The Pharmacokinetics of Insulin After Continuous Subcutaneous Infusion or Bolus Subcutaneous Injection in Diabetic Patients

TETSURO KOBAYASHI, SHINJI SAWANO, TOKUJI ITOH, KINORI KOSAKA, HIROKI HIRAYAMA, AND YASUJI KASUYA

SUMMARY

Pharmacokinetic models of insulin were examined in order to describe a plasma concentration-time profile after subcutaneous (s.c.) administration of insulin to the patients with insulin-dependent diabetes mellitus (IDDM) or non-insulin-dependent diabetes mellitus (NIDDM). Diabetic subjects were restricted to those with fasting plasma insulin levels around the lowest limit for insulin assay (5 μU/ml). A one-compartment open model with first-order absorption and elimination was appropriate for estimating the plasma concentration-time profile of insulin injected or infused subcutaneously. In the case of continuous s.c. insulin infusion (CSII) for 1 h at the rate of 3 ml/h (2–3 U/ml), the absorption rate constant (Ka), elimination rate constant (Ke), and distribution volume (Vd) were 0.026 ± 0.001 min^{-1} (mean ± SEM; absorption half-life: 27 min), 0.013 ± 0.005 min^{-1} (elimination half-life: 53 min), and 1.99 ± 0.49 L/kg body wt, respectively. These values did not differ significantly from those generated by single bolus s.c. injection of undiluted insulin (40 U/ml). The calculated areas under the plasma insulin concentration-time curves from time zero to infinity ($[AUC]_0^\infty$) did not differ after each mode of administration, while the $[AUC]_0^\infty$ after CSII was about 32% of that following intravenous bolus injection ($P < 0.01$).

The following conclusions can be drawn from these results: (1) the plasma concentration-time profile of insulin after CSII or bolus s.c. injection can be analyzed by pharmacokinetic modeling, (2) the absorption kinetics of insulin did not differ significantly between two modes of s.c. insulin administration in the patients with IDDM or NIDDM, and (3) the insulin after CSII or single bolus s.c. injection seems to be degraded at the s.c. site to the same extent. DIABETES 32:331–336, April 1983.

From the Department of Endocrinology and Metabolism, Toranomon Hospital, Okinaka Memorial Institute for Medical Research and Asahi Life Institute for Adult Diseases (T.K., S.S., T.I., and K.K.), 2-2-2 Toranomon, Minato-Ku, Tokyo 105, Japan; and the Department of Clinical Pharmacy, Tokyo College of Pharmacy (H.H. and Y.K.), 1432-1 Horinouchi, Hachioji, Tokyo 192-03, Japan.
Address reprint requests to Dr. Tetsuro Kobayashi, Department of Endocrinology and Metabolism, Toranomon Hospital, Okinaka Memorial Institute for Medical Research, 2-2-2 Toranomon, Minato-Ku, Tokyo 105, Japan.
Received for publication 28 July 1980 and in revised form 19 November 1982.

Continuous subcutaneous insulin infusion (CSII) using a portable insulin delivery system (open-loop system) has been proposed as a means of achieving sustained near-normoglycemia in diabetics.[1] However, subcutaneous (s.c.) insulin infusion schedules are usually determined by trial and error for several days, and the administration form is variable. Usually the following modes of administration are employed: basal continuous s.c. infusion together with either meal-time bolus s.c. injection[2] or square wave-form s.c. infusion.[1] A more practical and possibly more accurate approach for determining a suitable insulin delivery schedule may be to apply the pharmacokinetic method, which would elucidate the relationship between the amount of s.c.-administered insulin and plasma level-time profiles. However, there are a few reports describing this relationship with the exception of absorption studies, in which the disappearance of isotopically labeled insulin from the s.c. site was measured.[3–6] In the present study, we examined in diabetic subjects the appropriate pharmacokinetic model for evaluating the relationship between the amount of s.c.-injected or -infused unlabeled insulin and plasma level-time profiles of the insulin.

