

## Letters to the Editor

### Lactic acidosis due to metformin therapy in a low risk patient

Sir,

We should like to take issue with Drs D.J. Tymms and B.A. Leatherdale (*Postgraduate Medical Journal* 64: 230-231) in their description of their patient as low risk. We believe she was, in fact, at high risk. A serum creatinine of 91  $\mu\text{mol/l}$  in a 46 kg female does not indicate normal renal function. Serum creatinine is related to lean body mass and 91  $\mu\text{mol/l}$  represents a considerable reduction of renal function. Moreover the dose of metformin used, 850 mg three times a day, is exceptionally high since drug therapy should be tailored to metabolic body size and not simply to a blanket maximum of 3 g/day.

The use of metformin as a first line drug in high dosage schedule in underweight individuals is not usually advised not the least for its probable lack of efficacy under such conditions and its reputed anorexic effect. In view of the patient's degree of renal insufficiency not only was metformin contraindicated in March 1984 but so also was her sulphonylurea therapy. Chlorpropamide is a long acting drug cleared largely through the kidneys. The patient should have been changed to a shorter acting sulphonylurea which does not rely on normal renal function to maintain a normal half life.

The patient's biochemistry on presentation was that of acute renal failure with circulatory collapse and hypoglycaemia. There is no evidence presented to suggest that metformin was the direct cause nor that lactic acidosis secondary to metformin therapy was the primary pathology.

The renal failure itself would be sufficient to increase lactic acidemia, and her presenting arterial pH was sufficiently low to account for further uncontrolled lactic acid production by the liver. At a pH of less than 7.1 the liver becomes a net lactic acid producer as opposed to the main lactate metabolizing group.

J. Broom  
I.S. Ross  
P.H. Whiting  
*Department of Chemical Pathology,  
University of Aberdeen,  
University Medical Building,  
Foresterhill,  
Aberdeen AB9 2ZD, UK.*

*This letter has been shown to Drs Tymms and Leatherdale who reply:*

Sir,

We thank Drs Broom, Ross and Whiting for their considered comments about our case report but we believe that their conclusions are based on theoretical considerations rather than published evidence. Although it is possible that our patient did have some impairment of renal function, in practice 'clinical risk' is assessed on serum creatinine without measurement of glomerular filtration rate. We are, however, unaware of any report of metformin-related lactic acidosis in a patient whose serum creatinine and urea concentrations

were within the normal range, except in cases of metformin overdose<sup>1</sup> or alcohol abuse.<sup>2</sup> In a review of 330 cases of biguanide-related lactic acidosis<sup>3</sup> the lowest serum creatinine concentration in the 12 metformin cases was 265  $\text{mmol/l}$  and other reports have suggested that metformin-related lactic acidosis occurs only with marked renal impairment.<sup>4</sup>

Similarly, we are not aware of any work to show that body weight influences the metabolism or the clearance of metformin from plasma. Pharmacokinetic studies<sup>5,6</sup> have shown that it is renal function which is the main determinant of metformin clearance.

The hypoglycaemia noted on the day of admission was easily corrected and had probably developed because the patient had not eaten breakfast. If the chlorpropamide had accumulated more prolonged hypoglycaemia would have been expected and this was not seen. We believe that metformin was causally related to the lactic acidosis for a number of reasons. The plasma metformin level was very high at 56.8  $\mu\text{g/ml}$  which is twice the value of 26  $\mu\text{g/ml}$  reported in one other fatal case of metformin-related lactic acidosis.<sup>4</sup> Also the lactate level was high and similar to the mean level of 16.9  $\text{mmol/l}$  reported in 330 cases of biguanide-induced lactic acidosis.<sup>2</sup> These cases had degrees of acidosis and renal failure similar to our case and yet the lactic acidemia was clearly due to the biguanide drugs. We think it is unlikely that hepatic lactic acid production was significant in our patient as the pH was 7.027 and there is evidence to suggest that significant amounts of lactate are only produced at levels below 7.0.<sup>7</sup>

We, of course, agree with the statement that metformin was not an ideal drug for this patient. As reported, she was repeatedly advised to change from oral hypoglycaemic agents to insulin but refused to do this.

D.J. Tymms  
B.A. Leatherdale  
*Royal South Hants Hospital  
Southampton SO9 1BG, UK.*

### References

1. Bismuth, C., Gaultier, M., Conso, F., Heuclin, C. & Assan, R. Acidose lactique induite par l'ingestion excessive de metformine. *Nouv Presse Med* 1976, 5: 261-263.
2. Ryder, R.E.J. Lactic acidotic coma with multiple medication including metformin in a patient with normal renal function. *Br J Hosp Pract* June 1984: 229-232.
3. Luft, D., Schmulling, R.M. & Eggstein, M. Lactic acidosis in biguanide treated diabetics. A review of 330 cases. *Diabetologia* 1978, 14: 75-87.
4. Assan, R., Heuclin, Ch., Ganeval, D., Bismuth, Ch., George, J. & Girard, J.R. Metformin induced lactic acidosis in the presence of renal failure *Diabetologia* 1977, 13: 211-217.
5. Hermann, L.S. Metformin: a review of its pharmacological properties and therapeutic use. *Diabetes Metab* 1979, 3: 233-245.
6. Tucker, G.T., Casey, C., Phillips, P.J., Connor, H., Ward, J.D. & Woods, H.F. Metformin kinetics in health subjects and in patients with diabetes mellitus. *Br J Clin Pharmacol* 1981, 12: 235-246.
7. Cohen, R.D. & Woods, H.F. Clinical and biochemical aspects of lactic acidosis. Blackwell Scientific Publications, Oxford, 1976.



## Lactic acidosis due to metformin therapy in a low risk patient

D.J. Tymms and B.A. Leatherdale

*Postgrad Med J* 1989 65: 57

doi: 10.1136/pgmj.65.759.57-a

---

Updated information and services can be found at:  
<http://pmj.bmj.com/content/65/759/57.2.citation>

---

### Email alerting service

*These include:*

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

---

### Notes

---

To request permissions go to:  
<http://group.bmj.com/group/rights-licensing/permissions>

To order reprints go to:  
<http://journals.bmj.com/cgi/reprintform>

To subscribe to BMJ go to:  
<http://group.bmj.com/subscribe/>