4-Dimethylamino Phenol

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Thomas Zilker and Peter Eyer

Contents

In normal intermediary metabolism, six adenosine triphosphates (ATPs) are created by passing two pairs of electrons down the respiratory chain from two reduced nicotinamide adenine dinucleotides to molecular oxygen. In the course of this mitochondrial ATP synthesis, the iron in cytochrome aa_3, the terminal oxidative respiratory enzyme, is oxidized from the ferrous (Fe^{2+}) to the ferric (Fe^{3+}) form. Cyanide has a special affinity for the ferric heme, blocking oxygen consumption and oxidative phosphorylation. Blood contains a great quantity of ferrous heme within hemoglobin that can be converted to the ferric form (methemoglobin) by the use of methemoglobin-generating agents. If methemoglobin is formed in excess of total body cytochrome aa_3, the cyanide ion binds to methemoglobin, restoring normal cellular respiration (Fig. 1).

The use of nitrite for methemoglobin formation was suggested by Chen and colleagues [1] in 1933, and nitrite is still used to treat cyanide poisoning. A theoretical disadvantage of nitrite therapy, however, is that methemoglobinemia is induced slowly. The originally suggested dose of 4 mg/kg intravenously results in 6% of methemoglobin after only 40 min [2]. A high dose of nitrite, if given too quickly, may lead to vasomotor relaxation and hypotension [3]. Amyl nitrite, which is administered by inhalation, creates little methemoglobin [4], but similar to nitrite, it has a vasodilating effect. Another cyanide antidote, dicobalt ethylenediamine tetraacetic acid ("cobalt EDTA"), can cause severe reactions, such as

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urticaria, hypotension, convulsions, and laryngeal edema [5, 6].

The antidote with the least side effects is hydroxocobalamin, which is discussed in the chapter on Cyanide-Binding Antidotes [7]. The latter is expensive, however, and has practical disadvantages. It can be given only in a large volume 5gr in 250 mL, and the lyophilized powder must be first reconstituted. This process may be too time-consuming in a critically poisoned patient. A compound that quickly creates sufficient methemoglobin with few adverse effects would be preferable. 4-Dimethylaminophenol (4-DMAP) may have advantages regarding these criteria.

History

4-dimethylaminophenol was developed and studied in the laboratories of the Walther Straub Institute for Pharmacology and Toxicology of the Ludwig Maximilian University in Munich, Germany. The German army supported its development because it was thought that hydrogen cyanide might be used as a chemical warfare agent.

In 1969, Kiese and Weger [8] reported that 4-DMAP was the most potent methemoglobin-forming agent among a series of aminophenols tested in humans for the treatment of cyanide poisoning. 4-Dimethylaminophenol was used in human cyanide poisoning successfully by Daunderer et al. in 1972 [9]. Because severe cyanide poisoning has become rare, only single case reports have been published since. A series of 13 cases in which 4-DMAP was given to humans between 1973 and 1979 has been described in a thesis from our department; however, these cases have not been published elsewhere [10]. A further series of nine cases from our department, from 1981 to 1991, was published as an abstract [11]. We are aware of the use of 4-DMAP in Austria and the Netherlands [12]. 4-Dimethylaminophenol is registered as a pharmaceutical by the German authorities (BfArM). Permission for its use was extended in 2003. At the very moment, it is not acquirable as the firm has to alter the way of synthesis. But stocks are still on most German emergency ambulances (Notarztwagen NAW). The producer of this drug is the company Dr. Franz Koehler Chemie GmbH, Bensheim, Germany.

Properties

The properties of 4-DMAP are summarized as follows:

Chemical name: Dimethyl (para) aminophenol hydrochloride (Fig. 2)
Chemical formula: $C_8H_{11}ON\ HCl$
Relative molecular mass: 173.5
Appearance: White crystals
CAS (Chemical Abstracts Service) number: 619-60-3
Raw material: White colorless crystals
Melting point: 145 °C ± 1 °C
Solubility: Soluble in water. The solution is oxidized by contact with air and changes from colorless to black-brown.

Pharmacodynamics

4-Dimethylaminophenol produces methemoglobin by catalytic transfer of electrons from ferrohemoglobin to oxygen. This process is terminated by binding of oxidized 4-DMAP to compounds that possess free SH groups (see Fig. 1).

