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Effectiveness of Intramuscularly Administered Cyanide Antidotes on Methemoglobin Formation and Survival

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Key words:

Successful first aid therapy for cyanide intoxication is dependent upon immediate administration of antidotes which directly or indirectly interact with the cyanide ion to remove it from circulation. Owing to the severe respiratory, cardiovascular and convulsive episodes following acute cyanide intoxication, the most practical approach is to administer antidotes by intramuscular injection. Exceptionally rapid methemoglobin formers—hydroxylamine hydrochloride (HH) and dimethylaminophenol (DMAP)—are usually able to prevent the lethal effect of cyanide following intramuscular injections in doses sufficient to induce 20% methemoglobin (HH = 20 mg kg^{-1} and DMAP = 2 mg kg^{-1}). Sodium nitrite, the methemoglobin inducer approved for military use, must be administered by intravenous infusion because it is not an effective cyanide antidote by the intramuscular route. In the normal unintoxicated animal an intramuscular injection of 20 mg kg^{-1} sodium nitrite will form 20% methemoglobin; however, in acute cyanide intoxication the associated severe bradycardia appears to limit the rate of absorption and thus the rapid formation of methemoglobin. If the bradycardia is prevented or reversed by atropine, the rate of absorption of sodium nitrite and the formation of methemoglobin is able to reverse the otherwise lethal effects of cyanide. Thus, an intramuscularly administered combination of 20 mg kg^{-1} sodium nitrite and 1 mg kg^{-1} atropine sulfate, rapidly absorbed from the intramuscular site, appears to achieve the same degree of effectiveness against acute cyanide intoxication as intramuscularly administered HH or DMAP. It would appear from these studies that HH, DMAP and sodium nitrite with atropine are all potentially effective intramuscular antidotes for acute cyanide poisoning.

INTRODUCTION

Cyanide is an extremely toxic poison due to its rapid absorption into the blood and to its ability to inhibit cytochrome oxidase, thereby arresting cellular respiration.[1–3] Reports indicate that cyanide toxicity has been implicated in suicidal and homicidal attempts through the ingestion of cyanide salts.[2,4,5] Cyanide is also evident in exposure to aerosols during industrial processes such as electroplating and in the case hardening of steel.[6,7] Problems have also arisen in medical treatment of acute hypertension with sodium nitroprusside, a drug which, on metabolism in the body, releases cyanide.[8–10] Exposure to smoke and gases from fires in which cyanide is produced when polyurethane or other polymers containing nitrogen are burned in air have likewise been an area of increasing concern to both the aviation industry and to commercial manufacturers.[2,11–14] In addition cyanide has been used by psychopaths who add it to the contents of analgesic tablets, drinking water and soft drinks in attempts to kill unsuspecting individuals. Of even greater importance is the possible use of cyanide in chemical warfare.[1,16,17]

Unclassified threat briefing has stressed the possibility that cyanide, as well as nerve agents, could be used in areas of high troop concentration to inflict huge losses without destroying the existing ground installations.[18,19] It is further estimated that concentrations of cyanide necessary to kill could be easily attained by existing conventional weapon systems.[20] The resulting 'mass casualty' situation would require a treatment regimen that would have to be not only immediately effective but one that could be self-administered, or, at worst, be used by employing the buddy system. There is little question that medical support *per se* in such a situation would be totally overwhelmed, and that the resulting casualties would require a treatment which could be administered by other than the intravenous route. The currently available treatment regimen, sodium nitrite with follow-up sodium thiosulfate, while effective intravenously, might be difficult if not impossible to employ in many of the above situations.[21] Recognizing the speed with which cyanide appears to be capable of producing its lethal effects further reinforces the need for a readily available, easily administered, fast acting, preferably intramuscular form of therapy.[22] This study was carried out therefore to assess the ability of several treatment regimens to meet these criteria and successfully treat acute cyanide poisoning.

Materials and Methods

A total of 41 adult beagle dogs weighing between 8 and 12 kg anesthetized with sodium pentobarbital

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(30 mg kg^{-1}) were used in this study. All animals were continuously monitored for changes in arterial and venous blood pressure, electrocardiogram (ECG), heart rate and respiratory function. The dogs were also intubated and instrumented to allow for blood samples to be taken and analyzed for cyanide and methemoglobin determinations. An OSM-3 Hemioxmeter 6 g Radiometer instrument was used for both measurements. Therapy, when given, was administered 2–3 min after cyanide. No artificial respiration was given to any of the dogs in this study.

After a 30-min period of equilibration, all dogs were given sodium cyanide (2.5 mg kg^{-1}) i.v. The total dose was dissolved in 10 ml of sterile saline and injected into the catheterized femoral vein. The first group of 10 dogs (Group I) served as controls, and were given neither artificial respiration nor drug therapy. Group II, five animals, were given 20 mg kg^{-1} sodium nitrite i.v. at 2–3 min following the lethal dose of cyanide. The drug was given over a 15–30 s period of time. The five dogs in Group III were each given 2.0 mg kg^{-1} dimethylaminophenol (DMAP) i.m. The DMAP was dissolved in 2.0 ml of sterile saline. Group IV was composed of 10 dogs treated with 20.0 mg kg^{-1} hydroxylamine hydrochloride (HH) i.m. The hydroxylamine was also diluted in 2.0 ml of sterile saline.

