ISSN 1391-0736

The Sri Lanka Prescriber

March 2008; Volume 16, No. 1

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The Sri Lanka Prescriber is sponsored by the State Pharmaceuticals Corporation of Sri Lanka as a service to the medical profession.

The Sri Lanka
Prescriber

Copies of the *Sri Lanka Prescriber* and inquiries from M. P. Kuruppu, Deputy General Manager, Marketing, and Ms Sujathi Jayaratne, Manager/Marketing, State Pharmaceuticals Corporation, P. O. Box 1757, 75, Sir Baron Jayathilake Mawatha, Colombo 1. Telephones 2328507, 2435441.

Price per copy Rs 50.00 (students Rs 25.00). Personal callers may also obtain copies from the Departments of Pharmacology at the Medical Faculties in Colombo, Galle and Sri Jayewardenepura.

Published by

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Printed by

Ananda Press
82/5, Sir Ratnajothi Saravanamuttu Mawatha,
Colombo 13.
Telephone: + 94 11 2435975
E-mail: anpress@sltnet.lk

Should beta blockers remain first-line drugs for hypertension?

Interpretation of the evidence

Although regarded as high level evidence, meta-analyses are only as useful as the trials they include. Meta-analyses that include heterogeneous trials, even when this is accounted for in the statistical modelling, need to be interpreted cautiously. In many ways they should be regarded as hypothesis generating rather than hypothesis proving.

Conclusion

It is unlikely there will ever be a single ideal first-line drug for hypertension and most patients will eventually need multiple drugs to control their blood pressure. Treatment needs to be individualised for all patients.

The choice of treatment should be influenced not only by underlying cardiovascular risk factors, comorbidities and potential adverse effects, but also by the age of the patient. Beta blockers remain a viable option in the treatment of hypertension and they should not necessarily be discontinued if the clinical condition is stable and controlled or if there is another indication for their use.

Conditions where beta blockers are useful or indicated

- Ischaemic heart disease – angina (stable and unstable), postmyocardial infarction
- Tachyarrhythmias – supraventricular and ventricular tachycardia, atrial fibrillation, atrial flutter
- Chronic heart failure
- Palpitations
- Anxiety
- Essential tremor
- Migraine
- Glaucoma
- Thyrotoxicosis
- Portal hypertension

Elsik M, Krum H. Should beta blockers remain first-line drugs for hypertension? *Australian Prescriber* 2007; **30**: 5-7.

(Published courtesy of *Australian Prescriber*, by special arrangement)

Cover picture

The first official pharmacopoeia (1498 A.D.)

The first governmentally sanctioned Pharmacopoeia was published in Florence in 1498. Physicians and Pharmacists collaborated in preparing it; and the monk, Savonarola, current Florentine leader, served as political advisor.

One of a series: *A History of Pharmacy in Pictures*, presented by Parke, Davis & Company.

George A. Bender, Director Robert A. Thom, Artist

Quality assurance of medicines

Quality assurance is essential to ensure cost-effective outcomes from the use of medicines. There are procedures in place to ensure the quality of medicines in government and private sectors. They include the following steps.

1. Pre-marketing quality assurance through registration
2. Pre- and post-shipment inspections
3. Proper storage and transport
4. Appropriate dispensing
5. Product problem reporting

1. Registration

Medicine registration procedure usually includes three essential steps to assess the quality of a finished pharmaceutical product: a) manufacturing plant inspection b) document evaluation c) quality testing of samples.

Manufacturing plant inspection

Every local manufacturer is inspected annually by the Ministry of Health for renewal of the licence. The quality of a final medicinal product is determined by compliance with the Good Manufacturing Practices (GMP) by the manufacturer. These standards are often specific to individual dosage forms. WHO has established standards for GMP which are similar to those enforced by national medicine regulatory agencies of developed countries. They include criteria for personnel, facilities, equipment, raw materials (both active and inactive), manufacturing operations, packaging, labelling, stability testing, quality control and documentation. A GMP inspector should be appropriately qualified and knowledgeable in all these aspects. In addition, some regulatory agencies require the inspectors to possess experience in pharmaceutical manufacture.

