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PHARMACOLOGY PART 3A: INTERVENTIONAL MEDICATIONS IN RENAL AND BILIARY IMAGING.

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ABSTRACT

Pharmacology principles provide key understanding that underpins the clinical and research roles of nuclear medicine practitioners. Indeed, the scope of practice of the nuclear medicine technologist demands knowledge and understanding of indications, contraindications, warnings, precautions, proper use, drug interactions, and adverse reactions for each medication to be used. This article is the third in a series of articles that aims to enhance the understanding of pharmacological principles relevant to nuclear medicine. This article will build on the introductory concepts, terminology and principles of pharmacology explored in the first two articles in the series. Specifically, this article will focus on the pharmacological principles associated with interventional medications encountered in renal and biliary imaging. A companion article (3B) will examine the less commonly used interventional medications in general nuclear medicine and prototype adjunctive medications. Future articles will address the pharmacology related to nuclear cardiology, emergency trolley (crash cart), and contrast media associated with computed tomography (CT) and magnetic resonance imaging (MRI).

INTRODUCTION

Patients presenting to the nuclear medicine department may be taking medication that can interfere with the nuclear medicine procedure. Typically these represent cessation medications and the period of cessation is largely dependent on the half life of the medication combined with a clinical decision about the patients health when that medication is withheld (eg. other angiotensin converting enzyme (ACE) inhibitors when performing renal scanning in renovascular hypertension). This interference can, however, allow the nuclear medicine procedure to be enhanced by controlling the introduction of the medication, deliberately altering physiology and examining that response (eg. the role of morphine in contracting the sphincter of Oddi in biliary scanning). These represent interventional medications which may also be referred to as imaging medications. Interventional medications not only enhance the physiological process being evaluated but can also increase the sensitivity and specificity of the procedure (*1,2*). It may also be necessary to administer a medication to a patient to alter their condition in some way but without deliberately influencing the physiological response being examined (eg. sedation of a patient to gain compliance). These are referred to as adjunctive medications and will be addressed in the companion article in this edition of the *JNMT* (*3*).

The scope of practice for a nuclear medicine technologist (*4*) requires that they display a thorough understanding and knowledge of indications, contraindications, warnings, precautions, proper use, drug interactions, and adverse reactions for each medication to be used. That understanding and knowledge needs a command of the principles of pharmacology provided in earlier articles in this series (*5,6*). Indeed, the content conveyed in these previous articles should be considered assumed knowledge for this article and those that follow in the series. To that end, those foundation principles will not be redefined here. The list of medications used as either interventional or adjunctive medications is long and an exhaustive examination of all medications used in nuclear medicine is beyond the scope of this article.

The scope of practice for a nuclear medicine technologist (*4*) defines interventional (imaging) medications as those medications used to evoke a specific physiological or biochemical response used in conjunction with diagnostic imaging or therapeutic procedures (eg. captopril and dipyridamole). The same document (*4*) defines adjunctive medications as those medications used to respond to a patient's condition during a nuclear medicine procedure (eg. chloral hydrate and aminophylline). For interventional medications routinely used in renal and biliary imaging, this article will identify indications for their use, outline the dosage and administration modes, explain the mode of action and pharmacology, and describe precautions, contraindications and adverse reactions. These characteristics have been summarized in table 1 and 2.

INTERVENTIONAL RENAL SCANS

Interventional renal scans are among the most commonly performed procedures in general nuclear medicine. Diuretic and ACE inhibition renal imaging (renogram) are the principle interventional applications discussed below and summarized in table 1.

Furosemide (Lasix)

General information / drug class:

Diuretics generally increase urine volume by inhibiting reabsorption of sodium and chloride in the nephron (*7-11*). There are three main classes of diuretics and the fourth class is added to this discussion because it has an interventional application in brain scanning (figure 1):

1. Loop diuretics (eg. lasix / furosemide).
2. Thiazide diuretics (eg. hydrochlorothiazide).
3. Potassium sparring diuretics (eg. amiloride).
4. Carbonic anhydrase inhibitors (eg. acetazolamide).

Furosemide is a sulfamoylbenzoic acid based loop diuretic that increases urine volume by inhibitting reabsorption of sodium, potassium and chloride (*1,8-10,12*). While this can occur in proximal and distal tubules in the nephron, it is predominantly situated at the ascending aspect of the loop of Henle; hence the name loop diuretic (*1,8-12*). Loop diuretics are characterized by rapid onset and potent diuretic effects but typically of a short direction (*7-9*). Furosemide is active inside the lumen of the loop of Henle and, therefore, relies on adequate glomerular filtration and secretion of furosemide to have its effect (*8-10*). Consequently, furosemide may have a truncated response in renal impairment.

Increasing the flow rate of urine with furosemide allows differentiation of the obstructed kidney (post lasix clearance half life greater than 20 min), from the unobstructed kidney (post lasix clearance half life less than 10 min) and the dilated but not obstructed kidney (post lasix clearance half life between 10 and 20 min) (*13-15*). Furosemide is the diuretic of choice because it has superior peak effects (*15*).

Mode of action:

There are 2 sodium (Na^+), potassium (K^+) and chloride ($2Cl^-$) co-transporters (NKCC); $NKCC_1$ and $NKCC_2$ (*7-10*). The former is primarily involved in secretion and the latter primarily absorption; loop diuretics have an affinity for $NKCC_2$ (*7-9,11*). Transport effectively relies on simultaneous binding to all three ion sites and, thus, blockaid of just one results in inhibition (*9,10*). Furosemide binds to the chloride binding site and by doing so inhibits transport of sodium, potassium and chloride in the loop of Henle (figure 1) (*7-11,16*). The increased urinary excretion of sodium, potassium, chloride, calcium and magnesium results in low osmolality which inhibits the reabsorption of water by the kidney, increasing urine volume (*8-11,16*). A secondary effect changes the charge difference across the lumen wall which inhibits calcium and magnesium transport (*8,9*). Furosemide also releases vasodilating prostaglandins which produce short duration veno-dilation (*8-11*).

