CAN DILTIAZEM BE USED AS A *ROUTINE* ADJUVANT DRUG IN PATIENTS WITH HYPERTHYROIDISM?

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ABSTRACT

Objective: To assess the possibility of using diltiazem as a routine adjuvant drug in hyperthyroidism by evaluating the effects of combined therapy of diltiazem and carbimazole on the adrenergic manifestations of hyperthyroidism and thyroid function tests, and to compare these effects with those of combination of propranolol and carbimazole.

Material and methods: This prospective, interventional study included 45 newly diagnosed patients of hyperthyroidism attending the out patient department of Institute of Radiotherapy and Nuclear Medicine, Peshawar. Patients were randomised to two groups. Patients in group I (n = 20, male/female ratio 2:18, mean age: 41.75 ± 11.13 years) took diltiazem 30 mg + carbimazole 10 mg three times a day for 6 weeks. Patients in group II (n = 25, male/female ratio 4:21, mean age: 37.72 ± 8.90 years) took propranolol 20 mg + carbimazole 10 mg three times daily for 6 weeks. Clinical assessment was done before starting therapy and then after 6 weeks (± 3days) using standardised and modified hyperthyroid symptom score (HSS). Biochemical assessment was done by measuring serum FT_4 in the beginning and then after 6 weeks (± 3 days) of starting therapy.

Results: In group I, FT_4 decreased from 38.43 ± 6.67 to 34.30 ± 6.50 after 6 weeks of therapy with diltiazem and carbimazole ($p < 0.001$). HSS decreased from 15.80 ± 2.35 to 8.25 ± 2.53 ($p < 0.001$). In group II, FT_4 decreased from 37.47 ± 7.75 to 34.21 ± 7.89 after 6 weeks of therapy with propranolol and carbimazole ($p < 0.001$). HSS decreased from 14.88 ± 2.01 to 8.36 ± 1.91 ($p < 0.001$). Mean decline in FT_4 in group I (4.12 ± 3.19) when compared with mean decrease in FT_4 in group II (3.21 ± 3.47), the difference was non-significant ($p > 0.05$). Similarly, mean decrease in HSS in group I (7.55 ± 2.11) when compared with mean decline in HSS in group II (6.52 ± 1.92), the difference was non-significant ($p > 0.05$).

Conclusion: Combination of diltiazem and carbimazole is as effective as the combination of propranolol and carbimazole. As there are very few clinical limitations of diltiazem as compared to propranolol, it can be used as a **routine** adjuvant drug in the management of hyperthyroidism.

Key words: Diltiazem, propranolol, carbimazole, hyperthyroidism, adrenergic manifestations, free T_4 concentration.

INTRODUCTION

Adjuvants are necessary to be added to antithyroid drugs for early amelioration of adrenergic manifestations of hyperthyroidism because antithyroid drugs act primarily to decrease the biosynthesis of thyroid hormones and have no effect on the release of thyroid hormones previously stored in the gland; it takes 3-4 weeks before these follicular stores of thyroid hormones are depleted.[1]

Guanethidine and reserpine, which deplete tissue catecholamines, were used in the past in addition to antithyroid drugs but these drugs had serious adverse effects, e.g. orthostatic hypotension, mental depression and parkinsonian symptoms, and were soon replaced by β-blockers once they were available.[2]

Propranolol, the prototype β-blocker, is now usually added as an adjunct to antithyroid drugs but there are clinical conditions where b-blockers are contraindicated or hazardous, e.g. AV conduction defects,[3,4] asthma and COPD,[5] diabetes,[6] and hyperlipidaemia.[7] Roti et al (1988), Milner et al (1990) and Kelestimur et al (1993) suggested diltiazem, a calcium channel blocking drug, as adjunctive therapy in hyperthyroidism where β-blockers are contraindicated.[2,8,9] Marwat and his colleagues (2006) suggested diltiazem as a routine adjuvant drug; however, they were of the opinion to wait for further elucidation of the matter in future studies.[10]

The present study was, in fact, a continuation of the efforts to investigate the clinical efficacy of diltiazem in combination with carbimazole and to compare it with the combined effects of propranolol and carbimazole. We were additionally interested in assessing the biochemical effectiveness of these combined therapies.

