PAPERS AND ORIGINALS

Treatment of Diabetic Coma with Continuous Low-dose Infusion of Insulin

M. McB. PAGE, K. G. M. M. ALBERTI, R. GREENWOOD, K. A. GUMAA, T. D. R. HOCKADAY, C. LOWY, J. D. N. NABARRO, D. A. PYKE, P. H. SÖNKSEN, P. J. WATKINS, T. E. T. WEST

British Medical Journal, 1974, 2, 687-690

Summary

Thirty-eight patients in diabetic coma from four different centres were treated with a continuous low-dose intravenous infusion of insulin at an average dose of 7.2 IU/hr. All patients recovered rapidly except for one profoundly shocked patient who died. The mean fall in plasma glucose was 58% four hours after the start of insulin. Blood ketone bodies and plasma free fatty acids showed a similar response. There was no significant difference in plasma glucose response according to severity of acidosis or previous treatment with insulin. Hypokalaemia was uncommon. In the treatment of diabetic coma this technique has proved simple, safe, and effective.

Introduction

Many different regimens of insulin administration have been

Diabetic Department, King's College Hospital, London SE5 9RS

M. McB. PAGE, M.R.C.P., Registrar (Present appointment: Research Fellow British Heart Foundation)

D. A. PYKE, M.D., F.R.C.P., Consultant Physician

P. J. WATKINS, M.D., M.R.C.P., Consultant Physician

Nuffield Department of Clinical Medicine and Division of Medicine Radcliffe Infirmary, Oxford

K. G. M. M. ALBERTI, D.Phil., M.R.C.PATH., Medical Assistant, (Present appointment: Professor of Chemical Pathology, Southampton General Hospital)

T. D. R. HOCKADAY, D.Phil., F.R.C.P., Consultant Physician

Department of Medicine and Department of Metabolic Diseases, St. Thomas's Hospital Medical School, London S.E.1

P. H. SÖNKSEN, M.D., M.R.C.P., Senior Lecturer

C. LOWY, M.Sc., M.R.C.P., Senior Lecturer

T. E. T. WEST, M.R.C.P., Lecturer

R. GREENWOOD, M.R.C.P., Registrar

Middlesex Hospital, London W1P 7PN

J. D. N. NABARRO, M.D., F.R.C.P., Consultant Physician

K. A. GUMAA, M.B., Ph.D., Research Fellow, Biochemistry Department (Present appointment: Senior Lecturer, Department of Biochemistry, University of Khartoum)

advocated in the management of diabetic ketoacidosis, but none has been generally accepted. Some authors stress the importance of ketonaemia in deciding the initial dose of insulin, and others are guided by blood glucose levels. In the presence of severe ketoacidosis amounts of 300-400 IU of insulin have been advocated (Bradley, 1971; Hockaday and Alberti, 1972). Most regimens include complex advice about further doses to be given every two or four hours according to the response of the blood glucose. There is a common impression that the more severe the acidosis the more insulin is needed (Phear, 1963) though recent work has cast doubt on this (Hockaday and Alberti, 1972). In one prospective study no difference in clinical response was found between groups of patients receiving 80, 160, or 240 IU of insulin initially (Smith and Martin, 1954).

There is no valid evidence that large doses of insulin are needed, and they may carry risks, in particular hypokalaemia (Alberti, 1974), hypoglycaemia, and hyperlactataemia (Alberti *et al.*, 1973). Over the last 50 years occasional reports have appeared on the use of small doses of insulin (Faber and Holst, 1927; Katsch, 1946; Menzel and Jutzi, 1970), but they have had little impact on clinical practice. In normal subjects maximal hypoglycaemic activity is achieved by blood insulin levels in the range of 20-200 μ U/ml (Christensen, 1968; Sönksen, *et al.*, 1973). Sönksen *et al.* (1972) have also shown that the rate of fall of blood glucose in uncontrolled diabetes is uniformly rapid with blood insulin concentrations in this range, and that these concentrations can be achieved by insulin infusion at rates of 2-12 IU/hr. Alberti *et al.* (1973) used small hourly doses of insulin given intramuscularly to achieve blood concentrations in this range and found them to be effective in ketoacidotic patients.

The technique of constant intravenous infusion offers advantages over intermittent dose regimens—insulin action begins at once and a steady blood concentration in the effective range can be maintained and can be altered or ended almost instantaneously. Since the half life of insulin in blood is between three and five minutes (Turner *et al.*, 1971; Sönksen *et al.*, 1973) risk of hypoglycaemia is negligible once the infusion is stopped.

