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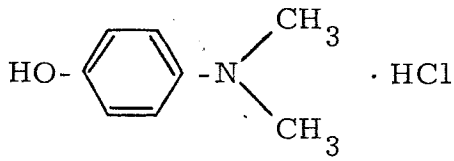
INTRODUCTION

This documentation includes the description of 4-DMAP, a preparation for the treatment of poisonings with cyanides, hydrocyanic acid and nitriles, also possibly of poisonings with hydrogen sulphide.

The experimental examinations with animals and the basic clinical experiments were conducted almost exclusively at the Pharmakologische Institut der Universität München (Pharmacological Institute of the University of Munich) where Docent Nikolaus Weger M.D. has concerned himself with the problem of the formation of methaemoglobin for the treatment of cyanide poisoning for more than 10 years. The results of relevant examinations have been recorded in numerous publications and scientific reports for the "Sanitäts-Lehr- und Arbeitsgruppe ABC-Schutz" ("Medical, Eductional and Working Group ABC Protection").

In the following, 4-DMAP is always understood as 4-Dimethylaminophenol hydrochloride.

Chemical and Physical Properties

Structural formula: 

Molecular formula: $C_8H_{11}ON \cdot HCl$

Molecular weight: 173.5

4-DMAP forms snow-white crystals which are very readily soluble in water and which melt at 145.1°C. 4-DMAP is rapidly oxidized in an aqueous solution giving rise to intensively brown to blackish-brown coloured derivatives due to polycondensation of the corresponding quinone.

The determination of the decomposition kinetics of 4-DMAP solutions leads to the result that, in an aqueous solution of the active substance at 20°C and a pH value of 5.0, the standard of the active substance drops from 100 % to 96.8 % in the course of 8.2 years. In this respect, a 4-DMAP solution can be described as remarkably stable.

See also:

C. Bannert and N. Weger: 4-Dimethylaminophenol für intramuskuläre und intravenöse Injektion; scientific report from the Akademie des Sanitäts- und Gesundheitswesens der Bundeswehr München 1973 (Academy of the Sanitary and Public Health Service of the Federal Army Munich 1973)

Quantitative Composition of the Injection Solution

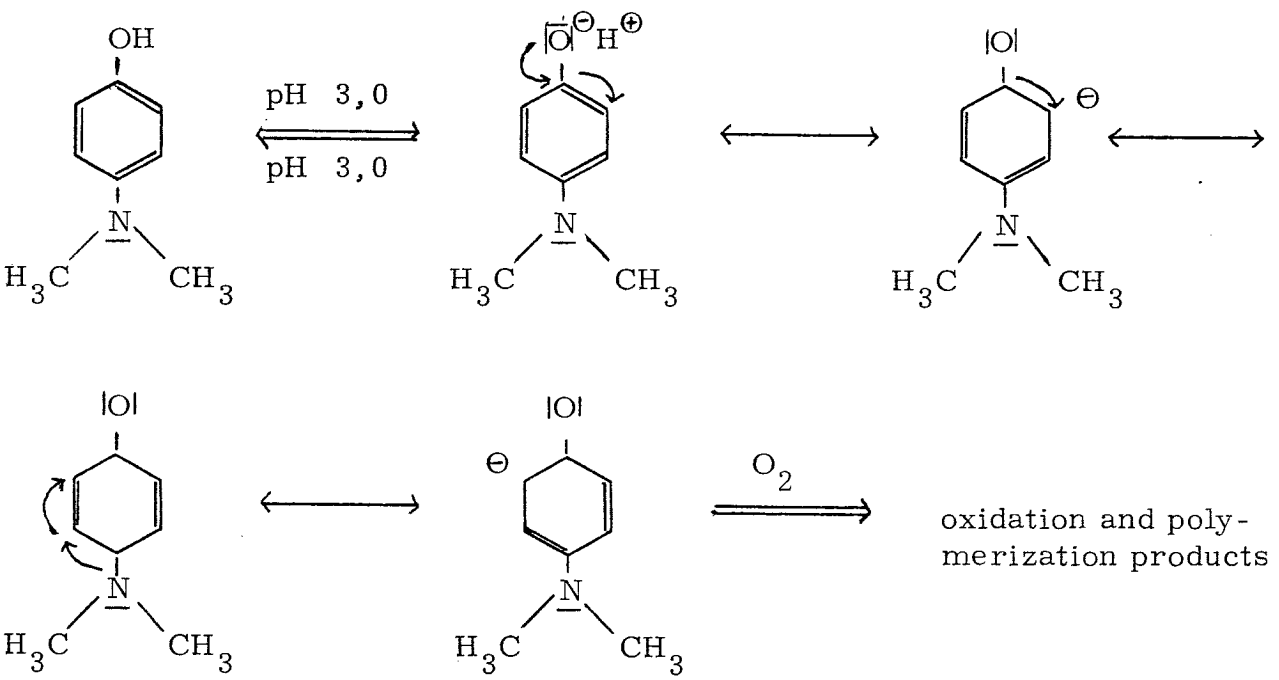
5 ml contain:

