

*PHARMACOLOGY CLINICAL
CORRELATIONS
HYPERTHYROIDISM:
GRAVES' DISEASE
CASE # 62*

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*OVERVIEW
Graves' Disease*

- 60-90% cases of hyperthyroidism is due to Graves' disease
- autoimmune disorder
- associated with other autoimmune diseases (DM, MG, pernicious anemia)
- more prevalent in women (Haddad, 1998)

LEARNING OBJECTIVES

- Describe s/s, lab parameters assoc with hyperthyroidism and relate to pathophysiology of the disease
- select and justify appropriate patient specific initial and follow-up pharmacotherapy
- develop a monitoring protocol for pharmacotherapy
- design patient counseling database for drug therapy

CHIEF COMPLAINT

- I'm here for follow-up of lab tests. I still feel really weak and unwell.

HISTORY OF PRESENT ILLNESS

- WS, 65 yo man who presented to the ED 3 days ago with the following complaints:
 - weakness
 - inability to sleep
 - feeling anxious
 - waking up at night with rapid heart rate
 - denies shortness of breath or chest pain
 - rapid heart rate relieved by taking deep breaths
 - muscle tremors when he writes
 - heat intolerance

MANAGEMENT IN ED

- Atenolol for sinus tachycardia
- labs for serum electrolytes and TFT's

HEALTH HISTORY

- PMH - HTN diagnosed 5 years ago
- FH - one sister with “thyroid problems”
- SH - owns a gas station and convenience store; 25 pack year history of cigarette smoking, none in past 5 years; 1-2 drinks of brandy/week
- Meds (prior to ED visit) - HCTZ 25 mg po qd; tylenol prn for knee pain

HEALTH HISTORY (CON'T)

- Allergies - NKDA
- ROS - increasing weakness and fatigue past 3 months; unable to rise out of chair last 2 days; increased frequency of BM, watery; 10 lb. weight loss past 6 weeks with notable increase in appetite

PHYSICAL EXAMINATION

- GEN - pleasant, thin man in NAD, blinking rapidly
- VS - BP 130/83; P 130, regular; R 16;
- T 36.4oC
- HEENT - NC/AT; PERRLA; EOMI, R eye slight ptosis and lid lag with upward gaze; no diplopia; proptosis index 17mm bilaterally; oropharynx clear, no exudate or erythema

PHYSICAL EXAM (CON'T)

- NECK - supple, enlarged thyroid, non-tender; no bruit; no nodules, masses or lymphadenopathy
- COR - tachycardia, regular rhythm, normal S1 and S2; no S3 or S4, no murmurs
- RESP - CTA, (+)BS, no crackles or rales
- ABD - soft, non-tender, hyperactive bowel sounds

PHYSICAL EXAM (CON'T)

- EXT - smooth skin, no cyanosis or edema
- NEURO - A&O X 3, CN II-XII intact; no focal abnormalities; reflexes 2+ in all four extremities; pulses equal and bounding; slight intention tremor on finger-to-nose testing

LABS (from ED visit)

• Na 137 mEq/L	K 4.2 mEq/L
• Cl 100 mEq/L	BUN 17 mg/dL
• CO2 content 29 mEq/L	Ca 9.2 mg/dL
• serum Cr 0.9 mg/dL	AST 35 IU/L
• glucose 105 mg/dL	alb 4.1 g/dL
• TSH <0.1 uIU/ml	free T4 4.4 ng/dL

OTHER RESULTS

- CXR - no infiltrates or effusions
- ECG - sinus tachycardia with ventricular rate of 120, no ST elevation or depression, no LVH

PROBLEM IDENTIFICATION

- SIGNS/SYMPTOMS
- weakness, easy fatigability
- anxiety
- insomnia
- tachycardia
- tremors
- heat intolerance
- frequent BM
- weight loss
- increased appetite
- ptosis with lid lag
- exophthalmos
- non-tender thyroid enlargement
- smooth skin
- hyperactive bowel sounds
- LABORATORY DATA
- normal
- TSH <0.1 uIU/mL 0.5 - 5
- free T4 4.4 ng/dL 1.0-2.0
- ECG - sinus tachycardia
- no data on RAIU 10-30%
- no T3 level 45-135ng/dL
- no TBG level 15-35mg/mL

