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Effect of Insulin Glargine on Cardiovascular Risk Analysed by Mean HRV

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Abstract

Type 2 diabetes mellitus is an insidious disease that is increasingly present in geriatric population [1]. The greatest difficulty is represented by glycaemic control in geriatric patients often not very compliant with diet therapy and drug therapy. A new insulin glargine 300 units/ml formulation seems improve patient compliance due to the lower volume of insulin to be injected and improved glycaemic control over 24 hours. The HRV signal, derived from digital electrocardiographic recording, is the simplest and most immediate analysis that consists in calculating some temporal parameters [2]. HRV is a simple statistics derived from beat-beat intervals of sinus origin expressed as units of time in milliseconds. Data in the literature indicate that a decrease in HRV, measured with time domain analysis, denotes a worse prognosis and/or an increased risk of mortality in patients with heart disease, especially in the elderly ones.

Keywords

Insulin Glargine, Diabetes, HRV, Cardiovascular Risk, Geriatry

1. Background

Type 2 diabetes mellitus is increasingly present geriatric population [1]. Recently, a new 300 units/ml insulin glargine formulation has been introduced in clinical practice to improve patient compliance due to lower volume of insulin to be injected and improved glycemic control within 24 hours. The HRV signal, derived from digital electrocardiographic recording, allows us to calculate some temporal parameters [2]. Data in the literature indicate that a decrease in HRV,

measured by the analysis of the time domain, shows a worse prognosis in particular in the elderly.

2. Aim

The aim of our study is to evaluate, through the Heart Rate Variability study, the possible influence of the new insulin glargine formulation 300 units/ml [3] on the neurovegetative tone and on the arrhythmic cardiovascular risk.

3. Materials and Methods

In the period between February 2018 and April 2018 we enrolled 30 patients. 5 patients (16.6%) are not compliant and therefore the real number of enrolled patients is 25 (13 male and 12 female) with an average age of 75 ± 13 years with type II diabetes mellitus. All patients gave their informed consent and ethical approval. In the enrolment phase, the patients underwent the evaluation of the glycaemic profile at 20.00 by means of glucostick and the subsequent digital electrocardiographic recording by means of a Medixai electrocardiograph. Elegibility patient have diabetes mellitus treated with insulin glargine. Exclusion criteria are the presence of atrial fibrillation for BIAS in HRV evaluation. At the end of the enrolment, the patients were treated with the new insulin glargine formulation 300 units/ml at the same dosage as the old insulin glargine. After 1 hour from insulin administration, the patients were again subjected to the evaluation of the glycaemic profile by means of glucostick and to the subsequent recording of digital control electrocardiography. The pre and post-treatment glycaemic values were used as a parameter to confirm the action of insulin glargine, administered to patients.

The analysis of the HRV in the time domain was performed using the Kubios software for Windows XP. For this study were used statistical parameters of STD variability or standard deviation of the R-R intervals with respect to the mean; NN50 or number of consecutive intervals with difference > 50 msec; pNN50 or percentage of the NN50 intervals compared to the total of the measured intervals (a threshold of 20 msec can demonstrate superior discrimination between physiological and pathological HRV) [4]; RMSSD or square root of the mean squared differences between adjacent R-R intervals; SDNN or calculation of the standard deviation of a series of intervals NN, AR LF/HF or regression analysis of the LF/HF ratio. Statistical analysis was performed with Paired T-test for small group of the patients using the Sigmastat 3.5 software for windows XP.

4. Results

The results of our study have shown that the new formulation of insulin glargine (300 units/ml) [5], even though it has determined a statistically significant reduction in glycaemic values due to insulin glargine activity (Table 1) before the electrocardiographic recording performed as a control, and a statistically significant increase of the Heart Rate index of a reduction in heart rate frequencies

Table 1. Descriptive statistics: RRvar STD (standard deviation of the R-R intervals compared to the mean); NN50 (number of consecutive intervals with difference > 50 msec); pNN50 (percentage of the NN50 intervals with respect to the total of the measured intervals, with a threshold of 20 msec); RMSSD (square root of the average of the squared differences between adjacent R-R intervals); SDNN (calculation of the standard deviation of a series of intervals NN); AR LF/HF (regression analysis of the LF/HF ratio). "*": statistically significant changes.

