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A STUDY OF EFFECTS OF HARMIDINE ON C.N.S. OF ANIMALS

M. K. BABAR* AND Z. QURESHI
Pharmacology Department, J.P.M.C., Karachi

ABSTRACT:

Effect of various doses of harmidine, a harmala alkaloid were evaluated on voluntary motor activity of rats, and on normal body temperature of mice. It was observed that harmidine antagonised the motor activity decreasing, Ptosis and miosis producing and hypothermic effects of reserpine like M.A.O. Inhibitors, as well as it prevented these effects of reserpine through a direct stimulant effect like amphetamine and imipramine. Further studies are suggested.

Introduction

Various medicinal properties have been ascribed to the seeds of Peganum harmala from the time of Dioscorides, Ist Century A.D. [13] Several alkaloids as harmine, harmaline and harmalol have been isolated from the roots and seeds of this plant. The pharmacological properties of these alkaloids were first investigated by Gunn in 1913. Siddiqui in 1962, isolated a new alkaloid harmidine from the seeds of P. harmala obtained from West Punjab. He reported that harmaline, was actually a mixture of bar-mine (15%) and harmidine (85%). The preliminary pharmacological activities of harmidine were carried out by Oureshi, in 1969. She found that some pharmacological actions of harmidine were similar to those of harmine and harmaline but the therapeutic index of harmidine was 4 times higher than that of harmine. Harmine and Harmaline have been shown to be monoamine oxidase inhibitors (MAO-I).[15] Akhtar (1971) suggested that like other harmala alkaloides, harmidine was most probably also a MAO-I. It therefore seemed interesting to investigate the effects of harmidine.

Materials and Methods

A) Animals used:

Male albino rats, weighing between 250-350 G and 3-4 months of age and male albino mice, weighing between 30-40 G. and 3-4 months of age, reared at 27°C

*Present address: Quaid-e-Azam Medical College, Bahawalpur.

temperature in the animal house of J.P.M.C. Karachi were used. They were fed ad lib. with food and water.

B) Drugs used:

i) Harmidine lid
Supplied by the Chemistry Department, University of Karachi.

ii) Research (Serpasil), Ciba Laboratories (Pak.) Ltd. Karachi, was supplied as 23 mg/ml in solution form.

iii) Solution of harmidine Hcl were prepared just before use in distilled water and concentrations expressed in terms of their bases. Further dilutions were made in normal saline.

C) Grouping of animals:

The animals were divided into 8 groups, including 25 rats in each group for evaluation of effect on voluntary motor activity and 10 mice/group for evaluation of effect on normal body temperature.

D) Experimental procedure:

I) For evaluation of effects on voluntary motor activity

The animals were left in the chamber of actophotometer about 30 minutes before starting the experiment to get them adopted to the new surroundings so that their exploratory activity should have come to a minimum. In all groups such signs as ptosis or miosis, shivering and tone of muscles were also noted at the same time.

II) For evaluation of effect on normal body temperature

The room temperature was kept between 26°C-27°C. The rectal temperature of animal was recorded with a clinical thermometer, kept in the rectum for 1 minute and three readings were taken each after 1 minute interval and the mean was then taken. Animals showing much variation from the mean were discarded. The animals were also observed for such signs as ptosis ormiosis and shivering.

Observations and Results

A) Effect on voluntary motor activity of rats:

i) There was significant increase in motor activity of saline treated rats at 0 minute after treatment as compared to untreated group ($P<.01$). There was no significant

difference between untreated and saline treated group at other time intervals (P <.1) Table-I, Fig.l.

ii) In rats treated with 3 mg/kg B.W. 6 mg/kg B.W. and 12 mg/kg B.W doses of harmidine, there was significant decrease in motor activity (P < .01). The effect started at 15 minutes after administration of the drug and remained upto 2 hours with 3 mg dose and upto 24 hours (Table-I) with 6 and 12 mg dose. There was no ptosis or miosis in all the animals treated with harmidine alone but shivering, tremors and increased tone of skeletal muscles were present.

iii) In rats treated with reserpine, 2 mg/kg B.W doses, afterone hour, there was significant decrease in motor activity (P < .01). This effect of reserpine remained upto 24 hours (Table-II Fig). There was ptosis and miosis in 80% rats at one hour interval and in 100% rats at 24 hours.

