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In the treatment of diabetes mellitus, the non-homonal hypoglycemic agents are of great importance because of convenience of administration and low cost of treatment since these agents are equally effective. Sulphonylureas still continue to be the mainstay in the treatment of maturity onset diabetes. Since, the discovery of sulphonylureas as a potential group of equally effective hypoglycemic agents, a large number of derivatives have been synthesized, tested and clinically introduced in therapy. Tolbutamide is the oldest sulphonylurea and it still finds favour from physicians due to high margin of safety and low incidence of side effects. The newer sulphonylureas, although similar to tolbutamide in mechanism of action and clinical efficacy but enjoy additional superiority primarily due to longer duration of action and hence less frequency of administration (chlorpropramide once a day, glibenclamide once or twice a day and tolbutamide 2-4 times a day). But many clinicians still believe administering a hypoglycemic agent with each meal of day and consider to be more effective to maintain normal blood sugar level than longer acting drugs.

Elevated incidence of cardiovascular diseases in general and hypertension and coronary diseases in particular in diabetes mellitus is well documented (Claussen and Elle.
Beta-adrenergic blocking agents are a major group of drugs in the management of cardiovascular diseases in the present clinical practice. Thus use of beta-blockers in diabetic patients with cardiovascular complications is quite common. These drugs also possess certain effect on glucose metabolism and affect blood sugar level (Kotler et al., 1988). It is therefore very likely that beta-blocker is concurrently administered to a diabetic patient and it may affect the response of an antidiabetic agent used. Although a large number of evidence of adverse drug interactions with tolbutamide and various beta-blocker have accumulated but still it is difficult to draw a definite conclusion about mode of concurrent therapy with these groups of drugs. It is so because beta-blockers with selective action are being introduced and it is after some time that their interaction potential with other drugs is brought to light. It was, therefore, felt worthwhile to conduct further drug interaction studies in animals between beta-blockers and tolbutamide.

Anti-inflammatory analgesics are also a very common group of drugs in the symptomatic relief of musculoskeletal pain and are very frequently prescribed in all patients. Use of anti-inflammatory agents is also associated with disturbances in blood sugar level and thus they also
The correlation coefficient ($r = -0.97$) is statistically significant at $p < 0.001$. The correlation of tolbutamide (50 mg/kg) in normal rabbits shows regression line between blood sugar change and serum concentration.

**Fig. 19:** Shows regression line between blood sugar change and serum concentration of tolbutamide.

**Correlation between Hypoglycaemic Response and Serum Concentration of Tolbutamide:**

- $r = -0.97$
- $p < 0.001$
influence blood sugar control by oral anti-diabetics.

In the present study beta-blockers and anti-inflammatory drugs were included in the interaction study with tolbutamide, amongst the beta-blockers the cardio-selective and among the anti-inflammatory drugs the newly introduced nonsteroidal agents were chosen as drug interaction studies with them are quite limited.

In this investigation tolbutamide was found to produce a dose dependent hypoglycemic effect in normal as well as in alloxan induced diabetic rabbits. However, the effects were qualitatively and quantitatively similar in both types of animals excepting an earlier peak response in diabetic animals (6 hours) as compared to normal animals (8 hours). Tolbutamide at an oral dose of 80mg/kg produced a marked hypoglycemia (about 63%) in the normal and diabetic animals at maximal hypoglycemic response and this effect persisted over nine hours.

The extent of hypoglycemia produced by tolbutamide was found to be dependent on the blood concentration of tolbutamide attained. At the peak response the tolbutamide concentration was the highest and it gradually diminished along with serum tolbutamide concentration (Fig. 20). In addition further information could be deduced from the
present study about the minimum serum level of tolbutamide required to induce and maintain the pharmacologic response. Our data showed that after 9 hours of administration of tolbutamide the blood sugar level returned (96.5 % in normal rabbits and 101 % in diabetic rabbits) to normal with serum level of 126.83 ± 4.68 in normal rabbits and 192.30 ± 6.85 mg/dl in diabetic rabbits. The serum concentration of tolbutamide less than 125 - 150 mg/dl seemed to be ineffective to evoke hypoglycemic response.

Aspirin, tolmetin and trimetrex have been used at doses less than their B.D.0.5 doses; the anti-inflammatory B.D.0.5 values for aspirin, tolmetin and trimetrex are 23, 49 and 109 mg/kg respectively (Sharma, 1982). Aspirin (40 mg/kg) and tolmetin (50 mg/kg) produced significant hypoglycemic whereas trimetrex (100 mg/kg) did not show any effect on blood sugar level. The anti-inflammatory agents produce anti-inflammatory action through a common mechanism of prostaglandin synthesis inhibition (Farrar et al., 1972; vanoy, 1972) but the decrease in blood sugar changes by these agents is difficult to explain. However, aspirin produces hypoglycemia (Langston, 1970) or hyperglycemia (Flower et al., 1980) in toxic doses. In this study aspirin in therapeutic doses produced hypoglycemia. Flumetrex, tolmetin and indomethacin despite of being potent anti-inflam-
symptomatic drugs do not change blood sugar level to any significant extent (Bethanich, 1983; Shama et al., 1981). Prostaglandins are known to exert insulin-like action (Shama, 1973). Anti-inflammatory agents by prostaglandin synthesis inhibition are rather theoretically accepted to raise blood sugar level by anti-insulin effect. It seems that hypoglycemic induced by some anti-inflammatory agents is probably not related to prostaglandin synthesis inhibition. The underlying mechanism for the effect is unclear and requires further investigations for elucidation.

