Carcinoid Syndrome

Carcinoid Tumors are GI endocrine tumors that synthesize, store, and release a variety of polypeptides, biogenic amines, and prostaglandins. Although rare (1-2 per 100,000), carcinoid is the most common GI endocrine tumour. Approximate 2-5% of these patients will exhibit carcinoid syndrome, the hallmark of which is flushing with diarrhea hemodynamic instability +/- bronchospasm. Carcinoid heart disease is present in 20-40% patients with carcinoid tumours.

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ANESTHETIC CONSIDERATIONS:	
• Cone	cerns of malignancy:
	• 4 Ms: mass, medications, metastatic conditions, metabolic.
• Dete	ermine presence of carcinoid syndrome:
	• Airway:
	 Obstruction secondary to airway or bronchial tumours
	Respiratory:
	 risk of bronchospasm (rare in patients with normal pulmonary function, higher risk in asthmatics)
	• CVS:
	 carcinoid heart disease (20-40%)
	 tricuspid regurgitation - avoid increased PVR
	 pulmonic stenosis
	 typically R sided heart lesions because the lung inactivates humoral substances prior to reaching the L heart
	 hemodynamic instability (secondary to release of vasoactive substances – histamine, prostaglandins, etc.)
	• GI
	Diarrhea (associated hypovolemia and electrolyte abnormalities)
• Oth	
011	Hypoproteinemia_possibly altered drug pharmacology
	• Pellagra (niacin deficiency)
	Prevent/manage perioperative carcinoid crisis
	 Avoid sympathetic stimulation (nain, avogenous catecholamines, stress response) due to increased hormone release from tumor
	Avoid sympanetic similation (pain, vxogenous categorius, suess response) due to increase normone release normanies.
	Prenedicate with any lottics and correctide
	Findedate with anticipates and observed to have MEN 1) Findedate strands of the server (10% also have MEN 1)
	- Evaluate presence of coexisting diseases (10/0 also have welly-1)
ANESTHETIC GOA	NT S'
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Avoid perioperative carcinoid crisis by preventing sympathetic surges

Avoid:

- sympathomimetics
- 5HT releasing agents
- pain
- hypercarbia
- acidosis
- hypovolemia
- Perioperative administration of octreotide to prevent vasoactive mediator release

HISTORY

- ** Determine the local effects of the tumor, the extent of multisystem disease and to decide if this is an "active" tumor with carcinoid symptoms**
 - Carcinoid symptoms =
 - o Episodic cutaneous flushing often with predictable triggers such as stress, eating, BM, alcohol consumption = most common presentation
 - Hypertensive headache
 - Syncope with flushing
 - Palpitations
 - Lacrimation
 - O Nausea / vomiting, episodic watery diarrhea, chronic abdominal pain
 - Episodic asthma poorly responsive to medications
- Local tumor effects =
 - O Endobronchial tumor with obstructive symptoms +/- focal wheeze
 - 0 GI obstructive symptoms, abdominal pain, GI bleeding
- Carcinoid heart disease =
 - Palpitations, pedal edema, ascites
 - Investigations
- Treatment
 - O Medications octreotide available as IM once-monthly slow-release preparation
 - Previous de-bulking surgery ? Complications ?
 - 0 Heart failure management medications (often loop diuretics + digoxin), fluid + salt restriction

PHYSICAL

- VITALS may see histamine-induced hypotension and vasodilatation or serotonin-induced hypertension
- HEENT airway or endobronchial tumor with obstruction
- RESP bronchospasm, wheeze, focal wheeze if airway obstructing lesion
- CVS
 - \circ Assess adequacy of fluid balance can be hypovolemic due to chronic vasoconstriction and diarrhea
 - Assess right-sided valvular status
 - Tricuspid regurgitation: elevated JVP with prominent V wave, RV heave and S3 gallop, pansystolic murmur along lower left sternal border (louder with inspiration), Afib, ascites, edema, hepatomegaly

- Pulmonary stenosis: may see prominent A wave on JVP, pulsatile liver, RV heave, thrill in suprasternal notch and at LUS border, wide split S2, loud P2, may have S4, systolic ejection click (varies with respiratory), SEM at LUS border, radiates infraclavicularly, axillary or to the back
- Small percentage will also have left-sided disease so look for LH failure as well
- GI Hepatomegaly, pulsatile liver, abdominal masses, tenderness, ascites