Pharmacokinetics:

Furosemide has variable oral bioavailability (10-100%) while IV provides 100% bioavailability (*9*). It has 95-99% plasma protein binding, 50% is excreted unchanged in urine and the remaining 50% is metabolized in the kidney (conjugated with glucuronic acid in kidney) (*8,9,16*). The elimination half-life is 1.5-2 hours (*9*) but this can be substantially extended in end stage renal disease (10 hours) and hepatic dysfunction (50-327 min) (*16*). After IV administration, onset of action occurs within 5 minutes with peak activity seen at 15-30 minutes and effects of significance lasting 2-3 hours (*1,8,9,16*).

Usual indications:

The clinical role of furosemide tends to be to manage edema in congestive heart failure patients (*1,2,7,8,10,11*). It can also be used to treat hypertension (*7,8,10,11,16*).

Use in nuclear medicine:

Evaluation of obstructive uropathy with renography (*1,2,12*).

Proper use and dose administration:

The standard adult IV dose is 20-40mg and pediatric doses are 0.5-1 mg/kg administered IV over 1-2 minutes (*1,2,12,15*). Given the time to peak activity, it can be administered pre-emptively 15 minutes before the administration of the radiopharmaceutical. More typically, furosemide is administered 15-20 minutes after the radiopharmaceutical if radiopharmaceutical retention in the renal pelvis is apparent (*1,2*).

Contraindications:

Furosemide is contraindicated in anuric patients, known hypersentivity (furosemide specifically or sulfonamides generally) and those significantly dehydrated or with sodium depletion (*1,9,12*).

Warnings and precautions:

Furosemide should be administered with caution to prevent injury or suture tearing in patients having recent urologic procedures (*1*). Patients should be adequately hydrated prior to administration (*1,12*). It should be used with caution in known kidney or liver disease, pregnancy, diabetes, gout and lupus (*16*). Furosemide is excreted in breast milk (*16*).

Adverse reactions:

Adverse reactions to a single dose of furosemide are usually mild and transient and include nausea, vomiting, diarrhea, dizziness, hypotension, headache, tinnuitus, rash, electrolyte imbalance and dehydration (*1,9,10*). These adverse reactions are more common in cases where furosemide is being used therapeutically. Therapeutic doses of

furosemide may also cause vision disturbance, sun sensitivity, hearing impairment, confusion, arrhythmia, limb numbness, tingling and pain, yellow eyes and skin, and abdominal pain (*7,16*). Allergic reactions are possible (*16*). Hearing adverse effects can be minimized with slower injection rates at 4mg/minute (*16*).

Common interactions:

Furusomide can enhance nephrotoxity of cephalosporin antibacterials and hearing impairment associated with aminoglycoside antibacterials (*16*). It can reduce the effect of antieplileptics like phenytoin (*16*). Cumulative effect with other diuretics can lead to electrolyte imbalance and dehydration (*16*). Hypotension can be more severe when used concurrently with ACE inhibitors or ARBs (*9*). Furosemide can increase the risk of toxicity of lithium, digoxin, cisplatin and aminoglycosides (*9,16*). Non-steroidal anti-inflammatory drugs (NSAIDs) decrease diuresis and can exacerbate side effects (*9,16*).

Captopril (Capoten)

General information / drug class:

The kidneys play an important role in blood pressure regulation through the negative feedback mechanism of the renin-angiotensin-aldosterone system (RAAS) (*7-11*). A decrease in blood flow through the kidneys (decreased arterial blood pressure) triggers a pressure gradient change between afferent and efferent arterioles in the Bowman's capsule (*8-11*). This leads to reduced glomerular filtration and release of renin which facilitates the production of angiotensin I (*8-11*). As illustrated in figure 2, an angiotensin converting enzyme (ACE) converts angiotensin I to angiotensin II leading to vasoconstriction and increased blood volume which, in turn, increases blood pressure (*7-11*). The presence of a hemodynamically significant renal artery stenosis initiates this cascade resulting in restoration of glomerular filtration (near normal renogram) and hypertension (*8,9*). A 75% stenosis is typically considered necessary for hemodynamic significance although there is variability in reported cut-offs down to 50% stenosis. Bilateral renal artery stenosis has increased renin production from both kidneys while unilateral disease has increased renin in the diseased kidney and suppressed renin production in the normal kidney.

Captorpil is an ACE inhibitor that competitively blocks the ACE to decrease blood pressure (*1,2,8-12*). While captopril is the prototype ACE inhibitor, it differs from most other ACE inhibitors in that it is not an ester prodrug (*9*). This allows more rapid onset of action and shorter duration of effect, making it ideal for an interventional study. Prodrugs like enalopril have slower onset, longer duration and, therefore, therapeutically they allow a once per day dosing regime (*9*).

Mode of action:

Captorpil blocks the conversion of angiotensin I to angiotensin II (*1,2,7-13,15*). This inhibits the compensatory vasoconstriction response in the efferent arterioles in the kidney and this leads to decreased glomeruli filtration in a kidney with a hemodynamically significant renal artery stenosis (*1,2,7,11,12,15*).

