Hyperparathyroidism: An Overview

The four parathyroid glands, normally located behind the four poles of the thyroid gland, secrete parathyroid hormone (PTH), which regulates extracellular calcium levels. Hyperparathyroidism, which can be primary, secondary, tertiary or quaternary, results in excess production of PTH. Excessive PTH secretion may be due to hyper-function in the glands themselves, in which case it is referred to as primary hyperparathyroidism and leads to hypercalcemia (elevated calcium levels). In these cases, oversecretion of PTH is due to adenoma, hyperplasia or, rarely, carcinoma of the parathyroid glands. It may also occur in response to low calcium levels, as encountered in various situations such as chronic kidney disease (CKD) and Vitamin D deficiency; this is referred to as secondary hyperparathyroidism. Secondary hyperparathyroidism can also result from malabsorption (chronic pancreatitis, small bowel disease, malabsorption-dependent bariatric surgery) in that the fat soluble vitamin D cannot get reabsorbed or rarely, long-term lithium treatment. Tertiary hyperparathyroidism is seen in patients with long-term secondary hyperparathyroidism which eventually leads to hyperplasia of the parathyroid glands and a loss of response to serum calcium levels. Quaternary hyperparathyroidism is rare and may be observed after surgery due to primary hyperparathyroidism, when it has led to renal damage that now again causes a form of secondary (quaternary) hyperparathyroidism that may itself result in autonomy (quintary) hyperparathyroidism. Additionally, quaternary hyperparathyroidism may develop from hungry bone syndrome after parathyroidectomy.

Etiology

Low circulating serum calcium concentrations stimulate the parathyroid glands to secrete PTH which increases the release of calcium and phosphate from bone matrix. PTH also stimulates the kidneys to reabsorb calcium and convert 25-hydroxyvitamin D3 (produced in the liver) to the active form, 1,25-dihydroxyvitamin D3 (calcitriol), which, in turn, stimulates intestinal absorption of calcium. Thus, overproduction of parathyroid hormone results in elevated levels of plasma calcium. High serum calcium concentrations have a negative feedback effect on PTH secretion, depressing its secretion.

In chronic kidney disease, overproduction of parathyroid hormone occurs in response to hyperphosphatemia, hypocalcemia and impaired 1,25-dihydroxyvitamin D production by the diseased kidneys. Failing kidneys do not convert enough vitamin D to its active form, calcitriol, and they cannot adequately excrete phosphate. Phosphate retention (hyperphosphatemia) inhibits renal activation...
When we think of DVT’s, or deep vein thrombosis, we traditionally think of our post-op patients or our immobile, elderly residents in our LTC facilities. Do we ever actually think about getting a DVT ourselves? No, historically, we probably don’t.....but, yes, it can happen to you!

Have you ever needed to get caught up on a little extra work and before you know it, found yourself sitting at your workplace for two or three hours without getting up and moving about? Well, the lack of circulation in your legs during that time is all it takes and you, too, could develop a blood clot or DVT in your legs. That may sound a bit far fetched; but several months ago, it happened to me. No additional risk factors required.....and in the right circumstances, you too could develop a blood clot, and find yourself giving Lovenox injections and daily Coumadin doses to yourself.

So, what’s the big deal with developing a DVT? Depending on the location of the blood clot, or thrombosis, it can become dislodged and make its way to your lungs and become a PE, or pulmonary embolism. This DVT complication can actually be fatal. Most clots that form in the leg are below the knees. These clots are less dangerous as they are much less likely to dislodge. As such, they are often left untreated. The concern lies in those clots that form above the knee. These are the clots that have a much greater chance of moving to the lungs and becoming a pulmonary embolus, and are therefore treated very aggressively.

Once a DVT is detected or confirmed by a doppler or ultrasound of the lower extremity, the individual is often admitted to the hospital. Strict bed rest and an aggressive anticoagulant regimen is initiated, often consisting of low molecular weight heparin injections and oral warfarin therapy, requiring very frequent blood work monitoring. Once oral warfarin therapy is therapeutic, the LMWH injections can be discontinued. In these cases, oral warfarin therapy is typically continued for an additional three to six months.