• DERM

- Pellagra (niacin deficiency) = dermatitis, diarrhea, dementia (develops secondary to increased shunting to production of 5HT from tryptophan and relative deficiency of other tryptophan metabolites)
- Hyperkeratosis, hyperpigmentation
- Venous telangiectasia

INVESTIGATIONS

- Labs
 - CBC
 - 0 Lytes, BUN, creatinine dehydration and electrolyte abnormalities from diarrhea
 - Hyperglycemia d/t to excess serotonin
 - 0 LFTs, albumin (hypoalbuminemia), INR, PTT
 - 0 Urine 5-HIAA (5-hydroxyindoleacetic acid) renally cleared serotonin metabolite used to diagnose carcinoid
 - Levels are normal in 20% of cases
 - Reference value < 50 µmol/L per 24 hours is normal

• Imaging

- o Bowel imaging (barium x-ray series, U/S, CT, MRI, nuclear medicine scans) to localize primary and metastatic tumors
 - Carcinoid heart disease diagnosed by TTE and urinary 5-HIAA levels
 - Expect levels up to 10-fold when heart is involved
- o ECG

0

- ECG typically shows nonspecific findings (sinus tachycardia, A.fib) and is not useful for screening for CHD
- 0 CXR, CT chest for suspected bronchial carcinoids

OPTIMIZATION

- Endocrinology, cardiology consults
 - Octreotide preoperatively: bolus 50-100 mcg (one source says 300 mcg) SC
 - Reaches peak levels within 30 min, $T^{1/2} = 100$ min
 - There is no ceiling dose, up to 4000 mcg used intraoperatively
 - IV peak concentration in 3 minutes (can give 25-100 mcg)
 - Consider premed even in patients on long-acting IM octreotide
 - Octerotide alternatives: vasopressin
 - Judicious premed for anxiolysis

ANESTHETIC OPTIONS

- GA,
 - regional,
 - neuraxial
 - local
 - With regional and neuraxial, avoid sympathetic stimulation by providing adequate anxiolysis
 - With neuraxial technique, consider epidural or CSE rather than spinal to avoid hypotension and reflex sympathetic stimulation

ANESTHETIC SETUP

- Drugs
 - Octreotide in room prior to induction
 - Phentolamine, esmolol, phenylephrine available (brief, direct-acting drugs to control labile hemodynamics)
 - Avoid:
 - Drugs with indirect sympathetic stimulation (ephedrine, epinephrine, norepinephrine, dopamine)
 - Sympathomimetics (ketamine, pancuronium)
 - Drugs that cause reflex sympathetic stimulation (nitroprusside)
 - Drugs that cause histamine release (morphine, meperidine, atracurium, mivacurium)
- Equipment
 - Usual CAS monitors, 5-lead ECG
 - Large-bore IV access
 - Invasive monitors: a-line preinduction
 - Consider CVP to guide fluid status (interpretation is difficult in right-sided heart lesions)

MANAGEMENT OF ANESTHESIA

- Induction
 - Slowly titrated induction and NMR, goal = stable hemodynamics
 - See above list of drugs to avoid
 - o SCh causing tumor mediator release due to abdominal fasciculations? mainly a theoretical concern (but should probably avoid)
- Maintenance
 - Any technique acceptable
 - Isoflurane suggested as volatile of choice (least sympathomimetic)
 - 0 May have decreased MAC with elevated serotonin levels
 - Avoid hypothermia, hypercarbia, pain (sympathetic stimulation)
 - Maintain good communication with surgeon to anticipate times of tumor mediator release and give octreotide 25-50 mcg IV bolus before surgical manipulation of the tumor (repeat PRN)

- O Consider octreotide 50 mcg/h IV infusion to prevent mediator release
- Emergence
 - Good pain control essential
 - Ondansetron as antiemetic and 5-HT blocker
 - May experience delayed emergence from elevated serotonin levels
 - Octreotide management depends on presence / absence of residual tumor consult endocrinology for octreotide management (usually some tumor is left and if patient was on octreotide preoperatively, it is maintained postoperatively)
 - If discontinuing perioperative octreotide infusion, do so gradually

