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Pharmacological Properties of Ametantrone

Właściwości farmakologiczne ametantronu

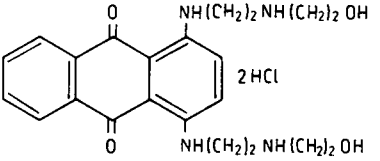
INTRODUCTION

In the recent years a great number of substances possessing aminoalkylaminoantraquinones (aa) structure have been synthetized (7). They are closely related to anthracycline antibiotics such as doxorubicine, daunorubicine and mitoxantrone (4). Though antracyclines are among the most useful cytotoxic anticancer drugs they have some serious side effects. The most important problem is their cardiotoxicity, which is characterized by ECG changes, cyanosis, dyspnea, irreversible heart failure (3, 10). The experiments carried out on animals have shown that aa possessed a significant anticancer activity agains *in vivo* trasplantable tumour models: L1210 and P388 lymphoid leukaemias, B16 melanoma, colon tumours, ovarian carcinoma and mammary adenocarcinoma (1, 14). The biological activity profile of these compounds resembles that of antracycline antibiotics (2). In addition they are cross resistant to the doxorubicin and daunorubicin-resistant leukaemia P388 sublines (13, 19). The ease of synthesis of the aa, the fact that both compounds have similar spectra of anticancer activity and high toxicity of anthracyclines evokes largely increased interest in aa substances. The particular attention is paid to their toxicity.

The following studies were designed to evaluate the toxicity and some general pharmacological properties of ametantrone dihydrochloride (synthetized in the Institute of Pharmaceutical Industry in Warsaw) in the healthly animals.

MATERIAL AND METHODS

The experiments were carried out on male Albino-Swiss mice and male Wistar rats. Ametantrone dihydrochloride (AM):



1,4-bis [2-(hydroxyethyl)-amino] ethyloamino -9, 10-anthracenedione dihydrochloride

synthetized in the Warsaw Institute of Pharmaceutical Industry, was administered i.p. in the volume of 0.1 ml/10 g (mice) or 0.5 ml/100 g (rats) of body weight. Control animals received equivalent volumes of solvent. The following experiments were carried out:

1. Acute toxicity

Acute toxicity was assayed as LD_{50} according to Litchfield and Wilcoxon (11). The number of survivals was evaluated after 24, 48, 72 hrs and additionally 7 and 14 days after single administration of ametantrone.

2. Cumulative toxicity

According to Lim et al. (10) mice were divided into two subgroups (5 animals in each). AM was given i.p. in a dose corresponding to 4.4% of acute LD_{50} for 4 consecutive days. Every four days the dose was increased gradually to 6.6%, 10% of LD_{50} etc. until all the animals in the tested groups died. C-LD_{50} was expressed as a percentage of median lethal dose/24 hr as described by Thompson (16).

3. General pharmacological properties

Mice ($n = 10$) received AM (i.p.) in the doses of 34 mg/kg (1/10 LD_{50}) and 17 mg/kg (1/20 LD_{50}) for 3 consecutive days. 60 min after administration of the last dose the experiments were performed and the following parameters were estimated:

A. Body temperature.
B. Spontaneous locomotor activity.
C. Amphetamine-induced hyperactivity (D,L-amphetamine, 5 mg/kg i.p).
D. Motor coordination.
E. Intestinal peristalsis (aqueous dilution of China ink, 1:1, p.o.).
F. Hexobarbital-sleeping time (hexobarbital sodium, 70 mg/kg i.p.).
G. Shaking behaviour (tranylcypromine 10 mg/kg i.p., 5-metoxytryptamine 5 mg/kg i.p.).

4. Subacute toxicity

AM in the doses of 3.8, 7.5, 15 and 30 mg/kg was injected i.p. for five consecutive days and after one week's interval again for three consecutive days. In the course of treatment the number of survivals in each group and body weight of each animal were estimated. The day after last treatment blood samples were taken by a heart puncture under a slight ether anaesthesia. The following parameters were assayed: hemoglobin content, hematocrit, the number of erythrocytes, leucocytes and platelets, the percentage of separate type of leucocytes, colour index (PCV), mean volume of erythrocyte (MCV), mean mass of hemoglobin (MCH), mean concentration of hemoglobin in erythrocyte (MCHC). The protein level in plasma according to Folin and Ciocalteau (5) and activity of AlAt and AspAt transaminases by the use of Reitman and Frankel (15) method were also measured. The animals were decapitated and the mass of internal organs (livers, kidneys, hearts, spleens) was estimated.

