

# Theophylline Therapy for Near-Fatal Cheyne–Stokes Respiration

## A Case Report

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**Background:** Cheyne–Stokes respiration is characterized by periodic breathing that alternates with hypopnea or apnea.

**Objective:** To describe the effect of theophylline on near-fatal Cheyne–Stokes respiration.

**Design:** Case report.

**Setting:** Tertiary referral center.

**Patient:** A 48-year-old diabetic woman with a history of three cardiorespiratory arrests, a normal coronary arteriogram, normal left ventricular function, and severe Cheyne–Stokes respiration.

**Measurements:** Oxygen saturation, intra-arterial blood pressure, central venous pressure, chest wall movement, electrocardiography, electromyography, electroencephalography, electro-oculography, minute ventilation, arterial blood gases, and serum theophylline levels.

**Results:** After intravenous administration of 1.2 mg of theophylline at 0.6 mg/kg per hour (serum level, 5.6  $\mu\text{g}/\text{mL}$ ), both Cheyne–Stokes respiration and oxygen desaturation were markedly attenuated. After infusion of 2.4 mg of theophylline (serum level, 11.6  $\mu\text{g}/\text{mL}$ ), Cheyne–Stokes respiration resolved completely. No change was seen with placebo. Cheyne–Stokes respiration did not recur during outpatient treatment with oral theophylline.

**Conclusion:** Theophylline may be a rapid and effective therapy for life-threatening Cheyne–Stokes respiration.

Cheyne–Stokes respiration is a common and occasionally serious condition characterized by periodic breathing in which apneas or hypopneas alternate with hyperventilation in a crescendo–decrescendo pattern (1, 2). This respiratory pattern is frequently seen in severe heart failure, in which it may be associated with increased morbidity and mortality (3). Cheyne–Stokes respiration is also seen in preterm infants (4) and may occur in normal persons during sleep and at high altitudes (5). Neurologic causes include stroke, tumors, meningitis, encephalitis, and trauma (6). Potential treatments include oxygen, carbon dioxide, and methylxanthines (3). One week of oral theophylline therapy attenuated nocturnal Cheyne–Stokes respiration in patients with heart failure (7).

We describe a patient with profound Cheyne–Stokes respiration associated with several cardiac arrests requiring cardiopulmonary resuscitation. We describe effective, prompt, and sustained elimination of Cheyne–Stokes respiration with intravenous and, subsequently, oral theophylline therapy.

## Case Report

A 48-year-old woman with a 25-year history of diabetes mellitus and resulting retinopathy, neuropathy, and end-stage renal disease (for which she underwent dialysis) was noted to have Cheyne–Stokes respiration. This condition was initially mild but worsened progressively over several years. The Cheyne–Stokes respiration resulted in profound oxygen desaturation accompanied by three cardiopulmonary arrests. The cause of cardiopulmonary arrest was initially unknown and was suspected to be cardiogenic in nature. She experienced her first cardiopulmonary arrest requiring cardiopulmonary resuscitation when she was given midazolam, a benzodiazepine that sometimes causes respiratory depression, for placement of a gastric feeding tube. Her next cardiac arrest occurred 1 year later, toward the end of a hemodialysis session; a third cardiorespiratory arrest occurred the following day. The third episode was preceded by documented oxygen desaturation and ST-segment depression. At that time, her medications were oral acetaminophen (Tylenol, McNeil Consumer Products Co., Fort Washington, Pennsylvania), 650 mg every 4 hours as needed; aluminum hydroxide (Amphojel, Wyeth-Ayerst Laboratories, Philadelphia, Pennsylvania), 30 mL every 4 to 6 hours as needed; oral prochlorperazine (Compazine, SmithKline Beecham, Pittsburgh, Pennsylvania), 10 mg every 6 hours; sodium polystyrene sulfonate (Kayexalate, Sanofi Pharmaceuticals, New York, New York), 15 g/d by feeding tube; oral aspirin, 81 mg/d; oral levothyroxine (Syn-

This paper is also available at <http://www.acponline.org>.

*Ann Intern Med.* 1999;130:427-430.

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throid, Knoll Pharmaceutical Co, Mount Olive, New Jersey), 0.1 mg/d; oral ferrous sulfate, 325 mg every night at bedtime; cisapride (Propulsid, Janssen Pharmaceutica, Titusville, New Jersey), 20 mg every night at bedtime; paroxetine hydrochloride (Paxil, SmithKline Beecham), 10 mg every night at bedtime; and trazodone, 400 mg every night at bedtime.

Electrocardiographic changes resolved once the patient's oxygenation improved, and myocardial infarction was ruled out. The patient was transferred to our tertiary care center. Her profound Cheyne-Stokes respiration during wakefulness and sleep, which triggered repetitive oxygen desaturation to less than 40%, was noticed only after therapy with supplemental oxygen was discontinued. She was minimally conversant and markedly somnolent during the daytime.

