

## BLOOD LACTATE LEVELS IN DIABETICS RECEIVING PHENFORMIN THERAPY †

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### INTRODUCTION :

The association between lactic acidosis and biguanide therapy has been reported by many workers. (Tranquada, Bernstein and Martin, 1963; Searle and Siperstein, 1975; Blumenthal and Streeten, 1975; Conlay and Lowenstein, 1975; Krishnaswamy et al. 1977) and this has led to the re-evaluation of these drugs in many countries. In the treatment of Maturity onset Diabetes we have been using phenformin in combination with glybenclamide, in those who do not respond to diet alone, with good results. (Viswanathan, 1973; Viswanathan, Ramachandran and Mohan Viswanathan, 1975; Viswanathan et al, 1976).

At the Diabetes Research Centre, Madras, the lactate and pyruvate levels are being studied in patients on phenformin therapy. This paper presents the details of a study undertaken to evaluate the blood lactate and its associated parameters in diabetics on phenformin therapy.

### MATERIALS AND METHODS :

Blood levels of lactate, pyruvate and the lactate/pyruvate ratio (L/P ratio) were estimated in 25 normal controls (Group A), 90 newly detected diabetics (Group B), and 100 diabetics treated with the combination therapy of phenformin and glybenclamide

(Group C). The age of the patients varied between 30 to 72 years. There were 15 men and 10 women in Group A, 62 men and 28 women in Group B, and 65 men and 35 women in Group C. In Group C, the dose of phenformin varied between 25 to 75 mg/day (Mean  $35 \pm 16.4$  mg) and that of glybenclamide between 2.5 to 5 mg/day. Blood urea, creatinine, 24 hour urinary proteins and creatinine clearance were estimated in all the patients prior to the treatment. Patients with renal, hepatic or cardiac complications were not given this therapy.

Fasting samples of blood were drawn for the estimation of lactate and pyruvate. Blood lactate was estimated by the method of Barker and Summerson (1941) and pyruvate by the method of Friedmann, and Haugen (1943). The lactate/pyruvate ratio was calculated in each case.

Serum electrolytes were measured and the anion gap was calculated.

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## RESULTS :

Blood levels of lactate, pyruvate and the L/P ratio in the three groups are presented in Table 1.

Statistically significant elevations were observed in lactate concentration in untreated, newly detected diabetics (Group B). The mean lactate value in patients who received phenformin (Group C) was slightly lower than that in controls (Group A), but the difference was not statistically significant.

The pyruvate concentration was higher in Group C, in comparison with Group A, but was lower than that in Group B.

The L/P ratio was a highest ( $16.1 \pm 6.7$ ) in Group B and lowest in Group C ( $9.3 \pm 6.2$ ). The difference in L/P ratio in the 3 groups was not significant statistically.

The anion gaps in Group B and C were  $14.2 \pm 5.3$  (SD) mEq/l and  $13.6 \pm 4.1$  mEq/l respectively. These values did not vary significantly from the mean anion gap of  $13.1 \pm 4.8$  mEq/l in the control group (Group A).

## DISCUSSION :

Blood lactate levels have been reported to be higher than normal in uncontrolled diabetics (Alberti and Hockaday, 1972; Wise et al, 1976). The pyruvate levels are also elevated in these patients (Fry and Butterfield, 1962; Rastogi and Singhal, 1969). Statistically significant elevations in lactate and pyruvate are seen in untreated diabetics (Group B) in our study also. However, the L/P ratio is not very much different from the normal levels due to the concomitant increase in both the parameters.

Biguanide therapy has been incriminated as one of the causes of lactic acidosis in diabetics. Dembo et al (1975) have shown that phenformin induces lactate accumula-

tion by direct and indirect mechanisms. The main mechanism is the inhibition of gluconeogenesis from its precursors like lactate, pyruvate and alanine resulting in accumulation of these metabolites. High concentration of phenformin reduces the conversion of NADH to NAD in the mitochondrial electron transport chain and this increased level of NADH favours the formation of lactate from pyruvate. Indirectly, pyruvate dehydrogenase activity is reduced by phenformin decreasing the oxidation of pyruvate via the TCA cycle, the accumulated pyruvate getting converted to lactate.

Increased levels of lactate have been reported by many workers, in diabetics treated with phenformin. (Tranquada, Bernstein and Martin, 1963; Searle and Siperstein, 1975; Blumenthal and Streeten, 1975; Conlay and Lowenstein, 1975; Krishnaswamy et al, 1977). A few other workers (Jackson et al, 1976; Christacopoulos et al, 1976; Czyzyk et al, 1976) have reported that no significant alterations occur in the blood lactate levels on treatment with biguanides.

The risk and the degree of hyperlactatemia is dependent to a great extent on the dose of biguanides used (Craig et al, 1960; Alberti and Natrass, 1977) and also on the presence of complications leading to the accumulation of the drug. (Wise et al, 1976). It is impossible to predict which diabetic will develop lactic acidosis while on treatment with phenformin. Conlay et al, (1977) are of the opinion that even patients without complications may go in for lactic acidosis and this might occur even with moderate doses of the drug. Alberti and Natrass (1977) noticed that if the cases with renal, hepatic and myocardial diseases are excluded, the number of phenformin-induced lactic acidosis will be small.

TABLE 1  
BLOOD LACTATE PYRUVATE AND THE L/P RATIOS IN THE STUDY GROUPS

Study Group	No.	Lactate mg/100 ml		Pyruvate mg/100 ml		L/P ratio ±SD
		Range	Mean±SD	Range	Mean±SD	
Controls (Group A)	25	6 - 20	14 ±4.6	0.5-1.1	0.9±0.2	15.9±4.5
		12.5-52.5	25.8±3	0.8-3.5	1.6±0.9	16.1±6.7
New Diabetics (Group B)	90		P<0.01		P<0.01	N.S.
Diabetics on Phenformin therapy (Group C)	100	7.7-20	12.5±1.3	0.8-1.9	1.3±0.3	9.3±6.2
			N.S.		P<0.01	N.S.

P value in comparison with Group A. N.S.: Non significant.

In our study, 100 patients in Group C, who received phenformin in the dose of 25-75 mg/day for periods varying from 6 months to 5 years have not shown any increase in the blood lactate level. The factors responsible for this may be (1) the selection of cases for the use of phenformin, i.e. exclusion of patients with renal and hepatic diseases and (2) the comparatively lower doses of the drug used namely  $35 \pm 16.4$  mg/day. Actually, in these patients the blood lactate levels are found to be lower than in the normal controls. The significance of this finding is unclear. This may be a reflection of the improved metabolic status of these patients. Perhaps, the combination therapy using phenformin and glybenclamide has a potentiating effect on the lactate turnover.

Serum electrolytes and the anion gap are also found to be within normal limits in all the cases.

From our preliminary results, it appears feasible to conclude that phenformin therapy, when used in small doses in carefully selected diabetics does not elevate blood lactate level.

#### SUMMARY

Blood lactate and pyruvate levels, in fasting state, were measured in normal controls (Group A), newly detected or untreated diabetics (Group B) and in patients receiving the combination of phenformin + glybenclamide for varying periods (Group C).

In Group B, lactate and pyruvate levels were increased to statistically significant levels. Group C showed no elevation in blood lactate level.

From this study, it appears that phenformin, if used in small doses in carefully selected cases, does not cause any increase in blood lactate level.

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