5. AM toxicity after twenty-onefold administration

Mice were injected i.p. with 1.8, 3.8, 7.5 and 15 mg/kg of AM once a day for 21 successive days. The observations were carried out as described above.

6. The influence of AM on aconitin-induced cardiac arrhythmias in rats

AM in the dose of 34 mg/kg was injected i.p. for 3 consecutive days. 60 min after the last dose the rats were anaesthetized with ethyl urethane (1.4 mg/kg, i.p.) and ECG changes were recorded by means of Simplicard electrocardiograph. As soon as the ECG became normal the rats received an i.v. injection of aconitin (Aconitin, Roth) in the dose of 2.5 and 10 mg/kg. The ECG was evaluated 30 and 60 sec later and additionally 2, 3, 10, 20, 30, 40 and 60 min after the aconitin injection. ECG changes induced by aconitin (control group) were compared with AM treated group.

7. The influence of AM on blood pressure, heart action and respiratory activity

Rats were anaesthetized with ethyl urethane (1.4 mg/kg, i.p). Blood pressure was measured using Condon manometer connected with the common carotid artery. Heart action estimated by means of Simplicard electrocardiograph. Respiration frequency was scored by Marey's tambour connected with trachea. AM was given i.v. in the raising doses from 2 do 32 mg/kg.

The results were evaluated statistically with Student's t test. LD_{50} was calculated according to Litchfield and Wilcoxon. C-LD_{50} was estimated by the use of Thompson method.

RESULTS

1. Acute toxicity (Table 1)

LD_{50} value of AM (i.p.) after 24 hr was calculated as 340 mg/kg and, respectively, after 48 hr — 260 mg/kg, 72 hr — 115 mg/kg. After seven days' period the tested drug became more toxic: 52.5 mg/kg and after 14 days — 40 mg/kg.

2. Cumulative toxicity

AM revealed strong tendency to cumulate in mice organism. C-LD_{50} value was 11.6% of acute LD_{50}.

3. General pharmacological properties:

A. AM given i.p. for 3 consecutive days in the dose of 34 mg/kg, but not 17 mg/kg caused a significant decrease of body temperature — about 1°C (Table 2).

B. AM (34 mg/kg) had no effect on spontaneous locomotor activity.

C. The experiments with AM in the dose of 34 mg/kg showed the significant diminution of amphetamine-induced hyperactivity in the first 30 min. (Table 3).

D. The tested drug did not disturb motor coordination.

E. No significant disturbances in the intestinal peristalsis were observed.

F. AM in the dose of 34 mg/kg caused a significant prolongation of hexobarbital-sleeping time in comparison with control mice (Table 4).

G. No influence on the number of head twitches was observed after AM administration.

Table 1. Acute intraperitoneal toxicity of ametantrone in mice

Time	LD_{50} (confidence limit) mg/kg
24 hrs	340.0 (322.3—358.7)
48 hrs	260.0 (221.2—293.9)
72 hrs	115.0 (155.3— 85.2)
7 days	52.5 (61.4— 44.9)
14 days	40.0 (44.0— 36.4)

Table 2. Effect of threefold administration of ametantrone

Treatment	Body temperature before drug administration	Mean ($x \pm$SE) of tempe		
		15 min.	30 min.	60 min.
Control	36.92 ±0.02	−0.07 ±0.04	−0.03 ±0.03	−0.09 ±0.05
Ametantrone 17 mg/kg	36.91 ±0.04	0.01 ±0.01	0.12 ±0.01	0.04 ±0.01
Control	36.59 ±0.07	0.19 ±0.06	0.08 ±0.05	0.09 ±0.05
Ametantrone 34 mg/kg	36.81 ±0.06*	−1.25 ±0.16*	−1.32 ±0.15*	−1.26 ±0.13*

* $p<0.001$ in comparison with control.