We describe here the use of a continuous low-dose intravenous infusion of insulin in the treatment of diabetic "coma."

Patients and Methods

Patients from four different centres with severe uncontrolled diabetes mellitus were studied. All needed emergency treatment with intravenous fluids and insulin. There were 38 cases: 21 from King's College Hospital, five each from the Radcliffe Infirmary and the Middlesex Hospital, which were consecutive admissions, and seven cases from St. Thomas's Hospital which were consecutive admissions on two of four medical firms.

Plasma glucose, urea, and electrolytes were measured in routine laboratories. Enzymatic methods were used for the measurement of blood 3-hydroxybutyrate and acetoacetate (Williamson *et al.*, 1962), lactate and pyruvate (Hohorst *et al.* 1959), and glycerol (Kreutz, 1962). Plasma free fatty acids (F.F.A.) were measured colorimetrically (Duncombe, 1963; Itaya and Ui, 1965). Serum insulin (Soeldner and Slone, 1965) was measured by double antibody radioimmunoassay using M.R.C. 66/304 and human insulin (Wellcome Laboratories) as standards.

The term "ketone bodies" refers to the total of 3-hydroxybutyrate and acetoacetate. Results are given as means $\pm$ S.E. Statistical significance was assessed by Student's *t* test.

Clinical Details

Of the 38 patients 31 were ketoacidotic, five were hyperosmolar non-ketotic, and two had uncomplicated hyperglycaemia. Seventeen patients had never previously received insulin. There were 15 males and 23 females. The age range was from 9-86 years with six patients under 14 years and five over 70 years. Twenty-eight patients had a depressed level of consciousness—one was totally unresponsive, seven responded to pain and loud noise only, and 20 were drowsy but obeyed commands—and the remaining 10 were fully conscious. Three patients were hypotensive with systolic blood pressure < 80 mm Hg and a further three were hypothermic with rectal temperature $< 35^{\circ}\text{C}$. Arterial blood pH was measured in 12 patients and in three was below 7.0.

There were five cases of bronchopneumonia, five of urinary tract infections, two of upper respiratory tract infections, and one case each of gastroenteritis, pyrexia of unknown origin, and cardiac failure as complicating factors on admission.

BIOCHEMICAL VALUES ON ADMISSION

Plasma glucose ranged from 295-2,010 mg/100 ml, mean 809 ± 57 , and blood ketone body concentrations from 2.7-18.6 mmol/l., mean 11.3 ± 0.8 ($n = 25$). Other mean values were blood urea 92 ± 11 mg/100 ml ($n = 38$), lactate 2.11 ± 0.21 mmol/l. ($n = 24$), pyruvate 0.092 ± 0.010 mmol/l. ($n = 15$), glycerol 0.24 ± 0.03 mmol/l. ($n = 15$), and plasma F.F.A. 1.64 ± 0.26 mmol/l. ($n = 13$). Serum potassium ranged from 2.8-8.4 mEq/l., mean 5.3 ± 0.8 . In the 17 patients who had never previously received insulin admission concentrations averaged $5 \mu\text{U/ml}$ and ranged from unrecordable—that is, $< 2 \mu\text{U/ml}$ —to $14 \mu\text{U/ml}$.

TREATMENT

Insulin.—On admission all patients received intravenous normal saline, and insulin infusion was begun a quarter of an hour to three hours afterwards. At King's College Hospital insulin was administered as follows: 24 IU of soluble insulin was added to a plastic syringe and the volume made up to 20 ml with saline. Using a mechanical pump the insulin was given in all but one case at a rate of 5 ml (6 IU) hourly via a four-way tap directly into the intravenous fluid line. A fresh insulin solution was prepared every four hours immediately before use. The rate of insulin administration was independent of the intravenous drip flow rate. At the other centres the procedure was similar but

0.5 g/100 ml human albumin (Lister Institute) was added to the insulin solution, and the solution was administered at rates from 3-24 IU/hr (average 8.6 IU/hr). Saline and insulin infusion was continued until the plasma glucose was between 100 mg and 250 mg/100 ml, when glucose infusions were begun. On termination of the insulin infusion subcutaneous insulin was given immediately and as needed.