National medicine regulatory agencies of 138 countries have agreed to participate in the WHO certification scheme on the quality of pharmaceuticals moving in international commerce. They have agreed to certify that drug products are registered in the exporting country, that the manufacturer's facilities have been inspected and that they comply with GMP. The reliability of the WHO certification scheme depends on:

- the reliability of the medicines regulatory agency of the exporting country and,
- capability of the medicines regulatory agency of the exporting country to perform inspection according to the requirements of the certification scheme.

The authenticity or the validity of the certificates submitted by importers is doubtful in many cases. Collaboration among the medicine regulatory agencies of importing and exporting countries is extremely useful in such situations.

Document evaluation

This is a procedure to assess the quality of the product by evaluating manufacturing and quality control data, stability reports, packaging, labelling and the various certificates included in the registration application.

Sample testing

Often testing of samples of all the products submitted for registration is not possible because resources are limited. Laboratory testing is costly in terms of human resources, equipment and reagents, so priorities can be set based on the following criteria.

- Drugs with a low therapeutic index
- Drugs with inherent bioavailability problems
- Modified release preparations
- Products from new suppliers and suppliers with problems in the past

2. Pre- and post-shipment inspections

The quality of products received needs to be verified as soon as possible after arrival both by physical inspection of each shipment and by laboratory testing of selected products. Selection can be based on the credibility of the manufacturer and products which are vulnerable to quality problems. WHO advocates a system of economical, less technically demanding, basic tests for commonly used drugs, that can be done in simple laboratories.

3. Proper storage and transport

Procedures to help maintain drug quality begin with proper storage at the port and prompt release. Stability of a drug product can be affected to a great extent by processes such as oxidation, hydrolysis and photo-chemical reactions. Environmental factors such as temperature, humidity and light are the main causes for these reactions. Appropriate storage conditions are needed to ensure maintenance of potency, to prevent deterioration, spoilage and degradation, and to maintain physical integrity. Most drugs can be kept at uncontrolled room temperature. If the product has no special instructions, normal storage conditions apply. This means storage in dry, clean, well-ventilated premises at temperatures up to 30°C. Less stable drugs must be stored in specific conditions to maintain their effectiveness and to prevent contamination. Storage conditions are product specific. Different brands of the same generic drug may have different storage requirements because of different packaging or formulation. The storage conditions recommended by a manufacturer for a product are always related to the shelf-life assigned to it. Therefore manufacturer's storage recommendations should be followed. The following categories of drugs require special storage facilities.

- Products that must be kept frozen (-10° to -20°C).
- Products sensitive to heat that require refrigeration (2°-8°C).
- Products that have a reduced shelf-life at uncontrolled room temperature and need mechanical ventilation or air-conditioning (15°-25°C).

Distribution of medicines should be done strictly according the government regulations on transport of medicines. Appropriate storage conditions should be maintained in the vehicles used for transport, and it should be done under the custody of a reliable person.

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4. Appropriate dispensing

Inappropriate dispensing procedures contribute to drug product deterioration and contamination, or medication errors. The following procedures help maintain the quality of drug products:

- use of proper dispensing containers. (The paper envelopes often used for dispensing do not protect tablets and capsules. Sometimes airtight or light resistant containers are necessary).
- clear labelling (with name of patient, name of drug, strength, instructions for use and storage, and expiration date).

The prescriber and dispenser should counsel the patient on the proper use of medications. They should explain what the drug is, why the patient needs it, how to take it and where and how to store it until treatment is completed.

5. Product problem reporting

It is important that all healthcare providers report suspected lapses in drug or packaging quality to the Ministry of Health. All reports should be carefully analysed using laboratory testing as required, and appropriate action must be taken. The reporter should be informed about the results and the action taken, even if products are not defective, to encourage such reporting.

Reference

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Management of deep leg vein thrombosis

The lack of simple non-invasive diagnostic facilities for venous thromboembolism (VTE) and the high prevalence of microfilaria in blood samples at screening in Sri Lanka contributed to the belief that most extremity swellings in our population were filarial. The availability of duplex ultrasound in the last decade has been a revelation, and it is now clear that deep vein thrombosis (DVT) is an important cause of morbidity and mortality among Sri Lankans, probably similar to its prevalence in the western world.

Treatment for established venous thrombosis

Before the introduction of heparin, symptomatic thromboses of deep leg veins progressed from calf to thigh or to the opposite leg in about 60%, embolised in about 40%, and about half the patients with pulmonary embolism died. With the introduction of immediate heparin and long term warfarin, expected symptom progression or embolism is less than 5%. Deaths from pulmonary embolism should be below 2%.