MATERIALS AND METHODS

Subjects. Subjects were nine patients with insulin-dependent diabetes mellitus (IDDM) and three patients with non-insulin-dependent diabetes mellitus (NIDDM). Their clinical characteristics are given in Table 1. To minimize the interference of the kinetic analysis of exogenously administered insulin by endogenous insulin, the subjects were restricted to those having fasting plasma insulin levels around the lowest limit for insulin assay (5 μU/ml). Cases 1–5 received intermediate insulin treatment up to 2 days before the experiment. On the previous day they received three s.c. injections of short-acting insulin (Actrapid MC, 40 U/ml, Novo

TABLE 1
Clinical characteristics of the 12 diabetics

Patient	Age/sex	Wt (kg)	Type of diabetes	Duration of diabetes	Insulin antibodies (%)	Fasting plasma insulin (μU/ml)	Experiments performed*
1	19/M	49	IDDM	4 yr	32	<5	a
2	23/M	50	IDDM	9 yr	37	<5	a
3	29/F	60	IDDM	7 yr	58	<5	a
4	26/M	54	IDDM	6 yr	26	<5	a
5	28/M	60	IDDM	4 yr	91	<5	a
6	45/M	59	IDDM	1 mo	5	5	a, b
7	17/M	59	IDDM	2 mo	6	<5	a, b
8	26/F	40	IDDM	1 mo	10	6	a, b
9	46/F	41	NIDDM	2 mo	7	5	a, b, c
10	35/M	58	NIDDM	2 yr	5	7	a, b, c
11	43/M	60	NIDDM	4 mo	4	7	a, b, c
12	48/M	40	IDDM	3 mo	10	<5	a, c

*a: single bolus s.c. insulin injection; b: CSII; c: single bolus i.v. insulin injection (see text).

Industries, Denmark). Cases 6–12, on the other hand, did not receive any insulin injection on the day before testing. All subjects were tested after fasting overnight.

Protocol. Highly purified porcine insulin (Actrapid MC) was administered by one of three techniques: (1) a single bolus s.c. injection of 0.15 U/kg body wt (6–9 U/subject), (2) continuous s.c. infusion of the same dose as that of technique 1, or (3) a single bolus intravenous (i.v.) injection of 4 U of undiluted insulin. For technique 2, insulin was diluted with 3 ml of normal saline (2–3 U/ml) and infused over a 1-h period. Some of the above-mentioned protocols were carried out in the 12 diabetics in randomized order. The protocols performed on each case are shown in Table 1. When patients underwent successive experiments, it was so scheduled as to finish all studies within 12 days.

Injection or infusion technique. A 23-gauge butterfly needle (14 mm length) was inserted subcutaneously, approximately 7 cm aside from the umbilicus for insulin injection or infusion. The antecubital vein was selected for bolus i.v. insulin injection. Bolus i.v. or s.c. insulin injection was done by a 500-μl microsyringe with the minimal scale of 5 μl (Terumo Co., Tokyo, Japan). Subcutaneous infusion was performed using a peristaltic rotary pump (Nikkiso Co. Ltd., Tokyo, Japan). Insulin recovery in the infusates averaged 98 ± 5% (mean ± SEM).

Blood sampling. Blood samples were taken through a 21-gauge butterfly needle from the opposite side of the antecubital vein every 20 min. Additional samples were taken at 5-min intervals for the first 20 min for technique 3 and at 10-min intervals for the first 60 min for technique 1.

