CASE REPORT

# Noncardiogenic Pulmonary Edema Associated with Hydrochlorothiazide

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Thiazide diuretics have been rarely reported to cause noncardiogenic pulmonary edema.[1-19] This report presents a case of pulmonary edema thought to be caused by a hydrochlorothiazide(HCTZ)-containing preparation. The literature is also reviewed to alert pharmacists to this potentially life-threatening reaction.

## CASE

A 61 year old female was admitted to hospital for management of pulmonary edema. She had a history of effort dyspnea, hypertension and angina-like pain with angiographically demonstrated normal coronary arteries. Medications at the time of admission included digoxin 0.25 mg daily, captopril 12.5 mg bid, furosemide 40mg daily, potassium chloride 10mEq daily. There was an unconfirmed history of allergy to pentazocine. Physical examination in the emergency department revealed a blood pressure of 200/110 mmHg, heart rate of 130 beats/minute, and respiratory rate of 30/minute. Her cardiovascular exam showed a jugular venous pulse (JVP) of approximately 4-5cm above the clavicle at 45 degrees. There was an $S_3$ heart sound present and a possible slight mid-systolic click. There was no peripheral edema. She had decreased breath sounds at the bases of both lungs with widespread crackles. On admission her serum electrolytes and complete blood count were normal. Creatine kinase and lactate dehydrogenase were also within normal limits. Blood gases revealed a $PO_2$ of 64 mmHg, $PCO_2$ of 33 mmHg, pH of 7.46 and bicarbonate of 23 mEq/L on 40% oxygen. The electrocardiogram showed sinus tachycardia with a left bundle branch block. The chest X-ray showed interstitial edema with Kerly B's and an increased cardiac silhouette.

In the emergency department the patient was treated with nitroglycerin paste 5cm, furosemide 40mg IV, morphine 2mg IV (three doses) and salbutamol 1mL in 2mL normal saline by nebulizer (two doses) which relieved her chest pain and shortness of breath. Her blood pressure decreased to 150/90 mmHg and heart rate to 107 beats/minute.

In hospital, the patient was treated with intravenous and oral furosemide and captopril. Despite this, the patient continued to be hypertensive and on day 11 of her hospital stay was prescribed Moduret®, (hydrochlorothiazide 50mg and amiloride 5mg) one tablet daily. Within two hours of receiving the first dose of Moduret®, the patient developed shortness of breath and she was noted to be confused. At the same time, her blood pressure decreased to 80/50 mmHg, her heart rate was 85-100 beats/minute and marked hypoxemia was observed, with a measured $PO_2$ of 38 mmHg. Chest X-ray showed pulmonary edema with a diffuse interstitial pattern. She was treated with morphine 2mg IV, furosemide 40mg IV, salbutamol 1mL in 2mL normal saline and 100% oxygen by mask. Her shortness of breath improved and blood pressure increased to 130 mmHg systolic.

She continued to receive the hydrochlorothiazide-containing diuretic for two more doses and her hypoxemia persisted (Table I). The diuretic was stopped on day 14 and thereafter her hypoxemia improved and oxygen was discontinued on day 21.

An isolated subsequent $PO_2$ of 43 mmHg was obtained at a time when the patient was not symptomatic. It was considered to be spurious in view

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**Table I: Blood Gases**

| Day | Time | $PO_2$ (mmHg) | % Oxygen |
|---|---|---|---|
| 1 | 17:15h | 64 | 40 |
| 11 | 15:57h | 70 | R/A |
| 12 | 00:25h | 38 | 100 |
| 12 | 00:50h | 44 | 100 |
| 12 | 01:50h | 78 | 100 |
| 12 | 11:30h | 109 | 100 |
| 13 | 11:26h | 73 | 35 |
| 18 | 13:10h | 67 | 2 L NP |
| 19 | 11:40h | 78 | 2 L NP |
| 19 | 15:13h | 43 | 2 L NP |
| 21 | 12:55h | 79 | R/A |

**Day** = day in hospital course
**R/A** = room air
**NP** = nasal prongs

of her continued clinical improvement.

The patient did not encounter further episodes of pulmonary edema during her hospitalization and was discharged after a prolonged hospital stay on captopril 25mg bid, digoxin 0.25mg daily, furosemide 20mg daily, and enteric coated ASA 650mg bid. At the time of discharge, the patient was instructed to avoid hydrochlorothiazide-containing preparations in the future.

The patient required a subsequent admission to hospital for further investigations which showed a stenosis of an accessory right renal artery. Balloon dilatation of this stenosis was subsequently accomplished, but continued therapy with captopril and furosemide was necessary for control of hypertension. No further episodes of pulmonary edema have been encountered.

