Case Report

Low Dose Captopril in Insulin Receiving Diabetics

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Introduction

Episodes of mild to severe hypoglycaemia symptoms are known to occur in ambulant patients where the causes like missing the meals, strenuous physical work or exercise, overdoses of anti-diabetic are well documented. In diabetics when hypertension is co-existing, there is need of individualisation of therapy for better glycemic control, and for this vasodilators - particularly ACE Inhibitors have been found to be effective in not only hypertension, but other benefits including no adversity on glycemic control, sexual functions, myocardial functions, better patient compliance, improved quality of life and positive role on micro-albuminuria.

Hypertension with glucose intolerance is known to cause risk of development of diabetes mellitus and/or ischemic heart disease, if patient also develops dyslipidemia. All these, when coexist in obese, there is risk of causing not only slow response to antimicrobials in infections due to undetected Insulin resistance, but also Syndrome-'X'. At this stage, oral co administration of insulin receptor sensitizing agent is one of measures to achieve glycemic control which may facilitate antimicrobials agents to cure infection early. On the other hand hypertension in an insulin unresponsive patient on outdoor basis treated by vasodilator along with appropriate anti-diabetic therapy, vasodilators do not worsen the existing dyslipidemia.

The present work was undertaken after receiving information of episode of hypoglycemia in two diabetics, 15 days after starting initial low doses of captopril, data of blood sugar and particulars of therapy was collected from records available with intimating private consultant.

Review of literature

Increase in Insulin sensitivity after injection of captopril was related to an accumulation of bradykinin in blood stream[1]. ACE inhibitors block kininase-II enyme to cause accumulation of bradykinin. It has been demonstrated that reduction in blood pressure is significantly related to change in bradykinin concentration in blood plasma[2]. Captopril administration causing increase in plasma or urinary bradykinin concentration[3]. This indicates kininase-II inhibition preventing inactivation of bradykinin and kallidin, which themselves are generated by action of kallikrein on HMW and LMW kininogens respectively. Kallikrein and kinins have been implicated in regulation of glucose uptake in working and hypoxic skeletal muscle [4].

Recent studies have suggested that Angiotensin II may promote impaired glucose metabolism through its effects on Insulin signalling pathways, tissue blood flow, oxidative stress, sympathetic activity and adipogenesis[5,6]. ACE inhibitors may have capacity to increase Insulin sensitivity[7,8]. Antidiabetic properties of ACE inhibitors may be largely mediated through increase in bradykinin level, nitric oxide and GLUT4 glucose transporters[9]. In a previous study, during treatment with captopril, insulin sensitivity was improved by about 11%[10]. Insulin influences eNOS and nitric oxide to reduce blood sugar by reduction in elevated $ONOO^-$ (peroxinitrite) and iNOS, in obese elevated $ONOO^-$ and iNOS are the cause of reduced glucose uptake and availability to myocytes[11]. Several studies have shown that PPAR-gamma increases insulin sensitivity of obese rodents and humans[12]. Metabolic studies on animals lacking bradykinin-B2 receptors, and in animals treated with both an ACE inhibitor and a bradykinin antagonist suggest that the Insulin sensitizing effects of ACE inhibitors involve more than just reduction in Angiotensin II levels[12].

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Aims and Objectives

With above said links in literature, along with collected data of those two patients who developed hypoglycaemia with initial low dose captopril, case report study undertaken to test low dose captopril, for any possible reduction in blood sugar in ambulant and working non-obese diabetics receiving maintenance doses of Insulin and are ill controlled (fasting blood sugar >150 mg%). Also to see whether there is insulin dose reduction or possibility of shifting the patients to oral hypoglycaemic agent.

Materials and Methods

The inclusions (n=4) non pregnant, uncomplicated, ambulant, non obese diabetic females receiving maintenance doses of Insulin attending diabetic clinic of govt. hospital, Nagpur, after approval from institutional ethics committee. These four patients mentioned below as case report, were on insulin and their fasting blood sugar was > 150 mg% , three were receiving 50-60 units of insulin, fourth patient being on 24 units. Tab. Aceten (captopril) 25 mg. was divided into four equal parts and was administered in 6.25 mg dose twice/ thrice daily before meals. Blood sugar was estimated by glucometer, by same technician using similar brand strips. Test drug was administered for a period of 3-6 wks starting with 6.25 mg twice daily. The dose was modified in 4th,5th and 6th wk, not exceeding 12.5 mg twice daily which is lower than its antihypertensive dose.

Results

Data Collected Case-1: 60 yrs old obese female, who was receiving monotard 40, and acrapid 24 units daily, with her blood sugar 138F, 191PP was on SARBITRATE, ANGISPAN,DITIDE, THROMBO-SPORIN for her cardiac ailment, was started captopril 6.25 mg once daily before meals. Her blood sugar after 2 wks was 12 random during hypoglycemic episode. Hypoglycemia treated effectively, insulin and captopril therapy stopped and patient was switched to tab Glipizide. All these were collected from record available with clinician.

*Data Collected Case-2***:** 60 yrs old obese male patient who was on monotard 20, acrapid 10,20 and co-therapy (sarbitrate, frusemide, tegretol and deriphylline for associated illnesses) was administered captopril 12.5 mg three times a day before meals. He developed hypoglycaemia 2 wks after captopril therapy which was effectively treated. He was re-titrated for insulin and requirement as 16 units acrapid (10M,6E). These two patients whose data was collected were receiving sarbitrate / angispan for coexisting angina-pectoris, one on 50 units and second on 64 units of insulin.

