Effect of Time Between Monochloroacetate Exposure and Glucose Infusion in “Golden Hour”

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Key words: chemical exposure, emergency treatment, glucose infusion, golden hour, monochloroacetate

ABSTRACT

We present the effect of the time elapsed between monochloroacetate exposure and antidotal glucose infusion in rat model during the first sixty minutes after exposure, commonly known as "golden hour".

Glucose infusion was performed at 0 (Group A), 15 (Group B) and 30 min (Group C) intervals after exposure. The 14-day survival rate, blood glucose and blood lactate were observed.

The survival rate was 90% (Group A), 68% (Group B) and 52% (Group C). Significant difference was observed between groups A and C (p<0.05). We confirmed a distinct improvement of the survival rate by opportune glucose infusion and a serious adverse outcome if the infusion is not administered in due time.

All groups showed a similar trend of the blood glucose level. The blood lactate levels of groups B and C reached an initial peak at about 3 mM as group A at 2-3 h and remained in the 2.0-4.0 mM range during the later phase, which was substantially higher than group A.

This animal experimental model is proposed to approach a management protocol for monochloroacetate exposure. We emphasize that the life-saving glucose infusion should be administered as soon as possible following exposure, within the time frame of the golden hour.

INTRODUCTION

Monochloroacetate (MCA) is widely used as a chemical intermediate in the synthesis of various organic compounds [1]. Dermal contact is a major route of MCA exposure for workers. Exposure to less than 10 % of body surface to MCA can be lethal requiring emergency treatment [2-5]. Poisoning by MCA results in systemic toxicity due to inhibition of a number of different enzymes including glycer-
aldehyde-3-phosphate dehydrogenase (GAPDH) in the glycolytic pathway and aconitase in the tricarboxylic acid (TCA) cycle [6,7]. Such metabolic blockage damages high energy-demand organs such as the heart, the central nervous system and muscles, leading to metabolic acidosis and hypoglycemia [3,8].

It has been recognized that a fatal event occurs after a “golden hour”, the first sixty minutes that represent the difference between life and death [9,10]. During this critical period it is recommended that contaminated clothes be removed and that the skin is rinsed with a stream of water for several minutes to reduce the risk of prolonged exposure. Administration of ethanol, dichloroacetate or glycerol has been suggested as part of standard antidotal treatment during golden hour [2], but the problem of time limitation and lack of a specific treatment remains.

Using experimental animals, we previously reported that continuous parenteral infusion with a glucose solution [11] or octreotide [12] as antidotes soon after MCA exposure can be an important lifesaving therapy for the prevention of hypoglycemia and metabolic lactic acidosis. In the present study, male Sprague-Dawley rats were used to establish differences in survival rate, blood glucose and blood lactate resulting from the length of time between MCA exposure and glucose infusion. We propose that this animal experimental model points at the great importance that should be given to the opportunite administration of glucose as part of the treatment for industrial MCA exposure.

MATERIALS and METHODS

Experimental ethics

The study was conducted following the Guidelines for Animal Experiments at Osaka Medical College, the Law Concerning the Care and Control of Animals (No.105) and the Japanese Government Notification on Feeding and Safekeeping of Animals (Notification No. 6 of the Prime Minister’s Office).

Animals

Thirty ten-week-old, 300 g male Sprague-Dawley rats were obtained from Japan SLC, Hamamatsu, Shizuoka, Japan. The rats were kept in an air-conditioned room maintained at 22 ± 1°C in 12-h light/ dark cycles. The rats were kept on a MM-3 commercial diet from Punabashi Farm, Funabashi, Chiba, Japan allowing them free access to food and tap water.

Chemicals

Pure grade sodium monochloroacetate (Nacalai Tesque, Kyoto, Japan), a 10% glucose solution (Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan) and distilled water were used in all our experiments.

Dosing and analytical procedure

The rats were maintained under observation for one week to verify that they were all healthy. For the experiments, they were fasted for 14-hours and then injected subcutaneously with 0.3 ml of a solution of 80 mg MCA per kilogram body weight, representing the LD99 for MCA established by Shimizu et al. [11].

The animals were then divided into three groups of ten rats each.

Antidotal 10% glucose infusion was performed (2 ml/h for 10 hours) under phenobarbital anesthesia by syringe pump (Model PHD 200P, Harvard Apparatus, Inc., Holliston Massachusetts, USA.) via a catheter placed in the right cervical vein at 0 (Group A), 15 (Group B) and 30 min (Group C) intervals after MCA exposure, respectively.

Capillary blood samples were obtained by puncturing the rats’ tails for determination of blood glucose and blood lactate. The measures were made at the beginning of the MCA exposure and at 1-hour intervals during the 10-h infusion. Glucose was determined with a Dextro-ZII blood glucose meter and lactate with a Lactate Pro™ lactate analyzer (ARKRAY, Japan). The survival rates of the rats in all groups were observed for 14 days after administration of MCA. The overall experimental design is illustrated in Figure 1.

Statistical analysis

The SPSS v. 11.0 statistical software was used for treatment of the data. The chi-square test was used to establish differences in 14-day survival rates between groups and the Mann-Whitney test to establish differences in blood lactate and glucose. The level of significance was set at p<0.05.

