

## ASPIRIN AND ANTICONVULSANT INTERACTION

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**Abstract:** Aspirin (360 mg/kg, po) *per se* had anticonvulsant activity in MES model. No effect was observed at lower doses and in other models. Aspirin 216 mg/kg, po (a subanticonvulsant dose) protected animals, receiving subanticonvulsant doses of phenytoin, phenobarbitone and carbamazepine against MES.

**Key words:** aspirin carbamazepine drug interaction  
phenytoin phenobarbitone

### INTRODUCTION

Neuromodulators such as prostaglandins (PG) are being investigated for their possible role in epileptogenesis (1). Supporting evidences for their involvement in epilepsy include: increased PG formation in epilepsy (2), their alleged role in epilepsy that is seen in children who in early life have had febrile convulsion lasting more than 2-3 min (3), increased concentration of PGD<sub>2</sub> and PGF<sub>2α</sub> following pentylentetrazol induced seizures (4), PGE<sub>1</sub> and PGE<sub>2</sub> have excitatory effects on cerebral cortex (5) and phenobarbitone and carbamazepine prevent release of PG from cortex, and prostaglandin synthesis inhibitors like diclofenac, indomethacin and paracetamol inhibit PTZ and MES seizures (6).

Such reports prompted the present study to investigate if aspirin, a prototype of prostaglandin synthesis inhibitors has any anticonvulsant activity *per se*, and whether it modifies the anti-convulsant activity of commonly used anticonvulsants.

### METHODS

Albino rats of either sex weighing 150-200 g were allocated to various drug groups (n=6). Over night fasted animals received orally either 0.5 ml/kg of 2% gum acacia mucilage or mucilage containing the total dose of assigned drug or drug combinations. After a time gap for near peak-plasma concentration of administered drug(s), either electro/chemoconvulsions were induced by conventional procedure.

Three doses of aspirin were employed by computing for rats, 54, 216, 360 mg/kg (7) the highest, the average and the lowest clinically recommended human doses (8), and were administered 0.5 hr before MES challenge.

The anticonvulsant and subanticonvulsant doses in mg/kg respectively phenobarbitone (10.8, 4.5), phenytoin (18, 13.5) and carbamazepine (18, 11.25) were administered 1, 2 and 4 hrs prior to MES challenge.

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In a preliminary study anticonvulsant dose was determined and a smaller dose which just failed to protect against the convulsions was selected.

Maximum electroshock seizures (MES) was produced with an AC 150 mA delivered through ear clip electrode for 0.2 sec and hind limb extension serving as end point.

Minimum electroshock threshold (MET) was arrived at by delivering AC shock of 0.25 mA for 0.2 sec with increments of 0.25 mA till head jerk appeared. The current strength at this point was noted as MET.

pretreatment reduced the anticonvulsant dose of phenobarbitone (Table I).

The anticonvulsant dose of carbamazepine had no anticonvulsant action against PTZ, but did so, in the presence of aspirin significantly ( $P < 0.001$ ).

Prostaglandin synthesis inhibiting property of aspirin may be involved in its antiseizure activity, as well as its potentiating effect on other anticonvulsants. The above suggestion is supported by the earlier reports that PG synthesis inhibitors like diclofenac, indomethacin and paracetamol protect against

TABLE I: Potentiation of the anticonvulsant action by aspirin on MES (n=6)

Drug (mg/kg)	Protection Number	Percent
Vehicle (0.5 ml)	0	00
Phenobarbitone (4.5)	0	00
Phenobarbitone (4.5) + Aspirin (216)	5	86.6
Phenytoin (13.5)	0	00
Phenytoin (13.5) + Aspirin (216)	6	100
Carbamazepine (11.25)	0	00
Carbamazepine (11.25) + Aspirin (216)	6	100

Phentylenetetrazol (PTZ) in the dose of 50 mg/kg, ip was given to produce clonic/tonic convulsions within 2-3 min. The duration of clonic/tonic convulsions were noted in presence or absence of test drugs.

## RESULTS AND DISCUSSION

Aspirin in a dose of 360 mg/kg protected the rats against MES. The response was similar to phenobarbitone phenytoin and carbamazepine. Lower dose of 216 mg/kg that had failed to exhibit anticonvulsant protection against MES, significantly potentiated anticonvulsant activity of the three drugs in their subanticonvulsant dose.

Pretreatment of aspirin did not affect the threshold of MET challenge. Phenobarbitone in a dose of 10.8 mg/kg provided significant ( $P < 0.001$ ) protection against PTZ induced convulsions. Aspirin

experimentally induced convulsions and that phenytoin sodium also exerts prostaglandin inhibition (9).

Though plausible, the above assumption has its own weakness because firstly unlike phenytoin, carbamazepine and phenobarbitone whose activity has been potentiated by aspirin in this study are not reported to be prostaglandin inhibitors; secondly aspirin could protect against MES as well as PTZ convulsions, whereas, other prostaglandin inhibitors like diclofenac, indomethacin etc protected against MES as well as PTZ convulsions (6).

The potentiating interaction between aspirin and other anticonvulsants could be pharmacokinetic as well. Salicylates displace phenytoin from plasma binding sites (10), thus raising its level in plasma and producing anticonvulsant effect.

Epileptics receiving anticonvulsants may on occasion take aspirin like drugs for some intercurrent indications, hence the nature, the extent and significance

of interaction between aspirin and anticonvulsants need further exploration both in laboratory and in clinical setting.

## REFERENCES

1. Campbell WB. Lipid derived autocooids; Eicosanoids and platelet activating factor. In Gilman GA, Rall TW, Nies AS, Taylor P, eds. The pharmacological basis of therapeutics. New York, Pergamon Press 1990; 600-617.
2. Wolfe LS. The role of prostaglandin in CNS. *Ann Rev Physiol* 1979; 41 : 669-684.
3. Adam RD, Victor M. Epilepsy and other seizure disorders. In Adam RD, Victor M. eds. Principles of Neurology. McGraw Hill Information Services Company 1990; IV 249-301.
4. Fortermann U, Heldt R, Hertting G. Increase in brain prostaglandin during convulsion is due to increased neuronal activity and not to hypoxia. *Arch Int Pharmacodyn* 1983; 263 : 180-188.
5. Bradley PB. Synaptic transmission in the CNS and its relevance for drug action. In Pfeiffer CC, Symthies JR, eds. The International review of neurobiology. London. Academic Press 1968 ; II : 2-56.
6. Bhaduri J, Acharya SB. Effect of some prostaglandin synthesis inhibitors on experimental convulsions. *Ind J Pharmacol* 1990; 2 : 3.
7. Paget GE, Barnes JM. In Lawrence DR, Bacharach AL eds. Evaluation of drug activities, pharmacometries. London Academic Press 1964; 1 : 125-166.
8. Paul AL. Analgesic antipyretic and antiinflammatory agents. Drugs used in the treatment of rheumatoid arthritis and gout. In Gilman GA, Rall TW, Nies AS, Taylor P, eds. The Pharmacological basis of therapeutics. New York Pergamon Press 1990; 638-681.
9. Weaver LC, Swinyard EA, Goodman LA. Pentylenetetrazol. *Fed Proc* 1953; 12 : 379-395.
10. Leonard RF, Knott J, Rankin GO, Robinson DS, Melnick DE. Phenytoin salicylate interaction. *Clin Pharma Therap* 1981; 29 : 56-60.