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Cover picture

STANISLAS LIMOUSIN, PHARMACAL INVENTOR (About 1886)

The French retail pharmacist, Stanislas Limousin, introduced many devices to Pharmacy and Medicine. His greatest contributions were invention of glass ampoules; the medicine dropper; and apparatus for inhalation of oxygen.

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

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

Management of acute bleeding in the upper gastrointestinal tract

Summary

Acute upper gastrointestinal haemorrhage is common. Patients require simultaneous resuscitation and clinical assessment followed by referral for endoscopy. There have been significant developments in terms of the acute endoscopic and medical treatment of upper gastrointestinal haemorrhage, as well as the development of prognostic tools to help guide management.

Preventing recurrent haemorrhage is also important. This requires an understanding of both the aetiology and risk factors for recurrence, as well as the medical and endoscopic treatments available to reduce these risks

Key words: peptic ulcer, varices, endoscopy, haemorrhage

(Aust Prescr 2005; ***28****: 62-6)*

Introduction

Acute upper gastrointestinal haemorrhage (bleeding proximal to the duodenojejunal flexure) is a common medical emergency (170 per 100 000 adults annually). Although its incidence may be declining, the mortality rate of upper gastrointestinal haemorrhage remains high, approximately 6-8%.[1] Depending on the site and rate of bleeding, a patient may present with melaena (black, tarry stool), haematemesis (vomiting 'coffee-grounds' or fresh blood), haematochezia (red blood per rectum) or syncope. Melaena may also result from bleeding into the more distal small intestine or proximal colon.

The majority of patients with upper gastrointestinal haemorrhage require hospital management. General practitioners have an important role in assessing and resuscitating patients and then managing them following discharge to reduce the risk of recurrent bleeding.

Initial assessment

Initial clinical assessment is directed towards the haemodynamic stability of the patient and the requirement for immediate resuscitation.

History

The presenting symptom, past medical history and current medications are important for establishing the aetiology (see box and Table 1) and severity of haemorrhage. A history of recent dyspepsia, or use of aspirin or another non-steroidal anti-inflammatory drug (NSAID) may suggest a bleeding ulcer. The presence of chronic liver disease raises the possibility of variceal haemorrhage. Haematemesis that follows prolonged vomiting or retching may be the result of a Mallory-Weiss tear.

A history of syncope may reflect haemodynamically significant bleeding. Vomiting frank blood suggests severe haemorrhage from an arterial or variceal source. In contrast, 'coffee-grounds' emesis is unlikely to reflect active bleeding.

Approximately 50 – 100 mL of blood is needed to produce melaena. Haematochezia may occur with brisk upper gastrointestinal haemorrhage and is usually accompanied by haemodynamic compromise.

Common causes of upper gastrointestinal haemorrhage

peptic ulcer disease

gastric erosions

oesophagitis

oesophageal or gastric varices

emetogenic injury (Mallory-Weiss tear)

malignancy

angiodysplasia

Table 1. Drugs associated with gastrointestinal haemorrhage

Drugs	Mechanism
Aspirin and non-steroidal anti-inflammatory drugs, including COX-2 inhibitors Prednisolone	Mucosal toxicity
Warfarin Clopidogrel and other antiplatelet drugs Aspirin Heparin (both fractionated and unfractionated) Selective serotonin reuptake inhibitors	Impaired haemostasis

Examination

It is critical to assess the patient's haemodynamic status by measuring heart rate, blood pressure and postural changes. In haemodynamically compromised patients a fall in blood pressure may follow only a minor change in posture, for example from lying flat to sitting at a 45° incline. Variceal haemorrhage is more likely if stigmata of chronic liver disease are present, particularly if there is evidence of portal hypertension, for example ascites and splenomegaly. An ulcer may cause epigastric tenderness. Digital rectal examination is important to confirm the presence of true melaena.

Investigations

Haemoglobin needs to be measured in all patients but may initially underestimate true blood loss, due to delayed haemodilution of the vascular space. Blood should be sent urgently to transfusion services for cross-matching. Other important tests include platelet count, urea:creatinine ratio, coagulation indices and liver function tests including albumin. Patients with end stage liver disease may have normal liver enzymes, yet have impaired synthetic liver function as evidenced by low albumin, or reduced clotting factors.

