BIOCHEMICAL EFFECT OF DILTIAZEM IN HYPERTHYROIDISM

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ABSTRACT

Objective: *To evaluate the effect of diltiazem on thyroid function tests.*

Material and Methods: *This prospective, interventional study was conducted on 19 newly diagnosed patients of hyperthyroidism attending the out patient department of Institute of Radiotherapy and Nuclear Medicine, Peshawar. All patients took diltiazem 30 mg three times a day for 6 weeks. Serum free thyroxine (FT4) measurements were done before starting diltiazem and then serially after 2, 4 and 6 weeks (+ 3 days) of therapy.*

Results: *FT4 decreased from 33.29 ± 7.77 pmol / L to 32.77 ± 8.15 pmol / L after 2 weeks (P = 0.509), to 31.86 ± 8.15 pmol / L after 4 weeks (P = 0.138) and then to 31.50 ± 7.80 pmol / L after 6 weeks (P = 0.i37).*

Conclusion: *Diltiazem has some although not significant biochemical effectiveness in decreasing the thyroid hormone levels after 4–6 weeks of therapy.*

Key Words: *Diltiazem, Hyperthyroidism, Free T4 Concentration.*

INTRODUCTION

The cytosolic free calcium concentration [Ca^{2+}_{1}] is an important intracellular messenger system. Changes in [Ca^{2+}]$_i$ constitute one of the major pathways by which information is transferred from extracellular signals (drugs, hormones, neurotransmitters, etc) received by the cell to intracellular sites. In a resting cell, [Ca^{2+}]$_i$ is kept very low by Ca^{2+} pumps. However, in response to a variety of stimuli, it rises to a level which initiates Ca^{2+}-dependent cellular processes resulting in a diverse range of physiological and pathological events. The rise in [Ca^{2+}]$_i$ occurs through Ca^{2+} influx across the plasma membrane or through Ca^{2+} release from intracellular stores, but more characteristically, from both the routes.[1]

[Ca^{2+}]$_i$ also plays crucial role in the synthesis of thyroid hormones. The thyroid plasma membrane contains a Ca^{2+}-regulated NADPH-dependent H_2O_2 generating system providing H_2O_2 for the thyroperoxidase (TPO)-catalysed biosynthesis of thyroid hormones under the following reaction:

$$NADPH + O_2 + Ca^{2+} \xrightarrow{\text{NADPH oxidase}} H_2O_2 + NADP^2$$

H2O2 is an essential substrate for TPO and is the limiting factor for the downstream chemical processes which lead to the synthesis of thyroid hormones.[3] The thyroid cells generate for the synthesis of thyroid hormones appropriate amounts of H_2O_2 that may be toxic in other cell types.[4–6]

Generation of H_2O_2, on the other hand, is dependent on cytosolic free Ca^{2+} concentration as shown by Takasu and his colleagues who demonstrated that [Ca^{2+}]$_i$ is an important factor in the regulation of H_2O_2 generation and thereby in the regulation of iodination and thyroid hormone synthesis.[7]

BASELINE AND POST-INTERVENTION CHARACTERISTICS REGARDING FREE T_4

Characteristic		FT_4 (pmol/L)	P- value*
Baseline		33.29 ± 7.77	–
Post-intervention	Week 2	32.77 ± 8.15	0.509
	Week 4	31.86 ± 8.15	0.138
	Week 6	31.50 ± 7.80	0.137

**P* values between means of baseline FT_4 (before starting therapy) and post-intervention FT_4 (after starting diltiazem).

Table 1

In an attempt to see for the effects of calcium channel blockers on the synthesis of thyroid hormones, Roti et al (1988) evaluated the effect of diltiazem on serum levels of thyroid hormones but observed no significant effect on these hormones.[8] Kelestimur and Aksu studied the effect of diltiazem on thyroid function tests and reached the conclusion that diltiazem does not significantly reduce thyroid hormone levels.[9] But in both of these studies, the biochemical effects of diltiazem on thyroid hormones were assessed after 10 days of therapy. However, it takes 3-4 weeks before the stores of T_4 are depleted.[10]

Studies in animals (rabbits) have shown that a month-long therapy with calcium channel blockers significantly decreases serum levels of T_3 and T_4.[11]

The aim of the present study was to evaluate the effect of diltiazem on free thyroxine levels after at least 6 weeks of therapy. This calcium channel blocker is unique in having non-specific antiadrenergic activity more than any other calcium channel blocker used clinically. Also, diltiazem, a non-dihydropyridine, blocks tachycardia in calcium-dependent cells more selectively than do the dihydropyridines (e.g. nifedipine). Furthermore, significant reflex tachycardia in response to hypotension occurs most frequently with dihydropyridines but less so with diltiazem.[12] These pharmacological properties of diltiazem may make it a favourable calcium channel blocker in thyrotoxic patients.

