Transient Pulmonary Hypertension from the Intravenous Injection of Crushed, Suspended Pentazocine Tablets*

Harrison W. Farber, M.D.; Randall Falls, B.S.; and Frederick L. Glauser, M.D., F.C.C.P.

We describe a patient with biopsy-proven pulmonary talc granulomas (secondary to the long-term intravenous injection of crushed tablets of pentazocine) who had two episodes of transient pulmonary hypertension following the injection of this oral medication. We established a canine model and measured the right lymph duct flow, mean pulmonary arterial pressures, and pulmonary vascular resistance to determine the short-term effects on hemodynamics and the flow of lymph after intravenous administration of crushed pentazocine tablets (3 to 4 mg/kg of body weight) or pure talc (2.5 to 3 mg/kg). A typical response to both agents consisted of short-term elevations of mean pulmonary arterial pressure and pulmonary vascular resistance to approximately twice baseline values, with a slow decrement over 30 to 45 minutes. The average flow of lymph tripled, peaking at approximately two hours after injection. The lymph contained high levels of albumin. We concluded that the talc filler in oral tablets of pentazocine induces the pulmonary hypertension, probably by mechanical obstruction of the pulmonary vasculature. Associated with this transient pulmonary hypertension is an increase in the permeability of the pulmonary microvasculature.

We report the findings in a patient with biopsy-proven talc granulomatosis who experienced acute transient pulmonary hypertension following the intravenous injection of crushed, suspended tablets of pentazocine (Talwin). In addition, we established a canine model and injected crushed pentazocine pills and powdered talc intravenously and followed pulmonary hemodynamics and pulmonary lymphatic flow as a reflection of pulmonary microvascular permeability.

Case Report

This 28-year-old man, a known abuser of intravenously administered pentazocine for several years, came to the emergency room in September 1977 (following the injection of four 50-mg tablets of pentazocine), complaining of dyspnea. The blood pressure was 90/60 mm Hg, the respiratory rate was 35/min, and the pulse rate was 120 beats per minute. Diffuse end-inspiratory rales were present in both posterior pulmonary fields. The findings from cardiac examination were within normal limits, except for a sinus tachycardia. The arterial oxygen pressure (PaO₂) was 59 mm Hg (fractional concentration of oxygen in the inspired gas \(FIO_2\), 0.21), the arterial carbon dioxide tension (PaCO₂) was 23 mm Hg, and the pH was 7.46; the PaO₂ quickly fell to 45 mm Hg (5 L of oxygen per minute by nasal cannula). The initial chest x-ray film (Fig 1) disclosed a normal cardiac shadow with diffuse reticular nodular interstitial markings and a superimposed alveolar infiltrate.

The patient was treated with intravenously administered fluids, vasopressor drugs, and 10 cm H₂O of positive end-expiratory pressure (PEEP); and eight hours after admission, a balloon-tipped flow-directed catheter was inserted for hemodynamic monitoring. Initial values were a pulmonary arterial pressure of 44/20 mm Hg and a pulmonary wedge pressure of 10 mm Hg, with a simultaneous PaO₂ of 118 mm Hg (\(FIO_2\) 1.0), PaCO₂ of 28 mm Hg, and pH

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Figure 1. Anteroposterior chest x-ray film from initial admission. Note reticular-nodular infiltrates, particularly in right upper and left lower pulmonary fields. In addition, interstitial and alveolar infiltrates are present. There is haziness of perihilar areas and cephalad redistribution of flow of blood. Pulmonary arterial size is normal.

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and perivascular foreign-body granulomas, fibrosis (Fig 2), and, by polarizing microscopic examination, numerous bi-refracti
ent crystals. Following the biopsy a nine-month course of therapy with prednisone (60 mg daily for one
week and then 60 mg qod) resulted in no improvement in clinical findings or pulmonary function. During this period
the patient abstained from drug abuse.

