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Intravenous Cobinamide Versus Hydroxocobalamin for Acute Treatment of Severe Cyanide Poisoning in a Swine (*Sus scrofa*) Model

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Abstract

Study objective—Hydroxocobalamin is a Food and Drug Administration–approved antidote for cyanide poisoning. Cobinamide is a potential antidote that contains 2 cyanide-binding sites. To our knowledge, no study has directly compared hydroxocobalamin with cobinamide in a severe, cyanide-toxic large-animal model. Our objective is to compare the time to return of spontaneous breathing in swine with acute cyanide-induced apnea treated with intravenous hydroxocobalamin, intravenous cobinamide, or saline solution (control).

Methods—Thirty-three swine (45 to 55 kg) were intubated, anesthetized, and instrumented (continuous mean arterial pressure and cardiac output monitoring). Anesthesia was adjusted to allow spontaneous breathing with FiO_2 of 21% during the experiment. Cyanide was continuously infused intravenously until apnea occurred and lasted for 1 minute (time zero). Animals were then randomly assigned to receive intravenous hydroxocobalamin (65 mg/kg), cobinamide (12.5 mg/kg), or saline solution and monitored for 60 minutes. A sample size of 11 animals per group was selected according to obtaining a power of 80%, an α of .05, and an SD of 0.17 in mean time to detect a 20% difference in time to spontaneous breathing. We assessed differences in time to death among groups, using Kaplan-Meier estimation methods, and compared serum lactate, blood pH, cardiac output, mean arterial pressure, respiratory rate, and minute ventilation time curves with repeated-measures ANOVA.

Results—Baseline weights and vital signs were similar among groups. The time to apnea and cyanide dose required to achieve apnea were similar. At time zero, mean cyanide blood and lactate concentrations and reduction in mean arterial pressure from baseline were similar. In the saline

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solution group, 2 of 11 animals survived compared with 10 of 11 in the hydroxocobalamin and cobinamide groups (P<.001 between the 2 treated groups and the saline solution group). Time to return of spontaneous breathing after antidote was similar between hydroxocobalamin and cobinamide (1 minute 48 seconds versus 1 minute 49 seconds, respectively). Blood cyanide concentrations became undetectable at the end of the study in both antidote-treated groups, and no statistically significant differences were detected between the 2 groups for mean arterial pressure, cardiac output, respiratory rate, lactate, or pH.

Conclusion—Both hydroxocobalamin and cobinamide rescued severely cyanide-poisoned swine from apnea in the absence of assisted ventilation. The dose of cobinamide was one fifth that of hydroxocobalamin.

INTRODUCTION

Background

Hydroxocobalamin is a Food and Drug Administration–approved antidote for treating acute cyanide poisoning.[1–3] However, because of its poor water solubility, it must be administered in a relatively large volume intravenously. In the out-of-hospital setting of cyanide gas release, such as an industrial accident, terrorist attack, or commercial or residential fire, intravenous access can be difficult and particularly problematic for providers wearing hazardous material protective gear; thus, nonintravenous antidotes are urgently needed.[4–7] To address this concern, federal agencies, including the National Institutes of Health and the US Army Medical Research Institute of Chemical Defense, are actively seeking nonintravenous, potent new antidotes.[4,5] Cobinamide is a water-soluble analog of hydroxocobalamin that has a much higher affinity for cyanide than hydroxocobalamin and binds 2 moles of cyanide permole compared with 1 mole of cyanide for each mole of hydroxocobalamin. Cobinamide has been shown to be 3 to 10 times more potent than hydroxocobalamin[6] in both mice and rabbitmodels of acute cyanide intoxication,[7,8] but to our knowledge it has not been studied in a critically ill large-animal model of cyanide poisoning.

Goals of This Investigation

Our goal was to compare the time to return of spontaneous breathing among 3 groups of swine after 1 minute of acute cyanide-induced apnea. This model has been previously validated as a model of acute cyanide toxicity and was developed to have a potential low survival rate in untreated animals.[3,9,10] If intravenous cobinamide is as efficacious as hydroxocobalamin in treating cyanide poisoning in a large animal, future studies could test the efficacy of cobinamide administered by the intramuscular route.

MATERIALS AND METHODS

Study Design and Setting

This investigation was a nonblinded randomized study approved by the Wilford Hall Clinical Research Division Institutional Animal Care and Use Committee. All animal experiments complied with the regulations and guidelines of the Animal Welfare Act, the National Institutes of Health Guide for the Care and Use of Laboratory Animals, and the

American Association for Accreditation of Laboratory Animal Care. Animals were housed and the study was conducted in the Animal Care Facility.

