Original Research Article

A retrospective study to analyse the effect of Carbimazole therapy on the Grave's disease patients in a tertiary hospital of Patna, Bihar

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Abstract

Introduction: Grave's disease is a relatively prevalent autoimmune thyroid disorder and it is most frequent cause of thyrotoxicosis. Antithyroid drugs are directed at reducing thyroid hormone production, which is ultimately responsible for the symptoms and signs of thyrotoxicosis. **Aim:** The present study is an attempt to analyse the effect of Carbimazole treatment on Grave's disease. **Methodology:** It was a retrospective study done on 53 patients attending OPD in Patna Medical College, Bihar, India. **Results:** There was significant difference between the mean age of males and females. As a result of our intervention of carbimazole therapy, 73.6% patients showed improvement in their clinical profile. Only 3 patients didn't show any improvement.

Keywords: Grave's disease, carbimazole, hyperthyroidism

Introduction

Grave's disease is a relatively prevalent autoimmune thyroid disorder and it is most frequent cause of thyrotoxicosis. Overt hyperthyroidism affects 1.3% of people in iodine-replete populations and if untreated is associated with a catabolic state characterized by weight loss, reduced bone mineral density, atrial fibrillation, and thromboembolic events[2,3].

Graves' disease is the commonest cause of hyperthyroidism accounting for up to 80% of cases [4,5]with a lifetime prevalence of 3% in women and 0.5% in men. The symptoms of thyrotoxicosis are often nonspecific, so patients with Grave's disease may present in numerous ways[1]. Frequently reported symptoms include tremor, palpitations, heat intolerance, weight loss and anxiety. Physical examination may reveal warm, tremulous extremities, a trial fibrillation, signs of thyroid orbitopathy and a goitre with a bruit. Treatment of thyrotoxicosis due to grave's disease relies on the use of anti-thyroid treatment, or thyroidectomy. Anti-thyroid drug have been a mainstay of treatment of patients with Grave's disease for almost > 70 years. Despite advances in the treatment of thyrotoxicosis after the introduction of antithyroid drugs some practical problems remain, particularly in gauging the doses required. Antithyroid drugs are directed at reducing thyroid hormone production, which is ultimately responsible for the symptoms and signs of thyrotoxicosis. Many of these clinical features result from secondary changes, however, including increased tissue sensitivity to catecholamines, which may not be rapidly reversed when the thyroid hormone excess is controlled [4-6].

Three thionamide derived antithyroid drugs, ATDs, are currently used: carbimazole [CBZ], rapidly converted to its active metabolite, methimazole [MMI] and propylthiouracil [PTU]. These drugs mainly exert their effect by reducing thyroid hormone synthesis through inhibition of the enzyme thyroid- peroxidise[2]. The beneficial effect obtained with anti-thyroid drugs in the treatment of Graves's disease is not only due to the blockade of thyroid hormone synthesis but also to the capacity of these agents to suppress cell-mediated immune responses and the production of specific autoantibodies. Both propylthiouracil (PTU) and carbimazole (CBZ), which is converted into its active metabolite methimazole (MMI), have been shown to possess immunosuppressive action [7,8]

According to a nationwide survey conducted to determine the trends in management of Grave's disease amongst leading thyrologists in India, the majority preferred ATD as the mainstay of treatment [3].

Objectives

1. To analyse the profile of Grave's disease
2. To analyse the effect of medical treatment with Carbimazole on Grave's disease

Methodology

The present study is a two year retrospective analysis of thyrotoxic patients who presented to the endocrine OPD of Patna medical college, Patna, in the year 2015-17. Elevation of one or both serum free thyroid hormones together with an undetectable TSH confirms the diagnosis of thyrotoxicosis. In the presence of clear extra thyroidal signs, of Grave's disease, no further testing beyond free thyroid hormones and TSH is necessary. The gold standard test is a highly sensitive TSH-R stimulating antibody assay. We included 53 patients of Grave's disease. All patients were treated with B blocker and carbimazole 20 mg initially. The dose of carbimazole was uptitrated to 30mg and 40 mg at two months interval if required.

Carbimazole treatment efficacy will be analysed by normalization of biochemical investigation FT3, FT4 and TSH and symptoms of thyrotoxicosis. Verbal and written consent were taken from patients.

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Results

We included 53 patients of Grave's disease in our study. Mean age of patients was 39.5 years and there were 42 females and 11 males.

