The Comparison of the Effects of "Trometamol; Tris-Hydroxymethylaminomethane" and "Sodium Bicarbonate" Treatments on Mortality and Survival Time in Experimental Metabolic Acidosis Induced by Methanol Intoxication

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Abstract

Aim: Metabolic acidosis is the most serious complication of methanol intoxication, which needs urgent treatment. The aim of this study was to investigate effects of "Trometamol; Tris-hydroxymethylaminomethane" (THAM) and "Sodium Bicarbonate" (NaHCO3) treatments on mortality and survival time in rats with metabolic acidosis induced by intragastric-administered methanol.

Materials and Methods: In 21 rats, a cannula was inserted in the right common carotid artery; the esophagus of each rat was penetrated with a branul. Baseline arterial blood gas samples were taken, and a 6 g/kg dose of methanol was injected into the cannula in the esophagus. The rats with confirmed acidosis were separated into three groups as "THAM," "$NaHCO_3$," and "control" for the treatments. The control group received no medication, and the THAM and $NaHCO_3$ groups were administered corresponding treatments intravenously.

Results: A statistically significant difference was determined between the survival times of the THAM and $NaHCO_3$ groups (p=0.036) and the THAM and control groups (p=0.002).

Conclusion: The results of this study support the use of THAM, which is a biological, low-toxicity, inert amino alcohol, instead of $NaHCO_3$ in the treatment of metabolic acidosis induced by intragastric methanol intoxication.

Keywords: Metabolic acidosis, methanol, Tris-hydroxymethylaminomethane, sodium bicarbonate, rat

Introduction

Methanol is a clear colorless alcohol obtained by the distillation of wood and has a smell and taste similar to ethanol. It is highly toxic by absorption through the skin, inhalation, or ingestion. Normally, it is used only in industry. However, when ingested accidentally or for suicide, it may cause methanol intoxication with high mortality rates (1, 2). Following the uptake, methanol is rapidly metabolized to formaldehyde in the liver, and the formaldehyde is converted to the toxic metabolite, formic acid, which causes serious complications (3). The

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most serious complication of methanol intoxication is metabolic acidosis; moreover, cardiovascular instability, ocular toxicity resulting in blindness, and death may also occur (2). The prognosis of methanol intoxication correlates with the degree of metabolic acidosis, with more severe acidosis conferring a poorer prognosis (4, 5).

In metabolic acidosis caused by methanol intake, particularly when pH drops below 7.2, myocardial contractions are suppressed and serious arrhythmias may be observed (6, 7). Yanturali et al. (8) reported a case of metabolic acidosis after hydrochloric acid intake in which the patient developed acute myocardial infarction; Sodium Bicarbonate ($NaHCO_3$) was used to treat metabolic acidosis, but the patient died. The authors claimed that if acidosis could be treated effectively, there would be a better prognosis. The treatment of metabolic acidosis is based on the control of the underlying pathophysiological process and the reversal of organ dysfunction. Despite a lack of data on the effect of $NaHCO_3$ therapy, many emergency physicians attempt to alkalinize blood with intravenous (IV) $NaHCO_3$ administration as part of metabolic acidosis treatment. However, benefits of $NaHCO_3$ administration in metabolic acidosis of sepsis are controversial in clinical practice. In addition, alkali therapy with $NaHCO_3$ has specific side effects, such as hypernatremia, hyperosmolality, and volume overload (4, 9, 10). Therefore, effective drugs to correct acidosis are required.

Tris-hydroxymethylaminomethane (THAM) is a biologically inert amino alcohol of low toxicity, which has the ability to buffer carbon dioxide and acids in vitro and in vivo. At 37°C, a weak base with a pK of 7.8 has been proposed as an alternative alkalinizing agent. THAM is a proton acceptor (11) that can bind both carbon dioxide and metabolic acid, and due to its favorable buffer properties, THAM has been propagated as an effective alkalinizing agent in either respiratory or metabolic acidosis (3, 5, 12).