The result of inadequate initial therapy is an increased risk of extension, recurrence and embolism – a constant finding of thrombosis treatment trials regardless of whether the fault was too little or no heparin at the beginning. Why too little heparin at the start should lead to recurrence weeks or months later, when the patient is taking an oral anticoagulant remains unknown.

Although VTE in patients who are known to be at high risk (surgery, injury, acute medical illness) can be largely prevented with compression stockings and a single daily subcutaneous injection of heparin, a majority of patients with VTE have no apparent predisposition.

Diagnosis

All patients with clinically suspected VTE must have appropriate diagnostic testing to confirm the diagnosis. Clinical suspicion alone is insufficient, since symptoms and signs of VTE are highly non-specific. Ultrasound imaging is the investigation of choice for proximal (popliteal or femoral) vein thrombosis, but venography is important in suspected calf vein thrombosis (where ultrasound is relatively insensitive), or in recurrent disease. A negative ultrasound examination for calf symptoms should be followed by a repeat examination during the following week to rule out extension of an undetected calf clot. A normal lung scan rules out pulmonary embolism, and a 'high probability' ventilation-perfusion lung scan is sufficient evidence to treat. Venous ultrasound imaging, spiral CT-scanning or pulmonary angiography may help to guide management in patients with a 'non-diagnostic' lung scan.

Anticoagulant therapy: benefits and risks

Deep leg vein thrombosis is a strong indication for anticoagulant therapy because of the high risk of early extension and embolism, and of subsequent recurrence. The bleeding risk is highest soon after surgery. It is increased by old age, low body weight, female gender, and malignancy, although none of these is an absolute contraindication. Interruption of the vena cava (see below) is an alternative to anticoagulant therapy within 24-48 hours of major surgery, or when there is active bleeding. There is a need for extra care with laboratory control of standard heparin and warfarin therapy if the bleeding risk is high.

Standard heparin

Regimens of administration of heparin vary, but a typical regimen would be an initial intravenous bolus of 5000 IU, followed by a continuous infusion. Infusion starts at about 1000 IU per hour, and is adjusted to prolong the activated partial thromboplastin time (APTT) to 1.5-2 times the control level or about 50-80 seconds (depending on the laboratory reagent used). Twice daily subcutaneous heparin, starting with 12 500-15 000 IU, and adjusted according to the APTT 4 hours after injection, is also effective. This method is not routinely recommended as the dose requirement is too variable and dose adjustment too cumbersome.

Low molecular weight heparins

These are much simpler to use than standard heparins. Given once or twice daily by subcutaneous injection, with the dose adjusted for weight as recommended, there is usually no need for monitoring. The antifactor Xa activity varies little between individuals and the APTT is not useful. Excretion is predominantly renal, so there is

a case for measuring antifactor Xa activity in renal failure, although this test is weak at predicting bleeding or recurrent thrombosis.

Recent large trials indicate that low molecular weight heparins, given once or twice daily, and standard heparin produce similar results.

Oral anticoagulants

Warfarin is started together with heparin or a low molecular weight heparin. The dose required varies so much between individuals that much depends on trial and error, although dose-response algorithms help. One popular regimen is to give a first dose of 10 mg followed by 5 mg on the next day, with subsequent doses adjusted to achieve an international normalised ratio (INR) of 2-3. Starting with 5 mg/day is advisable in the elderly and the maintenance dose is often quite small. Heparin can be stopped after a minimum of 4 days and once the INR has been greater than 2.0 for 2 consecutive days.

Warfarin is continued for 3-6 months. Three months is usually enough for calf vein thrombosis and when patients have a clear-cut predisposing event such as surgery. Six months is probably better for extensive thrombosis, and in patients with 'idiopathic' thrombosis where the risk of recurrence is greater and lasts longer. Those with 'idiopathic' thrombosis may warrant treatment beyond 6 months. Prolonged treatment is required when there is an ongoing underlying hereditary or acquired thrombophilia (a 'hypercoagulable' state).

Failure of anticoagulant therapy

Some of the most difficult management dilemmas result from major bleeding or clinically suspected recurrent thrombosis during anticoagulant therapy.

Major bleeding is best handled by stopping the anticoagulant and reversing its effects. This means vitamin K and clotting factor replacement for warfarin, and protamine sulphate for standard heparin. Low molecular weight heparins have no complete antidote, although protamine sulphate has some effect. A vena cava filter is considered when the risk of embolism is high.

