A Descriptive Study on Individually Titrated Levothyroxine in the Management of South African Hypothyroid Patients (DeuTSH)

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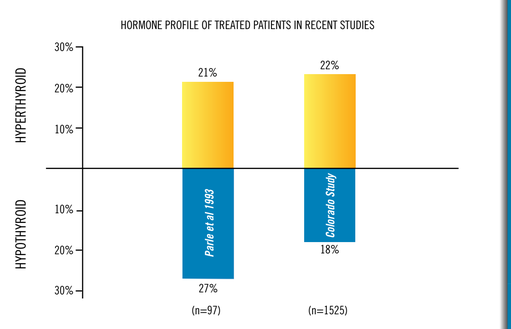
BACKGROUND

Currently few data regarding hypothyroidism in South Africa exists, but from the international literature it is evident that a significant number of patients fail to reach target TSH levels. [i] [ii]

FIGURE 1: THYROID STATUS OF TREATED PATIENTS



Adapted from Canaris, Ross, Parle & Hollowell [2,3]

OBJECTIVES

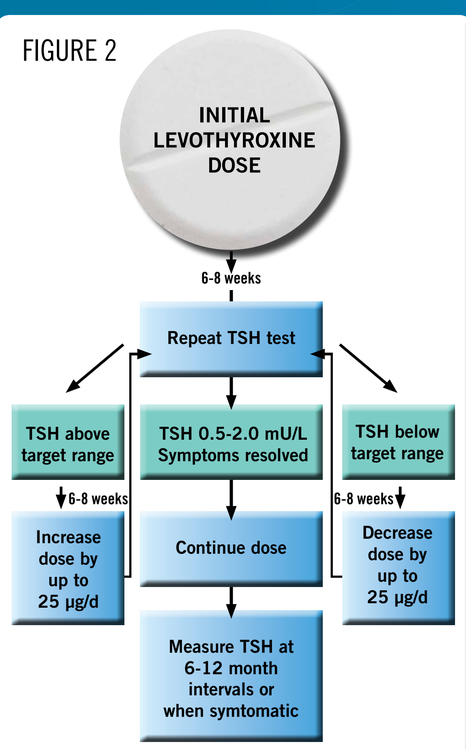
This observational study measured the efficacy of individually titrated doses of levothyroxine to achieve a euthyroid state. Target TSH utilised was set at 0.4 – 4.0 mIU/L. (initially 0.4-2.5 mIU/L in younger patients, but adapted after the publication of new hypothyroidism guidelines[iii] .) Secondary objectives were the evaluation of mean dose per kg bodyweight to reach euthyroidism, predictive value of initial TSH in determining therapeutic dosage, and assessment of the value of a 25 microgram formulation.

METHODS

Patients with hypothyroidism, treatment naïve or insufficiently controlled on any levothyroxine formulation, with a confirmed laboratory TSH value outside the target range, were included in the study. Investigators made an independent decision to prescribe levothyroxine (Euthyrox®) to patients, prior to consideration for inclusion in the study. Physicians were provided with a published treatment guideline and algorithm as well as education on hypothyroidism. Patient follow-up occurred every seven weeks until an outcome was reached. An outcome was defined as reaching the target range or withdrawal from the study for any reason. The 4 follow up visits were scheduled every 7 weeks with ± 5 day flexibility. Patients were followed up for a maximum of 28 weeks. TSH levels, levothyroxine dose changes, compliance, concomitant medication use, weight and changes in disease symptoms were assessed at each visit.

The following flow diagram from Demers et al was used to train the participants on dose titration[iv]:

FIGURE 2

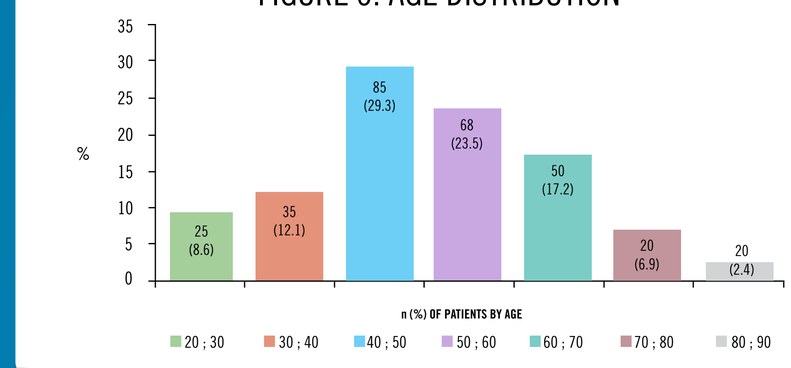


Demers LM, et al. *Clin Endocrinol (Oxf) 2003;58:138–140*

RESULTS

290 evaluable patients were enrolled.
The age distribution of participating patients can be seen in the following graph:

FIGURE 3: AGE DISTRIBUTION



The majority of patients were in the age-group 40-60 years.

