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# High Dose Oseltamivir Induced Hypothermia and Respiratory Suppression in Elderly: A Case Report

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***Authors' contributions***

*This work was carried out in collaboration between both authors. Author MT wrote the first draft of the manuscript. Author NK managed and revised the case report. Both authors read and approved the final manuscript.*

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***Case Study***

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## ABSTRACT

**Introduction:** Oseltamivir is an antiviral drug, used for influenza treatment. Neurological side effects of this drug, including hypothermia and respiratory arrest, were demonstrated in animal models.

**Case Presentation:** We reported a case of an elderly male who presented with influenza B pneumonia and respiratory failure. He received high dose and extended duration of Oseltamivir. He developed hypothermia and central hypoventilation, complicated with prolonged weaning. At that time, there were no sedative and neuromuscular blocking agents, and no evidence of brain stem dysfunction and endocrine crisis. Concerning of rare reported adverse reactions of Oseltamivir in animal models, this drug was discontinued. Consequently, his symptoms improved and he was successfully liberated from mechanical ventilation.

**Conclusion:** We hereby report a case of Oseltamivir associated respiratory suppression and hypothermia in human.

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## 1. CASE PRESENTATION

A 95 year-old Thai man presented with fever and dry cough for 1 day. On physical examination, he looked drowsy and had fever with hemodynamic instability. He had oxygen desaturation (SpO2 85% at ambient air) and fine crepitation at the left lung. Chest X-ray showed infiltration in both lower lungs. (Fig. 1) Lab investigations showed leukocytosis, azothemia and mild hyponatremia with wide gap metabolic acidosis. (Table 1) He was initially diagnosed with community acquired pneumonia with septic shock and consequently stabilized with fluid resuscitation, vasopressor and oxygen supplement. Levofloxacin and ceftriaxone were prescribed.

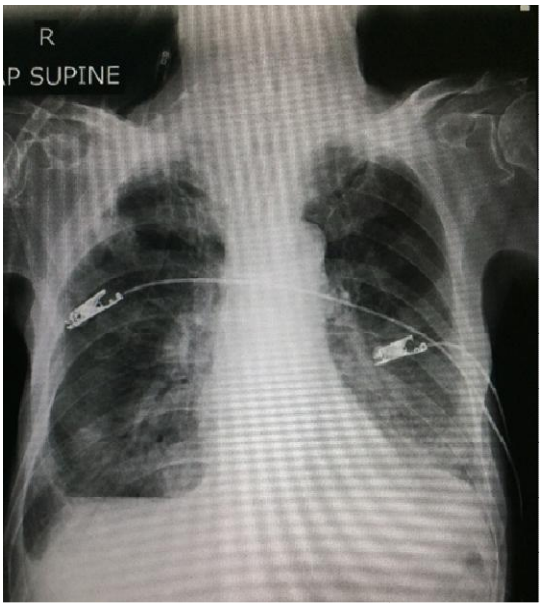


**Fig. 1. Chest X-ray reveals alveolar infiltration in both lower lungs**

Two days later, he developed acute respiratory failure and was assisted ventilation. His chest X-ray revealed progressive infiltration at the right lower lung. Rapid test for influenza B was positive, resulting in administration of oseltamivir (75 mg twice-daily). As a result, his symptoms and arterial oxygenation improved.

However, during the second week of admission, he could not breathe spontaneously and got a new onset of fever, anemia and thrombocytopenia. (Figs. 1,2) Sputum culture showed heavy growth of *Acenitobacter baumannii* without new infiltration on chest X-ray and no other sources of infection. Ventilator associated tracheobronchitis was diagnosed, so antibiotics were switched to Carbapenem, Colistin, and Ampicillin/Sulbactam. Besides, Oseltamivir was extended due to concerning of immune response to influenza-B.

His condition gradually recovered until the third week of treatment, after the 2 weeks duration of Oseltamivir, he developed unexplained hypothermia, occasional hypotension and central hypoventilation despite no sedative drugs and neuromuscular-blockades. (Fig. 2) At that time, his neurological signs including brainstem reflexes were intact. His ventilatory parameter showed low minute ventilation and apnea alarm. Additionally, there was no evidence of new infection. His morning cortisol and thyroid function test were absolutely normal. Subsequently, adverse drug reactions were considered, thus we discontinued Oseltamivir. Noticeably, his temperature, blood pressure, respiratory rate and PaCO2 returned to baseline within 5 days after Oseltamivir withdrawal. Finally, he was successfully liberated from the ventilator.