Before the beginning of the experiment, animals were randomly assigned, using a commonly used online medical research randomization plan generator (http://www.randomization.com) to one of the 3 following intravenous interventions: (1) hydroxocobalamin, the positive control and standard antidote; (2) cobinamide, the experimental antidote; or (3) saline solution, the negative control.

Yorkshire swine (*Sus scrofa*) (n=33, weighing 45 to 55 kg, female) were premedicated with intramuscular ketamine 10 mg/kg. General anesthesia was induced with isoflurane by nose cone. After intubation, the animals were mechanically ventilated with a volume-limited, time-cycled ventilator (Fabius GS anesthesia machine; Drager-Siemens, New York, NY) and maintained with inhaled isoflurane (1% to 3%) and oxygen (FiO_2 of 0.4 to 0.45). The tidal volume was initially 8 to 10 mL/kg and respiratory rate was 12 breaths/min. The minute ventilation was adjusted to maintain an end tidal CO_2 of 38 to 42 mm Hg as measured by inline capnography. Lead II of the surface ECG was monitored continuously. Animal body temperature was maintained at 37.5°C (99.5°F) to 39.0°C (102.2°F). Baseline biochemical variables (arterial blood gas, hemoglobin, and electrolytes) were measured.

Interventions

Invasive hemodynamic variables were measured with an 8-French Swan-Ganz CCOmbo pulmonary artery catheter (model 746HF8) and the Edwards Vigilance II monitor (Edwards Lifesciences, Irvine, CA). Measurements included continuous cardiac output, systemic vascular resistance, mixed venous oxygen saturation, central venous pressure, pulmonary artery pressure, and core temperature. Catheter ports were flushed with saline solution, and the catheter was placed by cutdown in the right external jugular. Aortic pressure was measured continuously through the femoral artery. An 8.5-French introducer (Arrow, Reading, PA) was placed in the carotid artery for laboratory sampling and another was placed in the femoral vein for medication administration. The animals received a warmed saline solution intravenous bolus (15 mL/kg) during procedure setup. Heparin (100 U/kg) was administered intravenously after catheters were inserted. The Fabius GS anesthesia data collection software embedded in the ventilator's computer was used for data acquisition at 1-minute intervals.

Baseline biochemical measurements included oxygen saturation, $PaCO_2$, PaO_2, and pH (ABL 800 Flex blood gas analyzer; Radiometer America, Westlake, OH), hemoglobin (OSM3 Hemoximeter; Radiometer, Westlake, OH), and electrolytes (Piccolo Chemistry Analyzer; Abaxis, Union City, CA). Ventilation and oxygenation variables were also collected and included tidal volume, respiratory rate, minute volume, and pulse oximetry.

After a 10-minute acclimation period, isoflurane was reduced to 1% to 1.5%, the FIO_2 was adjusted to room air (0.21), and the mechanical ventilator was turned off. Thus, the animals breathed spontaneously for the remainder of the experiment. Once the animals had sustained spontaneous respirations for 5 minutes, a 0.4% potassium cyanide solution (potassium cyanide; Sigma Aldrich, St. Louis, MO; normal saline solution) was infused continuously

until apnea occurred and was confirmed by capnography for 20 seconds. At this point (apnea), the cyanide infusion was stopped. After capnographic confirmation of 1 additional minute of apnea (time zero), animals were administered the antidote or saline solution intravenously as a bolus injection. The cobinamide was infused in less than 1 minute and the hydroxocobalamin was infused during 2 to 3 minutes to administer the larger volume. Animals received equal volumes of 90 mL during the infusion with 10 mL of saline solution given before and 10 mL infused after each drug administration. Cobinamide was infused in 4 to 8 mL, with an additional 80 to 85 mL of saline solution, hydroxocobalamin was infused in 90 mL, and 90 mL of saline solution was infused for control animals. The dose and infusion duration for cobinamide and hydroxocobalamin were based on previous published animal models and preliminary experiments in our laboratory.[3,8–10]

The animals were monitored for 60 minutes after treatment. Death was defined as a mean arterial pressure less than 20 mm Hg for 5 minutes. Animals that died were observed for an additional 20 minutes or until the end of the experiment to evaluate for a possible delayed therapeutic effect. At death or the conclusion of the study, animals were euthanized with intravenous sodium pentobarbital 100 mg/kg.