iv) In rats treated with harmidine (6 mg/kg B.W) one hour after reserpine (2 mg/kg B.W) there was significant decrease in motor activity (P < .01) at all time intervals (Table-II). However at one hour after harmidine treatment and 2 hours after reserpine treatment, there was no ptosis or miosis present in any animal. This effect of harmidine persisted upto 24 hours when there was ptosis and miosis in only 40% rats.

v) In rats treated with reserpine, one hour after the harmidine, there was significant increase in motor activity at 30 minutes, 1 hour and 2 hours intervals after reset-pine treatment (P < .01) as compared to saline treated animals, reserpine-alonetreated and harmidine-alone-treated groups. Ptosis and miosis were not present at one hour interval. Then it was present in 40% rats at 2 hours interval. At 4 hours and 24 hours intervals after reserpine treatment there was significant (P < 0.01) decrease in motor activity as compared to saline treated group, but there was significant increase in motor activity as compared to reserpine alone treated group (P < .01) Table-III, Fig.l. Also there was significant increase in motor activity as compared to harmidine-alone-treated group (Table-IV), at 4 hours interval but there was significant decrease at 24 hours intervals. Ptosis and Miosis were present in 60% rats at 4 hours interval and in 100% rats at 24 hours interval.

B) Effect on normal body temperature of mice:

i) There was no significant difference (P > .1) of body temperature in mice of untreated group and mice of saline treated group at all time intervals, Table-VI, Fig.3.

ii) There was no significant fall of body temperature ($P > .1$) in mice treated with 3 mg/kg B.W. dose of harmidine at all time intervals (Table-V), Fig. 3. Ptosismiosis, shivering and tremors were not present.

iii) The 6 mg/kg B.W and 12 mg/kg B.W. doses of harmidine produced a significant fall ($P < .01$) in body temperature. The effect started at 15 minutes and remained upto 4 hours (Table-II, Fig). There was no ptosis or miosis but shivering and tremors were present.

iv) In mice treated with 2 mg/kg B.W dose of reserpine, there was a significant fall in body temperature at 2 horns as compared to saline treated group ($P < .01$) Table-VI), Fig. 4. This effect lasted upto 24 hours. Plosis and miosis were present.

v) In mice treated with harmidine, one hour after reserpine, there was significant increase in body temperature at one hour to 4 hours intervals after harmidine treatment as compared to reserpine-alone-treated group (Table VII), Fig. 4, and harmidine-alone-treated group (Table VIII).

vi) In mice treated with resrpine, one hour after harmidine. There was significant fall in body temperature from 0 minute after reserpine treatment upto 60 minutes as compared to reserpine- alone treated group (Table-VII), Fig.4, but from 2-24 hours intervals there was no significant difference in temperature (Table-VII), Fig. 4. From 30 minutes to 2 hours interval, there was significant increase in body temperature as compared to harmidine alone treated group, then the temperature started falling (Table-VIII, Fig.5).

Discussion

Central nervous system depressants, lime hypnotics, sedatives and tranquillizers, decrease voluntary motor activity of experimental animals.[6] Impiramine, a tricyclic antidepressant, produces, hypothermia, ataxia and decreases the voluntary motor activity of Lab. animals.[2] The decrease in voluntary motor activity, Ptosis, miosis and hypothermia induced by reser ine, are antagonized by MAO - Inhibitors only if given sometime before reserpine[4,7,8,10]. C.N.S. stimulants like amphetamine and antidepressants like imipramine can antagonize and depressant effects of reserpine both ways, either given before reserpine or after reserpine.[14]

Harmine and harmaline have been shown to be MAO inhibitors.[16] Holzer and Horny kiewice (1959) have shown that harmine raised the brain 5-HT and NE concentration (cited by Robson and Stacy, 1962). Akhtar (1971) observed a rise in hypothalmic content of 5-HT and NE in rats treated with harmidine and suggested that like other harmala

alkaloids harmidine most probably is also a MAO inhibitor. In present studies harmidine decreased the voluntary motor activity of rats significantly ($P < .01$), treated with 3 mg, 6 mg and 12 mg/kg B.W doses of harmidine. Shivering, tremors and increased tone of skeletal muscles were present, but there was no ptosis or miosis. Possibly this spacticity of the limbs could be the cause of decrease in voluntary motor activity of rats.