It often takes 3 to 4 weeks for one to become therapeutic on oral warfarin therapy. Thus.... three to four weeks out of work! And no, that IS NOT three to four weeks out shopping at the mall or playing golf. That is three to four weeks lying flat on your back! NOT FUN!!

So.....let’s talk prevention. How can we make sure that we work safely and minimize our risk of developing a DVT? Fortunately, preventing a deep vein thrombosis is far easier than treating it after is has occurred.

Common Preventive Measures

- Exercise your lower calf muscles: Ideally, one should sit no longer than 45 minutes to an hour without getting up and walking around. Sit with your legs stretched out in front of you and not pulled back underneath your chair. Flex your feet and ankles out in front of you frequently, pointing your toes and pulling them back toward your body often. Also, try raising and lowering your heels while keeping your toes on the floor, then raising your toes while your heels are on the floor. These movements help promote the circulation of blood in your legs and deter clot formation.

- Make lifestyle changes: Lose weight, quit smoking and control your blood pressure. Obesity, smoking, and high blood pressure all increase your risk of deep vein thrombosis.

- Wear compression stockings: The use of compression stockings or hose can help prevent the formation of blood clots in the legs.
Risk Factors for Developing DVT’s
- Sitting for long periods of time, such as driving or flying
- Heredity: Inheriting a blood-clotting disorder
- Prolonged bed rest or paralysis
- Injury or surgery
- Pregnancy
- Cancer
- Inflammatory bowel disease
- Heart Failure
- Birth control pills or hormone replacement therapy
- Pacemaker
- History of DVT or pulmonary embolism (PE)
- Family history of DVT or PE
- Being overweight or obese
- Smoking—>60 years old
- Being Tall: taller men are at greater risk of blood clots

Symptoms of a DVT
Unfortunately, in about half of all DVT cases, the thrombosis occurs without any noticeable symptoms. When symptoms do occur, they can include:
- Swelling in the affected leg, including swelling in the ankle and foot.
- Pain in the affected leg, which can include the ankle and foot. Pain often starts in the calf and can feel like cramping or a charley horse.
- Warmth over the affected area.
- Changes in skin color: can be pale, red or blue.

Warning Signs of a Pulmonary Embolism
- Unexplained sudden onset of shortness of breath
- Chest pain or discomfort that worsens when you take a deep breath or when you cough.
- Feeling lightheaded or dizzy, or fainting
- Rapid pulse
- Sweating
- Coughing up blood
- A sense of anxiety or nervousness

In summary, the risk of development of deep vein thrombosis, or blood clots is not limited to our residents. It can happen to us, too. Be mindful of your movement! Do not sit at your desk or workplace for more than 45 minutes to an hour at a time. If you find yourself sitting for extended periods, keep moving! Exercise those calf muscles to keep that blood flowing in your lower legs. When traveling in your car for extended periods of time, stop and get out for a quick walk. If traveling by air, get up and move about the plane from time to time. Don’t just sit there......remember the risk of DVT.....IT CAN HAPPEN TO YOU!!

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of Vitamin D, which in turns reduces gut absorption of calcium as well as directly decreases blood ionized calcium. Hyperphosphatemia can directly stimulate PTH synthesis and parathyroid hyperplasia and indirectly promotes secondary hyperparathyroidism by decreasing free calcium levels.

Low blood calcium concentrations cause PTH secretion from the parathyroid glands to restore normal blood calcium and phosphorous concentrations. Decreased production of 1,25-dihydroxyvitamin D3 (calcitriol) results in a reduction in intestinal absorption of calcium. Both processes lead to hypocalcemia and hence secondary hyperparathyroidism.

The development of secondary hyperparathyroidism results from many factors, including deficiency of active Vitamin D (calcitriol) via renal disease, diet combined with lack of sun exposure, retention of phosphorus, a decrease in the activation of the calcium-sensing receptor (CaR) in the parathyroid gland, and skeletal resistance to the calcemic effect of PTH. All of these factors contribute to the development of hypocalcemia, which is the impetus for an increased production of PTH. More recently, fibroblast growth factor-23 (FGF-23), which increases early in the course of CKD possibly as a consequence of phosphorus retention, has been found to suppress calcitriol synthesis, in turn leading to increased PTH.

