CLINICAL RESEARCH

Oral glucose decreases hepatic extraction of insulin

OWAIN M GIBBY, C NICHOLAS HALES

Abstract

Peripheral venous (plasma) insulin and C-peptide concentrations were measured in eight normal subjects given oral or intravenous glucose sufficient to produce similar plasma glucose concentrations. The expected increased insulin response to oral as compared with intravenous glucose was not matched by a comparable increase in C-peptide concentration. The ratio of insulin to C-peptide concentrations doubled 30 minutes after oral glucose was given; no comparable rise was seen with intravenous glucose ($p=0.01$).

This finding is interpreted as evidence for decreased hepatic extraction of insulin after administration of oral glucose. Such a decrease could account for at least half of the well known difference in peripheral insulin concentrations after administration of oral as compared with intravenous glucose.

Introduction

Peripheral insulin concentrations are greater after an oral or jejunal glucose load than after an intravenous load.^{1,2} It was postulated that gastrointestinal factors that stimulated the release of insulin were released during glucose absorption. Recently several gastrointestinal hormones have been studied to determine whether they fulfil the criteria³ for a hormone responsible for part or all of the enteroinsular axis.⁴ It is also possible that the nervous system may play a part in the enhanced insulin response to oral glucose.

An investigation⁵ of the C-peptide secretory response to oral as compared with intravenous glucose in diabetics with heterotopic pancreatic grafts showed no difference between the responses. One report of the insulin and C-peptide responses to oral and intravenous glucose in normal subjects⁶ suggested

that the C-peptide response to oral as opposed to intravenous glucose was not as augmented as that of insulin. As this finding appeared to have been neglected and no confirmatory data or further studies had been published we reinvestigated the problem. The explicit assumption underlying these studies is that insulin and C-peptide are released in equimolar amounts.⁷

Subjects and methods

We studied eight normal male volunteers (mean $\pm$ SD age 26.5 ± 3.8 years, mean weight 74.0 ± 9.3 kg, mean percentage of ideal body weight $99.8 \pm 8.8\%$). After an overnight fast an intravenous cannula was inserted (into one arm for the study of oral glucose; into both arms for the study of intravenous glucose). The subject remained supine throughout the test and did not smoke, eat, or drink. Studies of oral and intravenous glucose were performed within, or usually at, an interval of one week. In the study of oral glucose 50 g glucose as Lucosade was given at time 0. During the intravenous study infusion of 50% dextrose (Phoenix Pharmaceutical, Gloucester) was begun at time 0. The rate of infusion was adjusted so that concentrations of glucose during this test were similar to those achieved during the study of oral glucose.

Blood was taken at -15, 0, 5, 15, 30, 90, 120, 150, and 180 minutes for estimation of plasma glucose, insulin, and C-peptide concentrations. Glucose concentration was measured by the glucose oxidase method and insulin⁸ and C-peptide⁹ concentrations by radioimmunoassay. The interassay variation for insulin was 10.4% and intra-assay variation 4.9%. For C-peptide the variations were 12.7% and 3.8% respectively. The sensitivity of the insulin assay was 0.025 nmol/l (15 ng/100 ml) and of the C-peptide assay 0.01 nmol/l (3 ng/100 ml). Informed consent was given by the volunteers after the study had been approved by the hospital ethical committee. The Wilcoxon matched pairs signed rank test was used for all statistical analyses.

Results

Glucose—Plasma concentrations of glucose (fig 1) were not significantly different between the oral and intravenous tests except at 90 minutes, when the plasma glucose concentration during the oral test was significantly lower than that during the intravenous test ($p=0.05$). Thus at no time were the glucose concentrations achieved by the oral tests significantly higher than those achieved during the intravenous test; during the critical early stage the concentrations were very similar between the two tests.

Insulin—Basal concentrations of insulin were similar in both tests.

Department of Clinical Biochemistry, University of Cambridge, Addenbrooke's Hospital, Cambridge CB2 2QR

OWAIN M GIBBY, MRCP, MRC training fellow (now lecturer in medicine, University of Birmingham)

C NICHOLAS HALES, PHD, MD, professor of clinical biochemistry

Mean plasma insulin concentrations rose rapidly in response to the oral glucose load compared with the intravenous load and were significantly greater at 30 minutes ($p=0.01$). During the intravenous test, however, the insulin concentration rose at a slower rate and reached a peak at 60 minutes, compared with 30 minutes for the peak in the oral test. Only when the insulin concentrations had

FIG 1—Plasma glucose, insulin, and C-peptide concentrations (means $\pm$ SEM) after oral and intravenous administration of glucose. * $p=0.05$; ** $p=0.01$.

Conversion: SI to traditional units—Glucose: 1 mmol/l $\approx$ 18 mg/100 ml. Insulin: 1 nmol/l $\approx$ 0.6 μ g/100 ml. C-peptide: 1 nmol/l $\approx$ 0.3 μ g/100 ml.

FIG 2—Ratios of insulin to C-peptide concentrations after oral and intravenous administration of glucose. ** $p=0.01$.

returned to baseline values after the oral glucose load was the insulin concentration greater after the intravenous load than after the oral load ($p=0.05$ at 120 minutes); this reflected the significantly greater glucose concentration at 90 minutes.

