Diabetologia 14, 71–74 (1978)

Diabetologia

Editorial

Biguanides

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The wisdom of using biguanides in the treatment of diabetes has been under discussion in recent years. In the last few months the antagonists have gained a marked advantage over the protagonists with the banning of biguanides in several countries. The problem has been highlighted with the action of the Food and Drug Administration in the United States banning the general use of phenformin as of October 1977. This has caused considerable unhappiness amongst many members of the medical profession for several reasons. First, phenformin was the only biguanide available in the U. S. A. so that effectively all use of biguanides has now ceased in that country. This may have deleterious effects on at least some patients who have been treated successfully thus far, and where there may be compelling reasons for not changing them to other agents. Second, there is a considerable feeling that legal and bureaucratic interference in a medical matter does not necessarily achieve the right result for the right reasons. It could, however, be said that it is a sad indictment of the medical profession that it abused these drugs for so long that bureaucratic intervention was inevitable. Third, many doctors may feel that although the banning of phenformin was a correct decision, the arguments and data which led to this end result were wrong.

It is perhaps timely, therefore, when these drugs are still available in many countries, to re-examine the problem of the biguanides and particularly the reasons which have led them to be withdrawn from several markets. That there is still considerable interest in these compounds is exemplified by the presence in this issue of Diabetologia of three papers on the subject.

In the United States the main attention was directed toward the University Group Diabetes Program which reported an increased cardiovascular mortality in diabetics treated with phenformin [1]. In addition to the extensive criticism of this report a number of other groups have failed to confirm the findings with regard to phenformin [2, 3]. In view of this, European diabetologists have concentrated more upon the metabolic effects of biguanides, particularly phenformin, and the role they play in the development of lactic acidosis [4, 5].

There are more than 300 reported cases of phenformin associated lactic acidosis in the literature and since this number is sufficient to discourage further reporting of isolated cases the true incidence is undoubtedly far in excess of this. In addition to frank lactic acidosis small, but significant effects upon lactate metabolism [6, 7] and circulating lactate concentrations have been observed in phenformin treated diabetics, in the fasting state [8], during oral glucose tolerance tests [9], and during 12 hour studies [10]. The elevated blood lactate concentrations observed occur in patients treated by phenformin alone, and in combination with a sulphonylurea [11].

The focussing of attention upon lactate metabolism has overshadowed a number of other metabolic effects produced by biguanides. Abnormally elevated concentrations of blood alanine, pyruvate, and total ketone bodies as well as the lactate/pyruvate ratio and 3-hydroxybutyrate/acetoacetate ratio occur during therapy with phenformin [11, 12], metformin [11], and buformin [13] and it is clear that the abnormal blood lactate elevation is but one part of the metabolic derangement by which biguanides achieve a hypoglycaemic effect. These effects may, however, be more important overall than lactic acidosis. The latter is relatively rare, although largely lethal when it does occur, while the less severe abnormalities appear to be present in *all* patients receiving the drugs. The significance to the patient of

these abnormalities over an extended time period remains uncertain.

The question arises: can the use of phenformin be restricted to those patients in whom it might be considered safe? In search of an answer a number of authorities have examined retrospectively reports of cases of phenformin-associated lactic acidosis. Contra-indications to its use include hepatic, renal and cardiovascular disease [4, 5, 14, 15]. Detecting the presence of these contra-indications before the instigation of therapy may present problems. Patients with retinopathy and high blood lactate concentrations, for example, may have normal serum creatinine concentrations but impaired renal function [16]; thus renal impairment should be assessed by creatinine clearance estimation. Furthermore the development of these associated conditions during therapy places an additional burden upon the awareness of the physician. Who could guarantee that all their biguanide-treated patients would have this inconvenient investigation performed every 6 or 12 months during therapy, and indeed which time interval is appropriate and what magic number marks the boundary between safety and potential disaster. In addition a proportion of lactic acidosis cases occur when an acute episode such as myocardial infarction, or cerebro-vascular accident, or septicaemia complicate phenformin therapy when the most meticulous previous screening for contra-indications is unlikely to be fruitful.