Kinetic model. As shown in Figure 1, a one-compartment open model with first-order absorption and elimination kinetics was employed for the data obtained by single bolus s.c. injection. The formula is presented in equation 1. That is,

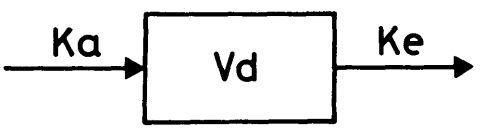

FIGURE 1. Schematic representation of a one-compartment model: where Ka is the apparent first-order absorption rate constant and Ke is the first-order elimination rate constant. Vd is the distribution volume.

$$C = \frac{Ka \cdot D}{Vd \cdot (Ka - Ke)} \cdot (e^{-Ke \cdot t} - e^{-Ka \cdot t}) \quad (1)$$

where C is the insulin concentration at time t, Ka and Ke are the apparent first-order rate constants for absorption and elimination, respectively, Vd is the apparent distribution volume, and D is the injection dose of insulin. The time course of insulin concentration after continuous s.c. infusion at a constant rate (RI) for a given period may be calculated by the following three equations based on a one-compartment model:

$$C = \frac{RI}{Vd \cdot Ke} \cdot (1 - e^{-Ke \cdot t}) + \frac{RI \cdot (e^{-Ke \cdot t} - e^{-Ka \cdot t})}{Vd \cdot (Ke - Ka)} \quad (2)$$

where C is the insulin concentration at time t during infusion period (τ), and Ka, Ke, and Vd are pharmacokinetic parameters.

$$X' = \frac{RI}{Ka} \cdot (1 - e^{-Ka \cdot \tau}) \quad (3)$$

where X′ is the amount of insulin left in the s.c. depots at the time when the insulin infusion is terminated. In our study τ equals 60 min.

$$C = \frac{Ka \cdot X'}{Vd \cdot (Ka - Ke)} \cdot (e^{-Ke \cdot t'} - e^{-Ka \cdot t'}) + C' \cdot e^{-Ke \cdot t'} \quad (4)$$

where C is the insulin concentration at the postinfusion time t′ and C′ is the insulin concentration at the time of terminating infusion.The concentration versus time curve in the case of a single bolus i.v. insulin injection was analyzed according to a two-compartment model (Figure 2) given as equation 5:

$$C = \frac{Xo \cdot (\alpha - K_{21})}{Vc \cdot (\alpha - \beta)} \cdot e^{-\alpha \cdot t} + \frac{Xo \cdot (K_{21} - \beta)}{Vc \cdot (\alpha - \beta)} \cdot e^{-\beta \cdot t} \quad (5)$$

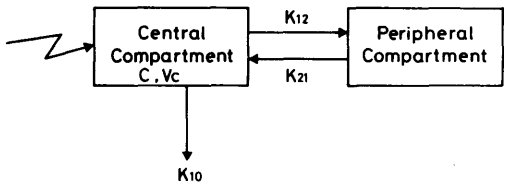

FIGURE 2. Schematic representation of a two-compartment model consisting of a central compartment and a peripheral compartment: where K_{12} and K_{21} are apparent first-order intercompartmental rate constants, and K_{10} is the apparent first-order elimination rate constant from the central compartment. C is the concentration of insulin and Vc is the apparent volume of the central compartment.

where C is the insulin concentration at time t, Xo is the amount of insulin in the central compartment at time zero and is equal to the i.v. dose, and Vc is the apparent volume of the central compartment. As shown in Figure 2, K_{21} and K_{12} are the apparent first-order intercompartmental distribution rate constants, and K_{10} is the apparent first-order elimination rate constant from the central compartment. α and β are complex constants that serve to replace the following relations, that is,

$$\alpha + \beta = K_{12} + K_{21} + K_{10} \quad (6)$$

and

$$\alpha \cdot \beta = K_{21} \cdot K_{10} \quad (7)$$

The model was fit to the data on a CBM 3032 computer using a MODFIT program.[7] Starting with initial estimates, parameter values were adjusted by an iterative procedure until a least squares fit was obtained.

In all calculations the pretested level was subtracted from the measured insulin level.