Whole blood cyanide levels, which includes cyanide bound to cobinamide and hydroxocobalamin, were measured spectrophotometrically at a referral laboratory (Michigan State University, Diagnostic Center for Population and Animal Health, Lansing, MI).[11] This method generates hydrogen cyanide gas, converts it to a cyanogen chloride, and measures a barbituric acid complex.[10,11]

Methods of Measurement and Outcome Measures

The primary outcome was time to return of spontaneous breathing after 1 minute of cyanide-induced apnea. This outcome was defined before the study and based on our previous research.[3,7,12] We also assessed survival and compared cardiac output, pulse rate, mixed venous oxygenation, pH, lactate, base excess, serum bicarbonate, cyanide concentrations, and inflammatory markers. Vital signs and hemodynamic measurements were recorded at 1-minute intervals and analyzed at 5-minute intervals. Blood sampling was obtained at baseline, 5 minutes after start of the cyanide infusion, at the onset of apnea, after 1 minute of apnea, and at 10, 20, 30, 40, 50, and 60 minutes after treatment.

Primary Data Analysis

The average time (in minutes and seconds) to return of spontaneous breathing after the antidote/saline solution was administered was compared among the 3 groups with the Kruskal-Wallis test. This nonparametric statistical analysis was used because the data were not normally distributed (Shapiro-Wilk test). Additional analysis was performed among the 3 groups to assess the differences in time to death, using Kaplan-Meier estimation methods of the survival distribution and log-rank testing to compare survival among the groups.

Secondary outcome variables (cardiac output, pulse rate, systemic vascular resistance, respiratory rate, mean arterial blood pressure, mixed venous oxygenation, and inflammatory markers) were modeled with repeated-measures ANOVA, with adjustment for treatment, time, and the interaction of treatment by time with an autoregressive covariance structure

assumed. Because only 2 of the control animals survived after 30 minutes, the control group was not included in secondary outcome variable analysis so that those data would not unduly influence the results of the comparison between the 2 antidote intervention groups. Post hoc analysis was performed on all variables that showed a significant treatment-by-time interaction, for which treatment contrasts were measured at each posttreatment point with a Bonferroni adjustment for multiple testing applied. Values for arterial blood pH, lactate, cyanide, bicarbonate, base excess, and potassium concentrations were compared among groups with repeated-measures ANOVA for times zero to 60 minutes.

All statistical testing was 2 sided, with a significant level of α=.05, and was completed with SAS (version 9.3; SAS Institute, Inc., Cary, NC). All graphic presentations were made with R version 2.15.1. Sample size calculations were based on our previous animal experiments of acute cyanide toxicity. A sample size of 11 animals per group was determined to be sufficient according to obtaining a power of 80%, an α=.05, and an SD of 0.17 (based on previous experiments) in mean time to detect a 20% difference in time to spontaneous breathing. Sample size calculation was performed with PASS 12 (version 12; NCSS, LLC, Kaysville, UT; http://www.ncss.com).

RESULTS

Characteristics of Study Subjects

At baseline and at apnea, the groups had similar vital signs and biochemical variables (Tables 1 and 2). At time zero, predefined as apnea of 1 minute's duration, there were no significant differences among groups (Table 3). Reduction in mean arterial blood pressure from baseline was also similar among groups (29%, 38%, and 36% decrease; *P*=.35).

Main Results

The time to return of spontaneous breathing between the 2 antidote-treated groups was similar: hydroxocobalamin group (1 minute 48 seconds [SD 29 seconds]), and cobinamide group (1 minute 49 seconds [SD 31 seconds]). This was significantly different from the control group (5 of 11 animals had return of spontaneous breathing and 6 of 11 remained apneic; 4 minutes 5 seconds [SD 40 seconds]; *P*=.005). One animal in the hydroxocobalamin group, 1 animal in the cobinamide group, and 9 animals in the control group died before completion of the experiment, ie, between receiving the antidote or saline solution at 1 minute after onset of apnea and 60 minutes later (Figure 1). Consequently, the 3 groups showed a difference in the Kaplan-Meier survival estimation (90% survival in hydroxocobalamin and cobinamide animals, 10% in control) and time to death compared with controls (*P*<.001). Outcome variables for the control group are reported until more than half of the animals died, which occurred at 30 minutes after time zero. Of the antidote-treated animals that survived, respiratory rate, mean arterial pressure, pulse rate, cardiac output, and central mixed venous oxygenation all trended toward baseline after treatment (Figure 2*A* through *E* and Figure E2 available at www.annemergmed.com)). There were no significant differences in respiratory rate, cardiac output, or mixed venous oxygenation between treatment groups from time zero to 60 minutes. Mean arterial pressure was significantly different between the 2 antidote-treated groups (*P*<.05) such that pigs in the