PATHOPHYSIOLOGY OF THE DISEASE

- thyroid stimulating antibodies (TSAb) (Cherner, 1997; McIver, 1998)
- extrathyroidal manifestations of Graves' disease (Reasner, 2000; Ringel, 1996)
- genomic point mutation
- increased human leukocyte antigens (HLAs) (Reasner, 2000)

PATHOPHYSIOLOGY OF THE DISEASE

- Signs/symptoms are attributed to 2 reasons:
 - beta adrenergic stimulation
 - thyrotoxicosis

LABORATORY DATA

- diagnosis of Graves' disease can be confirmed by:
 - suppressed or undetectable levels of TSH
 - elevated serum levels of T3 and T4
 - increased radioactive iodine uptake on thyroid scan (RAIU)
 - positive thyroid stimulating immunoglobulin test (TSAb) (Cherner, 1997)

*DESIRED OUTCOME
GOALS FOR MANAGEMENT*

- to normalize the production of thyroid hormone
- to minimize the symptoms and long term consequences of the disorder
- to provide individualized therapy based on the type and severity of disease, patient age and gender, existence of non-thyroidal conditions and response to previous therapy (Wells, et al, 2000)

THERAPEUTIC ALTERNATIVES
NON-PHARMACOLOGICAL INTERVENTION
SURGERY

- should be euthyroid prior to surgery
 - ATD e.g. PTU (propylthiouracil) or methimazole (tapazole) about 6-8 weeks)
- followed by iodides (500mg/d) for 10-14 days
- propranolol 20-40 mg q 6 hrs. given before and after surgery

CANDIDATES FOR SURGERY

- young pts
- pregnant pts
- large multinodular goiters
- pts with coexistent suspicious nodules
- pts who refuse other treatments (Kaplan, et al, 1998)

SIDE-EFFECTS OF SURGERY

- laryngeal nerve paralysis
- hypothyroidism
- hypoparathyroidism
- bleeding (Ryan, 1999)

NON- PHARMACOLOGICAL INTERVENTION
- Radioactive Iodine 131I

- Colorless, tasteless liquid
- dose: 4000-8000 rads
- Contraindicated in pregnancy
- best for most pts >40 yo
- moderate hyperthyroidism
- relatively small goiters
- those unresponsive to ATDs

Radioactive Iodine 131I

- treatment of choice in the US
- up to 20% of pts require a 2nd dose
- at least 6 months should elapse before 2nd dose is given
- precaution on older pts with CV disease

RADIOACTIVE IODINE 131I

- variables that influence outcome:
 - gender
 - race
 - size of thyroid
 - severity of disease
 - level of TSAb (Reasner, 2000; Dipiro, 2000)

SIDE-EFFECTS
RADIOACTIVE IODINE ¹³¹I

- Acute
 - radiation thyroiditis
 - hyperthyroidism exacerbation
- Long term
 - worsening of ophthalmopathy
 - hypothyroidism
 - no relationship has been estb between RAI and thyroid CA or fetal abnormality in subsequent generations (Bahn, 1993; Burch, 1993; DeGroot, 1997; Marcocci, 1992)

PREVENT RAI SIDE-EFFECTS

- ATDs especially for elderly and those at risk for cardiac complications (Cooper, 1998; Reasner, 2000; Dipiro 2000)
- glucocorticosteroids
- iodides 3-7 days *after* RAI

PHARMACOLOGICAL INTERVENTION
ATDs

- ACTION - thiourea drugs
 - block synthesis of thyroid hormone (Madison, 1998; Schilling, 1997; Dipiro, 2000; Reasner, 2000; Wells, 2000; Cooper, 1998)

*PHARMACOLOGICAL INTERVENTION
ATDs*

- methimazole (Tapazole)
 - once daily dosing
 - maybe given during pregnancy and lactation
 - initial dose is 20-30 mg qd
- propylthiouracil (PTU)
 - at high doses inhibit T4-to-T3 conversion
 - useful in thyroid storm
 - can be given during pregnancy and lactation
 - initial dose: 100-150 mg q 8 hrs.