In clinically suspected recurrence or extension, objective confirmation is essential. Usually, this rules out recurrence as it is quite rare when anticoagulant treatment has been adequate, and there is no underlying malignancy. If diagnostic tests confirm or fail to rule out recurrence, then the options include better heparin or warfarin control, a switch from warfarin to heparin or a low molecular weight heparin, or from standard heparin to a low molecular weight heparin, or caval interruption.

Treatment of leg vein thrombosis at home

Patients can be taught to self-inject a fixed, weight-adjusted dose of low molecular weight heparin at home. Two recently published large randomised trials of home treatment for proximal (femoral or popliteal) deep vein thrombosis have found that this gives results similar to those obtained in hospital with intravenous standard heparin (panel). Recurrence and bleeding were not significantly different when patients were treated at home. The patients managed at home felt, on average, better about their illness. Economic analysis overwhelmingly favours home therapy.

The enthusiasm for home treatment must be tempered with caution. Patients enrolled in clinical trials were carefully selected because of their willingness to be managed at home and low bleeding risk. Plans for home treatment must include contingencies for handling recurrence and bleeding. Starting warfarin requires daily blood tests until the maintenance dose is known. Clinically suspected thrombosis should not be treated without objective confirmation, just because home treatment is simple. In Sri Lanka home management of venous thrombosis using the well established public health nurse network may be feasible and needs to be explored.

Calf vein thrombosis: to treat or not to treat?

There is a debate about whether or not patients presenting with symptomatic calf vein thrombosis require treatment.

There is a high clinical recurrence rate during the next 3 months if patients with symptomatic calf vein thrombosis are managed with short term unfractionated heparin treatment in hospital alone, and are not given warfarin therapy. This is quite unlike the natural history of the small and asymptomatic calf clots frequently detected after surgery by routine screening tests during thrombosis prevention trials, which usually resolve without clinical complications. Symptomatic calf vein thrombosis is not a clinically trivial event, and should be treated with heparin followed by warfarin.

Panel

Treatment of proximal vein thrombosis with twice daily subcutaneous (sc.) low molecular weight heparins (LMWH) at home, compared with continuous intravenous (iv) infusion of heparin in hospital. Incidence of major bleeding and recurrence, extension or embolism (VTE) during 3 months of follow up while taking warfarin

Drug	sc. LMWH	iv. heparin
Enoxaparin (1 mg/kg):	patients = 247	patients = 253
• treated entirely at home	120	0
• days in hospital for inpatients	2.2 ± 3.8	6.5 ± 3.4
• recurrent VTE during 90 days	13 (5.3%)	17 (6.7%)
• major bleeding during heparin	5 (2.0%)	3 (1.2%)
Nadroparin (weight-based*):	patients = 202	patients = 198
• treated entirely at home	72	0
• discharged within 48 hours	44	0
• recurrent VTE during 90 days	14 (6.9%)	17 (8.6%)
• major bleeding during 90 days	1 (0.5%)	4 (2.0%)

* dose if <50 kg = 4100 IU; if 50-70 kg = 6150 IU; if >70 kg = 9200 IU

Thrombosis and embolism in pregnancy

About one-third of venous thromboses or pulmonary embolisms arise during the pregnancy, but the majority occur soon after delivery and up to six weeks thereafter. Warfarin crosses the placenta but standard or low molecular weight heparins do not. Warfarin during the first trimester is teratogenic, and at the end of pregnancy causes fetal as well as maternal bleeding. Recommended treatment for confirmed thrombosis during pregnancy is standard heparin, although increasing experience with subcutaneous low molecular weight heparins indicates that they are also effective and relatively safe. Warfarin is safe during lactation although it is present in breast milk.

The major concerns about the prolonged use of high-dose standard heparin therapy in pregnancy are osteoporosis and heparin-induced thrombocytopenia. These complications seem much less with low molecular weight heparins.

Thrombolytic therapy or surgery for deep vein thrombosis?