Pharmacokinetics:

Captopril has an oral bioavailability of 70-75% (*9,16*). It has 30% plasma protein binding, 40-50% is excreted unchanged in urine and the remaining 50-60% is metabolized in the liver (*9,16*). The elimination half-life is 2-3 hours (*9,16*) but this can be increased in renal dysfunction (*16*). After oral administration, onset of action occurs within 15 minutes with peak activity seen at 45-70 minutes and effects of significance lasting 6-12 hours (*1,9,16*).

Usual indications:

Captopril is not the front-line ACE inhibitor, but is used for treatment of hypertension in heart failure and post myocardial infarction (*1,7-11,16*). The properties that make it the preferred ACE inhibitor for renal imaging are the same properties that make it inferior to other ACE inhibitors for therapy. This includes onset, half life and duration of effect.

Use in nuclear medicine:

Captopril is used in conjunction with renal imaging (renogram) for the detection and characterization of the hemodynamic significance of renal artery stenosis in renovacular hypertension (*1,2*).

Proper use and dose administration:

Patients should discontinue ACE inhibitor therapy prior to the study (*1*). This should also includes angiotensin receptor blockers (ARBs). The standard dose is 25mg orally 60 minutes prior to commencement of the renal scan, however, 50 mg may be required if the requisite change in blood pressure does not occur (*1,2,12,15*). Patients should be monitored for the 60 min after captopril (blood pressure) and kept hydrated (1 litre). Improved absorption and bioavailability can be achieved by crushing the tablet prior to administration (*1*).

Contraindications:

Captopril is contraindicated where there is known hypersensitivity to captopril, and in patients with angioedema, high renin levels, dehydration, salt depletion, recent dialysis and aortic stenosis (*9,12,16*). Captopril use should be avoided during pregnancy (*7,9,16*).

Warnings and precautions:

Captopril should be used with caution in patients with scleroderma, lupus, depression, diabetes and liver dysfunction (*9*). Therapeutically, captopril is not recommended in patients with renovascular disease like renal artery stenosis, however, a single dose for an interventional procedure can be safely undertaken with patient supervision (*9,16*). Captopril is excreted in breast milk but unlikely to be harmful to a nursed infant with relative infant doses in the order of 0.02% of the mother (*16*). It should be used with caution in the elderly or those with peripheral vascular disease (*16*).

Adverse reactions:

Single doses of captopril for interventional studies may elicit a number of adverse reactions including hypotension, dizziness, tachycardia, chest pain, loss of taste, fever and a rash (*1,7-10,16*). Longer term therapy may lead to a dry cough, proteinuria, neutropenia and thrombocythemia (*1,7*). The intractable dry cough associated with ACE inhibitors is well documented, has implications for therapeutic compliance and drives some patients toward ARB therapy. The dry cough is thought to be due to incidental inhibition of the enzyme that breaks down bradykinin (*9*).

Common interactions:

Other ACE inhibitors and ARBs need to be withheld for 3 days prior to the captopril scan (*15*). This need only be 1 day if the patient is being treated therapeutically with captopril. The patient may experience severe hypotension if captopril is administered concurrently with diuretics or antihypertensive medications (*9,16*). The most serious interaction for ACE inhibitors is hyperkalemia due to the additive effect of potassium retention with diuretics and NSAIDs (*9*). Potassium sparing diuretics and any potassium

supplements should be ceased prior to ACE inhibition therapy (*9,16*). Captopril can decrease lithium and digoxin excretion and increase the risk of toxicity for both (*9,16*). Antacids reduce the bioavailability of captopril (*16*).

Enalapril (Vasotec)

General information / drug class:

Enalopril is not an ACE inhibitor itself but rather an ester pro-drug that is enzymatically converted in the liver to the active metabolite enalprilat (*1,9,11*). The principles, mode of action, usual indiations, use in nuclear medicine, contraindications, warnings and precautions, adverse reactions, and common interactions are as per captopril discussed above.

Pharmacokinetics:

Enalopril has an oral bioavailability of 60% and is rapidly biotransformed to enaloprilat (*9,16*). Enalopilat has 50-60% plasma protein binding, 90% is excreted in urine and the remaining 10% is excreted in feces (*9,16*). The elimination half-life is 11 hours (*9,16*) but is multi-phasic (*16*). After oral administration, onset of action occurs within 60 minutes with peak activity seen at 4-6 hours and effects of significance lasting 24 hours (*1,9,16*). The onset and peak times can be reduced to 15 minutes and 60 minutes respectively with IV administration (*9,16*).

Proper use and dose administration:

Enalapril can be administered by oral tablet or IV routes, however, the benefits of enalopril over captopril (more predictable action) are best demonstrated with an IV route (*1*). A dose of 0.05 mg/kg diluted in 10 mL of saline is injected IV slowly over 5 minutes (*1,2,12*). If the blood pressure drops more than 30% from baseline, the saline infusion should be increased until blood pressure is back to reference (*1*). The renal scan can be commenced at 10-15 minutes post enalapril in response to changes in blood pressure (*1,12*).

Adverse reactions:

Adverse effects from IV enalapril can be reduced using the slow IV infusion rate (5 min) and this is particularly helpful in reducing the risk of significant hypotension (*1*).

INTERVENTIONAL HEPATOBILIARY STUDIES

Interventional hepatobiliary scans are performed frequently in general nuclear medicine. Sincalide stimulation of the gallbladder and morphine augmentation are the principle interventional applications discussed below and summarized in table 2. The less commonly utilized phenobarbital intervention in the jaundiced neonate is also discussed.