Chronic overproduction of parathyroid hormone in patients with renal failure can manifest as one of two types of renal osteodystrophy (dystrophic bone growth): either a high turnover state known as osteitis fibrosa, or, in combination with low bone turnover, known as mixed uremic osteodystrophy. Consequences of these includes: marrow fibrosis that can exacerbate the anemia of CKD; abnormal bone mineralization and fractures; bone pain; myopathy and muscle weakness; spontaneous tendon rupture; pruritis; cardiovascular calcification; soft tissue calcification; endocrine disturbances; compromised immune system and neurobehavioral changes.

Diagnosis

Hyperparathyroidism is diagnosed by elevated parathyroid hormone level, hypercalcemia and measuring phosphate levels. If primary hyperparathyroidism is suspected, a procedure in nuclear medicine, a sestamibi scan, can be performed to identify parathyroid adenomas.

Radioimmunoassays for the intact PTH (iPTH) molecule, intended to detect only relatively intact and biologically active PTH molecules, is the recommended method to test for PTH and monitor hyperparathyroidism. Once an elevated PTH has been confirmed, goal of diagnosis is to determine whether the hyperparathyroidism is primary or secondary in origin by obtaining a serum calcium level. Low or normal calcium levels usually indicate secondary hyperparathyroidism while high calcium levels likely indicate primary hyperparathyroidism. Hypercalcemia is diagnosed by a serum Ca concentration >10.4 mg/dL or ionized serum Ca >5.2 mg/dL. When no cause is obvious, concentrations of serum Ca <11 mg/dL suggest hyperparathyroidism or other nonmalignant causes, whereas concentration >13 mg/dL suggest cancer. In hyperparathyroidism, the serum Ca is rarely >12 mg/dL, but the ionized serum Ca is almost always elevated.

In primary hyperparathyroidism, serum phosphate levels are abnormally low as a result of decreased renal tubular phosphate re-absorption. However, this is only present in about 50% of cases. This contrasts with secondary hyperparathyroidism, in which serum phosphate levels are generally elevated because of renal disease. Alkaline phosphatase levels are usually elevated in hyperparathyroidism. Isoenzyme studies using electrophoresis can confirm the source of the ALP, which would be elevated for ALPL, marker for liver/bone/kidney (tissue nonspecific) dysfunction.

Symptoms

Hyperparathyroidism is often diagnosed before signs or symptoms of the disorder are apparent. When symptoms do occur, they are the result of damage or dysfunction in other organs or tissues due to high calcium levels circulating in the blood or too little calcium in bones.

Symptoms may be so mild and nonspecific that they don’t seem at all related to parathyroid function, or they may be severe. The range of signs and symptoms include: fragile bones that easily fracture (osteoporosis), kidney stones, excessive urination, abdominal pain, tiring easily or weakness, depression or forgetfulness, bone and joint pain, frequent complaints of illness with no apparent cause, and nausea, vomiting or loss of appetite.

Treatment

Treatment depends on the type of hyperparathyroidism. Patients with primary hyperparathyroidism who are symptomatic benefit from surgery to remove the parathyroid tumor (parathyroid adenoma). In asymptomatic hyperparathyroidism, surgery is only indicated if 24-hour urinary calcium > 400 mg,
Phosphate binders and non-calcium based agents including Sevelamer carbonate (Renagel®, Renvela®) 800 to 3200mg or lanthanum carbonate (Fosrenol®) 250 to 1000 mg with each meal are non-calcium based options for patients who develop hypercalcemia while taking Ca-containing phosphate binders. Nurses please note the importance of giving phosphate binders with meals as their mechanism of action is binding dietary phosphate in the gut and preventing absorption into the blood stream.