Risk assessment scores

The Blatchford score predicts the need for therapy and thus admission. Patients are unlikely to need treatment and therefore may not require admission if they satisfy the following criteria:

- urea less than 6.5 mmol/L
- haemoglobin greater than 130 g/L (men) or 120 g/L (women)
- systolic blood pressure greater than 110 mmHg
- pulse less than 100 beats per minute (excluding those with syncope).

This 'fast-track' triage could be used in an emergency department to avoid unnecessary admissions.[2] Likewise in regional areas, such a scoring system could help the general practitioner decide if a patient requires immediate transfer to a tertiary referral centre, or whether it is reasonable to discharge the patient with a view to arranging an early outpatient endoscopy at the closest facility. The safety of using the management algorithm in this way is yet to be formally evaluated, and thus patients should continue to be managed on a case by case basis.

The Rockall score is frequently used for risk categorisation (Table 2). The score is the sum of each component, calculated before and after endoscopy. This predicts rates of re-bleeding and mortality and can be used in management algorithms, for example whether to admit a patient to an intensive care unit. Post-endoscopy risk scores of 2 or less are associated with a 4% risk of re-bleed and 0.1% mortality. In one study about 30% of patients had post-endoscopy risk scores of 2 or less and thus significant health savings could be achieved by early endoscopy and discharge.[3]

Resuscitation

Until cross-matched blood is available, resuscitation proceeds with crystalloid or colloid solutions aiming for a systolic blood pressure of greater than 100 mmHg. Thiamine replacement should be considered when there is a history of alcohol abuse.

Table 2. Rockall score for the prognostication of upper gastrointestinal bleeding[3]

	Score			
	0	**1**	**2**	**3**
Pre-upper gastrointestinal endoscopy				
Age	<60 years	60-79 years	≥80 years	
Shock	No shock BP >100 mmHg and pulse <100	Tachycardia BP >100 mmHg and pulse > 100	Hypotension BP < 100 mmHg	
Comorbidity	No major comorbidity	Ischaemic heart disease, cardiac failure, any major comorbidity		Renal or liver failure Disseminated malignancy
Post-upper gastrointestinal endoscopy				
Diagnosis	Mallory-Weiss or no lesion found, and no major stigmata of recent haemorrhage	All other diagnose	Gastrointestinal malignancy	
Major stigmata of recent haemorrhage		None or dark spot only	Blood in upper gastrointestinal tract, non-bleeding visible vessel, spurting vessel or adherent clot	

BP systolic blood pressure
Patients with a score of 0, 1 or 2 have a lower risk of haemorrhage, whereas approximately 50% of patients with a post-endoscopy score of 8 or more will re-bleed