Table 3. The influence of ametantrone on amphetamine-induced locomotor hyperactivity in mice

Treatment	Dose mg/kg	0—30 min.	30—60 min.	60—90 min.	90—120 min.
Control	—	890.4 ±97.3	531.2 ±89.1	250.1 ±51.2	120.3 ±39.8
Ametantrone	17.0	713.1 ±81.5	391.8 ±51.2	309.0 ±69.8	98.7 ±35.2
Control	—	1007.8 ±131.8	617.9 ±111.9	422.8 ±60.6	284.0 ±40.5
Ametantrone	34.0	585.9 ±92.4*	365.0 ±67.8	401.0 ±63.2	291.3 ±58.9

* $p<0.05$ in comparison with control.

Table 4. The influence of ametantrone on hexobarbital sleeping-time

Treatment	Dose mg/kg	Mean value of sleeping time (in min.)
Control	—	31.0 ±4.5
Ametantrone	17	40.3 ±7.9
	34	74.7 ±9.3*

* $p<0.005$ in comparison with control.

4. Subacute toxicity

A. Mortality. AM in the doses of 3.8, 7.5, 15, 30 mg/kg induced mortality of 5, 5, 10 and 20% mice, respectively.

B. Body weight. AM given in the doses of 3.8 and 7.5 mg/kg inhibited the increase of body weight on the 5th day of the experiment, while a marked decrease of body weight was noted when the animals were treated with AM in the doses 15 and 30 mg/kg. After 1 week's interval body weight of mice injected with AM in the lower dose ranges (3.8, 7.5, 15 mg/kg) was similar to that of control

on mice body temperature

rature change (in °C)			
90 min.	120 min.	150 min.	180 min.
−0.09 ±0.04	−0.12 ±0.05	−0.14 ±0.04	−0.12 ±0.05
−0.12 ±0.09	0.16 ±0.08	−0.13 ±0.07	−0.14 ±0.04
0.05 ±0.08	0.07 ±0.05	−0.05 ±0.05	0.02 ±0.06
−1.73 ±0.19*	−1.35 ±0.08	−0.89 ±0.12*	−0.46 ±0.13*

animals. On the last day of experiment significantly lower increase of body weight was observed when mice were treated with AM in the doses of 7.5 and 15 mg/kg. But when the dose of 30 mg/kg was given, a gradual, time dependent loss of body weight was noted.

C. Transaminases activity (Table 5). AM (7.5, 15, 30 mg/kg) slightly increased AlAt and AspAt activity (about 20—30%).

D. Serum protein level (Table 5). AM in the doses of 3.8, 7.5, 15, 30 mg/kg did not change the total protein content in mice serum.

E. Blood morphology (Table 6). A decrease of the total number of leucocytes with marked lymphocytes reduction and increase of the percentage of segments and monocytes was observed after treatment with 15 and 30 mg/kg of AM. A tendency to thrombocytopenia was also observed. There was no effect on red cell count, hemoglobin and hematocrit value.

F. Mass of internal organs. AM decreased the mass of spleen. Mass of liver, kidneys and heart remained unchanged.

5. AM toxicity after twenty-onefold administration

A. Mortality. After twenty-onefold administration of AM in the doses of 1.8, 3.8, 7.5 and 15 mg/kg 10, 20, 30, 65% of of death cases were observed, respectively.

Table 5. Effect of eightfold administration of ametantrone on the AlAt and AspAt activity and proteins level in mice plasma

Treatment i.p.	AlAt i.u.	AspAt i.u.	Proteins g%
Control	56.6 ±3.33	45.2 ±1.72	8.03 ±0.22
Ametantrone 3.8 mg/kg	49.2 ±3.86	46.8 ±1.94	9.00 ±0.34*
Ametantrone 7.5 mg/kg	56.1 ±4.56	61.85 ±2.70	7.56 ±0.14
Ametantrone 15 mg/kg	66.8 ±3.10	56.3 ±1.97	7.66 ±0.11
Ametantrone 30 mg/kg	72.12 ±3.24*	57.5 ±1.39*	7.33 ±0.47

* $p < 0.05$ in comparison with control.