In July 1979, the patient was readmitted, complaining of dyspnea following injection of four 50-mg tablets of
pentazocine. The findings on physical examination were similar to his original presentation. The PaO2 was 61 mm
Hg (FIO2 0.21), the PaCO2 was 16 mm Hg, and the pH was 7.37. A chest x-ray film again disclosed the reticular
nodular pattern and a superimposed alveolar pattern. The patient was treated with 10 cm H2O of PEEP, vasopressor
drugs, and intravenously administered fluids. A Swan-Ganz
catheter was inserted, and the pulmonary arterial pressure was 70/52 mm Hg, with a pulmonary wedge pressure of
15 mm Hg. A simultaneously determined PaO2 was 108
mm Hg. The patient’s condition improved slowly, and four
days later, he had a pulmonary arterial pressure of 38/18
mm Hg, with a pulmonary wedge pressure of 12 mm Hg.

CANINE EXPERIMENTS

Ten mongrel dogs were anesthetized with intravenously
administered pentobarbital (30 mg/kg of body weight) and
were ventilated with a respirator (Harvard) at a respi-
atory rate of 15 to 18 breaths per minute and a tidal volume
of 5 to 7 ml/kg. The animals were grouped as follows: (1)
in group 1, tablets of pentazocine (50-mg tablets) for a
dosage of 3 to 4 mg/kg of body weight were crushed
and suspended in 5 to 10 ml of a 0.9 percent solution of sodium
chloride and injected intravenously (four dogs); (2) in
group 2, pure t alc (2.5 mg/kg) was suspended in 5 to 10
ml of a 0.9 percent solution of sodium chloride and injected
intravenously (four dogs); and (3) in group 3, pentazocine
for intravenous use (3 to 4 mg/kg) was injected intra-
venously (two dogs).

All animals had the following procedures performed:
Under pressure monitoring (Electronics for Medicine VR-6
physiologic recorder and Statham pressure transducer), a
No. 7 balloon-tipped flow-directed catheter was inserted
into the pulmonary artery for readings of mean pulmonary

<table>
<thead>
<tr>
<th>Data</th>
<th>Baseline</th>
<th>1</th>
<th>30</th>
<th>60</th>
<th>120</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac output, L/min</td>
<td>1.4 ± 0.8</td>
<td>1.8 ± 0.7</td>
<td>1.4 ± 0.6</td>
<td>1.5 ± 0.5</td>
<td>1.5 ± 0.3</td>
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<tr>
<td>PaO2, mm Hg</td>
<td>90 ± 6</td>
<td>89 ± 6</td>
<td>90 ± 7</td>
<td>87 ± 7</td>
<td>76 ± 7†</td>
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<tr>
<td>Mean pulmonary arterial pressure, mm Hg</td>
<td>16 ± 4</td>
<td>35 ± 7†</td>
<td>24 ± 4‡</td>
<td>18 ± 5</td>
<td>17 ± 4</td>
</tr>
<tr>
<td>Pulmonary wedge pressure, mm Hg</td>
<td>5 ± 2</td>
<td>6 ± 3</td>
<td>5 ± 2</td>
<td>6 ± 2</td>
<td>6 ± 2</td>
</tr>
<tr>
<td>Pulmonary vascular resistance, dynes<em>sec/cm</em></td>
<td>560 ± 160</td>
<td>1,120 ± 320†</td>
<td>770 ± 180</td>
<td>560 ± 160</td>
<td>560 ± 210</td>
</tr>
<tr>
<td>Lymphatic flow, ml/30 min</td>
<td>0.4 ± 0.2</td>
<td>. . .</td>
<td>0.8 ± 0.2</td>
<td>1.0 ± 0.3†</td>
<td>1.2 ± 0.4†</td>
</tr>
<tr>
<td>Lymph/plasma albumin ratio</td>
<td>0.80 ± 0.20</td>
<td>. . .</td>
<td>0.85 ± 0.20</td>
<td>0.82 ± 0.20</td>
<td>0.80 ± 0.15</td>
</tr>
</tbody>
</table>

*Injections of crushed, suspended pentazocine (3-4 mg/kg). Table values are ± SD.
**Data for 150, 180, and 210 minutes after injection are not included, since they do not significantly differ from 120-minute values.
†P < 0.01.
‡P < 0.05.

