Graded Reduction of Arterial Pressure in Man by Means of a Thiophanium Derivative (Ro 2-2222)

Preliminary Observations on Its Effect in Acute Pulmonary Edema

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The authors describe the use of a ganglionic blocking agent which acts almost entirely as a peripheral vasodilator with minimal side effects in man. This substance acts almost instantaneously when given intravenously, with the depressor effect quantitatively controlled by regulating the infusion rate without tachyphylaxis over several hours. Depressor effect of the drug disappears 2 to 15 minutes after stopping the infusion and is blocked promptly by intravenous ephedrine, neosynephrine or norepinephrine. The authors discuss its use in the treatment and elucidation of the basic mechanisms of acute pulmonary edema.

Randall, Peterson, and Lehmann have described a ganglionic blocking agent which reduces arterial pressure in anesthetized dogs and cats. This compound, d-3,4-(1',3'-dibenzy1-2'-ketoimidazolido)-1,2-trimethylene thiophanium d-camphor sulfonate, will be called by its code number, Ro 2-2222, for convenience. It effectivelly lowers arterial blood pressure at much lower dosage levels than tetraethylammonium chloride. Furthermore, during recent investigations on the role of the autonomic nervous system in experimentally induced pulmonary edema, Ro 2-2222 has been found to lower pulmonary venous pressure to normal from previously induced levels of 20 to 70 mm. Hg. These favorable experimental data have prompted us to investigate and report the action of Ro 2-2222 in man.

Method

Administration. After preliminary investigation, Ro 2-2222 was given intravenously 27 times to 13 hypertensive patients and twice to two normotensive patients in one of two ways: (a) as single or multiple injections of either 0.1 or 0.2 mg. per kilogram of body weight, given in 30 seconds intravenously; or (b) as a continuous intravenous drip of 1 or 2 mg. of the drug per cc. in a 5 per cent dextrose solution.

After an intravenous infusion of 5 per cent dextrose had been established, control observations were made and the infusion of Ro 2-2222 in 5 per cent dextrose was started by turning a three-way stopcock in the line in such a manner that the patient was probably unaware of the change. This continuous infusion method was thought by the authors to yield the most significant information. Table I lists the patients.

Arterial pressure was recorded by means of the sphygmomanometer adhering to the criteria of Ragan and Bordley. In one patient brachial and pulmonary arterial pressures were recorded directly by means of the electromanometer. The heart rate was counted with the aid of a stopwatch. All patients were studied in the horizontal position with one pillow under the head except (a) the pulmonary edema patients described below, and (b) one patient with hypertensive encephalopathy, to whom Ro 2-2222 was given while in the lateral decubitus position in order to obtain readings of cerebrospinal fluid pressure.

Skin temperatures were taken either by means of the Rauh apparatus or the continuously recording, multiple lead, Brown potentiometer as used in previous studies.
When the continuous drip method was employed, the dripper was calibrated in terms of drops per cubic centimeter so that conversion to milligrams per minute could be made. The data obtained will be presented in that form. The cold pressor test was performed by immersing one hand up to the wrist in ice water for two minutes.

**Observations**

*Single or Multiple Intravenous Injections of Ro 2-2222.* The effects of single or multiple intravenous injections are shown in figure 1. Figure 1A shows the brevity of the depressor response when 0.2 mg. per kilogram was used.

