

Toxicological aspects of dimethyl-ether

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RÉSUMÉ

Les auteurs décrivent ici les résultats obtenus lors d'une série d'expériences pratiquées sur des souris et des lapins, dans le but de déterminer les effets toxiques de l'inhalation de diméthyl-éther. Pour la souris, la concentration létale moyenne (LC_{50}) et le temps létal moyen (TL_{50}) ont été évalués. Pour le lapin, on a aussi évalué les effets toxiques de de l'inhalation de diméthyl-éther sur certains paramètres physiologiques (pouls, battement cardiaque, gaz sanguin et pH).

Key-words : Dimethyl-ether; Gas poisoning; Blood gas analysis; Toxicology.

Introduction

Dimethyl-ether ($CH_3 - O - CH_3$) has been proposed as a possible substitute for liquid Petroleum gas (LPG), since its physical properties (1-4) are similar. Although the caloric power of Dimethyl-ether (DME) is lower than that of LPG, DME could be preferred as a comburent because of its reduced oxygen requirements. Moreover, DME's lower vapor pressure and higher specific gravity strongly suggest its utility for the purpose.

At present, little is known about the toxicology of DME (5). Some mention of the general anaesthetic properties of the gas is found in the literature (5-8), but precise pharmacological and toxicological characterization are lacking.

Thus, in view of this potential use as a fuel substitute it seemed desirable to investigate its toxicological properties.

This paper reports the results of the studies conducted on the toxic effects of DME in mice and rabbits.

Methods

1. — *Acute inhalation toxicity in the mouse.* Male Swiss strain mice (18-22 g), fasted for 16 hours, were

exposed in groups of four to DME in a 2.5-liter belljar chamber connected by a Palmer respiratory pump to a spirometer of the Tissot-type. Two series of experiments were performed, for determining: a) Median lethal concentration (LC_{50}) of the gas, in p. p. m., *i. e.*, the concentration which kills 50 % of the animals. Each of the following concentrations was tested on 8 animals: 100×10^3 ; 200×10^3 ; 300×10^3 ; 400×10^3 ; 500×10^3 ; 600×10^3 ; 800×10^3 and $1,000 \times 10^3$ p. p. m.; b) Median lethal time (LT_{50}), in minutes, *i. e.*, the time in which a fixed concentration of DME causes death of 50 % of the animals. Exposure times of 5, 10, 15, 30, 35 and 40 minutes to DME (400,000 p. p. m.) were assayed on 8 mice for each time period. The LC_{50} 's and LT_{50} 's, and their confidence limits (c. l.), were calculated by probits analysis (9).

2. — *Physiological measurements.* These include studies on the effects of DME on the cardiovascular system (blood pressure, heart rate) and on some blood parameters (pH, pO_2 , pCO_2). The tests were carried out on male New Zealand rabbits (3.5 kg), fasted for 16 hours and locally anaesthetized by subcutaneous injection of Lidocaine 1 %. Blood pressure was recorded from the left carotid artery by means of a capacitative transducer on a polygraphic apparatus (Batta-

glia-Rangoni, Bologna, Italy). Blood pO_2 , pCO_2 and pH data were determined on blood samples drawn at 5-minute intervals from the right carotid artery and at 15-minute intervals from the right jugular vein, by a Radiometer pH/blood gas analyzer mod. RH/302. For this purpose the artery was interrupted and the two branches were cannulated by two polyethylene catheters (PE 120) joined together by means of a small plexiglas cylinder (12 mm diameter, 20 mm length). A hole of the same diameter as the polyethylene tubing, drilled lengthwise through the cylinder, permits connecting the catheters by means of adapters to opposite ends. A third adapter, containing a rubber membrane, is connected to a vertical opening in the center of the cylinder which was drilled to join with the horizontal orifice. A hypodermic needle inserted through the membrane permits drawing blood samples without interrupting blood flow. Venous blood samples were obtained *via* a Gordh needle connected to a PE 120 catheter inserted into the vein. The animals were given, *via* the cannulated trachea, a respiratory mixture of DME (40 %) + atmospheric air (60 %). This was contained in a 10-liter Tissot-type spirometer and administered under intermittent positive pressure by a Palmer respiratory pump connected to it. The rate and volume of respiration ranged between 20 and 35 strokes/minute, each stroke varying from 30 to 50 ml according to the animal's body weight and normal respiratory rate, so as to obtain an administration of DME of about