The aim of thrombolytic therapy is to achieve clot lysis soon enough to preserve delicate vein valves and so prevent post-phlebitic venous insufficiency. Repeat venography done after 3-5 days of streptokinase infusion shows total lysis in about 30% of patients treated within 5 days of the start of symptoms, partial lysis in about 30% and no lysis in the rest. Results with tissue plasminogen activator have been no better, the bleeding risk is high, and there has been little clear-cut evidence of long term benefit in the small clinical follow up

studies done to date. As a result, thrombolytic therapy is considered only in young people with a low bleeding risk seen soon after the onset of extensive thrombosis. Thrombectomy may have a place in patients with impending venous gangrene.

Placing a filter in the inferior vena cava may be appropriate when anticoagulants have failed because of recurrence or bleeding, or when they are contraindicated because of active bleeding or a very high bleeding risk. There is no good evidence that the venographic or ultrasound image of a 'floating' thrombus indicates an unusually high risk of embolism, and this appearance alone is not an indication for interrupting the vena cava or for thrombectomy.

Further reading

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Gastro-oesophageal reflux disease

This is the commonest oesophageal disorder. One-third of the population will experience symptoms of gastro-oesophageal reflux disorder (GORD) at least once in 6 months. It should only be considered a disease when the symptoms are sufficiently severe to impair the quality of life or when there are complications [1]. Reflux oesophagitis should only be diagnosed when endoscopy reveals that the oesophageal mucosa is breached by the action of refluxed contents.

Aetiology

In most patients reflux occurs as a result of defective neural control of the lower oesophageal sphincter. Hiatus hernia is common in patients with reflux disease and it causes displacement of the sphincter. The hiatus formed by the diaphragmatic crura provides extrinsic support to the sphincter and helps to maintain gastro-oesophageal competence especially during straining.

Panel 1. Factors predisposing to GORD

Disordered anatomy	Hiatus hernia
	Obesity
	Surgery for achalasia
	Oesophageal stent
Myogenic	Systemic
Hormonal	Pregnancy
External influences	Smoking
	Ingestion of fat or chocolate
	Coffee/tea
	Alcohol
	Large meals
	Drugs
	Large meals

Diagnosis and assessment of severity

The history is pivotal for diagnosis because of the lack of an inexpensive diagnostic test. Upper gastro-intestinal endoscopy (UGIE) is the first choice for diagnosis as it can grade oesophagitis. Biopsy is useful to diagnose columnar metaplasia. However, a negative endoscopy does not exclude GORD as most of the patients do not have evidence of mucosal damage.

Oesophageal manometry and ambulatory pH monitoring are useful in patients with troublesome symptoms without endoscopic signs of oesophagitis. Patients who are being considered for anti-reflux surgery should also undergo oesophageal pH monitoring.

Treatment

Life-style modifications. Obesity is a major causal factor and weight loss is beneficial for the obese. Raising the head end of the bed by 20cm or more discourages nocturnal acid reflux. Avoidance of heavy meals, especially at night, is also useful. Coffee, chocolates and fatty foods lower the lower oesophageal sphincter (LOS) pressure and therefore should be avoided. Drugs such as calcium channel blockers and nitrites should be avoided. Smoking should also be discouraged (panel 1).

Drug treatment. In mild cases an antacid taken before meals is useful. In patients with persisting symptoms a proton pump inhibitor combined with a prokinetic drug for 6-8 weeks is useful. Proton pump inhibitors (PPI) reduce gastric acid secretion. Prokinetic drugs increase the LOS tone and stimulate gastric emptying. Relapse after stopping treatment occurs in 30-80% of patients with erosive oesophagitis. They require maintenance therapy with an antacid or a PPI for 6-12 months. There have been concerns about the safety of long term acid suppression ever since the introduction of histamine-2 receptor antagonists. So far, follow up of patients treated for 10 years or more with acid suppression has shown no evidence of significant ill effects.

Surgery. The aim of surgical treatment of GORD is the restoration of cardio-oesophageal competence and control of hiatus hernia. The operation involves fundoplication ie. wrapping the fundus of the stomach around the lower oesophagus. This creates a high pressure zone in the lower oesophagus which reduces reflux. The operation can be performed either laparoscopically or by open

Panel 2. Treatment of GORD and oesophagitis

Simple measures
- Lose weight
- Raise head end of bed on blocks
- Avoid bending

Avoid aetiological factors which reduce LOS pressure
- Smoking
- Ingestion of fat or chocolates
- Coffee/tea
- Alcohol

Drugs to reduce gastric acid secretion
- H2 receptor antagonists (cimetidine, ranitidine, famotidine)
- Proton pump inhibitors (omeprazole, pantoprazole, lansoprazole)