In vivo, THAM completes the buffering capacity of blood bicarbonate system, accepts proton, generates bicarbonate, and reduces the partial pressure of carbon dioxide in arterial blood. Unlike bicarbonate, it does not need open circulatory systems to reveal the effects of carbon dioxide elimination during buffering. THAM may show the buffering effect both in half-open and closed circulatory systems. Buffering power continues during states of hyperthermia. THAM can improve organ functions by rapidly correcting blood pH and maintaining acid–base balance in a state of acidemia, which has the potential to create organ dysfunction due to metabolic acid accumulation or carbon dioxide retention (13). It is used to correct hypercapnia in the treatment of respiratory failure. In addition, renal and diabetic acidosis, salicylate and barbiturate intoxication, and cerebral trauma associated with increased intracranial pressure are other indication areas where it can be used (11).

However, to the best of our knowledge, there are no studies in the literature comparing effects of $NaHCO_3$ and THAM in metabolic acidosis induced by methanol intoxication. Because of the lack of data on the use of THAM in life-threatening metabolic acidosis, this study aimed to evaluate the in vivo effect of $NaHCO_3$ and THAM treatments on rats with metabolic acidosis.

In this study, short-term effects of IV THAM and $NaHCO_3$ treatments on mortality and survival time were investigated in an experimental rat model of metabolic acidosis induced by intragastric-administered methanol.

Materials and Methods

The research was conducted at the Dokuz Eylul University Faculty of Medicine Multidisciplinary Experimental Animal Laboratory. The study was approved by the Dokuz Eylul University Faculty of Medicine Experimental Animal Research Ethics Committee (Ethics Committee approval: protocol no., 71/2013; dated August 14, 2013).

Study design

In previous studies on methanol intoxication, effects of methanol and its toxic metabolite formic acid on Wistar albino rats were observed. Toxic methanol levels were detected in the blood of the rats 30 min after methanol administration. It reached its peak level after 60 min and began decreasing after the 120 min (14). With reference to this, in our study, arterial blood gas samples were taken from the rats 30 min after methanol administration to check for the development of metabolic acidosis. Acidosis developed in all the rats in each group. Medication was given to each rat according to its group. Sixty min after methanol administration, arterial blood gas samples were taken again to observe the response to the metabolic acidosis treatment. The response to the treatment was evaluated. Rats were observed for a two-hour period after methanol administration, and the number of minutes each rat in each group survived and the number of rats that survived the intoxication were recorded.

A total of 21 male Wistar Albino rats, each weighing 200-210 g, were obtained from the Dokuz Eylul University Faculty of Medicine Multidisciplinary Experimental Animal Laboratory, Izmir, Turkey. Throughout the study, the animals were housed in standard laboratory conditions (12-h light and dark cycle, 20°C-22°C room temperatures, and 50%-60% humidity). Daily nutrition standards were provided for all the animals in the same way, with free access to unlimited water and standard rat food.

At the beginning of this study, equal numbers of rats were randomly assigned to each group. A cannula was inserted in the right common carotid artery, and the esophagus was penetrated with a branul in all rats. Baseline arterial blood gas samples were taken, and methanol was injected into the cannula in the esophagus.

During these surgical procedures, one rat from the THAM group and one rat from the control group died. After 30 min, arterial blood gas samples were taken again. The rats with acidosis confirmed by the arterial blood gas sample results were separated into three groups namely THAM, $NaHCO_3$, and control. No medication was applied to the control group, and the THAM and $NaHCO_3$ groups were treated with the corresponding medications administered intravenously. At 30 min after the treatment, arterial blood gas samples were taken again. The rats were then observed for 60 min, the survival time of each rat was recorded, and the experiment was completed (14).

Anesthesia and surgical procedures

The rats were anesthetized with 50 mg/kg ketamine (Ketalar®, Pfizer, Istanbul, Turkey) and 7.5 mg/kg xylazine (Xylazine Bio®, Pana-life Bio-Chemical, China). After 60 min, 20 mg/kg ketamine and 5 mg/kg

xylazine were intraperitoneally administered for the maintenance of anesthesia.

