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Comparison of theoretical doses of insulin detemir and insulin glargin estimated from insulin action indices in Japanese diabetic patients

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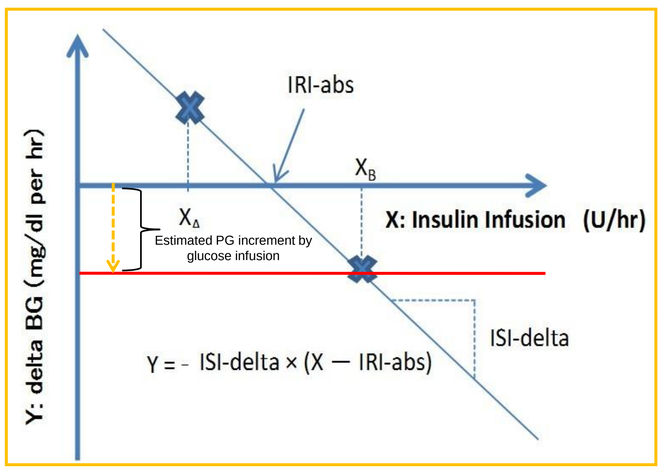
Aim

Adjustment of insulin doses is usually conducted by changing responsible insulin to reach an affected plasma glucose concentration to a target level. However, the optimal dose of insulin is difficult to be obtained. Clinical action of insulin can be defined by two parameters, ISI-del (decremental concentration of plasma glucose by a fixed increment of insulin [mg/dl per U]) and IRI-abs (an absolute amount of insulin to keep fixed glucose turnover and keep BG constant. [U/hr]) (Nutr Metab Cardiovasc Dis 20:79, 2010). From the plasma glucose concentration and insulin administration doses, it is possible to simulate glucose metabolism and estimate ISI-del and IRI-abs. From the ISI-del and IRI-abs, it is possible to calculate the theoretical doses of insulin. The purpose of this study is to compare the actual insulin doses and theoretical insulin doses of insulin detemir (DET) or insulin glargin (GLA) concomitantly used with ultra rapid-acting insulin.

Methods

Daily excursion of plasma glucose concentration, contents of carbohydrate in meals, and insulin doses were recorded. Glucose distribution volume was estimated from height and body weight. One compartment mathematical model was used to estimate IRI-abs and ISI-delta from the observed data. Duration of action of DET and GLA was set to 14 hours and 24 hours, and that of ultra rapid-acting insulin was set to four hours, Theoretical replacement dose of basal insulin was calculated by IRI-abs x 24, and that of bolus insulin was calculated by (CHO / 0.9 / 4 x 1000) / (BW x r / 100 x 10) / ISI-del, where CHO: dose of carbohydrate[g], BW: body weight [kg], and r%: proportion of water content (usually 25).

Insulin administration and BG changes

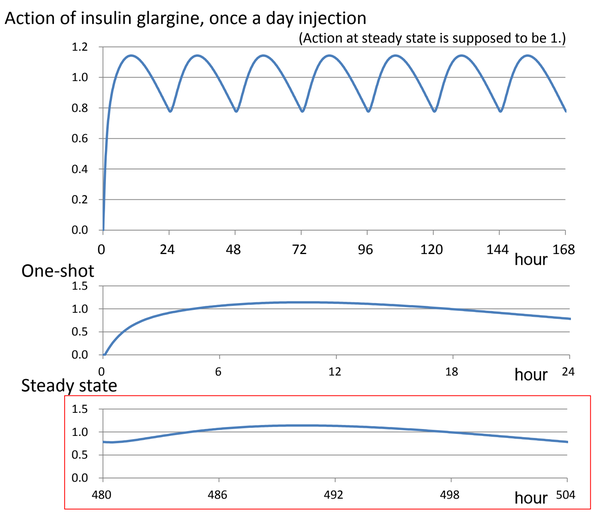


Glucose distribution space was estimated by height and weight during exogenous glucose infusion. Since interval of sampling of PG was more than one hour, equal distribution of glucose allowed us to calculate the estimated PG increment.

To fix the dose-response curve (line), we moved X-axis by the estimated PG increment downward.

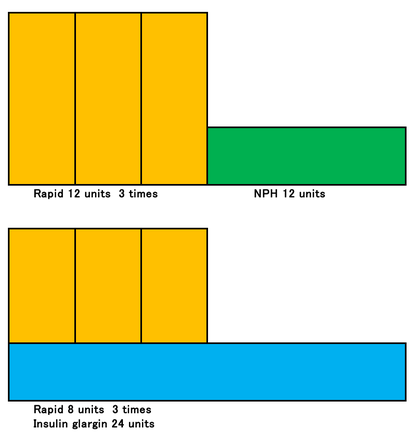
Assumption of the action of insulin according to the time after an injection

Action of insulin glargine, once a day injection
(Action at steady state is supposed to be 1.)



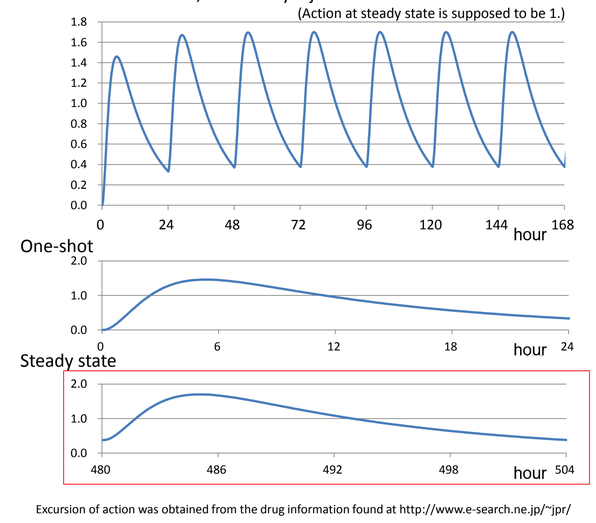
Excursion of action was obtained from the drug information found at http://www.e-search.ne.jp/~jpr/

Theoretical ways of administration, resulting equal action.



