

## PHYSOSTIGMINE REVERSAL OF CARBON MONOXIDE COMA

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Carbon monoxide (CO) poisoning is a worldwide phenomenon which causes considerable morbidity and mortality. Although CO has been removed from most domestic gases, it is still the most common fatal poison in many countries.<sup>1</sup> Carbon monoxide reacts readily and reversibly with hemoglobin, forming carboxyhemoglobin (COHb), which makes hemoglobin unavailable for oxygen transport and shifts the oxyhemoglobin dissociation curve to the left. The resultant hypoxia is the main cause of morbidity and mortality in man. It is also possible that CO has a direct toxic effect at the cellular level by hindering mitochondrial respiration. Such an effect may be longer-lasting than the rise in COHb concentration.<sup>2,3</sup>

Oxygen has been proposed as a suitable antidote to CO poisoning, because an elevated oxygen tension will increase the amount of oxygen in solution in plasma and will compete with CO for hemoprotein-binding sites. In addition, oxygen has been shown to inhibit the lipid peroxidation that follows CO exposure. Allopurinol and acetylcysteine were used with success in a patient with CO poisoning.<sup>4</sup>

Central anticholinergic syndrome (CAS) has not been described before in association with CO poisoning. This syndrome is caused by pharmacological substances that have anticholinergic actions. The central and peripheral manifestations of CAS are those of acetylcholine-competitive inhibition and appear to involve muscarinic receptors. Of the three muscarinic antagonists commonly used during anesthesia, atropine sulfate and scopolamine hydrobromide are known to cause this syndrome.<sup>7</sup>

Physostigmine (anticholinesterase) has only recently been used for the treatment of CAS. Physostigmine, which is chemically a tertiary ammonium compound, readily crosses the blood-brain barrier and reverses the central manifestations of CAS.<sup>6</sup> We describe a patient who

presented with coma following CO poisoning and who achieved a complete recovery as a result of physostigmine.

### Case Report

A 35-year-old male patient was found unconscious in his room beside a coal-heating oven. He was brought immediately to the accident and emergency department of our hospital. No definite history could be taken, since the patient was unaccompanied. On examination, he was deeply comatose with a Glasgow coma scale of 4. He could move all limbs on deep painful stimuli and both pupils were constricted and reactive to light. Heart rate was 104 beats/min, blood pressure 100/50 mm Hg and body temperature was 36.0°C. Chest x-ray was normal. The patient was cyanosed. His arterial blood gases (ABG) showed a pH 7.36, PaCO<sub>2</sub> 27 mm Hg, PaO<sub>2</sub> 42.7 mm Hg and oxygen saturation of 76.4% on room air.

Carboxyhemoglobin (COHb) blood level measured at this stage was 24.3% (normal 2%). The diagnosis of CO poisoning was made. Tracheal intubation was facilitated with succinylcholine 100 mg intravenously. Lungs were ventilated with an FIO<sub>2</sub> 1.0. The patient was transferred to the surgical intensive care unit (SICU) for further investigation and management. The patient started to recover and became restless when sedation was started with propofol 2-4 mg/kg/hr. Arterial and central venous lines were inserted.

In the SICU, elective ventilation with an FIO<sub>2</sub> 1.0 was continued. Arterial blood gases after admission to the SICU were pH 7.37, PaCO<sub>2</sub> 38 mm Hg, PaO<sub>2</sub> 357 mm Hg, HCO<sub>3</sub> 22 mm Hg and saturation 99.8%. The following investigations were normal: full blood count, biochemical profile including urea and electrolytes, blood glucose, liver enzymes and thyroid function tests.

The patient was given one dose of allopurinol 100 mg through the nasogastric tube and N-acetylcysteine intravenous infusion was started in the following order: 150 mg/kg in 200 mL dextrose 5% over 15 min, 50 mg/kg in 250 mL over four hours and 100 mg/kg in 500 mL over 16 hours. Ranitidine 50 mg i.v. every six hours and methylprednisolone 1.8 g were also given.

Serial assays of COHb level showed a gradual decrease of the CO level. On the second, third and fifth hour of

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elective ventilation, these levels were 3.5%, 1.6% and 0.4% respectively. Since the COHb level returned to normal, an attempt to wean the patient off the ventilator was started. Propofol was discontinued one hour later. After two hours, the patient was breathing spontaneously via T-piece with pH 7.42, PaO<sub>2</sub> 160 mm Hg, PaCO<sub>2</sub> 32 mm Hg and oxygen saturation of 99% under FIO<sub>2</sub> 0.3. Neurological examination revealed that the patient was comatose responding only to deep painful stimulation, but with no response to verbal commands. Two hours later the patient's condition did not change. At this stage the diagnosis of CAS was considered.

Physostigmine 2 mg i.v. was administered over 20 minutes. The patient then opened his eyes spontaneously and upon verbal commands he moved his limbs purposefully. The trachea was extubated 10 minutes later. After two days, the patient was discharged to the medical ward and one day later he was sent home with an appointment in the medical clinic for further follow-up. We were not able to detect any late sequelae of CO poisoning, since the patient did not show up in the medical clinic.