C-peptide—Basal plasma concentrations of C-peptide were similar in both tests. Like the insulin responses, plasma C-peptide concentrations rose more rapidly after oral glucose than after the intravenous load, the difference reaching significance at 30 minutes ($p=0.05$) and 60 minutes ($p=0.01$). C-peptide concentrations were raised in the late stages of the intravenous test, when the plasma glucose concentrations were raised. Plasma C-peptide concentrations

returned to baseline at 150 minutes after the oral test compared with 120 minutes for the plasma insulin concentrations, reflecting the longer half life of C-peptide.

The ratio of insulin to C-peptide concentrations in molar terms is shown in fig 2. In the basal state the concentration of C-peptide was about 10 times that of insulin, reflecting the prolonged half life of C-peptide. In contrast to during the intravenous test, when the ratio tended to fall slightly, after oral glucose the ratio rose sharply, reaching significance at 30 minutes ($p=0.01$), by which time it had doubled. It then fell gradually to a value similar to that in the basal state and to that observed after intravenous glucose.

Discussion

This study shows a clear difference in the responses of C-peptide and insulin, as measured by peripheral plasma concentrations, when stimulated by oral and intravenous glucose in normal subjects. The rise in peripheral insulin concentration during stimulation by oral glucose was greater than would be expected on the basis of the rise in C-peptide concentration. Our findings thus agree closely with those of Faber *et al.*⁶ A major difference between the metabolism of insulin and C-peptide is that the liver extracts at least half of the insulin delivered to it^{9,10} but only a small or negligible amount of C-peptide.¹¹ One obvious explanation of the present findings is that when secretion of insulin is stimulated by oral glucose, hepatic extraction of insulin is reduced with a consequent increase in the peripheral insulin:C-peptide ratio. Consistent with this explanation is the *in vitro* finding that no appreciable hepatic extraction of insulin occurs in the perfused rat liver pancreas preparation in the fed state, whereas after a fast the liver removes about half of the insulin released into the portal vein.¹³ Many of the published animal data, however, are contradictory.¹⁴

The possibility that a change in hepatic extraction of insulin might be responsible for some or all of the observed difference in the peripheral concentrations of insulin achieved when oral as opposed to intravenous insulin is the stimulus appears to have been neglected before the study by Faber *et al.*⁶ The present results suggest that at least half of the difference may be accounted for by such a mechanism. Studies of release of C-peptide by heterotopic pancreatic grafts have shown no difference in the C-peptide concentrations after oral and intravenous glucose.⁵ Both results suggest a role for the nervous system. The failure hitherto of studies of gastrointestinal hormones to account satisfactorily for the enhanced secretion of insulin after oral glucose¹⁴ can probably, however, be largely accounted for by the importance of changes in hepatic extraction of insulin.

Several interesting questions arise from the present observation. Firstly, what is the mechanism of the effect and what nutritional elements will produce it? Does the effect alter during the day? What is the consequence of the potential redistribution of insulin's action from the liver to the periphery during the change from the fasted to the fed state? Concern is often expressed that diabetics are habitually treated by insulin administered through the peripheral rather than the portal route. Is it possible that in the fed state this is a reasonable approximation to normal physiology? Finally, what is the meaning of the concept of a half life of insulin if its destination and hence presumably rate of destruction can be altered so dramatically? The present study indicates the importance of enterohepatic interactions and the need for work on this and the questions outlined above.

OMG was in receipt of an MRC training fellowship. We are grateful to Mrs J Mackman, research sister, and to Mrs M Loke, research technician, for their excellent help. This work was supported by grants from Thomae, Novo Laboratories Ltd, Allen and Hanburys Ltd, and the British Diabetic Association.

We are grateful to Mrs M Neaves and Mrs L Creswell for secretarial help and to the department of medical illustration, Queen Elizabeth Hospital, Birmingham.

Requests for reprints should be sent to Dr O M Gibby, Department of Medicine, University of Birmingham, Queen Elizabeth Hospital, Edgbaston, Birmingham B15 2TU.