2500 mg 4-Dimethylaminophenol hydrochloride
2,5 mg Sodium-disulfite, $Na_2S_2O_5$
0,5 mg Na_2EDTA

pH = 4.7, reached with app. 10 mg Sodium-hydrogencarbonate

A patent for the procedure of the preparation of stable aqueous 4-DMAP solutions has been applied for at the Bundespatentamt (Federal Patent Office) in Munich under No. P 25 07 955.4.

Aqueous solutions of 4-DMAP give, in the presence of oxygen and at pH values above 3.0, intensive discolourations within 12 hours. The rate of oxidation processes hereby taking place and which are followed by colour producing polymerisation processes, is determined by the degree of dissociation of the proton of the phenolic OH-group according to the following equation:



Upon raising the pH value to above 3,0, preferably above 5,0, which is necessary for application technical reasons, the oxidation of 4-DMAP in aqueous solution is already effected by traces of oxygen dissolved.

The complete elimination of oxygen by use of inert gas while filling 4-DMAP solutions into ampoules is ensured only by the addition of effective antioxidant agents because of the subsequent contact with air which is technically only difficult to avoid during the form-turning of the ampoules or phials. This aspect forms the basis of the aforesaid patent application.

Information about the Analytics:

1. 4-DMAP Pure Substance

Determined are:

a) Melting point

b) Content: by titration
by elementary analysis

c) I.R.-spectrum

d) Chromatogram

e) Drying loss

f) Sulphate ash

g) Heavy metals

2. 4-DMAP Ampoules

a) Identity

b) pH value

c) Drying residue

Range of Indications of 4-DMAP:

In case of poisonings with hydrocyanic acid, cyanides and nitriles, also possibly in case of poisonings with hydrogen sulphide.

Quality Control:

1. Sterility

The quality controls of 4-DMAP are executed according to the standards and terms of the DAB VII - Deutsches Arzneibuch VII (German Pharmacopoeia VII).

The examination of the sterility is carried oud with

4 filling units (ampoules) at the beginning of the sterilising filtration,
4 filling units in the middle of the sterilising filtration and
4 filling units at the end of the sterilising filtration.

In detail, the procedure of the proof of sterility is as follows:

10-15 ml of standard-I-nutrient bouillon (Merck, Art. No.7882) is incubated with 3 ml of 4-DMAP feed, to be examined, at 37°C for 6 days. Any turbidity must not occur.

Furthermore, a plate test is carried out as a control:

a) Standard-I-N-agar for the detection of particular germs

b) Sabouraud-glucose 2 % agar for the growing and isolation of pathogenic fungi and yeasts and

c) Thioglycolate bouillon according to USP XVIII (Merck, Art.No.8190 and 8191) for the test on anaerobic microorganisms

is poured into sterile Petri dishes. The 4-DMAP feed to be examined is spread lege artis into these culture media.

The culture media are incubated

a) at 37°C and

b) at 25°C

for 6 days.

According to the observations made so far, an aqueous solution of 4-DMAP proves itself to be autosterile in a therapeutically designated concentration.

2. Absence of Pyrogens

For toxicological reasons, the execution of the pyrogenic test on rabbits according to the regulations of the DAB VII - Deutsches Arzneibuch VII (German Pharmacopoeia VII) cannot be realized with an adequate volume of the 4-DMAP solution.

Toxicological Properties:

1. Acute toxicity:

According to the investigations of N. Weger et al., the LD_{50} for dogs is 26 mg/kg of animal, whereby about 85 % of ferrihaemoglobin (methaemoglobin) is formed. The animals die of anoxia because only 15 % of the haemoglobin is available for the transport of oxygen. With a ferrihaemoglobin content under 80 % of the total haemoglobin, all the animals survive.

The therapeutical dose of 3-5 mg of 4-DMAP/kg of human being oxidizes only 30-50 % of the haemoglobin to ferri-haemoglobin.