The five dogs in Group V were treated with 20 mg kg^{-1} sodium nitrite i.m. The sodium nitrite was dissolved in 2 ml of sterile saline and given into the hind limb of the anesthetized dog.

Group VI dogs were given a combination of 20 mg kg^{-1} sodium nitrite and 1.0 mg kg^{-1} atropine. The drugs were dissolved in 2.0 ml of sterile saline and injected i.m. into the hind limb of the six dogs comprising this group.

Results

The results obtained in these studies are shown in the following figures and are summarized in Table 1.

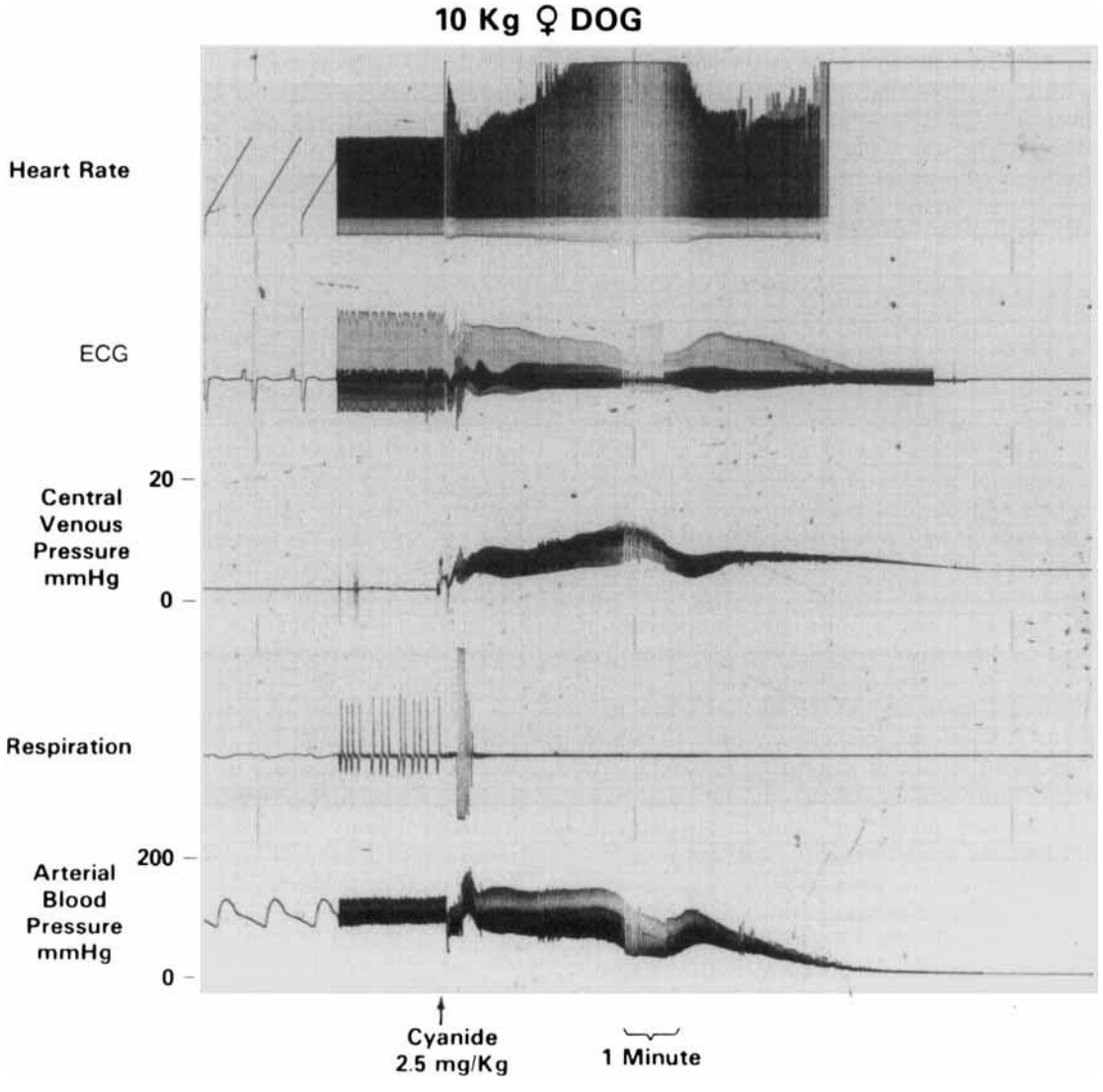

Figure 1. Effect of 2.5 mg kg^{-1} sodium cyanide i.v. on heart rate, ECG, central venous pressure, respiration and arterial blood pressure.