Sincalide (Kinevac)

General information / drug class:

Cholecystokinin (CCK) is an endogenous, 33 amino acid polypeptide hormone secreted in the duodenum in response to a fatty meal (*9,17*). Sincalide is the exogenous active portion (octapeptide) of CCK (*2,17*).

Mode of action:

Sincalide is a synthetic peptide representing the active portion of the endogenous CCK hormone (*2,12,15,17*). CCK / sincalide is released from the duodenal mucosa in response to fat stimuli which stimulates the contraction of the gallbladder (*17*). CCK / sincalide stimulates the dorsal vagus complex which, through vagal efferents, relax the sphincter of Oddi, contract the gallbladder and stimulate bile production (figure 3). The primary mechanism for gallbladder contraction, however, is CCK / sincalide entering the bloodstream to act directly on the gallbladder. Gallbladder contraction occurs when the serum CCK / sincalide levels reach a threshold (*2,14,15,17,18*). Since gallbladder contraction only occurs when serum CCK / sincalide levels reach a threshold, IV introduction of a synthetic active portion is associated with 5 times higher potency (*2,15,18*).

Pharmacokinetics:

There is limited pharmacokinetic data available for sincalide (kinevac). Sincalide has an IV bioavailability of 100% (*9,16*). After IV administration, onset of action occurs within 5-15 minutes with peak activity seen at 40 minutes (*1,9,16*). The gallbladder should start emptying within 2 minutes of IV administration of sincalide and complete by 11 minutes (*1*). A 35% gallbladder ejection fraction or greater is considered normal (*1,2*).

Usual indications:

The usual use of sincalide is to contract the gallbladder as an adjunct to cholecystography (*16*). It has also been used as a function test of the pancreas in combination with secretin (*16*). Endogenous CCK has been used to manage obesity because CCK inhibits gastric motility and increases satiety (*8,9*).

Use in nuclear medicine:

Sincalide is used to assess gallbladder function and patency of the biliary system post gallbladder contraction including calculation of the gallbladder ejection fraction (*1,2,17,18*). Sincalide intervention can enhance the specificity of the procedure and shorten the time to reporting the study (*1,17,18*).

Proper use and dose administration:

The patient should have fasted for a minimum of 4 hours and a maximum of 6 hours to ensure that gallbladder filling of the radiopharmaceutical is not impeded by residual endogenous CCK (45 min half life) contracting the gallbladder or a full gallbladder due to absence of any endogenous CCK for a long period (*1*). The dose of sincalide is 0.02mcg/kg IV over 5 min (*1,12,15,17,18*). A larger second dose of 0.04mcg/kg diluted in 10 mL of saline administered IV over 5 min may be used if gallbladder contraction is not achieved with the first dose (*1,12*).

Contraindications:

Sincalide is contraindicated in known hypersensitivity or intestinal obstruction (*1,12*). It is contraindicated in pregnancy due to the risk of spontaneous abortion.

Warnings and precautions:

Sincalide should not be administered after morphine (*12*).

Adverse reactions:

Adverse reactions are common but transient for sincalide and include abdominal pain and nausea (*1,12,16*). Less commonly patients may experience dizziness, flushing and the urge to defecate (*1,16*). Adverse reactions can be minimized using a diluted dose (10 mL) and slow IV infusion (5 min) (*1*).

Common interactions:

There are no documented drug interactions as a result of sincalide's short lived and mild action. Morphine and other opiates should, however, be stopped for 3 half lives.

Morphine

General information / drug class:

Morphine is an opioid agonist that is mostly selective for μ receptor (OP_3) but can interact with other opioid receptors (κ and δ) at high doses (*7-11,16,18*). As an analgesic, the mechanism of action of opiods is not well understood but inhibition of substance P release from neurons is a key aspect (*8-11*). Opioid receptors are G-protein-coupled transmembrane receptors that can be activated (agonists include morphine), inhibited (antagonists include naloxone) or partially agonised (eg. buprenorphine) (*8-11*).

Mode of action:

Morphine increases smooth muscle tone, particularly the sphincters of the gastrointestinal and biliary tracts (*8,16-18*). Morphine contracts / constricts the sphincter of Oddi at the junction of the common bile duct and duodenum (figure 3) which causes back pressure in the common bile duct (*1,2,9,12,15,17,18*). The back pressure in the common bile duct will allow a patent cystic duct to fill the gallbladder with bile and radiopharmaceutical (*1,2,12,15,17,18*). In doing so, this allows differentiation of chronic cholecystitsis (incomplete cystic duct obstruction) from acute cholecystitis (complete cystic duct obstruction). It should be noted that for this intervention to be successful, there needs to be adequate clearance of the radiopahrmaceutcal from the liver after morphine administration. Newer radiopharmacetucials with rapid clearance may require a second small (top up) dose of radiopharmaceutical to avoid false positive studies for acute cholecystitis.

Pharmacokinetics:

Morphine can be administered via numerous routes but for hepatobiliary augmentation, the dose is administered IV. Sub-analgesic doses of 0.04 mg/kg IV over 3 min deliver 100% bioavailability. It has 35% plasma protein binding, 50% is metabolized in the liver (conjugated with glucuronic acid) to morphine-3-glucuronide which is inactive and excreted by kidneys (*16*). A further 5-15% is metabolized to morphine-6-glucuronide which is more potent than morphine (1-2 hour half life) (*8,9,16*). 10% is excreted in the

kidneys unchanged and 10% is excreted as conjugates in bile and feces (*16*). The elimination half-life is 2 hours (*9,16*) but morphine-3-glucuronide has an elimination half life of 2.4 to 6.7 hours (*16*). After IV administration, onset of action occurs within 5 minutes with peak activity seen at 20 minutes and effects of significance lasting 4-5 hours (*1,9,16*). Morphine crosses the placenta and enters breast milk (*16*).