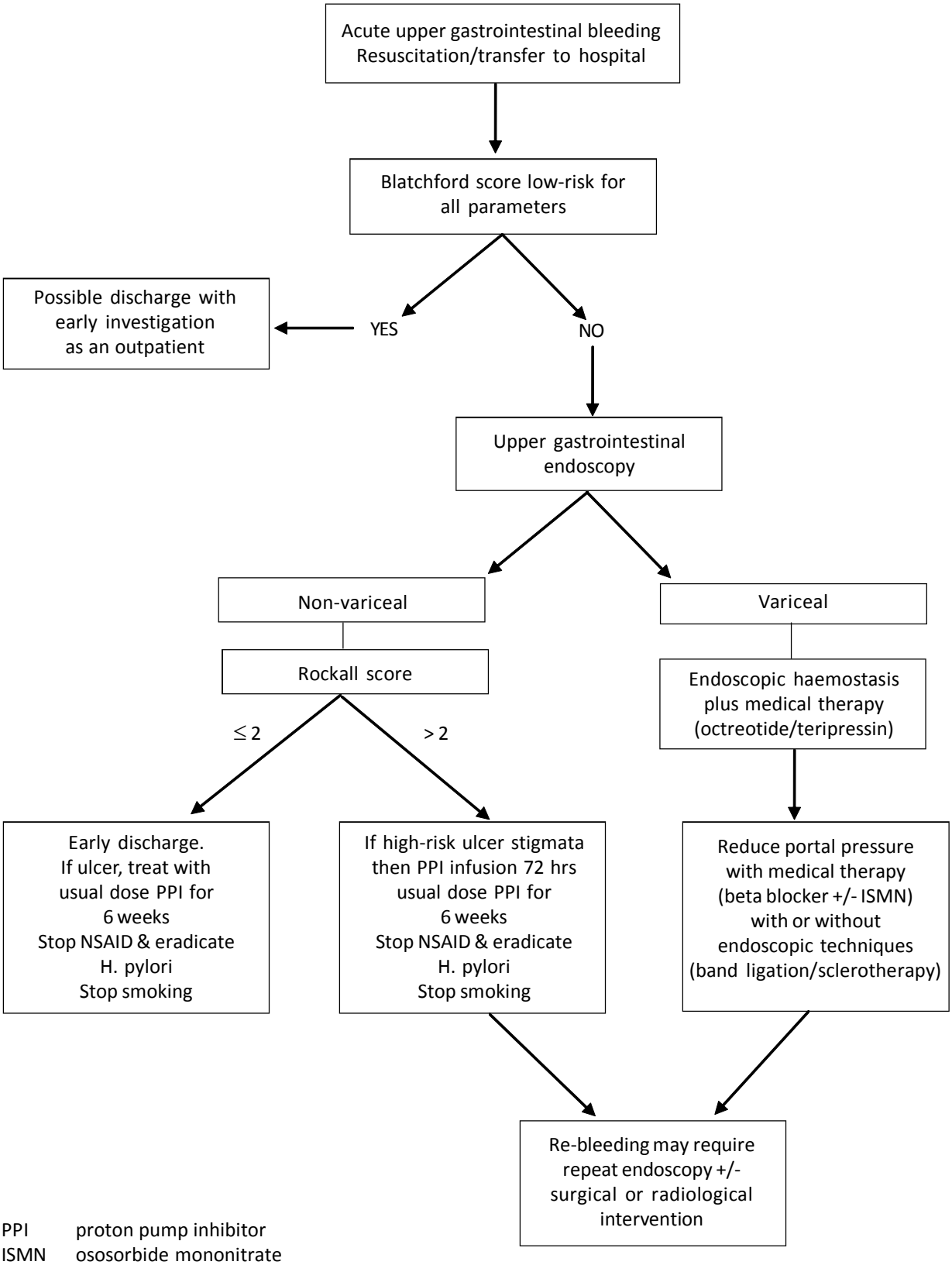
The target haemoglobin concentration is contentious. Some advocate 70-80 g/L for otherwise healthy individuals, without active bleeding, who are haemodynamically stable.[4] In patients older than 65 or those with cardiovascular disease a target concentration of 90-100 g/L may be more appropriate.

Endoscopy – diagnosis and management

After resuscitation an endoscopy is arranged. Some patients with profuse haemorrhage require emergency endoscopy, however the majority can be scheduled on the next routine list. The endoscopy should, however, take place within 24 hours of presentation, both to guide management and to facilitate the early discharge of patients with a low risk of recurrent bleeding.

When high-risk lesions are seen (ulcers with active spurting vessel or non-bleeding visible vessel) endoscopic therapy significantly reduces re-bleeding rates and mortality.[1] A dual-modality endoscopic approach is currently recommended, with a combination of (1:10 000) adrenaline injection and thermal coagulation. Band ligation and sclerotherapy are the two main endoscopic techniques for treating acute oesophageal varices.[5] These procedures are less successful in gastric varices, although injection with tissue adhesive may be effective.