In human volunteers, 3.25 mg/kg of 4-DMAP given intravenously oxidized about 30% of the total hemoglobin to methemoglobin (Fig. 3) [13]. The spontaneous reduction of methemoglobin back to ferrohemoglobin was 8% per hour at 30% to 20% of methemoglobin levels [14]. In vivo, 1 molecule of 4-DMAP is capable of converting 15 molecules of hemoglobin to methemoglobin [13]. Methemoglobin formation by 4-DMAP occurs rapidly. In experiments on seven volunteers [2], an intravenous bolus of 3.25 mg/kg of 4-DMAP resulted in 15% methemoglobin after 1 min and 28.5% after 10 min. The peak of 30% was attained after 20 min.

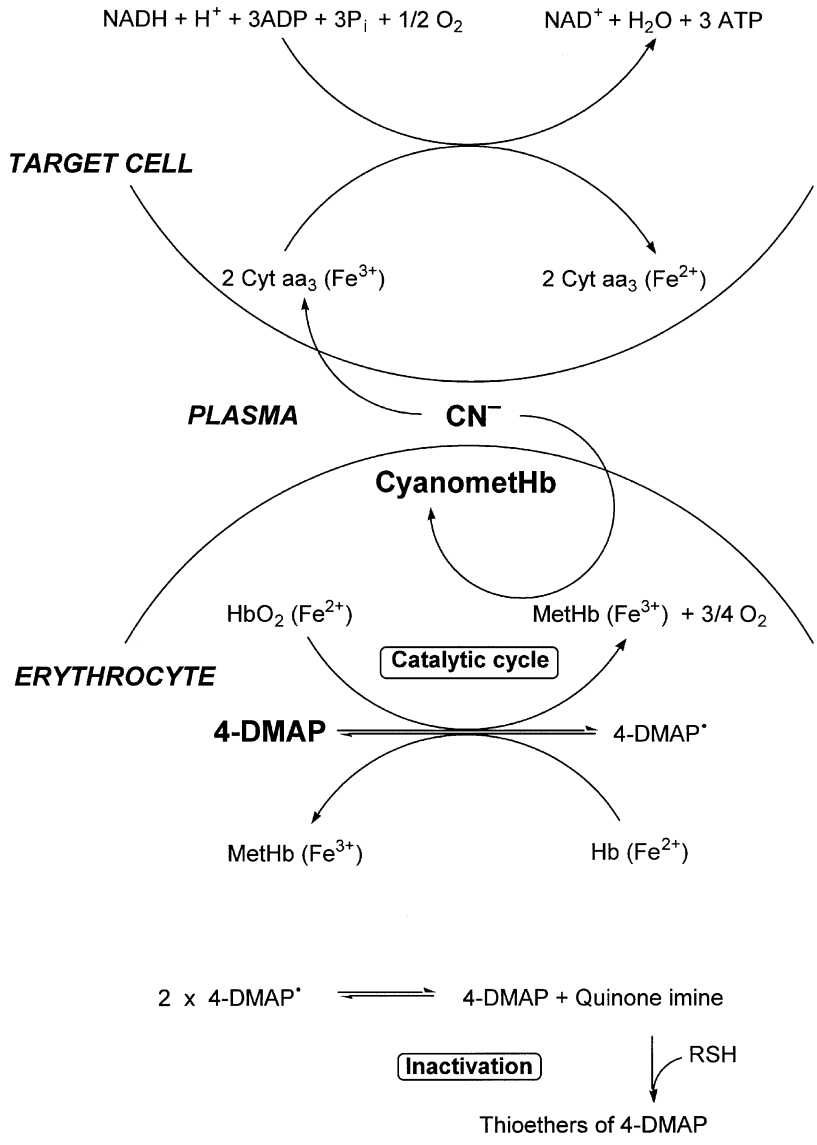

Fig. 1 Mechanism of action of cyanide, 4-DMAP, and methemoglobin. *Cyta*$_3$ cytochrome *aa*$_3$

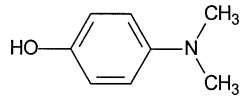

Fig. 2 Chemical structure of 4-dimethylaminophenol

4-Dimethylaminophenol can be administered intramuscularly or orally. The intramuscular injection of 3.5 mg/kg of 4-DMAP in human volunteers (n = 6) resulted in a maximal measured methemoglobin concentration of 30% after 45 min. The administration of 12 mg/kg of 4-DMAP orally (n = 5) created 27% methemoglobin within 30 min, but the actual oral bioavailability is uncertain [13].