## DISCUSSION

Twenty-one cases of acute pulmonary edema secondary to HCTZ were found in the English literature (Table II).[1-19] Kavaru et al[19] reviewed the literature on this topic and cited 17 cases. Since their report, another four cases have been described.[16-18] In these patients, HCTZ was prescribed for the treatment of hypertension[1,2,6,8-11,15,17] or for the management of peripheral edema[3,5,7,16,19], which could indicate some underlying heart failure. Only one patient was being treated for congestive heart failure.[13] In all of these previous cases, the patient had ingested the HCTZ outside the hospital and then presented to the emergency department with shortness of breath. The reaction in these patients appeared to be more severe than in the present case, often requiring invasive monitoring, intubation and inotropic support. In this case, the patient was already in the hospital when the reaction occurred and was treated promptly. This may have avoided the more aggressive treatment required in the other cases.

Symptoms of this reaction are usually manifested within 60 minutes after ingestion of the HCTZ. The most common manifestations are: nausea, diaphoresis, hypotension and hypoxemia. Auscultation of the chest and chest X-ray are consistent with the presence of pulmonary edema. The JVP, while elevated in acute cardiogenic pulmonary edema, is normal in drug-induced noncardiogenic pulmonary edema. Unfortunately, there are no patient specific factors that can be used to determine if a person is at risk of developing this reaction.

The pathogenesis of HCTZ-induced pulmonary edema is unknown. Several mechanisms have been proposed including: idiosyncratic reaction[5,16] and antigen-antibody complex mediated endothelial damage[4]. In the present case, the patient denied prior use of HCTZ and thus suggests an idiosyncratic reaction.

The reaction described in this report was felt to be due to HCTZ for several reasons. First, the temporal relationship to the ingestion of HCTZ, both for the onset and reversal of the signs and symptoms was similar to the other reports. In this case, the patient received multiple doses of the HCTZ-containing diuretic and her hypoxemia persisted

**Table II: Clinical Features of Reported Cases of Hydrochlorothiazide-induced Pulmonary Edema**

| Case No. | Author | Onset (min) | Recovery (days) | Initial $PO_2$ (mmHg)(% $0_2$) | Initial BP (mmHg) |
|---|---|---|---|---|---|
| 1 | Steinberg(1) | 45 | 2 | n/a | 100/70 |
| 2 | Steinberg(1) | 15 | 1 | n/a | 110/80 |
| 3 | Beaudry(2) | 60 | 5 | n/a | 140/90 |
| 4 | Weddington(3) | 30 | 6 | n/a | 80/40 |
| 5 | Farrell(4) | 45 | 1 | 33 (R/A) | 100/60 |
| 6 | Bell(5) | 20 | 3 | 41 (R/A) | 80/0 |
| 7 | Gould(6) | 30 | 1 | 38 (n/a) | 170/110 |
| 8 | Dorn(7) | 60 | 4 | 38 (n/a) | 230/110 |
| 9 | Carlson(8) | 30 | 7 | 54 (100) | n/a |
| 10 | Prupas(9) | 150 | 4 | n/a | 90/60 |
| 11 | Wagner(10) | 60 | 1 | 83 (n/a) | 106/75 |
| 12 | Parfrey(11) | 20 | 1 | n/a | n/a |
| 13 | Levay(12) | 30 | 2 | 58 (n/a) | 74/0 |
| 14 | Kounis(13) | 10 | 3 | 63 (n/a) | 80/50 |
| 15 | Alted(14) | 60 | 4 | 49 (R/A) | 90 (SBP) |
| 16 | Klein(15) | 30 | 8 | 38 (6L) | 146/110 |
| 17 | Grace(16) | 30 | 2 | 51 kPa (R/A) | 130/90 |
| 18 | Grace(16) | 30 | 1 | n/a | 80/45 |
| 19 | Anderson(17) | 60 | 3 | 50 (10L) | 70/0 |
| 20 | Hoegholm(18) | n/a | n/a | 67 kPa (n/a) | 60 (SBP) |
| 21 | Karavu(19) | 90 | 4 | 65 (10L) | 60/0 |
| 22 | Current case | 90 | 3 | 38 (100) | 80/50 |

**n/a** = not available
**R/A** = room air
**SBP** = systolic blood pressure

(Table I). The manifestations of this episode were also consistent with the other reported cases. As with many adverse drug reactions, it is difficult to unequivocally prove cause and effect in this case. A rechallenge with the suspected agent may have answered this question, but it was felt to be unethical.

In conclusion, the incidence of pulmonary edema secondary to HCTZ is probably greater than what has been detected and reported. Patients treated with HCTZ may have a history of congestive heart failure or other cardiac disease and the reaction to the drug may be mistaken for a cardiovascular etiology. Pharmacists need to be aware of this rare but potentially life-threatening reaction.

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