Figure 1. Management of acute upper gastrointestinal haemorrhage



PPI proton pump inhibitor
ISMN ososorbide mononitrate
NSAID non-steroidal anti-inflammatory drug (including aspirin)

Medical management of upper gastrointestinal bleeding (Fig. 1)

Non-variceal

In gastrointestinal haemorrhage there is enhanced mucosal fibrinolytic activity, impairing haemostasis.[6] Suppressing acid secretion blunts this escalation in fibrinolysis. In this setting high-dose proton pump inhibitor therapy reduces the risk of recurrent bleeding.[7]

Proton pump inhibitor therapy can be administered parenterally (either intermittently or by infusion) or orally. When high-risk features are present at endoscopy it may be advisable to administer high dose intravenous proton pump inhibitor therapy, that is omeprazole 80 mg (or equivalent) bolus followed by an infusion rate of 8 mg/hour for 72 hours. Where the cost of intravenous proton pump therapy is prohibitive and especially when there are no high-risk ulcer features, an oral proton pump inhibitor may be satisfactory.[7]

Variceal

Medical therapy reduces variceal bleeding by lowering portal venous pressure. The available drugs include vasopressin and its synthetic analogue terlipressin, as well as somatostatin and its synthetic analogues octreotide and vapreotide. The relative merits of these drugs are unclear. The addition of an octreotide infusion to endoscopic therapy improves bleeding control and reduces transfusion requirements[5], therefore a combination of endoscopic and medical treatment is probably the best approach. However, only terlipressin has been shown to reduce mortality rates following variceal bleeding[8], but it is currently only available in Australia under the Special Access Scheme.*

* http://www.tga.gov.au/docs/html/sasinfo.htm [cited 2005 May 10]

Prevention of recurrent bleeding

Non-variceal

Prevention of recurrent bleeding in ulcer disease should be directed towards the underlying cause. All patients should be asked about aspirin and other NSAID use and be tested for *Helicobacter pylori*. Patients who smoke should be advised to stop.

NSAID-induced ulcers

NSAIDs should be discontinued where possible. The ulcer may then be healed with an H2-receptor antagonist or a proton pump inhibitor over a period of six weeks.[9] Current clinical practice favours proton pump inhibitor therapy over H2-receptor antagonist for ulcer healing. No further endoscopy is required for duodenal ulcers, but repeat endoscopy at eight weeks is advisable for gastric ulcers to ensure healing and exclude malignancy.

In patients requiring ongoing NSAID therapy, a concomitant proton pump inhibitor achieves a greater rate of ulcer healing than H2-receptor antagonists.[10] An alternative approach is to substitute paracetamol or a COX-2 selective drug for the conventional NSAID. In terms of the rate of recurrent bleeding, this strategy is comparable to taking a conventional NSAID with a proton pump inhibitor.[11] The rate of recurrent haemorrhage in this group, however, is still relatively high. It is important to remember that the gastrointestinal advantages of COX-2 selective inhibitors are negated by concomitant aspirin therapy, and that there has been recent concern about the cardiovascular safety of this class of drug. A proton pump inhibitor reduces the risk of recurrent bleeding when long-term aspirin therapy is required. The timing of the resumption of a medication which may have contributed to the gastrointestinal haemorrhage should balance the likelihood of re-bleeding, the indication for the drug and whether safer alternatives are available.

H. pylori-associated ulcers

All patients with ulcer disease should be tested for *H. pylori*[12] and the bacteria eradicated if found. Successful eradication, usually a seven day regimen of triple therapy, significantly reduces the risk of ulcer recurrence.[13] Once *H. pylori* eradication is confirmed and the ulcer has been healed by six weeks of treatment with an H2-receptor antagonist or proton pump inhibitor, no further therapy is required.

Idiopathic ulcer

A number of patients have ulcers without a clear aetiology. These patients should have their ulcers healed with either an H2-receptor antagonist or a proton pump inhibitor for 6-8 weeks.[9] However, they may require long-term acid suppression.