Table 1. Summary of results for cyanide-challenged dogs (2.5 mg kg^{-1} I.V.)

Therapy	Route of administration	Dose mg kg^{-1}	Survivors
Control			0/10
Sodium nitrite	i.v.	20	5/5
DMAP	i.m.	2.0	5/5
Hydroxylamine·HCl	i.m.	20.0	10/10
Sodium nitrite	i.m.	20	0/5
Sodium nitrite + atropine	i.m.	20	6/6

Figure 1 shows the effect of 2.5 mg kg^{-1} of sodium cyanide on heart rate, ECG, central venous pressure, respiration and arterial blood pressure. Immediately following the cyanide there was a slight decrease in arterial blood pressure, hyperventilation, an increase in central venous pressure and bradycardia. This was followed by an increase in pulse pressure, apnea and a progressive decrease in heart rate. At 5–7 min, all animals showed progressive hypotension, marked bradycardia, terminal apnea and hypoxia ECG changes. At death, central venous pressure remained high (14–20 mmHg). None of the 10 control animals survived.

Figure 2 shows the effect of an i.v. injection of 20 mg kg^{-1} sodium nitrite on heart rate, ECG, central venous pressure, respiration and arterial blood pressure, after the i.v. administration of cyanide. The sodium nitrate produced a subtle increase in the heart rate accompanied by some arrhythmias, and a rather erratic recovery of arterial blood pressure. At ca. 8 min, central venous pressure decreased and arterial pressure stabilized. Spontaneous breathing resumed in 5–7 min. All of the five animals treated in this manner survived.

Figure 3 shows the effect of 2.0 mg kg^{-1} DMAP i.m. on heart rate, ECG, central venous pressure, respiration and arterial blood pressure in dogs given the lethal dose of cyanide. Therapy, as in the other studies, was given at time of complete apnea and when marked decreases in heart rate and blood pressure were apparent (2–3 min after cyanide). Two minutes after treatment, heart rate and blood pressure increased as central