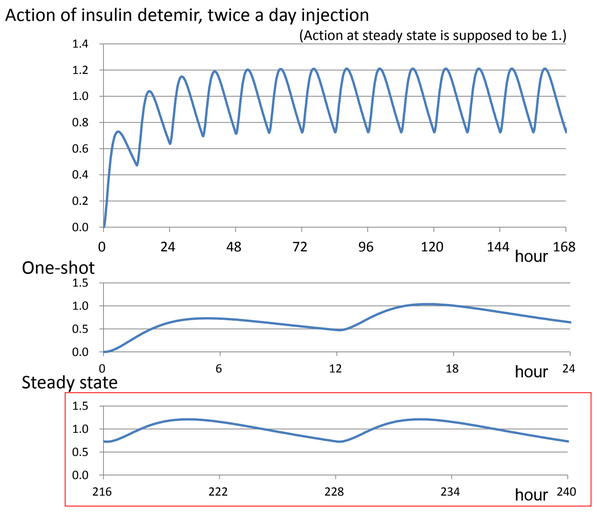
Assuming that rapid acting insulin, NPH insulin, and insulin glargin act for 4, 12, and 24 hours individually.

Action of insulin detemir, once a day injection
(Action at steady state is supposed to be 1.)



Excursion of action was obtained from the drug information found at http://www.e-search.ne.jp/~jpr/

Action of insulin detemir, twice a day injection
(Action at steady state is supposed to be 1.)



Calculation of theoretical basal and bolus doses from IRI-abs, ISI-delta

$Y = 1000 \div (BW \times r \times 10)$ mg/dl

where, Y (mg/dl) is the theoretical increment of plasma glucose concentration when 1g (=1000mg) of glucose is given to a person with a body weight of BW (kg). Glucose distribution space (r) is assumed to be 20 – 25 % of the body weight with specific gravity is assumed to be 1.

$G = D \times 0.55 \div 0.9 \div 3 \div 4 \times 1000$ mg

where, G is the glucose administration rate (mg/hour) after an ingestion of a meal containing D kcal of energy. 55% of energy intake is supposed to be carbohydrate and glucose is divided by 0.9. A meal is to be absorbed during four hours.

Bolus insulin replacement dose (for 4 hours each injection)

G × Y ÷ ISI-delta × 4 × I units
(I: for incretin action)

Basal insulin replacement dose

IRI-abs × 12 units twice a day injection
IRI-abs × 24 units once a day injection

Subjects

	Glargine	Detemir
n (M/F)	20 (12/8)	12 (8/4)	8 (4/4)
Age (y.o.)	58.8 ± 4.1	59.8 ± 5.1	57.3 ± 7.9
BMI (kg/m^2)	26.3 ± 1.8	26.5 ± 2.6	26.0 ± 2.7
Duration(years)	12.1 ± 3.2	12.3 ± 4.3	11.7 ± 5.7
HbA_{1C} (%)	10.0 ± 0.6	10.3 ± 0.9	9.6 ± 0.3
FBG (mg/dl)	141 ± 10	135 ± 14	150 ± 13
Meal (kcal)	1520 ± 80	1533 ± 112	1500 ± 129
Glucose (g)	232 ± 12	234 ± 17	229 ± 20
Bolus insulin (total/day)	22.2 ± 6.7	25.4 ± 5.5
Basal insulin	12.0 ± 7.9	10.1 ± 6.6

(mean ± SEM), FBG was the average of 3 consequtive days analyzed.
Urinary C-peptide excretion was less than 10 micro g per day.

Results

	Glargine	Detemir
Calculation		
ISI-delta	80.8 ± 14.7	87.8 ± 20.0	78.4 ± 23.9
IRI-abs	0.49 ± 0.13	0.49 ± 0.15	0.50 ± 0.25
Rapid acting insulin		
Actual dose (units)	22.2 ± 6.7	25.4 ± 5.5
Theoretical bolus dose (units)	23.4 ± 5.6	22.4 ± 6.9
Long acting insulin		
Actual dose (units)	12.0 ± 7.9	10.1 ± 6.6
Theoretical basal dose (units)	11.7 ± 3.6	11.9 ± 6.1
Bolus/Basal ratio		
Actual (based on insulin products)	1.9 ± 0.4	2.5 ± 0.4*
Theoretical	2.0 ± 0.3	1.9 ± 0.3

(mean ± SEM), *:p<0.05 vs theoreitcal

ISI-delta of GLA and DET were 87.8 ± 20.0 and 78.4± 23.9 mg/dl per U (p=N.S.) respectively, and IRI-abs values were similar (0.49 ± 0.15 and 0.50 ± 0.25 U/hr). Theoretical bolus/basal insulin ratio was 2.0 ± 0.3 in GLA and 1.9 ± 0.3 in DET, while actual ratio was 1.9± 0.4 in GLA and 2.5 ± 0.4 in DET (p<0.05 vs theoretical) individually. In this analysis, bolus insulin is needed more in the DET group, although their insulin demands are similar or less.

Conclusion

There must be a discrepancy in bolus/basal replacement doses in DET and GLA, since their duration of action is not equal. In Japanese, bolus/basal ratio seems to be higher than 1 (i.e. ~2), indicating less hepatic insulin resistance. The dosages of DET should be different from those of GLA, and the clinical use of those different kinds of insulin needs special caution.

There is no conflict of interest in this study.