PROPRANOLOL PREPARATION FOR THYRIODECTOMY IN TOXIC NODULAR GOITRE

THESIS

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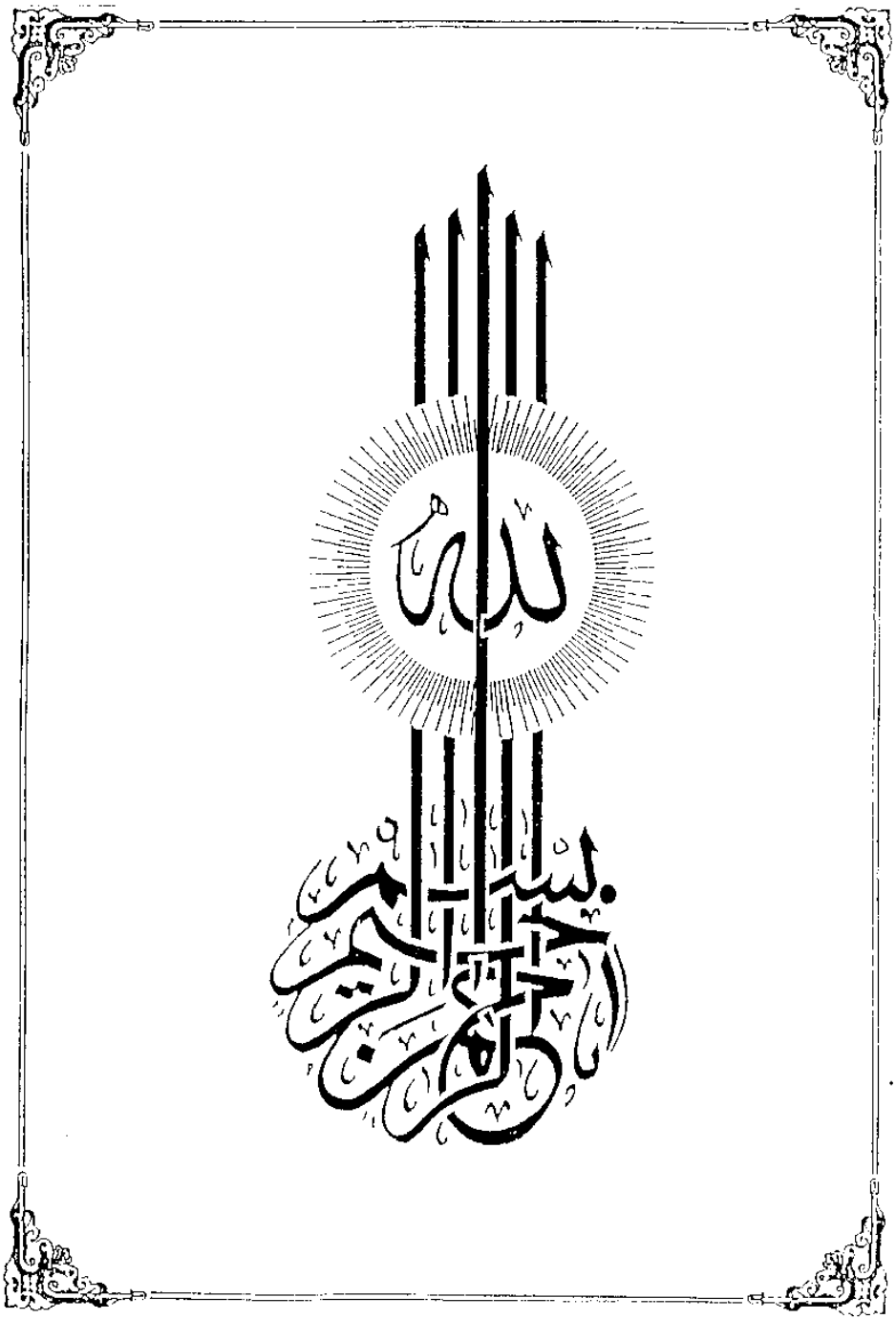
TO MY DAUGHTER SALMA



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INTRODUCTION

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Surgery still remains, in most centres, the line of choice in the management of hyperthyroidism (Simms and Tablot, 1983; Sawyers et al., 1972) even after the introduction of radioactive iodine (Block, 1967; Annotations, 1969) and potent relatively safe antithyroid drugs. The aim of pre-operative preparation is to bring the patient safely to an euthyroid state in a reasonably short time. Various drugs have been introduced, but the thionamides and iodine hold the priority.

Recently, propranolol, a beta-adrenergic receptor blocking agent has been introduced for rapid and safe preparation of thyrotoxic patients (Lee et al., 1973; Michie et al., 1974).

The aim of this work is to compare the different methods of preparation and, evaluate the efficiency of each method. Propranolol as the sole drug used in the preparation of thyrotoxic patients will be stressed in this thesis.