After anesthesia, the tails of the rats were cleaned with 10% povidone-iodine (Poviiodeks®, Kimpur Drug Lab, Istanbul, Turkey), and the dorsal tail veins were cannulated with a 24-G branul (B-CAT IV cannula; Bıçakçılar Company, Istanbul, Turkey). The neck regions were also wiped with 10% povidone-iodine and shaved. Blunt and fine dissection was applied through skin and subcutaneous incisions. The right common carotid artery was identified, suspended with 3/0 silk, and cannulated. The mean arterial pressure (MAP) and heart rate (HR) of the rats were monitored. Following the dissection, the esophagus was identified, penetrated with a 24-G branul, and the tip of the branul was advanced toward the stomach. The branul was fixed inside the esophagus with 3/0 silk at 0.1 cm distal of the insertion hole. A 0.3 mL blood sample was taken for measuring the baseline arterial blood gas values. During these surgical procedures, one rat from the THAM group and one rat from the $NaHCO_3$ group died.

Intragastric methanol administration

Methanol (99.9% purity) (Galenik Pharmaceuticals and Chemicals Storage, Izmir) was diluted to 50% concentration with saline solution (NaCl 0.9%, Eczacibasi-Baxter Hospital Supply Company, Istanbul), and a 6 g/kg dose was intragastrically administered through the cannula placed in the esophagus (15). After 30 min of methanol administration, arterial blood gas samples were taken again to evaluate acidosis. In literature, different cutoff levels of pH have been stated for the diagnosis of acidosis. In this study, a pH value of <7.29 was accepted as acidosis (16-18). Acidosis was observed in each rat. The rats with confirmed acidosis were randomly separated into three equal treatment groups namely THAM, $NaHCO_3$, and control.

Treatment groups

THAM Group (n=6): Metabolic acidosis developed, and IV infusion of THAM (Tribonat™ flk, Fresinus Kabi, Norway) was administered for the treatment. The THAM dose was individually calculated for each rat using the following formula: mmol buffer=0.3(×)body weight(×) base deficit.

$NaHCO_3$ Group (n=7): Metabolic acidosis developed, and IV infusion of $NaHCO_3$ (Sodium bicarbonate flk, Osel Lab, Istanbul) was administered for the treatment. The $NaHCO_3$dose was individually calculated for each rat using the following formula: mmol buffer=0.3(×)body weight(×)base deficit.

Control Group (n=6): Metabolic acidosis developed, and no treatment was applied.

Evaluated parameters

Mean arterial pressure and HR were recorded using a monitor before methanol administration as a baseline and after 30 and 60 min of administration. A volume of 0.3 mL of arterial blood gas samples were taken from the right common carotid artery before methanol administration as a baseline and after 30 and 60 min after administration. Blood gas analysis was employed using the Irma Trupoint Blood Analysis System (ITC Med, USA) device. For each blood gas sample, the measured pH, $PaCO_2$, PaO_2, Na^+, K^+, and base excess (BE) values were recorded in data sheets.

All rats were observed for 90 min after initiating the treatment. The time of death was recorded in the data sheets for all dead rats. The study was terminated at the 90th min after the start of treatment. Rats that were still alive were euthanized under high-dose halothane anesthesia.

Statistical analysis

Data obtained was entered into SPSS for Windows version 15.0 statistics program (SPSS Inc., Chicago, Illinois, USA). The Kolmogorov–Smirnov test was used to analyze compliance with normal distribution. Data were stated as mean±standard deviation (mean±SD). The Kruskal–Wallis Test was used for the comparison of variables determined by between-group measurements, and the Mann–Whitney U test was applied to compare two groups. The Fisher's Exact Test was used to compare categorical values between groups. The time elapsed until death was recorded for survival analysis. The Mann–Whitney U test was applied for the comparison of two groups. The Kaplan–Meier Survival analysis was performed, and survival curve was generated. A value of $p<0.05$ was considered statistically significant.