In rats treated with harmidine after reserpine although the motor activity decreased significantly ($P < 01$), Fig. 2, one hour after reserpine and remained significantly decreased upto 24 hours but ptosis and miosis were absent at 2 hours and 4 hours intervals after harmindine. This shows that harmidine did antagonize the depressant effect of reserpine to some extent and most probably through its direct stimulant effect on brain stem and most probably through the release of NE as NE release has also been shown by harmine and harmaline.[12] In rats treated with reserpine after harmidine, the motor activity was increased significantly ($P < .01$) after one hour and ptosis and miosis were also not present. These results indicate that harmidine pretreatment had increased NE levels of brain, most probably through MAO inhibition.

In mice treated with 6 mg/kg B.W and 12 mg/kg B.W doses of harmidine there was significant fall in body temperature ($P < .0l$) and shivering and tremors were present. This hypothermic effect of harmidine could be due to increased concentration of NE at temperature regulating centre in hypothalamus, brought about by MAO inhibition or through release of NE or through both. Feldberg and Myers (1964) have shown that even very small quantities of NE produced hypothermia in fever as well as when the temperature was normal. Physiologically also whenever there is hypothermia, shivering starts to increase the metabolic heat production. In mice treated with harmidine after reserpine, harmidine effectively antagonized the reserpine induced hypothermia ($P < .05$) most probably through its direct stimulant action like amphetamine and impiramine. In mice treated with reserpine after harmidine again there was an increase in body temperature. From this observation it can be inferred that harmidine most probably also antagonized the reserpine induced hypothermia in-directly through MAO inhibition but this action of harmidine is a weaker action. There is also a possibility that shivering, tremors and increased spasticity of skeletal muscles in rats and mice by harmidine is brought about by a central anti-dopaminergic action. Further studies in this respect are required to determine the possible mechaism of action and the site of action of harmidine in the brain.

Acknowledgement

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Table-I

Showing effect on voluntary motor activity of rats

Time of observation after treatment	Mean number of movements * ± S.E. untreated group(1)	Mean number of movements ± S.E. Saline treated group(2)	Percentage decrease or increase	'P' Value	Mean number of movements ±S.E. harmidine 3 mg/kg treated group(3)	Percentage decrease or increase as compared to Saline treated group	'P' Value	Mean number of movements ± S.E. Harmidine 6 mg/kg treated group (4)	Percentage decrease or increase as compared to saline treated group	'P' Value	Mean number of movements ± S.E. Harmidine 12 mg/kg treated group(5)	Percentage decrease or increase as compared to saline treated group	'P' Value
0 minute	86 ± 2.2	95 ± 1.9	10.4% Increase	P < .01	90 ± 2.4	5.2% Decrease	P > .1	90 ± 2.2	5.2% Decrease	P > .1	91 ± 1.8	4.2% Decrease	P > .1
15 minutes	73 ± 1.7	70 ± 1.7	4.1% Decrease	P > .1	51 ± 1.56	27% Decrease	P < .01	45 ± 2.3	35.7% Decrease	P < .01	31 ± 1.3	55.7% Decrease	P < .01
30 minutes	72 ± 1.0	69 ± 1.5	4.1% Decrease	P > .1	45 ± 2.3	34.7% Decrease	P < .01	38 ± 1.4	45% Decrease	P < .01	18 ± 1.4	74% Decrease	P < .01
60 minutes	60 ± 1.4	64 ± 2.2	6.6% Increase	P > .1	41 ± 1.4	36% Decrease	P < .01	34 ± 1.0	47% Decrease	P < .01	15 ± 1.0	76% Decrease	P < .01
2 hours	55 ± 2.0	54 ± 1.4	1.8% Decrease	P > .1	41 ± 1.26	24% Decrease	P < .01	27 ± 1.0	50% Decrease	P < .01	14 ± 1.3	74% Decrease	P < .01
4 hours	64 ± 1.8	61 ± 1.0	4.6% Decrease	P > .1	56 ± 1.26	8% Decrease	P > .1*	30 ± 0.89	50% Decrease	P < .01	26 ± 0.83	57.3% Decrease	P < .01
24 hours	88 ± 0.9	90 ± 2.2	2.2% Increase	P > .1	90 ± 1.4	-	-	75 ± 1.0	17% Decrease	P < .01	72 ± 1.4	20% Decrease	P < .01

*Standard Error (S.E.)