Drugs to increase gastric emptying and LOS tone
- Metoclopramide
- Domperidone

Drugs to protect oesophageal mucosal lining
- Alginic acid containing antacid
- Carbenoxolone

Drugs to neutralise gastric acid
- Antacids

Surgery

surgery. At present it is the most widely practiced surgical approach for GORD. Surgery is most beneficial in patients who have had recurrent progressive oesophageal injury despite medical treatment. Patients having reflux induced asthma respond poorly to PPI and may benefit from surgery. The advantages of anti-reflux surgery should be balanced against the risk of complications. Recognised complications include dysphagia, gastric perforation, left-sided pneumothorax, pneumomediastinum, and rarely intraoperative bleeding from the inferior vena cava, left hepatic vein, inferior phrenic artery or abdominal aorta [2].

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Management of renal colic

Introduction

Renal colic is one of the most common presentations at emergency units. It causes significant patient morbidity, and imposes a heavy burden on healthcare expenditure. Most patients can be managed non-surgically, but a few will need intervention to prevent morbidity such as recurrent pain and renal impairment.

Presentation

Renal or ureteric colic occurs due to obstruction of the upper urinary tract ie. either at calyceal level, the pelviureteric junction or the ureter. The pain radiates from the flank, along the lateral and anterior aspects of the abdominal wall to the groin and perineal region. The symptoms may provide a clue to the position of the stone eg. renal stones will cause upper abdominal pain whereas lower ureteric stones will cause pain which radiates towards the groin. Stones impacted at the vesicoureteric junction (VUJ) can cause lower urinary tract symptoms (LUTS) eg. urinary frequency and urgency. It is important to elicit certain associated factors [1] which have management implications (panel 1).

Panel 1

Associated factors in renal colic with management implications

- Infection
- Obstruction
- Renal impairment or single kidney
- Risk factors for recurrence
  - eg. bilateral / multiple calculi, young age. (<25 years), strong family history of stone disease

Features of infection and obstruction are important to elicit as this combination can lead to rapid deterioration of renal function, often within 48 hours. However, obstruction or urinary tract infection, if not coexistant, can be safely managed conservatively in certain circumstances. A urology referral is advisable in these circumstances (see panel 1).

Examination generally reveals an anxious, restless and agitated patient who classically keeps moving about and changing positions, trying to obtain some relief from the pain. There is tenderness in the costovertebral angle, and on deep palpation in the region where the stone is situated, but guarding and rigidity are absent.

Differential diagnosis

Causes of abdominal pain such as appendicitis, biliary calculi, acute gastritis, acute gastroenteritis, acute pancreatitis, twisted ovarian cyst, salpingitis and ectopic pregnancy are some of the conditions which can mimic renal colic.

Diagnosis

An acute episode of renal colic is characteristic. Nevertheless clinical features should be supported by imaging. The ultimate diagnosis in renal colic rests on imaging.

Initial basic studies should include a urine analysis which will show haematuria in about 90% of patients [2]. Presence of many pus cells and bacteria are important indications of urinary infection. This should lead to urine culture, antibiotic sensitivity testing (ABST) and white blood cell counts.

The choice of imaging will depend on resources available. Reasonable options are listed in panel 2.

Panel 2

Options for imaging in renal colic

- Xray kidney ureter bladder (KUB) and ultrasound KUB
- Intravenous urogram (IVU)
- Non-contrast computed tomography

A majority of renal calculi are radiopaque. The sensitivity of an xray KUB for renal calculi is about 45% with a specificity of 77% [3]. It will not show radiolucent stones (eg. uric acid, cystine), and can be influenced by the adequacy of bowel preparation. To assess for obstruction

and infective complications, combination with ultra-sound imaging is required. Apart from assessing obstruction, this can identify renal stones ≥ 4mm and also some ureteric stones.

Intravenous urography has been the gold standard in the diagnosis of renal colic. It will show most stones, give an indication of the site of obstruction, and some idea of the function of each kidney. Non-contrast computerised tomography of the abdomen is a new imaging modality which is popular in developed countries as the first line investigation for renal colic [3]. It has the advantage of being a rapid investigation which is contrast free, with a sensitivity of 96-100% and a specificity of 95.5-100%. Small stones, even 2mm in diameter and radiolucent stones become visible. Other confusing diagnoses can also be eliminated with this method. Disadvantages are the higher cost and radiation exposure.