Intravenous Fluids.—Normal saline (0.154 mol/l.) was infused initially. This was changed to half-strength saline in the four patients with plasma sodium above 155 mEq/l. A mean of 3.66 l. (range 1.5-6) was given in the first six hours and 5.51 l. (range 2.75-9.0) in the first 12 hours. Mean potassium supplements were 54 mEq (range 13-124) by six hours and 89 mEq (range 13-260) by 12 hours. Only 15 patients received bicarbonate, in an average dose of 156 mEq (range 33-403).

Results

GLUCOSE

Plasma glucose concentration fell on infusion of saline alone in 12 out of 18 patients in whom values were measured twice before the start of insulin. After insulin had been started the rate of fall of glucose was rapid and steady in all but one case. The individual plasma glucose responses to treatment are shown in fig. 1.

FIG. 1—Individual plasma glucose concentrations during insulin infusion.

There was no significant difference in this relatively small study in plasma glucose response according to age, severity of acidosis, or previous treatment with insulin. The magnitude of fall by four hours was 59% in the 10 patients with the highest blood ketones compared with 55% in the 10 with the lowest ketones. In the six patients with proven bacterial infections the fall at four hours was 33% compared with 60% in those without infection ($0.1 > P > 0.05$).

KETONE BODIES

Blood ketone body concentrations fell steadily from an average admission value of 11.3 mmol/l. ($n = 26$) and by four hours had reached about half this value, 5.73 mmol/l. (fig. 2). The main

FIG. 2—Individual blood ketone body concentrations during insulin infusion.

fall was in 3-hydroxybutyrate but there was also a slow and steady fall in acetoacetate. By five hours the ratio of 3-hydroxybutyrate to acetoacetate had fallen from over 4 to about 1.

LACTATE

Blood lactate fell from an average of 2.11 mmol/l. on admission to a level of 1.50 mmol/l. after four hours ($n = 24$). The highest blood lactate concentrations showed the greatest fall and concentrations less than 1.5 mmol/l. generally showed a slight rise at four hours.

FREE FATTY ACIDS AND GLYCEROL

Plasma F.F.A. declined from an average of 1.84 mmol/l. on admission to reach a value of 0.92 mmol/l. after four hours. Glycerol levels fell in the first four hours and then rose slightly (fig. 3).

SERUM INSULIN

Serum insulin concentrations were measured by different

FIG. 3—Mean (± 1 S.E. of mean) plasma free fatty acids (F.F.A.) and glycerol and serum insulin concentrations during insulin infusion. Numbers of patients are given in parentheses.

techniques in the various centres, but cross-sampling showed close comparability of results. Values were nearly all in the range of 20–200 μ U/ml. There was considerable variation both within and between individual patients (see fig. 3), but after half an hour of starting insulin infusion there was no significant difference between concentrations with the passage of time except in those receiving stepwise increases in infusion dose. There was also no difference in insulin concentrations between patients treated with and without albumin.

POTASSIUM

Hypokalaemia (plasma potassium < 3 mEq/l.) was present in two patients on admission. In one of these plasma potassium fell from 2.8 to 2.5 mEq/l. after two hours despite supplements of 59 mEq of potassium but subsequently rose. Concentrations of 3.0 mEq/l. at one hour and 2.4 mEq/l. at 12 hours developed in two further patients. In the second of these two patients plasma glucose and potassium had been normal nine hours previously. Another patient with gross hyperlipidaemia and pseudohyponatraemia of 101 mEq/l. had a potassium concentration of 2.8 mEq/l., but the corrected value was over 3.0 mEq/l. In the other cases plasma potassium values were and remained within the normal range.

MORTALITY

One patient died. He was a 69-year-old previously undiagnosed diabetic who arrived moribund and had two cardiac arrests before treatment could be started. He remained in cardiogenic shock throughout and died at 10 hours. Though his plasma glucose initially rose for three hours (see fig. 1), until his insulin infusion was increased from 6 IU to 12 IU/hr (and later to 24 IU/hr), his blood ketone bodies and lactate decreased steadily from the start of insulin treatment. The delayed fall in blood glucose may have been related to his treatment with 200 mg of hydrocortisone intravenously immediately after the cardiac arrests.

