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Introduction/Objectives

- Regardless of diabetes status, patients admitted to the hospital for acute ischemic stroke (AIS) are frequently observed to have hyperglycemia [1].
- Hyperglycemia is associated with poor stroke outcomes [2], and no conclusive evidence exists that normalizing serum glucose during the acute phase of ischemic stroke improves outcomes [1], unlike other groups of critically ill patients [3].
- Not stratifying patients according to their pre-stroke glycemic status [4] and differential pathophysiology of insulin regulation during the acute phase [5] may explain the inability to demonstrate the expected benefit.
- In general, hyperglycemia is secondary to a relative insulin deficiency in diabetic patients, whereas is part of the systemic stress response and not a hypo-insulinemic state in non-diabetic patients [6].
- Different treatment approaches that consider the diabetic status should improve stroke outcomes.
- We aimed to develop a pharmacokinetic model of regular SC insulin (Actrapid) therapy for hyperglycemia during acute ischemic stroke among stroke patients with and without pre-existing diabetes.

Methods

- A prospective study conducted in two-stroke centers in Malaysia.
- AIS patients with or without pre-existing diabetes who developed hyperglycemia within 72 hours of admission and were treated with SC insulin were recruited.
- Pre-existing diabetes status was confirmed by A1C level ≥ 6.5%.
- At least three blood samples were collected sparsely at 0, 0.5, 1.5, 3, 4, 6, and 8 hours of the SC insulin therapy.
- One and two-compartment models with additive, exponential, and combined additive and exponential error models and lag absorption models were investigated
- potential covariates were added considering the physiological plausibility and statistical significance.
- Parameters uncertainty was estimated by sampling importance resampling (SIR)
- NONMEM v.7.4 and PsN v.5.3.1 were used.

Results

- Fifty-three AIS diabetic patients (DM) and twenty-nine nondiabetic patients (non-DM) were included.
- A one-compartment model with first-order absorption and elimination was selected for both populations.
- A combined additive and exponential error model for the DM model and an exponential error model for the non-DM model were selected.
- DM patients' absorption rate increased by 32% every five years after 60 ( $Ka=\theta_1*(Age/60)^{5.97}$ ).
- The clearance decreased exponentially by approximately 10% for each 1 kg/m<sup>2</sup> increase in the body mass index (BMI) after 25.6 kg/m<sup>2</sup> ( $CL= \theta_2*e^{-0.128*(BMI-25.6)}$ ) and for each 0.5 mmol/l increase in urea concentration above 5.3 mmol/l during the acute state ( $CL= \theta_3*e^{-0.207*(Urea-5.3)}$ ).
- Non-DM patients with modified Rankin Score (MRS)>2 showed a six-time increase in regular SC insulin clearance compared to patients with MRS≤2.

Table.1: Final parameters estimates of developed popPK model of regular SC insulin (Actrapid) given to 53 diabetic patients during acute ischemic stroke

| Parameter             | Typical Value (95%CI)   | RSE, % | Shrinkage, % |
|-----------------------|-------------------------|--------|--------------|
| Ka (h <sup>-1</sup> ) | 1.22 (0.76, 1.84)       | 25.9   | -            |
| IIV (Ka), %           | 22.36 (17.6-26.64)      | 12.16  | 18           |
| Age/Ka                | 5.97 (2.92, 9.01)       | 30.62  | -            |
| CL/F (L/h)            | 26.7 (17.04, 36.05)     | 22.05  | -            |
| IIV (CL), %           | 80.87 (64.42-96.74)     | 12.09  | 18           |
| BMI/CI                | -0.128 (-0.18, -0.07)   | 26.9   | -            |
| Urea/CI               | -0.207 (-0.29, -0.11)   | 27.45  | -            |
| V/F (L)               | 247.18 (181.79, 339.38) | 19.16  | -            |
| IIV (V), %            | 56.64 (43.26-69.92)     | 13.99  | 18           |
| Corr, (Ka, CL)        | 42.81 (33.36-48.57)     | 10.15  | -            |
| Corr, (Ka, V)         | 35.77 (27.92-41.17)     | 10.71  | -            |
| Corr, (CL, V)         | 67.70 (53.54-77.56)     | 10.57  | -            |
| E. insulin (μU/ml)    | 6.25 (3.74, 8.79)       | 24.9   | -            |
| R1 (h <sup>-1</sup> ) | 0.15 (0.09, 0.24)       | 30.3   | -            |
| Add (μU/ml)           | 8.54 (6.93, 11.17)      | 15.33  | -            |
| Prop, %               | 22.8 (18.29, 29.25)     | 14.54  | -            |