REVIEW OF LITERATURE

The thyroid gland secretes thyrocalcitonin which appears to be important in lower animals by preventing hypercalcemia. In human, it is used to treat hypercalcemia and as a tumour marker for medullary carcinoma of the thyroid. The main function of the thyroid gland is to synthesize and secrete thyroid hormones necessary for overall metabolism. This depends upon several processes, including; (1) idoine metabolism, (2) the production, storage, and secretion of thyroid hormones, and (3) the effects of the hormones on various systems (Kaplan, 1984).

Iodine Metabolism

Ingested iodine is converted to iodide and absorped. The fate of the absorped iodide is summarized in figure 1. In the thyroid, iodide is actively transported from the ciculation to the colloid by "iodide trapping mechanism" or "iodide pump". The thyroid cell is about 50 mv negative relative to the interstitial space and the colloid. Iodide is pumped into the cell at its base against this electrical gradient into the colloid. The active transport mechanism is stimulated by TSH, and depends also on Na^+-K^+-AtPase. The ratio of thyroid to plasma or serum free iodide (T/S ratio) ranges from 10 to over 100 (Ganong, 1985).

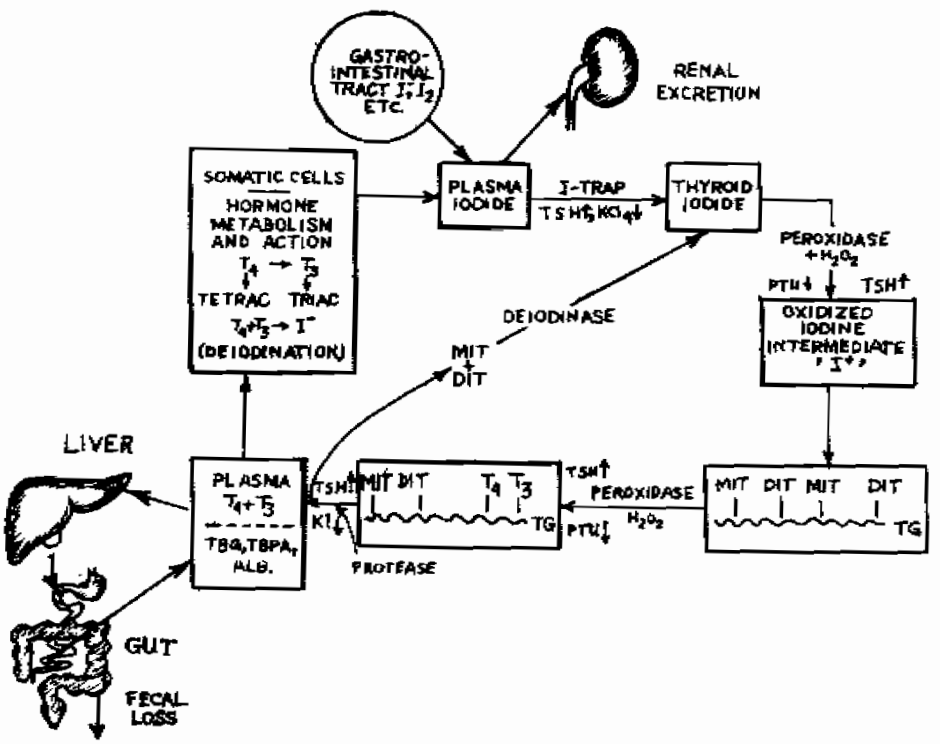

Figure 1. The Iodide Cycle. Ingested iodide is trapped in the thyroid, oxidized, bound to iodotyrosines in the thyroglobulin to form T_4 and T_3. Hormones secreted in plasma are transported to cells where some T_4 is deiodinated to T_3. Hormone exerting its metabolic effect intracellularly is ultimately deiodinated, and the iodide is reutilized or excreted in the kidney. A second cycle goes on inside the thyroid, with deiodination of iodotyrosines generating iodide, which is reutilized without leaving the gland (DeGroot and Stanbury, 1975).

Synthesis, Secretion and Turnover of Thyroid Hormones

In the thyroid, iodide is oxidized to iodine by thyroid peroxidase. It is rapidly incorporated into thyroglobulin, where tyrosine radicals are iodinated to form 3-monoiodotyrosine (MIT), and 3-5-diiodotyrosine (DIT). The coupling of these inactive iodotyrosines leads to the formation of active triiodothyronine (T_3), and tetraiodothyronine (thyroxine, T_4) which are held in peptide linkage with thyroglobulin (Kaplan, 1984).

Proteolysis of thyroglobulins release T_4 and much smaller amounts of T_3. Circulating T_4 is derived entirely from the thyroid. In contrast, about 85% of circulating T_3 is derived from the extra-thyroidal deiodination of T_4, principally in liver, kidney and muscle (Loose and Wartofsky, 1984).

The thyroid hormones are transported from the thryoid to their sites of action in the plasma, in which they circulate predominantly and reversibly bound to plasma proteins. Thyroxine - binding globulin (TBG) is the most important and binds neerly 70% and 80% of the circulating T_4 and T_3 respectively; thyroxine-binding pre-albumin and albumin are less important. The binding of T_4 and T_3 to these proteins is such that more than 99.95% of circulating T_4 and neerly 99.5% of the T_3 are bound. It is generally accepted that only the minute free hormone fraction is able to cross the plasma membrane and affect intracellular metabolism. However, protein binding may selectively direct thyroid hormones to target organs (Hoffenberg and Ramsden, 1983).