Usual indications:

Morphine is primarily a strong opioid analgesic (*1,7,8,10,11*) when given in therapeutic doses. Morphine is used for the relief of moderate to severe pain and to relieve anxiety associated with severe pain (*7,8,10,11,16*). It has been used as a hypnotic for insomnia due to pain (*7,8,10,11,16*).

Use in nuclear medicine:

Morphine helps to differentiate chronic and acute cholecystitis. Morphine increases the specificity and shortens the duration of the biliary study in these patients (by avoiding delayed imaging) (*1,2,17-19*).

Proper use and dose administration:

If the gallbladder is not visualized 60 minutes after administration of the biliary radiopharmaceutical, but common bile duct and duodenum are evident, morphine could be considered to avoid delayed imaging (*1,2,12,17-20*). Morphine has no role in the non-visualised gallbladder in post cholecystectomy patients. If the duodenum is not visualized, morphine should not be administered (*1*). An IV administration over 1-3 minutes of 0.04 mg/kg of morphine is the standard dose with imaging continuing for 30 minutes (*1,2,17-20*).

Contraindications:

While the doses being used in this interventional application are sub-analgesic, morphine remains contraindicated in patients with a known allergy to morphine and respiratory depression (*1,12,16,19*). It should not be used in the comatosed patient (*16*).

Warnings and precautions:

Morphine should be used with caution in patients with seizures, head injuries, asthma, chronic lung disease, hypothyroidism, adrenocortical insufficiency, pheochromocytoma, kidney or liver dysfunction, prostatic hyperplasia, hypotension, shock, inflammatory or obstructive bowel disorders, myasthenia gravis and pancreatitis (*1,9,16*). Caution should be employed in cases of opioid addiction (*16*). Caution should also be exercised in pregnancy and morphine is excreted in breast milk (*16*).

Adverse reactions:

While severe adverse reactions are uncommon with sub-analgesic doses, a number of adverse reactions can occur including repiratory depression, dizziness, drowsiness, sedation, nausea, vomiting, constipation, and sweating (*1,7-10,16,19*). With longer term use patients may experience dry mouth, facial flushing, headache, vertigo, bradycardia, tachycardia, palpitations, orthostatic hypotension, hypothermia, restlessness, changes of mood, decreased libido, hallucinations and miosis (*7,8,16*). Large doses of opioids produce respiratory depression and hypotension; circulatory failure and coma are possible (*7,16*). Morphine has a dose-related histamine-releasing effect (unlikely to be of significance in biliary scan doses) that can cause urticaria, pruritus and hypotension (*16*).

Common interactions:

Therapeutic doses of narcotic analgesics need to be ceased for 5 half lives to avoid interference with the biliary scan (*15*). While morphine augmentation studies employ sub-analgesic doses, consideration should be given to potential interactions with other medications. Morphine interacts with alcohol and other central nervous system (CNS) depressants to enhance respiratory and CNS depression, and hypotension (*9*). Monoamine oxidase inhibitors can enhance the effects of morphine and rifampicin can reduce analgesic effects of morphine (*9,16*). There is an additive effect with benzodiazepines and H_2 histamine anatagonists inhibit morphine metabolism (*16*). Clomipramine and amitriptyline increase the plama availability of morphine (*16*).

Naloxone is a narcotic antagonist and can be used with doses of 0.4 mg IV as an adjunctive medication in response to a severe allegric reaction to morphine (*1*).

Phenobarbital (Luminal):

General information / drug class:

Phenobarbital is a long acting barbiturate sedative and hypnotic that acts through $GABA_A$ receptor agonism (positive modulation) (*10,21*). It also acts as an anticonvulsant (*8,10,21*).

Mode of action:

Phenobarbital enhances and accelerates radiopharmaceutical excretion by the biliary system which allows differentiation of biliary atresia from neonatal hepatitis in the jaundiced neonate (*15*). Phenobarbital enhances the entire hepatic transport system independently of vagal induction (*15*). Phenobarbital induces microsomal enzymes in the liver which increases uptake and excretion of a number of compounds including bilirubin (figure 3) (*1,12*). Consequently, phenobarbital enhances biliary excretion (including biliary radiopharmacetuticals) if the biliary system is patent but not in biliary atresia (*1,12*).

Pharmacokinetics:

Phenobarbital has significant variability with respect to pharmacokinetics. Phenobarbital has an oral bioavailability of 90% (*16*). It has 45-60% plasma protein binding, 25% is excreted unchanged in urine and the remainder is only partially metabolized in the liver (*16*). The elimination half-life is 75-120 hours (*16*). After oral administration, onset of action occurs within 30-60 minutes with peak activity seen at 2-12 hours and effects of significance lasting 4-48 hours (*1,16*).

Usual indications:

Phenobarbital is used as an anti-epileptic to control partial and generalized tonic clonic seizures (*10,16*). It can also be used in the emergency management of acute seizures (*10,16*).

Use in nuclear medicine:

To differentiate biliary atreasia from neonatal hepatitis in the jaundiced neonate and to increase the sensitivity and specificity of the procedure (*1,2*).

Proper use and dose administration:

Phenobarbital is administered orally for 5 days prior to the biliary study at a dose rate of 5mg/kg/day usually split into 2 doses (ie. 2.5mg/kg twice daily for 5 days) (*1,2*).

Contraindications:

Phenobarbital is contraindicated where there is a known allergy to it and in patients with severe respiratory depression (*1,2,16*).