Table.2: Final parameters estimates of developed popPK model of regular SC insulin (Actrapid) given to 29 nondiabetic patients during acute ischemic stroke

| Parameter          | Typical Value (95%CI)   | RSE, % | Shrinkage, % |
|--------------------|-------------------------|--------|--------------|
| Ka (h-1)           | 3.92 (1.91, 5.99)       | 30.2   | -            |
| IIV (Ka), %        | 35.88 (17.6-26.64)      | 13     | 35           |
| CL/F (L/h)         | 25.8 (13.34, 39.07)     | 30.4   | -            |
| IIV (CL), %        | 108.2 (91.32, 139.1)    | 13.6   | 35           |
| MRS/CI             | 6.18 (3.45, 9.31)       | 28.6   | -            |
| V/F (L)            | 76.3 (34.8, 113.13)     | 19.16  | -            |
| IIV (V), %         | 181.1 (157.16, 231.27)  | 13.42  | 35           |
| Corr, (Ka, CL)     | -62.36 (-66.93, -41.59) | 10.74  | -            |
| Corr, (Ka, V)      | -80.62 (-86.84, -56.27) | 10.59  | -            |
| Corr, (CL, V)      | 140 (92.08, 152)        | 10.83  | -            |
| E. insulin (μU/ml) | 13.8 (6.72, 20.40)      | 29.19  | -            |
| R1 (h-1)           | 0.568 (0.29, 0.84)      | 28.74  | -            |
| Prop, %            | 72.4 (38.35, 105.35)    | 27.99  | -            |

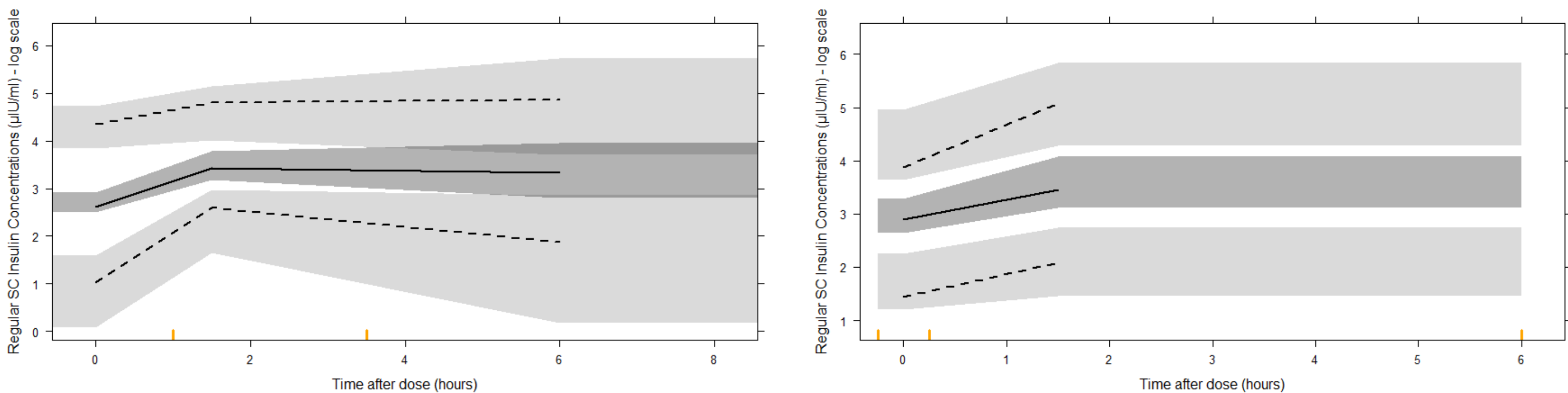


Figure.1: Prediction corrected visual predictive checks (pcVPC) plots of popPK model for diabetic AIS patients (Left) and nondiabetic AIS patients (Right).

Conclusions

- Regular SC insulin dose adjustment is needed in diabetic and nondiabetic patients during AIS.
- Dose reduction is necessary for AIS diabetic patients above 60, with a BMI above 25.6 kg/m2, and having a urea level above 5.3 mmol.
- At the same time, the dose should be increased for nondiabetic patients with MRS>2.

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