### Discussion

Carbon monoxide (CO) intoxication can cause injury to hypoxia-sensitive tissues, such as the brain and the heart, resulting in permanent damage or death. In addition, delayed neurologic deterioration following significant CO exposure may also occur after a lucid interval ranging from two days to six weeks. Because charcoal briquettes appear to burn clearly, individuals are often unaware that they emit significant quantities of CO. Cases of CO exposure from indoor burning of charcoal briquettes have been reported.<sup>7</sup>

The toxic mechanisms of CO are not well understood. Consequently the optimal treatment has not yet been established. It is still widely believed that CO is toxic only because of its binding to hemoglobin (Hb) and the consequent reduction in tissue oxygenation. However, it has been shown that CO has a significant toxicity unrelated to tissue oxygen delivery, although carboxyhemoglobin (COHb) is not toxic.<sup>8,9</sup>

It was shown in previous studies that the patient outcome does not correlate well with COHb levels and titration of treatment against the COHb concentration is often successful. Body stores of CO remain elevated after COHb levels have returned to normal.<sup>10</sup> Neurological dysfunction, particularly reduced consciousness, is the most prominent presentation of CO poisoning.<sup>11</sup> Cardiovascular manifestations are less common and include ST segment changes, cardiac dysrhythmias, hypotension, pulmonary edema and cardiorespiratory arrest. The often cited cherry-red coloration is rare, late

and is much less common than cyanosis. The assessment of severity of CO poisoning based on COHb levels has been unsuccessful.<sup>12</sup> Myers et al.<sup>10</sup> reported a series in which 213 patients were divided into mild and severe groups on the basis of neurological and psychometric examination and COHb levels. The 82 patients with mild poisoning were given normobaric O<sub>2</sub> and 10 of these patients (12.2%) developed neurological sequelae. The remaining 131 patients with severe poisoning were treated with hyperbaric O<sub>2</sub> and, with the exception of one patient, no neurological sequelae were seen.

The aim of treatment of CO poisoning is to increase the inspired O<sub>2</sub> tension. Oxygen is a competitive antagonist to CO for hemoprotein binding, where increased O<sub>2</sub> in solution in the plasma will offset the reduced tissue O<sub>2</sub> delivery secondary to COHb formation and O<sub>2</sub> will inhibit lipid peroxidation secondary to CO. Initial treatment with 100% O<sub>2</sub>, or preferably, hyperbaric O<sub>2</sub> (HBO) if available is recommended. We do not have such a facility in our hospital. At 3 atmosphere, HBO reduces the biologic half-life of CO to 23.5 minutes and may awaken the patient rapidly after treatment is initiated or within 24-48 hours. However, HBO may carry risks of its own, due to the liberation of toxic oxygen reduction products, where xanthine oxidase (NAD<sup>+</sup>-dependent dehydrogenase enzyme) becomes an oxidase and utilizes oxygen to generate superoxide radicals and hydrogen peroxide, thereby causing tissue damage.<sup>13</sup> In theory, allopurinol inhibits xanthine oxidase, and thiol compounds such as N-acetylcysteine reverse the conversion of xanthine oxidase to an oxidase and so inhibit the formation of oxygen radicals. This prompted Howard et al.<sup>4</sup> to use allopurinol and acetylcysteine for treatment of poisoning in a 26-year-old man who was unconscious for 35 hours and remained in a coma for five days, when he had a slow and progressive recovery. Our patient received the same regimen of allopurinol and acetylcysteine used by Howard et al. without improvement, although his COHb level became normal.

Since the central nervous system manifestations of CAS could be either deep coma or hyperexcitation, we considered the diagnosis of CAS in this patient. Physostigmine, which has been used to reverse excitement and depression caused by antihistamines,<sup>14</sup> was used with success in this patient. In order to clarify whether or not physostigmine can accelerate the restoration of normal vigilance, in-patients received no anticholinergic drugs during the recovery period in a randomized double blind study on 60 patients after general anesthesia. It was found that patients who received physostigmine showed significant superior and more rapid restoration of consciousness compared to the control group.<sup>6</sup> In our case, physostigmine resulted in dramatic and complete recovery of the patient.

The association between CO poisoning and CAS has not been reported before. We demonstrate a dramatic recovery of coma following CO poisoning after administration of physostigmine.

### References

1. Meredith T, Vale A. Carbon monoxide poisoning. *BMJ* 1988;296:77-9.
2. Zimmermann SS, Truxal B. Carbon monoxide poisoning. *Pediatrics* 1981;68:215-24.
3. Piantadosi CA. Carbon monoxide, oxygen transport and oxygen metabolism. *J Hyper Med* 1987;2:27-44.
4. Howard RW, Blake DR, Pall H, et al. Allopurinol/N-acetylcysteine for carbon monoxide poisoning. *Lancet* 1987;2:628-9.
5. Longo VG. Behavioural and EEG effects of atropine and related compounds. *Pharmacol Rev* 1966;18:965-70.
6. Schneck G, Handelshausen BV, Tempel G, Borsh R. The influence of physostigmine on the vigilance in the postoperative period. *Anaesthesist* 1985;36:456-9.
7. Hampson NB, Kramer CC, et al. Carbon monoxide poisoning from indoor burning of charcoal briquets. *JAMA* 1994;271:52-3.
8. Haldane JBS. Carbon monoxide as a tissue poisoning. *Biochem J* 1927;21:1068-75.
9. Orellano T, Dergel E, Alijani M, et al. Studies on the mechanism of carbon monoxide toxicity. *J Surg Res* 1976;20:485-7.
10. Myers RAM, Snyder SK, Emhoff TA. Subacute sequelae of carbon monoxide poisoning. *Ann Emerg Med* 1985;14:1163-7.
11. Gorman DF. Problems and pitfalls in the use of hyperbaric oxygen for the treatment of poisoned patients. *Med Toxicol Adverse Drug Exp* 1989;4:393-9.
12. Gorman DF, Runciman WB. Carbon monoxide poisoning. *Anaesth Intensive Care* 1991;19:506-11.
13. Kindwall EP. Hyperbaric treatment of carbon monoxide poisoning. *Ann Emerg Med* 1985;14:1233-4.
14. Lee JH, Turner H, Poppers PJ. Physostigmine reversal of antihistamine-induced excitement and depression. *Anesthesiology* 1975;43:683-6.