Measurement of bioavailability. The bioavailability of insulin was measured by calculating the areas under the plasma concentration versus time curve (AUC) from time zero to infinity after s.c. and i.v. administration. The AUC from time zero to infinity ($[AUC]_0^\infty$) was expressed as the sum of AUC from time zero to time T ($[AUC]_0^T$) and AUC from time T to infinity ($[AUC]_T^\infty$), that is,

$$[AUC]_0^\infty = [AUC]_0^T + [AUC]_T^\infty \quad (8)$$

Time T is the last sampling point and $[AUC]_0^T$ is calculated by the trapezoidal rule, whereas $[AUC]_T^\infty$ can be calculated by employing

$$[AUC]_T^\infty = \frac{C_T}{K'} \quad (9)$$

where C_T is the plasma concentration of insulin at time T and K′ is the apparent first-order elimination rate constant. K′ equals Ke in a one-compartment model and β in a two-compartment model.

Assay methodology. Plasma immunoreactive insulin (IRI) was measured by the double antibody method using Dinabot Kit (Dinabot Radioisotope Labs., Tokyo, Japan), free-IRI was measured according to the method of Nakagawa et al.,[8] and plasma glucose was measured by the glucose-oxidase method. Insulin antibodies were detected by immunoprecipitation using ^{125}I-insulin[9] (normal range: less than 13%).

Statistical analysis. Student's *t* test for paired data was employed.

RESULTS

Kinetics of subcutaneously injected insulin to the patients with insulin antibodies. In the first experiments, the concentration-time profiles of free-IRI after single bolus s.c. injection of insulin were analyzed in diabetics with insulin antibodies. A one-compartment open model as described by equation 1 proved to be appropriate for evaluating the plasma free-IRI versus time curves after s.c. bolus insulin injections. Calculated pharmacokinetic parameters are listed in Table 2. In case 5, who had an elevated titer of insulin antibodies, Vd attained an extremely high value.

Kinetics and bioavailability of subcutaneously administered insulin to the patients without insulin antibodies. The computer-generated curves derived from equations 1, 2, 3, and 4 are shown in Figure 3. The upper panel shows the results after single bolus s.c. injection and the lower panel after CSII. These curves were generally indicative of the typical "fit" of the individual datum. In the case of CSII, plasma IRI concentration reached the maximal level of 35.8 ± 5.0 μU/ml (mean ± SEM) 100 min after the initiation of infusion. The pharmacokinetic parameters, namely Ka, Ke, and Vd, obtained by CSII were 0.026 ± 0.001 min^{-1}, 0.013 ± 0.005 min^{-1}, and 1.99 ± 0.49 L/kg body wt, respectively (Figure 4, right panel). The absorption half-life, which was calculated by 0.693/Ka, was 27 min. Similarly, the elimination half-life (0.693/Ke) was 53 min. On the other hand, plasma IRI levels began to rise and reached peak values 60 min after the s.c. injection of insulin (0.15 U/kg body wt), and then showed a monoexponential decay pattern. There was a time lag of 7 ± 1 min before s.c.-administered insulin appeared in the

TABLE 2
Pharmacokinetic parameters in IDDM cases with insulin antibodies

Patient	Ka (min^{-1})	Ke (min^{-1})	Vd (L/kg)	Time lag (min)
1	0.068	0.024	1.02	5
2	0.018	0.013	1.30	6
3	0.024	0.014	1.42	6
4	0.023	0.013	1.03	7
5	0.030	0.020	14.00	5
Mean ± SEM	0.033 ± 0.008	0.017 ± 0.002	3.75 ± 2.28	5.8 ± 0.3