DISPOSITION & MONITORING

Observation in ICU/obs unit postoperatively

COMPLICATIONS

- Carcinoid crisis may occur at any point perioperatively
 - O Typically, occurs with surgical tumor manipulation, sympathetic stimulation or secondary to drugs that cause histamine or catecholamine release
 - Symptoms:
 - Hypotension
 Wheezing/bronchoss
 - Wheezing/bronchospasm
 - Diarrhea
 - Flushing
 - Immediately inform surgeon to stop
 - Administer 100% oxygen
 - Discontinue anesthetic if hypotension present
 - Restore intravascular volume, administer phenylephrine
 - O Administer drugs that decrease mediator release or effect:
 - First line = Octreotide 25-100 mcg IV (up to 1000 mcg boluses, repeat PRN) controls flushing, hypotension, wheeze, diarrhea in 75% cases
 - Other drugs used =
 - Histamine blockers (H₁ and H₂)
 - Aprotinin (kallikrein inhibitor)
 - Ondansetron (may limit serotonin symptoms and is the antiemetic of choice in these patients)
 - Bronchospasm
 - Usually responds to octreotide
 - β₂-agonists, theophylline, epinephrine may exacerbate it
 - Corticosteroids, inhaled ipratropium bromide and antihistamines may be safely used

PATHOPHYSIOLOGY

- Incidence of clinically diagnosed cases = 1-2/100,000 (higher at autopsy)
- Usually presents in 5-7th decade of life
- Carcinoid tumors are neuroendocrine tumors which secrete proteins and monoamines
 - Serotonin is the most common mediator released
 - O Others are histamine, bradykinin, kalikrein, substance P, prostaglandins, gastrin, corticotropin, neurokinin
 - 70-90% of tumors are found in the GI tract, the rest are in bronchi, breast, ovaries
- Metastatic lesions almost always go to the liver
- Carcinoid syndrome is seen in 2-5% patients with carcinoid tumor
- Higher incidence of carcinoid syndrome is seen with extra-GI tumors or liver mets (GI tumours release vasoactive mediators into the portal venous circulation and they are metabolized by the liver before they reach systemic circulation)
- Carcinoid heart disease = high levels of circulating serotonin causes myocardial fibrosis which affects the right side of the heart (TR, PS, plaques in vena cava, coronary sinus and PA) and may result in right heart failure
 - o Vasoactive mediators are inactivated by metabolism in the lungs so left-sided involvement is rare
- Tryptophan (essential amino acid) stores are depleted in the production of serotonin, so proteins and niacin synthesis is impaired = hypoproteinemia (hypoalbuminemia) and pellagra (dermatitis, diarrhea, dementia from niacin deficiency)
- Tumors are treated with surgery (limited response to chemo, resistant to radiation)
- 10-20% patients with carcinoid have another coexisting malignancy
- 10% of carcinoid tumors are associated with MEN-1 (parathyroid, pancreatic, pituitary)
- Common scenarios = OR for tumor de-bulking, relief of intestinal obstruction, "appendicitis", liver resection or transplant, heart valve replacement, thoracic surgery for lung or bronchial carcinoid resection
 - Occasionally, patients are undergoing surgery unrelated to their disease and carcinoid tumor is diagnosed based on intraoperative carcinoid crisis in previously undiagnosed patient
- Hepatic tumours may be treated with hepatic artery embolization in the radiology suite same anesthetic considerations and management as if they were an
 open resection plus: abdominal pain, fever, N / V +/- liver dysfunction post-procedure
- Patients at highest risk of perioperative complications are those with carcinoid heart disease and high urine levels of 5-hydroxyindoleacetic acid (5-HIAA metabolite of serotonin)
 - These complications are greatly reduced if octreotide used
 - Octreotide acetate = long-acting somatostatin analogue
 - It inhibits serotonin, gastrin, vasoactive intestinal peptide, secretin, motilin and pancreatic polypeptide release
 - Acute administration has no significant side effects
 - It can be given IV, SC or IM

REFERENCES

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