Data collected of these two obese diabetic patients who were on angispan / sarbitrate co-therapy for coexisting IHD, their blood sugar reduced after starting captopril 6.25 mg bd/tds. Both these patients had developed hypoglycemia in 3-4 wks. Insulin was stopped, hypoglycemia was effectively treated and captopril withdrawn. One of these was switched to oral anti-diabetic while other patient required reduced dose (16 u) of insulin for diabetic control.

Study Case 1: 36 yrs old female patient weighing 46 kg on Lente Insulin 40 units (morning) and 10 units crystalline Insulin (morning-evening) with blood sugar 193 fasting, and 227 postprandial, with her blood pressure 154/108 was administered Captopril (Aceten) 6.25 mg(1/4 tab of 25 mg) twice daily , before meals which was increased to 6.25 mg three times a day after 3 wks and was stopped in seventh week. Fasting blood sugar of 194 mg was observed with 35 (M) + 15 (E) units of respective Insulins at the end of 6 wks. Blood pressure was 130/92mmHg. Patient was referred to clinician for further management.

Study Case 2: 40 yrs old female patient weighing 30 kg on Lente Insulin 15 units (morning) 10 units (E) and crystalline Insulin (15 morning-10evening) with blood sugar 185 fasting, and 375 postprandial, with her blood pressure 180/108 was administered Captopril (Aceten) 6.25 mg (1/4 tab of 25 mg) once daily, before meals for three wks, increased to 6.25 mg twice daily in fourth wk, and thereafter 12.5mg (M), 6.5 mg (E)in 5th week. It was further increased to 12.5 mg twice daily in 6th week. All these doses were given before meals and stopped in 7th week. Her blood sugar in 6th week was 194mg fasting and 224 mg postprandial with Insulin requirement of total 40 units (Lente 15,10crystalline and 10,5 respectively morning and evening). Blood pressure reading was 144/92. Patient was referred to clinician for further management.

*Study Case 3***:** 40 yrs old female patient weighing 41 kg on Lente Insulin 20 units (morning) 10 units (E) and crystalline Insulin (10 morning- 5evening) with blood sugar 155 fasting, and 255 postprandial, with her blood pressure 150/82mmHg, was administered Captopril (Aceten) 6.25 mg (1/4 tab of 25 mg) once daily , before meals for three wks, increased to 6.25 mg twice daily in next three wks before meals, and was stopped after 6 weeks. Her blood sugar in 6th week was 102mg (F) and 196mg (PP) with Insulin requirement reduced to 25 units (Lente 10,5 and crystalline 5,5 morning evening respectively). Patient developed giddiness in 7th week. Her blood sugar was 98mg (F) and 141mg (PP). Patient was switched to tab.Daonil ½ twice daily and was sent to physician for further titration of dose.

Study Case 4: 33yrs old female patient weighing 40 kg on crystalline Insulin 12 units twice daily with blood sugar 186 fasting, and 246 postprandial, with her blood pressure 130/86mmHg, was administered Captopril (Aceten) 6.25 mg twice daily , before meals. Her blood sugar after 4 weeks was 184mg (F) and 244mg (PP), showing no reduction therefore Insulin doses continued in pretreatment doses.

In study case 3 above, fasting blood sugar reduced gradually to 98mg% after 6 wks of captopril administration. This patient was switched to oral anti-diabetic after consulting the clinician (Tab. Daonil ½ twice daily) as 45 units of insulin requirement reduced down to nil.

In study case 1 and 4, there were no obvious changes in blood sugar levels in 6 wks captopril co-therapy. Insulin requirement remained unaltered.

In study case 2, it was observed that either postprandial blood sugar, along-with insulin dose requirement was reduced (by 10 units) in 6 wks co-therapy with captopril. Pretreatment blood sugar levels were attained with reduction in insulin dose. Captopril withdrawn and pretreatment insulin dose reinstated.

Impression

From the collected data reported by clinician, it was clear that when vasodilators were used for coexisting diseases, hypoglycaemic episode is possible. Study case 3 above was normotensive and hence improvement in Insulin responsiveness. Recent studies have suggested that antidiabetic properties of ACE inhibitors may be mediated through increase in bradykinin levels, nitric oxide and the GLUT4 glucose transporter, the mechanisms in addition to but different from correction of angiotensin-II mediated deranged glucose metabolism. In study case 1 and 2, hypertension might have been factor (cytokines generation affecting PPAR-y function), and in study case 4, low crystalline insulin dose requirement from entry in study. It is important to carry out a separate clinical study on large number of patients using other ACE inhibitors like Enalapril and Ramipril which are now preferred over Captopril.

Overall, three (1 under study+2 data collected) out of six patients showed reduction in insulin requirement after starting low doses of captopril, up-to six wks of therapy. Two (i.e.one each from studied and data collected patients) out of six were switched to oral anti-diabetic. Two showed reduction in insulin dose requirement. The risk of hypoglycaemia is higher if patient is already on other vasodialators for IHD, and Captopril added for hypertension, micro-albuminuria, impending cardiac failure or any other indication.

Approval for further study with other vasodilator antihypertensive drugs has been given by institutional ethics committee, GMC, Nagpur.

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