**Table 1.—Clinical Findings in Thirteen Hypertensive and Two Normotensive Patients**

<table>
<thead>
<tr>
<th>Name</th>
<th>Age</th>
<th>Admission Blood Pressure</th>
<th>Maximum Urine S. G.</th>
<th>Blood Trea Pressor</th>
<th>Capillary</th>
<th>Cardiac Failure</th>
<th>Encephalopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I. N.</td>
<td>68</td>
<td>240/140</td>
<td>1.019</td>
<td>14</td>
<td>+</td>
<td>O</td>
<td>+</td>
</tr>
<tr>
<td>2. V. H.</td>
<td>34</td>
<td>220/140</td>
<td>1.010</td>
<td>18</td>
<td>+</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>3. H. H.</td>
<td>26</td>
<td>220/155</td>
<td>1.018</td>
<td>20</td>
<td>+</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>4. A. M.</td>
<td>50</td>
<td>250/170</td>
<td>1.014</td>
<td>85</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>5. H. G.</td>
<td>50</td>
<td>225/155</td>
<td>1.019</td>
<td>12</td>
<td>+</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>6. W. S.</td>
<td>41</td>
<td>190/130</td>
<td>1.009</td>
<td>85</td>
<td>+</td>
<td>+</td>
<td>O</td>
</tr>
<tr>
<td>7. M. D.</td>
<td>45</td>
<td>230/120</td>
<td>1.024</td>
<td>12</td>
<td>+</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>8. E. M.</td>
<td>42</td>
<td>250/160</td>
<td>1.020</td>
<td>21</td>
<td>+</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>9. F. G.</td>
<td>40</td>
<td>220/125</td>
<td>1.010</td>
<td>13</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>10. F. M.*</td>
<td>42</td>
<td>130/90</td>
<td>1.024</td>
<td>10</td>
<td>O</td>
<td>O</td>
<td>+*</td>
</tr>
<tr>
<td>11. J. H.</td>
<td>44</td>
<td>184/110</td>
<td>1.012</td>
<td>27</td>
<td>+</td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>12. W. M.</td>
<td>39</td>
<td>250/178</td>
<td>1.024</td>
<td>1.015</td>
<td>37</td>
<td>+</td>
<td>O</td>
</tr>
<tr>
<td>13.† E. G.</td>
<td>32</td>
<td>220/140</td>
<td>1.010</td>
<td>25</td>
<td>+*</td>
<td>O</td>
<td></td>
</tr>
<tr>
<td>14.† A. L.</td>
<td>14</td>
<td>170/120</td>
<td>1.012</td>
<td>203</td>
<td>+*</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>15.† G. H.</td>
<td>45</td>
<td>70/60</td>
<td>1.017</td>
<td>47</td>
<td>+*</td>
<td>O</td>
<td></td>
</tr>
</tbody>
</table>

* Normotensive patient with central nervous system syphilis.
† Patients with acute pulmonary edema.

Figure 1B indicates the reproducibility of the depressor response when a second dose was given 22 minutes after the first. Figures 1C and 1D suggest that a reasonable type of dose-response relationship exists insofar as can be determined from the depressor effects of 0.1 and 0.2 mg. per kilogram. Figure 1C further shows the similarity of the depressor response to a dose of 0.2 mg. per kilogram given to the same patient on two successive days.

In figure 1E is shown the effect of a single dose of 0.2 mg. per kilogram on cerebrospinal fluid pressure in a patient with hypertensive encephalopathy. About 12 cc. of spinal fluid had been removed just prior to the period during which the observations were made, and the cerebrospinal fluid pressure was returning to its previous level when the intravenous injection of Ro 2-2222 was made. A temporary and slight reduction in cerebrospinal fluid pressure occurred. Unfortunately, no data were obtained during the more prolonged depressor effect obtained with the continuous drip technique as described below. (See addendum.)

As seen in figure 2A, tachyphylaxis did not occur when a total of 1 mg. per kilogram was administered in divided doses over a period of 31 minutes. This figure confirms the nature of the dose-response relationship as seen above, since 0.1 mg. per kilogram given at the beginning and end of the sequence had less of an effect than doses of 0.2 mg. per kilogram administered in the interim. The over-all effect was an irregular lowering of arterial pressure. However, the reproducibility of the response was demonstrated.

*Ro 2-2222 Administered as a Continuous Intravenous Drip.* In figure 2B the effect on arterial pressure of a continuous infusion of 3 mg. per minute can be seen. The cold pressor test, which yielded a substantial rise of both systolic and diastolic pressures during the control period, did not produce a pressor response during the administration of Ro 2-2222. Cessation of the infusion was followed by a prompt return of arterial pressure to control levels.

Figure 3 shows the effect on arterial pressure of varying the rate of infusion. Note that different degrees of reduction in arterial pressure could be obtained and that this depended upon the rate of administration of the drug. In addition, changes in arterial pressure levels occurred promptly so that the new level was apparent within a few minutes after changing the rate of administration. The induced fall of arterial pressure could be made either abrupt or gradual and to those levels found desirable to meet the therapeutic or experimental requisites.