100 ml/kg/min. In some instances, administration of the mixture was interrupted after 30 minutes, in order to control the reversibility of changes induced by DME on the parameters under study.

Results and conclusions

1. — *Acute inhalation toxicity in the mouse.* The results are given in Tables I and II. Table I reports the percentages of lethality obtained in the animals exposed, for different periods of time, to different concentrations of DME. The LC_{50} values were : 494.36 p. p. m. (c. l. 447.68-545.91 p. p. m.) after a 15-minute exposure, and 385.94 p. p. m. (c. l. 334.63-445.11 p. p. m.) after a 30-minute exposure. The lethality data for mice exposed to 400,000 p. p. m. for varied periods are listed in table II. An LT_{50} value of 24.4 minutes (c. l. 20.15-29.72) was calculated. In lethal doses, DME induced sedation, a progressive depression of motor activity, loss of the righting reflex, hypopnea, coma and, finally, death. No deaths occurred in the 72 hours following exposure to DME. From this we may infer that the gas does not have any delayed lethal toxic effect.

2. — *Physiological measurements.* The results are reported in tables III and IV. As shown in table III, inhalation by the rabbit of DME (40 % in the respiratory mixture) is followed, after a slight increase in the heart rate of 15 minutes duration, by a progres-

Table I
Lethality values obtained in mice exposed to different DME concentrations.

DME concentration (1×10^3 ppm)	No. of mice	Cumulative lethality values (%)										
		at different post-exposure intervals										
		2'	4'	6'	7'	10'	15'	20'	30'	40'	50'	72h*
100	8	0	0	0	0	0	0	0	0	0	0	0
200	8	0	0	0	0	0	0	0	0	0	25	25
300	8	0	0	0	0	0	0	0	25	50	50	50
400	8	0	0	0	0	12.5	12.5	37.5	50	87.5	100	100
500	8	0	0	0	12.5	37.5	50	62.5	75	100	100	100
600	8	0	0	0	25	62.5	87.5	100	100	100	100	100
800	8	0	0	0	37.5	100	100	100	100	100	100	100
1000	8	12.5	50	87.5	100	100	100	100	100	100	100	100

*Values obtained 72 hrs after the end of exposure

LC_{50} (at 15 mins.) = 494.36 ppm; c.l. : 447.68 - 545.91 ppm (P 0,05)

LC_{50} (at 30 mins.) = 385.94 ppm; c.l. : 334.63 - 445.10 ppm (P 0,05)

Table II

Lethality values obtained in mice exposed to a fixed DME concentration for different periods of time.

DME concentration (1×10^3 ppm)	No. of mice	Exposure time	Lethality at 72 hrs (%)
400	8	5'	0
400	8	10'	0
400	8	15'	12.5
400	8	30'	50
400	8	35'	87.5
400	8	40'	100

 $LT_{50} = 24.44$ mins. c.l. : 20.15 - 29.62 mins. (P 0,05)

sive depression of arterial blood pressure lasting up to 40 to 45 minutes and by the death of the animal. Simultaneously, as soon as exposure to the DME begins, both the arterial and venous pO_2 values decrease while the venous pCO_2 and blood pH values increase (see table IV). In rabbits in which DME was replaced 30 minutes later by oxygen, the normal values for blood pressure, pO_2 , pCO_2 and pH and the previous anaesthetic state were restored.

From these experiments the anaesthetic properties of DME, as revealed by the appearance of typical

signs of general anaesthesia, are confirmed. The signs become evident when the blood pressure decreases and parallel the depth of anaesthesia up to the death of the animal.