Results

MAP and NR

When the baseline and 30th-min MAP and HR values were compared, no statistically significant difference was observed between the study groups (Kruskal-Wallis test, $p>0.05$). When the 60th-min MAP and HR values were compared, no statistically significant difference was observed between the THAM and $NaHCO_3$ groups (Mann-Whitney U test, $p>0.05$).

Arterial blood gas values

When the baseline and 30th-min values of arterial blood PaO_2, $PaCO_2$, Na^+, K+, and BE were compared, no statistically significant difference was observed between the study groups (Kruskal–Wallis test, $p>0.05$). When the 60th-min values of arterial blood PaO_2, $PaCO_2$, Na^+, K^+, and BE were compared between the THAM and $NaHCO_3$ groups, no statistically significant difference was observed (Mann-Whitney U test, $p>0.05$).

When the baseline and 30th-min values of arterial blood pH were compared, no statistically significant difference was observed between the study groups (Kruskal-Wallis test, $p>0.05$). When the 60th-min values of arterial blood pH were compared between the THAM (pH: 7.31±0.02) and $NaHCO_3$ (pH: 7.26±0.01) groups, the pH values were significantly higher in the THAM group (Mann–Whitney U test, $p=0.02$) than those in the $NaHCO_3$ group.

Survival times

A statistically significant difference was observed between the survival times of the THAM and $NaHCO_3$ groups (Mann-Whitney U test, $p=0.036$). A statistically significant difference was observed between the survival times of the THAM and control groups (Mann-Whitney U test, $p=0.002$). No statistically significant difference was observed between the survival times of the $NaHCO_3$ and control groups (Mann-Whitney U test, $p=0.828$) (Table 1 and Figure 1). At the end of the study, six rats from the THAM group and three rats from the $NaHCO_3$ group survived, whereas all six rats in the control group died (Table 2).

Table 1. Mean survival times of THAM, NaHCO3, and Control groups

	THAM group (n=6)	**$NaHCO_3$ group (n=7)**	**p**
Survival time (min)	90±0	64.5±23.8	0.036
	$NaHCO_3$ group (n=7)	**Control group (n=6)**	
Survival time (min)	64.5±23.8	50.17±5.3	0.828
	THAM group (n=6)	**Control group (n=6)**	
Survival time (min)	90±0	50.17±5.3	0.002

Min: minute; THAM: trometamol; Tris: hydroxymethylaminomethane; $NaHCO_3$: sodium bicarbonate

Table 2. Distribution of dead rats in groups

	Alive (n) (%)	**Dead (n) (%)**
THAM group (n=6)	6 (100%)	0
$NaHCO_3$ group (n=7)	3 (42.86%)	4 (57.14%)
Control group (n=6)	0	6 (100%)

THAM: trometamol; Tris: hydroxymethylaminomethane; $NaHCO_3$: sodium bicarbonate; N: number

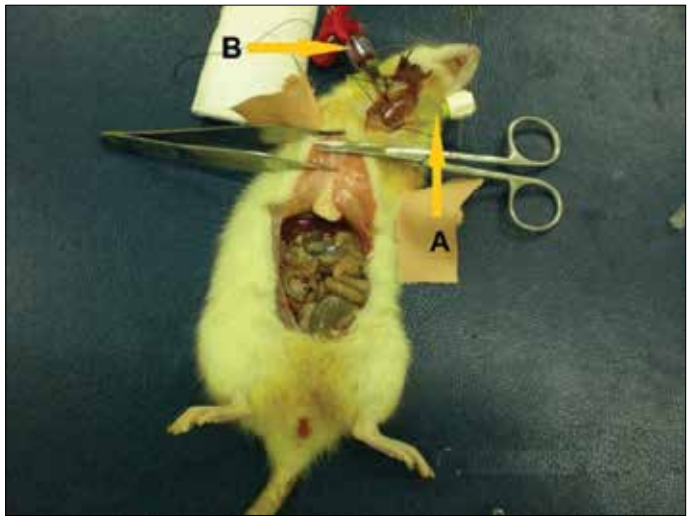

Figure 1. The rat with cannulated right common carotid artery (A) and the esophagus (B)