4-Dimethylaminophenol (3.25 mg/kg) given intravenously to dogs 1 min after poisoning with potassium cyanide (4 mg/kg) that is twice the lethal dose in dogs [15] resulted in the survival of all dogs [16]. The peak concentration of methemoglobin was 32% ± 1.9% [16].

4-Dimethylaminophenol has other effects on physiologic functions. Although the venous lactate

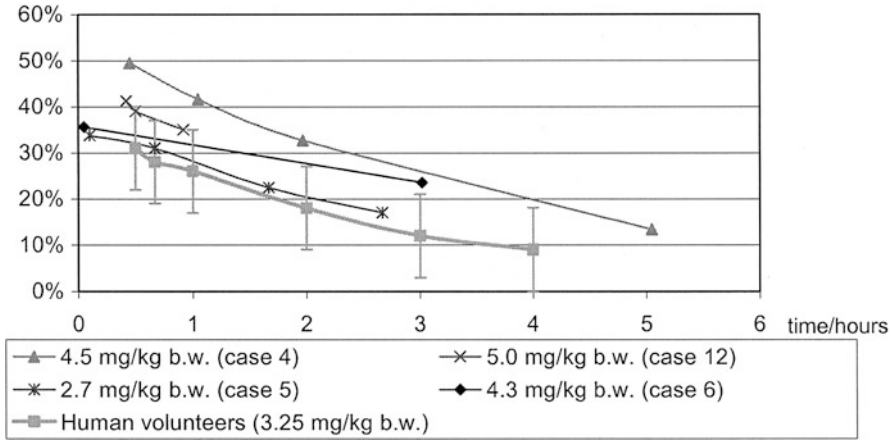

Fig. 3 Course of methemoglobin concentrations in cyanide-poisoned patients and human volunteers after intravenous administration of 4-DMAP [10]. *bw* body weight

concentration did not change, the pyruvate concentration increased by 30% after 4-DMAP administration. This effect also was found in canine blood in vitro, most probably caused by the lactate-induced methemoglobin reduction [14, 17].

In dogs [17], the mean arterial pressure after 4-DMAP (3.25 mg/kg intravenously) increased by 15% within 5 min, and the effect was maintained for 1 h. The respiratory minute volume increased by 30%. Both effects may be advantageous in cyanide poisoning. The arterial PO_2 increased within 1 min from 95 to 190 mmHg, after which it normalized by 10 min. This increase has been attributed to the release of oxygen from oxyhemoglobin during the formation of methemoglobin. It is possible that in a critically ill, cyanide-poisoned patient, this may improve tissue oxygenation [17]. When cerebral blood flow was measured in canine brain [18], 4-DMAP evoked a dose-dependent increase in cerebral blood flow. The positive cerebral blood flow response did not occur until at least 10% methemoglobin was formed. As long as the methemoglobin concentration was less than 40%, the canine brain could compensate for the diminished oxygen transport capacity by elevating oxygen use as indicated by a decrease of pO_2 in the sinus sagittalis. At higher methemoglobin concentrations, oxygen use no longer could be improved [18]. A 4-DMAP dose producing more than 40% methemoglobin is not advisable. As long as methemoglobin is less than 40%, most physiologic reactions to 4-DMAP seem to be favorable for treating cyanide poisoning.

Pharmacokinetics

In humans and dogs, 4-DMAP (3.25 mg/kg intravenously) is cleared rapidly from the blood with a half-life of less than 1 min [19]. This rapid clearance is due to various first-pass effects [13]. Using [14]C-labeled 4-DMAP in canine experiments, approximately one third of 4-DMAP equivalents were found in red blood cells, and two thirds were found in plasma and the extracellular space (apparent volume of distribution 0.17 L/kg) [20]. To understand the particular pharmacokinetics of 4-DMAP, one must differentiate between the metabolism in erythrocytes and elsewhere, mainly in the liver.