The response of skin temperature during the administration of Ro 2-2222 is shown in figure 3B, wherein it can be seen that the cutaneous temperatures of the right and left great toe.
rose during the hypotensive periods and fell when arterial pressure rose toward control levels. The injection of 50 mg. of ephedrine sulfate intramuscularly elevated arterial pressure and lowered skin temperature while the administration of Ro 2-2222 was being continued.

In figure 3C, data from a normotensive patient, the administration of 50 mg. ephedrine sulfate intravenously produced a marked elevation of arterial pressure from the hypotensive level produced by Ro 2-2222. In this patient, as in the patient of figure 2B, the cold pressor test failed to elevate arterial pressure during the administration of the drug.

The response of the pulse rate seen in figure
2B was the greatest change observed. In one other instance it rose 15 beats per minute but returned to control levels during the continued administration of the drug. In other patients the pulse rate changed less than 10 beats per minute and most frequently decreased.

In one patient (previous data shown in fig. 3B), Ro 2-2222 was given as a continuous infusion while the patient was on the artificial kidney. Figure 4 shows the reduction in pulmonary arterial pressure that accompanied the reduction in systemic arterial pressure 3.5 min-

utes after the start of the infusion of Ro 2-2222 at the rate of 3.7 mg. per minute.

Acute Toxicity. Insofar as the gross observation of the patient is informative, the acute toxicity of Ro 2-2222 in the doses administered was as follows:

One patient (fig. 1A) had restlessness and a temporary clouding of the sensorium during the hypotensive period after the arterial pressure had been abruptly lowered. These symptoms also occur with abrupt hypotension induced by other means, such as tetraethylammonium chloride or high spinal anesthesia. They were not seen in those patients in whom the continuous infusion method was used. In two patients with hypertensive encephalopathy, gastrointestinal symptoms were observed when the intravenous drip was increased to the point of tolerance. Nausea, retching, and the passage of flatus occurred in one, and nausea and vomiting in the other. Although both patients had been nauseated and had vomited several times previously on the same day, the reaction, coming as it did at the time of the highest dose level, was attributed to the drug. This occurred, however, at a dosage level several times higher than was required for an effective depressor response. In two other patients, the hypotensive phase during the administration of Ro 2-2222 was accompanied by persistent yawning, frequent eructation, and the passage of flatus. Yawning accompanied the continuous administration of Ro 2-2222 in all the hypertensive patients to whom it was given in effective depressor doses, except in the patients with acute pulmonary edema described below. It did not occur in the one normotensive patient studied.

When the agent was administered for any length of time, dryness of the mouth always
occurred. This can reasonably be attributed to the parasympatholytic activity of the drug as described by Randall and co-workers.\textsuperscript{1} No other side reactions were observed.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig3a-c.png}
\caption{Effect of varying the rate of administration of Ro 2-2222. Drug given as a solution containing 2 mg. per cc. in 5 per cent dextrose. Changes in skin temperature shown in B. Note effect of 50 mg. ephedrine sulfate intramuscularly in B and ephedrine sulfate, 50 mg., intravenously in C. This latter was given at 5:33 p.m. C.P.T. = cold pressor test.}
\end{figure}

\textbf{Case Reports}

\textbf{Case 1. Treatment of Acute Pulmonary Edema Associated with Hypertension}

E. G. (No. 8B756) was a 32 year old single man with hypertension for 10 years, admitted because of paroxysmal dyspnea and mild edema. He was a well developed, well nourished man, often sweating and apprehensive. Blood pressure was 220/140 with a definite pulsum alternans; pulse, 88; respirations, 20. The fundi showed fresh and old hemorrhages and exudates, marked narrowing of the arterioles and arteriovenous nicking, and grade I papilledema. The chest was clear to percussion and auscultation. The heart was enlarged with a heaving apex impulse, normal sinus rhythm, and a diastolic gallop at the apex.