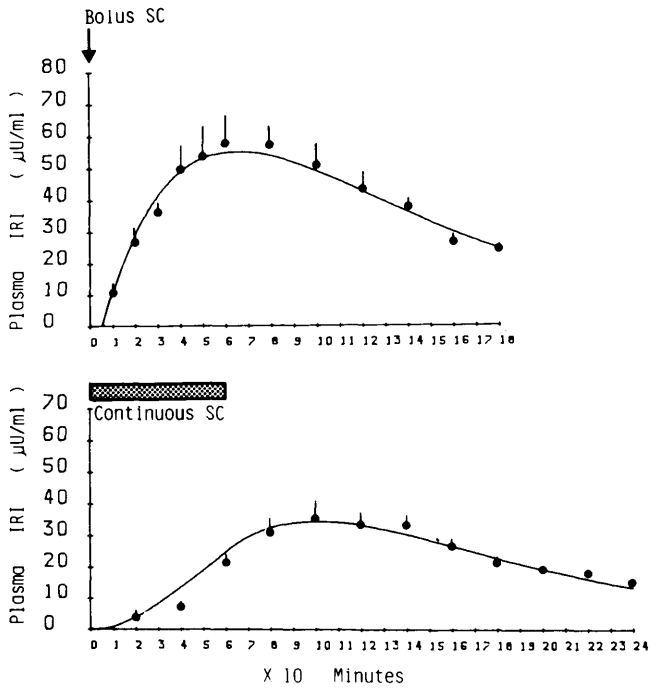

FIGURE 3. Computer matching (solid line) of mean plasma insulin values using the one-compartment model. Filled dots denote experimental mean (± SEM) plasma insulin concentration after bolus s.c. injection (upper panel) or continuous s.c. infusion (lower panel).

compartment. These pharmacokinetic parameters obtained by each mode of s.c. administration did not show any significant differences (Figure 4). Single bolus i.v. insulin injection produced a prompt plasma IRI peak and showed a biexponential decrease (Figure 5). The pharmacokinetic parameters, K_{12}, K_{21}, K_{10}, α, and β, obtained by a two-compartment model given by equation 5, were 0.0492 ± 0.0008 min^{-1}, 0.0203 ± 0.0019 min^{-1}, 0.1936 ± 0.0448 min^{-1}, 0.2478 ± 0.0475 min^{-1}, and 0.0154 ± 0.0012 min^{-1}, respectively.

In the case of CSII performed at a rate of 3 ml/h, the $[AUC]_0^\infty$ per one unit of insulin was 1010 ± 103 μU · min/ml (mean ± SEM) as shown in Figure 6. This value was not significantly different from that obtained by single bolus s.c. injection. However, the $[AUC]_0^\infty$ per one unit of insulin after bolus i.v. injection was approximately threefold greater than those after CSII ($P < 0.01$).

There was no significant difference among the initial plasma glucose concentration before starting the three protocols. The values were 253 ± 12 mg/100 ml in the single bolus i.v. study, 209 ± 15 mg/100 ml in the single bolus s.c. study, and 226 ± 27 mg/100 ml in CSII. Plasma glucose concentration declined after initiation of each study to a nadir level of 197 ± 17 mg/100 ml with single bolus i.v. injection at 40 min, 144 ± 17 mg/100 ml with single s.c. injection at 140 min, and 155 ± 22 mg/100 ml with CSII at 160 min. The nadir level did not differ significantly between single bolus s.c. injection and CSII.

DISCUSSION

We demonstrated that a one-compartment open model with first-order absorption and elimination was appropriate for