Metabolism of 4-DMAP in Erythrocytes

The distribution of 4-DMAP between plasma and erythrocytes is not known because of the ultrashort lifetime of 4-DMAP within red blood cells. 4-Dimethylaminophenol is cooxidized quickly with oxyhemoglobin to form methemoglobin

and a phenoxyl radical. The phenoxyl radical oxidizes deoxyhemoglobin, sustaining the catalytic cycle of methemoglobin formation [21]. Alternatively, the phenoxyl radical disproportionates to form 4-DMAP and a quinone imine that is bound covalently to hemoglobin SH groups [22]. In the presence of high glutathione concentrations, such as occurs in erythrocytes, the quinoneimine undergoes sequential addition/oxidation reactions with formation of mono-glutathione, bis-glutathione, and tris-glutathione adducts of 4-DMAP [23]. The trisubstituted conjugate is not oxidized further but is actively excreted from the erythrocyte into plasma [24]. This conjugate has a half-life of about 1 h in plasma and is processed further by the kidneys and excreted mainly as a tris-cysteinyl derivative of DMAP [25], as has also been observed in dogs [20]. It has been calculated that probably all 4-DMAP thioethers excreted (15% of the dose) originate from the metabolism of 4-DMAP within the red blood cells. About the same amount of 4-DMAP is bound covalently to the hemoglobin SH groups.

Metabolism of 4-DMAP in the Liver

About 50% of the 4-DMAP administered intravenously to humans is transformed in the liver to the glucuronide and sulfate conjugate. In urine, 41% 4-DMAP glucuronide and 12% 4-DMAP sulfate were detected [13, 25]. This conjugation seems to occur rapidly, as shown in the isolated, hemoglobin-free perfused rat liver, in which covalent binding to liver proteins or formation of glutathione conjugates were of no importance [26]. The first-pass effect in the liver may be the reason for the much higher oral dose compared with the parenteral dose of 4-DMAP required to obtain an equivalent degree of methemoglobin [13].

Toxicity

The toxicity of 4-DMAP has been studied in mouse, rat, and dog. The median lethal doses are listed in Table 1. In all studies, the cause of death was severe methemoglobinemia. Single intravenous injection of 4-DMAP (100 mg/kg) to rats was followed by a large amount of necrosis and inflammation of the convoluted tubules without affecting the glomeruli and papillae. No changes were found in the liver, heart, and spleen [27]. In isolated, hemoglobin-free perfused rat kidneys, 4-DMAP underwent a sharp increase of covalent binding to kidney proteins at concentrations greater than 15 μM. Microautoradiography [14] showed that the high binding was particularly prominent in the proximal convoluted tubules [31].

Table 1 Median lethal doses in mice, rats, and dogs

Route/species	Median lethal dose (mg/kg)
Intravenous/mouse	50–70 [27, 28]
Oral/mouse	946 [28]
Intravenous/rat	57 [29]
Oral/rat	689–780 [28]
Intravenous/dog	26 [30]

Special Populations

No data for neonates or children are available. In our series of 23 patients in whom 4-DMAP was used, the eldest person was 66 years old (case 13) (Tables 2 and 3). This patient received 9.3 mg/kg of 4-DMAP. He developed mild hemolysis, with an increase in lactate dehydrogenase to 378 U/L, a decrease in hemoglobin from 13.8 to 10 g/dL within 5 days, and an increase in bilirubin to 3 mg/dL. Because this was nearly three times the recommended dose and hemolysis occurs in younger patients at similar doses, we could not detect a difference between elderly and younger people in reacting to this dose.

Contraindications

Patients with glucose-6-phosphate dehydrogenase deficiency who are unable to reduce methemoglobin by the pentose phosphate shunt are at risk of developing long-lasting methemoglobinemia after 4-DMAP and may have severe hemolysis.

To our knowledge, the drug was never used in such a case. On theoretical grounds, glucose-6-phosphate dehydrogenase deficiency is a contraindication for the use of 4-DMAP. Given the desperate situation of a potentially fatally poisoned patient, we recommend that this be considered only a relative contraindication in cyanide poisoning. If a glucose-6-phosphate dehydrogenase-deficient patient were treated with 4-DMAP, because the enzyme deficiency was unrecognized or it was thought that the treatment was mandated because of life-threatening cyanide poisoning, the induced hemolysis could be treated by transfusion or blood exchange. In whites in Europe, glucose-6-phosphate dehydrogenase deficiency is a rare disease.

Clinical Experiences with Use of 4-DMAP in Cyanide Poisoning

Limited data are available for the use of 4-DMAP in cyanide poisoning because of the rarity of such poisonings and because few such poisoned persons are found alive. Some single case reports are published [9, 12, 32–34] (Grade III evidence). All but one of these case reports describe patients who survived, probably reflecting a publication bias.