Variceal

Variceal bleeding recurs in approximately two-thirds of patients.[5] Both endoscopic and medical strategies are used in an attempt to reduce recurrent oesophageal variceal bleeding. Regular endoscopic

treatment, usually 3-4 sessions (initially weekly, then every 2-3 weeks), with either sclerotherapy or banding can obliterate oesophageal varices. Band ligation is preferred because of greater efficacy and a lower incidence of oesophageal strictures.[5] Alternatively, reducing portal pressure with a non-selective beta blocker (propranolol, nadolol (not approved in Australia) with or without a long-acting nitrate has proven effective. The combination of nadolol and isosorbide mononitrate therapy was superior to band ligation alone in preventing recurrent variceal bleeding.[14] It is possible, however, that combination endoscopic and medical therapy (in this study the medical treatment was nadolol and sucralfate) may be more effective than either alone.[15] Some patients require specialist techniques such as porto-systemic shunting by surgery or by a trans-jugular intrahepatic porto-systemic shunt. Other patients may not be able to have optimal medical treatment because of contraindications or adverse effects. In the case of alcoholic liver disease, failure to stop drinking increases the risk for recurrent haemorrhage, so abstention from alcohol is critical.

Conclusion

Management of acute upper gastrointestinal haemorrhage begins with clinical assessment and resuscitation. Endoscopy is required for diagnosis and initial therapy. A combination of medical and endoscopic strategies are used to reduce the risk of recurrent bleeding.

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Management of gastro-oesophageal reflux disease

Gastro-oesophageal reflux disease (GORD) occurs due to chronic reflux of gastric contents into the oesophagus. It is one of the commonest conditions presenting to primary care physicians and specialists in the field of gastroenterology.

The diagnosis of GORD is primarily clinical in the majority of patients who present with the typical symptoms of heartburn and regurgitation. Upper gastrointestinal endoscopy (UGIE) is warranted in the following circumstances:

- In the elderly
- In those with alarm symptoms (i.e. anorexia, weight loss, melaena, anaemia, dysphagia, and odynophagia)
- When complications (eg. strictures) are suspected
- Follow up after proton pump inhibitor (PPI) therapy in those with severe erosive oesophagitis at initial endoscopy
- Persistent symptoms despite 4-8 weeks of PPI therapy

Endoscopic examination enables the differentiation of GORD into erosive oesophagitis (EO) or non-erosive reflux disease (NERD), based on the presence or absence of mucosal erosions in the distal oesophagus. Cardiac investigation may be required when chest pain is the primary presentation. This review focuses on the management of patients where a diagnosis of GORD has been established. The main objectives of treatment in GORD include:

- symptomatic relief
- healing and prevention of recurrent mucosal lesions, ie. reflux oesophagitis
- prevention of complications such as strictures, bleeding and columnar metaplasia (ie. Barret's oesophagus)

The management strategy of GORD is determined by the:

- frequency of symptoms
- severity of symptoms
- presence of erosive oesophagitis on UGIE

Symptomatic relief is the most important reason for patients seeking medical attention and is achieved by a combination of lifestyle modification and drug therapy

Lifestyle and dietary modification

The following lifestyle modifications are recommended as the first line of management in patients with GORD.

- Weight loss in those who are overweight or have recently gained weight
- Elevation of the head of the bed where nocturnal or laryngeal symptoms (eg. cough, hoarseness, throat clearing) are predominant
- Avoidance of large meals and consumption of small frequent meals
- Avoidance of the supine position soon after meals, and avoidance of meals two to three hours before bedtime
- Avoidance of specific foods (oily food, caffeine, chocolate, spicy food, carbonated beverages, and peppermint) that trigger GORD symptoms
- Avoidance of tight fitting garments that raise intra-gastric pressure
- Promotion of salivation through oral lozenges or chewing gum to neutralise refluxed acid and enhance oesophageal acid clearance
- Avoidance of tobacco and alcohol, as both reduce lower oesophageal sphincter (LOS) tone, and smoking also diminishes salivation
- Abdominal breathing exercises to strengthen the anti-reflux barrier of the LOS

Drug therapy

Two strategies are described for the treatment of patients with GORD.

- Step up – this involves an incremental increase in the potency of therapy until symptomatic control is achieved
- Step down – this begins with potent anti-secretory agents and a gradual reduction in the potency of therapy until breakthrough symptoms define the treatment necessary for symptom control

The former, recommended for patients with mild and intermittent symptoms, minimizes the use of proton pump inhibitors (PPIs) and its associated costs and side-effects, whereas the latter provides rapid symptomatic relief to those with severe symptoms or EO.