Table-II

Showing effect on voluntary motor activity of rats

Time of observation after treatment	Mean number of movements * ± S.E. Saline treated group	Mean number of movements ± S.E. Reserpine 2 mg/kg treated group (6)	Percentage increase or decrease as compared to saline treated group	'P' Value	Mean number of movements ± S.E. harmidine after reserpine treated group (7)	Percentage increase or decrease as compared to Saline treated group	'P' Value	Mean number of movements ± S.E. reserpine after harmidine treated group (8)	Percentage increase or decrease as compared to saline treated	'P' Value
0 minute	95 ± 1.9	91 ± 1.8	4.2% Decrease	P > .1	38 ± 1.7	60% Decrease	P < .01	34 ± 1.0	65.2% Decrease	P < .01
15 minutes	70 ± 1.7	73 ± 1.7	4.2% Increase	P > .1	14 ± 1.8	80% Decrease	P < .01	48 ± 1.7	31.4% Decrease	P < .01
30 minutes	69 ± 1.5	68 ± 1.0	1.4% Decrease	P < .1	6 ± 1.2	91.3% Decrease	P < .01	82 ± 1.8	18.8% Increase	P < .01
60 minutes	64 ± 2.2	48 ± 1.4	25% Decrease	P < .01	2 ± 0.54	96.8% Decrease	P < .01	80 ± 2.3	25% Increase	P < .01
2 hours	54 ± 1.4	8 ± 1.2	85% Decrease	P < .01	0	100% Decrease	P < .001	63 ± 1.4	16.6% Increase	P < .01
4 hours	61 ± 1.0	5 ± 0.64	91.3% Decrease	P < .01	0	100% Decrease	P < .001	53 ± 2.0	13.0% Decrease	P < .01
24 hours	90 ± 2.2	5 ± 0.14	94.4% Decrease	P < .01	4 ± 0.54	95.5% Decrease	P < .01	26 ± 1.4	71.0% Decrease	P < .01

*S.E. = Standard Error

Table-III

Showing comparison of voluntary motor activity of rats

Time of observation after treatment	Mean number of movements * ± S.E. 2 mg/kg treated group	Mean number of movements ± S.E. Harmidine after reserpine treated group	Percentage increase or decrease as compared to reserpine treated group	'P' Value	Mean number of movements ± S.E. reserpine after Harmidine group	Percentage increase or decrease as compared to Reserpine treated group	'P' Value
0 minute	91 ± 1.8	38 ± 1.7	58.2% Decrease	P < .01	34 ± 1.0	62.6% Decrease	P < .01
15 minutes	73 ± 1.7	14 ± 1.8	80.8% Decrease	P < .01	48 ± 1.7	34.2% Decrease	P < .01
30 minutes	68 ± 1.0	6 ± 1.2	91% Decrease	P < .01	82 ± 1.8	20.5% Increase	P < .01
60 minutes	48 ± 1.4	2 ± 0.54	95.8% Decrease	P < .01	80 ± 2.3	66.6% Increase	P < .01
2 hours	8 ± 1.2	0	100% Decrease	P < .001	63 ± 1.3	87.5% Increase	P < .001
4 hours	5 ± 0.64	0	100% Decrease	P < .001	53 ± 2.00	90.5% Increase	P < .001
24 hours	5 ± 0.14	4 ± 0.54	20% Decrease	P = .01	26 ± 1.4	80.7% Increase	P < .001