Overall 221 (76.2%) patients reached TSH target levels of which 135 (46.6%) reached target levels by follow-up visit 1.

TABLE 1: TSH LEVELS AT ENROLMENT AND WHEN AN OUTCOME WAS REACHED

TSH, mIU/L	TSH Level at	TSH Level at the follow-up visits when an outcome was reached:			
	Enrolment	Follow-up visit 1 Week = 7	Follow-up visit 2 Week = 14	Follow-up visit 3 Week = 21	Follow-up visit 4 Week = 28
All patients					
n	290	148	70	29	27
Mean	15.8	2.4	4.8	2.4	2.6
Std dev	39.6	6.4	13.6	3.4	3.2
Median (QR)	6.6 (4.6 – 11.2)	1.8 (1.0 – 2.6)	1.6 (0.9 – 2.8)	1.3 (0.6 – 2.4)	1.5 (0.2 – 4.8)
Min / Max	0 / 530.40	0.1 / 78.0	0.0 / 81.0	0 / 14.4	0 / 11.7

Of the 290 patients at enrollment 16 patients withdrew from the study after the baseline visit for different reasons: lost to follow-up, missing data, withdrawn consent. 148 patients reached an outcome at Follow-up visit 1. Either outcome, target TSH or withdrawal from the study, was reached from the first follow-up visit onward, except for the final visit at week 28, at which point the study was ended, regardless of TSH value.

The mean TSH at the start of the study was 15.8 mIU/L and the median 6.6 mIU/L.

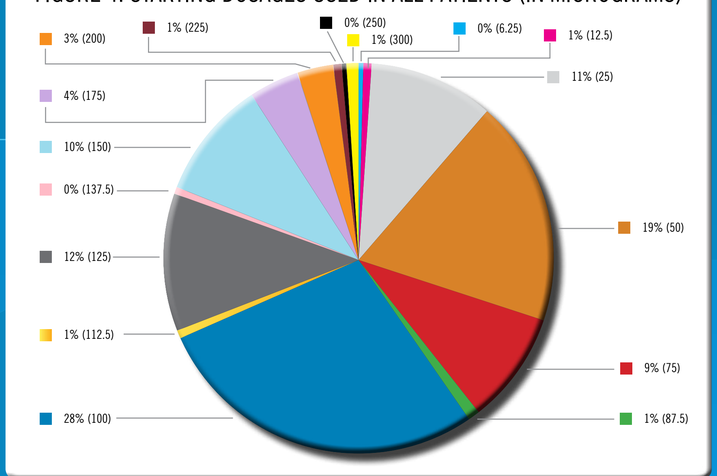
Health Care Physicians (HCPs) used the starting dose as per their usual practice, but following the algorithm as trained.

TABLE 2: PRESCRIBED STARTING DOSE AT VISIT 1

Prescribed starting dose	Number (%) of patients	
	Naive	Pretreated
6.25	1 (0.8)	-
12.5	2 (1.5)	-
25	24 (18.2)	7 (4.4)
50	42 (31.8)	12 (7.6)
75	2 (1.5)	24 (15.2)
87.5	-	3 (1.9)
100	44 (33.3)	37 (23.4)
112.5	-	2 (1.3)
125	6 (4.5)	28 (17.8)
137.5	-	1 (0.6)
150	7 (5.3)	22 (13.9)
175	1 (0.8)	10 (6.3)
200	2 (1.5)	7 (4.4)
225	-	2 (1.3)
250	-	1 (0.6)
300	1 (0.8)	2 (1.3)
Total	132 (100)	158 (100)
n	132	158
Mean	75.8	114.9
Standard deviation	45.6	49.5
Median (Quartile range)	50 (50 - 100)	100 (75-150)
Minimum / Maximum	6.25 / 300	25 / 300

Table 2 shows different starting dosages for treatment naïve and pretreated patients. Unsurprisingly, higher dosages were prescribed more frequently in pre-treated patients compared to naïve patients. Mean starting dose in the naïve group was 75.8 µg/day(median of 50 µg/day). Mean starting dose in the pretreated group was 114.9 µg/day (median of 100 µg/day).