Summarizing, the results of our investigations suggest that DME acts on the CNS with a mechanism similar to that of other general anaesthetics of the ethyl-ether class. DME's systemic and lethal effects and its LC_{50} , in fact, are comparable to those of these compounds and are completely acceptable for use as described in the introduction.

Table III

Effects of DME inhalation on blood pressure and heart rate, in the rabbit.

Parameters	Post-exposure time (in minutes)									
	0' (n=6)	5' (n=6)	10' (n=6)	15' (n=6)	20' (n=6)	25' (n=6)	30' (n=6)	35' (n=6)	40' (n=5)	45' (n=4)
Blood pressure (mm/kg)(mean \pm SE)	158.88 ± 8.10	164.38 ± 8.10	159.38 ± 16.27	153.13 ± 19.97	131.88 ± 26.20	106.25 ± 21.34	86.25 ± 12.70	66.88 ± 6.58	58.13 ± 7.41	41.25 ± 7.76
Heart rate (beats/min.)(mean \pm SE)	238.47 ± 36.82	235.97 ± 29.56	261.07 ± 28.78	288.25 ± 15.39	326.10 ± 9.90	326.30 ± 13.98	318.82 ± 16.33	309.07 ± 17.09	297.10 ± 21.76	252.52 ± 37.01

Table IV

Effects of DME inhalation on blood pO_2 , pCO_2 and pH, in the rabbit.

Parameters		Post-exposure time (in minutes)									
		0' (n=6)	5' (n=6)	10' (n=6)	15' (n=6)	20' (n=6)	25' (n=6)	30' (n=6)	35' (n=6)	40' (n=5)	45' (n=4)
pO ₂ (mean±SE)	Arterial	97.10 ±5.01	78.90 ±7.77	67.30 ±6.73	55.83 ±2.67	51.88 ±2.91	47.65 ±1.55	44.53 ±2.80	43.53 ±7.19	44.58 ±9.47	50.35 ±10.80
	Venous	52.43 ±4.08	-	-	34.20 ±5.82	-	-	24.78 ±3.94	-	-	18.55 ±2.77
pCO ₂ (mean±SE)	Arterial	26.05 ±2.73	30.85 ±3.47	33.78 ±4.36	41.58 ±2.23	41.15 ±3.37	40.83 ±3.74	39.35 ±5.02	39.83 ±5.52	36.33 ±7.06	30.18 ±9.90
	Venous	29.20 ±3.12	-	-	37.73 ±3.48	-	-	42.63 ±4.91	-	-	52.03 ±6.50
pH (mean±SE)	Arterial	7.426 ±0.04	7.380 ±0.03	7.333 ±0.02	7.253 ±0.01	7.207 ±0.01	7.210 ±0.02	7.199 ±0.05	7.178 ±0.05	7.209 ±0.07	7.227 ±0.09
	Venous	7.381 ±0.04	-	-	7.266 ±0.005	-	-	7.142 ±0.01	-	-	7.085 ±0.03

SUMMARY

The authors report the results of a series of investigations on the toxic effects produced in mice and rabbits by inhalation of Dimethyl-ether. Median lethal concentration (LC_{50}) and Median lethal time (LT_{50}) were determined in the mouse. Also the effects of DME inhalation on some physiological parameters (blood pressure, heart rate, blood gas and pH data) were evaluated in the rabbit.

ZUSAMMENFASSUNG

Die Autoren berichten über die Ergebnisse von Forschungen über die durch Inhalation von Dimethyläther bei Mäusen und Ratten ausgelösten toxischen Wirkungen. Bei der Maus hat man die mittlere letale Konzentration (LC_{50}) und die mittlere letale Zeit (LT_{50}) bestimmt. Man hat ebenfalls die Wirkungen der Dimethyläther-Inhalation auf einige physiologische Parameter (Blutdruck, Herzfrequenz, Blutgase und pH-Angaben) beim Kaninchen bewertet.

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