Management

Management of the acute episode

Pain management is the first priority. In severe colic, oral analgesics may not be sufficient, and medication may need to be given as suppositories or parenterally (panel 3).

Panel 3

Analgesics in acute renal colic

- Suppository
  Dicolfenac sodium (maximum daily dose is 150 mg)
- Parenteral
  Pethidine intramuscularly or intravenously
  Morphine
  Tramadol

NB: The use of diclofenac sodium intramuscularly is **banned** in Sri Lanka

Even if the diagnosis is not confirmed, it is safe to give analgesics as long as an experienced clinician has evaluated the patient and decided on the appropriate investigations and management plan. Once the pain is controlled, investigations can be performed to confirm the diagnosis. Management of the calculus is by one of the following methods.

1. Conservative management.
2. Extracorporeal shock wave lithotripsy.
3. Surgery.

Conservative treatment

Uncomplicated small renal and ureteric stones in a urinary system with no distal obstruction will pass spontaneously. Stones which are ≥ 4mm have an 80% chance of spontaneous passage, but those ≥ 7mm have only a small chance of passing without intervention [1]. The recent joint American and European Urology Guidelines state that stones <10 mm can be managed conservatively initially if uncomplicated [4]. Distal ureteric stones are more likely to pass than proximal ones. Suitability for conservative management also depends on other factors (panel 4).

Panel 4

Indications for intervention

- Obstruction of the urinary tract **with associated infection***
- Severe uncontrollable or recurrent pain
- Obstruction in a single kidney*
- Bilateral obstruction*
- Large stones (> 7mm)
- Social reasons eg. occupation eg. airline pilot

* Decompression of the urinary tract with either a percutaneous nephrostomy or intraluminal stent bypassing the stone should be the minimum if a definitive stone intervention is not contemplated.

Medical therapy to facilitate the passage of stones, ie. medical expulsion therapy (MET), has an evidence base to justify its use [4]. The evidence is stronger with alpha receptor blockers (eg. terazosin, tamsulosin) than with the calcium channel blockers (eg. nifedipine). Patients selected for this form of initial management should be free of sepsis and severe pain, and have no renal impairment. Regular follow up is required to confirm progression of the stone and to assess for hydronephrosis.

Extracorporeal shock wave lithotripsy (EWSL)

This is a non-invasive method of fragmenting stones using shock waves. The procedure can generally be done under cover of analgesics. Sometimes sedation or general

anaesthesia may be required (especially in children). Stones in the kidney and upper ureter are especially amenable to this method of treatment. Generally the stones should be less than 1.5-2 cm in size. Visualisation of the stone by either fluoroscopy or ultrasound is essential to focus the shock waves.

Complications of EWSL are urinary infection, further ureteric colic with passage of fragments, haematuria, stone fragments lining up along the ureter ('steinstrasse'), failure of fragments to pass (especially with lower calyceal stones) and non-fragmentation of stones (ie. failure of treatment method).

Surgical treatment

This may be endoscopy, laparoscopy or open surgery.

Endoscopy

Ureteric or renal stones can be definitively treated using an endoscope passed via the urethra. The ureter can be accessed with rigid, semi-rigid or flexible ureteroscopes and the stones fragmented using electrohydraulic, pneumatic or ultrasonic lithotriptors, or laser energy. Stone fragments or the entire stone can be extracted using baskets and stone forceps. Renal stones (small) can be tackled using flexible uretero-renoscopes and laser energy (not availabe in Sri Lanka). Larger stones can be accessed via endoscopes introduced into the kidney percutaneously ie. nephroscopes.

Complications of these procedures include iatrogenic injury to the ureter and kidney, bleeding, sepsis, and residual stones. Endoscopic procedures can be combined with ESWL to reduce residual stone volumes.

Laparoscopy

This is reserved for large ureteric stones which are considered too large to be treated endoscopically. Some centres in Sri Lanka offer this treatment modality. The ureter is generally approached retroperitoneally.

Open surgery

The usage of this tried and tested method of treating urinary calculi will depend on the resources and expertise available in a particular centre. Large ureteric stones may still require open surgical intervention (ureterolithotomy). However, the proportion of open surgery (vs. endoscopic procedures) for renal stones performed in the west is probably <1%. Lack of resources and also pressures of workload have meant that open renal surgery remains an important treatment method in Sri Lanka.

