Serum bicarbonate: can it be a marker of metformin induced acidosis in geriatrics?

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ABSTRACT

Metformin is an oral antidiabetic agent, widely used in the treatment of type 2 diabetes mellitus.The serious side effect of metformin therapy is lactic acidosis. Contraindications for metformin therapy include renal insufficiency. A cut off value of 60ml/min in creatinine clearance is suggested. Hundred type 2 diabetics receiving metformin as monotherapy or in combination with insulin/other oral antidiabetic agents, were enrolled in the study. Patients were on metformin for atleast one month prior to being enrolled. Patients' demographic data were taken. Baseline serum creatinine and bicarbonate were estimated. Creatinine clearance (Clcr ml/min) was calculated. Patients were grouped into group1-4 depending upon the doses of metformin they received. Patients were again grouped based on their Clcr as groupA (Clcr<60ml/min), group B (Clcr>60.01ml/min). Data was analysed using student's *t* test. Out of 100 patients 52 were males, 48 females. Mean age and SD of males and females were 69.92±6.95 and 66.85±5.72 respectively. Comparison of mean bicarbonate level in different doses of metformin did not show any statistical significance. But comparison of bicarbonate levels based on Clcr were highly statistically significant (p=0.0084). In three patients whose bicarbonate level was very low (15, 16.4 and 19.2mmol/L), doses of metformin was reduced and after one month their bicarbonate levels returned to normal (27.4, 25.6 and 26.2mmol/L). Hence serum bicarbonate can be a marker to assess metformin induced acidosis in geriatrics patients with low creatinine clearance.

Keywords: Diabetes mellitus, metformin, serum bicarbonate, geriatrics, creatinine clearance.

INTRODUCTION

The burden of diabetes mellitus type 2 (DM2) is increasing world wide.[1] Diabetes mellitus is a common disease in older people, with almost 50.0% of type 2 diabetic patients being over 60 years of age.[2] Metformin is a biguanide that has been used for more than 40 years in the management of type 2 Diabetes Mellitus.[3,4] Intensive treatment with metformin has been shown to reduce the cardiovascular and total mortality rates compared with insulin, sulfonylurea use, or diet alone.[5] Combinations of metformin with insulin, sulfonylureas and thiazolidinediones have shown to be effective as treatment strategies.[6,7] Metformin lowers the blood glucose concentration without causing hypoglycemia. It acts by enhancing the sensitivity to insulin by a decrease in the hepatic glucose production and an increase in its peripheral use.[8]

Metformin is absorbed mainly in the small intestine; not bound to plasma proteins; and is excreted unchanged in urine. The $t_{1/2}$ is about 2 hours and is given in the maximum recommended daily dose of 2g in two to three doses after meals.[9]

Contraindications for metformin therapy include renal insufficiency: serum creatinine ≥ 1.5 mg/dl for men; ≥1.4 mg/dl for women with adjustments for age.[6] The best parameter to assess renal function is creatinine clearance, as in patients with reduced muscle mass such as elderly patients; the serum creatinine concentration may underestimate the glomerular filtration rate.[6,10] A cut off value of 60ml/min in creatinine clearance is suggested.[11]

The serious side effect of metformin therapy is lactic acidosis. Biguanides cause a shift in the intracellular redox potential to anaerobic metabolism, increases cellular lactate production and decreases bicarbonate level.[12] Lactic acidosis may be fatal in one half of cases and can still occur as a complication of biguanide therapy.[6] To minimize the risk of lactic acidosis, the patient's renal function should be assessed prior to initiating metformin. And consideration must be given to whether there are other problems such as hepatic disease, a past history of lactic acidosis of any cause, cardiac failure requiring pharmacological therapy, chronic hypoxic lung disease which might make metformin dangerous to use.[13]

Some studies have revealed that the most important pharmacokinetic change in old age is a decrease in the

Table-1: Demographic data

	Male	Female
Number of Patients	52	48
Mean Age±SD	69.92±6.95	66.85±5.72

(SD, standard deviation)

