Effect of Bretylium Tosylate (Darenthin) on Pulmonary Circulation


Bretylium tosylate (Darenthin, Burroughs Wellcome), is one of the series of benzyl quaternary ammonium compounds which blocks selectively the peripheral sympathetic nervous system without antagonizing the effects of epinephrine. This block occurs without depression of the parasympathetic or central nervous system. Its effect on the pulmonary circulation has not hitherto been investigated.

Methods

Experiments were carried out on eight sheep ranging from 40 to 45 Kg. The fasting supine animals were anesthetized with 10 to 15 mg./Kg. thiopental (Thiopentone) injected intravenously. This dose was followed by a continuous intravenous saline drip of 2.0 to 2.5 ml./min. containing 0.20 to 0.25 mg./Kg./min. thiopental and 0.15 to 0.20 mg./Kg./min. heparin. A cuffed Magill tube (no. 12) was used for intubation of the trachea and a no. 7 cardiac catheter was passed through the femoral vein and introduced into the pulmonary artery. In two animals a no. 8 double-lumen catheter was used instead with the distal end wedged into the artery to measure pulmonary "capillary" pressure. A cannula was inserted into the femoral artery and a thermometer into the rectum. Oxygen content of the systemic (Ca) and pulmonary (Cv) arterial blood and total hemoglobin were determined spectrophotometrically. Expired air (VE) was collected for 1% to 2 minutes in Douglas bags; their composition was analyzed by the Haldane method. Carbon dioxide content and pH were measured in the arterial blood of three animals. Their arterial CO2 tension (PaCO2) and alveolar ventilation (VA) were calculated as described elsewhere.

Pulmonary arterial (Ppa) and systemic arterial (Psa) pressures were measured by transducers and recorded on a Sanborn multichannel direct-writing oscillograph. In two animals pulmonary arterial wedge pressure (Ppaw) and right ventricular pressure (Pv-r) were recorded simultaneously. A point 10 cm. above the back of the supine animals was used for reference level. Pressures were determined before and after the collection of expired air. Blood samples were taken in the midperiod of collection of expired air.

The Fick principle was used to calculate cardiac output (Q), and the shunt-equation \( (C_{O2} - C_{O2} \cdot C_{O2}) \) was used to calculate venous admixture \( Q_s \), expressed in per cent of Q. Oxygen content of the pulmonary capillary blood \( C_{O2} \) was estimated by subtracting 0.60 volume per cent from the oxygen-carrying capacity of the arterial blood.

Total pulmonary \( (R_{pulm}) \) and systemic \( (R_{sys}) \) resistances were calculated by the usual formulas and expressed in dynes/sec./cm.5. Flows, resistances, and ventilated volumes are expressed on basis of one square meter of body surface area.

After a control period, 10 mg./Kg. bretylium were slowly injected into the pulmonary artery. Twenty-five minutes later all measurements were repeated. In two animals 100 per cent oxygen breathing was commenced subsequently for 10 minutes.

Results

Results are shown in table 1. The slight, not statistically significant, increase in \( V_E \) and \( V_t \) may be coincident to a significant rise in \( Q_s \) (0.02 < \( P < 0.05 \)) and the resulting hypoxemia. The slight increase in Q and the equally small fall in \( P_{pa} \) resulted in a decrease in \( R_{sys} \) of questionable statistical significance (0.05 < \( P < 0.10 \)). A rise in \( P_{paw} \) has also occurred in both cases investigated (fig. 1). Alveolar oxygen tension \( (P_{AO2}) \) was calculated in three animals (nos. 116, 121, and 123). It was normal during the control period and increased slightly after the administration of bretylium. The inhalation of 100 per cent oxygen resulted in a fall in \( P_{paw} \) and \( P_{paw} \) in both animals (fig. 1).

Discussion

It is not without precedent that a systemic hypotensive agent should act as a pressor substance in the pulmonary circulation: Apresoline has a similar effect. This action of bretylium is apparently unrelated to its sym-
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patholytic properties. Other adrenergic neuronal blocking agents, e.g., Hydergine or Dibenamine, fail to increase P_p.a..

The simultaneous rise in P_p.a.w. indicates that bretylium-induced pulmonary hypertension has a precapillary and postcapillary component. The rapid return of both pressures to normal during oxygen breathing appear to suggest that the rise in pressure was caused by a constriction or increase in tone of the arterioles and venules.