2. Chronic toxicity:

With regard to the application of 4-DMAP according to regulations, the examination of the active substance under the conditions of the chronic toxicity is not necessary. Despite this, in the dog experiment, 3 mg of 4-DMAP/kg of animal was intravenously applied twice a week during a period of 13 weeks. This dose oxidizes 35 % of the haemoglobin, but does not cause changes, either macroscopically or microscopically, on the liver, spleen, kidney, heart, on the blood count or transaminases and creatinine.

See also:

M. Kiese, L. Scinicz, N. Thiel and N. Weger: Wirkung des 4-Dimethylaminophenols und 4-Aminophenols auf Organe von Hunden und Ratten; scientific report from the Pharmakologische Institut der Universität München 1973 (Pharmacological Institute of the University of Munich 1973).

Teratogenic Properties:

Examinations with 4-DMAP for effects which are detrimental to the cells of propagation have not been carried out in view of the range of indications of this active substance.

Pharmacological Properties:

The detoxification of cyanides, hydrocyanic acid and nitriles proceeds according to the following scheme:

1st Step:

4-DMAP + haemoglobin ($Fe^{2+} \cdot O_2$) $\longrightarrow$ ferrihaemoglobin (Fe^{3+})

2nd Step:

CN^- + ferrihaemoglobin (Fe^{3+}) $\rightleftharpoons$ ferrihaemoglobin-CN-complex ($Fe^{3+}CN^-$)

3rd Step:

CN^- + sodium thiosulphate $\xrightarrow[\text{rhodanase}]{}$ thiocyanate (SCN^-)

For the therapy of poisonings with cyanides, hydrocyanic acid and nitriles, about 30 % of the haemoglobin must be oxidized to ferrihaemoglobin. After an intravenous application of approx. 3 mg of 4-DMAP/kg of body weight, the semi-maximum concentration of ferrihaemoglobin is reached within one minute, the maximum concentration after 5-10 minutes.

The physiological reduction of ferrihaemoglobin to haemoglobin can be observed already after 30 minutes, 10 % of the total haemoglobin still being present as ferrihaemoglobin in the human being after approx. 4 hours after the application.

In case of an overdosage of 4-DMAP, the reduction process can be shortened to 30-15 minutes by an intravenous application of 2-4 mg of o-toluidine blue/kg of body weight.

After an intravenous injection of 4-DMAP, disorders, either in the coronary circulation system or in the carbohydrate and protein metabolism, are not observed. Heinz inner bodies are not found. The activity of the transaminases remains unchanged.

After the conversion of the haemoglobin-cyanide complex into the ferrihaemoglobin-cyanide complex by 4-DMAP, the detoxification of the cytochrome oxidase blocked by the cyanide must be completed by high doses of sodium thiosulphate. That means, in a second step of the therapy, the cyanide is converted into the relatively non-toxic thiocyanate with the help of the endogenic rhodanase. This secondary detoxification process is decisively accelerated by intravenous administrations of 50-100 mg of sodium thiosulphate/kg of body weight. Thiocyanate is excreted up to 80 % in the urine. Ferrihaemoglobin is physiologically reduced to haemoglobin.

See also:

N. Weger: Therapie der Blausäurevergiftung durch Ferrihämoglobinbildung; Habilitations-Thesis from the Pharmakologische Institut der Universität München 1969 (Pharmacological Institute of the University Munich 1969).

N. Weger: Aminophenole als Blausäureantidote; Arch. Toxikol., 24 (1968), 49-50.

P. Eyer, M. Kiese, G. Lipowsky and N. Weger: Reactions of 4-Dimethylaminophenol with Hemoglobin, and autoxidation of 4-Dimethylaminophenol; Chem.-Biol. Interactions, 8 (1974), 41-59.

M. Kiese, R. Klimmek, L. Szinicz and N. Weger: Wirkung von 4-Dimethylaminophenol und Co-Histidin auf Atmung, Kreislauf und verschiedene Parameter des Blutes bei Beagle Hunden nach akuter Cyanidvergiftung; Scientific Report from the Pharmakologische Institut der Universität München 1974 (Pharmacological Institute of the University of Munich 1974).

M. Kiese, R. Klimmek, L. Szinicz and N. Weger: Wirkung von 4-Dimethylaminophenol auf Atmung, Kreislauf und verschiedene Parameter des Blutes bei Beagle Hunden; Scientific Report from the Pharmakologische Institut der Universität München 1974 (Pharmacological Institute of the University of Munich 1974).

Dosage and Mode of Application:

After the diagnosis of a poisoning with hydrocyanic acid, cyanides or nitriles, 3-4 mg of 4-DMAP/kg of body weight is immediately injected intravenously within 30 seconds, that means: For an adult, approximately 1 ampoule of 5 ml containing 250 mg of active substance.