	Base ± DS	Control ± DS	Probability (P)
Glucose (mg/dl)	242.500 ± 77.768	190.500 ± 72.109	P < 0.001*
RR var (ms)	811.717 ± 176.049	839.942 ± 177.081	P = 0.035*
NN50 (ms)	58.542 ± 66.835	61.833 ± 69.133	P = 0.691
pNN50	23.242 ± 26.540	23.600 ± 26.317	P = 0.892
RMSSD	53.600 ± 46.600	57.508 ± 54.778	P = 0.577
SDNN	43.271 ± 36.614	43.500 ± 41.433	P = 0.961
AR LF/HF	1.457 ± 1.965	1.390 ± 2.208	P = 0.910

(Table 1), but does not establish any statistically significant changes in neurovegetative tone, that would negatively affect the cardiovascular risk in geriatric patients with multiple co-morbidities.

5. Discussion

Insulin glargine is a human insulin analog designed to have a low pH neutral solubility while the solubility is highest for pH values equal to 4. After subcutaneous injection, the acidic insulin solution is neutralized giving rise to the formation of precipitate insulin which gradually releases small amounts of insulin glargine.

The administration of the new insulin glargine formulation (300 units/ml) allows improving the glycaemic profile in 24 hours as reported by the pharmacodynamic studies that have shown how the insulin effect persists up to 36 hours, due to the prolonged release of insulin glargine from the precipitate of this new formulation. This can be attributable to the reduction in injection volume of about 2/3. Such reduction in injection volume leads to a decrease in the area of the precipitate responsible for the release of soluble glargine insulin. The dosage of the new insulin glargine can be optimized by adding 10% - 20% of the usual dosage of the old-generation insulin glargine (100 units/ml) since the insulin glargine of the old generation (100 units/ml) and the new formulation of insulin glargine (300 units/ml) are not bioequivalent and are not directly interchangeable.

According to the data sheet, the dosage of the new generation glargine insulin (300 units/ml) can be calculated with the formula 0.2 units/kg of body weight or increasing the dosage of the new generation insulin by 10% - 20% (300 units/ml) compared to the old glargine insulin dosage (100 units/ml). The new insulin glargine formulation ensure a good control of glycaemia [6] and ensure a neutrality in terms of effects on arrhythmic cardiovascular risk, which represent a highly represented problem in the geriatric population affected by co-morbidities such as heart failure, atrial fibrillation and electrolyte disorders, concomitant with chronic renal function abnormalities.

6. Conclusion

Preliminary data obtained from our study shown that the new insulin glargine formulation 300 units/ml represents a new therapeutic option that allows improving the glycaemic profile (Figure 1), given the best solubility in relation to the minor surface of the precipitate [6] and improve with a statistically significant variation the RR-variability (confirmed by the data deriving from the analysis of the RR variability index) (Figure 2) without altering the neurovegetative structure and therefore the cardiovascular risk (confirmed by the data deriving from the regression analysis of the LF/HF ratio). Our data give comfortable results but further evaluations are needed to have conclusive results.
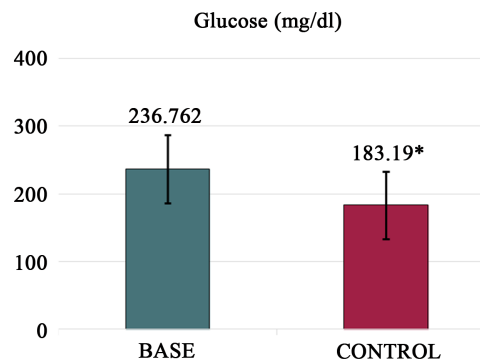
Figure 1. Descriptive statistics about glucose value. "*": statistically significant changes.
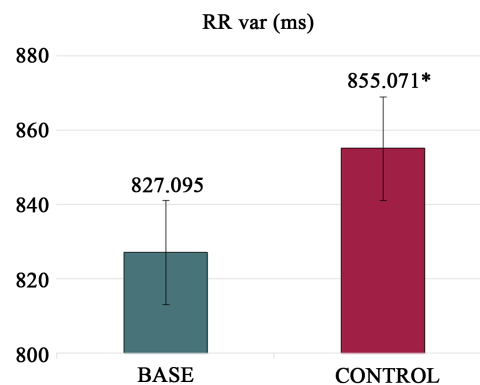
Figure 2. Descriptive statistics about R-R variability index. "*": statistically significant changes.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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