Warnings and precautions:

Caution should be exercised in children and elderly, acute pain and in depression (*16*). Caution is also required for impaired liver, kidney or lung function (*16*).

Adverse reactions:

While sedation is the most common adverse reaction, phenobarbital can produce a number of common side effects including respiratory depression, drowsiness, lethargy, rash, nausea, vomiting and a paradoxical hyper-excitement in pediatrics (*1,8,10,12,16*). Mood changes and depression can be seen with longer term use (*16*). Nystagmus and ataxia might occur at high doses (*16*). Hypersensitivity is uncommon but can occur (*16*).

Common interactions:

By virtue of the role of phenobarbital in activating microsomal enzymes in the liver, it can have a significant negative effect on drugs metabolized in the liver including analgesics, antibacterials, antiarrythmics, antidepressants, antiepileptics, antipsychotics, antivirals, beta blockers, calcium channel blockers, digoxin, ciclosporin, diuretics, theophylline and some vaccines (*16*). Phenobarbital effects can be enhanced by CNS depressants and alcohol (*16*).

CONCLUSION

An understanding of basic pharmacology for renal and biliary interventional medications allows enhanced practice. Specifically, this deeper understanding of pharmacology, indications, contraindications, warnings, precautions, proper use, drug interactions, and adverse reactions for each medication to be used ensures the nuclear medicine technologist meets the minimum capabilities for their scope of practice (*4*). This in turn translates to safer practice and better patient outcomes.

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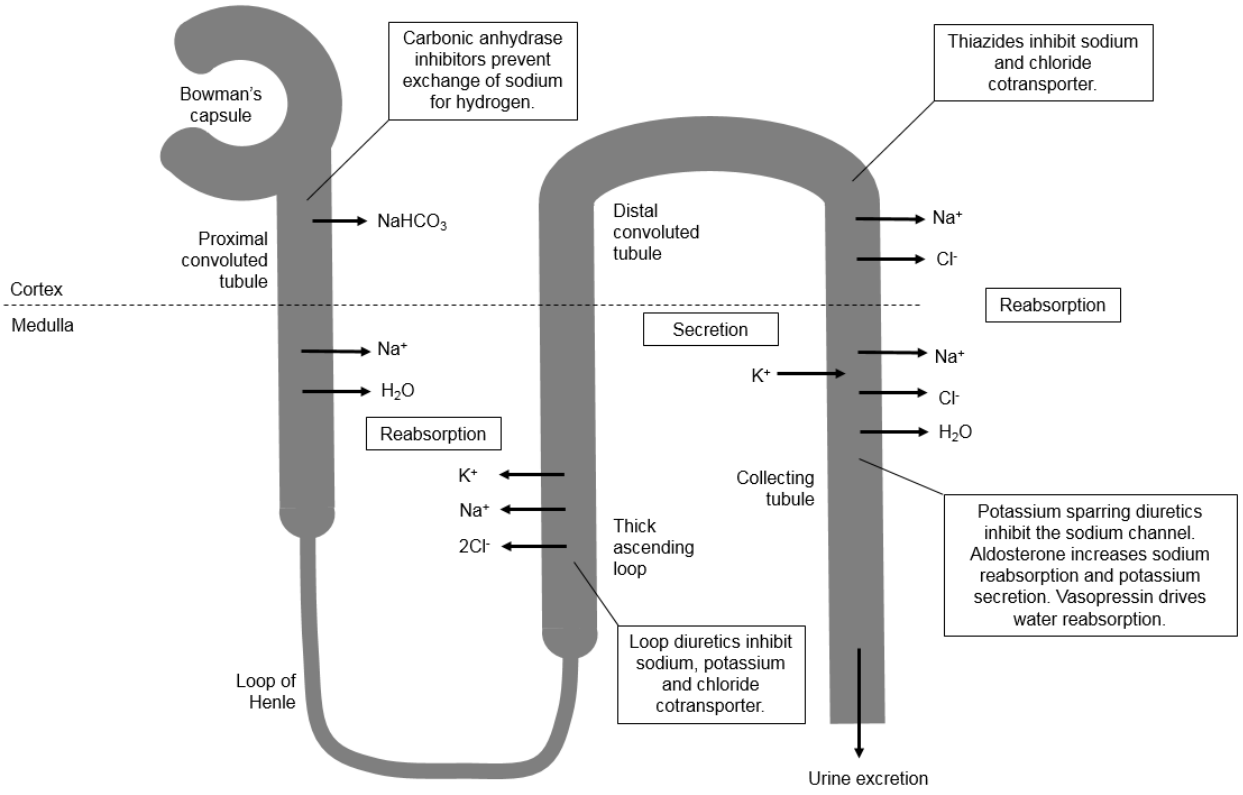

Figure 1: Schematic representation of the sites of action of different classes of diuretics. Furosemide is a loop diuretic acting on the thick ascending loop of the loop of Henle in the nephron.