Since 1972, our department has accumulated 23 cases of cyanide poisoning treatment by 4-DMAP either before or at the time of admission and one case in which 4-DMAP was used by mistake (see Tables 2 and 3): 13 cases were published in a thesis by Werner in 1979 [10], 1 case (number 10) was published by Daunderer and coworkers [9], and 9 additional cases were published in an abstract [11].

In the original Werner series, the indications for administering 4-DMAP were less strict than they are today. Of the 13 patients, only 4 (see Table 2), found in coma, seemed to meet the absolute indications we use today. Three of these four patients survived. In two further cases (cases 8 and 9 in Table 2), the indications for 4-DMAP were questionable. One patient was somnolent and still arousable. The other patient was in a coma, but 5 h had elapsed since the poisoning. In 1981 (when the first author joined the department), the indications for 4-DMAP administration were clarified. Cases of mild cyanide poisoning were treated with sodium thiosulfate. Since 1981, nine patients received 4-DMAP: five survived, three died, and one was dead for an unknown period before he was found. From the eight remaining cases, three had to be resuscitated at the scene. In all three cases, it was possible to restore circulation after the administration of 4-DMAP. Two of the patients died of irreversible brain damage or edema after brain death had ensued, and one fatally rearrested after 3 h. All patients who were found in deep coma without cardiac arrest or without severe circulatory failure survived. Of the group of 12 patients (excluding the one who was found dead, the one who got the antidote after 5 h, and all the cases in which the indication was doubtful), 8 survived and 4 died. 4-Dimethylaminophenol has not been studied in a controlled trial comparing its efficacy with other cyanide antidotes.

Dose

Considering the optimal 4-DMAP dose for a severely poisoned patient, the clinician has to keep in mind that exact dosing is difficult for the patient in extremis, the exact weight or height of the patient is unknown, and calculations under stress are difficult. We recommend that a standard dose, based on animal studies and clinical experience, be one ampule (equivalent to 3.25 mg/kg of 4-DMAP in a 76-kg person). As can be seen from Table 2, 125 mg was administered in 2 cases (cases 3 and 20), and 250 mg was administered in 13 cases. One patient (case 21) who could not be saved had mild hemolysis. One patient received 375 mg of 4-DMAP (case 19) in two divided doses and died on day 5 with severe hemolysis. All five patients (cases 7, 13, 14, 15, and 16) who were given 500 mg showed mild-to-severe hemolysis. One patient (case 18) received 1000 mg and developed severe hemolysis with a peak methemoglobin content of 73%; the patient survived. Another patient treated with 1000 mg of

Table 2 Data in 23 patients in whom 4-DMAP was administered[a]

Case no./year	Cause/route of poisoning	4-DMAP dose/interval before administration	Indication	Adverse effects	Outcome
1/1975	Accident/transdermal	250 mg/ 12 min	None; not in coma	None	Recovery
2/1976	Accident/inhalation	250 mg/ 55 min	None; not in coma	None	Recovery
3/1976	Accident/transdermal	125 mg/2.5 h	None; not in coma	None	Recovery
4/1976	Accident/oral	250 mg/1.5 h	None; not in coma	None	Recovery
5/1977	Accident/inhalation	250 mg/5.5 h	None; not in coma	None	Recovery
6/1978	Accident/almond type with high amygdaline content (cyanogenic glycoside)	250 mg/9.5 h	None; not in coma	None	Recovery
7/1979	Accident/bitter almond	500 mg/2 h	None; not in coma	Severe hemolysis, Hb from 13 to 5.9 within 3 days	Recovery
8/1973	Suicidal/oral	250 mg/ 15 min	Questionable somnolence	None	Recovery
9/1978	Suicidal/oral	250 mg/ 15 min	Questionable blood level 3 mg/L	None	Recovery
10/1972 (published 1974)	Accident	250 mg/ 45 min	Yes; deep coma	Circulatory suppression due to additional cobalt EDTA	Recovery
11/1973	Suicidal/oral	250 mg/5 h	Yes; deep coma	None	Recovery
12/1977	Accident/transdermal	250 mg/2 h	Coma	None	Recovery
13/1979	Suicidal/oral	500 mg/?	Yes; coma	Mild hemolysis, Hb from 13.8 to 10 bilirubin (maximum): 3	Recovery
14/1985	Suicidal, oral	250 mg/ 10 min; 250 mg/3 h	Yes; deep coma	Mild hemolysis. Hb from 13.3 to10.3 bilirubin (maximum): 4.7	Recovery
15/1987	Suicidal, oral	500 mg/1.5 h	Yes; coma	Mild hemolysis, Hb from 15 to 13.4 bilirubin (maximum): 4.4	Recovery
16/1989	Suicidal, oral	500 mg/ 20 min	Yes; deep coma	Hemolysis, Hb from 13.6 to 9 bilirubin (maximum): 9.3	Recovery
17/1991	Suicidal, oral	250 mg/ 15 min	Yes; deep coma	None	Recovery
18/1986	Accident, inhalation	1000 mg/ 15 min; 73 % MetHb	Yes; deep coma	Severe hemolysis, Hb from 13.9 to 7.3 bilirubin (maximum): 8.9	Recovery