\textit{Laboratory Data}. The urine concentration was 1.025 with pH 5.5, 1 to 3 plus protein, occasional red cells, white cells, granular casts, and no growth on culture. Hematocrit was 45. Blood urea nitrogen values were 18 and 30 mg. per 100 cc. Vital capacity was 3900 cc. Urea clearance was 49 cc. per minute, maximum. Intravenous pyelograms were normal.

X-ray films and fluoroscopy of the lungs showed clear lung fields. The heart was 27 per cent enlarged with predominance of the left ventricular segment.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig4.png}
\caption{Upper tracing = pulmonary artery. Lower tracing = brachial artery. Slow speed = 1 mm. per second. Fast speed = 10 mm. per second. Solid black line represents electrically integrated (mean) pressures; other represents full pulse pressures. Tracings at right obtained 3.5 minutes after starting infusion of Ro 2-2222 at rate of 3.7 mg. per minute. Same patient as 3B on a different occasion.}
\end{figure}

On the thirteenth hospital day, following a period of obvious emotional stress, the patient developed extreme apprehension, orthopnea, and rales throughout both lungs up to level of the clavicle. Pulse rate rose to 156, respirations to 44, blood pressure to 280/160. He was unable to lie flat for even a few moments. There was a marked pulsum alternans. A polyvinyl tube was then inserted into the right basilic vein approximately 22 inches so as to pass into the superior vena cava. Ro 2-2222 was given at a rate of approximately 1 mg. per minute by continuous intravenous drip. Within 10 minutes, and coincident with a moderate fall in arterial pressure, his respirations slowed and were subjectively and objectively less labored. The pulse rate fell and venous pressure fell from 220 to 90 mm. Pulsus alternans disappeared and most of the rales had
ARterial Pressure in Man

cleared from his lungs. Within 20 minutes he was able to lie flat with comfort and remain so without an elevation of pulse or respiratory rate. At that time there were only a few scattered moist basal rales, and these were gone upon auscultation one hour later. (See figure 5 for details.)

FIG. 5. Data on central venous pressure (corrected), respiratory rate, pulse rate, and arterial pressure from patient in acute pulmonary edema treated with Ro 2-2222. At arrow 1 patient was orthopneic, sweating, markedly apprehensive, had bubbling rales up to the clavicle and was bringing up pink-tinged sputum. At arrow 2 the rales had become distinctly less audible. At arrow 3 the patient volunteered that his breathing felt considerably easier and at arrow 4 was able to tolerate the horizontal position. Auscultation revealed only scattered basal rales, and at arrow 5 he requested lunch. At arrow 6 he ate while the infusion of Ro 2-2222 was still going in. It was discontinued at 2:15 p.m.

After two hours and 12 minutes of intravenous medication, the drip was discontinued and the patient remained comfortable and asymptomatic for the remainder of the day. On the following day, a milder but comparable episode of acute pulmonary edema was promptly relieved following an injection of 0.1 mg. of provera.

Case 2. Acute Pulmonary Edema Associated with Uremia

A. L. (No. 8B04) was a 14 year old boy, admitted in extremis from renal failure following an attack of acute glomerulonephritis six months previously. His face was puffy, pale, and cyanotic; he was dyspneic and orthopneic, but not edematous. Blood pressure was 170/120; pulse, 104; respirations, 48; rectal temperature, 98.8. The heart was enlarged with regular sinus rhythm and no murmurs, and a rough pericardial friction rub. There were medium and coarse, moist rales throughout both lung fields. The urine showed a specific gravity of 1.012 with 3 plus protein and was loaded with red cells and white cells and occasional hyaline and granular casts. Hematocrit was 20. White blood cell count, 15,600 with 83 per cent polymorphonuclear leukocytes. The blood urea nitrogen was 203 mg. per 100 cc. The carbon dioxide combining power was 16 m.M. per liter. Serum sodium was 143 and serum potassium 8.9 mEq. per liter. Electrocardiogram was characteristic of moderate hyperkalemia.

He had already been given 5 mg. of digitoxin and 12 mg. of morphine sulfate. Oxygen therapy had been administered for three hours by means of a face mask. The administration of Ro 2-2222 in doses up to 2.5 mg. per minute failed to induce any objective evidence of improvement or lowering of blood pressure. The same negative result followed 0.12 mg. provera intravenously. The further administration of morphine sulfate and digitoxin had no significant effect, and the patient died four hours later following a series of convulsions. Autopsy permission was not obtained.