Propranolol is a nonselective beta-blocker but atenolol, atenolol, and acebutolol are cardioselective (β₁) beta-receptor blocking agents (Shama, 1983). Recent studies reveal that β₂ receptors present in liver and pancreatic islets of Langerhans are involved in autonomic mediation effects on glucose metabolism (Shama, 1983) and insulin release. Nonselective beta-adrenergic blocking agents nonselectively modulate glucose metabolism by inhibiting metabolite β₂ receptors; whereas cardioselective drugs are said to be free from metabolic effect. In this study propranolol produced hypoglycemia; this observation is in agreement with earlier reports (Shama, 1974). Metoprolol and acebutolol did not show any metabolic effect on blood sugar level. This finding again confirms the
nominivlement of cardioselective beta-blockers in glucose metabolism (Hanan, 1976). However, etomidate another
cardioselective beta-blocker exhibited hypoglycemic response.

Aspirin and tolbutamide when administered along with
tolbutamide increased tolbutamide hypoglycemic in normal
as well as alloxan induced diabetic rabbits but interestingly
the serum tolbutamide concentration was found significantly
lower than the corresponding normal values. This clearly
indicates that the potentiation of hypoglycemic by the
anti-inflammatory drugs under study is not by enhancing
tolbutamide bioavailability.

On the contrary, these anti-inflammatory agents
decreased serum tolbutamide level by some mechanism most
plausible by decreasing absorption of tolbutamide. However,
several reports mention that salicylates displace tolbuta-
mide from plasma protein binding sites and thus increase
unbound sulphonylureas in the blood (Harron, 1976). More-
over Lewis et al. (1988) have suggested that the potentiation
is due to intrinsic hypoglycemic action of anti-inflammatory
drugs. Our findings also confirm this contention as aspirin
and tolbutamide per se produced hypoglycemia. Furthermore, it
is reasonable to presume that if the anti-inflammatory agents
had not decreased the tolbutamide bioavailability, the hypogo-
llycemic potentiation would have been still more. Therefore,
it is probable that the hypoglycemic potentiation might be partly due to intrinsic hypoglycemic action of anti-inflammatory drugs. The lowering of serum concentration of tolbutamide appears to be due to decreased absorption by anti-inflammatory drugs but it requires further confirmation.

The other anti-inflammatory agent tocamil was found not to have any intrinsic hypoglycemic action or any effect on serum tolbutamide concentration. Tomaril did not produce any effect on tolbutamide hypoglycemia.

 Pretreatment with aspirin and tolmetin daily for a week but without concurrent administration with tolbutamide on the 5th day were found to increase tolbutamide hypoglycemia without any significant change in serum tolbutamide concentration. Moreover, in the control group, the hypoglycemic effect of aspirin and tolmetin remained persistent on the 5th day. Since these drugs did not change tolbutamide concentration significantly their effect on absorption, metabolism and excretion of tolbutamide is out of question. The possible mechanism of this potentiation might be due to persistent hypoglycemic action of aspirin and tolmetin after prolonged treatment.

 Furosemid and atenolol, among the beta-blocking drugs potentiated tolbutamide hypoglycemia in normal as well as in diabetic subjects. These drugs had no effect on
serum tolbutamide concentration pattern. It appears that
the tolbutamide hypoglycemic potentiating by beta-blockers
might be due to their hypoglycemic action through metabolic
B2 receptor blockade. But atenolol has been reported to be
a selective cardiac B1 blocker. Thus it is not expected to
produce hypoglycemic or potentiate sulphonylureas induced
hypoglycemia. In our study atenolol produced these effects.
It does possess intrinsic hypoglycemic action which may
not be B-receptor mediated.

Metoprolol and acebutolol, the other two cardiac-
selective beta-blockers, although did not produce any effect
in normal rabbits but potentiated tolbutamide hypoglycemia
in diabetic rabbits. It can be concluded that intrinsic
hypoglycemia in diabetic action and potentiation of tolbu-
tamide hypoglycemia by beta-receptor blockers is due to
metabolic B2 - receptor blockade. Although atenolol, meto-
prolol and acebutolol are selective B1 blockers but a minor
B2 blocking activity in these drugs can not be completely
ruled out. This study further shows that metoprolol and
acebutolol are more selective than atenolol.

Propranolol after a week-long treatment poten-
tiated the tolbutamide hypoglycemia on the 6th day but in
the general group the blood sugar level remained with in
normal range. Thus it appears the mechanism of potentiation
is not due to persistent hypoglycemic action of propranolol. Moreover, serum tolbutamide level was also not markedly changed. Therefore propranolol after prolonged treatment might not be affecting tolbutamide absorption, metabolism or excretion. From the present data it is not possible to explain the exact mechanism how chronic treatment with propranolol potentiated tolbutamide hypoglycemia. There are many possibilities including increased insulin release by tolbutamide due to some cellular change produced by chronic pretreatment with propranolol.

It can be concluded from the present investigation that anti-inflammatory and beta-blocking drugs when administered along with tolbutamide may give rise to therapeutically undesirable problems. Concomitant administration of these drugs with tolbutamide can lead to improper control of diabetes and in higher doses may lead to dangerous hypoglycemia. But two-vasodil and cardioselective beta-blockers like metoprolol and acebutolol, are comparatively safer in this respect.