The increase in Q_s is reminiscent of that following the administration of aminophylline, norepinephrine, and acetylcholine. No attempt was made to investigate its mechanism.

Pulmonary hypertension in bretylium-treated sheep was coincident to hypoxemia and reversed by oxygen breathing. This indicates the necessity to assess the possible role of hypoxia.

Hypoxemia was shown to increase P_p.a. in dogs in the presence of normal P_A provided the fall in P_A exceeded 10 per cent. Mean P_A in our animals decreased from 89.7 to 84.4 per cent. No correlation could be obtained between the increase in Q_s and the rise in P_p.a. As the most potent pulmonary vasodilator, oxygen is capable of abolishing several types of pulmonary hypertension etiologically unrelated to hypoxia. It appears, therefore, unlikely that hypoxemia would be a major factor in the genesis of the mild pulmonary hypertension induced by bretylium.

Table 1

<table>
<thead>
<tr>
<th>No. of experiment</th>
<th>116</th>
<th>119</th>
<th>121</th>
<th>122</th>
<th>123</th>
<th>126</th>
<th>Mean</th>
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<tbody>
<tr>
<td>V_E (L.min./M^2 BSA, BTPS)</td>
<td>C 9.6</td>
<td>8.2</td>
<td>7.9</td>
<td>10.7</td>
<td>4.3</td>
<td>5.3</td>
<td>7.7</td>
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<tr>
<td>V_t (ml./M^2 BSA, BTPS)</td>
<td>D 9.7</td>
<td>9.0</td>
<td>5.8</td>
<td>11.7</td>
<td>6.5</td>
<td>5.3</td>
<td>8.0</td>
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<tr>
<td>Q (L/M^2 BSA)</td>
<td>C 164</td>
<td>207</td>
<td>199</td>
<td>301</td>
<td>193</td>
<td>242</td>
<td>218</td>
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<tr>
<td>L/M^2 BSA</td>
<td>D 185</td>
<td>213</td>
<td>196</td>
<td>314</td>
<td>267</td>
<td>216</td>
<td>232</td>
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<tr>
<td>F_r,m, mm Hg</td>
<td>C 120</td>
<td>142</td>
<td>120</td>
<td>95</td>
<td>130</td>
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<td>124</td>
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<td>D 112</td>
<td>115</td>
<td>136</td>
<td>80</td>
<td>120</td>
<td>110</td>
<td>112</td>
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<td>R_arterial (dyne.sec./cm.^2/M^2 BSA)</td>
<td>C 3824</td>
<td>3158</td>
<td>3368</td>
<td>2256</td>
<td>4173</td>
<td>3781</td>
<td>3427</td>
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<tr>
<td>D 2334</td>
<td>2848</td>
<td>3487</td>
<td>1899</td>
<td>3019</td>
<td>3411</td>
<td>2833</td>
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<td>Q_per cent</td>
<td>C 20</td>
<td>25</td>
<td>8</td>
<td>6</td>
<td>21</td>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td>D 34</td>
<td>35</td>
<td>18</td>
<td>12</td>
<td>50</td>
<td>5</td>
<td>26</td>
<td></td>
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<tr>
<td>P_p.a., mm Hg</td>
<td>C 8</td>
<td>9</td>
<td>14</td>
<td>10</td>
<td>12</td>
<td>15</td>
<td>11</td>
</tr>
<tr>
<td>D 12</td>
<td>15</td>
<td>19</td>
<td>11</td>
<td>19</td>
<td>24</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>R_pulmonary (dyne.sec./cm.^2/M^2 BSA)</td>
<td>C 287</td>
<td>226</td>
<td>393</td>
<td>237</td>
<td>385</td>
<td>411</td>
<td>323</td>
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<td>D 250</td>
<td>371</td>
<td>487</td>
<td>261</td>
<td>478</td>
<td>744</td>
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</table>

*For abbreviations see Methods. C = control period; D = 25 minutes following the administration of bretylium. Statistical significance of changes is described in text.
Summary

In a dose sufficient to produce a mild systemic hypotension, bretylium increases pulmonary arterial pressure and venous admixture in the experimental animal. The clinical significance of these side effects appears to deserve some consideration.

Acknowledgment

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Addendum

After this manuscript was submitted, pulmonary hypertension occurring in humans treated with bretylium was described by Taylor and Donald (Lancet 2: 389, 1960).

References


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