T_3 and T_4 are conjugated in the liver to glucuronic acid and excreted in the bile. In the intestine, these conjugates are hydrolysed and a portion of free hormone is reabsorped in the enterohepatic circulation. The half-life of T_3 is about 3 days, while the half-life of T_4 is 7-8 days (Kaplan, 1984). However, T_3 level falls to normal range by 24 hours after thyroidectomy in toxic goitre (Toft et al., 1976). Also, T_4 half life ranges from 5 days (Caswell et al., 1978), 6.2 days (Sterling and Chodos, 1956) to 7.2 days (Lee et al., 1973).

Thyroid Hormone Actions

Fetal Development

Thyroid hormones are critically important in fetal development, particularly of the neural and skeletal system.

Effects on Intermediary Metabolism

Thyroid hormones increase O_2 consumption and calorigenesis. They stimulate protein synthesis. Glycogenolysis and gluconeogenesis are increased, presumbly in relation to regeneration of ATP consumed e.g. by increased Na^--K^+- ATPase activity. Cholesterol synthesis and degradation are both increased and since, the latter effect predominates, the serum cholesterol declines in thyroid overactivity and vice versa. Lipolysis increases possibly by enhancing the effect of catecholamine stimulation (Ganong, 1985).

Hematopoiesis and Endocrine System

Thyroid hormones increase erthropoiesis by increasing O_2 utilization by tissues leading to increased erythropoietin production. They increase 2,3-diphosphoglycate in erythrocytes that dissociates O_2 from hemoglobin increasing O_2 availability to the tissues. Thyroid hormones increase the metabolism and clearance of various hormones and pharmacologic agents. This explains hyperprolactinemia and menstrual disturbances in hypothyroidism, and increased insulin requirements in diabetics in hyperthroidism (Greenspan and Rapport, 1983).

Cardiovascular and Sympathetic System

Thyroid hormones increase the number of B-adrenergic receptors in the heart and consequently increase its sensitivity to the inotropic and chronotropic effects of catecholamines (Tsai and Chen, 1977). Available evidence suggests that thyroid hormone excess results in enhanced tissue responsiveness to endogenous catecholamines, an effect explained by increased B-adrenergic receptor densities in those target tissues (Wildenthal, 1972; Seino et al., 1980; Guarneieri et al., 1980).

Recently, T_3 thyrotoxicosis has been found to increase mononuclear leukocyte B-adrenergic density (Ginsberg et al., 1981). Also, the demonstration that spinal anaesthesia (Rea, 1944), sympathectomy (Jaboulay, 1897), reserpine (Canary et al., 1957), guanethidine (Gaffney et al., 1961) and propranolol

ameliorate clinical manifestations of thyroid hormone excess, supports inter-relationship of thyroid hormones and sympathetic nervous system (Lee et al., 1982).

Mechanism of Action of Thyroid Hormones

Thyroid hormones enter tissues cells and T_3 bind to specific receptors in the nuclei. T_4 can also bind, but not as avidly, and in many organs, much of T_4 is converted to T_3 in the cytoplasm. T_4 is often regarded as a prohormone although intrinsic activity of T_4 can not be excluded (Bernel and Refetoff, 1977; Oppenheimer et al., 1984).

T_3 binds to the non-histone acidic proteins in the chromatin and acts on DNA increasing synthesis of MRNA and ribosomal RNA. The MRNA dictates protein synthesis in the ribosomes and these act as enzymes that modify cell function.

Thyroid hormones stimulate plasma membrane Na^+-K^+- ATPase activity, which is coupled to Na^+ and K^+ transport. The increase in energy consumption associated with increased Na^+ transport is responsible for increased metabolic rate (Ganong, 1985).

Mitochondrial receptors of high affinity for thyroid hormones have recently been described, and their importance in mitochondrial function is being investigated (Greenspan and Rapoport, 1983).

Regulation of Thyroid Function

Thyroid hormone synthesis is controlled predominantly by the circulating level of TSH, which in turn is regulated by the negative feedback of free T_3 and T_4 at the hypothalamus and pituitary. Intrapituitary de-iodination of T_4 to T_3 is an important step in the inhibitory effect of thyroid hormones on TSH secretion (Kaplan, 1984).

TSH is furthur controlled by thyrotropin-releasing hormone (TRH) of hypothalamus. The pituitary acts as a "thyrostat" to maintain the hypothalamically determined levels of thyroid hormones (Seth and Beckett, 1985).

TSH receptors made of glycoprotein bound to a ganglioside have been studied in the thyroid gland. When TSH binds to the receptors, it activates adenylate cyclase in thyroid cell membranes, and the resultant increase in intracellular cyclic AMP brings about most of TSH effects (Ganong, 1985).

Autoregulatory control of thyroid function is also present. High concentration of intrathyroidal iodide decreased the rate of release of thyroidal iodine as T_4 and T_3 (Ingbar and Woeber, 1968).