Table 6. Effect of eightfold administration of ametantrone

Treatment	Dose mg/kg	Hemoglobin $x \pm SE$ g/100 ml	Hematocrit $x \pm SE$ %	Erythrocytes $x \pm SE$ mln/mm³	Leucocytes $x \pm SE$ thous./mm³	Thrombocytes $x \pm SE$ thous./mm³
Control	—	10.9±0.59	36.6±1.74	7.45±0.37	5.94±0.58	181.5±10.00
Ametantrone	3.8	10.3±0.21	33.2±1.95	6.45±0.49	4.45±0.51	145.80±6.92*
	7.5	11.5±0.37	38.8±1.34	6.73±0.41	3.96±0.33	152.34±8.50*
	15.0	10.6±0.41	35.0±1.23	6.45±0.27*	3.10±0.28**	115.93±7.69**
	30.0	9.9±0.37	33.3±1.13	6.88±0.25	1.81±0.31**	157.7±15.05

* $p<0.05$. ** $p<0.001$ in comparison with control.

B. Body weight. AM in the doses of 3.8, 7.5 and 15 mg/kg gradually inhibited the increase of body mass in comparison with control groups. The effect was dose-dependent. The lower dose (1.8 mg/kg) was without marked influence on body weight.

C. Transminases activity (Table 7). AM (7.5 and 15 mg/kg) increased the AlAt activity. The activity of AspAt was found to be increased after AM in the doses of 1.8, 3.8, 7.5 and 15 mg/kg.

D. Serum protein level (Table 7). There was noted a slight, dose-independent enhancement of protein content in mice serum after twenty-onefold AM administration.

E. Blood morphology (Table 8). No significant influence of 1.8 mg/kg AM on blood morphology was noted, the only exception was the increase of thrombocytes count. AM when administered in doses of 3.8, 7.5 and 15 mg/kg diminished markedly leucocytes content. The same doses lowered hemoglobin concentration and hematocrit. There was observed the reduction of erythrocytes count (7.5 and 15 mg/kg), lower colour index and some changes of MCV and MCH (15 mg/kg).

F. Mass of internal organs. AM in doses of 1.8, 3.8 mg/kg was without any significant influence on the mass of internal organs. When administered in higher doses it decreased the mass of spleen (7.5 and 15 mg/kg) and liver (only 15 mg/kg).

6. The influence of AM on aconitin-induced cardiac arrhythmias in rats

AM (34 mg/kg) given i.p. for 3 consecutive days did not increase the aconitin-induced ECG changes.

7. Blood pressure, heart action and respiratory activity

AM when given i.v. in the raising doses (2, 4, 8, 16 and 32 mg/kg) exerted dose-dependent hypotensive action in rats. There was observed the increase of

on the blood morphology in mice

Leucogram (x ±SE); %			PCV x±SE	MCV x±SE μM³	MCH x±SE pg	MCHC x±SE %
S	L	M				
15.0±2.62	84.3±2.62	0.7±0.26	0.49±0.04	49.87±3.22	14.94±1.05	29.89±0.35
15.7±3.87	81.2±4.18	3.0±1.04*	0.55±0.04	53.21±3.36	16.60±1.24	31.07±0.42*
15.4±3.24	83.0±3.29	1.6±0.40*	0.58±0.03	59.15±3.63	17.54±1.02	29.69±0.23*
32.8±3.31**	63.6±3.07**	3.6±0.65**	0.55±0.02	54.68±1.98	16.56±0.60	30.32±0.31*
33.7±4.69	63.1±4.35	3.2±0.49*	0.48±0.02	48.80±2.11	14.50±0.66	29.74±0.47*

Table 7. Effect of twenty-onefold treatment with ametantrone on the AlAt and AspAt activity and proteins level in mice plasma

Treatment i.p.	AlAt i.u.	AspAt i.u.	Proteins g%
Control	52.80 ±1.83	40.00 ±1.55	8.04 ±0.10
Ametantrone 1.8 mg/kg	55.70 ±3.72	47.25 ±1.78	11.00 ±0.28*
Ametantrone 3.8 mg/kg	53.80 ±2.50	47.00 ±2.16	10.05 ±0.35*
Ametantrone 7.5 mg/kg	62.20 ±3.91	67.15 ±1.72*	8.84 ±0.24*
Ametantrone 15 mg/kg	88.42 ±4.42	73.92 ±2.83	8.61 ±0.22*

*$p<0.05$ in comparison with control.