hydroxocobalamin-treated group demonstrated an increased mean arterial pressure at 5 minutes through 50 minutes postapnea. Moreover, pulse rate was significantly faster at times 5 to 15 minutes in the hydroxocobalamin-treated animals compared with cobinamide-treated animals. However, post hoc analysis at the individual times revealed no statistical difference by the end of the experiment (88 [SD 15.2] 15.2 mm Hg hydroxocobalamin and 71 [SD 10] 10 mm Hg cobinamide). The systolic blood pressure was also different between groups ($P<.05$) but similar at the end of the experiment (112 mm Hg SD [14.1] 14.2 mm Hg IV hydroxocobalamin, 91 [SD 15.1] mm Hg IV cobinamide).

No important difference was detected between treated groups in regard to lactate, bicarbonate, pH, or cyanide concentration levels from time zero through the end of the study (Figure 3*A* through *D* and Figure E3 available at www.annemergmed.com)). Lactate (1.2 versus 1.5 mmol/L), pH (7.44 versus 7.44), and bicarbonate (28 versus 28 mEq/L) at 60 minutes were similar in the treated groups. Immediately after treatment, cyanide was not detected in the blood of 10 of 10 hydroxocobalamin-treated animals and 7 of 10 cobinamide-treated animals. Cyanide was not detectable in any treated animal at the end of the study. The likely reason that blood cyanide was detected longer in the cobinamide-treated animals than the hydroxocobalamin-treated animals is that cobinamide binds more tightly to plasma proteins than hydroxocobalamin; thus, cobinamide was likely at a higher blood concentration than hydroxocobalamin, yielding higher cyanide concentrations.

LIMITATIONS

This study has several limitations, the principal one being that an animal model does not precisely reproduce human toxicity. However, it clearly is not possible to administer cyanide to humans, and animal models must be used. We have previously noted that pigs are an excellent choice for modeling cyanide exposure, given the similarities of their cardiovascular systems to that of humans.[3,13,14]

Another shortcoming is that we used intravenous cyanide as a substitute for inhalational exposure. Both routes have rapid onset, but the intravenous route provides a controlled method to induce toxicity compared with relatively uncontrolled cyanide absorption in an inhalational model. In addition, an inhalational route of cyanide exposure for a large animal puts the research staff at a greater risk than the intravenous route because of the potential for undetected leaks in the ventilation system.[10,12,15]

A third potential concern is that we used potassium cyanide, rather than sodium cyanide. However, the potassium dose received was small, about 0.67 mEq during 10 minutes.

A fourth limitation is that we observed the animals for only 60 minutes after treatment. A longer observation period may have shown a difference between the 2 antidote-treated groups.

Finally, our study was not blinded; however, we reported objective criteria (death, breathing-based capnography, blood pressure, and cyanide levels) to limit the subjectivity of interpretation of the results.

DISCUSSION

We expected cobinamide to provide a significantly faster and more complete rescue for cyanide-exposed animals compared with either hydroxocobalamin or saline solution. Previous investigations in our laboratory comparing the 2 antidotes in mice and rabbits suggested that cobinamide is 3 to 10 times more potent than hydroxocobalamin as a cyanide antidote, depending on the cyanide exposure model.[7,8] To our knowledge, this is the first investigation comparing the antidotes in a pig model of cyanide poisoning. We found no difference between cobinamide, an agent being developed as a cyanide antidote, and hydroxocobalamin, an established cyanide antidote, in terms of the primary outcome measure of time to return of spontaneous breathing after cyanide-induced apnea. Furthermore, we found both groups similar in terms of mortality, lacticemia, acidosis, and clearance of cyanide. Although we found differences in mean arterial pressure and pulse rate between the 2 antidote-treated groups, we find it difficult to speculate about these minor cardiovascular differences because this is a small controlled animal study. Moreover, these differences had abated by the conclusion of the study.

