Indian J Physiol Pharmacol 1991; 35(3): 209-211

LETTER TO THE EDITOR

EFFECT OF SOME NON-STEROIDAL ANTI-INFLAMMATORY AGENTS ON BLOOD SUGAR LEVEL AND ON INSULIN-INDUCED HYPOGLYCAEMIA IN ALBINO RATS

Sir,

(Received on August 31, 1990)

Arthritis is a common condition affecting middle aged obese individuals. Diabetes mellitus, which is often associated with it, is a predisposing factor for this ailment. Commonly employed antiarthritic drugs include aspirin, indomethacin, pyrazolone derivatives (eg. phenylbutazone, oxyphenbutazone), propionic acid derivatives (ibuprofen, ketoprofen) and piroxicam. The beneficial effects of nonsteroidal anti-inflammatory drugs (NSAIDs) is likely to be mediated by inhibition of prostaglandin biosynthesis (4). Futher prostaglandin biosynthesis in pancreatic islets has been well documented (2,5,7) and has also been implicated in the regulation of insulin secretion from this organ (6). Sadhana et al (11) have reported hypoglycaemic response by indomethacin Insel has reported potentiation of insulin hypoglycaemia by phenylbutazone (4). Therefore it was thought worthwhile to examine the effect of some NSAIDs on blood sugar level *per se* and on insulin induced hypoglycaemia, particularly since NSAIDs are likely to be co-administered in patients with arthritis and diabetes.

The study was conducted in healthy albino rats (Sprague-Dewley rats) of either sex, weighing 100-200 g fasted 18-20 hr prior to and during the acute study but allowed water *ad lib*. The animals were given usual laboratory diet i.e. soaked grams and green leafy vegetables. The rats were divided into 10 groups of 5 rats each. Blood samples were collected from infraorbital plexus of rats in fluoride vials and the blood sugar estimatation was done by the method as described by Somogyi (13).

In the first series of experiments, 5 groups of rats were used. Distilled water (2 ml, control) or an NSAID (as suspension in starch in 2 ml distilled water) were given (po) once a day for 10 consecutive days. Blood samples were collected at 0, 1, 2, 4, 6 and 24 hr intervals and after 10 days.

In the second series of experiments, the control rats were given crystalline insulin (2 units kg, sc). To remaining groups, various NSAIDs were given as above just before the administration of insulin. The samples were taken just prior to and at 0.5, 1, 2, 4 and 6 hr intervals after drug administration.

Insulin produced significant hypoglycaemia within 1 hr, peaking at 2 hr. Complete recovery was observed at 6 hr. (Table I).

Phenylbutazone (50 mg/kg) produced hyperglycaemia within 1 hr peaking at 6 hr and significant hyperglycaemia was seen even after 10 days (Table I). However when phenylbutazone was administered with insulin, it significantly potentiated the insulin hypoglycaemia at 2 hr. and recovery was not complete even after 6 hr. (Table I).

Piroxicam (2.5 mg/kg) produced significant rise in blood sugar level within 4 hr peaking at 24 hr. Administration of piroxicam with insulin antagonised insulin's effect at 1 hr, 2 hr and 4 hr. However the blood sugar returned to control value within 6 hr (Table I).

Indomethacin (5 mg/kg) produced a highly significant hypoglycaemia within 4 hr with peak effect at 6 hr; the effect persisted even after treatment for 10 days (Table I). Simultaneous administration of indomethacin and insulin significantly potentiated the peak effect of insulin at 2 hr prolonged the duration of action and delayed recovery (Table I).

TABLE I : Effect of some NSAIDs on blood sugar level and on hypoglycaemic effect of insulin in rats.

Group	Dose/kg	Blood sugar level as % (Values are Mean ± SEM)							
		0 hr.	1/2 hr	1 hr	2 hr	4 hr	6 hr	24 hr	10 days
1. Distilled water	2 ml	101.2±1.07	—	101.2±1.07	100.6±0.98	99.4±1.36	102.4±1.96	102.8±1.12	101.4±1.43
2. Insulin	2 units	101.0±1.18	82.2±1.02***	60.8±1.16***	49.8±0.66***	88.6±1.17***	97.2±0.97	—	—
3. Phenylbutazone	50 mg	103.0±0.95	—	111.6±3.16**	114.8±3.43**	116.0±1.92***	118.2±2.65***	115.2±1.46***	114.0±2.92**
4. Phenylbutazone Insulin	50 mg 2 units	102.4±1.12	79.2±0.49	60.0±0.89	45.0±0.84**	79.0±0.89**	91.4±0.75**	—	—
5. Piroxicam	2.5 mg	101.4±1.54	—	98.2±2.06	104.4±1.63	109.6±1.54**	111.2±3.22**	122.6±3.53***	115.6±1.47**
6. Piroxicam Insulin	2.5 mg 2 units	101.6±1.21	81.0±1.52	66.0±1.26**	54.6±1.57*	73.6±1.57**	94.6±1.72	—	—
7. Indomethacin	5 mg	98.8±1.85	—	98.4±1.17	89.4±1.78**	84.6±1.43***	81.8±1.2***	89.6±3.5**	89.2±1.85***
8. Indomethacin Insulin	2.5 mg 2 units	100.0±0.70	80.0±1.09	58.6±1.25	44.4±0.51**	67.0±1.0***	89.0±1.0***	—	—
9. Ketoprofen	15 mg	102.6±1.47	—	100.6±0.98	85.0±2.54***	86.2±2.48**	94.8±3.32*	100.8±2.67	95.0±1.96*
10. Ketoprofen Insulin	15 mg 2 units	102.6±1.17	80.8±1.24	60.2±0.66	50.0±0.70	87.0±0.05	96.4±0.93	—	—

There were 5 animals in each group
(*P< 0.05, **P <0.01, ***P < 0.001 as compared to respective controls 't' test)

Ketoprofen (15 mg/kg) produced significant hypoglycaemia at 2 and 4 hr only but not later. It did not produce any significant change when administered with insulin (Table I).