*PHARMACOLOGICAL INTERVENTION
ATDs*

- concurrent administration of L-thyroxine with thionamide therapy to improve remission rate - NOT consistently observed in all studies

*COMPARISON OF DOSE AND DURATION OF
THIOUREA DRUGS IN VARIOUS PLACES AND
HOW THIS INFLUENCE EFFECTIVENESS OF RX*

- Prospective randomized Japanese study (Hashizume, 1991)
- Similar study done in England several years later (McIver, 1996)
- another fairly recent study (Pfeilschifter, 1997) also did not support the results of the Japanese study

COMPARISON OF DOSE AND DURATION OF THIOUREA DRUGS IN VARIOUS PLACES AND HOW THIS INFLUENCE EFFECTIVENESS OF RX

- reasons for the differences in outcome are not clear
- differences in ethnic derivation (HLA-type) and iodine intake between the two study populations have been suggested as possible explanations

COMPARISON OF DOSE AND DURATION OF THIOUREA DRUGS IN VARIOUS PLACES AND HOW THIS INFLUENCE EFFECTIVENESS OF RX

- Sensitivity to ATDS and iodides
- theory
 - those with an endemic lack of iodine are more sensitive to the ATDS and iodides than pts in areas where iodine is readily available
 - dosing should be lower and must be monitored more closely

*PHARMACOLOGICAL INTERVENTION
ATDs*

- 6-18 months course of treatment
- recommended for the following pts.
 - Pregnant and lactating women
 - young patients <45 yo
 - pts with severe ophthalmopathy or cardiac arrhythmias
 - preliminary control in preparation for thyroid surgery or RAI treatment

ATDs FOLLOW-UP

- Monthly - changes in dose
- every 6-12 months after remission occurs
- if relapse occurs - alternate therapy with RAI preferred over 2nd course of ATD (Dipiro, 2000; Reasner, 2000)

PTS WHO DO WELL ON ATDs

- older pts > 40 yo
- low ratio of T4 to T3 (<20)
- small goiter (<50 gm)
- short duration of disease (<6 months)
- no previous history of relapse with ATDs
- duration of therapy 1-2 years
- low TSAb titers at baseline or reduction with treatment (Dipiro, 2000; Reasner, 2000)

ATDS SIDE-EFFECTS

- Fever
- skin rash (treated with antihistamine)
- liver dysfunction - elevation in transaminase
- arthralgia
- serum sickness
- vasculitis
- rare occurrence: agranulocytosis - maybe HLA linked

ATDS SIDE-EFFECTS

- Patients who have experienced a *major* adverse reaction to one thiourea drug should not be converted to the alternate drug because of cross sensitivity (Dipiro, 2000; Reasner, 2000)

*PHARMACOLOGIC INTERVENTION
ADRENERGIC BLOCKERS*

- Beta blockers (propranolol/Inderal)
 - used to ameliorate thyrotoxic symptoms
 - contraindicated in pts with:
 - CHF unless due to tachycardia bronchospasm
 - cardiomyopathy pregnancy (small fetal size, post natal bradycardia)
 - sinus bradycardia
 - MAO inhibitors
 - tricyclic antidepressants
 - spontaneous hypoglycemia

BETA-BLOCKERS and others

- propranolol
- cardioselective blocker e.g. esmolol
- use centrally acting sympatholytics (clonidine) and calcium channel antagonists (diltiazem) (Cooper, 1998)

*OTHER ADJUNCTIVE DRUG
THERAPIES*

*PHARMACOLOGIC INTERVENTION
IODIDES*

- action
 - block release of preformed thyroid hormone
 - decrease size and vascularity of thyroid gland
- uses
 - adjunctive therapy for surgery and RAI
 - thyroid storm by acutely inhibiting TH release

