

## Acute pulmonary edema after a single oral dose of acetazolamide

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### Abstract

**Introduction:** Anaphylactic shock and pulmonary edema are unusual but life-threatening adverse reactions to drugs. We encountered a case of serious anaphylactic shock and acute pulmonary edema caused by a single oral intake of acetazolamide, a frequently used medication by several medical specialties especially in ophthalmology.

**Case presentation:** An 80-year-old female was admitted to our emergency Coronary Unit presenting symptoms and signs of shock with acute pulmonary edema. Patient was hospitalised at the Ophthalmological Department with intention to undergo cataract surgery. Approximately, four hours before operation, half a tablet of acetazolamide 250 mg was given, in order to control her pre-operative intraocular pressure. Half an hour later, she complained of nausea, became cyanotic, and suffered acute respiratory failure with characteristic massive pulmonary edema. Ventilatory support was initiated and O<sub>2</sub> saturation increased to 89%. She was administered 2 ampoules of intravenously furosemide. The blood chemistry panel was normal, as well as myocardial cytolysis tests. Chest radiograph showed enlarged cardiothoracic index, ill-defined vessels, peribronchial cuffing, alveolar edema. An echocardiogram showed normal atria and ventricles, normal systolic function, and excluded pulmonary hypertension. Furosemide (40 mg/IV, S: 1x3) and oxygen (8 Lt/min) were administered for the following 24 hours. Clinical improvement was seen and the O<sub>2</sub> saturation was normalized. ECG controls were normal. The patient experienced a full recovery and was discharged 3 days later.

**Conclusion:** The relationship between anaphylactic shock with acute pulmonary edema and acetazolamide seems highly probable in this case, considering the short time between drug assumption and onset of symptoms (about 30 minutes) and the absence of previous diseases to which symptoms could be related. The patient was not previously treated with acetazolamide. Nowadays, the clinical use of acetazolamide is very limited. Its principal uses are in the preoperative treatment of closed angle glaucoma and continuative therapy of open angle glaucoma. Hippokratia 2013, 17, 2: 177-179

**Keywords:** Acetazolamide, acute pulmonary edema, anaphylactic

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### Introduction

Acetazolamide is a carbonic anhydrase inhibitor used to treat glaucoma or to remove excess body water<sup>1</sup>. It is sometimes useful, also, as an adjunct in the treatment of tonic-clonic, myoclonic, and atonic seizures, particularly in women whose seizures occur or are exacerbated at specific times in the menstrual cycle. The anticonvulsant activity of acetazolamide may depend on a direct inhibition of carbonic anhydrase in the CNS, which decreases carbon dioxide tension in the pulmonary alveoli, thus increasing arterial oxygen tension<sup>1</sup>. The diuretic effect depends on the inhibition of carbonic anhydrase, causing a reduction in the availability of hydrogen ions for active transport in the renal tubule lumen<sup>1</sup>. This leads to alkaline urine and an increase in the excretion of bicarbonate, sodium, potassium, and water<sup>2</sup>. On the contrary, there is very low probability of serious anaphylactic shock inducement and acute pulmonary edema after acetazolamide oral administration<sup>3</sup>.

### Case presentation

An 80-year-old female was admitted to our emergency Coronary Unit of Department of Cardiology presenting symptoms and signs of shock with acute pulmonary edema. The patient was hospitalised at the Department of Ophthalmology in order to undergo surgery for cataract under local anaesthesia at her left eye. All preoperative controls were normal, and no major disease was identified on anesthesiological examination, in particular, no signs of myocardial failure were observed.

Her previous included medical history is: arterial hypertension, diabetes mellitus, hyperuricaemia, obesity, dyslipidemia and hypothyroidism. Furthermore, her family history was clear as she mentioned. There was no history of allergy or hypersensitivity. She never smoked or consumed alcohol.

On admission, her blood pressure was regular, 115/70 mmHg, pulse rate was 70 beats per minute sinus rhythm, and she was in no acute distress at rest. Temperature was

36.7 °C. Her lungs revealed mild exhaling wheeze but had no decreased breath sounds in the bilateral bases. Cardiac examination revealed a regular heart with no murmur, rubs or gallop.

Approximately, four hours before the start of the operation, half a tablet of acetazolamide 250 mg (Diamox) was given in order to control her pre-operative intraocular pressure. Half an hour later, she complained of nausea, became cyanotic and suffered acute respiratory failure with characteristic massive pulmonary edema. At the initial evaluation, the following findings were noted: Arterial Systolic Pressure: 79 mm Hg, Arterial Diastolic Pressure: 52 mmHg, heart rate: sinus rhythm with 62/min, dyspnea, tachypnea (~40 breaths per minute), O<sub>2</sub> saturation 77 % and axillary temperature 36.7 °C. On chest auscultation, diminished alveolar murmur, simultaneously, with the presence of basilar crepitations-rales and prolonged expiration were found.