Case 3. Acute Pulmonary Edema Associated with Lower Nephron Nephrosis and Hyperkalemia

G. N. (No. 9B198) was a 45 year old housewife who was heavily exposed to a chlorinated hydrocarbon while spraying clothes in a closed room. Over the succeeding five days preceding admission, she became anorexic, developed diarrhea, abdominal cramps, nausea, vomiting, right upper quadrant tenderness, and finally drowsiness, oliguria, and hypotension.

Physical Examination. Her temperature was 102 F.; pulse, 94; respirations, 22; blood pressure, 70/40. She was semistuporous and dehydrated. There were a few moist rales at the right lung base. The heart was normal in size and showed no irregularities or murmurs. The abdomen was moderately distended with gas; peristaltic sounds were reduced but otherwise normal. There was definite tenderness and resistance in the right upper quadrant. There was 1 plus pitting edema of the legs.

Admission Laboratory Data. Findings in urine were: specific gravity, 1.017; pH, 5.0; 3 plus protein; 1 plus sugar; no acetone; 3 or 4 white blood cells, hyaline and granular casts but no red blood cells per
high-power field. Findings in blood were: hematocrit 38 per cent; white blood cell count, 26,500 with 98 per cent polymorphonuclear leukocytes; 16 eosinophils per cu. mm.; urea nitrogen, 47 mg. per 100 cc.; carbon dioxide combining power, 18.6 mEq. per liter; serum chloride, 88 mEq. per liter; serum sodium, 120 mEq. per liter; serum potassium, 3.4 mEq. per liter; serum bilirubin, 0.32 mg. per 100 cc.

Hospital Course. She was given 200 cc. of normal saline and 300 cc. of 3 per cent sodium chloride intravenously within the first five hours of admission which, without other medication, was accompanied by a rise in blood pressure to 100/70, a brisk resumption of urine output, and a rise in serum chloride level to 109 mEq. per liter. Hydration was continued over the ensuing 18 hours, but the hematocrit meanwhile fell to 32 per cent, and a slow transfusion was started. After 250 cc. had run in over three hours, the patient developed dyspnea, orthopnea, and both moist rales and asthmatic wheezing throughout both lung fields. The transfusion was discontinued immediately.

Ro 2-2222 was given, 20 mg. intravenously over two minutes. By this time the blood pressure had fallen from 144/92 to 90/66, the respiratory rate from 38 to 28, the venous pressure from 190 to 120 mm. Hg. Within five minutes after starting the drug, the patient noted subjective improvement in her wheezing and was able to tolerate the horizontal position without marked dyspnea. Within 25 minutes after stopping the injection, however, the blood pressure had risen again to 126/88, the respiratory rate to 36, the venous pressure to 155 mm. Hg., and orthopnea and wheezing had returned subjectively to a point comparable to the control period. At 30 minutes, 20 mg. of Ro 2-2222 was given at half the previous rate over four minutes, and the blood pressure fell again, to 90/68, again with relief of wheezing and orthopnea. Eight minutes after stopping this infusion, symptoms had again become severe with a rise of blood pressure to 120/90. This time Ro 2-2222 was given at 4 mg. per minute over 40 minutes with continued relief of orthopnea at a blood pressure level of 103/76. Wheezing virtually disappeared, and there were only scattered bilateral moist basal rales. The patient was then given morphine sulfate, 8 mg. subcutaneously, and Digoxin 1 mg., intravenously with continued relief of the symptoms of acute pulmonary edema.

A laparotomy was performed, under local anesthesia with supplementary doses of morphine, in order to rule out acute cholecystitis as the cause of the severe leukocytosis and right upper quadrant tenderness. An acutely swollen, exquisitely tender liver was found, biopsy of which showed pericholangitis and fatty infiltration consistent with a toxic hepatitis. The gallbladder and pancreas were normal. Diuresis continued over the next few days, with urine outputs of 2,000 to 5,000 cc. daily and gradual return of renal function to normal and without recurrence of acute pulmonary edema.

