A STUDY OF SOME PHARMACOLOGICAL ACTIONS OF CARBAMAZEPINE AND SODIUM VALPROATE

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(Received on August 8, 1983)

Summary : Carbamazepine (CA) and sodium valproate (SV) were studied for their actions of central nervous system and neuromuscular junction. CA and SV given ip neither possessed analgesic nor hypothermic activity in rats, nor did they alter the pentobarbitone sleeping time in mice. The drug had no effect on the frog rectus muscle nor did they alter its responses to acetylcholine. Both CA and SV produced a dose related decrease in indirectly evoked contractions of rat diaphragm and cat gastrocnemius muscle without much altering the directly evoked responses. This effect may be due to their local anaesthetic property, which was observed in infiltration test in guinea pigs.

Key words : carbamazepine, sodium valproate, neuromuscular junction, central nervous system

INTRODUCTION

Carbamazepine (CA) and sodium valproate (SV) are the two relatively recent additions to the group of anti-epileptic drugs. CA is a derivative of iminostilbene with carbamyl group at 5th position. SV is a simple branch chained carboxylic acid and has been marketed since 1978.

Few pharmacological actions of these anti-epileptic compounds have been reported. The present study was undertaken to study the effects of these compounds on central nervous system and on skeletal neuromuscular junction.

MATERIAL AND METHODS

Frog rectus abdominis muscle : Frog rectus abdominis was mounted in a bath of 10 *ml* capacity containing oxygenated frog Ringer solution at room temperature.

Phrenic nerve-diaphragm preparation of rat : Hemi-diaphragm of albino rat with phrenic nerve was dissected and set up in a bath (75 *ml*) containing oxygenated Tyrode

solution. It was stimulated indirectly and directly (square wave pulses, supramaximal voltage, at 1/10 sec; pulse width, 1 and 5 msec, respectively, for indirect and direct stimulaion). Contractions were recorded on kymograph paper with a Starling lever.

Gastrocnemius sciatic nerve preparation of cat : Cats (2.5-3 *kg*) of either sex were anaesthetized with chloralose (80 *mg/kg*, iv). The standard preparation was set-up as described by Sheth *et al.* (7). Direct and indirect contracions were recorded using Palmer isometric frontal writing lever, stimulation parameters were the same as described above.

Pentobarbitone induced sleeping time in mice : Modification of pentobarbitone sleeping time by CA (10-20 *mg/kg*, ip) and SV (50-100 *mg/kg* ip) was studied in 3 groups of 10 animals each, Pentabarbitone sodium (3.5 *mg/kg*, ip) was adminsitered 30 min after the pretreatment. The time interval during which the animal lost and regained the righting reflex was noted as the duration of sleeping time.

Analgesic activity : Thermal method as described by D'Amour and Smith (3) was used for testing the analgesic activity in rats.

Body temperature : Effect of pretreatent of CA (10-20 *mg/kg*, ip) and SV (5-100 *mg/kg*, ip) was studied on rectal temperature of albino rats at interval of 0, 15, 30, 60, 90 min in 6 groups of 5 animals each. Experiments were carried out in the morning The solutions of CA and SV were prepared in isopropylene glycol.

Local anaesthetic activity : Surface anaesthetic property of both the drugs was studied on rabbit's cornea in the concentration of 0.02-1% as described by Chance and Lobstein (2). Tests for intradermal infiltration anaesthesia were carried out in adult guinea-pigs as described by Bulbring and Wajda (1).

RESULTS

Rectus abdominis muscle : CA (50-100, $\mu g/ml$) and SV (100-500 $\mu g/ml$) had no effect on he muscle even though preparation were sentitive to acetylcholine (threshold dose, 0.8 to 3.0 $\mu g/ml$). Neither did CA nor SV alter the dose effect curves for acetylcholine in any fashion.

Phrenic-nerve diaphragm preparation ; Both CA (50-200 $\mu g/ml$) and SV (100-500 $\mu g/ml$) produced a dose-related decrease in the height of indirectly evoked contractions. Full effect was established in 4-5 mins (Table I).