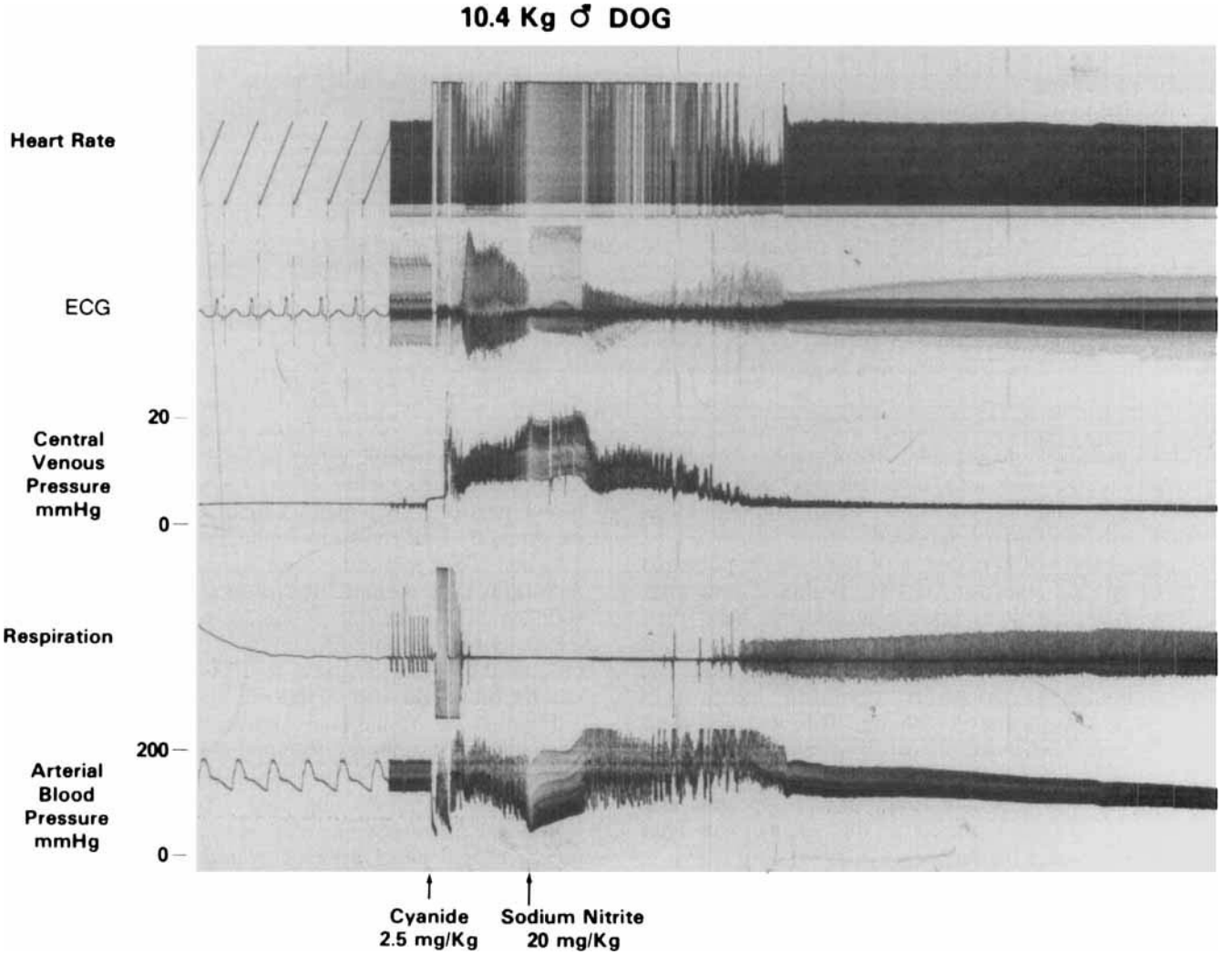

Figure 2. Effect of 20 mg kg^{-1} sodium nitrite i.v. on heart rate, ECG, central venous pressure, respiration and arterial blood pressure after a lethal dose of cyanide.

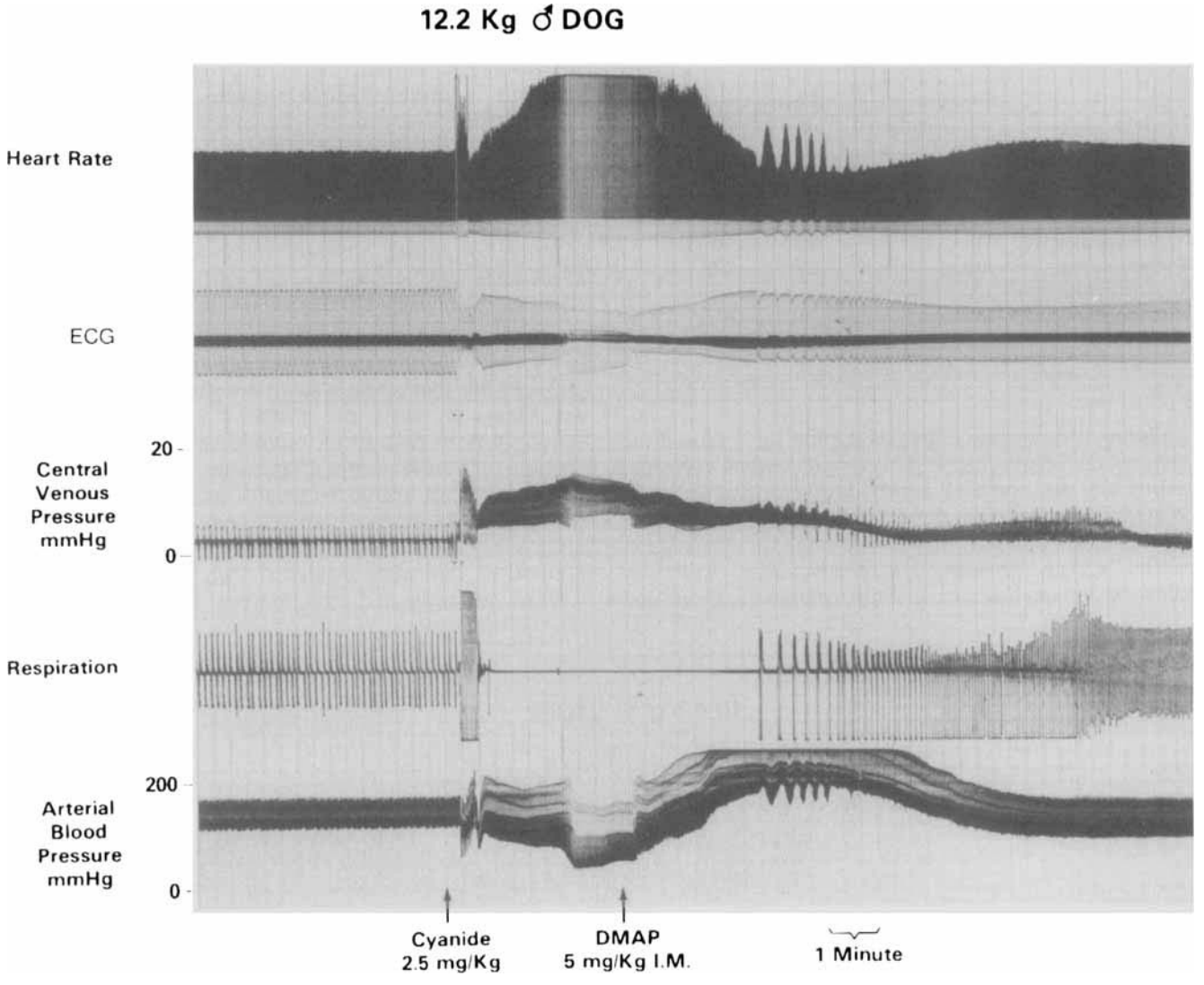

Figure 3. Effect of 2 mg kg $^{-1}$ dimethylaminophenol i.m. on heart rate, ECG, central venous pressure, respiration and arterial blood pressure following a lethal dose of cyanide.

venous pressure decreased. Spontaneous breathing returned at ca. 3–4 min after therapy and became normal only after 10–15 min. All of the five dogs treated with the DMAP survived.