Although no difference was noted between cobinamide and hydroxocobalamin in terms of the main outcome variable, the dose of cobinamide we used to rescue the animals was one fifth that of hydroxocobalamin, on a milligram-per-kilogram basis. This apparent increased potency may relate to the fact that each cobinamide molecule can bind, and therefore neutralize, 2 cyanide molecules compared with hydroxocobalamin, which can bind only 1 cyanide molecule.[6,8,16] This difference in binding capacity explains only a 2-fold increase in potency, suggesting other differences between cobinamide and hydroxocobalamin as cyanide antidotes. Two other explanations seem likely. First, cobinamide has a much higher affinity for cyanide than hydroxocobalamin ($K_{aoverall}$ 10^{22} M^{-2} for cobinamide and K_a 10^{12} M^{-1} for hydroxocobalamin).[17] This could allow cobinamide to more effectively remove cyanide from cytochrome c oxidase than hydroxocobalamin; we have previously shown that cobinamide is more potent than hydroxocobalamin in reversing cyanide inhibition of cellular respiration.[6] Cytochrome c oxidase is one of the primary molecular targets of cyanide and is part of complex IV of the mitochondrial electron transport system. Second, we have preliminary evidence that cobinamide is transported into cells more rapidly and completely than hydroxocobalamin. Together, these 3 differences between cobinamide and hydroxocobalamin of increased cyanide binding capacity, increased cyanide binding affinity, and increased cellular transport could explain the apparent increased potency of cobinamide as a cyanide antidote.

There are 2 major differences between our study and previous work on animal models of cyanide poisoning. First, we used 50-kg Yorkshire pigs instead of rodents, rabbits, or dogs, which have been more commonly used in studies of cyanide toxicity.[7,12,15,18] Second, ours was a strictly nonventilated model.

We chose pigs because they are close in size to humans, thereby minimizing scaling issues, and because their cardiovascular system is similar to that of humans.[3,13,14] Drug doses are generally converted from one species to another with body surface area, but this may not be appropriate for all drugs, and less scaling will usually lead to a more accurate estimate of the

proper human dose. The heart and brain are generally considered the 2 primary targets of cyanide, and thus, using an animal model that has a cardiovascular system close to that of humans allows one to apply the results to humans more confidently. In addition, we have reported swine models of cyanide-induced cardiac arrest and of shock.[3,9,10]

In the out-of-hospital setting of a major cyanide exposure such as a massive fire or a terrorist attack, it is extremely unlikely that sufficient time or resources will be available to intubate and ventilate the large number of cyanide-exposed victims.[8] Thus, we chose not to ventilate our animals as a means to more accurately simulate such a scenario. This considerably narrows the window of time available to rescue an animal from cyanide exposure, and we elected to treat the pigs after 1 minute of apnea. Although this could be considered a relatively short period of apnea, it is not realistic to think that humans can be rescued fully after several minutes of apnea. We believe that the advantages of simulating a mass casualty scenario of no artificial ventilation outweigh the disadvantage of treatment after 1 minute of apnea.

Now that we have shown that intravenous cobinamide is comparable to intravenous hydroxocobalamin in a swine model of acute cyanide toxicity, the next step is to evaluate cobinamide delivered by nonintravenous routes. To that end, we currently have multiple ongoing swine studies evaluating the efficacy of intraosseous and intramuscular administration of cobinamide in a similar model.

In conclusion, no difference was noted between intravenous cobinamide, at one fifth the dose, and intravenous hydroxocobalamin for return of spontaneous breathing after acute cyanide poisoning in a nonventilated swine model.

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Editor's Capsule Summary

What is already known on this topic

An intramuscularly administered antidote for cyanide toxicity would be desirable, particularly in the out-of-hospital environment. Cobinamide is a candidate agent, but its intravenous efficacy has not yet been evaluated.

