Inhalation Toxicology, 18:1047–1049, 2006

ISSN: 0895-8378 print / 1091-7691 online
DOI: 10.1080/08958370600904629

informa
healthcare

Hyperbaric Oxygenation in the Treatment of Life-Threatening Isobutyl Nitrite-Induced Methemoglobinemia—A Case Report

J. Lindenmann and V. Matzi
Division of Thoracic and Hyperbaric Surgery, Department of General Surgery, University Medical School, Graz, Austria

P. Kaufmann and P. Krisper
Department of Internal Medicine, University Medical School, Graz, Austria

A. Maier, C. Porubsky, and F. M. Smolle-Juettner
Division of Thoracic and Hyperbaric Surgery, Department of General Surgery, University Medical School, Graz, Austria

Methemoglobinemia usually results from exposure to oxidizing substances such as nitrates or nitrites. Iron within hemoglobin is oxidized from the ferrous (Fe^{2+}) state to the ferric (Fe^{3+}) state, resulting in the inability to transport oxygen and carbon dioxide. Clinically, this condition causes functional cyanosis. As methemoglobin levels increase, patients show evidence of cellular hypoxia in all tissues. Death usually occurs when methemoglobin fractions approach 70% of total hemoglobin. We describe the case of a 35-year-old female patient with severe life-threatening isobutyl nitrite-induced methemoglobinemia of 75% of total hemoglobin. Toluidine-blue was administered as first-line antidotal therapy immediately, followed by hyperbaric oxygenation. The patient recovered uneventfully and could be discharged 3 days later.

CASE REPORT

A 35-yr-old female drug addict combined the ingestion of alcohol and the inhalation of isobutyl nitrite vapors. At the site of the accident she vomited extensively and became comatose shortly afterward. After intubation and artificial ventilation, the emergency doctor administered 0.4 mg Naloxon hydrochloride and 0.5 mg Flumazenil, but the initial Glasgow Coma Scale (GCS) of 4 did not change.

At the time of admission the patient was unconscious, there was deep cyanosis with a tinge of gray, and limbs were cold and sweaty. A distinct smell of turpentine could be noticed. Physical examination of lung, heart, and abdomen yielded no pathological findings. The electrocardiograph (ECG) showed sinus rhythm, slight ST elevation, but no further signs of myocardial ischemia. Arterial blood pressure was 86/37 mm Hg; heart rate was 96. Laboratory tests were normal except for blood glucose (180 mg%) and lactate (4.3 mmol/L). Drug screening was positive for blood alcohol (2.67 ‰) and for tetrahydrocannabinol (THC) in the urine.

Under artificial ventilation with 100% oxygen, arterial blood gas analysis yielded pO_2 311 mm Hg, pCO_2 33.4 mm Hg, 87% O_2 saturation, and pH 7.36. Methemoglobinemia of 75.2% of total hemoglobin was documented (Table 1)

As an antidote, 3 mg/kg body weight toluidine blue was administered intravenously: The general condition improved, the limbs became warm, and the skin color changed to normal. The patient showed the first signs of regaining consciousness, whereupon a slight sedation with 25 mg Midazolam/h was initiated. Thirty minutes after injection of toluidine blue, methemoglobin concentration had decreased to 34.3%, lactate was 4.1, and the blood gas check parameters improved (Table 1).

Half an hour after toluidine blue injection, hyperbaric oxygenation (HBO) was performed according to the protocol otherwise used in CO intoxication (3 bara for 60 min, 2.2 for 30 min).

After 1 h of HBO treatment the blood gas check showed oxygen saturation 99.0%, pO_2 1185.0 mm Hg, pCO_2 40.1 mm Hg, pH 7.28 (Table 1).

Received 12 April 2006; accepted 13 June 2006.
Address correspondence to Joerg Lindenmann, MD, Department of Surgery, Division of Thoracic and Hyperbaric Surgery, University Medical School Graz, Auenbruggerplatz 29, 8036 Graz, Austria. E-mail: jo.lindenmann@meduni-graz.at

TABLE 1
Methemoglobin levels and arterial blood gas checks and lactate before and after treatment

	Met-Hb (%)	pO_2 (mm Hg)	pCO_2 (mm Hg)	pH	SO_2 (%)	Lactate (mmol/L)
At admission	75.2	311	33.4	7. 36	87	4.3
30 min After toluidine blue	34.3	335	19.2	7.44	99	4.1
During HBO	—	1185	40.1	7.28	99	1.5
After HBO	2.2	467	33.2	7.39	99	2.0
After extubation	1.2	73.8	35.2	7.48	97	0

After HBO therapy the methemoglobin level had decreased to 2.2% of total hemoglobin; lactate was 2.0 (Table 1).