Table 8. Effect of twenty-onefold treatment with

Treatment	Dose mg/kg	Hemoglobin $x \pm SE$ g/100 ml	Hematocrit $x \pm SE$ %	Erythrocytes $x \pm SE$ mln/mm³	Leucocytes $x \pm SE$ thous./mm³	Thrombocytes $x \pm SE$ thous./mm³
Control	—	12.3±0.27	40.3±0.87	6.81±0.34	6.75±0.89	261.09±10.33
Ametantrone	1.8	11.6±0.27	38.6±0.73	7.01±0.25	5.87±0.80	418.93±15.37**
	3.8	10.5±0.65*	35.4±1.89*	5.99±0.28	3.78±0.38**	395.30±24.42
	7.5	9.7±0.34**	32.3±1.03**	5.48±0.33*	4.40±0.44*	295.92±20.43
	15.0	7.2±0.79**	23.5±2.74**	4.82±0.46*	2.05±0.33**	291.93±19.06

* $p<0.05$. ** $p<0.001$ in comparison with control.

respiratory frequency by about 50—60%. The dose of 32 mg/kg (i.e. 1/10 LD_{50}) caused primarily the bradycardia, and next the heart action was stopped, which resulted in the death of rats.

DISCUSSION

Ametantrone is an antineoplastic agent with activity against a great number of solid transplantable tumours in animals (6, 13). The studies reported here were aimed at establishing the general pharmacological properties and toxicologic profile of this drug. Acute toxicity in mice was assayed as LD_{50} 24, 48 and 72 hrs after i.p. administration of AM and was, respectively: 340, 260 and 115 mg/kg. In the experiments AM appeared to be less toxic to mice than mitoxantrone and daunorubicin (8, 9). Watkins (17, 18) reported that intravenous LD_{50} value for mitoxantrone (5 mg/kg) was sevenfold lower than for AM (34 mg/kg). AM administered i.v. at a dose of 80 mg/kg caused immediate convulsions lasting about 10 sec., which were followed by respiratory distress and sometimes immediate death (7). Even extremely high doses (645 mg/kg) of AM, when injected i.p., did not result in such symptoms. Convulsions and death were also evoked by mitoxantrone given i.v. at the dose of 142 mg/kg. The authors (7) noted that the single dose of AM administered i.v., which was within the therapeutic dose range when injected i.p., might cause an immediate death. In the studies presented here AM was administered i.v. in doses ranging from 2 to 32 mg/kg, in rats being in urethane anaesthesia, to evaluate its influence on blood pressure. There was observed mild, dose-related hypotensia lasting 2 to 9 min. The dose of 32 mg/kg (1/10 LD_{50} i.p.) caused rats' death. To study the cumulative properties of AM mice were given the drug in raising dose levels. The tendency to cumulation was well observable, C-LD_{50} value equalled 11.6% of acute LD_{50}/ /24 hr. The extent of cumulation was lower as compared with mitoxantrone (C-LD_{50} = 6.8% LD_{50}). For examination of some general pharmacological properties of AM mice were treated with the drug for 3 consecutive days

ametantrone on the blood morphology in mice

Leucogram (x ±SE); %			PCV x±SE	MCV x±SE μM^3	MCH x±SE pg	MCHC x±SE %
S	L	M				
11.0±2.04	81.1±2.19	1.9±0.48	0.62±0.03	60.22±2.74	18.50±0.88	30.66±0.17
7.9±1.55	91.4±1.59	0.7±0.33	0.56±0.02	55.54±1.87	16.74±0.55	30.16±0.24
8.5±1.54	90.6±1.66	0.9±0.35	0.58±0.02	58.80±0.95	17.51±0.46	29.73±0.43
29.2±3.12**	63.3±3.55**	2.5±0.60	0.61±0.04	60.64±3.73	18.34±1.12	30.27±0.24
34.3±2.81**	61.8±2.96**	3.8±0.98	0.50±0.03*	48.67±3.14*	15.00±0.93*	30.83±0.42

(34 mg/kg). The following changes were noted: mild hypothermia, inhibited amphetamine-induced hypereactivity and prolonged hexobarbital-sleeping time. The above can suggest the influence of AM on central nervous system. No influence on intestinal peristalsis was observed. However Loesch (12) reported the incidence of diarrhea in dogs given AM.