RESULTS

The 14-day survival rates were 90% (Group A), 68% (Group B) and 52% (Group C). The difference between groups A and C is statistically significant (p<0.05).

The increasing trend of blood glucose in the three groups is shown in Figure 2. As shown in this figure, groups B and C showed similar trends between the 100- and 200-mg/dl range, with or without significant differences when compared to group
**Figure 1** Schematic of experimental protocol with the time-course, performed using 0.3 ml subcutaneous injection of MCA (80-mg/kg-rat BW) solution and antidotal 10% glucose infusion (2ml/h) for 10 hours. The survival rate at 14-day was examined with the time delay for glucose infusion treatment (0min for Group A, 15min for Group B and 30 min for Group C) after MCA exposure (n = 10 each for Group A, B and C).

**Figure 2** Changes in blood glucose levels in the three study groups ten hours after administration of a LD99 of monochloroacetate
- □ Group A; ○ Group B; △ Group C; (n = 10 each)
Mean values (symbols) and standard error (error bars) are shown,
*p<0.05 vs. Group A

**Figure 3** Changes in blood lactate levels in the three study groups ten hours after administration of a LD99 of monochloroacetate
- □ Group A; ○ Group B; △ Group C; (n = 10 each)
Mean values (symbols) and standard error (error bars) are shown,
*p<0.05, **p<0.01 vs. Group A
A. In these groups, the plateau level of blood glucose was between 130-200 mg/dl during the glucose infusion period.

Figure 3 shows the blood lactate trends in the three groups. Groups B and C showed higher blood lactate levels than group A, with or without significant differences except at 3 h after exposure. Although groups B and C reached the initial peak of about 3 mM as group A at 2-3 h, their fluctuation range of 2.0-4.0 mM in the later phase was substantially higher than that of the animals in group A.

DISCUSSION

Shimizu et al. [11] reported that MCA exposure in rats produced severe hypoglycemia and lactic acidosis, and that glucose infusion prevented these increases, improving the survival rate of the exposed animals. The present study was conducted to establish the effect of time-interval elapsing between exposure and glucose infusion within the golden hour.

Since the rats were given a lethal dose of MCA, the expected 14-day survival rate is only 1% if no treatment is given. The life-saving effect of opportune glucose infusion within the first 30-min of the golden hour is clear: the observed survival rates are much higher for all three groups in our study: 90% in group A, 68% for group B and 52% for group C.

It is also clear that time has a marked effect on the results. The survival rate decreases uniformly with the length of time treatment is delayed after exposure. Our results show that waiting for as short as 15 to 30 minutes can result in increasingly unfavorable outcomes.

Although the blood glucose in the three groups showed a similar increasing trend, the blood lactate trends in groups B and C showed the higher levels than group A. These results suggest that the time passed between exposure and glucose infusion had stronger effect on the blood lactate level than the blood glucose level. Thus, it should be noted that MCA induced lactic acidosis can not be prevented in groups B and C and showed lower survival rate than group A.

Absorbed MCA inhibits gluconeogenesis by the inactivation of GADPH and causes degradation of amino acids, resulting in lactic synthesis and lactic acidosis [7]. The absorption and diffusion of MCA is rapid and complete. In chemical burns, >95% of MCA is absorbed through the skin within 15 min and its concentration peaks in most of tissues 4 h after dermal exposure [13-18]. In this study we observed a rapid initial peak of lactate in 2-3 h after exposure, evidencing the quick diffusion of injected or absorbed MCA.

The Material Safety Data Sheets (MSDS) have become a useful catalog of hazardous chemical information, emergency and first aid procedures [19-21]. The MSDS recommendations for toxic dermal exposure describes prompt and thorough washing with water for about one hour to remove soluble material, followed by flushing of eyes or skin with plenty of water for at least 15 minutes while removing contaminated clothing and shoes for first aid measures.

These are general guidelines for chemical exposure that are not specific for MCA. In cases of MCA, it is also necessary to pay attention to occupational exposure controls, regulation strategy, appropriate personal protection use, release measures and safety handling as other chemicals.

The MSDS indicate that sodium dichloroacetate (SDCA) can be used as an antidote against MCA toxicity. Timely administration of intravenous SDCA may be life saving in cases of severe MCA intoxication. Sodium dichloroacetate was licensed as an antidote by the Swedish Medical Product Agency in 1999. It is used to treat MCA exposure at the world’s largest MCA producer Akzo-Nobel plant in Skoghall, Sweden.

However, SDCA and other antioxidants such as ethanol [2], glycerol monoacetate [2] and N-acetylcysteine [3] are not approved for medical use and most clinicians are unfamiliar with these specific antidotes, so that medical treatment is often limited to treat the symptoms and provide general medical support to the patient.

As confirmed by the previous experiments of Shimizu et al. [11] and by the present study, opportune glucose infusion improves survival rate of MCA-exposed rats and can be recommended as clinical antidotal therapy. It must be emphasized that the effectiveness of this therapy may decline rapidly even within the golden hour by delaying treatment for only 15-30 minutes.

Since glucose infusion is an easy and cost effective clinical procedure, health providers must be fully aware of all good and bad points of this therapy, which may be recommended as a new emergency treatment during the early minutes of the golden hour after MCA exposure.

REFERENCES

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Received March 10, 2008
Accepted March 26, 2008