*S.E. = Standard Error

Table-IV

Showing comparison of voluntary motor activity of rats

Time of observation after treatment	Mean number of movements * ± S.E. 6 mg/kg treated group (4)	Mean number of movements ± S.E. Harmidine after re-serpine treated group	Percentage increase or decrease as compared to Harmidine treated group	'P' Value	Mean number of movements ± S.E. reserpine after Harmidine treated group	Percentage increase or decrease as compared to harmi-dine treated group	'P' Value
0 minute	90 ± 2.2	38 ± 1.7	57.7% Decrease	P < .01	34 ± 1.0	62.2% Decrease	P < .01
15 minutes	45 ± 2.3	14 ± 1.8	68.8% Decrease	P < .01	48 ± 1.7	6.6% Decrease	P < .1
30 minutes	38 ± 1.8	6 ± 1.2	84.2% Decrease	P < .01	82 ± 1.8	52.3% Increase	P < .01
60 minutes	34 ± 1.0	2 ± 0.54	94% Decrease	P < .01	80 ± 2.3	42.4% Increase	P < .01
2 hours	27 ± 1.0	0	100% Decrease	P < .001	63 ± 1.4	57% Increase	P < .01
4 hours	30 ± 0.89	0	100% Decrease	P < .001	53 ± 2.0	43.3% Increase	P < .01
24 hours	75 ± 1.0	4 ± 0.54	94.6% Decrease	P < .01	26 ± 1.4	65.3% Decrease	P < .01

*S.E. = Standard Error

Table-V

Showing effect on normal body temperature of mice

Time of observation after treatment	Mean rectal temperature °C ± S.E. untreated group	Mean rectal temperature °C ± S.E. saline treated group	Increase or decrease °C	'P' Value	Mean rectal temperature °C ± S.E. harmidine 3 mg/kg treated group	Increase or decrease as compared to saline treated group °C	'P' Value	Mean rectal of temperature °C ± S.E. harmidine 6 mg/kg treated group	Increase or decrease as compared to saline treated group °C	'P' Value	Mean rectal temperature °C ± S.E. harmidine 12 mg/kg treated	Increase or decrease as compared to saline treated group °C	'P' Value
0 minute	37.4 ±0.18	37.33 ±0.69	0.07 Decrease	P > .1	37.35 ± 0.1	0.02 Increase	P > .1	37.26 ± 0.63	0.07 Decrease	P > .1	37.12 ± 0.1	0.21 Decrease	P > .1
15 minutes	37.5 ±0.22	37.5 ± 0.1	–	–	37.23 ± 0.06	0.27 Decrease	P > .1	36.3 ± 0.1	1.2 Decrease	P < .01	35.12 ± 0.1	2.38 Decrease	P < .01
30 minutes	37.54 ±0.14	37.57 ± 0.14	0.03 Decrease	P > .1	37.42 ± 0.07	0.15 Decrease	P > .1	35.1 ± 0.14	2.47 Decrease	P < .01	34.19 ± 0.14	3.38 Decrease	P < .01
60 minutes	37.55 ±0.17	37.82 ± 0.08	0.27 Increase	P > .1	37.3 ± 0.04	0.52 Decrease	P > .1	34.61 ± 0.14	3.21 Decrease	P < .01	33.61 ± 0.14	4.21 Decrease	P < .01
2 hours	37.45 ± 0.24	37.54 ± 0.58	0.09 Increase	P > .1	37.32 ± 0.08	0.22 Decrease	P > .1	35.67 ±0.2	1.87 Decrease	P < .01	34.61 ± 0.14	2.93 Decrease	P < .01
4 hours	37.48 ± 0.14	37.28 ± 0.08	0.2 Decrease	P > .1	37.22 ± 0.05	0.06 Decrease	P > .1	36.5 ± 0.17	0.78 Decrease	P < .01	35.37 ± 0.06	1.91 Decrease	P < .01
24 hours	37.35 ± 0.12	37.2 ± 0.08	0.15 Decrease	P > .1	37.1 ± 0.05	0.1 Decrease	P > .1	37.04 ± 0.14	0.06 Decrease	P > .1	36.6 ± 0.14	0.6 Decrease	P > .1