Figure 4 shows the response of the cyanide-poisoned dogs to an i.m. injection of HH. Within 2 min after therapy there was a remarkable increase in heart rate. Central venous pressure began a slow, sustained decrease as arterial blood pressure increased steadily. As physiological parameters stabilized there were attempts at spontaneous breathing. This was followed shortly by increased respiratory movement and, at 10 min after HH, heart rate, ECG, central venous pressure, respiration and arterial blood pressure all appeared near normal. All 10 dogs treated in this manner survived with no additional therapy.

Figure 5 shows the effect of 20 mg kg^{-1} sodium nitrite i.m. on heart rate, ECG, central venous pressure, respiration, and arterial blood pressure in dogs given a lethal dose of cyanide. The sodium nitrite produced no observable positive effects on monitored parameters. None of the five dogs survived.

Figure 6 shows the effect of i.m. sodium nitrite with atropine on heart rate, ECG, respiration and arterial blood pressure in animals administered a lethal dose of cyanide. There was an immediate increase in heart rate and blood pressure, with apnea persisting for ca. 3–5 min after therapy. Restoration of breathing was spontaneous, beginning as short gasps and returning to a near-normal breathing pattern in 8–10 min. No follow-up therapy was given to this group of animals, yet six of six dogs survived.

Figure 7 shows the comparative effectiveness of i.m. treatment with sodium nitrite and atropine, dimethylaminophenol and HH on methemoglobin levels.

All three therapies appeared capable of producing significant increases in methemoglobin even in the presence of a lethal dose of cyanide.

Discussion

Results of these studies indicate that a lethal dose of cyanide given i.v. into an anesthetized adult beagle