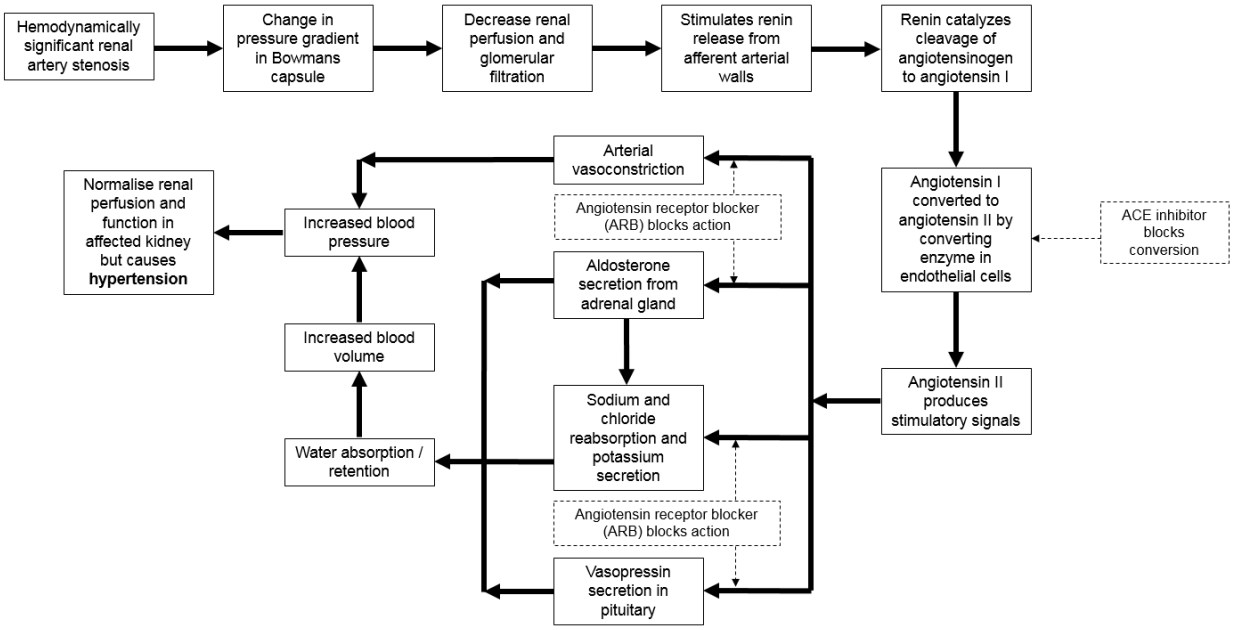

Figure 2: Flow chart of RAAS response to decreased blood flow (solid lines). Inhibition of this response can be undertaken (dashed lines) by ACE inhibitors acting to prevent conversion of angiotensin I to angiotensin II or by ARBs antagionising the angiotensin receptor at the numerous sites of action.

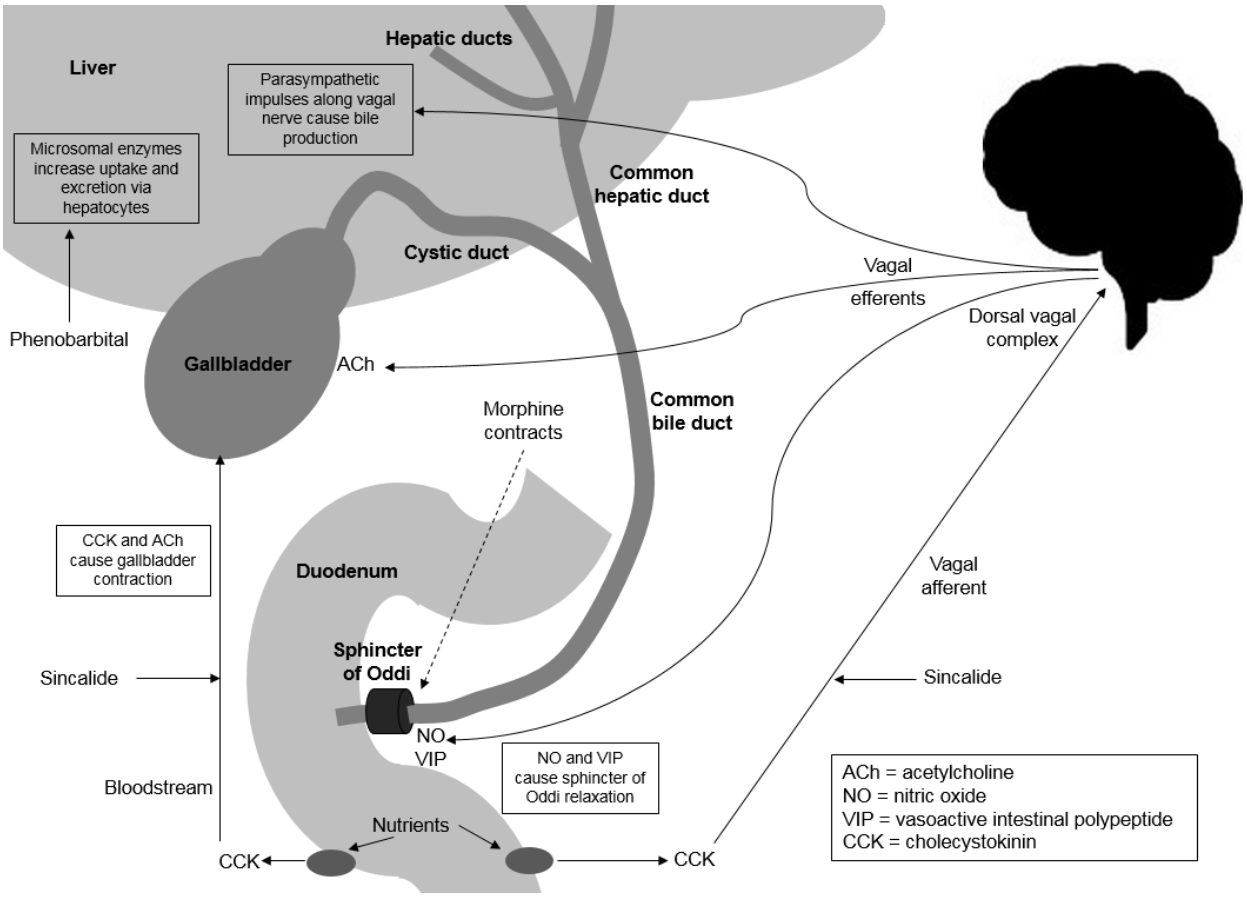

Figure 3: Schematic representation of the release of CCK to produce gallbladder contraction directly and via vagal afferents. The implications of exogenous sincalide are demonstrated. The relaxation (CCK) and contraction (morphine) effects on the sphincter of Oddi are illustrated. Phenobarbital stimulation of biliary excretion independently of the vagal nerve is also illustrated.

