Methemoglobinemia, Heinz Bodies, and Acute Massive Intravascular Hemolysis in Lysol Poisoning

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Two patients with poisoning by concentrated lysol are reported. One developed methemoglobinemia, a marked decrease in red cell glutathione level, and large solitary Heinz bodies associated with massive intravascular hemolysis 3 days later. The other patient, who had absorbed less lysol, developed methemoglobinemia and multiple small Heinz bodies that subsequently disappeared without frank hemolysis. No preexisting red cell defect was demonstrated in either patient, and in vitro experiments showed that these effects were due to a direct oxidant action of lysol and hydroquinone, a metabolite of phenol on the red cell.

Cyanosis due to methemoglobinemia and acute intravascular hemolysis associated with Heinz bodies occurred commonly among workers in the chemical industry who were exposed to aromatic compounds such as aniline, nitrobenzene, trinitrotoluene, phenylhydrazine, and various quinones. Lysol is a proprietary preparation of 50% cresol in a mixture of linseed oil, potassium hydroxide, and water. Cresol is closely related to phenol, and their absorption, metabolism, and toxicity are similar. In a review of phenol poisoning, Deichman made no mention of the hematologic effects of acute poisoning. Fisher reported methemoglobinemia and acute intravascular hemolysis with Heinz bodies in two Negro women after the use of abortificants containing phenol, but the underlying red cell defect was not studied in detail. The following report of two cases is intended to document the hematologic effects of acute lysol poisoning.

Case Report

Case I: W.L.F.

A Chinese woman, aged 37 yr, swallowed about 250 ml of lysol 2 hr before admission to hospital in deep coma. The buccal and pharyngeal mucous membranes were swollen and inflamed. Her respiration was rapid and shallow, temperature 36.5°C, pulse 100/min, and blood pressure 90/60 mm Hg. Aspiration of the stomach contents yielded 160 ml of concentrated lysol. After washing out the stomach with milk, 60 ml of castor oil were introduced. She was put on assisted respiration. The urine was found to contain a substance that reduced Benedict's solution, and this has been shown to be a glucuronide of cresol catabolism. On admission her hemoglobin (Hb) was 13 gm/100 ml, the packed cell volume (PCV) 35%, and the platelet and white cell counts normal. Forced diuresis with
intravenous fluid and mannitol was instituted. The urine output was maintained at approximately 500 ml/hr. Seven hours after admission the patient regained spontaneous movements and responded to pain. However, she became cyanotic with neither clinical nor radiologic evidence of abnormality in the lungs. At this juncture the Hb was 13 gm/100 ml, the PCV 35%, and methemoglobin 36%. No hemoglobin was detected in the serum. On staining with methyl violet, 50% of the red cells were found to contain 1–2 small Heinz bodies. The enzyme levels in the red cells were normal or slightly increased: glucose-6-phosphate dehydrogenase (G6PD), 233 U (μmol NADPH reduced/min per 100 ml red cells at 25°C); 6-phosphogluconate dehydrogenase (6PGD), 87 U; glutathione reductase (GR), 40 U; and pyruvate kinase, (PK) 209 U. The normal ranges in our laboratory are: G6PD, 100–227 U; 6PGD, 40–97 U; GR 23–67 U; and PK, 60–179 U. However, the glutathione level (GSH) was markedly reduced to 12 mg/100 ml of red cells (normal range = 50–100 mg), though it was stable after incubation with acetylphenylhydrazine. The hemoglobin pattern on starch gel electrophoresis and Hb F levels were normal and no H inclusions were detected. The patient was also given 100 mg of methylene blue and 500 mg of ascorbic acid intravenously. This resulted in a fall in methemoglobin to 23%. She regained consciousness, and the reducing substance disappeared from the urine 12 hr after the lysol was swallowed. In the following 36 hr the condition of the patient progressively improved, and at the end of this time assisted respiration and forced diuresis were discontinued. She remained cyanotic despite the administration of three further doses of methylene blue and ascorbic acid. Preparations of the blood stained with methyl violet now showed red cells containing moderately large solitary Heinz granules in increasing numbers (Fig. 1A). On the third day, the patient became jaundiced and had recurrent attacks of transient loss of consciousness. There was clinical and radiologic evidence of bronchopneumonia. The PCV dropped to 23%, methemoglobin was 20%, GSH level was 17 mg/100 ml, and there was both severe hemoglobinemia and hemoglobinuria. Large single Heinz bodies were demonstrated in all the red cells and in the numerous red cell ghosts that were present (Fig. 1B). The platelet count fell to 40,000/cu mm, but there was
no evidence of generalized bleeding. Packed red cells from 2 pints of blood were transfused. On the fourth day, the patient developed cardiac arrest, and after resuscitation the electrocardiogram revealed the changes of an anteroseptal myocardial infarction. The PCV fell further to 17.5%, and marked hemoglobinemia persisted. However, a methyl violet preparation now showed a normal population of red cells without Heinz bodies, presumably representing the recently transfused red cells and indicating that the agent producing the Heinz bodies had been removed. The blood urea was 207 mg/100 ml, potassium 4.1 meq/liter, and the base excess -15.9 meq/liter. The patient died despite hemodialysis.

