SOME CENTRAL NERVOUS SYSTEM ACTIONS OF 5-(3 DIMETHYLAMINO-2-METHYL-PROPYL) DIBENZO [A, D] [1, 4] CYCLOOCTADIENE HYDROCHLORIDE

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Summary: The influence of 5-(3-dimethylamino-2 methyl-propyl) dibenzo [a, d] [1. 4] cyclocctadiene hydrochloride, a dibenzo-tricyclic compound on the central nervous system of various experiemental animals was studied. The compound exhibited mainly depressant actions, and lowered temperature under normal and pyretic states in rats. It is an analgesic and antiemetic. The pentobarbital sleeping time was significantly increased only at high doses. No protection against electro-convulsions was observed. Chemically induced convulsions were enhanced. LD_{50} was calculated to be 249.46 *mg/kg*.

Key words: central nervous system actions 5-(3-dimethyl-amino-2-methyl-propyl) dibenzo [a,d] [1,4] cyclooctadiene

INTRODUCTION

Davis *et al.* (4) reported protective effect against electroshock seizures in mice of a series of tricyclic compounds like dibenzo [a, d] cycloheptadiene, dibenzo [a, e] cycloheptatriene-5-carboxamide, dibenzo [a, d] cycloctadiene and related analogues. One of these compounds 5-(3-dimethylamine-2-methyl-propyl) dibenzo [a, d] [1, 4] cyclooctadiene hydrochloride (Ayerst, Canada) (hereafter referred to as 'DDC') on preliminary investigation by the present workers (unpublished observations) revealed some centrally active properties. This was interesting in view of its structural similarity to amitriptyline. This study was planned to investigate the effects of 'DDC' on pentobarbitone induced sleep, yeast induced pyrexia and normal rectal temperature and emetic responses due to morphine and copper sulphate. It was also tested for analgesic and anticonvulsant activity.

MATERIALS AND METHODS

Drugs: 5-(3-dimethylamine-2-methyl-propyl) dibenzo [a, d] [1, 4] cycloctadiene hydrochloride, (soluble in water, acetone and chloroform) was used as one persent aqueous solution (pH 6.6-6.8).

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Procedures : Potentiation of Hypnosis : Pentobarbitone (40 *mg/kg*) induced sleep in mice was studied in three groups of 20 albino mice each, according to the method of Dandiya and Cullumbine (3).

Effects on temperature: The influence of 'DDC' (10 and 25 *mg/kg*, i.p.) on normal rectal temperature was studied in 40 albino mice according to the method of Koppyani and Kraczmar (11). Yeast pyrexia was induced in albino rats according to Burn *et al.* (2). 'DDC' (10 or 25 *mg/kg*) was injected intraperitoneally in two groups of 10 rats each.

Analgesic studies: The analgesic activity of 'DDC' in doses of 50 and 100 *mg/kg* i.p. was evaluated in 80 albino rats against thermal pain as described by Madan *et al.* (13) and pressure stimuli as per the method of Green and Young (8).

Anticonvulsant actions: In eighty albino rats divided in groups of 6-8, convulsions were provoked according to the method of Madan *et al.* (13) by subcutaneous injection of either pentylenetetrazol (100 *mg/kg*) or picrotoxin (4 *mg/kg*) or strychnine (0.5 *mg/kg*). Electroconvulsions were induced by an alternating current of 150 m.a intensity for a duration of 0.2 sec. delivered through corneal electrodes.

Antiemetic effects: The influence of 'DDC' (2.5, 5.0, and 25 *mg/kg*, i.m.) on emetic responses of morphine 1 *mg/kg*, i.p. (17) and Copper sulphte 40 *mg/kg*, i.p. was studied in 30 dogs.

Toxicological studies: 'DDC' was subjected to acute and subacute toxicological studies in albino rats, LD_0 of 'DDC' was calculated in 80 albino rats (110-140 g). Four groups of ten rats each (100-170 *g*) were used to assess the subacute toxic effects of 'DDC'; three groups received 10, 25 and 100 *mg/kg* of 'DDC' and the fourth group received 5 *ml* of normal saline daily by oral route. All the animals were sacrificed after 4 weeks of medication and the viscera examined for gross and histopathological studies (7).