Discussion

In the treatment of metabolic acidosis, IV $NaHCO_3$ is widely used worldwide. However, the effectiveness of $NaHCO_3$ use in acidosis is controversial in the literature. The correction of acidosis with $NaHCO_3$ administration aims to normalize extracellular and intracellular pH and improve outcome. However, many studies have suggested that this approach is overly simplistic, and the impact of $NaHCO_3$ administration on restoring hemodynamic and improving clinical outcomes is unknown. Despite a lack of data on the effect of $NaHCO_3$ treatment, many emergency physicians attempt to alkalinize blood with IV $NaHCO_3$ administration as a part of metabolic acidosis treatment. However, the benefit of $NaHCO_3$ administration in metabolic acidosis caused by sepsis is controversial in clinical practice. Alkali therapy with $NaHCO_3$ also has specific side effects for metabolic acidosis, including hypernatremia, hyperosmolality, and volume overload (4, 9, 10).

In some studies, $NaHCO_3$ has not been found to be effective for treating of lactic acidosis and ketoacidosis and has even been shown to increase mortality (10, 19). Main reasons for the increase in mortality are increased intracellular acidosis, decreased ionized Ca^{+2} level, and hyperosmolality. When the mechanism of action was examined, THAM was reported to increase HCO_3 production and decreases CO_2 levels in the arterial blood. Therefore, THAM can be effectively used for treating metabolic acidosis (12).

Trometamol; Tris-Hydroxymethylaminomethane, which has a weak base with a pK of 7.8, has been proposed as an alternative alkalinizing agent. THAM can bind both carbon dioxide and metabolic acid, and due to its favorable buffer properties, THAM has been propagated as an effective alkalinizing agent in either respiratory or metabolic acidosis (3, 5, 12).

In the current study, short-term effects of IV THAM and $NaHCO_3$ treatments on mortality and survival expectancy were investigated and compared in an experimental rat model of metabolic acidosis induced by intragastric methanol. The IV THAM treatment was determined to significantly reduce mortality, improve arterial blood pH, and extend the survival time of rats in the first 90 min compared with $NaHCO_3$ treatment in experimental metabolic acidosis induced by intragastric methanol intoxication.

In principle, THAM shows a long-term buffering effect on metabolic acidosis by correcting intracellular acidosis (19, 20). THAM prevents the formation of intracellular acidosis, and this may be one of the main reasons for the decrease in the mortality rate among the rats.

Yanturali et al. (8) reported a case of metabolic acidosis after hydrochloric acid intake. The patient developed cardiac arrhythmias, hypotension, and acute myocardial infarction. $NaHCO_3$ was used for treating metabolic acidosis, but the patient died. The authors claimed that if acidosis could have been treated effectively, the patient would not have died because of myocardial infarction. It is thought that $NaHCO_3$ treatment does not correct acidosis. In the findings of the current study, there was no difference in mortality between $NaHCO_3$ and control groups, which also supports this opinion.

Velissaris et al. (4) stated that routine $NaHCO_3$ administration for the treatment of lactic acidosis in sepsis remains debatable. Published evidence suggests that $NaHCO_3$ treatment is not beneficial in cases of metabolic acidosis in sepsis and may even cause harm. In a study of pigs, Scheiderman et al. (16) claimed that THAM treatment is effective for normalizing pH in respiratory acidosis. Moreover, Sirieix et al. (17) in an isolated rabbit heart model that THAM is a good buffer in correcting pH in acidosis, and when $NaHCO_3$ and THAM are used in combination, better results are obtained for correcting pH.

Rice et al. (10) compared $NaHCO_3$ with THAM for correcting hyperchloremic acidosis in their research and showed that both agents increased pH levels. However, in the current study, in the post-treatment 60th-min blood gas analysis, a statistically significant improve-

ment in pH levels was only determined in the THAM group. Nahas et al. (11) claimed that for the treatment of lactic acidosis, THAM is a better buffering agent than $NaHCO_3$ on the basis of a decrease in CO_2 and an increase in HCO_3.