Cerebral computed tomography (CT) scan performed immediately after hyperbaric oxygenation gave no evidence of cerebral ischemia or intracerebral edema.

Two hours after hyperbaric oxygenation, the patient could be weaned from artificial ventilation; oxygen supply at 3 L/min was continued.

On the next day, oxygen supply was discontinued. The patient did not show any signs of neurological disturbance. Arterial blood gas analysis yielded oxygen saturation of 97%, pO_2 73.8 mm Hg, $pCO_2$35.2 mm Hg, and pH 7.48. Methemoglobin was 1.2% (Table 1).

The further course of the patient was uneventful. She recovered without any signs of neurological damage and was discharged on the third day.

DISCUSSION

During methemoglobinemia, iron of deoxyhemoglobin is oxidized to the Fe^{3+} form which renders the molecule incapable of binding oxygen, resulting in hypoxia. Although lower levels of methemoglobinemia remain clinically undetected, levels of greater than 60 to 70% have been associated with collapse, coma, and death (Touze et al., 1983). Though many chemical substances can induce methemoglobinemia, the exposure to nitrobenzenes or nitrites is the most common cause. Inhalation of nitrous gases ("poppers") is often seen in multiple drug abuse. Its potential dangers are not widely known, with "poppers" being considered as an illicit "party drug" (Wu et al., 2005; Botnick et al., 2002).

Intravenous administration of toluidine blue is the first choice of treatment in patients with methemoglobinemia (Smith & Olsen, 1973; MacDonald & McGuigan, 1997; Svecova & Bohmer, 1998). Toluidine blue or methylene blue accelerates the enzymatic reduction of methemoglobin by NADPH-methemoglobin reductase.

Hyperbaric oxygenation (HBO) is based on the concept of oxygen physically dissolving in the plasma while the patient is breathing 100% oxygen under elevated ambient pressure. At 2 atm, paO_2 of about 1500 mm Hg and at 3 atm, paO_2 up to 2000 mm Hg can be achieved. The need for hemoglobin-bound oxygen transport is temporarily obviated under these conditions (Sinkovic et al., 2006).

The biochemical mechanism of HBO in reducing methemoglobin levels is based on prevention of the oxidation of hemoglobin by nitrite due to competitive binding. A first report of the usefulness of HBO in methemoglobinemia was made in 1973 by Smith and Olson (1973), who applied it alone or as an adjunct to systemic administration of methylene blue. Other authors corroborated their findings (Sheehy & Way, 1968; Ol'mezov et al., 2001; Lukin-Butenko et al., 1983; Goulon et al., 1966; Jansen et al., 2003). When used as the only treatment for methemoglobinemia, HBO at 2.2 atm has been found to decrease the methemoglobin level at a rate of about 8% per hour of exposure to HBO (Goldstein & Doull, 1971).

The rationale of using HBO in case of severe methemoglobinemia is not only the enhanced reduction of methemoglobin but also the possibility of instant, plasma-bound reoxygenation independent of the degree of methemoglobinemia.

An additional beneficial effect is the prevention and treatment, respectively, of posthypoxic and/or postischemic cerebral damage (Velkamp et al., 2005; Al-Waili et al., 2005). We used an HBO treatment protocol otherwise applied for severe carbon monoxide intoxication, based on the rationale that nitrous gas inhalation causes a temporary loss of hemoglobin function similar to the one found after CO exposure (Sinkovic et al., 2006). There was no evidence of edema on posttreatment cerebral CT scan, nor was there any clinical sign of persistent neurological damage.

The undisturbed clinical course without any neurological sequelae in the present case is noteworthy, considering the fact that methemoglobin levels exceeding 70% of total hemoglobin have been found to be lethal in the majority of patients (Touze et al., 1983). One may speculate whether only the concurrent use of toluidine blue and hyperbaric oxygenation played a major role, or whether the concomitant abuse of alcohol and other psychotropic drugs may have had a protective effect on the brain. There is, for example, evidence that cannabinol might reduce oxidative stress in binge-ethanol-induced neurotoxicity (Hamelink et al., 2005). On the other hand, alcohol in moderate doses has shown neuroprotective effects following craniocerebral injury (Dash et al., 2004).

In conclusion, the combination of toluidine blue or methylene blue administration, respectively, and hyperbaric oxygenation not only enhances the elimination of methemoglobin, but may have a protective effect against neurological sequelae of severe methemoglobinemia.