Antacids

Antacids are limited to on-demand use for symptomatic relief, especially when the symptoms are mild and infrequent ie. less than once a week. They usually contain a combination of magnesium trisilicate, aluminum hydroxide, or calcium carbonate. These neutralise gastric acidity and reduce the acid exposure of the oesophageal mucosa during episodes of reflux. They are taken after a meal and at bedtime, and provide relief from heartburn within 5 minutes but have a short duration of effect of 30 to 60 minutes.

Surface agents and alginates

Sucralfate is a surface agent that adheres to the mucosal surface and induces healing and protects from peptic injury. However, its short duration of action and limited efficacy compared to PPIs limits its use mainly to the management of GORD in pregnancy.

Sodium alginate is a polysaccharide derived from seaweed that forms a viscous gum that floats within the stomach and reduces the postprandial acid pocket in the proximal stomach. Its role in the management of GORD is not established.

Acid suppression therapy

Acid suppressionis the cornerstone of medical therapy and includes the H2 receptor-antagonists (H2RAs) and proton pump inhibitors (PPIs). Symptomatic relief is achieved in more than 75% of patients, especially with the latter.

Histamine 2 receptor antagonists (H2RAs)

H2RAs decrease acid secretion by inhibiting histamine-2 receptors on gastric parietal cells. However, the development of tachyphylaxis within 2-6 weeks of initiation of H2RAs limits their use as maintenance therapy. They also have limited efficacy in patients with EO, especially when severe.

Proton pump inhibitors

PPIs are the most potent inhibitors of gastric acid secretion by irreversibly binding to and inhibiting the hydrogen-potassium ATPase pump. PPIs are used in patients,

- who fail twice daily H2RA therapy
- with EO and/or frequent (two or more episodes per week) symptoms
- with severe symptoms that impair quality of life

PPIs are administered daily and are most effective when taken 30 minutes before the first meal of the day, because the amount of H-K-ATPase present in the parietal cell is greatest after a prolonged fast. PPIs at standard doses for 8 weeks relieve symptoms of GORD and heal oesophagitis in most patients with EO. There are no major differences in efficacy among PPIs, different dosages or dosing regimens. Limitations include a higher cost and potential side-effects such as interference with calcium homeostasis, aggravation of cardiac conduction defects and hip fractures in postmenopausal women.

Prokinetic medications and reflux inhibitors

Prokinetic agents may be effective in patients with mild symptoms and are usually prescribed along with PPIs. The usual adult regimen is metoclopramide or domperidone 10 mg/day. Long-term use of prokinetic agents is discouraged since they have serious complications.

Treatment of *Helicobacter pylori* infection

It is unclear whether chronic acid suppression with PPIs increases the risk of atrophic gastritis in patients with *H. pylori*. Hence, routine screening for *H. pylori* infection and empirical eradication of *H. pylori* are not recommended in patients with GORD. However, for *H. pylori* diagnosed in the setting of GORD, eradication has been associated with an improvement of symptoms in patients with antral gastritis.

Healing of oesophagitis

The healing of acute reflux oesophagitis usually requires marked acid suppression for a long period, and is dependent on the severity of the initial oesophagitis. Most such patients will require maintenance PPI therapy at a dosage of 20 mg/day, while a smaller group will require at least 40 mg/day.

Refractory symptoms

Patients who fail to respond to once daily PPI therapy are considered to have refractory GORD.Twice daily PPI therapy should be used to improve symptom relief in these patients.

Management of recurrent symptoms and maintenance therapy

Cessation of medication should be considered in all patients with GORD whose symptoms resolve with acid suppression. Exceptions include those patients with severe OE and Barrett's oesophagus, who should remain on long-term maintenance acid suppression with a PPI.

Up to 60% of patients with NERD and most patients with OE will relapse within 6 to 9 months when acid suppression is discontinued. Patients with recurrent symptoms should be managed with acid suppressive therapy, with incremental dose adjustment to control symptoms if required.