A newer class of medications, calcimimetics, one of which is commercially available as Sensipar® (cinacalcet), are FDA approved for use in patients on dialysis, but have not been approved for use in CKD pre-dialysis because, among other concerns, they can increase phosphorus levels. The calcimimetic, cinacalcet, modulates the set point of the Ca-sensing receptor on parathyroid cells and decreases PTH concentration in dialysis patients without increasing serum calcium. Nurses need to be reminded to give Sensipar® with a meal or directly after for maximum efficacy. Trials with cinacalcet indicate that early intervention in stage 3 and 4 chronic kidney disease can correct parathyroid hormone levels and could prevent renal bone disease and prolong patient survival. Treatment with calcimimetics such as cinacalcet leads to significant improvements in biochemical parameters, but patient-based benefits have not yet been demonstrated. The EVOLVE (Evaluation Of Cinacalcet HCl Therapy to Lower CardioVascular Events) trial was one of the first large-scale, randomized controlled trials in patients with ESRD to examine the treatment of secondary hyperparathyroidism with cinacalcet vs placebo along with standard of care phosphorous binders and Vitamin D analogs. Hyperphosphatemia and hyperparathyroidism have been associated with increased risk of death in ESRD patients and this trial was designed to see if there was a mortality benefit in the use of the non-calcium/non-Vitamin D analog cinacalcet in the ESRD population. The results of the trial demonstrated that cinacalcet did not result in improved mortality or improve cardiovascular endpoints. The use of cinacalcet did reduce the need for parathyroidectomy for refractory hyperparathyroidism. Of note, there was an increased risk of serious adverse events, namely hypocalcemia, with the use of cinacalcet. In conclusion, despite aggressive management of secondary hyperparathyroidism that is associated with increased mortality in ESRD patients, cinacalcet did not offer a cardiovascular or mortality benefit in this population of patients.

**Conclusion**

Hyperparathyroidism can mainly be related to secondary or less often as the primary disease state. The majority of hyperparathyroidism is related to CKD (secondary) and is treated based on phosphate dietary restriction as well as phosphate binders along with active Vitamin D or its analogs and/or calcimimetics. Recognition of prevention and treatment of skeletal and non-skeletal consequences is the focus of treatment to decrease morbidity and mortality in hyperparathyroidism.
Phenytoin (Dilantin®) is a commonly used anticonvulsant that can have serious toxicity affects when serum concentrations reach above 20 mcg/ml. This medication has a very narrow therapeutic range and is highly protein bound so its therapeutic effect and degree of toxicity are dependent upon the free fraction phenytoin concentrations which in turn depend upon the amount of drug bound to serum albumin. As serum albumin levels increase, the amount of free drug and its therapeutic effect decreases which can lead to insufficient quantities of the drug in the body and result in a seizure. At the same time if a person’s albumin level decreases, the amount of free drug increases along with its therapeutic effect which can lead to toxicity. The formula to calculate an approximate corrected or “free phenytoin” level is: Corrected phenytoin level = (measured phenytoin x 4.4) / measured albumin. The normal therapeutic concentration range is 10-20 mcg/ml, however some patients may be therapeutic at concentrations of 5-10 mcg/ml. Adjustment of dose is not only based on the level, but mostly on the clinical condition of the patient. Insufficient or hypoalbuminemia can alter phenytoin plasma protein binding leading to increased drug concentrations. Many disease states or conditions result in hypoalbuminemia such as liver disease, nephritic syndrome, pregnancy, cystic fibrosis, burns, trauma, malnourishment, and simply being elderly. So it is important that the serum concentration of phenytoin is checked regularly to maintain a concentration in the therapeutic range of 10-20 mcg/mL because small dose increases can result in disproportionately large increases in serum concentrations.

HgbA1c is not as useful for monitoring in a patient with diabetes and Chronic Kidney Disease. Some of the methods used to measure A1c, such as agar gel electrophoresis, are affected by ESRD. This is due, in part, to analytical interference from carbamylated hemoglobin formed in the presence of elevated concentrations of urea, leading to false elevations in the A1c level. Therefore in patients with CKD, it may be better to monitor blood glucose levels. A fructosamine level can also be used to estimate mean blood glucose; however, it is important to be aware that this level reflects mean values over a period of 1-2 weeks.

Chronic use of methotrexate requires supplementation with folic acid 1 mg/day. Methotrexate interferes with the cellular utilization of folic acid. Supplementation with folic acid has been found to reduce adverse effects seen with methotrexate.