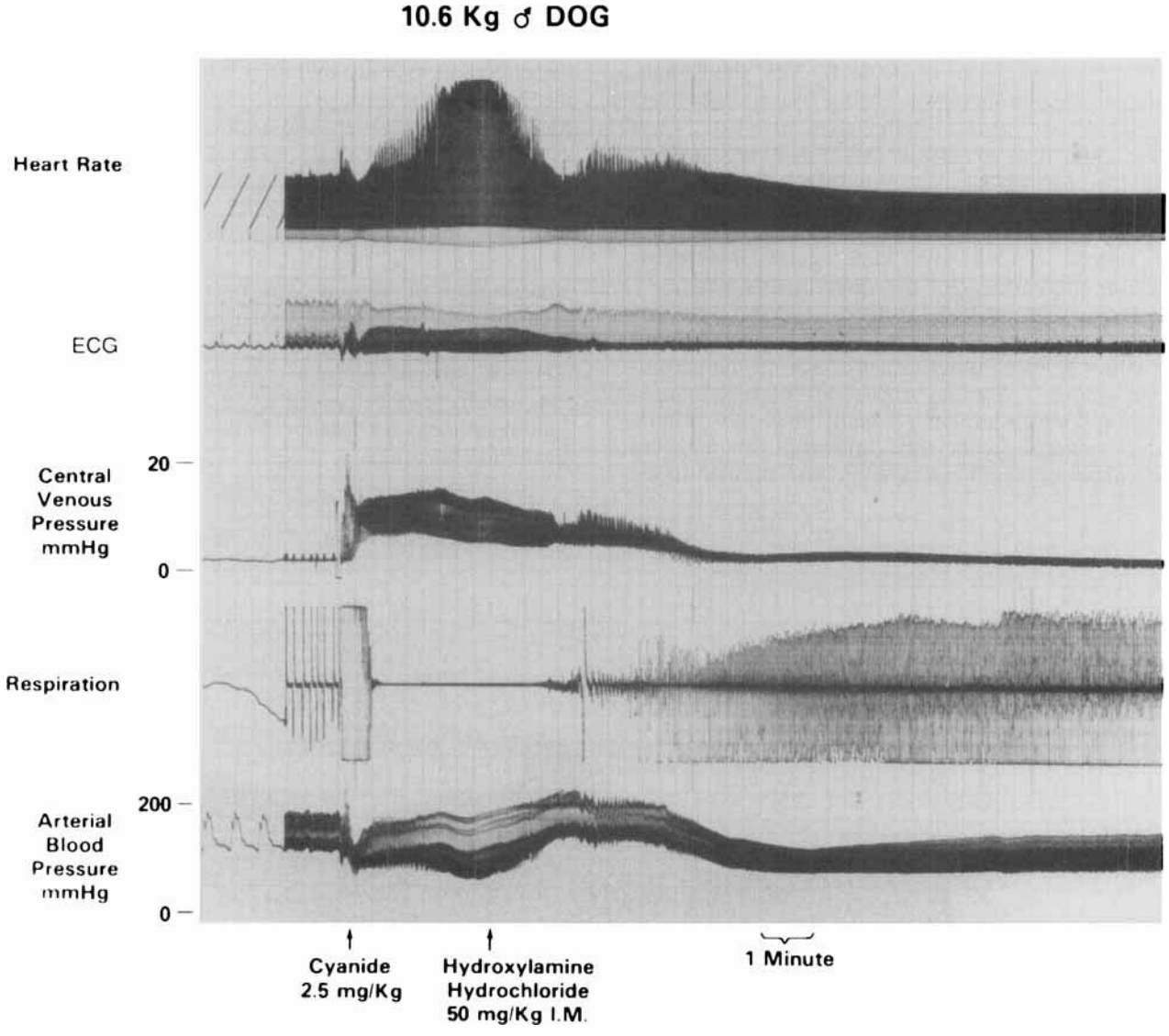

Figure 4. Effect of 20 mg kg ^{1} hydroxylamine hydrochloride i.m. on heart rate, ECG, central venous pressure, respiration and arterial blood pressure after a lethal dose of cyanide.

dog produces death within 8–12 min. Death is characterized by an increase in central venous pressure, an almost immediate interruption in breathing, a progressive decline in arterial blood pressure, profound bradycardia and electrocardiographic changes characteristic of acute myocardial hypoxia.[23] The three antidotes used in this study—sodium nitrite, DMAP and HH—rapidly form methemoglobin.[24] The ability of methemoglobin to prevent or reverse the toxic effects of cyanide is well recognized.[25–27]

Treatment of this form of poisoning with i.v. therapy such as sodium nitrite is theoretically possible and was found to be effective in this study; however, the use of i.v. forms of therapy in 'real life' situations, such as in accidental exposures, may be difficult at best. For example, the finding of a vein during severe circulatory collapse is potentially a very real problem. It was with these problems and concerns in mind that this study sought to determine the effectiveness of a number of candidate agents, namely i.m. sodium nitrite, DMAP and HH. This route of administration, if found to be successful, would allow for rapid and effective treatment of exposures to cyanide, without the obvious problems associated with attempting to administer an intravenous antidote.

In this study. i.m. sodium nitrite alone was found to be ineffective in restoring any of the vital physiological functions that had been embarrassed by the cyanide. All animals treated with this agent died within ca. 8–12 min, which is the time in which control animals died. It is thought that the severe bradycardia associated with cyanide poisoning might prevent both the absorption of the drug and the formation of enough methemoglobin to tie up the cyanide. The addition of atropine to the i.m. sodium nitrite appears to reverse this profound bradycardia, allowing for tissue perfusion, the uptake of the sodium nitrite, the formulation of methemoglobin and ultimately the survival of the animals. The most remarkable results in this study then were obtained not only with i.m. DMAP and HH but also with the combination of sodium nitrite plus atropine. These compounds, if administered i.m. prior to complete car-

diovascular collapse, were all effective in reversing the otherwise lethal effects of the cyanide. Within 2 min after the administration of DMAP, HH or sodium nitrite with atropine there was an increase in both heart rate and blood pressure, which was associated with a decrease in central venous pressure and recovery of spontaneous breathing. It is important to note that breathing was restored without the aid of artificial ventilation. Methemoglobin levels increased to ca. 20% in the animals treated with these agents, and seems optimal for the survival of the dogs in this study.

The mechanism by which nitrites reverse cyanide is thought to be through the formation of methemoglobin and possibly to some other direct action on the cardiovascular system[28]. Sodium nitrite has been shown to rapidly form methemoglobin which binds the cyanide as cyanomethemoglobin, thus allowing for recovery of the cytochrome–oxidase system and normal tissue oxygenation. Dimethylaminophenol likewise rapidly forms methemoglobin and is thought, in part, to reverse the effects of cyanide by this mechanism. Hydroxylamine has not previously been explored as an antidote for cyanide; however, these and other studies have shown that HH not only produces methemoglobin but has a positive inotropic effect on the heart.[29] In studies using isolated perfused Langendorff heart preparations, HH was shown to produce an increase both in force of contraction and heart rate.[19,30] It is possible that this combination of actions can most effectively restore physiological function to normal and allow for survival following a lethal dose of cyanide. Because DMAP, HH and sodium nitrite + atropine are all effective i.m., each has the potential of being an excellent candidate agent for treating acute cyanide poisoning in 'real life' situations.

