



PHARMACOLOGICAL SCREENING OF SOME NEW AMINOPYRIDINIUM DERIVATIVES

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ABSTRACT

Aminopyridinium derivative such as Ethyl-2-(4-chloroamino pyridinium) acetate (compound A), Ethyl-2-(4-bromoamino pyridinium) acetate (compound B), Ethyl-2-(3-chloroaminopyridinium) acetate (compound C) have been evaluated for analgesic, anti anxiety and locomotor activity. All the aminopyridinium derivative prepared by the dose (50&100mg/kg/i.p), which shown significant analgesic activity when compared to morphine (5mg/kg/i.p). In case of open field exploratory and elevated plus maze test, the aminopyridinium derivatives prepared by the dose (50&100mg/Kg/oral) reverse the anxiety behavior of the mice when compared to lorazepam (0.5mg/kg/oral). Among this, compound C (100/mg/kg) produce better effect than others. Locomotor activity in the activity cage, the reaction time of Aminopyridinium derivative A, B&C produce more effective Central nerve depressant effect than Diazepam (2mg/kg/i.p) drug.

Key words: Aminopyridinium, open field test, elevated-plus maze test, activity cage

INTRODUCTION

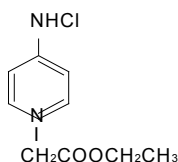
Aminopyridine derivatives were found to possess a wide range of biological activities such as analgesic, neuromuscular blocker and neuroprotective action. Aminopyridinium and their analogue are used in treatment of skin disorder and neurodegenerative disease etc¹. specially the 4-AP as a potential treatment for Spinal cord injuries was initiated in the late 1980s². Behavioral improvements attributed to 4-AP such as voluntary motor control, ambulation, continence, respiratory control along with

decreases in spasticity and idiopathic pain³⁻⁷. So in the light of the above fact we have evaluated the pharmacological activities of Aminopyridinium derivatives like Analgesic and Anti Anxiety effect

MATERIALS AND METHOD

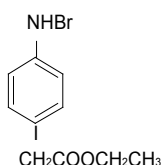
Selection of drugs

The compound aminopyridinium and its derivatives were obtained from department of chemistry, Bharathidasan University, Trichy



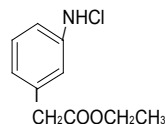
Ethyl-2-(4-chloroamino
pyridinium)acetate

Compound A



Ethyl-2-(4-bromoamino
pyridinium)acetate

Compound B



Ethyl-2-(3-chloroamino
pyridinium)acetate

Compound C

Open field exploratory behavior test⁸

Healthy Swiss male albino mice (22-30 g) were selected for this study. Experimental animals were selected for this study. Experimental animals were grouped into eight, contains six animals each and treated as follows: Group I received vehicle (0.2% CMC, 2 ml/kg/oral) and serve as control. Group II received Lorazepam (0.5mg/kg/oral) and serve as a positive control. The test treatments are, Group III and Group IV received compound A (50mg & 100mg/kg/oral) respectively. Group V and VI received compound B (50mg & 100mg/kg/oral) respectively. Group VII and Group VIII received compound C (50/100mg/kg/oral) respectively, the injections were administered in the above manner in 7 days. On the 8th day animals were subjected to behavioral studies such as Open field exploratory. Each mouse was placed in the center square of the open field and observed for 5mins. The behavioral parameters recorded include ambulation, rearing, grooming centre square entries and fecal bowel.

Elevated plus maze test⁹

Healthy Swiss male albino mice (22-30 g) were selected for this study. Experimental animals were grouped into eight, contain six each and treated as follows: Group I received vehicle (0.2% CMC, 2ml/kg/oral) serve as control. Group II received Lorazepam (0.5mg/kg/oral) serve as a positive control. The test treatments are, Group III and Group IV received compound A (50mg & 100mg/kg/oral) respectively. Group V and VI received compound B (50mg & 100mg/kg/oral) respectively. Group VII and Group VIII received compound C (50/100mg/kg/oral) respectively, the injections were administered in the above manner in 7 days. On the 8th day animals were subjected to behavioral studies such as elevated plus maze. Normally, the maze is kept 50cm above the floor in a dimly lit room the mouse were individually placed on the central square of the plus maze facing on the enclosed arm. Finally record the time spent and

number of entries made by the mice during next 5 minutes on open and closed arm.