Table-3: Mean serum bicarbonate levels based on creatinine clearance (Clcr)

	Group A	Group B	P value
Number of Patients	52	48	0.0084*
Mean±SD	26.20±4.04	27.98±3.23	

*P value is statistically highly significant.

excretory capacity of the kidney more than the decline in rate of hepatic drug metabolism.[14] Declining renal function, a reduction in both renal blood flow and glomerular filtration rate, is a major contributor to drug toxicity in the elderly.[15]

Metabolic acidosis has profound effects on respiratory, cardiac, and nervous systems. Both peripheral arterial vasodilation and central venoconstriction can be present. The decrease in central and pulmonary vascular compliance predisposes to pulmonary edema with even minimal volume overload. Central nervous system function is depressed, with headache, lethargy, stupor and, in some cases, even coma. Glucose intolerance may also occur.[16] The objective of present study is to evaluate the effect of Metformin on serum bicarbonate levels.

MATERIALS AND METHODS

Institutional ethical committee approval has been taken prior to the study. Written informed consent obtained from all the participants in the study. One hundred type 2 diabetics receiving metformin as monotherapy or in combination with insulin/other oral antidiabetic agents, were enrolled in the study. Patients were on metformin for atleast one month prior to being enrolled. Patients demographic data were taken. Baseline serum creatinine and bicarbonate were estimated. Creatinine clearance (Clcr ml/min) was calculated using COCKROFT GAULT FORMULA. Patients were grouped into group1-4 depending upon the doses of metformin they received. Group 1 included patients who received a total daily dose of metformin up to 500mg, Group 2 received a dose of upto 1000mg/day, Group 3 received a dose of upto 1500mg/day and grouped 4 was those who received a dose more than 1500mg. Patients were again grouped based on their Clcr as group A (Clcr<60ml/min), group B (Clcr>60.01ml/min). If serum bicarbonate of the patient is below the normal reference range (22-26mmol/L) the doses of metformin were reduced. After one month serum bicarbonate levels were rechecked. Data was analysed using student's *t* test.

Table-2: Mean serum bicarbonate levels in different doses of metformin

	Group 1	Group 2	Group 3	Group 4
Number of Patients	44	40	12	4
Mean±SD	27.22±3.71	27.04±3.23	26.32±5.79	27.65±3.13

P value >0.05 when each group was compared with the others.

RESULTS

Out of 100 patients 52 were males, 48 females. Mean age and SD of males and females were 69.92 ± 6.95 and 66.85 ± 5.72 respectively (Table-1). Comparison of mean bicarbonate level in different doses of metformin did not show any statistical significance (Table-2). Though differences of bicarbonate levels based on Clcr were statistically highly significant (p=0.0084), the values were within the normal reference range, hence there is no clinical significance to this finding (Table-3).

In three patients whose bicarbonate level was very low (15, 16.4 and 19.2mmol/L), doses of metformin was reduced and after one month their bicarbonate levels returned to normal (27.4, 25.6 and 26.2mmol/L) (Table-4).

Other antidiabetic agents used were second generation sulfonylureas like glibenclamide (25.0%), glimepiride (25.0%), glipizide (14.0%), gliclazide (7.0%); pioglitazone (28.0%) and insulin (17.0%). Antihypertensive agents used were metoprolol (19.0%), atenolol (19.0%), amlodipine (34.0%), enalapril (20.0%) and losartan (24.0%). Aspirin was prescribed in 45 patients and clopidogrel used in 11 patients. Among the diuretics, hydrochlorothiazide (10.0%), spironolactone (8.0%), furosemide (7.0%) and amiloride (2.0%) were used.