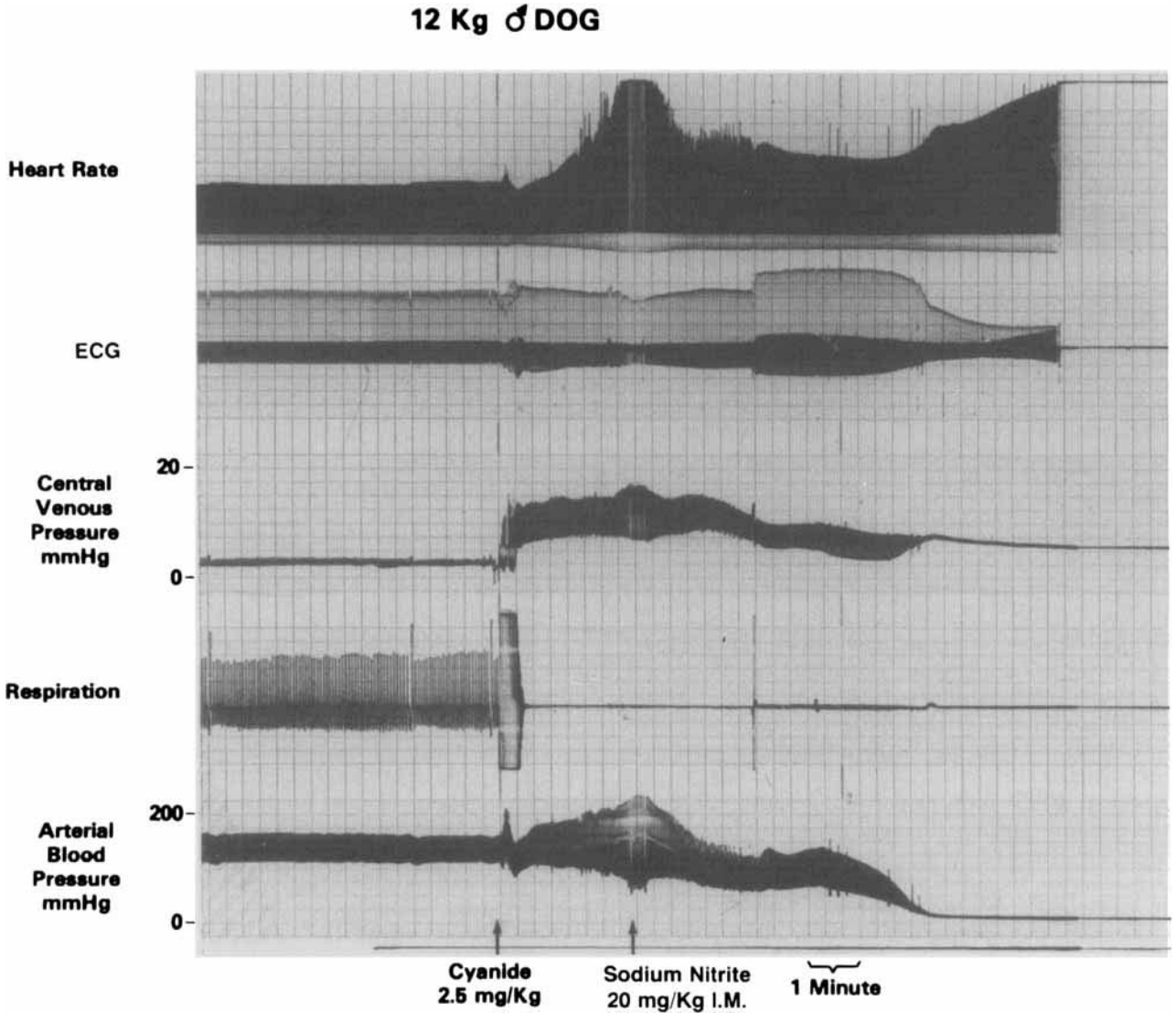

Figure 5. Effect of 20 mg kg $^{-1}$ sodium nitrite i.m. on heart rate, ECG, central venous pressure, respiration and arterial blood pressure following a lethal dose of cyanide.