Follow up management

Patients who have treatment for urinary calculi should be advised that absence of symptoms (especially pain) does not guarantee a stone free status. Imaging to confirm this is essential. Also, once a patient forms a stone there is a risk of developing another stone in the future, with recurrence rates approaching 50% [2]. Therefore with the aim of reducing the risk of stone recurrence, all patients should be advised to increase their fluid intake to produce at least 2L of urine per day [2]. They also should be advised to seek medical help if they develop flank pain or haematuria. Recurrent stone formers and young stone formers should be investigated for metabolic abnormalities that could contribute to the recurrence.

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Current information about drug registration

New chemical entities registered

Generic name	Brand name	Dosage form	Manufacturer	Importer	Therapeutic/class/use(s)
Gadoversetamide	Optimark	Injection, 0.5 mmol/mL	Mallinckrodt, USA	AJ Medichem	MRI contrast agent
Everolimus	Certican	Tablet, 0.25 mg	Novartis, Switzerland	Baurs	Organ transplantation
Tacrolimus	Pangraf 1 Pangraf 5 Vingraf 1 Vingraf 5	Capsule, 1 mg Capsule, 5 mg Capsule, 1 mg Capsule, 5 mg	Panacea, India Panacea, India Emcure, India Emcure, India	Nawakrama Nawakrama Gamma Gamma	Organ transplantation
Valganciclovir	Valcyte	Tablet, 450 mg	Roche, Switzerland	Baurs	Cytomegalovirus infection
Levetiracetam	Levitoz	Tablet, 500 mg	Atoz, India	Euro Asian	Antiepileptic
Temozolomide	Temodal	Capsule, 20 mg	Orion, Finland/Schering Plough	Baurs	Antineoplastic
Ertapenem	Invaz	Injection, 1 g	MSD, UK	Mansel	Beta-lactam antibiotic
Deferasirox	Asunra	Tablet, 125 mg & 500 mg	Novartis, Switzerland	Baurs	Iron chelator

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Self-assessment questions

(And clinical physiology in small doses)

(Select the *best* response in each question)

1. Low molecular weight heparins in deep leg vein thrombosis
   a. must be given intravenously every 8 hours
   b. has produced similar results to therapy with standard heparins in large clinical trials
   c. have a shorter half-life than standard heparins
   d. have unsatisfactory bioavailability compared to standard heparins
   e. need regular monitoring using APTT estimation

2. Which statement is *false* regarding sexually transmitted infections?
   a. about 80% of women infected with *Chlamydia trachomatis* are asymptomatic
   b. the Chlamydia PCR has a specificity of about 70-80% and sensitivity of about 70-75%
   c. the majority of rectal, pharyngeal and cervical infections with *Neisseria gonorrhoeae* are silent (ie asymptomatic)
   d. the newer nucleic acid amplification tests for gonorrhoea have a specificity >98% and a sensitivity >90% for swab samples
   e. over 99.5% of cervical cancers are positive for human papillomavirus DNA

3. The gut peptide hormone that has most influence on post-prandial satiety is
   a. secretin
   b. somatostatin
   c. gastrin
   d. vasoactive intestinal polypeptide
   e. oxyntomodulin

Answers to self-assessment questions

1. The correct response is b. Low molecular weight heparins are given by subcutaneous injection, have better bioavailability and a longer half-life than standard heparins, and do not require APTT monitoring. (See article by Professor Wijeyaratne in this issue).

2. The correct answer is b. Chlamydia PCR has a specificity of 99-100% and a sensitivity of 85-90%. Responses a, c, d and e are true, and b is the only **false** response. (See article by Catriona Ooi in *Australian Prescriber*, Volume 30, Number 1, Feb 2007).

3. The correct answer is e, oxyntomodulin. The other gut peptides known to produce post-prandial satiety are peptide yy (PYY), pancreatic polypeptide (pp) and glucagon-like peptide (GLP-1). (See (i) Wynne K, Stanley S, Bloom S. The gut and regulation of body weight. *Journal of Clinical Endocrinology and Metabolism* 2004; **89**(6): 2576-82, (ii) Druce MR, Small CJ, Bloom SR. Mini review: gut peptides regulating satiety. *Endocrinology* 2004; **145**(6): 2660-5).

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ISSN 1391-0736

Printed by Ananda Press, Colombo 13.