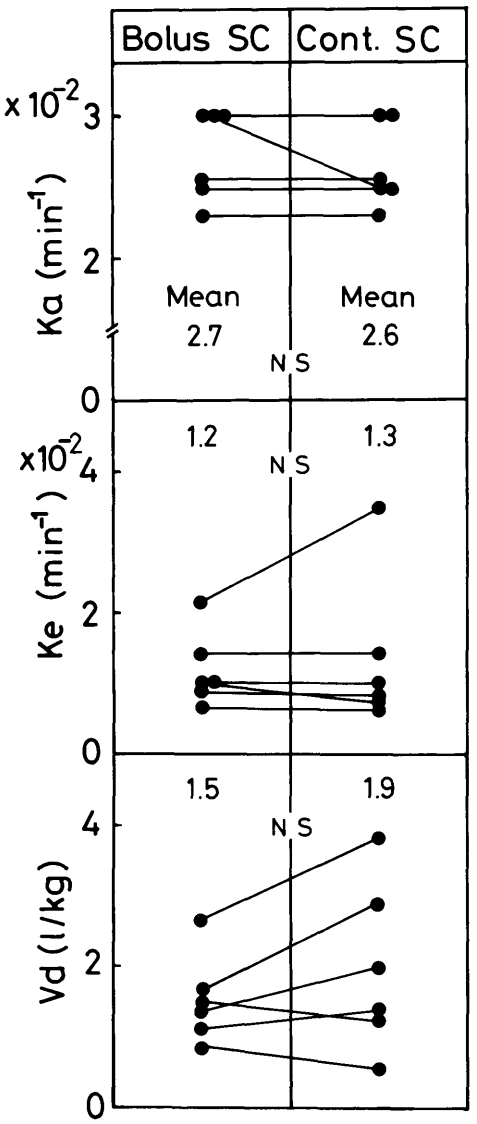

FIGURE 4. Individual computer-calculated pharmacokinetic parameters in the case of bolus s.c. insulin injection (Bolus SC) and continuous s.c. insulin infusion (Cont. SC).

estimating the kinetics of subcutaneously administered insulin irrespective of insulin antibodies in diabetic patients. The distribution phase, which was obvious upon i.v. insulin injection in our and other studies,[10–12] was not observed after single bolus s.c. injection or continuous s.c. infusion. This can be explained by the fact that s.c.-administered insulin is absorbed slowly, thereby not achieving sufficient plasma levels to produce the distribution phase.

It was found that the IDDM case with insulin antibodies of very high titer (case 5) had an extremely high Vd value. This might be attributed to the high levels of insulin antibodies in this case, i.e., most of the insulin absorbed from s.c. tissue was incorporated with the insulin antibodies in plasma and the remaining minute quantity of free-insulin caused a slight rise in plasma free-IRI, resulting in an extremely high Vd value.

Our pharmacokinetic technique can mathematically simulate the increase and decay of s.c. multiple-injected or continuously infused insulin in plasma. Therefore, this technique