Eddy's hot plate method¹⁰

Swiss male albino mice (22-30 g) were selected for this study. All the animals are fasted for 18 hrs. They were divided into eight groups of eight animals each. Group I received saline 2mg/kg/ip (intraperitoneal route) serve as control. Group II received morphine 5mg/kg/ip serve as positive control. The test treatments are Group III and Group IV received compound A (50mg & 100mg/kg/ip) respectively. Group V and VI received compound B (50mg & 100mg/kg/ip) respectively. Group VII and Group VIII received compound C (50/100mg/kg/ip) respectively. The injection was administered above manner. The time of reaction to pain stimulus of the mice placed on hot plate heated at 55°C was recorded at early phase 5 min and late phase 30 min only after the administration of the test and standard drug. The increase in reaction time against control group was compared and calculated

Locomotor activity by actophotometer¹¹

Swiss male albino mice (22-30 g) were selected for this study. They were divided into five groups of six animals each. Group I received saline (0.5ml/kg/i.p) serve as control. Group II received diazepam (2mg/kg/i.p) serve as positive control. The test treatments are, Group III compound A (100mg/kg/ip). Group IV received compound B (100mg/kg/ip). Group V received compound C (100mg/kg/ip) respectively. Place individually each mouse in the activity cage for 10 min. Note the basal activity score of all the animals. Inject Diazepam (2 mg/kg/ip), and after 30 min re-test each mouse for the activity scores for 10 min.

Note the difference in the activity, before and after Diazepam. Calculate per cent decrease in motor activity.

Statistical analysis

The results are expressed as Mean $\pm$ SEM. comparison between the groups was made by student t test. P value $P < 0.05$ was considered as significant.

RESULT AND DISCUSSION

Analgesic activity in the hot plate test the reaction time was significantly increased in (Table 1) Aminopyridinium derivatives of A,B,C. The effect was compared with morphine treated group, after over all, suggesting central analgesic effect present in Aminopyridinium derivatives. In open field exploratory test, a significant decrease in ambulation central activity rearing grooming behavioral along with increased fecal dropping observed in normal mice. It indicates anxiogenicity. All Aminopyridinium derivatives significantly reduced the alter behavior indicating the anxiolytic effect of this drug, especially compound C 100 mg/kg/ip, produce better effect than other derivatives. (Table 2). Normal mice show decrease and increase in time spent in open arms and closed arms respectively. All Aminopyridinium derivatives significantly reduced the alter behavior indicating the anxiolytic effect of this drug, especially compound C 100 mg/kg/ip, produce better effect than other derivatives. (Table 3). Locomotor activity logically measures the cognitive function with better precision. Locomotor activity in the actophotometer/activity cage, the reaction time of Aminopyridinium derivative A,B,&C produce more effective C.N.S depressant activity than standard drug. (Table 4)

Table 1 Analgesic effect of AP derivatives on Mice, Mean $\pm$ SEM

Treatment	Time spent in licking the paw sec.	
	Early Phase, 5 min.	Late Phase, 30 min.
Saline 2mg/kg i.p	1.06 $\pm$ 0.12	2.12 $\pm$ 0.08
Aminopyridinium (A), (50 mg/kg)	2.02 $\pm$ 0.16	4.22 $\pm$ 1.21
Aminopyridinium (A), (100 mg/kg)	3.04 ** $\pm$ 0.18	2.04 $\pm$ 0.20
Aminopyridinium (B), (50 mg/kg)	7.22** $\pm$ 1.41	4.63 $\pm$ 1.25
Aminopyridinium (B), (100mg/kg)	3.15 $\pm$ 0.07	8.62 $\pm$ 1.23
Aminopyridinium (C), (50mg/kg)	3.95** $\pm$ 0.24	10.04** $\pm$ 0.08
Aminopyridinium (C), (100 mg/kg)	2.16 $\pm$ 0.16	9.16** $\pm$ 1.12

Values are expressed as mean $\pm$ SEM of 8 animals. Symbol represents the statistical significance done by student t test
P values ** $P < 0.001$, indicates the comparison of all groups with control group.