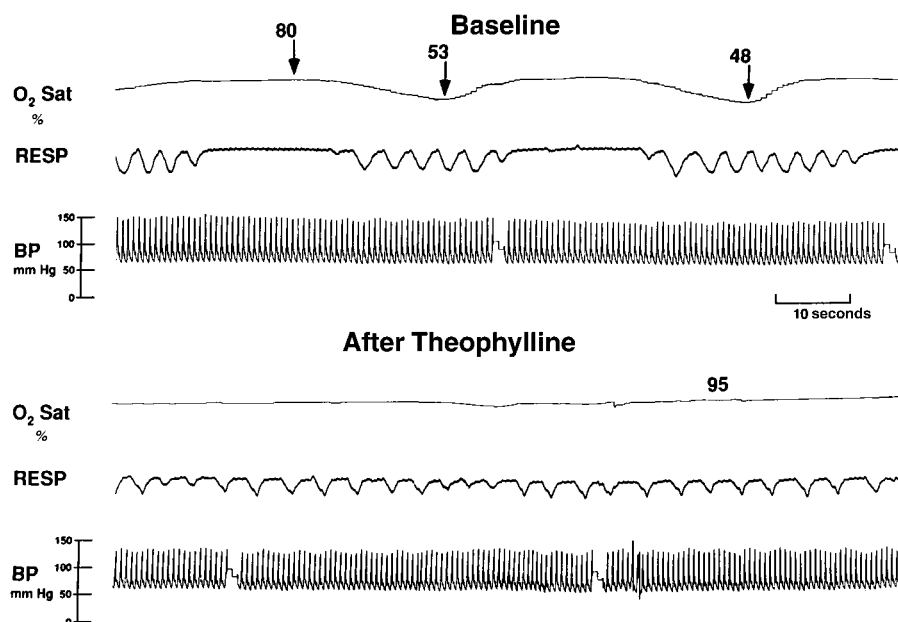
The patient weighed 60.2 kg, was 1.58 m tall, and had a body mass index of 24.1 kg/m<sup>2</sup>. The level of thyroid-stimulating hormone was normal (3.15  $\mu$ IU/mL). Transthoracic echocardiography revealed mild left ventricular hypertrophy with normal left ventricular function and right atrial enlargement. Magnetic resonance imaging of the patient's brain revealed an old thalamic lacunar infarction. Cardiac catheterization revealed normal coronary arteries. Polysomnography showed an apnea-hypopnea index of 35 events/h with 219 total apneas (26 central apneas, 192 hypoventilatory hypopneas, and 1 obstructive apnea). A trial of continuous positive airway pressure was initiated but was not tolerated. The patient was dependent on 2 L of oxygen by nasal cannula, which was only partially effective. Thus, we evaluated the effect of intravenous theophylline on her Cheyne-Stokes respiration.

## Methods and Results

Baseline studies done before initiation of theophylline therapy and after discontinuation of oxygen therapy showed apneic episodes lasting from 20 to 50 seconds with oxygen desaturation to as low as 40% (**Figure 1, top**). During intravenous infusion of theophylline (0.6 mg/kg per hour, 400 mg in 100 mL of normal saline), Cheyne-Stokes respiration resolved rapidly and completely. While breathing room air, the patient had no apneas or desaturation after approximately 3 mg of the theophylline was infused (theophylline level, 11.4  $\mu$ g/mL) (**Figure 1, bottom**).

The patient remained completely free of Cheyne-Stokes respiration for the remainder of that day and night and had no nocturnal desaturation while receiving 1 L of oxygen by nasal cannula. Her daytime somnolence resolved and cognitive function improved, as reflected in part by her ability to initiate and maintain conversations; she could do neither before theophylline therapy. At 7:00 the following morning, her theophylline level was 2.2  $\mu$ g/mL.

To determine the threshold for response to theophylline and to exclude any possible effects of the sleep state, we studied the patient at 11:00 the following morning. Supplemental oxygen therapy was discontinued. We obtained continuous measurements of heart rate (by electrocardiography), intra-arterial blood pressure, and central venous pressure. Oxygen saturation was monitored with a pulse oximeter (Nellcor Inc., Hayward, California). Chest wall movement was measured, and electromyography, electroencephalography, and electro-oculography were done. Minute ventilation was measured by



**Figure 1.** Recordings of oxygen saturation ( $O_2$  Sat), respiration (Resp), and blood pressure (BP) before and during intravenous theophylline therapy. **Top.** Before administration of theophylline, Cheyne-Stokes respiration was accompanied by marked oxygen desaturation; even the peak levels of oxygen saturation reached during Cheyne-Stokes respiration were low. Because of a lag in the oxygen saturation monitor, the oxygen saturation lows reached during the apneic period were only recorded subsequently during the hyperventilation period. **Bottom.** After theophylline therapy, respiration was regular, sustained, and free of apnea. Oxygen saturation was maintained at a consistently higher level.

using an S430 ventilation measuring system (KL Engineering, Vacumetrics, Inc., Ventura, California) with a precision, ultralight, unidirectional, inertia-compensated turbine flow transducer; during this measurement, the patient breathed through a mouthpiece with a nose clip to ensure exclusive mouth breathing.