## 2. DISCUSSION

The elderly man was diagnosed community acquired pneumonia resulting from Influenza B, and rapidly developed respiratory failure on the second day of admission. He received the prolonged course and high dose of Oseltamivir because of delayed clinical improvement. Subsequently, he developed unexplained hypothermia, hypotension and respiratory suppression, which dramatically recovered after withdrawal of Oseltamivir.

Tamiflu (Oseltamivir phosphate) is the prodrug of Oseltamivir carboxylate, an active form of neuraminidase inhibitor. A capsule of Oseltamivir phosphate dissolves in gastrointestinal tract to form 75 mg of Oseltamivir free base, which is absorbed to portal venous system and hydrolysed by hepatic carboxylesterase (hCE) to active Oseltamivir carboxylate. This drug is predominantly eliminated by urine as the active Oseltamivir carboxylate (>90%).

Neuropsychiatric manifestations are not uncommon central nervous system side effect of Oseltamivir. This side effect is mainly from

Oseltamivir phosphate in free base form, which penetrates through the blood brain barrier more than the active form, Oseltamivir carboxylate. There are two possible mechanisms potentiating the neurological side effects of Oseltamivir in acute phase of infection. Firstly, the plasma concentration of unchanged Oseltamivir free base may increase because of the reduction of hepatic carboxylesterase (hCE) by interleukin-6 [1,2]. Secondly, down regulation of P-glycoprotein, the critical drug efflux transporter at the blood brain barrier appears in acute phase of inflammation, resulting in increased Oseltamivir free bases at the blood brain barrier [1,2].

However, receptors, channels and actual mechanisms of the neurological suppression have not been known yet. The central hypoventilation was demonstrated in animals treated with the higher doses and longer duration of Oseltamivir than those used in clinics. Kimura S, et al. showed the dose-related hypopnea occurred in mature rats administered with intravenous Oseltamivir, and the dose of 200 mg/Kg led to respiratory arrest [3,4,5].

Up to our knowledge, the respiratory suppression was reported only in animal models. Interestingly, there were some suspected cases of respiratory depression presenting with sudden death during sleep, or dyspnea and cyanosis in human [6,7]. Symptoms such as hypothermia, decreased body movement and slow or abnormal breathing frequently appeared before the events.

**Table 1. Lab data**

| Day of admission | 1 | 20 | Normal values | units |
|---|---|---|---|---|
| **CBC** | | | | |
| Red cell count | 4.14 | 2.87 | 4.60 – 6.00 | X 10 6/uL |
| Hemoglobin | 12.3 | 8.1 | 13.0 - 17.0 | g/dl |
| Hematocrit | 39.7 | 24.6 | 39.0 – 51.0 | % |
| MCV | 95.8 | 86.3 | 80.0-100.0 | fl |
| RDW | 14.7 | 15.1 | 11.0 – 14.5 | % |
| Platelets counts | 153000 | 161000 | 150 -450 | X 10 3/uL |
| White cell count | 16200 | 11280 | 4.50 – 11.00 | X 10 3/uL |
| Neutrophils | 94.9 | 81.4 | 40.0 - 70.9 | % |
| Lymphocytes | 2.3 | 4.0 | 22.2 - 43.6 | % |
| Monocytes | 2.5 | 11.5 | 0.0 – 7.3 | % |
| Eosinophil | 0.02 | 1.9 | 0.0 – 4.1 | % |
| Basophils | 0.0 | 0.0 | 0.0 – 1.8 | % |
| **Blood chemistries** | | | | |
| BUN | 37 | 22 | 7 - 20 | mg/dl |
| Creatinine | 2.77 | 1.73 | 0.70 – 1.20 | mg/dl |
| GFR | 30.15 | | | % |
| Calcium | 9.4 | 8.8 | 8.5 – 10.5 | mg/dl |
| Phosphate | 2.8 | 4.4 | 2.5 – 4.5 | mg/dl |
| Magnesium | 0.74 | 0.8 | 0.7 – 1.0 | mmol/L |
| Total protein | 6.6 | | 6.4 – 8.3 | g/dl |
| Albumin | 3.3 | 2.2 | 3.5 – 5.0 | g/dl |
| Total bilirubin | 0.76 | 0.35 | 0.2 – 1.2 | mg/dl |
| Direct bilirubin | 0.44 | 0.21 | 0.0 – 0.5 | mg/dl |
| SGOT | 32 | 34 | 5 – 35 | U/L |
| SGPT | 22 | 12 | 0 – 40 | U/L |
| Alkaline phosphatase | 62 | 119 | 40 – 120 | U/L |
| Sodium | 133 | 127 | 136 – 145 | mmol/L |
| Potassium | 4.5 | 3.9 | 3.5 – 5.1 | mmol/L |
| Chloride | 100 | 95 | 95 – 105 | mmol/L |
| Carbon dioxide | 16 | 26 | 22 – 29 | mmol/L |