TSH stimulates the synthesis of T3 and T4 by the thyroid gland. T3 and T4 inhibit the secretion of TSH, both directly and indirectly by suppressing the release of TRH. Therefore, it TSH levels are high, there is little T3 and T4. If TSH levels are low, there is too much T3 and T4. Patients with primary hypothyroidism who are taking levothyroxine replacement therapy can be monitored by assessing the serum TSH. If serum TSH is high, the dose needs to be increased; if it is low, the dose needs to be reduced.

Barrett’s esophagus occurs when the normal cells that line the lower part of the esophagus (squamous cells) are replaced by a different cell type (intestinal cells). This occurs as a result of repetitive damage to the inside of the esophagus by longstanding GERD. The intestinal cells that develop have a risk of transforming into cancer cells. Goal of therapy is to control
gastric reflux symptoms. First-line therapy is a PPI (usually dosed once or twice daily).

**Primidone (Mysoline®)** has 2 active metabolites: phenobarbital and phenylethylmalonamide (PEMA). Half-life elimination is age dependent: primidone 5-15 hours, PEMA 16 hours. Since the elderly metabolize phenobarbital at a slower rate than younger adults, it is suggested to measure both primidone and phenobarbital serum concentrations together. Checking both levels helps show if the patient is clearing the metabolites appropriately. In rare instances or when toxicity is suspected, primidone, phenobarbital, and PEMA levels can be checked.

**Huntington’s Disease** or cholera is a genetic disorder that causes wasting away of brain nerve cells. As the disease gets passed along from generation to generation, the development of symptoms become apparent at a younger age.

There are two forms of Huntington’s disease:
- Adult onset
- Early onset

Adult onset occurs in the 30’s-40’s while early onset begins in childhood or adolescent years.

Symptoms of Huntington’s disease include but are not limited to: hallucinations, irritability, restlessness or fidgeting, psychosis, abnormal and unusual movements of the arms, legs, face, and other body parts, slowly worsening dementia, etc.

Tests to detect Huntington’s disease:
- Head CT
- Head MRI scan
- PET scan of the brain
- There are also genetic tests available to see if you are a carrier of the gene

Treatment: There is currently no treatment and no way of stopping the progression of the disease, but some medications are used in hopes of slowing down the progression or helping with the symptoms of Huntington’s. These include:
- Dopamine blockers
- Amantadine, Tetrabenazine
- Co-enzyme Q10 (evidence, but non-conclusive)

**Vitamin B12** is needed to produce proper red blood cell formation, neurological function, and DNA synthesis. If someone is deficient in B12 it can lead to serious side effects such as fatigue, weakness, loss of appetite, and neurological symptoms such as numbness and tingling. It can also produce signs of depression, dementia, and poor memory—many things we see our elderly patients being treated for with various antidepressants or antipsychotics. Knowing this, it is very important that we pay close attention to B12 levels in this age group to prevent over treatment or misdiagnoses.

The main causes of B12 deficiency include mal-absorption from food and post surgical mal-absorption, pernicious anemia, and dietary deficiency. In the older population, 10-30% are affected with atrophic gastritis. This can lead to lower acid levels in the stomach which can decrease the absorption of B12 and lead to the overgrowth of gut flora that use the B12.

Treatment: In order to treat B12 deficiency it is important to determine the patient’s ability to absorb the vitamin. B12 can be given orally or through injection. If the patient is able to absorb the vitamin B12 then high doses of oral agents may be given, if not then an injection of B12 can be given because it bypasses possible barriers to absorption.

*Short Subject contributions from Amanda Groppe and Logan Dawson, both Pharm D Candidates*
Greetings to all the PharmNotes Family,

Just thought I would share a few interesting quotes for you to think about this month……..

“People overestimate what they can do in a single day and underestimate what they can do in their whole lives.”

“Don’t look back…….you’re not going that way”.

“Never get so busy making a living that you forget to make a life”.

“You never know how strong you are…..until being strong is the only choice you have”

Till next time….

Cathy Fuquay
Pharm Notes Editor

...a note from the Editor