Arterial blood gases when breathing room air were PaO<sub>2</sub>: 70.9 mm Hg, PaCO<sub>2</sub>: 39.6 mm Hg, pH 7.296, HCO<sub>3</sub><sup>-</sup>: 16.9 mEq/l. Ventilatory support was initiated by using positive pressure assisted ventilation through a nasopharyngeal mask in combination with 35% oxygen administration and O<sub>2</sub> saturation increased to 89%. She was given positive inotropic and sympathetomimic substances intravenously such as dobutamine and dopamine. Her arterial pressure started to rise half an hour later. Then, she was administered 80 mg of intravenous furosemide. Blood chemistry panel was normal, as well as myocardial cytolysis tests.

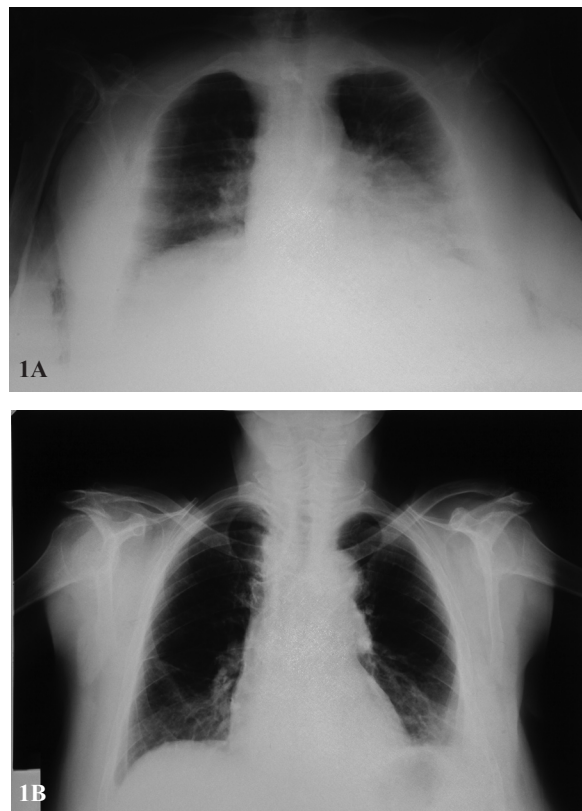
Chest radiograph showed enlarged cardiothoracic index, ill-defined vessels, peribronchial cuffing, alveolar edema, and aortic atheromasia (Figure 1 A). An transthoracic echocardiogram showed normal atria and ventricles, normal systolic function, and excluded pulmonary hypertension (Figure 2 A, B).

Furosemide (40 mg/IV, S: 1x3) and oxygen (8 Lt/min) were administered for the following 24 hours. Clinical improvement was seen and the ventilatory and haemodynamic support were discontinued, O<sub>2</sub> saturation normalized. ECG controls were normal. The patient experienced a full recovery and was discharged 3 days later (Figure 1 B, Figure 2 C, D).

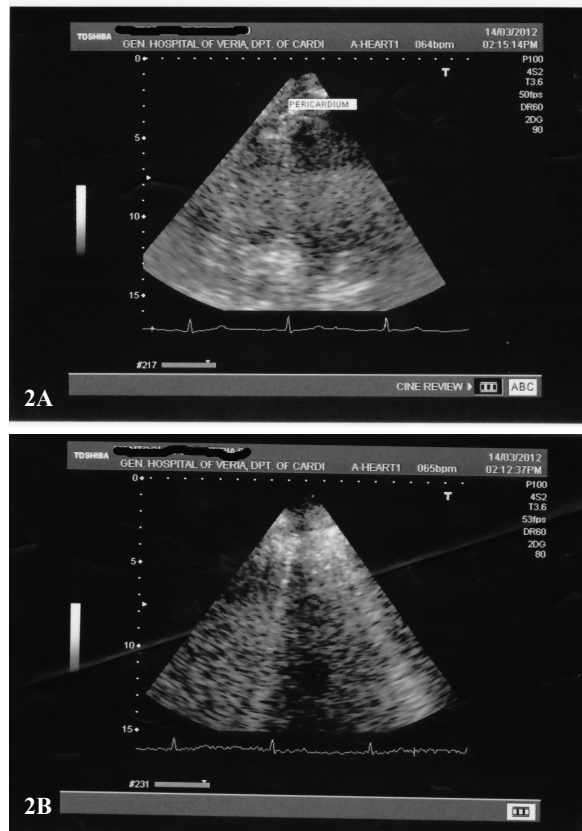
## Discussion

Acetazolamide is indicated for adjunctive treatment of edema due to congestive heart failure, drug-induced edema, centrencephalic epilepsies and chronic simple (open-angle) glaucoma<sup>1</sup>.