DISCUSSION

Peripheral vasodilatation induced by spinal anesthesia in patients with acute pulmonary edema has been shown previously to be followed by a prompt therapeutic response.9 Presumably, this was brought about by (a) the diminution in peripheral resistance against which the failing ventricle was working, and (b) a shift of blood from the pulmonary parenchyma to the peripheral vascular bed as a result of the peripheral vasodilation. The use of peripheral vasodilation as a means of treating acute pulmonary edema has since received firm confirmation in laboratory experiments.2-4 The fall in blood pressure following the spinal block in one patient was precipitous, however, and the patient became much worse in the few minutes before the therapeutic effect of the procedure set in. More recently, as little as 30 mg. of procaine in the third lumbar intercostal space provoked a drastic and sudden fall of arterial pressure from 180/100 to 60/35 mm. Hg within five minutes in a hypertensive patient.

The ganglionic blockade produced by Ro 2-2222, however, has distinct therapeutic advantages over spinal anesthesia. After producing severe arterial hypertension and pulmonary venous pressures up to 70 mm. Hg. by stimulating medullary cardiovascular centers,2-4 Ro 2-2222 administration promptly lowered pulmonary venous pressure to control levels and significantly raised the cardiac output, but with only a slight or moderate lowering of peripheral arterial pressure. The effect was in sharp contrast to the often drastic and unpredictable fall in arterial blood pressure produced by spinal anesthesia. Phlebotomy, under the same experimental conditions, lowered pulmonary venous pressure, but failed to elevate, and occasionally even depressed, cardiac output.

It was largely with the acute pulmonary edematous state and the above experiences with spinal anesthesia in mind that a compound was sought which would provide a quantitative method of diminishing peripheral resistance in a gentler and more promptly controllable
manner than has been possible by other means. From the above data it appears that the continuous graded, intravenous administration of Ro 2-2222 furnishes such a method. The first case report cited above would seem to confirm the previous experimental data which relate peripheral vascular tone to the acute pulmonary edema state in hypertension.

The lack of a therapeutic effect in the second patient might be attributable to either (a) the fact that the pulmonary edema of uremia is not predominantly a result of increased pulmonary capillary pressure, (b) the fact that the peripheral vasomotor tone is not predominantly under neural influence but rather is a result of blood chemical changes, (c) the fact that the total peripheral arteriolar bed has been constricted by chemically irreversible organic vascular changes, or (d) inadequate dosage. It is apparent that more specific experimental data is needed regarding the mechanism of acute pulmonary edema in uremia.

The third patient with acute pulmonary edema had nearly normal blood pressure. Pulmonary edema occurred on the second hospital day following intensive fluid replacement therapy for shock and oliguria. The primary difficulty appeared to be a lower nephron nephrosis following exposure to a chlorinated hydrocarbon, with azotemia and hypochloremia severe enough to produce oliguria and severe hypotension. As the hypotension and oliguria were relieved by infusion of hypertonic saline and finally by 250 cc. of blood, congestive failure and acute pulmonary edema appeared. The extremities were warm and dry and the blood pressure 145/95. The liver was enlarged and tender, and there were rales as well as asthmatic wheezes throughout both lung fields, suggesting that hypervolemia was a major factor in producing the acute pulmonary edematous state. Again marked clinical improvement following injections of Ro 2-2222 were associated with a fall in peripheral arterial and venous blood pressure, relief of wheezing and orthopnea, and no significant change in pulse rate. It was not possible to judge whether the patient's azotemia played a role, per se, in producing pulmonary edema. The hemodynamic considerations regarding both pathogenesis and treatment by peripheral dilatation seemed to apply to this case of pulmonary edema in a normotensive individual fully as well as to the previous case with hypertension.

The depressor response to Ro 2-2222 in man, when given as a single intravenous dose, is brief. This characteristic of the drug, however, makes possible the prompt reversibility of the induced depressor reaction when given as a continuous infusion and thus facilitates the precise regulation of arterial pressure. If, as presumed, this graded reduction of arterial pressure is due to quantitative ganglionic blockade, the means is at hand for the continuous regulation of peripheral vascular resistance over a period of hours. Observations for more prolonged periods have not yet been made.