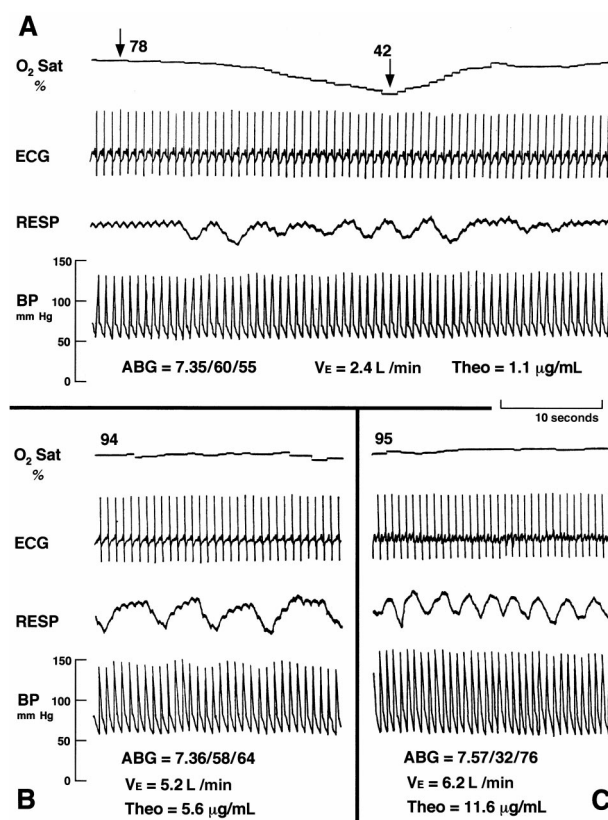
At baseline, the patient's theophylline level was 1.1  $\mu\text{g/mL}$  (**Figure 2A**). Measurement of arterial blood gases revealed a pH of 7.35, a  $\text{PaCO}_2$  of 60 mm Hg, and a  $\text{PaO}_2$  of 55 mm Hg while breathing room air. Minute ventilation was 2.4 L/min. She manifested repetitive and progressively worsening Cheyne–Stokes respiration with hypercapnia and oxygen desaturation as low as 29%; these symptoms were consistent with her initial clinical presentation. Measurements were not affected by a placebo infusion of saline. Polysomnography showed that desaturations to these levels occurred during both wakefulness and drowsiness, but the patient did not sleep. These desaturations were accompanied by ST-segment depression (**Figure 2**). No reflex bradycardia was evident during apnea.

We then initiated therapy with theophylline, 0.6 mg/kg per hour. After intravenous infusion of 1.2 mg of theophylline, the patient's Cheyne–Stokes respiration began to decrease, with marked attenuation of oxygen desaturation. At this time, her theophylline level was 5.6  $\mu\text{g/mL}$ ; her arterial blood gas measurements were a pH of 7.36, a  $\text{PaCO}_2$  of 58 mm Hg, and a  $\text{PaO}_2$  of 64 mm Hg; and her minute ventilation was 5.2 L/min (**Figure 2B**). When we further infused theophylline to a total dose of 2.4 mg, Cheyne–Stokes respiration resolved completely. At this time, her theophylline level was 11.6  $\mu\text{g/mL}$ ; her blood gas measurements were a pH of 7.57, a  $\text{PaCO}_2$  of 32 mm Hg, and a  $\text{PaO}_2$  of 76 mm Hg; and her minute ventilation was 6.2 L/min (**Figure 2C**). Both the decrease in somnolence and improvement in alertness were remarkable.

The patient was discharged to home with orders to take oral theophylline in a sustained-release form (Theo-Dur, Key Pharmaceuticals, Inc., Kenilworth, New Jersey), 200 mg twice daily; this dosage was estimated to maintain a theophylline level of approximately 8 to 12  $\mu\text{g/mL}$ . At 18 months of follow-up, she continued to do very well while taking oral theophylline. Her serum theophylline levels were 8.0  $\mu\text{g/mL}$  at 3 months, 11.6  $\mu\text{g/mL}$  at 12 months, and 11.5  $\mu\text{g/mL}$  at 18 months. The patient and her husband reported marked subjective improvement in her quality of life.