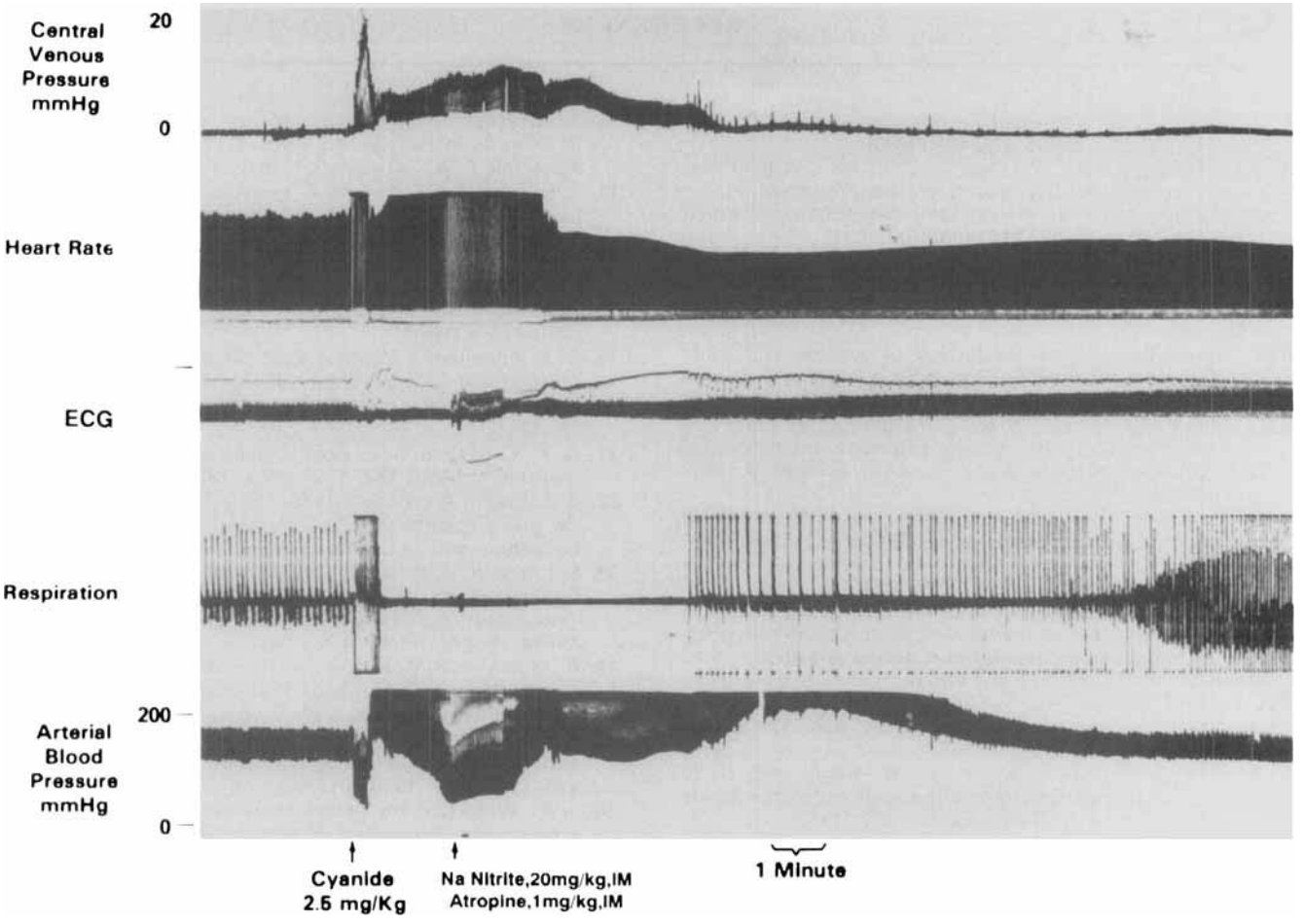

Figure 6. Effect of 20 mg kg $^{-1}$ sodium nitrite and 1 mg kg $^{-1}$ atropine i.m. on heart rate, ECG, central venous pressure, respiration and arterial blood pressure after administration of a lethal dose of cyanide.

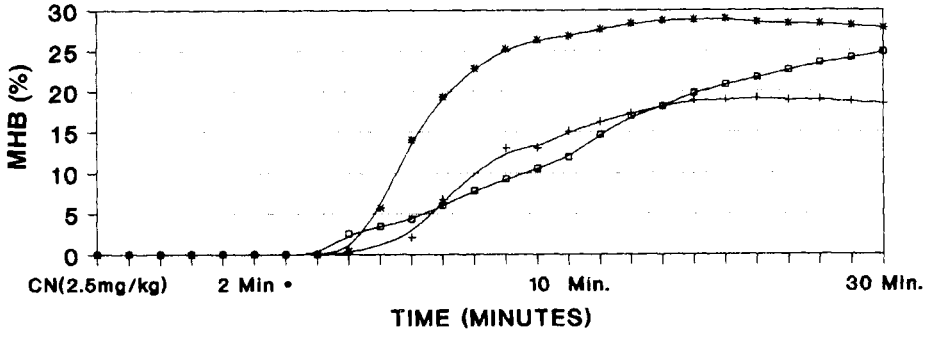

Figure 7. Effect of 20 mg kg $^{-1}$ sodium nitrite and 1 mg kg $^{-1}$ atropine (N + A) i.m. 20 mg kg $^{-1}$ hydroxylamine hydrochloride (HH) i.m. and 2 mg kg $^{-1}$ dimethylaminophenol (DMAP) i.m. on methemoglobin (MHb) levels after a lethal i.v. dose of 2.5 mg kg $^{-1}$ cyanide (□ MHb levels, CN (N+A); *MHb levels, CN, HYD.H; +MHb levels, CN, DMAP).

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