Postmortem examination showed confluent bronchopneumonia in both lower lobes of the lung, no gastrointestinal ulcerations, and no evidence of myocardial infarct, but the heart was moderately enlarged. There were moderate fatty liver changes, and the kidneys showed fibrin clumps in the glomeruli and moderate tubular degeneration compatible with intravascular thrombosis.

**Case 2: Y.S.Y.**

A Chinese female, aged 20 yr, swallowed about 100 ml of lysol (B.P., Evans) 1½ hr before being admitted semiconscious to hospital. There were multiple superficial burns on the face, limbs, and trunk, and the oral mucosa was swollen. Her temperature was 39°C, pulse 85/min, blood pressure 140/90, and the respiration was rapid. Gastric aspiration yielded 50 ml of concentrated lysol, and after gentle lavage with milk, 60 ml of castor oil were introduced. Urine examination showed the presence of a reducing substance by the Benedict reaction (vide case 1). Forced diuresis was started, and 5 hr later the patient’s conscious state improved, and the reducing substance disappeared from the urine. Forced diuresis was discontinued. On admission, her Hb was 14.9 g/100 ml, PCV 45%, and the white cell and platelet counts were normal. The reticulocyte count was 2.2%, methemoglobin 6.7%, and red cells showed no Heinz bodies. The level of G6PD was 201 U, GSH 60 mg/100 ml and stable after incubation with acetylphenyhydrazine, and Hb pattern by electrophoresis was normal. Methylene blue and ascorbic acid were not given. Six hours after admission, her Hb was 12.7 gm/100 ml, PCV 39%, and reticulocytes 1.8%. There was no methemoglobin, but 10% of the red cells contained 2–3 small Heinz bodies. Over the subsequent 48 hr there was no change in the Hb level, reticulocyte count, or increase in urine urobilinogen; no methemoglobin was found, GSH levels remained normal, and the Heinz bodies remained unchanged until their disappearance at the end of 48 hr. She made an uneventful recovery.

