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Effects of Second Generation Sulfonylureas on The Thyroid

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While it has long been known that first generation sulfonylureas have goitrogenic effects, knowledge about the effects of second generation sulfonylureas on the thyroid is insufficient. In this study, we aimed to investigate the effects of second generation sulfonylureas on the thyroid.

Twenty four (15 females and 9 males, age 51.9 ± 2.1 years) diabetic patients were studied. They were treated with gliclazide ranging from 80 mg to 320 mg daily. Thyroid volume were calculated by thyroid ultrasound, 2-hour and 24-hour RAIU and thyroid function tests (FT_3, FT_4, TSH, TU, FTI) were evaluated before and four months after treatment.

Thyroid volume was found to be 17.0 ±1.3 ml before sulfonylurea treatment and 18.3 ±1.4 ml after treatment and the increase was statistically significant (P< 0.01). 2-hour RAIU was found to be 20.0 ± 2.4 % before and 16.0 ±1,5 % after treatment. 24- hour RAIU was found to be 36.9 ± 3.3 % before and 30.2 ± 2.4 % after treatment. The decrease in the 24-hour RAIU was statistically significant (P< 0.05*). No changes were observed for thyroid function tests.**

These results suggest that second generation sulfonylureas may have a goitrogenic effect, so it may be useful to investigate the effects of second generation sulfonylureas on the thyroid with more extensive studies.

KEY WORDS Sulfonylurea Thyroid

Introduction

Sulfonylurea drugs have been used in the treatment of non insulin dependent diabetes mellitus since 1955. The antithyroid and goitrogenic activity of sulfonylurea compounds was clearly recognized at the time of their introduction for the treatment. Early studies showed that, in animals receiving large doses of sulfonylureas, the weight of the thyroid gland is increased, its histological appearance is changed and its iodine content and fixation of radioiodine are reduced (1).

Sulfonylurea drugs are a class of compounds that are developed from sulfonamide drugs by some modifications, but their effects on iodine metabolism are different from sulfonamides. Sulfonylureas decrease the uptake of iodide whereas

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sulfonamides prevent conversion of iodine to diiodotyrosine and thyroxine, but don't prevent uptake of iodide by the thyroid (2, 3).

Also studies showed a higher incidence of hypothyroidism in diabetics treated with the first generation sulfonylureas than in control groups treated with diet alone or insulin (4, 5). In most patients that are hypofunctional after sulfonylurea therapy, the pituitary is able to compensate for their effect and maintain a euthyroid state by increased synthesis of TSH (compensated hypothyroidism), and goiter is the most striking and best known outcome of excessive TSH secretion (1, 6).

The electrophoretic studies showed that sulfonylureas inhibit the binding of T_3 and T_4 to TBG competitively. Reduced protein-bound iodine (PBI) and elevated resin uptake has been used as evidence of their antithyroid property (7, 8).

Carbutamide has a strong antithyroid effect when compared with other first generation sulfonylureas. In contrast with the other drugs, carbutamide contains a para-aminobenzene ring and this is the probable basis for the strong antithyroid effect (2, 7, 8).

Knowledge about effects of second generation sulfonylureas on the thyroid is insufficient. There are a few studies and different results (9-11). It is important to know whether second generation sulfonylureas have antithyroid and goitrogen effects or not for selection of the drug in the treatment. In spite of the fact that the antithyroid potency of the sulfonylurea drugs is apparently not very high, there are several reasons for a serious consideration of this side effect. In the majority of cases, oral antidiabetic treatment means a continuous consumption of a goitrogen over a period of years or even decades. One other reason is the increased antithyroid and goitrogen effect of sulfonylurea drugs when combined with iodine deficiency, which is endemic in many regions of our country (1).

In this study, we investigate the effects of second generation sulfonylureas on the thyroid.

Materials and Methods

Twenty four (15 females and 9 males, age 51.9 ± 2.1 years) diabetic patients were studied. Patients had not used sulfonylurea drugs before and could not be controlled by diet only, and also they did not have thyroid disease.

They were treated with gliclazide ranging from 80 mg to 320 mg daily. Patients were evaluated before and four months after treatment.

Thyroid ultrasound examination was performed with a real-time instrument (Toshiba SSA-340A) using a 7,5 mHz linear transducer. Thyroid volume was calculated according to the formula of the ellipsoid model:

Width x Length x Thickness x 0.52 (for each lobe) (12).

Counts were obtained in 364 keV photopeak and 20% window by using a gamma camera (GE 400 AC/T) fitted with a pinhole collimator. A tracer dose of 30 µCi I^{131} was given to the patient orally and an equal dose was measured and saved for reference counting. The count rate over the neck was measured after 2 and 24 hours. The extrathyroidal background activity was assessed by measuring the count rate over the thigh. The percentage uptake was counted by the formula below:

$$\text{Uptake \%} : \frac{\text{Neck count - thigh count}}{\text{Reference tracer dose}} \times 100$$

Thyroid function tests were measured by the chemiluminescence method using a Ciba-Corning ACS-180 instrument and Ciba-Corning kits.

Statistical analyses were performed using the t test, paired t test, X^2 test and Pearson product correlation. All laboratory data are expressed as mean ± SEM.