It seems appropriate to state why it seemed worthwhile to investigate the use of an agent which requires an intravenous drip for the best results in the therapy of what is frequently an emergency situation. This consideration becomes even more pointed in view of the similarity in the type and rapidity of relief obtained in the same patient treated with a continuous infusion of Ro 2-2222 on one day and on the following day with a single injection of protovatrine. Although the patient's second attack of pulmonary edema was apparently not as severe as the previous one, the relief obtained with the single injection of protovatrine closely resembled the result obtained with continuous infusion of Ro 2-2222. The reasons for preferring the continuous infusion method follow. They presume the desire to achieve the ideal rather than the approximate in the management of the acute pulmonary edematous state.

As suggested elsewhere,\textsuperscript{3--5, 9} it is desirable to treat acute pulmonary edema by inducing peripheral vasodilation in order (a) to diminish the resistance against which the left ventricle is working and also (b) to decrease pulmonary blood volume by shifting blood into the peripheral vascular bed. However, there is reason to believe that in patients with hypertension and vascular disease, it is wise to avoid a sudden and drastic lowering of arterial pressure. Theoretically, at least, this revolves around the necessity of preventing a critical lowering
of perfusion pressure in the arteries leading to the heart, kidney, and brain. When a depressor agent is to be given as a single injection, selection of the dose in terms of the depressor response desired will require previous information regarding how much of that drug will achieve the desired depression in that particular patient. This is rarely available. On the other hand, when it is possible to titrate the response by regulating the rate of administration, such previous information is unnecessary.

Finally, in such normotensive individuals as case 3, where the choice is between pulmonary edema and shock, a well-known clinical dilemma exists in which customary measures aimed at treating pulmonary edema are apt to aggravate shock. In such situations one must walk a physiologic tightrope on which a readily reversible, quantitatively regulated agent has obvious advantages. That acute pulmonary edema associated with coronary insufficiency may be effectively treated by means of careful peripheral vasodilation is suggested by previous data on one such patient to whom spinal anesthesia was administered.9

Chronic toxicity studies on this agent have not yet been completed, and the number of patients who have received the drug is small. A prolonged clotting time is produced by large amounts of this substance in the dog, but not in the mouse, rat, rabbit, guinea pig, cat, or monkey.1 Clotting times were not found to be elevated in the three patients in whom this determination was made after the administration of Ro 2-2222.

When Ro 2-2222 was administered at effective rates intravenously, most patients experienced a desire to yawn repeatedly. In two patients this was followed by actual nausea with retching or vomiting, of which yawning is a common symptomatic precursor. Both of these patients had already been chronically nauseated and vomiting intermittently because of advanced uremia, but there seemed to be little doubt that Ro 2-2222 accentuated this symptomatology. Accurate dosage regulation was apparently responsible for minimizing the undesirable gastrointestinal side effects so commonly observed with most depressor agents.

The apparent freedom from tachyphylaxis, insofar as determined by the above studies, suggests the possible use of this substance in the control of hypertension for longer periods than have been herein described.

The practice of maintaining low arterial pressures during surgery in order to diminish blood loss has been recently revived. Ro 2-2222 has the characteristics of an agent suitable for such a purpose since the degree of depressor response can be regulated from moment to moment and can be reversed readily in a controlled fashion. Under ether and cyclopropane anesthesia, the intraoperative arterial pressures have been lowered to and maintained at levels of 65/45 mm. Hg throughout the following four procedures: radical mastectomy (1), spinal cordotomy (1), and removal of large intracranial meningiomas (2). Intraoperative blood loss and postoperative transfusion requirements appeared to be materially diminished. The re-elevation of arterial pressure occurred as promptly in these four normotensive patients under anesthesia as in the patients described above following cessation of intravenous administration of Ro 2-2222. The results of further studies will be published subsequently.18