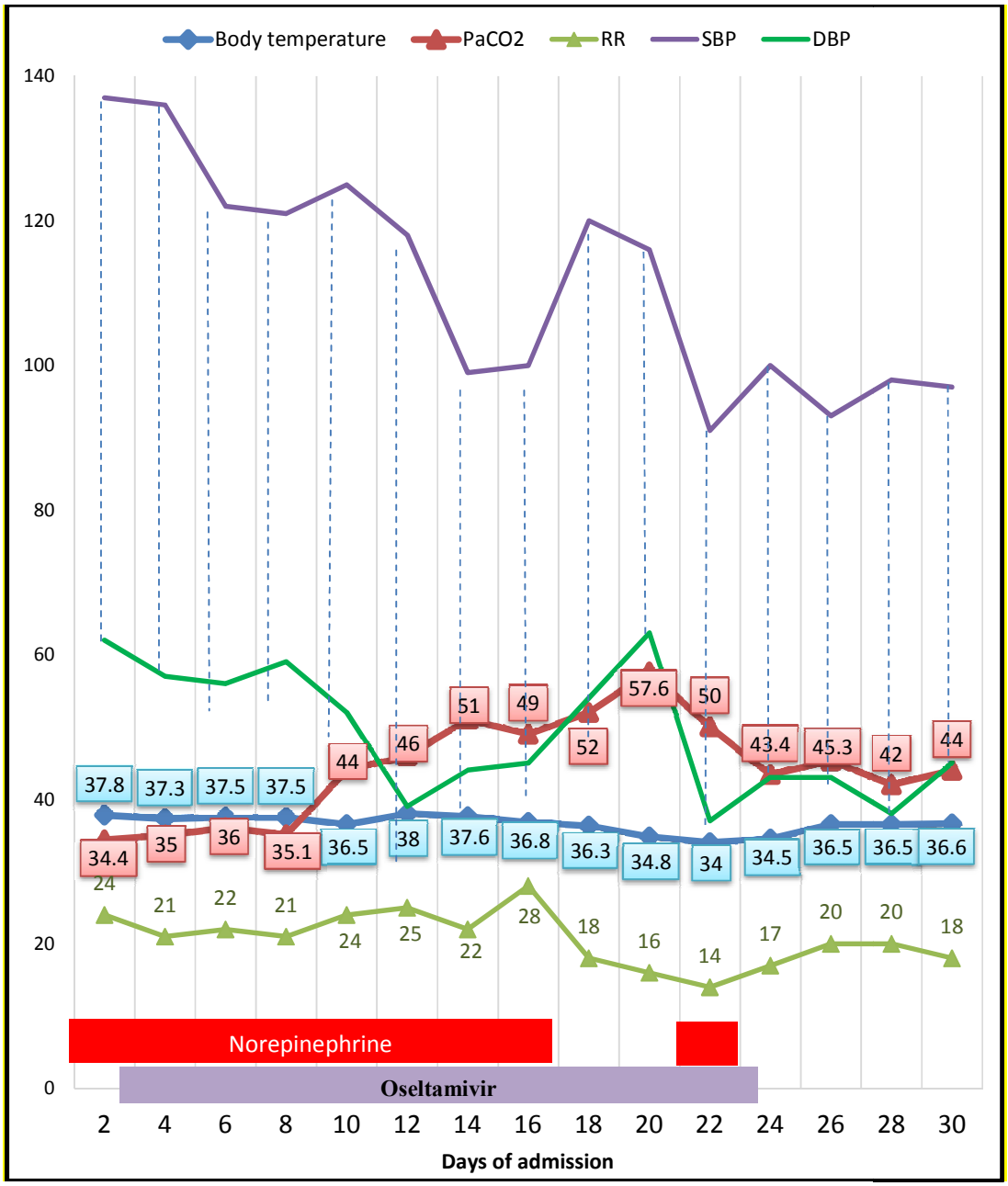


**Fig. 2. This figure shows changes of vital signs and PaCO2 during influenza B treatment**

According to the clinical presentation, our patient developed hypoventilation during the third week of treatment. This adverse reaction might be related to high cumulative dose of Oseltamivir.

## 3. CONCLUSION

Our report demonstrated the first human case of Oseltamivir associated respiratory depression and hypothermia, which were dose-dependent adverse reactions.

## CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the authors.

## ETHICAL APPROVAL

All authors hereby declare that the patient was explained before asking him to give

the permission. It is noted that this case report has already been examined and approved by the institutional ethics committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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