Results

Mean thyroid volume was found to be 17.0 ± 1.3 ml. before sulfonylurea treatment, and 18.3 ± 1.4 ml. after treatment. The increase was statistically significant. (P< 0.01**).

2-hour RAIU was found to be 20.0 ± 2.4 % before and 16.0 ± 1,5 % after sulfonylurea treatment. 24-hour RAIU was found to be 36.9 ± 3.3 % and 30.2 ± 2.4 % after treatment. The decrease in the 24-hour RAIU was statistically significant (P< 0.05*).

There was no difference in FT_3, FT_4, TSH, TU and FTI levels before and after treatment (Table 1).

Table 1. Thyroid volume, 2-hour and 24-hour RAIU and thyroid function tests before and after sulfonylurea treatment.

	Before treatment	After treatment	p
Thyroid volume (ml)	17.04 ± 1.3	18.3 ± 1.4	< 0.01**
2 - hour RAIU (%)	20.0 ± 2.4	16.0 ± 1.5	> 0.05
24-hour RAIU (%)	36.9 ± 3.3	30.2 ± 2.4	< 0.05*
FT3 (pg/ml)	2.57 ± 0.10	2.73 ± 0.06	> 0.05
FT4 (ng/ml)	1.17 ± 0.03	1.18 ± 0.03	> 0.05
TSH (μIU/ml)	2.09 ± 0.36	2.08 ± 0.31	> 0.05
TU	0.84 ± 0.01	0.83 ± 0.02	> 0.05
FTI	2.19 ± 0.08	2.04 ± 0.08	> 0.05

Discussion

Goitrogenic substances exert effects on the thyroid gland by disrupting one of several steps in the biosynthesis and secretion of thyroid hormones. These include inhibition of the iodine-trapping mechanism, blockage of organic binding of iodine and coupling of iodothyronines to form thyroxine (T_4) and triiodothyronine (T_3), and inhibition of thyroid hormone secretion by an effect on the proteolysis of active hormone from the colloid (13).

Studies showed that sulfonylureas decrease the uptake of iodide. Tranquada et al. examined the 24-hour I^{131} uptake in rats given sulfonylurea and they showed that the thyroid I^{131} uptake was decreased (3, 8). Also Skinner et al. examined the effects of sulfonylureas in patients following administration of chlorpropamide, and they found that 24-hour RAI uptake was 18.1 percent before sulfonylurea administration and 11.4 percent after treatment (14).

In our study, 2-hour and 24-hour RAI uptake were studied before and after sulfonylurea treatment. After treatment for 4 months, both 2-hour and 24-hour RAIU were decreased and the decrease in the 24-hour RAIU was statistically significant.

Studies that examined the effect of first generation sulfonylureas on the thyroid also showed their goitrogenic effect (2, 3, 8). However, the results of the studies about effects of second generation sulfonylureas were equivocal. England et al. found that there was no effect of glyburide on thyroid size after 6 weeks of treatment (11). However, 6 weeks may be insufficient to constitute the goitrogenic effect.

Three criterion standards have been used in assessing the accuracy of thyroid size determination: Weight measured after surgical or post-mortem removal, ultrasound assessment, and nuclear scintigraphy. Ultrasound assessments of thyroid weight correlate well with true gland weight as determined following excision, although there is lack of agreement as to the best formula to use for estimating size (15).

In this study, we used the ellipsoid model to calculate thyroid volume and found an increase in thyroid volume after sulfonylurea treatment.

Similar to the goitrogenic effect, studies aiming at evaluating the effects induced by treatment with sulfonylureas on thyroid function have led to conflicting results. Hunton et al. observed a higher incidence of hypothyroidism in diabetics treated for at least six months with tolbutamide and chlorpropamide. Some other studies reporting the effect of tolbutamide did not show any significant variation in thyroid function (4).

In the various series, there are no clear-cut alterations in thyroid function after short term administration. However, sulfonylurea-induced hypothyroidism can occur after long-term administration and the rate ranges from 3 to 15 percent (16). In the study by Portioli and Rocchi, in 200 patients treated with tolbutamide and followed up from 1 to 7 years, thyroid function tests suggested hypothyroidism in 3%, although clinically none of the patients was hypothyroid. But, the incidence of spontaneous primary myxedema among total hospital admissions in various large hospitals has been reported to be 0.01 % to 0.08 %. On the other hand, at the Joslin Clinic a survey revealed that among approximately 9000 diabetic patients who had ever received first generation sulfonylureas, very few -only 14 (0.15 %)- had developed hypothyroidism (5).

There is no large series with second generation sulfonylureas. In spite of the report of Heki et al. in which hypothyroidism was induced by administration of glibenclamide, the other studies demonstrated that glibenclamide and gliclazide had no influence on thyroid hormone metabolism (9 -11). In the present study no changes were observed for thyroid function tests.

In conclusion, in this study there is an increase in thyroid volume and decrease in RAIU after sulfonylurea treatment for 4 months. These results suggest that second generation sulfonylureas may have a goitrogenic effect, so it may be useful to investigate the effects of second generation sulfonylureas on the thyroid with more extensive studies.

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