## Discussion

Our patient had an unusual presentation of severe Cheyne–Stokes respiration during both wake-



**Figure 2.** Recordings of oxygen saturation ( $\text{O}_2$  Sat), electrocardiography (ECG), respiration measurement (Resp), and intra-arterial blood pressure (BP) at baseline, early during intravenous theophylline administration, and at the end of theophylline (Theo) infusion. Arterial blood gas (ABG) values are listed as follows: pH/ $\text{PaCO}_2$ / $\text{PaO}_2$ . **A.** On the morning of the second study, the patient's theophylline level was 1.1  $\mu\text{g/mL}$ . She had persistent Cheyne–Stokes respiration with oxygen desaturation to 42%. ST-segment depression is evident on the rhythm strip before institution of theophylline therapy. Arterial blood gas analysis showed carbon dioxide retention, a low  $\text{PaO}_2$ , and low minute ventilation ( $\text{V}_E$ ). Her blood pressure was 130/55 mm Hg, and her heart rate was 72 beats/min. **B.** During theophylline infusion (at 5.6  $\mu\text{g/mL}$ ), the patient's Cheyne–Stokes breathing began to decrease and her oxygen desaturation became attenuated; these events were accompanied by a decrease in  $\text{PaCO}_2$ , an increase in  $\text{PaO}_2$ , and an increase in minute ventilation. Her blood pressure was 140/60 mm Hg, and her heart rate was 78 beats/min. **C.** After intravenous infusion of 2.4 mg of theophylline, Cheyne–Stokes breathing resolved completely.

fulness and sleep; it was not related to congestive heart failure but may have been due to autonomic neuropathy that affected her chemoreceptor function. Central apneas have been reported in patients with type 1 diabetes, particularly in those with autonomic neuropathy (8). These patients also have an absence of the usual bradycardia–tachycardia response to apnea. This combination of central sleep apnea and lack of appropriate autonomic response has been implicated in cardiorespiratory arrest (9). Hypoxic ventilatory depression as part of a generalized central nervous system depression probably contributed to the lack of ventilatory response to progressive hypoxia. Cheyne–Stokes respiration occurred in our patient even during wakefulness and resulted in two spontaneous near-death episodes in 1 month. We cannot exclude the possibility that

midazolam therapy, dialysis, and diabetic microangiopathy contributed to her cardiopulmonary arrests.

Theophylline has been suggested as a possible therapy for Cheyne–Stokes respiration. Although theophylline's mechanism of action is not well understood, it may reduce Cheyne–Stokes respiration by reversal of hypoxic ventilatory depression (10), alteration of the respiratory center response to carbon dioxide (11, 12), or antagonism of adenosine at a central level (13, 14). A randomized, placebo-controlled study by Javaheri and colleagues (7) showed that oral theophylline decreased nocturnal apneas and attenuated oxygen desaturation in patients with congestive heart failure.

Our findings in an awake patient with normal cardiac function support those of Javaheri and colleagues. In addition, we show that intravenous theophylline rapidly eliminated Cheyne–Stokes respiration in a dose-responsive manner. Little information is available about what levels of theophylline may correct Cheyne–Stokes respiration or whether theophylline eliminates Cheyne–Stokes respiration during wakefulness. The normal cardiac function and normal epicardial coronary arteries in our patient allowed us to use intravenous theophylline with relative safety. In our patient, Cheyne–Stokes respiration resolved partially at a theophylline level of 5.6  $\mu\text{g}/\text{mL}$  and completely at 11.6  $\mu\text{g}/\text{mL}$ . Along with elimination of Cheyne–Stokes respiration, theophylline also increases minute ventilation, heart rate, and blood pressure (**Figure 2**).

Important aspects of our study are that rapid, sustained resolution of profound, near-fatal Cheyne–Stokes respiration was achieved in an awake patient without congestive heart failure; that intravenous theophylline can be used to evaluate the threshold for efficacy in preventing Cheyne–Stokes respiration; and that theophylline increased minute ventilation and decreased  $\text{PaCO}_2$  in the setting of hypoventilation. Although careful use of oral theophylline may be safe in patients with heart failure (3), caution must be exercised in the use of intravenous theophylline, especially in patients with clinically significant coronary artery disease. Our findings may also have implications for other patients with Cheyne–Stokes respiration, in whom a trial of intravenous theophylline may predict the response to long-term oral theophylline therapy.

*Grant Support:* Drs. Pesek and Cooley are supported by a National Institutes of Health (NIH) Interdisciplinary Cardiovascular Research Fellowship HL07121. Dr. Narkiewicz is a recipient of an International Research John E. Fogarty Fellowship from the NIH (3F5 TW05200) and a Perkins Memorial Award from the American Physiological Society. Dr. Weintraub is supported by an NIH Program Project Grant (HL9264-06) and an American Heart Association Clinician Scientist Award (96 004540). The study was also supported by a Sleep Academic Award from the NIH, an Established Investigator Grant from the American Heart Association, and NIH grant HL61560 (Dr. Somers).

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