What question this study addressed

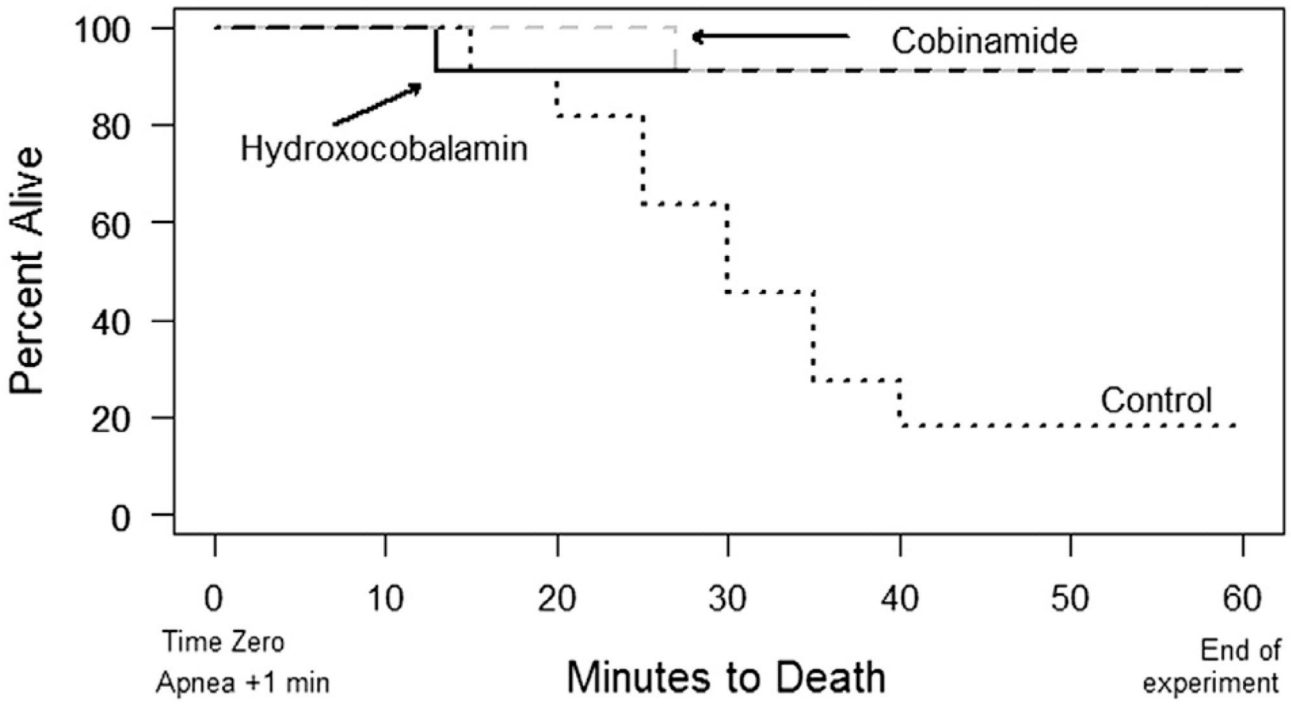
This nonblinded 33-pig study compared the efficacy of intravenous cobinamide, hydroxocobalamin, and placebo in a nonlethal model of cyanide poisoning.

What this study adds to our knowledge

The primary endpoint, time to return of spontaneous respirations after intravenous administration, was similar for both antidotes.

How this is relevant to clinical practice

If findings are confirmed with intramuscular administration, cobinamide may be an effective out-of-hospital antidote, especially during mass toxicologic events.



Number at Risk

Control	11	11	10	7	3	2	2
Cobinamide	11	11	11	10	10	10	10
Hydroxocobalamin	11	11	10	10	10	10	10

Figure 1.
Survival analysis using a Kaplan-Meier curse plot estimate comparing all the groups of cyanide-poisoned animals.

