SICU. The mortality rate for cardiac surgical patients discharged from the SICU within one week of surgery (comprising about 90 per cent of such patients) was 6 per cent, whereas those discharged after one week suffered 30 per cent mortality. Of the general surgical patients, 45 per cent of those discharged from the SICU in the first week and 60 per cent of those discharged after one week died. The median SICU stay of the cardiac surgical patients was 2.8 days, and that of the general surgical patients, 5.2 days. The estimated daily cost of SICU care was $761, including all drugs, tests, and procedures, and the daily cost was $187 for the rest of the hospitalization. Although the total hospital stays averaged 20.3 days for patients who died and 32.3 days for survivors, those who died stayed an average of 11 days in the SICU, as opposed to 5.6 days for the survivors. Therefore, the total hospital bill was only slightly higher for patients who died. Since the longer stay in the SICU implied more severe disease and less chance for survival, it would appear that cost of medical care is inversely related to survival. In order to effect more efficient utilization of the facility, patients in the SICU were considered to be in one of three classes according to the intensity of care needed. Monitoring, professional case, and laboratory studies were then utilized in relation to the severity of illness. (Cicetta, J.: The Inverse Relationship between Cost and Survival. J Surg Res 14: 265-269, 1973.)