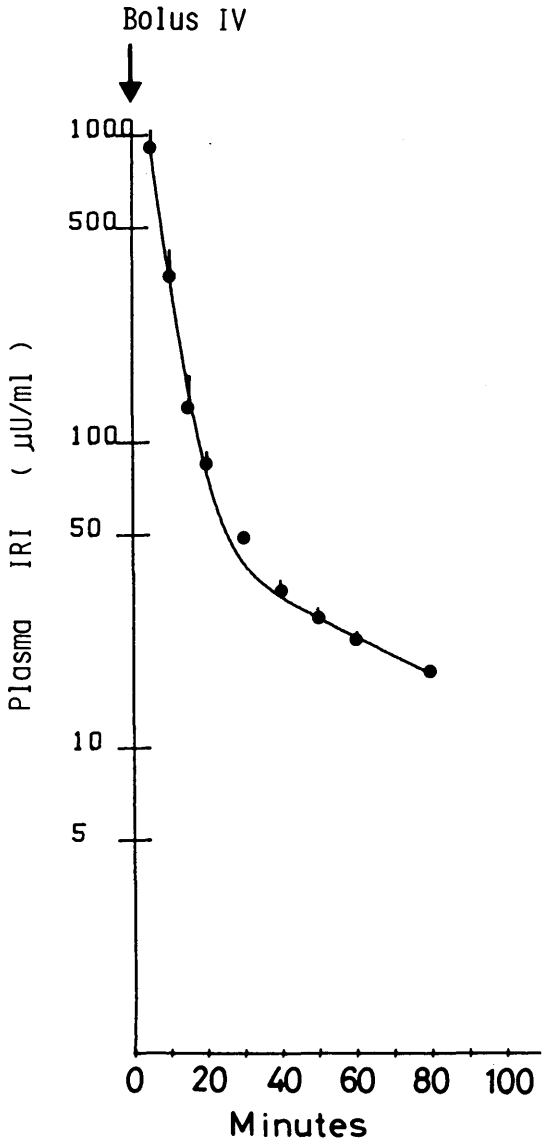

FIGURE 5. Computer matching (solid line) of mean plasma insulin values using the two-compartment model. Filled dots denote experimental mean (± SEM) plasma insulin concentration after bolus i.v. injection.

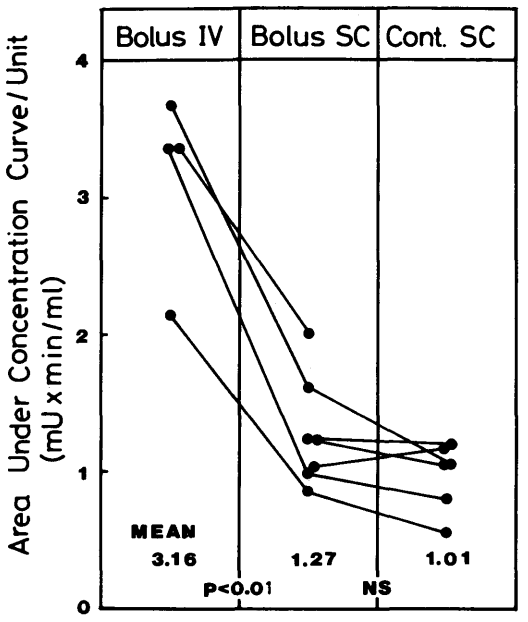

FIGURE 6. Area under the plasma insulin concentration versus time curve from time zero to infinity per 1 U of insulin. Bolus IV, Bolus SC, and Cont. SC represent the values obtained by bolus i.v. insulin injection, bolus s.c. insulin injection, and continuous s.c. infusion, respectively.

will contribute to studies on the dynamics of subcutaneously administered insulin or to the development of suitable insulin delivery schedules for an open-loop s.c. infusion system. Berger et al.[6] investigated the absorption kinetics of s.c.-injected ^{3}[H]-insulin in anesthetized pigs by the direct method. They extracted the insulin from the tissues, which were excised from the injection site en bloc, and measured the disappearance of intact ^{3}[H]-insulin separated from degraded products by column chromatography. They showed an absorption half-life of 59 min. Binder et al.[3] reported that in human beings the injection of ^{125}I-insulin (Actrapid insulin) into abdominal s.c. tissues in normal men yielded an absorption half-life of about 39 min. We investigated in the present study the absorption kinetics of unlabeled insulin by the pharmacokinetic method in diabetic patients with poor endogenous insulin reserve. The absorption half-life of insulin after bolus s.c. injection was about 26 min. The discrepancy between the findings of Binder et al.[3] and ours cannot be explained. However, the estimation of the ^{125}I-insulin in the abdominal wall with an external gamma-counter may not reflect actual insulin absorption. According to our kinetic model, there was a time lag of about 7 min before subcutaneously administered insulin appeared in the compartment. This time lag may reflect the transport of s.c. injected insulin to the general blood flow.

The $[AUC]_0^\infty$ after a single bolus s.c. injection or CSII attained approximately four-tenths of the $[AUC]_0^\infty$ after bolus i.v. injection. These results indicate that up to about 60% of the subcutaneously injected or infused insulin was likewise inactivated at the s.c. site. The extent of this inactivation at the s.c. site was general agreement with other recent reports on pigs[3] or rats[13] using different techniques.