The directly evoked contractions were not significantly affected. The tissue recovered fully within 25-30 min after wash. The partial blockade of indirectly evoked contractions was unaffected by physostigmine (10 $\mu g/ml$), $CaCl_2$ (100 $\mu g/ml$), tetraethylammonium (300 $\mu g/ml$), choline chloride (200 $\mu g/ml$), KCl (400 $\mu g/ml$) and adre-

TABLE I : Effect of carbamazepine and sodium valproate on indirectly evoked twitch responses of rat diaphragm.

Drug and bath concentration μg/ml	*n*	*Latency period min Mean±SEM*	*Time to half decay (in min) mean±SEM*	*Percentage blockade Mean±SEM*
Carbamazepine				
50	6	2.5	4.0	61.5±3.31*
100	6	2.0	3.5	71.42±4.02*
200	6	1.0	1.5	76.1±4.3*
Sodium valproate				
100	—	—	—	—
250	6	2.25	3.0	44.4±4.01*
500	6	1.00	1.5	99.2±5.03*

*Differs significantly ($P<0.05$) from the control (t-test)
n=number of observations.

naline hydrochloride (1 μg/ml). However, effect of d-tubocurarine (0.1 μg/ml) and CA and SV were apparently additive.

Gastrocnemius sciatic nerve preparation : Both CA (2-4 *mg/kg*) and SV (2.5-5 *mg/kg*) given intra-arterially produced a dose-dependent neuromuscular blockade of indirectly evoked twitches while the directly evoked contractions were not significantly affected.

The blockade of the indirectly evoked twitches was established in 4-5 min while it was not reversed till 60-80 min. Thepartial blockade of indirectly evoked twitches was unaffected by physostigmine (25 μg/kg), $CaCl_2$ (1 μg/kg), tetraethylammonium (50 μg/kg), choline chloride (50 μg/kg), KCl (2 μg/kg) and adrenaline hydrochloride (5 μg/kg). Effect of d-tubocurarine (0.1 μg/ml) and CA and SV were apparently additive.

C.N.S. actions : CA (10-20 *mg/kg*, ip) and SV 50-100 *mg/kg*, ip) did not significantly alter the pentobarbitone induced sleeping time in mice and rectal temperature in rats, or exhibitd any analgesic activity.

CA and SV (0.02-1%) failed to show any surface anaesthetic action on rabbits' cornea. Moreover, infiltration with CA (0.25 *ml*, 5 *mg/ml* solution) and SV (0.25 *ml*, 25 *mg/ml* solution). resulted in an almost total local anaesthetic effect.

DISCUSSION

Both CA and SV reduced the twitch response to indirect stimulation of the rat phrenic nerve diaphragm and cat sciatic nerve gastrocnemius préparation. CA and SV

produced complete neuromuscular blockade in a partially curarised preparaion while it did not alter the responses to direct stimulaion, indicatig that the site of action of CA and SV is similar to that of d-tubocurarine i.e. the motor-end plate.

Additive effect of CA with d-tubocurarine or SV with d-tubocurarine on the rat diaphragm should not be taken to indicate an essentially curare like action of CA and SV, as procaine also reduced responses to single shock in curarised muscle (4).

The blockade resisted physostigmine and agents which restore transmission by increasing acetylcholine out-put It is evident that CA and SV in the doses employed in present experiments produced neuromuscular blockade which is neither like d-tubocurarine nor decamethonium. The local anaesthetic activity of both the compounds may explain their neuromuscular blocking action. However, unlike procaine neither CA nor SV blocked the acetylcholine induced responses of rectus abdominus muscle This finding is difficult to explain at present, unless permeability of CA and SV in muscle is assume to be different than in case of procaine.

Sedation has been reported to occur in patients taking SV (6). In the present study, both CA and SV did not significantly alter the pentobarbitone induced sleeping time. Kapatonovic *et al.* (5) reported that SV increased the phenobarbitone levels in blood. This interaction might be possible in chronic treatment but was not evident in acute study. Thus SV and CA did not possess sedative or hypnotic property when they were administered acutely in mice. Moreover, CA and SV are also devoid of analgesic action and do not alter the normal body temperature in experimental animals.

ACKNOWLEDGEMENTS

This study was supported by a grant from Gujarat University, Ahmedabad.

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