IODIDES

- Precautions
 - do not initiate therapy until after the TH has been blocked for at least 48 hrs with ATDs
 - it should *not* be used before, but rather 3-7 days after RAI treatment

IODIDES

- Large doses of iodine may exacerbate hyperthyroidism (Jod-Basedow disease) - most commonly observed in iodine deficient areas

IODIDES

- Examples of iodides:
 - SSKI 2-3 drops q 8 hrs., po
 - Lugol's solution 3-5 drops q 8 hrs., po
 - ipodate sodium/ Oragrafin; sodium iopanoate/Telepaque (cholecystographic agents) 1 gm/day, po
 - sodium iodide 0.5g q 12 hrs. IV in an emergency (thyroid storm)

IODIDES SIDE-EFFECTS

- Hypersensitivity reactions
- salivary gland swelling
- iodism
- gynecomastia (Dipiro, 2000; Reasner, 2000)

*PHARMACOLOGIC INTERVENTION
LITHIUM CARBONATE*

- Action
 - inhibits thyroid secretion but clinical therapeutic experience is very limited

*PHARMACOLOGIC INTERVENTION
BILE ACID SEQUESTRANTS*

- Action
 - cholestyramine resin interfere with the enterohepatic circulation of T4, subsequently reducing the serum T4 levels (Dipiro, 2000)

Table 1. COMPARISON OF TREATMENT MODALITIES FOR THE CORRECTION OF HYPERTHYROIDISM

Treatment	Advantages	Disadvantages	Particularly Suitable for
¹³¹ I	Definitive, safe, single, predictable outcome	Likelying ¹³¹ I, treatment usually needed; unsuitable in pregnant patients and nursing mothers	Most patients
Antithyroid drugs	May avoid need for lifelong medication	Side effects; low long-term remission rate; more frequent visits needed	Pre-treatment before RAI; pregnant patients; patients afraid of radiation exposure; young patients with mild disease and small goiter
Surgery	Definitive, rapid; eliminates large nodular goiters	Expensive; requires general anesthesia and hospitalization; risk of recurrent nerve or parathyroid damage; outcome dependent on surgeon's expertise; lifelong ¹³¹ I treatment usually needed	Young patients with toxic autonomous nodules; pregnant patients not controlled by, or allergic to, ATD; large multinodular goiters with low RAI uptake; patients with consistent suspicious nodules; patients who refuse other treatments

*INITIAL PHARMACOTHERAPEUTIC
PLAN FOR WS*

- ATDs
 - PTU 100mg, po, q 8 hrs.
- beta-blocker
 - propranolol 20 mg, po, qid
- diuretic
 - HCTZ 25 mg, po, qd
- pain reliever
 - acetaminophen, NO aspirin or NSAIDS

*LABORATORY PARAMETERS TO
EVALUATE TREATMENT*

- monthly serum T3 and T4 levels
- TSAb titer
- utility of serum TSH measurements in the first few months of ATD is limited (Cooper, 1998)

*LABORATORY PARAMETERS TO
EVALUATE TREATMENT*

- serum drug levels (PTU) not helpful clinically (Cooper, 1998)
- baseline LFTs and WBC although will not be monitored monthly (Cooper, 1998; Reasner, 2000)

*CLINICAL PARAMETERS TO
EVALUATE TREATMENT*

- Objective improvement in 4-6 weeks
- changes in drug dose made on a monthly basis (Dipiro, 2000; Reasner, 2000)

*CLINICAL PARAMETERS TO
EVALUATE TREATMENT*

- monitor for persistent signs of thyrotoxicosis (tachycardia, tremor, anxiety, heat intolerance, etc.)
- evaluate for signs of developing hypothyroidism (bradycardia, weakness, lethargy, fatigue, depression, cold intolerance, etc)

*CLINICAL PARAMETERS TO
EVALUATE TREATMENT*

- monitor for drug side-effects
 - PTU - skin rash most common side-effect, if present, order antihistamine