In addition, we clearly demonstrated in diabetics without insulin antibodies that the mean pharmacokinetic parameters, namely Ka, Ke, and Vd, 1 h after the continuous s.c. infusion of diluted insulin (2–3 U/ml) at a rate of 3 ml/h did not differ significantly from those after single bolus s.c. injection of the same doses (6–9 U) of undiluted insulin. These findings suggest that, when the infusion rate is lower than 3 ml/h and the concentration of insulin is higher than 2–3 U/ml, the absorption kinetics of CSII are linear and are not different from those obtained by single bolus s.c. injection.

During CSII, prediction of the plasma insulin concentration or achievement of the desired plasma profile of insulin may be possible by inserting the pharmacokinetic parameters generated by single bolus s.c. injection into our appropriate multiple-dosing equations. For example, one can obtain the desired plasma level-time profile of insulin by applying equations 2, 3, and 4 in the case of square wave-form s.c. infusion,

or equations 1, 2, 3, and 4 in the case of meal-related bolus s.c. injection plus continuous s.c. infusion.

REFERENCES

[1] Pickup, J. C., Keen, H., Parsons, J. A., and Alberti, K. G. M. M.: Continuous subcutaneous insulin infusion: an approach for achieving normoglycemia. Br. Med. J. 1978; *1*:204–207.

[2] Tamborlane, W. V., Sherwin, R. S., Genal, M., and Felig, P.: Reduction to normal of plasma glucose in juvenile diabetes by subcutaneous administration of insulin with a portable infusion pump. N. Engl. J. Med. 1979; *300*:573–78.

[3] Binder, C.: Absorption of injected insulin. Acta Pharmacol. Toxicol. 1969; *27* (Suppl. 2):37–49.

[4] Koivisto, V. A., and Felig, P.: Effects of leg exercise on insulin absorption in diabetic patients. N. Engl. J. Med. 1978; *298*:79–83.

[5] Berger, M., Halban, P. A., Assal, J. P., Offord, R. E., Vranic, M., and Renold, A. E.: Pharmacokinetics of subcutaneously injected tritiated insulin: effects of exercise. Diabetes 1979; *28* (Suppl. 1):53–57.

[6] Berger, M., Halban, P. A., Girardier, L., Seydoux, J., Offord, R. E., and Renold, A. E.: Absorption kinetics of subcutaneously injected insulin: evidence for degradation at the injection site. Diabetologia 1979; *17*:97–99.

[7] McIntosh, J. E. A., and McIntosh, R. P.: Mathematical modeling and computers in endocrinology. New York, Springer-Verlag, 1980:250.

[8] Nakagawa, S., Nakagawa, H., Sasaki, T., Yoshino, K., Yu, Y. Y., Shinozaki, K., Aobi, S., and Mashimo, K.: A simple method for the determination of serum free insulin levels in insulin-treated patients. Diabetes 1973; *22*:590–99.

[9] Desbuquois, B., and Aurbach, G. D.: Use of polyethylene glycol to separate free and antibody-bound peptide hormones in radioimmunoassays. J. Clin. Endocrinol. Metab. 1971; *33*:732–38.

[10] Tranberg, K. G., and Dencker, H.: Modeling of plasma disappearance of unlabeled insulin in man. Am. J. Physiol. 1978; *235*:577–85.

[11] Sherwin, R. S., Kramer, K. J., Tobin, J. D., Insel, P. A., Liljenquist, J. E., Berman, M., and Andres, R.: A model of the kinetics of insulin in man. J. Clin. Invest. 1974; *53*:1481–92.

[12] Navalest, R., Pilo, A., and Ferrannini, E.: Kinetic analysis of plasma insulin disappearance in nonketotic diabetic patients and in normal subjects: a tracer study with ^{125}I-insulin. J. Clin. Invest. 1978; *61*:197–208.

[13] Stevenson, R. W., Tsakok, T. I., and Parsons, J. A.: Matched glucose responses to insulin administered subcutaneously and intravenously: evidence for subcutaneous inactivation of insulin. Diabetologia 1980; *18*:423–26.