(*continued*)

Table 2 (continued)

Case no./year	Cause/route of poisoning	4-DMAP dose/interval before administration	Indication	Adverse effects	Outcome
19/1977	Suicidal, oral	250 mg/1.5 h; 125 mg/5 h	Yes; deep coma	Severe hemolysis, Hb from 16.4 to 10.9 bilirubin (maximum): 18.4	Death after 4 days
20/1986	Suicidal, oral	125 mg (only)/1.5 h	Yes; resuscitation after 4-DMAP successful	None	Death after 4 days
21/1987	Suicidal, oral	250 mg/2 h	Yes; resuscitation after 4-DMAP successful	Mild hemolysis, Hb from 15.7 to 13.7 bilirubin (maximum): 4.4	Death after 5 days
22/1989	Suicidal, oral	250 mg/1 h	Yes; resuscitation after 4-DMAP successful	Too short to judge	Death after 3 h
23/1981	Suicidal, inhalation	500 mg/?	Dead for unknown time	Not possible to judge	Found dead

[a]Sodium thiosulfate was administered after 4-DMAP in all patients.
Hb hemoglobin, *MetHb* methemoglobin

4-DMAP was poisoned with parathion. This patient also survived with severe hemolysis and renal failure (not shown in Table 2 or 3).

Methemoglobin Formation

A dose of 250 mg of 4-DMAP (see Table 3, cases 4, 5, 6, and 12) seems to create methemoglobin concentrations between 33% and 49.5%, which disappeared with a half-life of around 140 min (see Fig. 3). The half-life is not influenced by the dose. In our patients, it was a little bit longer than in normal controls (117 min). As seen in case 7, 500 mg of 4-DMAP can lead to long-lasting methemoglobin formation. It is likely that most of the methemoglobin found in this case after 72 h stemmed from extracellular methemoglobin due to hemolysis.

From this limited experience, we conclude that in a healthy adult, 250 mg is theoretically sufficient, yet safe. Repeated 4-DMAP administrations do not seem to be necessary if sodium thiosulfate is administered subsequently.

Precautions

Before 4-DMAP is used in a patient, it should be certain to the degree practically possible that the patient is poisoned by cyanide. We recommend that 4-DMAP should be used only if the patient is in a coma (Grade III recommendation). We do not recommend its use in smoke inhalation patients because of the theoretical concern that carboxyhemoglobin and methemoglobin jointly may impair oxygen transport and delivery.

Table 3 Whole-blood cyanide and methemoglobin levels in 23 patients in whom 4-DMAP was administered

Patient	Cyanide level/time after intoxication	Dose 4-DMAP	Methemoglobin/time after 4-DMAP
1	Negative/1 h	250 mg	23 %/13 min
2	Not measured	250 mg; 4.38 mg/kg	Not measured
3	Negative/150 min	125 mg; 2.7 mg/kg	Not measured
4	Positive in breath/90 min	250 mg; 4.5 mg/kg	49.5 %/27 min
5	Positive in breath/5.25 h	250 mg; 2.7 mg/kg	33 %/9 min
6	0.18 mg/L/9 h	250 mg; 4.3 mg/kg	35.6 %/3 min
7	Not measured	500 mg; 8.3 mg/kg	35 %/72 h
8	1.5 mg/L/15 min	250 mg	Not measured
9	3 mg/L/15 min	250 mg; 4 mg/kg	14.7 %/1 h
10	Not measured	250 mg	Not measured
11	Not measured	250 mg; 3.57 mg/kg	22 %/13 min
12	2 ppm in breath/2 h	250 mg; 5 mg/kg	41.2 %/25 min
13	Not measured	500 mg; 9.3 mg/kg	Not measured
14	2.4 mg/L/2 h	250 mg/10 min; 250 mg/3 h	15.8 %/1 h; 37.7 %/155 min after second administration
15	6.0 mg/L/2.25 h	500 mg	Not measured
16	25 mg/L/1 h	500 mg	33.4 %/130 min
17	1.46 mg/L/130 min	250 mg	Not measured
18	Positive in breath	1000 mg	73 %/1 h; 46 %/3.5 h
19	2.65 mg/L	250 mg; 125 mg	Not measured
20	34 mg/L/1.5 h	125 mg	Not measured
21	10.9 mg/L/2 h	250 mg	19 %/15 min
22	14 mg/L	250 mg	14.8 %/45 min
23	Not measured	500 mg	Not measured