FIGURE 4: STARTING DOSAGES USED IN ALL PATIENTS (IN MICROGRAMS)



The chart above illustrates the wide variation in dosage strengths used as starting dosages.

TABLE 3: DEPARTURE RATES

Number (%) of patients that left the study after reaching an outcome				
Baseline Visit	Follow-up visit 1	Follow-up visit 2	Follow-up visit 3	Follow-up visit 4
16 (5.5)	148 (51.1)	70 (24.1)	29 (10.0)	27 (9.3)

Table 3 illustrates the numbers of patients that left the study at each visit, after an outcome was reached.

TABLE 4: TSH STATUS

Outcome	Number (%) of patients					
	Baseline visit	Follow-up visit 1	Follow-up visit 2	Follow-up visit 3	Follow-up visit 4	All
Controlled	-	135 (46.6)	55 (18.9)	20 (6.9)	11 (3.8)	221 (76.2)
Over-titrated	2 (0.7)	8 (2.8)	9 (3.1)	6 (2.1)	9 (3.1)	34 (11.7)
Uncontrolled	14 (4.8)	5 (1.7)	6 (2.1)	3 (1.0)	7 (2.4)	35 (12.1)
Total	16 (5.5)	148 (51.1)	70 (24.1)	29 (10.0)	27 (9.3)	290 (100)

After 2 follow-up visits, 65.5 % of the patients reached control.
The total control rate in the study was 76.2% (95% CI: 71.0% - 80.7%).
At study end, 34 (11.7%) of patients experienced over-treatment while 35 (12.1%) of patients still required up-titration to achieve control.

The most frequently employed dosages for treatment of naïve patients were 50 or 100 µg. In pre-treated patients it was 75 and 100 µg . The 25 µg thyroxin dosage was used in 46.4 % of patients and the 12.5 µg dosage in 8.2 % of patients.
The mean thyroxin dose per kg bodyweights were as follows:

- For naïve patients : 0.86
- For pretreated patients: 1.32
- For all patients together: 1.12.

DISCUSSION

The total control rate in the study was 76.2% (95% CI: 71.0% - 80.7%).
34 (11.7%) of patients were over-treated at the end of the study. On the other end of the spectrum, 35 (12.1%) of patients still needed to be up-titrated further to achieve control of the TSH value.
The variability in dosages used in the study, suggests that there is value in having several strengths of levothyroxine dosages for treating hypothyroidism.
The 25 µg and 12.5 µg dosage was used in 54.6% of patients.

The mean thyroxin dosage of 1.12 µg/kg body weight in controlled patients is lower than the recommended 1.6 µg/kg.

CONCLUSIONS

The value of treatment algorithms used to assist HCPs with titration of thyroxin dosages in hypothyroidism was confirmed in this study. The study also highlights the need of an initial early follow-up of TSH values (after 7 weeks) and regular monitoring until control is achieved. The total control rate of 76.2% in our study is superior to many important studies cited in this poster. The better outcome may be ascribed to the structured TSH determinations and adherence to the treatment algorithm.
This study further highlights that a high proportion (>50%) of patients required the small 25 µg and 12.5 µg dosages for optimal dose titration.

References:

[i] Canaris GJ, Manowitz NR, Mayor G, Ridgway C. The Colorado thyroid disease prevalence study. Arch Intern Med 2000; 160: 526–34
[ii] Parle JV, Franklyn JA, Cross KW, Jones SC, Sheppard MC. Prevalence and follow-up of abnormal thyrotrophin (TSH) concentrations in the elderly in the United Kingdom. Clin Endocrinol 1991; 34: 77–83
[iii] Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. Endocrine Practice 2012 Nov/Dec; 18(6).
[iv] Demers LM, Spencer CA for the AACE Thyroid Task Force. American As¬sociation of Clinical Endocrinologists medical guidelines for clinical practice for the evaluation and treatment of hyperthyroidism and hypothyroid¬ism. Endocr Pract. 2002;8:457-469

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