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arterial pressure and pulmonary wedge pressure. Polyethylene tubing (No. 260) was inserted into the femoral artery for readings of mean systemic blood pressure and into a femoral vein for sampling blood and injection. The right lymphatic duct was cannulated for determination of pulmonary lymphatic flow and the concentration of albumin, according to the technique of Vreim and Ohkuda. At baseline and at 1 and 30 minutes after injection of the specific substances and then every 30 minutes for three to four hours, the following values were monitored in all dogs: (1) duplicate determinations of cardiac output (liters per minute) by thermodilution, employing a computer (Lyons Cardiac Output Computer); (2) mean pulmonary arterial pressure; (3) pulmonary wedge pressure; (4) mean systemic blood pressure; \( \text{PaO}_2 \), \( \text{PaCO}_2 \), and pH, employing a blood gas analyzer (Instrumentation Laboratories 213). Blood gas levels were corrected for the animal's body temperature.

Lymphatic flow and lymph/plasma albumin ratios were determined every 30 minutes. The level of albumin was measured fluorometrically. Pulmonary vascular resistance (PVR in dynes·sec/cm\(^5\)) was determined by the following formula: PVR = (PAP - PWP)/CO \times 79.6 where PAP is mean pulmonary arterial pressure, PWP is pulmonary wedge pressure, and CO is cardiac output. Analysis of variance was employed to determine statistical significance.

**Results**

Following a 1-hour baseline (Table 1), crushed, suspended tablets of pentazocine (3 to 4 mg/kg) were injected intravenously over 10 to 15 seconds (group 1); and within one minute the mean pulmonary arterial pressure increased from 16 ± 4 to 35 ± 7 mm Hg (\( P < 0.01 \)), with a doubling of pulmonary vascular resistance from 560 ± 160 to 1,120 ± 320 dynes·sec/cm\(^5\) (\( P < 0.01 \)). There was no change in cardiac output, \( \text{PaO}_2 \), or pulmonary wedge pressure. Thirty minutes after injection, the mean pulmonary arterial pressure decreased towards normal but was still significantly higher than baseline values (\( P < 0.05 \)) while lymphatic flow doubled from baseline values of 0.4 ± 0.2 to 0.8 ± 0.2 ml/30 min (\( P < 0.05 \)). Over the ensuing 15 to 30 minutes, mean pulmonary arterial pressure and pulmonary vascular resistance returned to normal values. Lymphatic flow peaked at approximately three times baseline values two hours after injection. Lymph/plasma albumin ratios were maintained at all times of study. The \( \text{PaO}_2 \) did not significantly decrease until approximately 1 hour to 2 hours after injection. The results of a single typical experiment is shown in Figure 3.

When pure talc, in a dose (approximately 45 mg of talc for a 15-kg dog) adjusted to approximately that given with the pentazocine tablets, was injected (group 2), the same sequence of changes in hemodynamics, lymphatic flow, lymph/plasma ratios, and \( \text{PaO}_2 \) occurred (Table 2), except for the following: mean pulmonary arterial pressure and pulmonary vascular resistance increased slightly higher at one minute after injection of talc, compared to animals receiving crushed pentazocine (Tables 1 and 2). At 30 minutes after injection of talc, the mean pulmonary arterial pressure had decreased to 20 ± 6 mm Hg, which was not significantly higher compared to baseline values. This was in contrast to the animals injected with pentazocine, whose mean pulmonary arterial pressure (24 ± 4 mm Hg) 30 minutes after injection was significantly higher than baseline values (\( P < 0.05 \)).