In some studies, where THAM has been used for acidosis treatment, it has been claimed that CO_2 exchange is deteriorated. Bar-Joseph et al. showed that THAM decreases blood CO_2 levels significantly in their study, where Carbicarp, THAM, and $NaHCO_3$ were used to correct metabolic acidosis, which occurred during cardiopulmonary resuscitation in dogs (5). In the present study, after the THAM treatment, a moderate increase in blood CO_2 level was observed. This moderate increase may be mostly attributed to respiratory factors as the time elapsed from the administration of the drug until the collection of the last blood gas sample. The rats were not intubated during the study for them to be compatible models with daily emergency department setting, where patients are not routinely intubated. The rats were allowed to breathe spontaneously. In future studies, this variable, which affects acidosis, can be ruled out by intubating the rats.

Methanol is converted to formaldehyde by alcohol dehydrogenase, and formaldehyde is converted to formic acid by aldehyde dehydrogenase in the liver. Formic acid is the metabolite responsible for toxicity and metabolic acidosis in methanol intoxication. In methanol metabolism, the first step is performed by alcohol dehydrogenase, and this enzyme can be competitively inhibited by ethanol or fomepizole (Antizol®). Therefore, if these are used as an antidote in treatment, the formation of formic acid, which is the toxic metabolite of methanol, is prevented (2). In the current study, THAM was used to correct metabolic acidosis. THAM is a biological low-toxicity inert amino alcohol. Because THAM is an alcohol and has a structure similar to like ethanol, it could have reduced the blood methanol and formic acid levels of rats in this study (11). Thus, while correcting acidosis; THAM may also have effects on methanol metabolism. The blood methanol and formic acid concentrations of the rats were not evaluated because these were not a part of the study objectives. Therefore, whether THAM had this effect in this study remains unclear. Whether THAM could also be used as an antidote in methanol intoxication should be investigated in the future studies.

Study limitations

Mortality caused by methanol ingestion can be related with systemic, local, or both systemic and local effects. In this study, only systemic aspects of mortality were investigated. The local effects of ingested methanol on mortality can be examined in a future study.

Formic acid is the metabolite of methanol formed during methanol metabolism in the body and is responsible for toxicity and metabolic acidosis. It is thought that the severity of the resulting acidosis is correlated with blood levels of formic acid, and in the early phase of methanol intoxication, the acidosis substantially develops due to formic acid (2). Therefore, methanol and formic acid levels should be evaluated.

In this study, rats were allowed to breathe spontaneously. In future studies, the rats could be intubated so that the role of respiration is minimized in acidosis development.

Conclusion

There are studies in the literature analyzing effects of IV $NaHCO_3$ and THAM treatments on correcting acidosis and mortality in various metabolic acidosis models (hypoxic lactic acidosis, hypovolemic shock, tricyclic antidepressant poisoning, desipramine intoxication, etc.) (10, 18, 19). To the best of our knowledge, there are no studies of rats with metabolic acidosis induced by oral methanol intake comparing the effects of $NaHCO_3$ and THAM treatments. Therefore, this study can be considered original research.

In this experimental rat model of metabolic acidosis induced by intragastric methanol, THAM treatment significantly reduced mortality, improved blood pH, and extended the survival time of rats compared with the $NaHCO_3$ and control treatments in the first 90 min after the metabolic acidosis developed. Consequently, THAM, which is a biological low-toxicity inert amino alcohol, can be considered for use instead of $NaHCO_3$ treatment in methanol intoxication-induced metabolic acidosis. These results with additional support from further studies can become a novel clinical treatment approach.

Trometamol; Tris-Hydroxymethylaminomethane is a drug that is not available in the pharmaceutical market in Turkey. New animal and human studies using THAM treatment on the basis of this study, which has demonstrated that THAM is effective in metabolic acidosis treatment, could be officially introduced into the market in Turkey and could be used in the treatment of patients with metabolic acidosis.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Dokuz Eylul University Faculty of Medicine Experimental Animal Research Ethics Committee (protocol no., 71/2013; dated August 14, 2013).

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