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## CASI CLINICI

# Triazolam, obesity and non cardiac pulmonary edema

*Triazolam, obesità ed edema polmonare non cardiogeno*

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### KEYWORDS

Non cardiac pulmonary edema;  
Adverse drug reaction;  
Triazolam;  
Obesity.

### Summary

**Introduction:** Triazolam belongs to the group of benzodiazepines and may have side effects on the respiratory system which include not only respiratory depression, but also transient benign non cardiac pulmonary edema.

**Case report:** A 52 year old obese woman developed pulmonary edema after she was taking triazolam for almost two weeks without any other medications. All possible cardiogenic and non cardiogenic causes were excluded. The condition was severe enough to require non invasive ventilation.

**Discussion:** This case differs from the other report of triazolam associated non cardiac pulmonary edema for its severity requiring non invasive ventilation. The pathogenetic mechanism is unknown. Despite the lack of objective evidence to explain pulmonary venous hypertensive changes in our case, we want to advice that triazolam should be used with caution in obese patients, as obesity might aggravate this described drug adverse reaction.

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## Introduction

Triazolam belongs to the group of benzodiazepines and may have side effects on the respiratory system which include not only respiratory depression, but also transient benign non cardiac pulmonary edema [1]. This form of non cardiac pulmonary edema is not life threatening ( $\text{PaO}_2/\text{FiO}_2$  is always superior to 400), is usually auto-resolving within few hours and may be associated to many drugs (Table 1).

We report a severe form of triazolam associated non cardiac pulmonary edema in an obese patient requiring non invasive ventilation.

## Case report

A 52 year old woman (Body Mass Index 34) presented with severe dyspnea progressive increasing in few days. On examination heart rate was 120 bpm, blood pressure 150/80 mmHg,

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**Table 1** Causative drugs of transient benign non cardiac pulmonary edema according to references reported by Pneumotox On Line ([www.pneumotox.com](http://www.pneumotox.com)).

Acetazolamide	Gemcitabine	Propofol
Acetylsalicylic acid	Hydrochlorothiazide	Propranolol
Adrenaline	Ibuprofen	Prostacilin
Albumin	Immunoglobulins (IV)	Protamine
Amitriptyline	Insulin	Pyrimethamine-sulfadoxine
Amphotericin B	Interleukin 2	Retinoic acid
Basiliximab	Ketamine	Ritodrine
Buprenorphine	Lidocaine	Rituximab
Carbamazepine	Medroxyprogesterone	Rosiglitazone
Chlorpromazine	Metamizole	Salbutamol
Clomiphene	Methadone	Sulfasalazine
Codeine	Methotrexate	Sulfonamides
Colchicine	Minocycline	Terbutaline
Cotrimoxazole	Morphine (agonists/antagonists)	Thiazolidinediones
Cyclophosphamide	Nicardipine	Triazolam
Cyclosporin	Nitroglycerin	Troglitazone
Deferoxamine	Oxycodone	AbMo antitumor necrosis factor-alpha
Dexamethasone	Paclitaxel	Vasopressin
Dextran	Phenylbutazone	Vinorelbine
Diltiazem	Phenylephrine	
Erythromycin	Pioglitazone	

respiratory rate 40 breaths/min and temperature 36.7 °C. Auscultation of heart was normal, while chest auscultation revealed inspiratory crackles bilaterally. Peripheral edema and jugular venous distension were not present. The electrocardiogram showed only sinus tachycardia. The chest radiograph showed diffuse asymmetric bilateral infiltrates with normal cardiac size and vascular pedicle width; the distribution of blood flow in the lung was not inverted and Kerley lines were not seen. Transthoracic echocardiogram showed normal cardiac dimensions (luminal diameters and septal thicknesses), cardiac output as well as ejection fraction, valve areas and function; systolic pulmonary artery pressure of 41 mmHg, considered with the limitations of the method at the upper limit of normality [2]. Abdominal ultrasound was normal and there were no pleural effusions on chest echography.

Physical findings, chest radiograph and transthoracic echocardiogram were indicative of non cardiac pulmonary edema.

