LETTER TO THE EDITOR

INFLUENCE OF ANTIDIABETIC DRUGS ON THE ACTIVITY OF NONSTEROIDAL ANTI-INFLAMMATORY DRUGS IN CARRAGEENAN PAW EDEMA TEST IN THE RAT

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Interactions between anti-inflammatory drugs and anti-diabetic drugs particularly sulphonylureas are known. Nonsteroidal anti-inflammatory drugs (NSAIDs) like aspirin, phenylbutazone and oxyphenbutazone are known to potentiate (1, 4, 5) and indomethacin and ibuprofen are known to antagonise the hypoglycaemic effect of oral sulphonylurea drugs (2). On the other hand Wellinger *et al.* (12) reported that insulin and tolbutamide potentiate anti-inflammatory effect of indomethacin. As various NSAIDs interact differently with oral anti-diabetic drugs and insulin is reported to alter the prostaglandin synthesis (6), it was worthwhile to investigate the interactions of various anti-diabetic drugs with NSAIDs.

For the anti-inflammatory activity the carrageenan edema method of Winter *et al.* was followed (13). The percentage inhibition of oedema was calculated from drug treated and vehicle treated groups using mean oedema values. ED_{50} was calculated from the oedema values after 3-hr of carrageenan injection by probit analysis. The significance of the results was calculated by student's t test.

For the hypoglycaemic effect, blood was collected from the orbital sinus of the rats (male, 130-150 G, 5/dose group) with the help of a capillary tube at various intervals after treatment with drugs for blood glucose de.ermination. Blood glucose was determined by the enzymatic method (10).

Blood pressure was registered from the rat's (male 180-200 g, 5/group) right carotid artery using Statham P_{23} AC pressure transducer attached to a polygraph under pentobarbitone anaesthesia (40 *mg/kg*, ip).

TABLE I : Effect of insulin (I) 0.5 *IU/kg*, sc, tolbutamide (T) 50 *mg/kg*, po and phenformin (p) 25 *mg/kg*, po on the ED_{50} values of NSAIDs against carrageenan edema (given orally as aqeous suspension in 0.5% tragacanth 1 hr before).

Treatment group	*ED_{50}±SEM mg/kg, po of NSAID alone and in combination with I, T and P.*				*Relative potency*[1]		
	NSAID alone	*NSAID+I*	*NSAID+T*	*NSAID+P*	*NSAID+I*	*NSAID+T*	*NSAID±P*
Aspirin	74±9.0	40±6.9*	45±6.38*	66±10.0	1.85	1.64	1.12
Naproxen	23±3.5	8.8±2.4*	12±2.8*	20.5±3.8	2.61	2.16	1.12
Oxyphenbutazone	42±4.2	23±2.7*	26±4.0*	44±6.33	1.82	1.61	0.95
Ibuprofen	48±4.8	23±3.3*	27±3.2*	50±6.0	2.08	1.77	0.96
Indomethacin	3.7±0.32	2.2±0.3*	2.15±0.3*	4.2±0.5	1.68	1.72	0.88

[1]Relative potency is expressed by a quotient of ED_{50} of NSAID and ED_{50} of NSAID plus insulin or tolbutamide or phenformin.

*$P<0.05$ vs NSAID alone.

Insulin (2.5-5 *IU/kg*, sc) produced 28±3.8 and 52±4.5% inhibition of carrageenan oedema respectively. Tolbutamide (125+250 *mg/kg*, po) produced 32±5 3 and 48±3.6% inhibition of carrageenan oedema respectively. Insulin and tolbutamide below these doses had negligible effect. Phenformin had no significant effect upto 100 *mg/kg*, po dose levels. 0.5 *IU/kg*, sc of insulin, 50 *mg/kg*, po of tolbutamide and 25 *mg/kg*, po of phenformin were therefore chosen as doses of anti-diabetic drugs for further study.

Anti-inflammatory ED_{50} values of aspirin, oxyphenbutazone, naproxen, ibuprofen and indomethacin are given in Table I. Insulin and tolbutamide increase the activity of all the anti-inflammatory drugs studied, when the inhibition of the oedema with the anti-inflammatory drugs was 55% or less. The activity of the higher doses having more than 55% activity was not increased. The ED_{50} values of all the NSAIDs were significantly reduced when they were combined with insulin and tolbutamide. Phenformin did not alter the effect of NSAIDs (Table I). Insulin, tolbutamide and phenformin alone and their combination with ED_{50} doses of NSAIDs did not have any significant hypoglycaemic activity and also did not alter the blood pressure.

The alteration in the anti-inflammatory activity of NSAIDs may be due to the effect on one or more of the factors respondible for the inflammation and the anti-inflammatory activity of NSAIDs (3, 7-9, 11), such as Kininogen depletion and redueed production of PG and alteration in collegen by insulin.

Increase in anti-inflammatory activity by tolbutamide may be explained by its eflect on insulin release. As phenformin has no effect on insulin release, it has no effect on anti-inflammatory activity of NSAIDs. As anti-diabetic drug and their combinations with ED_{50} doses of anti-inflammatory drugs did not have signflcant hypoglycaemic or hypotensive effect, hypoglycaemia (6) and hypotension (12) are not involved in this increase in activity.

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