PATIENT COUNSELING

- inform about potential side-effects of medications
- seek medical attention
 - signs/symptoms of hypothyroidism
 - ATD serious side- effects (agranulocytosis, hepatitis)

*CLINICAL COURSE
FOLLOW-UP VISIT IN 2 WEEKS*

- Improvement in fatigue and anxiety symptoms
- tolerating drug therapy
- no change in thyroid size or composition
- no change in ocular symptoms
- HR 67/min
- no change in drug therapy

*FOLLOW UP VISIT AFTER 3 MONTHS
OF THERAPY*

- c/o dry eyes and blurring of vision
- anxious
- rapid heart rate esp at night
- improved appetite with 5 lbs weight gain
- no episode of heat intolerance
- PE - thyroid remains enlarged (60g); HR 63/min; TSH - 6.7uIU/mL; free T4 - 0.6ng/dL; TSAb - 35 units/ml

*EVALUATE DRUG EFFECTIVENESS AND WHAT
RECOMMENDATIONS CAN BE MADE*

- Pt is chemically euthyroid based on the results of the TSH and the free T4 but still suffers from the thyrotoxic effects clinically (anxiety, rapid HR at night and dry eyes with blurring of vision) which maybe brought about by persistent presence of thyroid antibodies (TSAb elevation)

*RTC IN 8 WEEKS FOLLOWING
CHANGES IN THERAPY*

- euthyroid and feeling much improved
- eye symptoms worse
- corticosteroid added to medications
- RAIU study requested - 57% in one hour
- I₁₃₁ was recommended in a few weeks in the hope of decreasing his TSAb

*ETIOLOGY AND PATHOGENESIS OF
OPHTHALMOPATHY*

- Autoantibodies also react with orbital muscle that cause the ophthalmopathy characterized by:
 - exophthalmos
 - diplopia
 - visual loss

OPHTHALMOPATHY

- common pt complaints related to the eye
 - dryness
 - burning
 - irritation
 - light sensitivity
 - foreign body sensation (Gladstone, 1998)

RECOMMENDED TREATMENT REGIMEN FOR OPTHALMOPATHY

- steroid therapy
- lubricating ointment at night and artificial tears during the day
- surgery to correct the exophthalmos if severe

TREATMENT REGIMEN AFTER SEVERAL RELAPSES FROM COURSES OF THIOUREA DRUGS AND 90% THYROIDECTOMY

- If patient has not achieved clinical and chemical euthyroidism, consider RAI therapy
- RAI preferred over 2nd course of ATD (Dipiro, 2000; Reasner, 2000)
- If patient became hypothyroid as a result of therapy, provide L- thyroxine (Synthroid) replacement therapy

✓ **Table 1. CONTACT INFORMATION FOR NORTH AMERICAN SUPPORT GROUPS FOR PATIENTS WITH THYROID CONDITIONS***

Group	Address	Phone	Internet Site	E-Mail
Thyroid Foundation of America	Ruth Sleeper Hall-FSL, 200 40 Parkmer St. Boston, MA 02114-2598	617-735-8338 or 800-833-8321	http://www.thyfaeb.org/jv/ifa	ts@tdaah.net
Thyroid Foundation of Canada	1940 Gardiners Rd., Box C Kingston, Ont K7P1R1 Canada	613-634-3428 800-367-8822 (Canada only)	http://www.tfcn.net/~thyroid Canada/ftm	thyroid@lineone.ksone.com
National Graves' Disease Foundation	2 Telle Court Brussels, NC 28713-4263	704-477-6261 (747-771-1125)	http://ngdf.org/	ngdf@alcom.net
Thyroid Society for Education & Research	1310 S. Main St., Ste. 545 Houston, TX 77028	713-799-8809 800-649-7643	http://www.the-thyroid-society.org	tsed@the-thyroid-society.org

*The organizations listed above are presently active in North America. Several books are available that provide valuable information (see refs. 1-4). Some of these books can be purchased in general or medical/book stores, the others can be obtained from one or more of the support groups listed.