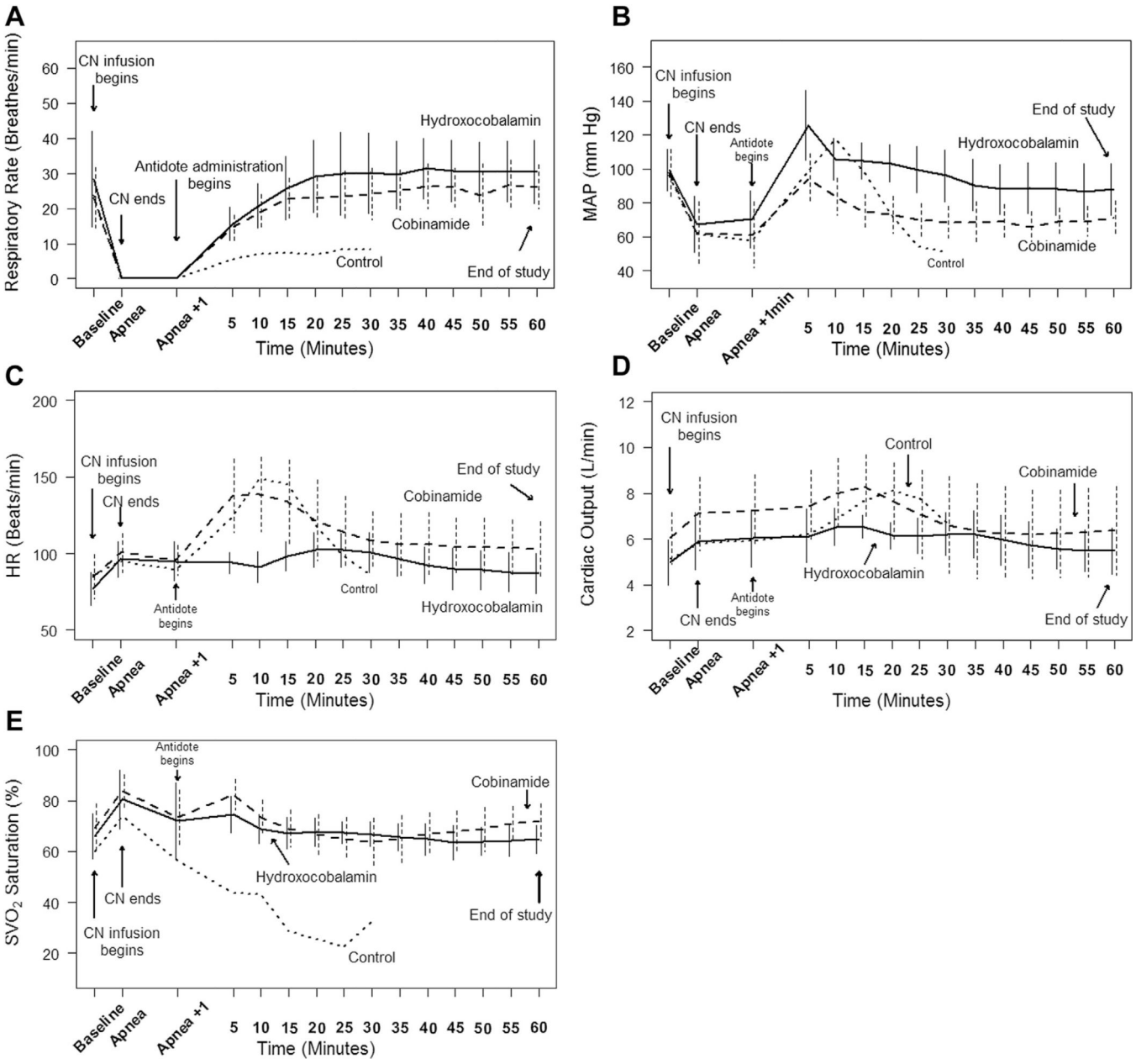


Figure 2.

Hemodynamic variables and vital signs (respiratory rate, mean arterial pressure, pulse rate, cardiac output, and mixed venous oxygenation [SVO_2] saturation) in cyanide-poisoned animals over time for the 3 groups. Values for the control arms were plotted until greater than 50% of the animals died (30 minutes). *MAP*, Mean arterial pressure; *HR*, pulse rate; *CN*, cyanide.