Adverse Effects

Two major adverse effects are related to the desired action of 4-DMAP: excessive methemoglobinemia and hemolysis. Our cases suggest that significant hemolysis does not occur at doses of 5 mg/kg body weight. The suggested dose of 3.25 mg/kg did not produce excessive methemoglobinemia. Only in one fatal case of cyanide poisoning was excessive methemoglobinemia observed using the recommended dose of 4-DMAP [12]. In vitro, the methemoglobin production rate at atmospheric oxygen pressure was only 60% of that at 40 mmHg, similar to that in venous blood [35]; this may be important in hypoxic patients when cardiopulmonary insufficiency is present. In our opinion, this fact should not lead to reducing the dose in such circumstances as long as the patient is ventilated with a fraction of inspired oxygen of 1.

Some minor adverse effects are of little relevance in severely poisoned patients. Phlebitis was observed 6–7 days after 4-DMAP was infused in the antecubital vein. After an intramuscular injection of 4-DMAP, slight pressure was felt after 5–10 min at the site of injection, slowly growing in intensity and finally resulting in severe pain in one patient. In another patient, shivering, sweating, and fever occurred approximately 10 h after the injection. In volunteers, after the intravenous injection of 4-DMAP (3.25 mg/kg), the total bilirubin concentration increased by 140%, conjugated bilirubin increased by 180%, and iron increased by 200%. Within 24 h of an intramuscular injection of this dose, the total bilirubin

increased by 270% and then declined rapidly, whereas the conjugated bilirubin concentration increased by 120% and iron increased by 50% [13].

Treatment of Adverse Effects

Excess methemoglobinemia may be corrected by 2 mg/kg of toluidine blue or by 1 mg/kg of methylene blue intravenously [36]. We suggest that this should be done only if within 1 h after the administration of 4-DMAP the methemoglobin level exceeds 50% (Grade III recommendation). Otherwise, cyanide can be released, and thiosulfate infusion is mandatory. Exchange transfusion is needed if the methemoglobin level remains high as this means that methemoglobin comes from erythrocytes that have lysed and therefore cannot reduce MetHb.

Administration

4-Dimethylaminophenol should be administered in a dose of 3.25 mg/kg intravenously in a comatose, cyanide-poisoned person (Grade III recommendation). In adults, it seems reasonable to administer one ampule of 4-DMAP, which contains 250 mg, if the exact weight is not known. It is possible to administer 4-DMAP in the same dose intramuscularly in mass poisoning.

Final Evaluation

Animal experiments and limited clinical data suggest that 4-DMAP is an effective antidote against cyanide poisoning. Although in most cases it was used in combination with sodium thiosulfate and therefore it is difficult to distinguish the efficacy of the two drugs. Single cases have received DMAP only successfully. There was, in most cases, an improvement shortly after its administration and before the use of sodium thiosulfate, suggesting that 4-DMAP is effective. In cases of severe cyanide poisoning, 4-DMAP is probably lifesaving, if administered in time. 4-DMAP produces more MetHb more rapidly than nitrites, although it has to be acknowledged that since both treatments have an equal chance of successful outcome, the speed of forming MetHb might not be of utmost importance. It should not be used in the case of smoke inhalation since the induced methemoglobinemia may be additive to CO poisoning. However, there is no evidence that it has ever been tested in such circumstances. The possibility to administer 4-DMAP intramuscularly might make it an appropriate antidote for severe cases in the industrial environment and for use in treatment of mass casualties, e.g., in terror attacks [37].

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