Table 1: Interventional medications used in renal scanning (*1,2,7-12,14-16,21*). Duration is the period of significant or measurable effect. Some adverse effects are more likely when used therapeutically than in single interventional doses.

Drug	Indication	Dose	Pharmacokinetics	Mechanism of Action	Contraindications / Cautions	Adverse Effects / Interactions
Furosemide	Diuretic challenge for obstructive uropathy on renal scan	20-40mg IV in an adult and 1 mg/kg IV over 1-2 min for pediatrics	• 5 min onset • Peak 15-30 min • Half life 1.5-2 hours • Duration 2-3 hours • 99% plasma protein bound	Loop diuretic by inhibiting sodium, potassium and chloride transport in the ascending portion of loop of Henle.	Contraindicated in anuria, sulphonamide hypersensitivity, and sodium or fluid depletion. Caution in kidney or liver disease, diabetes, gout, lupus, pregnancy, and after urologic procedures.	Tinnitus, allergic reaction, nausea, vomiting, dizziness, blurred vision, headache, hypotension, dehydration. Potential interactions with aspirin, diuretics, digoxin, lithium, antihypertensives and NSAIDs.
Captopril	Renal artery stenosis in renovascular hypertension renal scan	25-50mg tablet orally 60 min before renal scan	• 15 min onset • Peak 45-70 min • Half life 2-3 hours • Duration 6-12 hours • 30% plasma protein bound	Blocks conversion of angiotensin I to angiotensin II, blocking blood pressure compensation and reducing glomerular filtration.	Contraindicated in angioedema, high renin levels, dehydration, salt depletion, recent dialysis, aortic stenosis, pregnancy and hypersensitivity. Caution in scleroderma, lupus, depression, diabetes, liver dysfunction, peripheral vascular disease and dialysis.	Hypotension, dizziness, tachycardia, chest pain, loss of taste, fever and rash. Can cause a dry cough. Potential interactions with other ACE inhibitors or ARBs, diuretics, hypertensives, NSAIDs, digoxin and litium.
Enalopril		Oral dose 20-40mg 0.04 mg/kg in 10mL of saline IV over 3-5 min to maximum dose of 2.5mg	• 60 min onset • Peak 4-6 hours • Half life 11 hours • Duration 24 hours • 50-60% plasma protein bound If given IV, onset is 15 min and peak effect is 1 hour.	As for captopril except enalopril is an ester prodrug converted to enaloprilat in the liver after absorption.		

Table 2: Interventional medications used in biliary scanning (*1,2,7-12,14-16,21*). Duration is the period of significant or measurable effect. Some adverse effects are more likely when used therapeutically than in single interventional doses.

Drug	Indication	Dose	Pharmacokinetics	Mechanism of Action	Contraindications / Cautions	Adverse Effects / Interactions
Sincalide	Gallbladder ejection fraction on biliary scan	0.02 mcg/kg in 10 mL of saline IV over 3-5 min	• 5-15 min onset • Peak 40 min • Limited data	Synthetic active portion of CCK stimulates gallbladder contraction and relaxes sphincter of Oddi.	Contrainicated in known hypersensitivity, intestinal obstruction and pregnancy (spontaneous abortion). Caution with opioids.	Abdominal pain, nausea, dizziness, flushing, urge to defecate, and allergic reaction. No documented interactions.
Morphine	Differentiation of acute and chronic cholecystitis on biliary imaging	0.04 mg/kg in 10 mL of saline IV over 1-2 min (range of 2-4.6 mg). Note this is subanalgesic dose.	• 5 min onset • Peak 20 min • Half life 2 hours • Duration 20-50 min • 35% plasma protein bound	Opioid agonist that constricts sphincter of Oddi to increase pressure in common bile duct.	Contraindicated in known hypersensitivity, respiratory depression and the comatosed patient. Caution in renal or liver impairment, pregnancy, seizures, head injuries, asthma, hypotension, hypothyroidism, pheochromocytoma, addiction and dyspnea.	Respiratory depression, hypotension, vomiting, dysphoria, urinary retention, dizziness, sedation, nausea and constipation. Potential interactions with narcotic analgesics, CNS depressants, benzodiazepines, and Monoamine oxidase inhibitors.
Phenobarbital	Biliary imaging	2.5mg/kg/ twice daily orally for 5 days prior to study	• 30-60 min onset orally • Peak 2-12 hours • Half life 75-120 hours • Duration 4 hours to 2 days • 45-60%% plasma protein bound	Increases radiotracer uptake and biliary excretion by inducing hepatic enzymes.	Contraindictaed in known allergy to phenobarbital and severe respiratory depression. Caution in liver, kidney or lung dysfunction, the elderly, children and in acute pain.	Sedation, anxiety, respiratory depression, vomiting, dizziness, nausea, headache, and paradoxical excitement. Potential interactions with drugs metabolsied by the liver and CNS depressants.