Discussion

Treatment of diabetic ketoacidosis by infusion of small amounts

of insulin was effective in the 38 cases in this study. The technique of intravenous infusion in diabetic coma was first described in 1960 (Rossier *et al.*, 1960; Völlm, 1960) with an initial dose of 100 IU/hr, and further reports have followed using doses of 100 IU (Froesch *et al.*, 1966) and 50 IU/hr (Genuth, 1973). Infusion of low dose of insulin was first described by Sönksen *et al.* (1972), who used amounts from 1.5-12 IU/hr. Low dose insulin infusion maintains adequate blood concentrations of insulin. In 70-kg adults an infusion rate of 6 IU/hr produces an average steady state serum insulin concentration of 100 μ U/ml, but biological variation between patients in the factors determining the pharmacokinetics of insulin metabolism results in observed serum insulin concentrations ranging from 20 to 200 μ U/ml. (Sönksen *et al.*, 1972, 1973). In children a dose of 0.1 IU/kg/hr is theoretically sufficient to achieve an average blood insulin concentration of 100 μ U/ml. (Sönksen *et al.*, 1973).

Though continuous infusion is the most direct way of giving insulin previous work has discouraged its use. Insulin is variably adsorbed to glass and plastic, an effect which can be almost completely abolished by the addition of a small amount of human albumin to the insulin solution (Sönksen *et al.*, 1965). Weisenfeld *et al.* (1968) showed that the adsorption of insulin from non-protein-containing solutions may approach 30-40% depending on its concentration, the time in contact with an adsorbing surface, and the rate of flow and that adsorption is inhibited by the presence of negatively charged proteins such as human serum albumin. The degree of adsorption seems to be negligible when insulin is present in relatively high concentrations in the infusion syringe. Serum insulin concentrations and plasma glucose response were similar in our patients who were treated with and without albumin, and its addition therefore seems unnecessary. With insulin doses in the range used in this study the variability of adsorption due to different types and makes of plastic materials should not be important.

High doses of insulin have previously been used to anticipate insulin "resistance," thought to be a risk in some patients with severe acidosis, infection, or an excess of insulin antibodies. A striking feature in the present series was the lack of effect of ketoacidosis or previous insulin treatment on the glucose response to insulin. Alberti *et al.* (1973), using small doses of insulin given intramuscularly, also found a uniform response and did not encounter insulin resistance. The only patient to show a rise in plasma glucose during insulin infusion was the man who had two cardiac arrests. He had shown signs of early metabolic improvement—that is, a fall of ketones from the start of treatment—and had received a large dose of hydrocortisone, an insulin antagonist. His plasma glucose fell satisfactorily when the infusion rate was increased to 12 IU/hr. It is a simple matter to raise the circulating insulin concentration if the metabolic response is inadequate by increasing the infusion rate, when a new steady state is obtained within 10 minutes.

The rate of fall of blood glucose during low dose insulin infusion is similar to that when insulin is given by other routes in larger amounts. In the present series the mean plasma glucose four hours after insulin infusion had fallen by 58%, which is similar to the results in a previous series of 100 cases at King's College Hospital using conventional high doses of insulin given by intravenous and intramuscular injections (Sheldon and Pyke, 1968). Alberti *et al.* (1973) had similar results with a regimen of small intramuscular doses hourly. Furthermore, the rate of fall of plasma glucose was no greater with an insulin infusion rate of 50 IU/hr (Genuth, 1973). Blood glucose is known to fall with saline infusion alone (Alberti *et al.*, 1973), as was observed in 12 of 18 of our patients, but the rate of fall increases when insulin is added. Early and adequate intravenous fluid replacement remains an essential part of the treatment of diabetic "coma" whatever insulin treatment regimen is used.

There was a more rapid fall in 3-hydroxybutyrate than in acetoacetate (Stephens *et al.*, 1971). By five hours after the start of insulin the ratio of 3-hydroxybutyrate to acetoacetate had fallen to about 1, suggesting an earlier return to normal of the

mitochondrial redox state (Gumaa *et al.*, 1971).

The danger of hypokalaemia may be lessened by using small doses of insulin (Alberti *et al.*, 1973). Large doses of insulin seem to lead to a faster fall of plasma potassium, probably because of increased uptake in peripheral tissues. In our cases, relatively small amounts of potassium were added, but hypokalaemia was not a problem. It is possible that the steady insulin concentrations we achieved were effective in inhibiting hepatic gluconeogenesis without stimulating peripheral uptake of glucose and thus led to a fall in blood glucose without marked uptake of potassium by peripheral tissues.