S.E. = Standard Error

Table-VI
Showing effect on normal body temperature of mice

Time of observation after treatment	Mean rectal temperature °C ± S.E. treated group	Mean rectal temperature °C ± S.E. reserpine 2 mg/kg treated group	Increase or decrease °C as compared to saline treated group	'P' Value	Mean rectal temperature °C ± S.E. harmidine after reserpine treated group	Increase or decrease as compared to Saline treated °C	'P' Value	Mean rectal of temperature °C ± S.E. reserpine after harmidine treated group	Increase or decrease as compared to saline treated group	'P' Value
0 minute	37.33 ± 0.69	37.45 ± 0.08	0.12 Increase	P > .1	37.0 ± 0.17	0.33 Decrease	P > .1	34.61 ± 0.14	2.72 Decrease	P < .01
15 minutes	37.5 ± 0.1	37.39 ± 0.05	0.11 Decrease	P > .1	37.4 ± 0.17	0.1 Decrease	P > .1	35.0 ± 0.1	2.5 Decrease	P < .01
30 minutes	37.57 ± 0.14	37.45 ± 0.09	0.12 Decrease	P > .1	37.5 ± 0.17	0.07 Decrease	P > .1	35.6 ± 0.17	1.97 Decrease	P < .01
60 minutes	37.82 ± 0.08	37.25 ± 0.06	0.57 Decrease	P > .1	37.6 ± 0.14	0.22 Decrease	P > .1	36.0 ± 0.2	1.82 Decrease	P < .01
2 hours	37.54 ± 0.58	36.89 ± 0.09	0.65 Decrease	P > .1	37.6 ± 0.14	0.06 Decrease	P > .1	36.5 ± 0.17	1.04 Decrease	P < .01
4 hours	37.28 ± 0.08	35.5 ± 0.09	1.78 Decrease	P < .01	37.4 ± 0.17	0.12 Decrease	P > .1	36.0 ± 0.21	1.28 Decrease	P < .01
24 hours	37.2 ± 0.08	36.0 ± 0.04	1.2 Decrease	P < .01	36.0 ± 0.2	1.2 Decrease	P < .01	36.0 ± 0.14	1.2 Decrease	P < .01

*S.E. = Standard Error

Table-VII

Showing comparison of normal body temperature of mice

Time of observation after treatment	Mean rectal tempera-rature °C ± S.E. respire treated group	Mean rectal tempera-rature °C ± S.E. harmidine treated group	Increase or decrease °C as compared to reserpine treated	'P' Value	Mean rectal tempera-ture °C ± S.E. reserpine after harmidine treated	Increase or decrease °C as compared to reserpine treated	'P' Value
0 minute	37.45 ± 0.08	37.0 ± 0.17	0.45 Decrease	P < .05	34.61 ± 0.14	1.84 Decrease	P < .01
15 minutes	37.39 ± 0.05	37.4 ± 0.17	0.01 Increase	P > .1	35.0 ± 0.1	2.39 Decrease	P < .01
30 minutes	37.45 ± 0.09	37.5 ± 0.17	0.05 Increase	P > .1	35.6 ± 0.17	1.85 Decrease	P < .01
60 minutes	37.25 ± 0.06	37.6 ± 0.14	0.35 Increase	P < .05	36.0 ± 0.2	1.25 Decrease	P < .01
2 hours	36.89 ± 0.09	37.6 ± 0.14	0.71 Increase	P < .01	36.5 ± 0.17	0.39 Decrease	P > .1
4 hours	35.5 ± 0.09	37.4 ± 0.17	1.9 Increase	P < .01	36.0 ± 0.2	0.5 Increase	P = .05
24 hours	36.0 ± 0.04	36.0 ± 0.2	–	–	36.0 ± 0.14	–	–

