Methemoglobinemia After Infusion of Ifosfamide Chemotherapy*

First Report of a Potentially Serious Adverse Reaction Related to Ifosfamide

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Acute formation of methemoglobin is a life-threatening condition caused by multiple medications. In this article we report the first case of methemoglobinemia in a patient with metastatic uterine leiomyosarcoma, after infusion of ifosfamide chemotherapy. The patient recovered after prompt diagnosis and treatment of the condition. A mechanism for the formation of methemoglobin as a result of the ifosfamide infusion is offered. (CHEST 2000; 118:1208–1210)

Key words: ifosfamide; methemoglobin; methylene blue

Methemoglobinemia is a condition that results from formation of abnormal hemoglobin. Acute methemoglobinemia is life threatening. Multiple medications can cause methemoglobin formation, and the list is constantly growing, as more and more therapeutic agents enter the market. Prompt diagnosis, removal of the offending agent, and treatment can quickly reverse methemoglobin formation. We report the first case in the literature, to our knowledge, of methemoglobinemia induced by the chemotherapy agent ifosfamide, and we offer a mechanism for the formation of methemoglobin.

CASE REPORT

A 58-year-old African-American woman with stage IV metastatic leiomyosarcoma of probable uterine origin was admitted to the hospital for IV chemotherapy with mesna, adriamycin, ifosfamide, and dacarbazine (known as MAID). The cancer was diagnosed a month before admission, after metastases were found in the right shoulder. Past medical history was significant for hypertension, hypercholesterolemia, resection of an asymptomatic cerebral aneurysm in 1991, cholecystectomy, and fibrocystic breast disease. Her home medications included diltiazem for hypertension, hypercholesterolemia, resection of an asymptomatic cerebral aneurysm in 1991, cholecystectomy, and fibrocystic breast disease. Her home medications included diltiazem and enalapril for hypertension, fluvastatin for hypercholesterol.

Past obstetric history was significant for cystic breast disease. Her home medications included diltiazem and enalapril for hypertension, fluvastatin for hypercholesterolemia, and danazol. Ten months after the original episode, she has not had any repeated episodes of symptomatic or asymptomatic methemoglobinemia after receiving other chemotherapeutic regimens. Ten months after the original episode, she has not had any repeated episodes of symptomatic or asymptomatic methemoglobinemia after receiving other chemotherapeutic regimens.

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Methemoglobin is formed constantly in every RBC by the oxidation of iron (Fe) in hemoglobin from ferrous (Fe$^{2+}$) to ferric (Fe$^{3+}$) state. The nicotinamide adenine dinucleotide, the nicotinamide adenine dinucleotide phosphate, and the glutathione systems in the RBC reduce methemoglobin to hemoglobin and keep methemoglobin levels at around 1%. Methemoglobin has a different spectrum of light absorption than hemoglobin (631 nm vs 660 nm). This characteristic is useful in the diagnosis of methemoglobinemia. Blood gas machines measure the PaO$_2$ and calculate the percentage saturation of hemoglobin (oxygen saturation) from the hemoglobin saturation/desaturation curve and the pH. PaO$_2$ is not affected by the formation of methemoglobin, since it depends on the alveolar oxygen tension, shunt fraction, and diffusion of oxygen across the alveolar membrane. Pulse oximetry is also unable to diagnose methemoglobinemia, since most such devices detect only the wavelength of hemoglobin absorption. The presence of significant amounts of methemoglobin causes interference in the light absorption, and pulse oximetry devices show oxygen saturation between 85% and 88%. The diagnosis of methemoglobinemia requires a spectrophotometer that tests blood for methemoglobin and carboxyhemoglobin (co-oximetry).

**Figure 1.** Metabolism of ifosfamide. Reprinted with permission from Fleming.
Methemoglobin is unable to transport and unload oxygen in the tissues, effectively reducing the amount of available hemoglobin in the body for oxygen transport. Methemoglobin levels up to 25% can be well tolerated in otherwise healthy patients, but levels >50% are life threatening. High levels of methemoglobin cause a dark brown (chocolate) discoloration of blood, and patients appear cyanotic. Methylen blue, an electron donor, repletes the endogenous cellular antioxidant systems. Its effect is evident in minutes, and the effect lasts for up to 90 min. High doses (7 mg/kg) of methylene blue or its use in patients with glucose-6-phosphate deficiency can precipitate methemoglobinemia; it therefore needs to be used with caution.

Ifosfamide is an alkylating chemotherapeutic agent that is used in the treatment of testicular, lung, breast, cervical, ovarian cancers, and sarcomas. The parent compound can be administered IV or po, but it requires transformation to 4-hydroxy-ifosfamide by the cytochrome P450 enzymes of the liver. In tumor cells, this compound is transformed to the active cytotoxic metabolites ifosfamide mustard and acrolein as well as carboxyifosfamide, 4-ketoifosfamide, and 4-thioifosfamide (Fig 1). The latter compound reacts with glutathione and can deplete cell antioxidant stores. Some of the parent compound is converted to chloroethylnifosfamide and chloroacetalddehyde, which also react with glutathione. Ifosfamide has been shown to induce its own metabolism after administration of one dose (autoinduction).

Our patient was receiving phenobarbital, a potent inducer of the cytochrome P450 enzymes, and probably metabolized ifosfamide faster than expected. On the second day, ifosfamide autoinduction further increased its rate of metabolism, causing increased amounts of ifosfamide metabolites, which in turn reduced glutathione stores in RBCs. This caused overt methemoglobinemia leading to respiratory distress. Mesna, when used with ifosfamide, protects the urinary system, but not the RBCs, and therefore did not adequately prevent the depletion of the cellular reducing systems of the RBCs. The prompt reversal with only one dose of methylene blue suggests that the offending agent had been removed. An extensive review of the literature did not reveal an obvious mechanism for adriamycin or dacarbazine to cause methemoglobinemia, nor did it show any reported cases. Cyclophosphamide, a compound related to ifosfamide in structure and metabolism, is reported to cause methemoglobinemia.

Physicians need to have high clinical suspicion for methemoglobinemia in patients with cyanosis, respiratory symptoms out of proportion to their blood gas, equivocal oximetry, and use of new medications or medications known to cause methemoglobinemia.

Our report suggests that ifosfamide should be added to the list of drugs causing methemoglobinemia and offers a potential mechanism for ifosfamide-induced methemoglobinemia. Physicians using ifosfamide should be aware of this potentially life-threatening reaction, especially in patients who are receiving agents that induce the cytochrome P450 system.

### References


### Successful Treatment of Juvenile Laryngeal Papillomatosis-Related Multicystic Lung Disease With Cidofovir*

#### Case Report and Review of the Literature

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Cidofovir, a nucleoside analog antiviral agent, has been used with moderate success in the treatment of juvenile laryngeal papillomatosis (JLP) by direct intraleisional injection. We report the first case where IV cidofovir was used successfully to treat a rare but lethal multicystic lung disease complicating JLP. A 35-year-old woman with a history of JLP requiring multiple laser ablations of laryngeal papillomata each year presented with hemoptysis and was found on CT scan to have bilateral, multiple pulmonary nodules and cysts. The results of BAL fluid analysis demonstrated no evidence of malignancy, and cultures were negative for fungi and mycobacteria. Molecular DNA typing of a biopsy specimen ob-

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