Table 2 Effect of derivatives on open field exploratory (OFE) behavior in rats

Treatment	Ambulation	Rearings	Selfgroomings	Activity in center	Fecal droppings
Vehicle (0.2% CMC) 2ml/kg Oral	46.08 $\pm$ 5.40	9.66 $\pm$ 2.01	7.58 $\pm$ 1.67	1.25 $\pm$ 1.21	3.58 $\pm$ 1.37
Lorazepam (0.5 mg/kg Oral)	85.66*** $\pm$ 3.55	16.66*** $\pm$ 2.50	12.16*** $\pm$ 1.83	6.00*** $\pm$ 1.41	2.33* $\pm$ 0.81
Compound A (50mg/kg Oral)	74.00* $\pm$ 14.87	10.00*** $\pm$ 2.60	8.16*** $\pm$ 1.16	2.66*** $\pm$ 1.50	2.83* $\pm$ 0.75
Compound A (100mg/kg Oral)	83.83* $\pm$ 6.11	11.33*** $\pm$ 2.80	7.66*** $\pm$ 1.50	4.66* $\pm$ 2.16	3.16* $\pm$ 0.75
Compound B (50 mg/kg Oral)	62.00*** $\pm$ 11.00	18.82* $\pm$ 3.53	9.18*** $\pm$ 1.36	1.42*** $\pm$ 1.20	4.02*** $\pm$ 0.82
Compound B (100mg/kg Oral)	71.21** $\pm$ 13.92	13.54** $\pm$ 2.05	7.42*** $\pm$ 1.20	3.26*** $\pm$ 1.28	2.02* $\pm$ 0.95
Compound C (50mg/kg Oral)	75.12* $\pm$ 13.20	9.82*** $\pm$ 2.00	9.34** $\pm$ 1.26	4.26* $\pm$ 1.56	3.58*** $\pm$ 0.81
Compound C (100 mg/kg Oral)	90.36* $\pm$ 4.22	10.02*** $\pm$ 1.58	8.52*** $\pm$ 1.50	3.41** $\pm$ 1.98	1.92* $\pm$ 0.64

Values are Mean $\pm$ SEM

Values are expressed as mean $\pm$ SEM of 6 animals. Symbol represents the statistical significance done by student t test
P values * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, indicates the comparison of all groups with control group.

Table 3 Effect of AP on the elevated plus maze behavior in rats

Treatment	Time spent on (sec)		Entries on	
	Enclosed arm	Open arm	Enclosed arm	Open arm
Vehicle (0.2 % CMC)	214.94 ±4.65	28.72±1.79	7.83±2.79	2.75±0.75
Lorazepam (0.5 mg/kg Oral)	164.14***±4.65	70.16***±3.57	9.83*±1.94	7.66***±1.63
Compound A (50 mg/kg Oral)	180.48***±2.98	51.84***±3.11	8.08*±1.92	5.62*±2.02
Compound A (100 mg/kg Oral)	200.25***±3.72	66.21*±2.82	12.00**±1.08	6.42*±1.28
Compound B (100 mg/kg Oral)	182.00***±2.00	78.66***±3.12	6.40***±1.02	13.82***±1.16
Compound C (50 mg/kg Oral)	202***±2.98	82.00***±2.64	8.24*±2.02	8.12*±1.08
Compound C (100 mg/kg Oral)	175***±3.02	86.00***±2.32	6.12***±1.12	9.38*±2.02

Values are Mean ± SEM

Values are expressed as mean ± SEM of 6 animals. Symbol represents the statistical significance done by student t test

P values *P<0.05, **P<0.01, ***P<0.001, indicates the comparison of all groups with control group.

Table 4 Locomotor activity of AP derivatives on Mice

Treatment	Dose in mg/kg	Locomotor activity		% change in activity
		Before treatment	After treatment	
Saline	0.5 ml	120	122	1.66
Compound A	100mg/kg	126	51	40.47
Compound B	100mg/kg	128	65	50
Compound C	100mg/kg	139	68	48.04
Diazepam	2mg/kg	140	72	51

n= 6 animals in each group

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