A full understanding of the mode of action and variety of effects of the ganglionic blocking agents is not yet at hand. In the dog, for example, tetraethylammonium does not block the pressor response to asphyxia, whereas in the cat it does.10 Stone, Entwistle and Loew11 have recently shown that tetraethylammonium causes the discharge of a pressor substance from the adrenal gland, and Reiser and Ferris12 stated that tetraethylammonium produced a pressor rather than a depressor response in 6 of 20 hypertensive patients (30 per cent). A pressor response did not occur in any of the 14 hypertensive patients to whom Ro 2-2222 was administered. Recent work by Siems and Rottenstein13 suggests that tetraethylammonium has an effect on the vascular bed, distal to the point of ganglionic blockade. The use of tetraethylammonium in man has suggested to Fowler and co-workers14 that the drug has a direct cardiac effect, and Freis and associates15 found that tetraethylammonium intensified the pressor effect of epinephrine and norepinephrine in man. That the situation is equally complex...
in the case of the methonium compounds is suggested in the recent article by Paton.16

Mitchell and co-workers17 have recently reported that Ro 2-2222 produces the liberation of histamine when administered to dogs. The characteristic flush and headache that accompany the presence of higher than normal blood levels of histamine in man have not been encountered in the above described series of patients. Further, from the data of Randall and colleagues,1 the dog seems to react with a histamine response not observed in other species.

In view of the foregoing, the authors are keenly aware that, since a diverse body of information is not yet available in regard to Ro 2-2222 and clinical experience is limited to the studies presented herein, this report must be considered to be of a preliminary nature.

**Summary and Conclusions**

1. Ro 2-2222 in man produces a diminution in sympathetic activity, presumably by ganglionic blockade, which is evanescent in response to a single intravenous dose of 0.1 or 0.2 mg. per kilogram.

2. The depression of arterial pressure and rise in skin temperature responds in a satisfactory manner to various rates of administration when the continuous infusion technic is used. Either partial or apparently complete chemical sympathectomy can be achieved and a steady state maintained by regulation of the rate of administration of the agent.

3. The rate and the degree of sympathetic blockade achieved can be reasonably well controlled with minimal side effects so that either a precipitous or gentle lowering of arterial pressure results. On the basis of previous studies this suggests that the agent may be of use in the management of the acute pulmonary edema state.

4. Arterial pressure begins to return to control levels soon after discontinuance of the drug. Ephedrine is effective in elevating arterial pressure during the administration of the drug.

5. In the two patients so studied, the cold pressor test response was abolished during administration of Ro 2-2222.

6. Tachyphylaxis did not become apparent under the conditions of study observed above.

7. The results of treatment with Ro 2-2222 in three patients with acute pulmonary edema have been presented.

**Addendum**

Since this manuscript was submitted, the therapeutic effect of Ro 2-2222 upon acute pulmonary edema with essential hypertension has been confirmed in two additional patients, one of whom had not responded to intravenous morphine, oxygen by face mask, and tourniquets. Two patients with rheumatic valvular heart disease and mild pulmonary edema, but with normal arterial pressures, showed disappearance of orthopnea after slight peripheral vasodilatation with Ro 2-2222.

Three children, 8, 10, and 14 years of age, with hypertension accompanying acute glomerulonephritis, showed no fall in blood pressure following Ro 2-2222 administration, confirming the findings in our case report 2. One other patient in chronic pulmonary edema associated with severe uremia showed no clinical response to Ro 2-2222 even though reduction of arterial pressure was accomplished. One patient with acute pulmonary edema associated with a myocardial infarction did not respond in a convincing manner to Ro 2-2222. One moribund patient exhibited a sustained fall in cerebral spinal fluid pressure from 325 to 225 mm. of water, associated with a fall of arterial pressure from greater than 300/240 to 240/135 mm. Hg, and a fall of venous pressure from 315 to 165 mm. of water.

Three patients with acute bronchial asthma were not benefited by Ro 2-2222 administration, despite lowering of blood pressure, in contrast to the favorable effect of the drug in case 3 reported herein, in whom the asthma appeared to be on a cardiac basis. It is conceivable that this agent might occasionally be valuable in differentiating bronchial from cardiac asthma.

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Graded Reduction of Arterial Pressure in Man by Means of a Thiophanium Derivative (Ro 2-2222): Preliminary Observations on Its Effect in Acute Pulmonary Edema
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Circulation. 1952;6:63-73
doi: 10.1161/01.CIR.6.1.63

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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