DISCUSSION

Diabetes is becoming increasingly common in the elderly, affecting more than one person in five.[17] Changes associated with ageing may affect the pharmacokinetics and pharmacodynamics of both sulphonylureas (increasing the risk of severe hypoglycaemia) and biguanides (increasing the risk of lactic acidosis).[18] Metformin, an antihyperglycemic, is widely used in the treatment of type 2 diabetes mellitus.[19] The major benefit of metformin therapy in the elderly is the lack of hypoglycemia when the drug is used as monotherapy. Another positive metabolic effect is weight loss or

Table-4: Characteristic feature of individual patients whose serum bicarbonate level is <22mmol/L

Characteristics	Case Patient 1	Case Patient 2	Case Patient 3
Gender	Female	Female	Male
Age(yrs)	72	73	78
Duration of disease (years)	5	7	18
Serum Creatinine (mg/dl)	1.0	1.0	1.4
Creatinine Clearnce (ml/min)	49.48	52.99	48.59
Total daily dose of metformin at baseline (mg)	1000	1700	1500
Serum bicarbonate level at baseline (mmol/L)	16.4	15	19.2
Total daily dose of metformin after intervention (mg)	500	-	1000
Serum bicarbonate level after 1 month (mmol/L)	25.6	27.4	26.4
Comorbidity	Hypertension, Peripheral neuropathy	Hypertension, IHD, Perpheral neuropathy, Hypothyroidism	Hypertension
Concomitant medication	Enalapril, Amitryptylline	Metoprolol, Ecospirin, Thyroxine, Amitryptylline	Enalapril, Clonidine, Atenolol

stabilization.[17] A rare, but important complication associated with this drug is the development of lactic acidosis: Overall mortality of lactic acidosis is approximately 50.0%.[19] Biguanides increase the risk of lactic acidosis, a potentially lethal complication that may occur because of drug accumulation. Metformin is almost entirely (90.0%) cleared renally and does not undergo hepatic metabolism or biliary excretion. The risk of lactic acid accumulation increases with the degree of renal impairment.[17] Renal impairment is frequent in aged diabetic patients, notably with type 2 diabetes.[20] Mild kidney failure is common and frequently unrecognized in elderly people.[21] Renal function can appear to be normal when measured by serum-creatinine concentration in older patients with reduced muscle mass, but calculation of GFR often reveals impairment.[22] In our study serum creatinine of all the patients were normal but when creatinine clearance (GFR) was calculated 52.0% of the patients showed moderate renal impairment (Clcr<60ml/min). Calculating the creatinine clearance is recommended in elderly patients, and metformin should be avoided if the value is less than 60 mL/min.[17] The increasing use of metformin in older patients for the treatment of diabetes mellitus warrants renewed attention to this severe side effect.[22] In our study patients with low Clcr, bicarbonate levels were also low. In the present study three patients serum bicarbonate levels were very low (15, 16.4 and 19.2mmol/L) and it was clinically significant. Of these three patients two patients doses of metformin was reduced; after one month serum bicarbonate was rechecked and it has come back to normal. Metformin was completely stopped in one patient and serum bicarbonate was normal after one month. By this we can say that some of the geriatric diabetic patients with impaired renal function are more prone to develop metformin induced acidosis and it can be avoided by monitoring serum bicarbonate levels. Though some of the patients were on high doses of metformin with reduced Clcr but still they well tolerated metformin therapy. There are standard methods to check metformin induced lactic acidosis by checking the anion gap or by checking serum lactate level but in developing countries like India cost of the investigations also counts. Checking serum bicarbonate level before initiation of metformin therapy and one month after the treatment is one of the easiest method in geriatric diabetics to reduce metformin induced acidosis which might precipitate to lactic acidosis in susceptible individuals.

Metformin has been used for >40years as an effective glucose lowering agent in type 2 diabetes mellitus. Many patients are treated with metformin despite having clinical conditions that place them at risk for developing acidosis. Metformin associated acidosis is rare and could be avoided by checking serum bicarbonate level in those patients whose creatinine clearance is less than 60ml/min. Hence it can be used as a marker to assess metformin induced acidosis in geriatrics.

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