Table 1:Age & Sex distribution among study population.(n=53)

Age in Year	Total		Male		Female	
	No	%	No	%	No	%
18 - 30	12	22.6	02	18.2	10	23.8
31 - 40	18	34.0	01	9.1	17	40.5
41 - 50	15	28.3	02	18.2	13	30.9
51 - 60	04	7.5	02	18.2	02	4.8
61 - 70	04	7.5	04	36.3	00	00
Total	53	100.0	11	100.0	42	100.0
Mean & SD Value	39.471±10.79		48.181±16.26		37.190±7.59	
P Value			0.001			

There was significant difference between the mean age of males and females [p< 0.05].

Table 2:Distribution of weight & Duration of the disease according to Sex

	Male(n=11)		Female(n=42)		P Value
	Mean	SD	Mean	SD	
Weight(kg)	44.909	±4.63	46.571	±3.08	0.029(S)
Duration of the disease(months)	17.181	±8.28	13.357	±6.56	0.077(NS)

There was significant difference between the mean weights of the males against female patients. Though non-significant difference was seen in the duration of the disease among the two genders.

Table 3:Mean & SD value of TSH, FT3 & FT4 before treatment.

	Mean	SD
TSH	0.0436	±0.04
FT4	3.713	±0.66
FT3	1.209	±0.50

Table 4: Other Clinical assessment of study population

Clinical assessment of study population (n=53)			
	Status	N	%
Anti TPO antibody	Positive	21	39.6
	Negative	32	60.4
TSH RAb	Positive	21	39.6
	Negative	32	60.4
Goiter Grade	Grade-1	11	20.8
	Grade-2	23	43.4
	Grade-3	19	35.8
Class of Ophthalmopathy	N/F	11	20.8
	1	13	24.5
	2	24	45.3
	3	05	9.4

Table 5:USG finding of study population(n=50)

USG finding	Frequency	Percent
Diffuse Enlarged	11	20.8
Diffuse Enlarged Hetragenous	1	1.9
Enlarged Hetragenous	17	32.1
Enlarged Hetragenous cystic	1	1.9
Enlarged Nodular	1	1.9
Hetragenous	1	1.9
Hetragenous Cystic	2	3.8
Hetragenous Nodular	6	11.3
hetragenous with septiom	1	1.9
Smooth Enlarged	12	22.6
Total	53	100.0

It was evident from the USG findings that majority of the patients had smoothly or diffusely enlarged thyroid gland. On doing FNAC, 47.5% had thyroiditis, 22.6% had lymphocytic thyroiditis, 13.2% showed chronic thyroiditis, degenerative thyroiditis among 9.4% and rest had benign follicular thyroiditis, nodular goitre thyroiditis and Grave's thyroidits [3.8%].

Table 6: Comparison between Initial TSH and after 2nd, 4th, & 8th months of treatment.

One way ANOVA								
Comparison between Initial TSH and after 2nd ,4th, & 8th months of treatment								
TSH	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
Initial	53	.0436	.04358	.00599	.0316	.0557	.00	.10
2nd	53	.2747	.34853	.04787	.1786	.3708	.01	2.00
4th	52	3.7494	4.45725	.61811	2.5085	4.9903	.01	18.00
8th	52	5.4208	5.74184	.78870	3.8382	7.0035	.00	28.00
Total		2.3656	4.27939	.29461	1.7849	2.9464	.00	28.00
P Value	F 28.058 p Value <0.001(HS)							

From the above table it can be noted that, as the duration of treatment increases, the thyroid hormones decreased in the patients resulting in higher TSH.

Fig 1: Mean plot TSH

Table 7:Comparison between Initial FT3 and after 2nd ,4th, & 8th months of treatment .

One way ANOVA								
Comparison between Initial FT3 and after 2nd ,4th, & 8th months of treatment								
	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
Initial	53	1.2094	.50543	.06943	1.0701	1.3487	.70	4.20
2nd	53	.8196	.19979	.02744	.7646	.8747	.40	1.36
4th	52	.5038	.23202	.03187	.4398	.5677	.10	1.20
8th	52	.6192	.91862	.12618	.3660	.8724	.30	7.00
Total		.7880	.60525	.04157	.7061	.8700	.10	7.00
P Value	F 17.051 p Value <0.001(HS)							

As discussed, with the increase in duration of the treatment, the value of free T3 decreased among the patients and the decrease was found to be statistically significant. Following initiation of antithyroid treatment with carbimazole, both fT3 and fT4 decreased proportionately in a 1:1 ratio.

