Combination of Octreotide and Oral Glucose Maintains the Blood Glucose Level and Improves Survival Rate in Rats after Monochloroacetic Acid Exposure

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ABSTRACT

We report the combined therapeutic effect of subcutaneous injection of octreotide and oral glucose administration to monochloroacetic acid exposed rats.

The control rats group was subcutaneously injected with 80 mg/kg sodium monochloroacetate and infused with 2 mL/hour 10% glucose solution for 10 hours 60 minutes after exposure. Group A was given 2 g/kg oral glucose after exposure, and then infused with glucose as control. Group B was given 2 g/kg oral glucose and a subcutaneous injection of 30 µg/kg octreotide after exposure, and then infused with glucose as control.

The 14-day survival rate was 0.35 (control), 0.50 (group A) and 0.90 (group B). The blood glucose of group B increased to 188 mg/dl at the beginning of the glucose infusion, significantly higher than group A. Although there were significant differences in the lactate levels between the 3 groups, the levels were not abnormally high.

In conclusion, our study suggests that it is important to elevate the blood glucose levels within 60 minutes after monochloroacetic acid exposure. In addition, a combination of subcutaneous octreotide and oral glucose is advantageous to maintain high blood glucose level at early stages after exposure and may be an effective therapy for monochloroacetic acid intoxication.

INTRODUCTION

Monochloroacetic acid (MCA, CH₂ClCOOH) is widely used in the chemical industry as intermediate in the synthesis of carboxymethylcellulose and other compounds [1]. It is usually commercialized as an 80% solution for industrial use [2]. Accidental fatal exposures to MCA in chemical industries have been increasing in recent decades [2-5]. Accidental skin exposure to high concentrations of MCA solutions that only cover 25% of the body surface can cause lethal systemic poisoning. MCA is highly corrosive to tissues and is 25-40 times more toxic than acetic, dichloroacetic or trichloroacetic acids [5]. Systemic poisoning starts within a few hours and the reported symptoms include disorientation,
agitation, cardiac failure and coma. Damage occurs to various organs such as liver, heart, central nervous system and kidney [2,6]. The main toxic mechanism of MCA is its inhibition of glicerinaldehyde-3-phosphate dehydrogenase (GAPDH). Animal experiments have shown that MCA inhibits gluconeogenesis by inactivating GAPDH in the liver leading to hypoglycemia, which may involve degradation of gluconeogenic amino acids and result in the increase of pyruvic and lactic acid concentrations [7].

It is important to prevent hypoglycemia and maintain high blood glucose levels at the early stages after MCA exposure. It has been reported that continuous parenteral infusion of high-dose glucose solutions for 10 hours could be an effective therapy for MCA poisoning. Lactic acidosis caused by MCA was suppressed by a high-dose glucose infusion, with an excellent inverse linear relation between blood glucose and blood lactate levels [8]. Previous studies suggested increasing blood glucose after MCA exposure could be an effective measure, but if the glucose infusion is to be performed at a medical facility, the time it takes to transport MCA exposed individuals from their workplace to a suitable medical location and then start the treatment becomes a problem.

Oral glucose administration is the easiest way to increase glucose levels, but the increase of blood glucose may not be sufficient because of the insulin response caused by hyperglycemia. Thus an improved life-supporting therapy becomes necessary to rise the blood glucose concentration more efficiently.

Octreotide is a somatostatin analogue that suppresses many kinds of endocrine and exocrine systems, including the insulin secretory pathway. Octreotide suppresses the secretion of insulin [9], glucagon, and growth hormone [10]. It is used for the treatment of hypoglycemia of pancreatic islet cell tumors [11]. It was reported that during oral glucose (2 g/kg) loading in conscious rats, the subcutaneous administration of a high-dose (30 µg/kg) of the somatostatin analogue SMS 201-995 suppressed insulin secretion and caused a significant increase of blood glucose levels, whereas lower doses (1 µg/kg) of the analogue did not affect blood glucose levels [9].

As a procedure, it is easier to orally administer glucose concurrently with subcutaneous octreotide than to infuse glucose after MCA exposure. In the present study we report the therapeutic effects of combined octreotide and oral glucose administration on blood glucose, lactate, and survival rate of MCA-exposed rats.

**MATERIALS and METHODS**

Chemically pure grade sodium monochloroacetate (Na-MCA) was purchased from Nacalai Tesque (Kyoto, Japan). Na-MCA was dissolved in distilled water. Saline solution and 10% and 50% glucose solutions were purchased from Otsuka Pharmaceutical Co., Ltd. (Tokyo, Japan). Octreotide acetate was purchased from Wako (Kyoto, Japan).

This study was carried out in accordance with the Guidelines for Animal Experiments at Osaka Medical College, 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).

Sixty ten-week-old male Sprague-Dawley rats (mean weight 300 g) were used in this study. They were housed in an air-conditioned room at 22 ± 1°C in a 12-hour/day-illumination cycle. The rats were given free access to tap water and food (Funabashi Farm MM-3, Funabashi City, Chiba, Japan) for 7 days.

After starving the animals for 12 hours, the rats were subcutaneously injected with a LD99 dose (80 mg/kg) of Na-MCA [8] and divided into three groups. The control group (n=20) was infused with 2 mL/hour 10% glucose solution for 10 hours 60 minutes after Na-MCA exposure. Group A (n = 20) was given 2 g/kg oral glucose immediately after MCA exposure, and 60 minutes later they were infused with 10% glucose as described for controls. The rats in Group B (n = 20) were also given 2 g/kg oral glucose and a subcutaneous injection of 30 µg/kg octreotide immediately after exposure, and then infused with glucose as the other groups.