MATERIAL AND METHODS

Twenty newly diagnosed, untreated cases of hyperthyroidism attending the out patient department of Institute of Radiotherapy and Nuclear Medicine, Peshawar were selected in this prospective, interventional study using the following criteria:

Inclusion criteria:

- Subjects of 20–55 years of age of either sex,
- Mild to moderate, stable cases of hyperthyroidism with free thyroxine not more than 50 pmol / L, and
- Subjects who gave a written, well informed consent.

To improve supervision and minimize the drop out from the study, only those cases were registered who belonged to Peshawar and the suburbs, so that they could be approached in case of their failure to attend the follow up clinic. But even then, one patient was lost to follow up.

Exclusion criteria:

- Subjects with severe hyperthyroidism,
- Pregnant or lactating mothers, and
- Subjects with ischaemic heart disease or any other chronic illness like diabetes or renal failure.

All subjects took diltiazem (Dilzem – Park-Davis) 30 mg three times a day for 6 weeks. Serum free T_4 measurements were done before starting diltiazem and then serially after 2, 4 and 6 weeks (± 3 days) of therapy using radioimmunoassay technique. TSH measurements using coat-A-Count TSH IRMA and radioactive iodine uptake (RAIU) studies / thyroid scan were done once in the beginning for the purpose of diagnosis.

Data collected were analysed statistically with SPSS (statistical package for social sciences) using paired Student's t-test; value of '*P*' less than 0.05 was considered significant.

RESULTS

This study was conducted on 20 newly diagnosed, untreated cases of hyperthyroidism. After drop out, 19 patients (16 females and 3 males with a mean age of 35.31 ± 10.36 years) completed the study. Results are described as mean ± SD.

Free T_4 (FT_4) concentrations decreased from 33.29 ± 7.77 pmol / L to 32.77 ± 8.15 pmol/L after 2 weeks (P = 0.509). FT_4 further decreased to 31.86 ± 8.15 pmol/L and 31.50 ± 7.80 pmol/L after 4 and 6 weeks with P values of

BIOCHEMICAL CHARACTERISTICS (FT_4) OF THE SUBGROUPS AFTER AGE WISE CATEGORIZATION

Subgroup	Baseline FT_4 (pmol/L)	FT_4 (pmol/L) after 6 weeks
Group A (20-35 years) (n = 8)	35.38 ± 8.43	34.67 ± 6.43
Group B (36-55 years) (n =11)	31.77 ± 7.27	29.19 ± 8.16

Table 2

0.138 and 0.137 respectively (Table 1). Most of the decline in FT_4 (80 % of the total) has occurred after 4 weeks (Figure 1).

Characteristics of the patients when categorized on the basis of age (20–35 years versus 36–55 years) are shown in Table 2. Mean change in FT_4 after 6 weeks in subgroup A (0.71 ± 5.15 pmol/L) when compared with the mean change in FT_4 in subgroup B (3.12 ± 5.35 pmol/L), the difference was non-significant ($P > 0.05$).

The essential role of hydrogen peroxide (H_2O_2) as an oxidant for thyroperoxidase (TPO) activity and its generation by the thyroid cells was described in 1980s and an NADPH oxidase activity was suggested quickly to be the underlying mechanism[13,14] but it took one and a half decades from the discovery of this function to the identification of dual oxidases (DUOX) which are members of the NOX family of NADPH oxidases (both DUOX 1 and DUOX 2 are highly expressed in thyroid).[15–19]