In two animals, we injected increasing dosages (50 to 200 mg) of liquid intravenously prepared pentazocine and found no increase in lymphatic flow or changes in mean pulmonary arterial pressure or pulmonary vascular resistance. Above a single dose of 200 mg, the mean systemic blood pressure, mean pulmonary arterial pressure, and pulmonary wedge pressure, decreased dramatically.

**Discussion**

The chronic pulmonary hypertension associated
with the intravenous injection of crushed oral tablets is well documented and is believed to result from a talc-induced granulomatous involvement of the pulmonary vasculature, with subsequent thrombosis and vascular sclerosis. To our knowledge, ours is the first case where acute hypertension has been reported following injection of talc. The mechanism or mechanisms responsible for this transient pulmonary hypertension are speculative but may include the following: First, there is the vasoconstrictive effects of alveolar hypoxia, acidosis, and hypercapnia. Our patient did not experience hypercapnia or acidosis; and although he did have hypoxemia, he continued to exhibit pulmonary hypertension in spite of PaO₂ greater than 100 mm Hg. If the pulmonary hypertension were due solely to alveolar hypoxia, it should have quickly reversed with supplemental oxygenation. A second possible mechanism is the transient release of humoral vasoconstrictive substances. One can theorize that certain vasoactive/vasoconstrictive substances (serotonin, catecholamines, prostaglandins, etc	extsuperscript{11,12}) were released secondary to the injection of talc, leading to pulmonary hypertension; however, the duration of the hypertension, particularly during the patient's second episode, would seem inconsistent with this mechanism, although we cannot absolutely rule out this possibility. A third possible mechanism for the transient pulmonary hypertension is a hypersensitivity reaction. The eosinophilia (total count of approximately 1,000 cells per cubic millimeter) may indicate that a "hypersensitivity" (eg, immunologic response) occurred. Whether this eosinophilia was related to the pulmonary hypertension is unclear. A fourth possible mechanism is increasing pulmonary vascular obstruction. Since the patient's pulmonary vasculature was chronically and diffusely obstructed by a granulomatous reaction, the delivery of even more particulate material to previously perfused vessels could lead to enough mechanical obstruction to cause pulmonary hypertension. As talc was removed from the pulmonary vascular lumen, the pulmonary hypertension slowly resolved. Our canine studies bear on this question of mechanical obstruction and deserve some mention.

Following the intravenous injection of crushed, suspended tablets of pentazocine, a predictable response in hemodynamics and lymphatic flow occurred, ie, rapid elevations in mean pulmonary arterial pressure and pulmonary vascular resistance to approximately twice baseline values, with a slow decrement in these values to normal over 30 to 45 minutes (Table 1; Fig 3). Lymphatic flow increased within the first 30 minutes after injection, peaking at two hours and becoming stable at three times baseline levels (Table 1; Fig 3). At no time was there any decrease in lymph/plasma albumin ratios. Additionally, hypoxemia did not occur until 1.5 hours after injection. These findings were mimicked by an equivalent amount of pure t alc but were not induced by the injection of liquid pentazocine designed for intravenous use.

From these data, we believe that the transient pulmonary hypertension seen in this study is due to mechanical blockage of pulmonary vessels by the particles of talc. There is an increased flow of protein-rich lymph, indicating an increased pulmonary microvascular permeability to albumin. Whether this increased permeability is due to purely mechanical factors or some other cause or causes (leukocyte trapping, coagulation factors, release of humoral substances, etc	extsuperscript{11,12}) is not clear.

In conclusion, we have shown that transient pulmonary hypertension can occur following injection of talc.
of pentazocine and that this reaction is probably due to the talc and not the pentazocine itself. It is also possible that repeated injection of crushed tablets of pentazocine leads to persistent pulmonary hypertension due to granulomatous impaction on the pulmonary vasculature.

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REFERENCES

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