When symptom recurrence occurs three or more months after discontinuing therapy repeated, 8-week courses of acid suppressive therapy is recommended. However, if symptoms recur within 3 months, an UGIE is done to rule out complications of GORD and long-term maintenance acid suppression (PPI) therapy at the lowest effective dose is recommended. Although intermittent (on-demand) therapy is an alternative in the management of recurrent GORD, continuous therapy appears to provide better symptom control, quality of life, and higher endoscopic remission rates.

Prevention of complications

Aggressive medical therapy heals oesophageal ulcers and prevents recurrent bleeding. Barrett's oesophagus should be prevented owing to its malignant potential. Evidence suggests that it rarely develops de novo or progresses after effective control of oesophagitis. This supports the use of aggressive acid suppression in patients with severe oesophagitis. It appears unlikely that PPIs or surgery cause regression of established Barrett's oesophagus.

Pregnancy and lactation

The initial management of GORD in pregnancy consists of lifestyle and dietary modification. In patients with persistent symptoms, pharmacologic therapy should begin with antacids followed by sucralfate. In those who fail to respond, H2RAs and PPIs could be used.

While most antacids are safe during pregnancy and breast-feeding those containing sodium bicarbonate and magnesium trisilicate should be avoided. Where UGIE is indicated, it should be postponed to the second trimester or post-partum.

Indications for surgery

The Nissen fundoplication, a 360° transabdominal fundoplication is the most widely practiced procedure for GORD. It is increasingly done laparoscopically. Ambulatory pH studies and oesophageal manometry on or off therapy should be considered prior to surgery.

Indications for fundoplication include:

- patients with symptoms not completely controlled by PPI therapy
- patients with well-controlled GORD who desire definitive, one-time treatment
- presence of Barrett oesophagus
- presence of extra-oesophageal manifestations of GORD: ie. respiratory (eg. cough, wheezing, aspiration), ear, nose, and throat (eg. hoarseness, sore throat, otitis media) and dental (eg. enamel erosion)
- young patients
- poor patient compliance with medications
- postmenopausal women with osteoporosis
- patients with cardiac conduction defects
- costs of prolonged medical therapy

Further reading

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Some key points in the new National Medicines Regulatory Authority (NMRA) Act

Introduction

The Government of Sri Lanka published its National Medicinal Drug Policy (NMDP) in 2005. Since then, attempts that were made to get it through as an Act of Parliament ran into various difficulties, and the NMDP remained as yet another inactive government document. Attempts to operationalize it got a boost when the NMDP became an election slogan in the last few years. In June 2014, the then Minister of Health, appointed a committee to draft a National Medicines Regulatory Authority (NMRA) Act. This committee used the existing draft of an Act developed by a previous committee and modified it to accommodate the objectives of the NMDP as far as possible. The implementation of the NMDP was included in the "100 day programme" of the present government. The drafting committee had to work overtime to develop the NMRA Act in quick time. The proposed NMRA Act was presented to the Cabinet in February, and was approved by Parliament in March 2015. Salient points in the proposed NMRA Act are summarised in this article.

Throughout the Act the term medicine or pharmaceutical is used instead of the word 'drug'. This Act proposes to regulate medicines, medical devices and borderline medicinal products. However, the acronym NMRA is usedfor short. Cosmetics with medicinal claims are regulated under this Act as borderline products. Products which get classified as pure cosmetics which do not have any medicinal claims, such as simple soaps and toothpastes, will not be regulated under this Act. The government will have to develop a new mechanism to regulate such cosmetics.

Establishment of an independent "Authority"

Under the repealed Cosmetics Devices and Drugs Act No. 27 of 1980 (CDD Act), the Drug Regulatory Authority (DRA) of Sri Lanka came under the purview of the Department of Health Services and the Director General of Health Services (DGHS) functioned as the "Drugs Authority". With delegated authority, the Director, Medical Technology and Supplies (D, MT & S) functioned as the local DRA.

Under the proposed Act a National Medicines Regulatory Authority ("Authority") will be established outside the Department of Health Services, but answerable to the Minister of Health. This Authority will have 13 members, including a Chairman and the chief executive officer (CEO). The DGHS will be a member. Others include persons with training in pharmacology, pharmacy, medical specialists and other professionals. The Minister will make the appointments. It is expected that the responsibility of all aspects of medicines regulation will be with the Authority, and not on any single individual.