REFERENCES

Al-Waili, N. S., Butler, G. J., Beale, J., Abdullah, M. S., Hamilton, R. W., Lee, B. Y., Lucus, P., Allen, M. W., Petrillo, R. L., Carrey, Z., and Finkelstein, M. 2005. Hyperbaric oxygen in the treatment of patients with cerebral stroke, brain trauma, and neurologic disease. *Adv. Ther*. 22(6):659–678.

Botnick, M. R., Heath, K. V., Cornelisse, P. G., Strathdee, S. A., Martindale, S. L., and Hogg, R. S. 2002. Correlates of suicide attempts in an open cohort of young men who have sex with men. *Can. J. Public. Health* 93(1):59–62.

Dash, P. K., Moore, A. N., Moody, M. R., Treadwell, R., Felix, J. L., and Clifton, G. L. 2004. Post-trauma administration of caffeine plus ethanol reduces contusion volume and improves working memory in rats. *J. Neurotrauma.* 21(11):1573–1583.

Goldstein, G. M., and Doull, J. 1971. Treatment of nitrite-induced methaemoglobinaemia with hyperbaric oxygen. *Proc. Soc. Exp. Biol. Med*. 138(1):137–139.

Goulon, M., Nouailhat, F., and Gajdos, P. 1966. On a case of acquired methaemoglobinaemia with coma, treated with hyperbaric oxygen and methylene blue. *Rev. Neurol. (Paris)* 114(5):376–378.

Hamelink, C., Hampson, A., Wink, D. A., Eiden, L. E., and Eskay, R. L. 2005. Comparison of cannabidiol, antioxidants, and diuretics in reversing binge ethanol-induced neurotoxicity. *J. Pharmacol. Exp. Ther.* 314(2):780–788.

Jansen, T., Barnung, S., Mortensen, C. R., and Jansen, E. C. 2003. Isobutyl-nitrite-induced methaemoglobinaemia; treatment with an exchange blood transfusion during hyperbaric oxygenation. *Acta. Anaesthesiol. Scand*. 47(10):1300–1301.

Lukin-Butenko, G. A., Luzhnikov, E. A., Koldaev, A. A. 1983. Hyperbaric oxygenation in the complex treatment of acute poisoning with methaemoglobin formers. *Klin. Med. (Mosk)*. 61(9):121–125.

MacDonald, R. D., and McGuigan, M. A. 1997. Acute dapsone intoxication: A pediatric case report. *Pediatr. Emerg. Care* 13(2):127–129.

Ol'mezov, V. V., Ostanin, V. V., Borisov, Iu P., Barinov, A. V., Talalaev, S. F., Tikhonov, A. N., Il'menev, O. V., Nikiforov, A. E., and Sen'ko, V. L. 2001. Use of hyperbaric oxygenation and methylene blue in the treatment of a 10-year-old child with methaemoglobin producer poisoning. *Anesteziol. Reanimatol*. (1):69.

Sheehy, M., and Way, J. L. 1968. Effect of oxygen on cyanide intoxication. 3. Mithridate. *J. Pharmacol. Exp. Ther*. 161(1):163–168.

Sinkovic, A., Smolle-Juettner, F. M., Krunic, B., and Marinsekz, M. 2006. Severe carbon monoxide poisoning treated by hyperbaric oxygen therapy-a case report. *Inhal. Toxicol*. 18(3):211–214.

Smith, R. P., and Olsen, M. V. 1973. Drug-induced methaemoglobinaemia. *Semin. Hematol*. 10(3):253–268.

Svecova, D., and Bohmer, D. 1998. Congenital and acquired methaemoglobinaemia and its therapy. *Cas. Lek. Cesk*. 137(6):168–170.

Touze, M. D., Desjars, P., Baron, D., Tasseau, F., Delajartrem, A. Y., and Nicolas, F. 1983. Collective acute poisoning by nitrous gases. *Toxicol. Eur. Res.* 5(5):220–224.

Veltkamp, R., Siebing, D. A., Sun, L., Heiland, S., Bieber, K., Marti, H. H., Nagel, S., Schwab, S., Schwaninger, M. 2005. Hyperbaric oxygen reduces blood-brain barrier damage and edema after transient focal cerebral ischaemia. *Stroke*. 36(8):1679–1683. Epub 2005 Jul 14.

Wu, L. T., Schlenger, W. E., and Ringwalt, C. L. 2005. Use of nitrite inhalants ("poppers") among American youth. *J. Adolesc. Health*. 37(1):52–60.