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MATERIAL AND METHODS

This prospective, interventional study was conducted on 45 newly diagnosed, untreated cases of hyperthyroidism attending the out patient department of Institute of Radiotherapy and Nuclear Medicine (IRNUM) Peshawar. The total numbers of patients registered initially were sixty (60) who were then randomised to two matched groups using random number table. Each group had 30 patients but 15 patients were lost to follow up, 10 in group I and 5 in group II. So ultimately, 45 patients were left in the study (20 in group I and 25 in group II). Patients included in the study were between the ages of 20-55 years and were of either sex. Only mild to moderate, stable cases of hyperthyroidism were recruited in the study with serum FT_4 levels not more than 50 pmol/L (normal reference range for FT_4 followed by IRNUM is 11.5-23 pmol/L with values as high as more than 74 pmol/L in severe disease). Only those cases were registered in the study who gave a written, well-informed, Urdu version of the consent. Pregnant and lactating mothers were excluded from the study. Moreover, hyperthyroid patients with concurrent cardiovascular, renal or any other chronic illness like diabetes were not included.

Data were collected through detailed history proforma, laboratory investigations (serum free T_4, serum TSH, serum creatinine, blood glucose), ECG, x-ray chest and clinical assessment score (hyperthyroid symptom score). 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.

Group I (n = 20, with male/female ratio of 2:18 and having mean age of 41.75 ± 11.13 years) took diltiazem (Dilzem – Park-Davis) 30 mg three times a day and carbimazole (Neo-Mercazole – Reckit-Benckiser) 10 mg three times daily for 6 weeks.

Group II (n = 25, with male/female ratio of 4:21 and having mean age of 37.72 ± 8.90 years) took propranolol (Inderal – ICI) 20 mg (2 tablets of 10 mg each) three times a day and carbimazole 10 mg thrice daily for 6 weeks.

Biochemical assessment was done by measuring serum FT_4 in the beginning and then 6 weeks (± 3 days) after starting therapy, using radioimmunoassay technique. Clinical assessment was done on day 0 (baseline) and then after 6 weeks (± 3 days) of starting therapy using standardised and modified hyperthyroid symptom score (HSS).

The HSS is a clinician-rated instrument assessing the symptoms associated with hypermetabolic thyroid hormone conditions and based on an evaluation of symptoms available in the endocrine literature. Patients were asked to what extent each symptom (excessive sweating, trembling hands, heat intolerance, easy fatigability, nervousness, diarrhoea, increased appetite, palpitation, dyspnoea on exertion) was present during the week before the interview. Answers were scored from 0 (not present) to 3 (severe) with a maximum total score of 27.[11, 12]

Data collected were analysed statistically with SPSS (Statistical Package for Social Sciences) using paired and unpaired Student's t-test; value of *P* less than 0.05 was considered significant while that less than 0.001 was taken as highly significant.

RESULTS

Results are described as mean ± SD.

In group I, FT_4 decreased from 38.43 ± 6.67 to 34.30 ± 6.50 after 6 weeks of therapy with diltiazem and carbimazole. This decline in FT_4 concentration is highly significant ($p < 0.001$). HSS decreased from 15.80 ± 2.35 to 8.25 ± 2.53. This change is also highly significant ($p < 0.001$).

In group II, FT_4 decreased from 37.47 ± 7.75 to 34.21 ± 7.89 after 6 weeks of therapy with propranolol and carbimazole. This decline in FT_4 concentration is highly significant ($p < 0.001$). HSS decreased from 14.88 ± 2.01 to 8.36 ± 1.91. This change is also highly significant ($p < 0.001$).

The mean decline in FT_4 in group I (4.12 ± 3.19) when compared with mean decline in FT_4 in group II