References

- ¹ McIntyre N, Holdsworth CD, Turner OS. New interpretation of oral glucose tolerance. *Lancet* 1964;ii:20-1.
- ² Brown JC, Otte SC. Gastrointestinal hormones and the control of insulin secretion. *Diabetes* 1978;27:782-9.
- ³ Buchanan KD. The gastrointestinal tract and diabetes mellitus. In: Vallance-Owen J, ed. *Diabetes, its physiological and biochemical basis*. Baltimore: University Park Press, 1975:63-91.
- ⁴ Unger RH, Esentrant AM. Enteroinsular axis. *Arch Intern Med* 1969;123:261-6.
- ⁵ Gibby OM, Loke M, Sarson DL, Bloom SR, McMaster P, Calne RY. Disruption of the entero-insular axis in pancreatic transplantation. *Regul Pept* 1980;suppl 1:542.
- ⁶ Faber OK, Madsbad S, Kehlet H, Binder C. Pancreatic beta cell secretion during oral and intravenous glucose administration. *Acta Med Scand* 1979;suppl 624:61-4.
- ⁷ Horwitz DL, Starr JL, Mabo ME, Blackard WG, Rubenstein AM. Proinsulin, insulin and C-peptide concentrations in human portal and peripheral blood. *J Clin Invest* 1975;55:1278-83.
- ⁸ Hales CN, Randle PJ. Immunoassay of insulin with insulin antibodies precipitate. *Biochem J* 1963;88:137-46.
- ⁹ Heding LG. Radioimmunological determination of human C-peptide in serum. *Diabetologia* 1975;11:541-8.
- ¹⁰ Katz AI, Rubenstein AH. Metabolism of proinsulin, insulin and C-peptide in the rat. *J Clin Invest* 1973;52:1113-21.
- ¹¹ Stoll RW, Toubert JL, Menahan LA, Williams RH. Clearance of porcine insulin, proinsulin and connecting peptide by the isolated rat liver. *Proc Soc Exp Biol Med* 1970;133:894-6.
- ¹² Caniret B, Krebs BP. C-peptide uptake and excretion by the liver in man. *Horm Metab Res* 1980;12:229-30.
- ¹³ Striffler JS, Curry DL. Effect of fasting on insulin removal by liver of perfused liver-pancreas. *Am J Physiol* 1979;237:E349-55.
- ¹⁴ Sarson DL, Wood SM, Holder D, Bloom SR. The effect of glucose-dependent insulinotropic polypeptide infused at physiological concentrations on the release of insulin in man. *Diabetologia* 1982;22:33-6.

(Accepted 4 January 1983)

Rifampicin reduces effectiveness and bioavailability of prednisolone

W A C McALLISTER, P J THOMPSON, S M AL-HABET, H J ROGERS

Abstract

Rifampicin is an inducer of hepatic drug metabolising enzymes. This results in interactions with several drugs including oral anticoagulants, hypoglycaemics, and contraceptives. Concurrent treatment with prednisolone and rifampicin is given when tuberculosis coexists with a disease that is sensitive to steroids, when the diagnosis is uncertain, or occasionally in the treatment of severe tuberculosis. Two patients with respiratory disease were treated with both drugs: their condition improved considerably after rifampicin was withdrawn. Seven patients were then studied to assess the effect of rifampicin on the pharmacokinetics of prednisolone. Overall, rifampicin increased the plasma clearance of prednisolone by 45% and reduced the amount of drug available to the tissues (area under the plasma concentration time curve) by 66%.

The effectiveness of prednisolone may be considerably reduced when rifampicin and prednisolone are used in combination.

Introduction

Rifampicin is an inducer of the hepatic mixed function oxygenase enzymes involved in drug metabolism.^{1,2} Needle biopsy specimens of the liver from patients receiving rifampicin show an increase in cytochrome P₄₅₀³ and proliferation of smooth endoplasmic reticulum in the hepatocytes.⁴ Rifampicin induces its own metabolism⁵ during continuous treatment as demonstrated by a shortened half life. In addition, rifampicin can accelerate the elimination of the contraceptive pill,⁶ leading to menstrual disturbance and unwanted pregnancy. Tolbutamide, hexobarbitone,⁷ and oral anticoagulants⁸ are other drugs whose metabolism is similarly affected. Deterioration in renal⁹ and allograft function¹⁰ associated with concomitant rifampicin treatment may be cited as indirect evidence of the effect of this drug on steroid metabolism.

We report on two patients with respiratory disease in whom rifampicin affected metabolism of steroids; and we describe a study of the effects of rifampicin on the pharmacokinetics of prednisolone in seven patients.

Case reports

CASE 1

A 16 year old boy presented with a year's history of symmetrical polyarthropathy, early morning stiffness, and lassitude. Finger clubbing and a rheumatoid nodule at the elbow were noted, and investigation showed a high erythrocyte sedimentation rate and the presence of rheumatoid factor. Rheumatoid arthritis was diagnosed.

A chest x-ray film showed bilateral hilar lymphadenopathy and midzone reticular shadowing. As the most likely diagnosis was thought to be tuberculosis treatment with rifampicin and isoniazid was started. He developed pyrexia, which was ascribed to a possible hypersensitivity reaction to one of these drugs. In an attempt to limit the suspected reaction and because of uncertainty about the diagnosis he was treated additionally with prednisolone 30 mg daily for six weeks. The chest radiographic appearance and symptoms had not improved at the end of this time. Steroid dose was reduced gradually to 10 mg a day but continued at between 7.5 and 15 mg daily concomitantly with

Brompton Hospital, London SW3 6HP

W A C McALLISTER, MB, MRCP, senior registrar
P J THOMPSON, MB, FRACP, research fellow

Department of Clinical Pharmacology, Guy's Hospital Medical School, London SE1 9RT

S M AL-HABET, BPHARM, research fellow
H J ROGERS, PHD, MRCP, reader in clinical pharmacology

Correspondence to: Dr W A C McAllister, Chest Clinic, Westminster Hospital, London SW1.