We have also carried out 8 and 21 days' experiments. The influence of tested drug on blood morphology was estimated. In 8 days' experiment there were found numerous hematologic changes consisting of the decrease of the total number of leucocytes with lymphocytes reduction and increase of the percentage of segments and monocytes. Similar findings have been observed in experimental animals with mitoxantrone and daunorubicine (8). Moreover, contrary to mitoxantrone AM had no significant effect on red cells count. The eight fold injection of AM in the doses of 15 and 30 mg/kg resulted in mortality of 10 and 20% mice, respectively, the lower doses i.e. 3.8 and 7.5 mg/kg had no lethal effect. While daunorubicin caused 100% death at the dose 3 mg/kg, the same was the effect of 4 mg/kg of mitoxantrone. AM inhibited the increase of body weight when given i.p. (7.5 and 15 mg/kg) for 8 or 15 consecutive days. In the dose of 30 mg/kg it induced time-related loss of body mass. Daunorubicin and mitoxantrone induced similar changes in lower doses. The influence of these compounds on the mass of internal organs was similar. AM, daunorubicin and doxorubicin reduced the mass of spleen. The drugs had no influence on the heart, liver and kidneys mass, the only exception was daunorubicin which diminished the liver mass (1, 8).

In chronic toxicity studies mice were given 21 consecutive i.p. injections of AM in the doses of 1.8, 3.8, 7.5 and 15 mg/kg. Dose-dependent lethal effect and reduction of body weight were observed. The dose of 1.8 mg/kg which caused 10% lethal effect had influence neither on the body weight nor the mass of internal organs. That dose did not change the transaminases activity and the peripheral blood morphology. The higher doses diminished the mass of the spleen, increased the transaminases activity (about 60—70%) and caused some changes in hematological parameters. Leucopenia and low-grade anemia were

observed. The influence of AM on platelet count was no univocal. After eightfold injection thrombocytopenia occurred. The degree of thrombocytopenia was mild and appeared to be unrelated to the dose of AM administered. But there was noted a slight enhancement of thrombocytes at 21 days' experiment. Repeated doses of AM resulted in blue discoloration of mice viscera. The discoloration was related to the dose of AM administered and the time of administration. The most frequently described AM side effects in animals were: dose-related reversible leucopenia, thrombocytopenia, blue urine, blue stools, diarrhea, anorexia, weight loss and hypothermia (6, 12). AM was less cardiotoxic to animals than anthracycline antibiotics (4, 20). In our study threefold administration of the drug did not change the aconitin induced arrhythmias. Some authors (18) suggested that daunorubicin and doxorubicin cardiotoxicity was caused by aminosugar group which was absent in the chemical structure of AM. The ratio of the minimal cumulative cardiotoxic dose to optimum therapeutic cumulative dose in the P388 leucaemia model in rats was 1.44 and 1.03 for daunorubicine and doxorubicine. On the contrary, for AM it was 2.18, which proves lower toxicity for AM (4).

Summing up, the relatively low toxicity of aminoalkylaminoantraquinones compounds and their biological activity resemblance to the anthracycline antibiotics merit further oncological studies.

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STRESZCZENIE

Dwuchlorowodorek ametantronu, strukturalny analog antybiotyków antracyklinowych, jest związkiem o działaniu przeciwnowotworowym. Przeprowadzone badania miały na celu określenie właściwości ogólnofarmakologicznych i toksycznych tego leku. Oceniono toksyczność ostrą i kumulatywną, przeprowadzono testy zachowania się zwierząt, a także zbadano toksyczność podostrą (wpływ na masę ciała zwierząt, przeżycie zwierząt, morfologię krwi, poziom białek i aktywność enzymów w surowicy krwi). Badanie kardiotoksyczności, będącej najbardziej uciążliwym objawem ubocznym antracyklin, przeprowadzono na szczurach otrzymujących akonitynę. Uzyskane wyniki wskazują na mniej zaznaczoną toksyczność ametantronu w porównaniu z daunorubicyną, doksorubicyną i mitoksantronem.

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