Initially in the emergency room she was given by nursing staff high flow oxygen by a Ventimask with a FiO<sub>2</sub> of 40% to maintain arterial oxygen saturation of hemoglobin (SaO<sub>2</sub>) around 90-92%. Subsequently she was given 4 L/min oxygen by a Ventimask with a FiO<sub>2</sub> of 28% and arterial blood gas analysis revealed PaO<sub>2</sub> 64 mmHg, PaCO<sub>2</sub> 59 mmHg, HCO<sub>3</sub><sup>-</sup> 33 mmol/L, pH 7.37.

The PaO<sub>2</sub>/FiO<sub>2</sub> ratio of 229 was consistent with a severe hypoxemia, but not yet an acute respiratory distress syndrome (ARDS) defined by a PaO<sub>2</sub>/FiO<sub>2</sub> ratio of less than 200.

Laboratory investigation showed: erythrocyte sedimentation rate 10 mm/h; WBC 6,300 x 10<sup>3</sup>/μL with 64% neutrophils and 28% lymphocytes; RBC 4.76 x 10<sup>6</sup>/μL; HGB 14 g/dL; HCT 45.8% and PLT 205 x 10<sup>3</sup>/μL; BUN 19 mg/dL and serum creatinine 0.65 mg/dL; blood glucose 113 mg/dL; D-dimer 54 ng/mL; serum electrolytes and urine analysis normal.

Many possible causes of non cardiac pulmonary edema (intravenous fluid overload; neurogenic causes as seizures, head trauma and electrocution; inhalation of toxic gases; pulmonary contusion; aspiration of gastric fluid or other liquids; blood transfusions; severe infections; illicit drug use) were excluded on the basis of history, physical examination, instrumental and laboratory investigations. Pulmonary embolism, which rarely may be associated with non cardiac pulmonary edema, was excluded by the absence of any ECG and ultrasound signs of right heart acute overload and by serial measurements of D-dimer always normal. From history resulted that she was taking triazolam for almost two weeks without any other medications. Therefore we interpreted the pulmonary edema as an adverse side effect of this drug.

The patient had received intravenous furosemide (40 mg) and continuous intravenous infusion of nitrates (5 μg/min) in the emergency room. After the diagnosis of iatrogenic non cardiac pulmonary edema, she was empirically treated with high doses of intravenous steroids (prednisolone 1mg/kg body weight), but the focus was on maintaining adequate oxygenation with non invasive ventilation. We used a bilevel assisted spontaneous breathing pressure support non invasive ventilation with an inspiratory positive airway pressure

(IPAP) of 20 cm H<sub>2</sub>O and an expiratory positive airway pressure (EPAP) of 7 cm H<sub>2</sub>O, back up respiratory rate of 15 breaths/min and back up inspiratory/expiratory time ratio of 1:3. The patient oxygenation increased promptly and non invasive ventilation was withdrawn after almost 12 hours excluding the short periods off the ventilator. She continued to improve and was then discharged on the eighth hospital day in good and stable condition with the following arterial blood gases on air: PaO<sub>2</sub> 70.1 mmHg; PaCO<sub>2</sub> 47 mmHg; HCO<sub>3</sub><sup>-</sup> 29 mmol/L; pH 7.39.

## Discussion

The pathogenetic mechanism of non cardiac pulmonary edema is usually due to direct toxic stimulus, as in the case of aspiration of gastric contents, inhalation of toxic substances or closed chest trauma, or to systemic insults (infections and sepsis, trauma, repeated blood transfusions, pancreatitis, etc.) which cause the release of several inflammatory cells and mediators [3].

We report a case of non cardiac pulmonary edema associated with the use of triazolam. The pathogenetic mechanism of triazolam as well as many other drugs associated non cardiac pulmonary edema (Table 1) is unknown. This case differs from the other report [1] for its severity requiring non invasive ventilation. Pulmonary venous hypertension may be frequent in obese individuals as it has been found by an autopsic study of Haque et al. [4], but in our case the absence of echocardiographic signs of right ventricular overload and

of left ventricular dysfunction seems to not justify pulmonary venous hypertensive changes aggravating the condition.

In conclusion, despite the lack of objective evidence to explain the severity of this drug associated non cardiac pulmonary edema, previously described transient and benign [1], the take-home message from this report is that triazolam should be used with caution in obese patients, as obesity might aggravate this described drug adverse reaction and may have already determined compromised ventilatory performances in affected subjects.

## Conflict of interest statement

The authors have no conflict of interest to disclose.

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