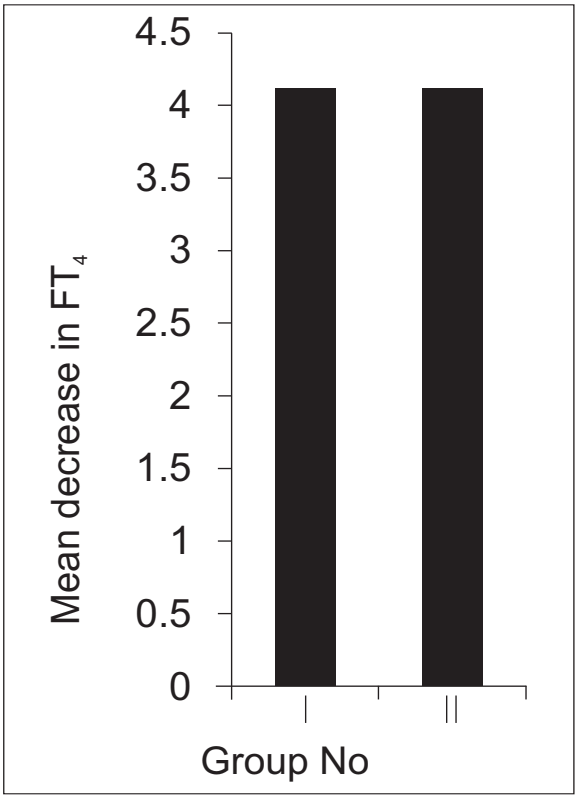

Figure 1. Mean decline in post-intervention FT_4.

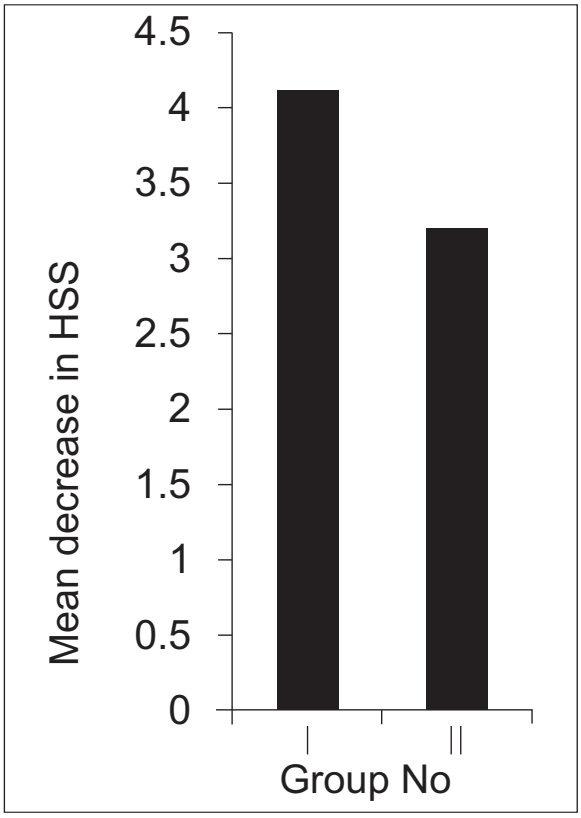

Figure 2. Mean decline in post-intervention HSS.

(3.21 ± 3.47), the difference was non-significant ($p > 0.05$). Similarly, the mean decrease in HSS in group I (7.55 ± 2.11) when compared with mean decline in HSS in group II (6.52 ± 1.92), the difference, though, was non-significant at the standard 5% level of significance but it was "approaching" significance ($p < 0.1 > 0.05$; exact value of $p = 0.094$); see tables 1 & 2 and figures 1 & 2.

DISCUSSION

Clinical trends are sometimes changed, especially when they have logical supports. Guanethidine and reserpine were replaced by β-blockers as adjuvant drugs in the management of hyperthyroidism. This substitution was very much logical as guanethidine and reserpine had serious adverse effects and â-blockers became available then. Propranolol, a non-selective β-blocker is now used almost exclusively as adjuvant drug in hyperthyroidism but there are clinical situations which limit the use of β-blockers including cardioselective β_1-antagonists.[13] Diltiazem, a nondihydropyridine calcium channel blocker, has been suggested by various workers as an adjuvant drug in situations where β-blockers are contraindicated. We conducted this study with the hypothesis if diltiazem could be used as a routine alternative to propranolol in the management of hyperthyroidism, thus, changing the trend as had changed once in favour of β-blockers.

Results of this study have shown that diltiazem in combination with carbimazole has worked very well in controlling the adrenergic manifestations of hyperthyroidism by bringing down the HSS from 15.80 ± 2.35 to 8.25 ± 2.53 ($p < 0.001$). These findings are in agreement with the results of the studies done by Kelestimur and Aksu,[14] and Marwat et al.[10] Kelestimur and Aksu demonstrated in a prospective, randomised and placebo-controlled study on 22 patients that diltiazem is an effective adjunctive therapy in hyperthyroid patients and can be safely combined with propylthiouracil. Marwat and his colleagues did a pro-

Table 1. Baseline and post-intervention characteristics regarding FT_4 and HSS.