Subsequently, 100-500 mg of sodium thiosulphate/kg of body weight is infused through the same needle.

See also:

N. Weger: Cyanidvergiftung und Therapie;
Wehrmed. Monatsschr., 19 (1975), 6-11.

M. Daunderer, H. Theml and N. Weger: Behandlung der Blausäure-vergiftung mit 4-Dimethylaminophenol (4-DMAP); Med.Klin., 69 (1974), 1626-1631

Compatibility:

In the investigations with the animal as well as in the application in man, 4-DMAP does not show any effect on the blood pressure and the flow velocity in the blood vessels.

Wenn applied according to the regulations, no other symptoms occured besides the cyanosis (formation of ferrihaemoglobin) to be expected.

The effect of 4-DMAP on newbornes and infants has not been investigated. Since the methaemoglobin reductase is not yet fully effective in newborns, there is the danger of a long lasting methaemoglobinemia.

4-DMAP does not cause any disorders in the carbohydrate and protein metabolism. The antidote does not form Heinz inner bodies and reacts inert in relation to the activity of the transaminases.

In experiments with dogs and rats, it was shown that a dose of 30 mg of 4-DMAP/kg of animal does not cause pathological changes in the kidney.

See also:

H. Offterdinger and N. Weger: Kreislauf und Atmung bei Blausäurevergiftung und Therapie mit Ferrihämoglobinbildnern und Kobaltverbindungen; Naunyn-Schmiedebergs Arch. Pharmak., 264 (1969), 289.

N. Weger: Therapie der Blausäurevergiftung; Med. Monatsschr., 23 (1969), 436-440.

M. Kiese, L. Szinicz, N. Thiel and N. Weger: Wirkung des 4-Dimethylaminophenols und 4-Aminophenols auf Organe von Hunden und Ratten; scientific report from the Pharmakologische Institut der Universität München 1973 (Pharmacological Institute of the University of Munich 1973).

Clinical Examinations:

Because the extent of action of 4-DMAP regarding the stoichiometric relations between the dose and the oxidative conversion of haemoglobin to ferrihaemoglobin is clarified in detail, and, on the other hand, because the detoxifying effect of ferrihaemoglobin on the cyanide-haemoglobin complex is also very well known, the therapeutic scope of action of 4-DMAP, when applied according to the regulations, can be exactly adjusted on this basis without hesitation. In this respect, clinical examinations are not necessary in case of provoked cyanide, hydrocyanic acid of nitrile poisonings, besides the fact that clinical experiments as defined in the regulations of the AMG - Arzneimittelgesetz (law governing the manufacture and prescription of medicines), under consideration of serious ethical aspects, cannot be realized.

See also:

M. Daunderer, H. Theml and N. Weger: Behandlung der Blausäurevergiftung mit 4-Dimethylaminophenol (4-DMAP) Med. Klin., 69 (1974) 1616-1631

M. Kiese, J.G. Schöber and N. Weger: Versuche am Menschen zur Kinetik der Ferrihämoglobinbildung durch Aminophenole und Nitrit; Naunyn-Schmiedebergs Arch. Pharmak., 260 (1968), 152.

M. Kiese, N. Weger: The Treatment of Experimental Cyanide Poisoning by Hemiglobin Formation; Archiv für Toxikologie, 21 (1965), 89-100.

M. Kiese and N. Weger: Hämiglobinbildung zur Behandlung der Cyanid-Vergiftung; Naunyn-Schmiedebergs Arch. Pharmak., 250 (1965), 263.

M. Kiese, N. Weger: Formation of Ferrihaemoglobin with Aminophenole in the Human for the Treatment of Cyanide Poisoning; Europ. J. Pharmacology, 7 (1969), 97-105.

Pharmacokinetics:

4-DMAP is excreted through the kidneys. In the average, 16 % of a dose administered intravenously is eliminated with the urine within 8 hours.

The following products of metabolism were detected as metabolites by means of radioactively marked 4-DMAP:

> 4-Methylaminophenol, quinone, hydroquinone, formaldehyde, dimethylamine, and a blue as well as a yellow pigment of unknown constitution.

See also:

W. Lörcher: Optimale Konzentration von Ferrihämoglobin zur Behandlung der Blausäurevergiftung; Inaugural-Dissertation - Tierärztliche Hochschule der Ludwig-Maximilians-Universität München 1973 (Veterinary Faculty of the Ludwig-Maximilian University of Munich 1973).