Reports are available indicating that PGs stimulate insulin release and thus have insulin like effects on carbohydrate metabolism (1, 8, 9, & 10). The hyperglycaemic effect observed after phenylbutazone and piroxicam can be explained through inhibition of PGE synthesis which in turn inhibits the release of insulin.

Indomethacin is known to inhibit angiotensin induced hyperglycaemia (12) and glucagon induced hepatic glucose production (3). Kelly and Laychock (6) had shown that indomethacin inhibited Islet's prostaglandin turnover and potentiated glucose stimulated insulin release in rats. Transient hypoglycaemia shown by ketoprofen may be because of its comparatively rapid metabolism and excretion.

All these drugs are inhibitors of cyclo oxygenase responsible for the biosynthesis or prostaglandins (4). As such the hypoglycaemic or hyperglycaemic effect of these drugs may be because of their variation in potency in inhibiting prostaglandin biosynthesis, thereby altering the release of insulin from Islet cells.

Phenylbutazone has been reported to do both, induce or inhibit the hepatic microsomal enzymes. The potentiation of insulin hypoglycaemia and delayed recovery may be because of inhibition of insulin metabolising enzymes. The potentiating effect of prioxicam and the antagonising effect of indomethacin on insulin hypoglycaemia can be explained by their respective hyperglycaemic and hypoglycaemic effect *per se*. Ketoprofen did not show any effect on insulin hypoglycaemia. This may be because of its very short duration of action.

If these findings are reproductive in man and if the effects are significant, they may have a therapeutic relevance.

N. GUPTA*, I. P. JAIN, M. K. SHARMA, J. N. PURI, M. B. MISRA AND R. K. MISRA**
Department of Pharmacology, G.S.V.M. Medical College, Kanpur - 208 002 (UP)

*Corresponding Author
**Department of Physiology, G.S.V.M. Medical College, Kanpur - 208 002 (UP).

REFERENCES

1. Campbell WB. Lipid derived autocoids. In, Goodman and Gilman's Pharmacological Basis of Therapeutics eds. AG Gilman, TW Rall, A Nies & P Taylor; McMillan Publishers N.Y. VIIIth ed 1990; pp 600–610.
2. Evans MH, Ace CS, Clements RS. Endogenous prostaglandin synthesis and glucose induced insulin secretion from the adult rat pancreatic islets. *Diabetes* 1983; 32; 509-515.
3. Ganguli S, Sperling MA, Ronald CF. Inhibition of glucose induced hepatic glucose production by indomethacin. *Am J Physiol* 1979; 236: 358-365.
4. Insel PA. Analgesic, antipyretic and anti-inflammatory agents. In, Goodman & Gilman's Pharmacological Basis of Therapeutics. eds AG Gilman, T Rall, A Nies & P Taylor; McMillan Publishers N.Y. VIIIth ed 1990; pp 638-681.
5. Kelly KL, Laychock SG. Prostaglandin synthesis and metabolism in isolated pancreatic islets of the rat. *Prostaglandins* 1981; 21: 759-769.
6. Kelly KL, Laychock SG. Activity of prostglandin biosynthetic pathway in rat pancreatic islets. *Prostaglandins* 1984; 27(6) 925-938.
7. Metz S, Robertson RP, Fujimoto WY. Inhibition of Prostaglandin E synthesis augments glucose induced insulin secretion in cultured pancreas. *Diabetes* 30: 551.
8. Metz S, Fujimoto WY, Robertson RP. Modulation of insulin secretion by cyclic AMP and Prostaglandin E. *Metabolism* 1982; 31: 1014-1022.
9. Pek S. Tai TY, Elster A, Fajans SS. Stimulation by prostaglandin E_2 of glucagon and insulin release from isolated rat pancreas. *Prostaglandin* 1975; 10, 493.
10. Pek S, Tai Ry, Elster A. Stimulatory effects of prostaglandin E_1, E_2 and F_2 on glucagon and insulin release *in vitro*. *Diabetes* 1978; 27: 801-809.
11. Sadhna, Sharma VV, Kulshrestha VK. Comparative biochemical and haematological study of enfenamic acid and some non-steroidal anti-inflammatory drugs. *Ind J Pharmacol* 1987; 19: 94-99.
12. Singh KN. Mishra V, Mullick V, Saxena VC. Modification of hyperglycaemic effect of angiotensin by indomethacin. *Ind J Physiol Pharmacol* 1978; 22: 378.
13. Somogyi M. Notes on sugar determination. *J Biol Chem* 1952; 195: 19.