*S.E. = Standard Error

Table-VIII
Showing comparison of normal body temperature of mice

Time of observation after treatment	Mean rectal tempera-rature °C ± S.E. harmidine 6 mg/kg treated group	Mean rectal tempera-rature °C ± S.E. harmidine treated group	Increase or decrease °C as compared to harmidine treated group	'P' Value	Mean rectal tempera-ture °C ± S.E. reserpine after harmidine treated group	Increase or decrease as compared to harmidine treated °C	'P' Value
0 minute	37.26 ± 0.63	37.0 ± 0.17	0.26 Decrease	P > .1	34.61 ± 0.14	2.65 Decrease	P < .01
15 minute	36.3 ± 0.1	37.4 ± 0.17	1.1 Increase	P < .01	35.0 ± 0.1	1.3 Decrease	P < .01
30 minute	35.1 ± 0.14	37.5 ± 0.17	2.4 Increase	P < .01	35.6 ± 0.17	0.5 Increase	P < .05
60 minutes	34.61 ± 0.14	37.6 ± 0.14	2.99 Increase	P < .01	36.0 ± 0.2	1.39 Increase	P < .01
2 hours	35.67 ± 0.2	37.6 ± 0.14	1.93 Increase	P < .01	36.5 ± 0.17	0.83 Increase	P < .01
4 hours	36.5 ± 0.17	37.4 ± 0.17	0.9 Increase	P < .01	36.0 ± 0.2	0.5 Decrease	P > .1
24 hours	37.04 ± 0.14	36.6 ± 0.2	1.04 Decrease	P < .01	36.0 ± 0.14	1.04 Decrease	P < .01

*S.E. = Standard Error

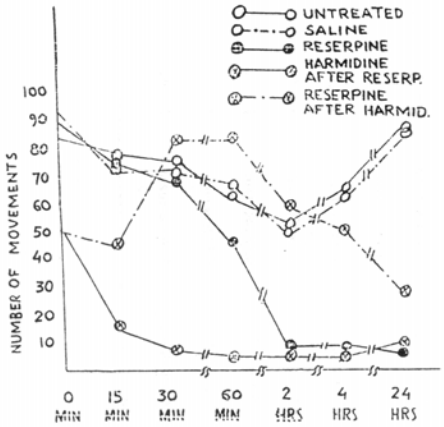

Fig. 1: Effect on voluntary motor activity.

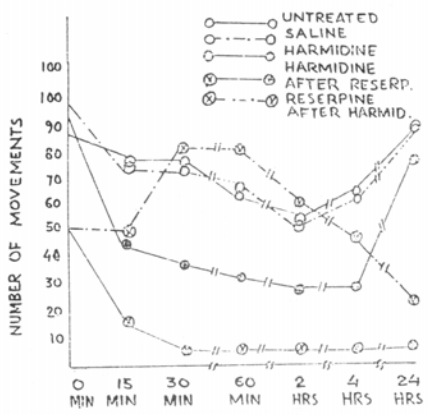

Fig. 2: Effect on voluntary motor activity.

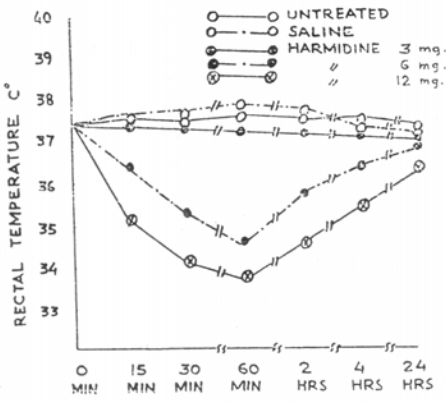

Fig. 3: Effect on voluntary motor activity.

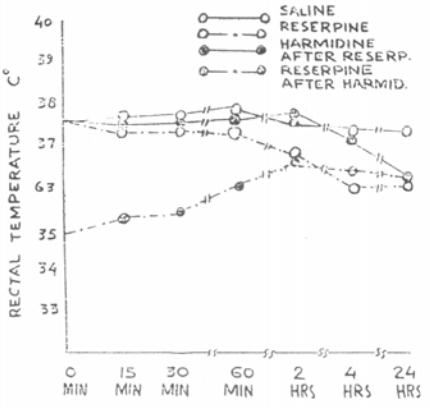

Fig. 4: Effect on normal body temperature.

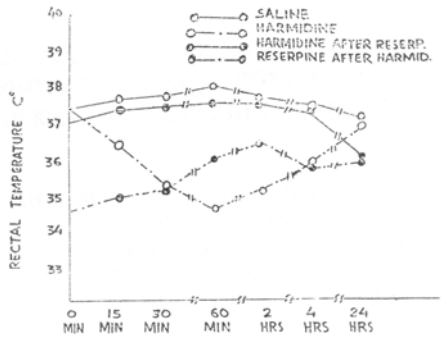

Fig. 5: Effect on normal temperature.

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