With the rats kept under phenobarbital anesthesia, the 10% glucose infusion was performed via a catheter placed in the right cervical vein for 10 hours at the rate of 2 mL/hour by means of a Model PHD 200P syringe pump from Harvard Apparatus, Inc., USA.

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 infusion and at 1-hour intervals during the 10-h infusion. Glucose was determined with a Dexter-ZII blood glucose meter and lactate with a Lactate ProTM lactate analyzer (ARKRAY, Japan). The survival rates of the rats in all groups were observed for 14 days after administration of Na-MCA.

The SPSS v. 11.0 software was used for the statistical treatment of the data. Chi-square analysis was used to analyze the 14-day survival rates in the three groups. The Mann-Whitney U test was used.
to establish differences in the mean values of blood glucose and lactate levels. A p value of less than 0.05 was considered statistically significant.

RESULTS

As shown in Figure 1 the 14-day survival rate was significantly higher in group B (0.9, p<0.05) than that of the controls (0.35). Group A survival rate was higher (0.5) but the increase was not statistically significant.

Figure 2 shows the results of the blood glucose levels. At the beginning of the glucose infusion the blood glucose levels showed a significant increase (about two-fold) in group B (188 mg/dl) and group A (144 mg/dl) relative to controls (93 mg/dl). The differences between groups A and B also were significant.

The blood lactate levels (Figure 3) in the controls showed increases at 7 and 8 hours from the beginning of the glucose infusion. The blood lactate levels in group A increased at 1 and 2 hours and those of group B hardly changed. The blood lactate levels in group B were significantly higher than those of the control group at the beginning of the glucose infusion. Although there were significant differences in lactate levels between the three groups, the values were not abnormally high.
DISCUSSION

Our previous research revealed that rats showed hypoglycemia of around 50 mg/dl after 2 hours of exposure to a LD99 dose (80 mg/kg) of Na-MCA [8]. However, hypoglycemia was not observed in this study as the glucose infusions were performed in all groups after 60 minutes of MCA exposure. The lowest blood glucose levels were observed in control group (93 mg/dl) at the beginning of the glucose infusion (Figure 2) and the survival rate was also lowest (0.35).

The 10% glucose infusions to LD99 Na-MCA exposed rats maintained higher blood glucose level of 150 mg/dl and survival rate of 0.80 comparing to the 5% glucose infusions group which showed blood glucose level of 100 mg/dl and survival rate of 0.14 [8]. It was therefore thought that increasing the blood glucose level within 60 minutes after exposure was of importance in the treatment of MCA exposure. Oral glucose administration is the easiest way to increase glucose levels, but we found that oral glucose administration immediately after MCA exposure was not sufficient (Figure 1).

The highest blood glucose levels were observed in group B (188 mg/dl) at the beginning of the glucose infusion (Figure 2). This group had also the highest survival rate. Although the blood glucose levels in group A (144 mg/dl) was also higher than in the controls (93 mg/dl), the survival rate in group A was not as high. It is possible that the blood glucose levels in the control group and group A increased gradually because of the continuation of high-dose glucose infusion. The combined effects of octreotide and oral glucose given 60 minutes at early stages after MCA exposure maintain the blood glucose level near 200 mg/dl. Octreotide alone without oral glucose did not prove effective to elevate the blood glucose levels. In the effect to rise of blood glucose levels, the blood glucose levels of the group of octreotide alone without oral glucose did not show distinct rise, the blood glucose levels of the group of oral glucose alone showed more increases [12].

Although the lactate levels in the three groups of this study were significantly different, the levels themselves were not abnormally high (Figure 3). It is possible that lactic acidosis was inhibited by the high-dose glucose infusion [8].

MCA inhibits gluconeogenesis by inactivating GAPDH in the liver of MCA-exposed rats, thereby causing hypoglycemia and increases the pyruvic and lactic acids concentrations [7]. Therefore, maintenance of high blood glucose levels in the early stages after MCA exposure may prevent hypoglycemia and metabolic lactic acidosis caused by MCA. This seems to be accomplished by the joint administration of subcutaneous octreotide and oral glucose.

In cases of accidental exposure in factories, the commonly accepted first-aid treatment for chemical burns involves immediate decontamination by removing clothing and flushing the chemical off the skin with warm water (using a shower for large areas) for 10 minutes. The start of therapeutic glucose infusion is delayed when there are no medical facilities in the proximity, or when the transport of patients takes a long time. For example a mean call-to-initial-recorded-electrocardiogram (ECG) interval of 11.1 min in patients with out-of-hospital cardiac arrest in Japan [13].

Various antidotes for MCA (ethanol and ethanol plus N-acetylcysteine) have been studied without conclusive evidence for their effectiveness. Dichloroacetic acid (DCA) has been licensed as an antidote by the Swedish Medical Products Agency since 1999. It has been used in clinical studies in the treatment of lactic acidosis from several origins [14,15].

CONCLUSION

The combined administration of subcutaneous octreotide and oral glucose promptly elevates the blood glucose levels. The procedure is easier than glucose infusion for in situ treatment of MCA exposure. It is recommended that first response personnel should have octreotide always ready for subcutaneous injection in conjunction with oral glucose administration as an effective therapy in cases of MCA exposure.

REFERENCES

4. Kusch GD, McCarty LP, Lanham JM.
Octreotide therapy for monochloroacetic acid exposure

Monochloroacetic acid exposure: a case report.


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