Teratogenic study was conducted on 30 chick embryos according to the method of Tubare (16). Chick embryo was selected because it is stated to be a sensitive indicator of teratogenic activity and that there is no excretion, which means that a constant level of the best drug can be maintained easily. 'DDC' was injected on the 8th day of incubation in 15 eggs in the dose of 200 mcg./egg. (in 0.1 *ml* normal saline). An equal number of control embryos were also handled similarly but received only requisite quantity of normal saline.

RESULTS

'DDC' in doses upto 200 *mg/kg* caused ataxia and sedation in animals. Doses above 200 *mg/kg* caused tremors, convulsions, irregular respiration and death in 10-20 min.

Hypnosis potentiation: The duration of sleep induced by pentobarbitone was increased by prior administration of 'DDC'. The group of mice that received barbiturate alone recorded a mean sleeping time of 31.5 ± 4.9 min. In other two groups the duration of hypnosis was

increased to 46.9±5.8 min. with 50 *mg/kg* of 'DDC' and to 63.3±2.5 min. ($P<0.01$) with 100 *mg/kg* of 'DDC'.

Rectal temperature of mice: 'DDC' given in doses of 10 *mg/kg* i.p. caused within one hr of its administration a fall in the rectal temperature from 101°F to 96.5°F. With 25 *mg/kg* there was a profound fall (9.5°F) in rectal temperature which lasted for two hrs. In both these groups the temperature returned to normal in 24 hr. Pentobarbitone (40 *mg/kg* i.p.) and chlorpromazine (2.5 *mg/kg* i.p.) caused a fall of temperature by 6.7°F and 3.1°F respectively and recovery in both cases occured in 6 hr (Fig. 1).

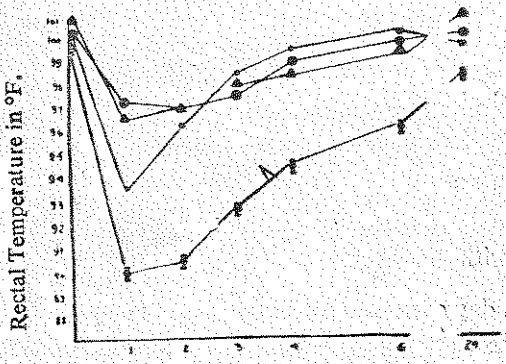

Fig: 1: Influence of 'DDC', pentobarbitione and chlorpromazine on rectal temperature of mice.

▲ — DDC 10 *mg/kg*.
● — 'DDC' 25 *mg/kg*.
■ — Pentobarbitone 40 *mg/kg*.
○ — Chlorpromazine 2.5 *mg/kg*.

Antipyretic activity in rats: The mean rectal temperature of rats was recorded to be 99.6°F. It was raised by 3.6-4.0°F after administration of 15% yeast in 2% acacia subcut. When these pyretic animals were treated with 10 *mg/kg* (i.p.) of 'DDC' a steady fall in temperature (6.8°F) lasting for two hr was observed. Then the temperature rose to prepyrexial state in 6 hr. : 25 *mg/kg* of 'DDC' intraperitoneally caused a greater fall of temperature (9.0°F and the recovery occured within 24 hr.

Analgesic activity: The reaction time of rats to thermal stimuli was increased from 4.8±1.7 min to 11.6±0.7 min after 40 min of administration of 50 *mg/kg* (i.p.) of 'DDC'. At 100 *mg/kg*, an increase in reaction time from 5.0±0.9 min to 15.1 ± 1.8 min was noted. The increase in reaction time in both cases was statistically significant ($P<0.01$).

Pressure analgesiometery: The animals that received 'DDC' required increased pressure to evoke a response and this increase is statistically significant at 100 *mg/kg* (i.p.) doses.