Few drugs, however, are totally devoid of side-effects and although the mortality of lactic acidosis is high [4, 5] the risk to the individual patient is small. It might even be considered justifiable if (a) careful prescribing reduced it still further, and (b) if the therapy was of undoubted value in these carefully selected patients. Biguanides are of value as an adjunct to caloric restriction in the obese maturity-onset diabetic, and when used to supplement sulphonylurea therapy where control of blood glucose is considered inadequate on sulphonylurea therapy only. In the latter case they may be used to delay the instigation of insulin therapy or obviate it entirely in unsuitable cases. Since there is no reasonable alternative at present in such situations many physicians would regret the withdrawal of biguanides and would prefer to maintain an option to prescribe a biguanide if not phenformin.

It is pertinent to question whether all three biguanides, phenformin, metformin, and buformin, produce the same degree of metabolic abnormality. Schäffer has delineated the subcellular site of action of guanidine derivatives explaining the metabolic effects through an alteration of the electrostatic surface potential of the mitochondrial membrane [7]. This mechanism may well explain the diverse effects upon intestinal absorption of glucose [18, 19], amino acids [20], other hexoses [21] and vitamins [22]; upon peripheral utilisation of glucose [23]; and upon hepatic gluconeogenesis [24, 25, 26]. While the qualitative effect upon membranes may be the same for all biguanides the quantitative effect is related to the length of the side-chain attached to the biguanide moiety [27]. Subcellular concentration of the particular biguanide is also important and it is clear that tissue distribution of the three drugs displays marked differences. Phenformin depends upon hepatic microsomal hydroxylation for inactivation [28] and concentrations markedly in excess of circulating concentrations are found intracellularly, particularly in liver and intestinal cells. Metformin, however, is excreted unchanged via the kidney [29]. It might be expected, therefore, that these differences in metabolism and distribution could be reflected in a difference of effect upon intermediary metabolism.

Regrettably the practical situation in patients is less clear. Subjects pretreated with one of the three biguanides and subjected to stimuli designed to raise blood lactate, e.g. fructose, or ethanol, showed no difference in hyperlactataemic response between biguanides [30]. Similarly, in random blood lactate estimation in clinic patients there was no significant difference in the hyperlactataemia observed between patients taking phenformin and those taking metformin [31]. It is possible, however, that short term experiments may bias results favourably towards phenformin, allowing insufficient time for intracellular accumulation of the drug, while in random samples from patients results may similarly be biased in favour of phenformin by the timing of the sample since the highest blood lactate concentrations are found after the midday or evening meal [10].

Arguing against the similarity of biguanides in their metabolic effects, however, is the wide discrepancy in the incidence of lactic acidosis. Despite heavy prescribing of metformin in countries such as France and Switzerland lactic acidosis remains extremely uncommon and the majority of cases have occurred in patients where its use would be considered by many to be totally inappropriate [32]. This is in stark contrast to the incidence of lactic acidosis during phenformin or buformin therapy and cannot be explained on the basis of a lower consumption of metformin than the other biguanides.

In addition, during 12 hour metabolic studies in the same patients during successive periods of therapy with phenformin and metformin, the former produced significantly greater abnormalities in

blood lactate, pyruvate, lactate/pyruvate ratio, alanine, total ketone bodies, 3-hydroxybutyrate/acetoacetate ratio, and glycerol, *despite similar concentrations of blood glucose* during the two therapies [10].

There is some evidence, therefore, that metformin produces less metabolic abnormality than either phenformin or buformin in exerting a hypoglycaemic effect, and clear evidence that metformin-induced lactic acidosis has a significantly lower incidence than lactic acidosis during phenformin or buformin therapy. Thus there would seem little beyond idiosyncratic preference and occasional gastro-intestinal intolerance to support the continued use of phenformin and perhaps buformin. Quite clearly, however, it remains necessary to assess patients fully, before and during metformin therapy with particular attention to renal function.

In conclusion biguanides may still have a role in the treatment of hyperglycaemia. Physicians must however be clear that they may not be treating all the metabolic complex that is diabetes but only one, albeit important, aspect, while creating by their very mechanisms of action further abnormalities. Metformin would appear to be the biguanide of choice but prescribers should be certain that in the individual patient metformin therapy is preferable to diet alone, sulphonylurea alone or insulin. Should phenformin have been banned in certain countries? On balance the answer is probably yes in view of its inappropriate administration to many patients but it is sad to have such decisions thrust upon the profession by legal pundits, when logic, knowledge and education are available to us all.

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