The method described here is simple and involves no complicated calculation of insulin dosage according to clinical state or biochemical findings. About 6 IU/hr given by continuous infusion was found to be a safe starting dose and this can be halved or doubled hourly at will on the basis of response to treatment. A standard regimen simplifies management for medical and nursing staff, but it should not lead to a false sense of security, as diabetic "coma" remains a medical emergency. Blood glucose and electrolytes need to be measured often and the results must be available quickly whatever type of treatment is used.

The technique of continuous intravenous infusion of low doses of insulin seems also to be suitable for the management of unstable or refractory diabetes in other circumstances—for example, after myocardial infarction or operation and during labour.

The use of a continuous infusion of insulin in low dose seems to have advantages over standard large dose regimens in the treatment of diabetic "coma" and in our experience has proved simple, safe, and effective.

We thank Mrs. Rowena Oakley, Miss Christine V. Tompkins, and Mr. John Perkins for biochemical studies and all the housemen and members of nursing staff who co-operated to make this study possible.

K.G.M.M.A. thanks the Wellcome Trust for generous financial support. K.G.M.M.A., T.D.R.H., J.D.N.N., and P.H.S. thank the British Diabetic Association for grant in aid.

References

- Alberti, K. G. M. M., Hockaday, T. D. R., and Turner, R. C. (1973). *Lancet*, **2**, 515.
- Alberti, K. G. M. M. (1974). *Symposium on Advanced Medicine*. In press.
- Bradley, R. F. (1971). In *Joslin's Diabetes Mellitus*, ed. A. Marble, *et al.* 11th edn., p. 381. Philadelphia, Lea and Febiger.
- Christensen, N. J., and Ørskov, H. J. (1968). *Journal of Clinical Investigation*, **47**, 1262.
- Duncombe, W. G. (1963). *Biochemical Journal*, **88**, 7.
- Faber, K., and Holst, J. E. (1927). *Acta Medica Scandinavica*, **65**, 461.
- Froesch, E. R., Bühlmann, A., and Rossier, P. H. (1966). *Verhandlungen der Deutschen Gesellschaft für Innere Medizin*, 72 Kongress, p. 199. Munich, Bergmann.
- Genuth, S. M. (1973). *Journal of the American Medical Association*, **223**, 1348.
- Gumaa, K. A., McLean, P., and Greenbaum, A. L. (1971). *Essays in Biochemistry*, **7**, 39.
- Hockaday, T. D. R., and Alberti, K. G. M. M. (1972). *Clinical Endocrinology and Metabolism*, **1**, 751.
- Hohorst, H. J., Kreutz, F. H., and Bücher, T. (1959). *Biochemische Zeitschrift*, **332**, 18.
- Itaya, K., and Ui, M. (1965). *Journal of Lipid Research*, **6**, 16.
- Katsch, G. (1946). *Die Gesundheitswesen*, **1**, 651.
- Kreutz, F. H. (1962). *Klinische Wochenschrift*, **40**, 362.
- Menzel, R., and Jutzi, E. (1970). *Die Gesundheitswesen*, **25**, 727.
- Phear, D. N. (1963). *British Medical Journal*, **2**, 1581.
- Rossier, P. H., *et al.* (1960). *Schweizerische Medizinische Wochenschrift*, **90**, 952.
- Sheldon, J., and Pyke, D. A. (1968). In *Clinical Diabetes*, p. 437. London, Blackwell.
- Smith, K., and Martin, H. E. (1954). *Diabetes*, **3**, 287.
- Söldner, J. S., and Slone, D. (1965). *Diabetes*, **14**, 771.
- Sönksen, P. H., *et al.* (1965). *Diabetologia*, **1**, 208.
- Sönksen, P. H., *et al.* (1972). *Lancet*, **2**, 155.
- Sönksen, P. H., *et al.* (1973). *Clinical Science and Molecular Medicine*, **45**, 633.
- Stephens, J. M., Sulway, M. J., and Watkins, P. J. (1971). *Diabetes*, **20**, 485.
- Turner, R. C., *et al.* (1971). *Journal of Clinical Endocrinology and Metabolism*, **33**, 279.
- Völlm, K. (1960). *Schweizerische Medizinische Wochenschrift*, **90**, 1080.
- Weisenfeld, S., *et al.* (1968). *Diabetes*, **17**, 766.
- Williamson, D. H., Mellanby, J., and Krebs, H. A. (1962). *Biochemical Journal*, **82**, 90.