Mean Plot

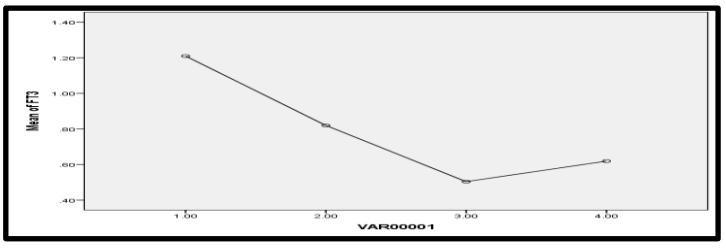

Fig 2: Mean plot TSH

Table 8:Final Outcome

Final Outcome		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Drop out case	1	1.9	1.9	1.9
	Improved	39	73.6	73.6	75.5
	Mild Improved	1	1.9	1.9	77.4
	No Improvement	3	5.7	5.7	83.0
	Partial Improvement	9	17.0	17.0	100.0
	Total	53	100.0	100.0	

As a result of our intervention of carbimazole therapy, 73.6% patients showed improvement in their clinical profile. Only 3 patients didn't show any improvement.

Discussion

Graves' disease (GD) is the most common cause of hyperthyroidism worldwide. In the present study, we report a pharmacodynamic relationship between the dose of carbimazole and the fall in thyroid hormone levels, to aid clinicians in the rapid achievement of euthyroidism whilst avoiding the sequelae of overtreatment and hypothyroidism. Current therapeutic options for GD include antithyroid drugs (ATD), radioactive iodine, and thyroidectomy. ATD treatment is generally well accepted by patients and clinicians due to some advantages including normalizing thyroid function in a short time, hardly causing hypothyroidism, and ameliorating immune disorder while avoiding radiation exposure and invasive procedures. Carbimazole exerts its pharmacological effect by converting to methimazole, so it has similar efficacy and features as methimazole [9,10]. In our study, 79% of the patients were females. Females have a higher incidence of GD than males[11].The reason for a different incidence in gender is unclear and might be associated with varying sex hormones. Estrogens influenced B-cell function and further regulated the immune system. In GD patients, the increased estradiol level is related to the positivity of TRAb[12].The mean age of 39 years of our cohort is consistent with the reported peak incidence of Graves' disease in the third to fifth decade[13].The key feature in untreated GD is the significant increase in the serum triiodothyronine (T3) level, which is caused by the elevated activity of intrathyroidal type 1 deiodinase[14].In addition, the serum TSH level also should get more attention. In our findings, mean TSH value started decreasing with treatment, as assessed at 2nd, 4th and 8th month of treatment. Large goiter size is a main clinical manifestation of GD patients, as seen in our 50% patients tool[15].These studies suggested that enlarged goiter size at the time of GD diagnosis and drug withdrawal is associated with a higher recurrence risk. The high recurrence rate is a major drawback of ATD therapy, and patients with recurrent GD often have a much higher recurrence risk than average[16]·Serum fT3 and fT4 levels were increased and fell proportionately in response to treatment in a _1:1 ratio. Carbimazole has a plasma half-life of _5.3 h, and traditionally was prescribed in divided doses[17].However, several studies have demonstrated that a single dose of carbimazole is just as effective at inducing euthyroidism [18-20].Furthermore, methimazole is concentrated in thyroid follicular tissue and has a longer biological duration of action than suggested by pharmacokinetic levels. Moreover, compliance is increased by once daily dosing of ATD .In patients with at least 2 months' duration of treatment, the majority achieved normal fT4 and fT3 levels. Euthyroid status, defined as having TSH, fT4, and fT3 all within range, was achieved by 76% of patients at a time range of 4-6 months. There is a paucity of data describing the relationship between carbimazole dose and the subsequent change in thyroid hormone levels. Thus, these data represent an important first step in establishing the relationship between dose and pharmacodynamic response to carbimazole. However, it is necessary to stress that as the models were developed using retrospective data, external validation of the predictions outlined in the present study is required prior to consideration for clinical use.

Conclusion

In summary, we have identified a pharmacodynamic relationship for medical therapy of Graves' disease with dose of carbimazole. The titration approach is desirable as it facilitates reduced cumulative exposure to ATDs and thus carries a lower risk of dose-related side effects. Whilst Graves' disease is one of the most common endocrine diseases treated, the pharmacodynamic response to carbimazole has been poorly defined, causing a residual significant risk of under- or overtreatment. Thus, the relationships described in the present study could aid in dose-selection and represents a useful initial step to the estimation of factors that influence the response to ATD therapy.

Conflict of Interest: Nil Source of support: Nil

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