Category of patients	Baseline characteristics	Post-intervention characteristics	*p* value
Group I, n = 20 (Diltiazem +Carbimazole)	FT_4: 38.43 ± 6.67 HSS: 15.80 ± 2.35	FT_4: 34.30 ± 6.50 HSS: 8.25 ± 2.53	$p < 0.001$ $p < 0.001$
Group II, n = 25 (Propranolol +Carbimazole)	FT_4: 37.47 ± 7.75 HSS: 14.88 ± 2.01	FT_4: 34.21 ± 7.89 HSS: 8.36 ± 1.91	$p < 0.001$ $p < 0.001$

Table 2. Group statistics regarding FT_4 and HSS.

Characteristics	Group I (Diltiazem+Carbimazole	Group II (Propranolol+Carbimazole)	Difference (Gp I vs Gp II)
Mean decline in FT_4	4.12 ± 3.19	3.21 ± 3.47	$p > 0.05$
Mean decline in HSS	7.55 ± 2.11	6.52 ± 1.92	$p > 0.05$ ($p < 0.1 > 0.05$)

spective, interventional study on 19 untreated cases of hyperthyroidism and pointed towards the possible routine use of diltiazem as adjuvant therapy. This capability of diltiazem to alleviate thyrotoxic symptoms may be due to its nonspecific antiadrenergic activity that is more than any other member of calcium channel blockers used clinically.[15]

Mean decline in HSS caused by the combined therapy of diltiazem and carbimazole when compared with that caused by the combination of propranolol and carbimazole, the difference was non-significant at the usual standard 5% level of significance. However, it was significant at 10% level of significance which, in statistical terminology, is sometimes called "approaching" significance ($p < 0.1 > 0.5$). To some extent, these findings are in accordance with the results of the study done by Milner et al who compared the efficacy of diltiazem and propranolol in a randomised, prospective, double-blind, crossover study in 6 patients with untreated thyrotoxicosis and observed that all subjects felt better with drug therapy, with 3 patients preferring diltiazem to propranolol. No significant difference in clinical response or in haemodynamic effect was noted between the agents.[8]

Biochemically speaking, combined therapy with diltiazem and carbimazole worked very well like the combination of propranolol and carbimazole and decreased FT_4 concentrations from 38.43 ± 6.67 to 34.30 ± 6.50 after 6 weeks of therapy ($p < 0.001$). Undoubtedly, this decline is due to carbimazole whose results become evident after 3-4 weeks of therapy but when we compared this decline in FT_4 in group I (4.12 ± 3.19) with that in group II (3.21 ± 3.47), the difference was non-significant ($p > 0.05$) showing that the combination of diltiazem with carbimazole is at least as effective as combined propranolol and carbimazole therapy. These results support the findings of the study done by Kelestimur and Aksu who compared diltiazem and propranolol along with propylthiouracil and found no significant changes in thyroid function tests in both the groups after 10 days of treatment[14] (though, the duration of the study period, in our opinion, is a limitation of the study because it takes 3-4 weeks before the thyroid hormone stores are depleted).[1] Before starting the study, an idea in our mind was that the combination of diltiazem with carbimazole might work synergistically as it is the cytosolic free Ca^{2+} concentration which is important for the generation of H_2O_2, that in turn is an essential substrate for thyroperoxidase activity.[16-18] But this hypothesis proved null and void, although, in contradiction to the findings of the study done by Mittal et al who showed that a month-long therapy with calcium channel blockers in rabbits significantly reduced serum levels of T_3 and T_4.[19]

CONCLUSION

Combined therapy with diltiazem and carbimazole is as effective as the combination of propranolol and carbimazole in reducing FT_4 levels and ameliorating the adrenergic manifestations of hyperthyroidism. As evident from the literature review,[3-7, 13, 20,21] there are very few limitations of calcium channel blockers as compared to b-blockers and their adverse effect profile is better than the β-blockers, we recommend **routine** use of diltiazem as adjuvant drug in patients with hyperthyroidism.

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