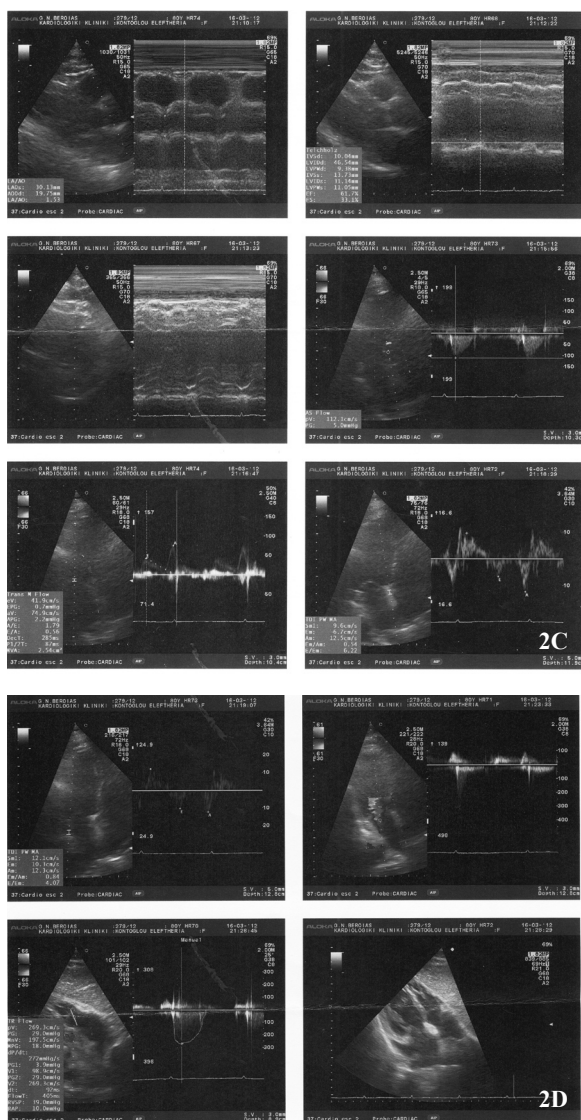
Serious anaphylactic reactions to carbonic anhydrase inhibitors, such as acetazolamide, are infrequent. Although, adverse effects of acetazolamide have been previously reported, there are only a few previous reports of anaphylactic shock and acute pulmonary edema caused by the oral intake of acetazolamide<sup>4-6</sup>. Our patient had not been treated with acetazolamide previously, so hypersensitivity due to prior administration to sulphonamides is excluded. On the other hand, the relationship between an-



**Figure 1:** A) After the oral administration of acetazolamide, B) After full recovery of the patient.



**Figure 2:** A, B) Transthoracic Echocardiogram of the patient.



**Figure 2. C, D)** Transthoracic echocardiogram of the patient after full recovery.

anaphylactic shock and acetazolamide was highly probable due to the short time between drug effect and onset of symptoms (less than 30 minutes) and the absence of previous diseases to which symptoms could be related<sup>7</sup>. The patient was not previously treated with acetazolamide.

Acetazolamide is a sulphonamide derivative and, like other sulphonamides, may cause bone marrow depression, skin toxicity, and allergic reactions in patients hypersensitive to sulphonamides<sup>8</sup>. The anaphylactic reaction in our patient could have been related to sulphonamide hypersensitivity caused by a cross sensitivity with other drugs in the same family such as carbonic anhydrase.

A previous study<sup>4</sup> reported a 66-year-old woman who developed anaphylactic shock associated with laryngeal edema, respiratory distress syndrome, and death after ingestion of 250 mg of acetazolamide. Tzanakis et al<sup>5</sup> described a 70-year-old man with sulphonamide hypersensitivity, who presented acute respiratory failure 30

minutes after taking 250 mg of acetazolamide. Gerhards et al<sup>9</sup> reported a 66-year-old female who developed irreversible anaphylactic shock with massive pulmonary edema after assumption of acetazolamide. The investigators hypothesized that this adverse effect was attributable to cross-reaction with sulphonamide. Riquelme et al<sup>10</sup> described a 33-year-old man who presented with hypotension and acute heart failure 30 minutes after acetazolamide assumption. The investigators hypothesized an etiopathogenetic mechanism similar to thiazide diuretics hypersensitivity.

The exact cause of the drug-induced acute pulmonary oedema remains unknown although recently an immunologically mediated mechanism has been described<sup>11</sup>. It is well known that acute allergic reaction is associated with vasculitis<sup>11</sup> which leads to increased permeability of pulmonary capillaries, a fact that cannot be proven for obvious reasons. To our knowledge there are no references in the literature supporting this theory.

## Conclusion

Clinicians and ophthalmologists should be aware if any sign of anaphylactic shock are experienced in patients who take acetazolamide orally. We also suggest the careful monitoring of patients with prior history of allergic reactions to sulphonamides or to other drugs during oral administration of the first dose of acetazolamide.

## Conflict of interest:

None declared.

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