Anticonvulsant action: Electroshock seizures were not significantly influenced by 'DDC' in the doses of 25 *mg/kg*, i.p. 'DDC' potentiated convulsions induced by pentylenetetrazol, strychnine and picrotoxin. Pentylenetetrazol, 100 *mg/kg* alone produced a simple twitch followed by myoclonic convulsions and extensor spasm and none of the animals died. But when this dose of pentylenetetrazol was preceded by 'DDC' (25 *mg/kg* i.p.), all the animals died. Convulsions induced with strychnine or picrotoxin were more intense in animals pretreated with 25 *mg/kg* of 'DDC'. Subconvulsive doses of pentylenetetrazol (60 *mg/kg*) picrotoxin (2 *mg/kg*) and strychnine (0.3 *mg/kg*) produced frank convulsions after pretreatment with 'DDC' 25 *mg/kg* i.p.

Antiemetic activity: 'DDC' at 5 *mg/kg* (i.m.) dose protected 80% of dogs against emesis induced by morphine. Copper sulphate emesis was not effected even when 25 *mg/kg* (i.g.) of 'DDC' was administrered. Chlorpromazine 5.0 *mg/kg*, however, afforded 100 per cent protection against morphine induced emesis and 20 percent against copper sulphate emesis.

Toxicological studies: LD_{50} calculated by Lagrange's method as described by Elhans (5) was found to be 249.46 *mg/kg*. No obvious gross or microscopic abnormality was noted in viscera and brain after 4 weeks of oral feeding with 'DDC'.

When the eggs were opened on the 20th day of incubation only eleven embryos in drug treated group and nine in control group had progressed after the injection of the materials. The development in rest of the embryos had stopped at an early stage. There was no developmental abnormality in the control group. In 'DDC' treated group, there was no gross abnormality in three chick embryos; ventral hernia was a prominent finding in four other chicks which were found to be otherwise normal. The remaining four 'DDC' treated embryos exhibited significant abnormalities in that they were very small in size and in one of them there was total absence of ventral abdominal wall, absence of one eye and mal-development of one side of head.

DISCUSSION

The pentobarbitone hypnosis in mice was increased by prior administration of 'DDC'. It potentiated pentobarbitone sleeping time only after administration of 'DDC' in high doses (100 *mg/kg*). The phenomenon of hypnosis potentiation is generally explained on the basis of inhibition of enzyme system inactivating the hypnotic agent (6), the sensitization of CNS to the stimulus of the anaesthetic (1), the arrest of continuous bombardment of reticular formation by sensory inflow of cortical impulses (9), the influence on absorption and distribution of the hypnotic agent (14), or the reduction of body temperature (10, 12). However it failed to cause potentiation at doses which caused profound fall in body temperature.

'DDC' in doses of 10 and 25 *mg/kg* caused significant decrease in normal rectal tmperature of mice ($P<0.01$). Pentobarbitone was less potent and chlorpromazine more potent then 'DDC' in producing hypothermia. 'DDC' also reduced yeast induced pyrexia in rats. By virtue of its profound influence on normal and raised body temperature the compound simulates chlor-

promazine group of drugs (14) and differs from salicylates and related agents which fail to influence the normal body temperature (7).

'DDC' at 100 *mg/kg* caused significant analgesic actions against thermal and pressure stimuli. However, at 50 *mg/kg*, it was less effective against pressure induced pain, but caused significant analgesia against thermal pain and thus it simulates the analgesic actions of morphine (15).

'DDC' (25 *mg/kg*) did not afford any protection against electroconvulsions. Chemoconvulsions were intensified.

In dogs 'DDC' effectively blocked the emetic response of morphine. Compared with 'DDC' chlorpromazine afforded a more effective protection against morphine emesis and the doses required were smaller.

'DDC' injection in eggs caused developmental abnormalities. Muscular tissue was affected in particular since a fair proportion of embryos showed ventral abdominal wall defects.

LD_{50} of 'DDC' was 249.46 *mg/kg*. On oral feeding of 'DCC' daily for four weeks in rats, no damage to vital organs was evident.

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