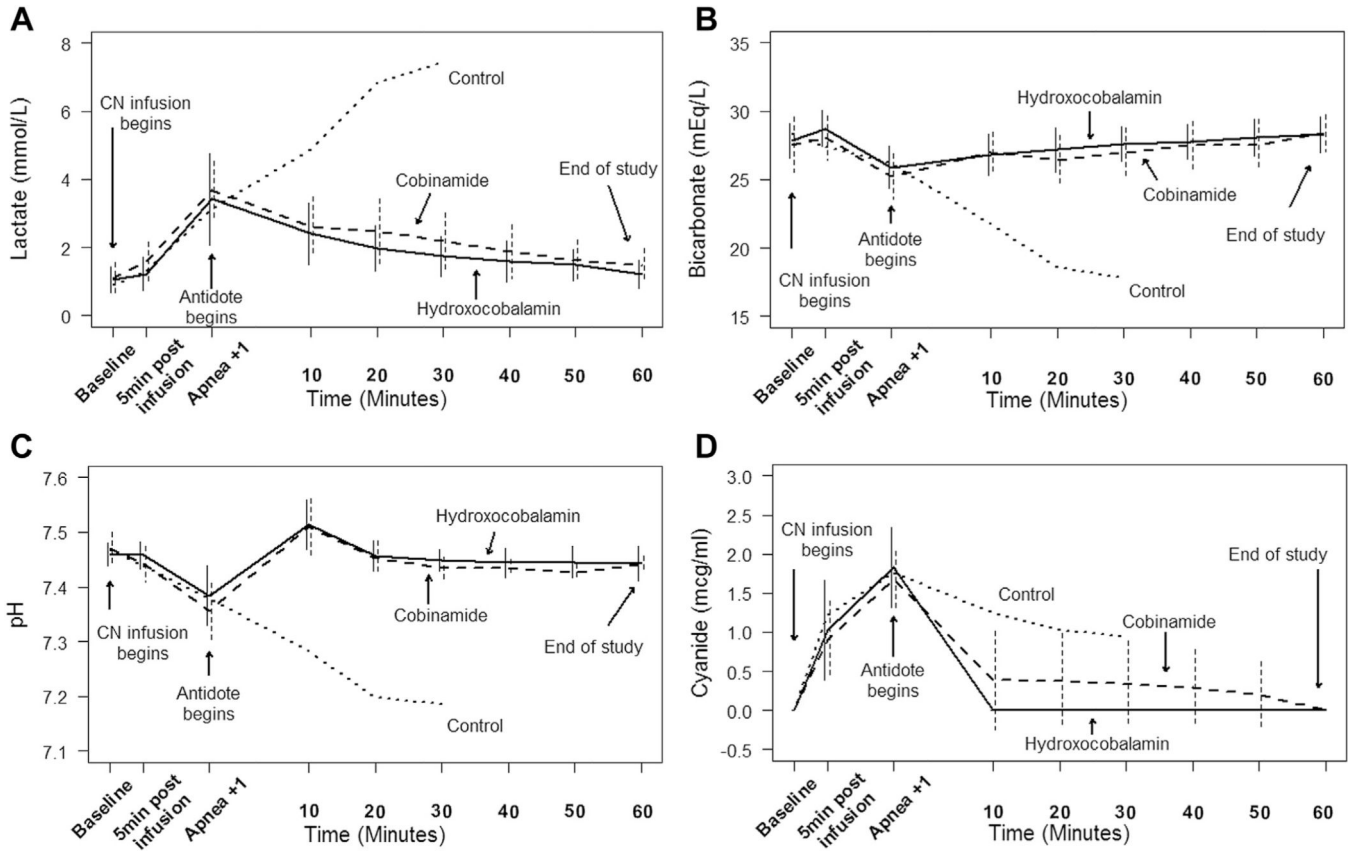


Figure 3.

Serum markers (lactate, bicarbonate, pH, and cyanide concentrations) of cyanide-poisoned animals over time for the 3 groups. Values for the control arms were plotted until greater than 50% of the animals died (30 minutes).

Table 1

Baseline characteristics of animals in each group before receiving cyanide infusion.*

Characteristics at Baseline	Hydroxocobalamin (65 mg/kg IV) (N = 10)	Cobinamide (12.5 mg/kg IV) (N = 10)	Control (Saline Solution) (N = 11)
Weight, kg	49.9 (3.9)	52.7 (3.09)	51 (2.86)
Pulse rate, beats/min	76.7 (10.69)	84.9 (14.72)	85.55 (23.56)
Systolic blood pressure, mm Hg	122.9 (12.42)	120.7 (16.46)	119.36 (16.75)
MAP, mm Hg	99.2 (12.35)	97.9 (13.86)	96.09 (17)
Cardiac output, L/min	4.97 (0.98)	6.03 (1.13)	5.13 (1.28)
Systemic vascular resistance, dynes-s/cm^5	1,564.2 (464.9)	1,244.9 (221.32)	1,418.9 (303.27)
pH, mEq/L	7.46 (0.02)	7.47 (0.03)	7.47 (0.02)
Bicarbonate, mEq/L	27.81 (1.26)	27.56 (2)	28.43 (2.24)
Lactate, mmol/L	1.06 (0.38)	1.1 (0.46)	0.89 (0.31)

IV, Intravenous, MAP, mean arterial pressure.

*Data are presented as mean (SD).

Table 2

Characteristics for each group at apnea of the cyanide-poisoned animals.*

Characteristics at Apnea	Hydroxocobalamin (65 mg/kg IV) (N = 10)	Cobinamide (12.5 mg/kg IV) (N = 10)	Control (Saline Solution) (N = 11)
Cyanide dose, mg/kg	1.91 (0.7)	1.85 (0.53)	1.67 (0.53)
Time to apnea, min:s	11:12 (04:04)	10:54 (03:07)	09:49 (03:05)

* Data are presented as mean (SD).

Table 3

Characteristics for each group at time zero (1 minute of apnea) of the cyanide-poisoned animals.*

Characteristics at 1 Minute of Apnea	Hydroxocobalamin (65 mg/kg IV) (N = 10)	Cobinamide (12.5 mg/kg IV) (N = 10)	Control (Saline Solution) (N = 11)
MAP at apnea, mm Hg	70 (17)	61 (20)	58 (27)
Lactate, mmol/L	3.4 (1.3)	3.7 (0.9)	3.2 (1.1)
Cyanide level, μg/mL	1.83 (0.51)	1.68 (0.36)	1.76 (0.59)
pH	7.38 (0.05)	7.36 (0.05)	7.38 (0.07)

* Data are presented as mean (SD).