**In Vitro Observations**

Venous blood was taken from three normal and three G6PD-deficient subjects into acid-citrate-dextrose (B.P.). To 2 ml of blood was added sufficient lysol (B.P.) to give a final concentration of 1:200 (2.5 × 10^-2 M cresol) or hydroquinone (BDH) to give final concentrations of 2.5 × 10^-2 M and 2.5 × 10^-3 M, respectively, and the mixtures were incubated at 37°C for 4 hr. Since small amount of phenol is metabolized to hydroquinone, this known oxidant, this latter substance was also used in the in vitro studies. Percentage hemolysis was determined as described by Selwyn and Dacie, except that Drabkin’s solution was used. The red cells were washed once with normal saline. The intracellular methemoglobin level was determined by the method of Tönz, and reduced glutathione (GSH) level by the method of Beutler et al. Lysol added immediately to the hemolysate did not interfere with the determination of methemoglobin or glutathione. The blood pH after the addition of lysol was in the range of 7.0–7.15. Complete absorption spectra of the hemolysates were recorded from 700 μm to 600 μm before and after the addition of cyanide, and in every instances only methemoglobin and oxy-
hemoglobin were detected. Intracellular methemoglobin formation and the decrease in GSH level were expressed as percentage after correction for hemolysis. The results are presented in Fig. 2. It can be seen that hemolysis, methemoglobin formation, and decrease in GSH level were produced in normal cells after incubation in a 1:200 concentration of lysol. With G6PD deficient cells, the same concentration of lysol resulted in more marked methemoglobin formation and decrease in GSH. When an equimolar concentration of hydroquinone (2.5 × 10⁻² M) was incubated with normal cells, methemoglobin formation and decrease in GSH were both more marked than when lysol was used, although the percentage of in vitro hemolysis was less. With G6PD-deficient cells, a 2.5 × 10⁻³ M concentration of hydroquinone resulted in changes similar to that found with a 2.5 × 10⁻² M concentration of hydroquinone on G6PD normal cells. Preparations of both normal and G6PD-deficient cells after incubation with lysol showed multiple small Heinz bodies in red cell ghosts. After incubation with hydroquinone, no Heinz bodies were detected.
DISCUSSION

In these two patients with lysol poisoning the rapid removal of the absorbed lysol by forced diuresis prevented its lethal action on the heart, blood vessels, kidneys, and central nervous system. However, subsequent Heinz body formation with acute intravascular hemolysis was not averted in case 1. Since the transfused red cells were not similarly affected, this delayed effect of lysol was unlikely to be associated with the persistence of a toxic dose of the agent. The markedly decreased GSH level and the high percentage of cells with large Heinz bodies in case 1 indicated irreversible damage to red cells before the toxic agent was removed. Methylene blue and ascorbic acid given to reduce the methemoglobinemia did not prevent the subsequent massive intravascular hemolysis that resulted in death from multiple thrombosis and acute renal failure. These large Heinz bodies are thus an ominous sign, and repeated examination for their presence in patients with lysol poisoning is important.

In case 2, a smaller amount of lysol was absorbed, the GSH level in the red cells remained normal, and only a small amount of methemoglobin was formed. The small Heinz bodies in red cells did not result in clinical hemolysis. The small Heinz bodies might have been “pitted” by the spleen comparable to the removal of siderotic granules in siderocytes described by Crosby. In fact the hematologic effects of lysol in case 2 might readily have been overlooked. Thus, methemoglobinemia and Heinz body formation with or without acute hemolysis may not be as rare as the paucity of reports in the literature suggests.

Considerable progress has been made in the understanding of the mechanisms that protect the red cell against oxidants. These include G6PD, the entry enzyme to the hexose monophosphate shunt that generates NADPH, and the related enzyme systems that maintain GSH in the reduced form and protect hemoglobin from irreversible oxidation. Heinz body anemias are found in individuals with defects in these protective mechanisms when they are exposed to oxidants in the form of chemicals or drugs that normally are not hemolytic. Spontaneous or oxidant-induced Heinz body anemias are also found in individuals with unstable hemoglobins, such as Hb Zurich and Hb H. In the two patients now reported there was no detectable underlying red cell defect, and the methemoglobinemia, formation of Heinz bodies, and acute intravascular hemolysis were due to the toxic effect of lysol or its metabolite. The low level of GSH in case 1 may be interpreted as an oxidant effect of lysol or its metabolite on the red cell thiol groups, an interpretation that is supported by the in vitro observations.

The finding that the incubation of normal red cells in a 1:200 dilution of lysol resulted in methemoglobin formation and a decrease in GSH is consistent with lysol having an oxidant effect upon the cell content. In equimolar concentration, hydroquinone is a stronger oxidant than lysol. The finding that lysol caused more marked in vitro hemolysis when compared with hydroquinone suggests that it has an additional direct effect on the red cell membrane. These effects of lysol and hydroquinone were even more pronounced in
G6PD-deficient red cells, indicating that an intact hexose monophosphate shunt exerts a protective effect against the action of both lysol and hydroquinone.

REFERENCES

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