The importance of cytosolic free calcium concentration ($[Ca^{2+}]_i$) as a regulating factor for the generation of H_2O_2 was established in their experiments by Bjorkman and Ekholm who demonstrated that H_2O_2 release from isolated open pig thyroid follicles was promptly increased about 10 times by the addition of a Ca^{2+} inophore A-23187 to Ca^{2+}-containing medium.[20] Takasu and his colleagues studied the effects of A-23187 and Bay K-8644, a calcium channel agonist, on $[Ca^{2+}]_i$ and H_2O_2 generation in cultured porcine thyroid cells and reached the conclusion that it is the cytosolic free calcium concentration which regulates the generation of H_2O_2 and, through that, regulates iodination and thyroid hormone synthesis.[7]

Roti et al studied the effects of diltiazem on serum levels of total T_4, T_3 and rT_3 in 11 hyperthyroid patients after 10 days of therapy but observed that no significant change occurred in levels of these three hormones.[8] Kelestimur et al evaluated the influence of diltiazem on serum concentration of total T_4 and T_3 in 20 hyperthyroid patients and concluded that diltiazem does not significantly reduce these hormones after 10 days of therapy.[21] Then Kelestimur and Aksu assessed the biochemical effect of diltiazem on thyroid function tests in 22 newly diagnosed patients with hyperthyroidism but observed that diltiazem had no significant effect on these hormones after 10 days of therapy.[9] Finally Mittal and his colleagues carried out a study in rabbits and reached the conclusion that calcium channel blockers significantly decreased the serum levels of T_3 and T_4 after a month-long therapy with these drugs.[11]

The present study was undertaken to explore further the biochemical efficacy of diltiazem regarding free thyroxine (FT_4) concentrations after a 6 weeks-long therapy. Serial measurements of FT_4 after 2, 4 and 6 weeks have shown that FT4 decreased to some extent with *P* values of 0.509, 0.138 and 0.137 respectively. All these *P* values are non-significant at the usual 5 % level of significance but the latter two values are highly 'sensitive' and are 'approaching' significance ($P < 0.15 > 0.05$).

The results of this study are in agreement with those shown by Mittal and his colleagues who demonstrated that a month-long therapy with calcium channel-blockers significantly decreased serum levels of T_3 and T_4 in rabbits.[11] However, our results are in contradiction to those shown by Roti et al (1988)[8], Kelestimur et al (1993)[21] and Kelestimur and Aksu (1996)[9] who concluded that

PERCENTAGE DECREASE IN MEAN FT_4 AFTER STARTING THERAPY WITH DILTIAZEM

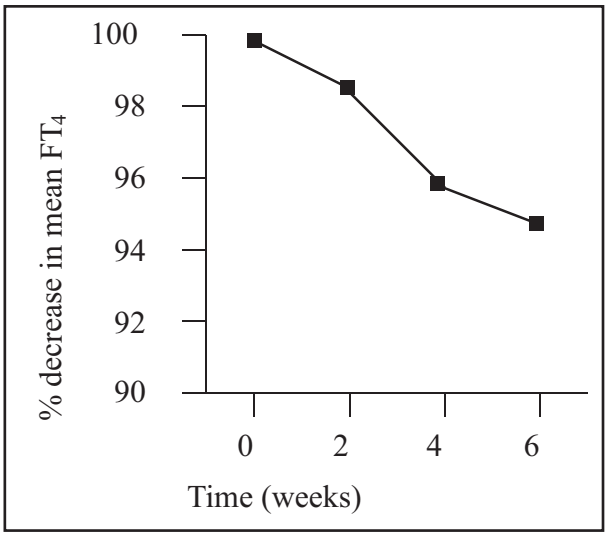

Figure 1

diltiazem did not significantly affect thyroid function tests. But in these three studies, the effect of diltiazem on thyroid hormone levels were evaluated after 10 days of therapy. In fact it takes 3-4 weeks before the stores of T_4 are depleted.[10] In the present study, the effects of diltiazem were studied for a period of 6 weeks.

Age wise categorisation of the patients (20–35 years versus 36–55 years) has shown that there is no significant difference between these two subgroups regarding the decline in FT_4 concentration ($P > 0.05$), thus indicating that intensity of biochemical response to diltiazem occurs irrespective of the age of the patient.

CONCLUSION

Diltiazem (30 mg three times per day) has some although not significant biochemical effectiveness in decreasing the thyroid hormone levels after 4–6 weeks of therapy. The matter needs elucidation in future studies with still higher doses of the drug and more prolonged duration of therapy with diltiazem.

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