Some key objects of the Authority are as follows.

(a) Ensure the availability of efficacious, safe and good quality medicines, medical devices and borderline products to the general public at affordable prices

(b) Function as the central regulator of all matters connected with regulation and licensing of medicines, medical devices and borderline products

(c) Ensure that activities pertaining to objective (b) are carried out in a transparent, sustainable and equitable manner

(d) Encourage local manufacture of good quality medicines with a view to assuring availability of essential medicines at affordable prices

(e) Promote safe and rational use of medicines to health care professionals and to consumers

(f) Regulate the availability of medicines, medical devices and borderline products

Divisions of the Authority

The Authority will have different divisions in it including the National Medicines Quality Assurance Laboratory (NMQAL), which will be one such division. Others include the Medicines Regulatory Division, Medical Devices Regulatory Division, Borderline Products Regulatory Division, Clinical Trials Regulatory Division (CTRD), Pharmacy Regulatory Division, Organization Development Division (dealing with

human resources, finance, administration and audit), Information Education Communication and Research Division (IECRD) and Vigilance and Inspectorate Division. The Authority shall have its own fund. Provision is provided to address conflict of interest issues of the members of the Authority and the committees. It is expected that most of the work pertaining to implementation of the NMRA Act will have to be done by qualified pharmacists. Their representation is provided in the appropriate committees.

The National Standing Committee

A National Standing Committee (NSC) consisting of 21 members is appointed to supervise the implementation of the NMDP and the NMRA Act by the Authority. The technical advisory committee (TAC) of the CCD Act is extinct, and some of the functions of the TAC will be vested with the National Advisory Committee.

Aspects of regulation

Areas of registration, import, local manufacture, wholesale sale, retail sale, storage, transport, advertising and promotion pertaining to medicines, medical devices and borderline products will be regulated through a process of registration, licensing, scheduling and listing.

Technical evaluation of the products will be done by 3 committees (Medicines Evaluation Committee, MEC; Medical Devices Evaluation Committee, MDEC, and Borderline Products Evaluation Committee, BPEC) whose membership is specified in the Act. In addition to the specified members there will be panels of experts to each committee and also the option to co-opt members. Criteria to be considered during evaluation of the products are efficacy, safety, quality, need and cost. In addition, provision has also been made to consider pharmacoeconomic aspects where appropriate. Registering of generic medicines would be subjected to evaluation of bioequivalence and biowaiver data.

With stringent criteria used during the registration process it is expected that only products which meet quality standards will be registered. With the operation of the "need clause" it is expected that the NMRA will be able to reduce the number of brands in the market.

Where relevant, compliance with various international guidelines is incorporated in the Act for different aspects of regulation. These include the WHO Good Manufacturing Practices (GMP), Good Pharmacy Practice, Good Distribution Practice, Good Review Practice guidelines etc.

All new applications will be granted registration initially for a period of one year. The Authority may renew the registration for a further period of 1 year or 5 years. In the case of new chemical entities the registration and renewal shall be granted for periods of 1 year each, up to a period of 3 years.

National Medicines Quality Assurance Laboratory (NMQAL)

Under the CCD Act the NDQAL was not under the Authority. In the NMRA Act the laboratory will be a division of the Authority, and function as its laboratory. The main function of the NMQAL is to test the quality of medicines, medical devices and borderline products submitted by the Authority, including articles submitted for registration, those collected at ports of entry to the country, complaint samples, post-marketing surveillance samples and others. Provision for testing at different points during the life-cycle of a medicine is provided. It is expected that the resources and the capacity of the laboratory will be increased enabling it to carry out these functions.

Clinical trials

Provision is made to establish a Clinical Trials Regulatory Division (CTRD) under the Authority. Reference is made to the new Clinical Trials Act for regulation of clinical trials, which is already drafted as a separate Bill to be passed by Parliament in the near future.

Pharmacies and prescribing

There is a separate division in the Authority to regulate pharmacies. Dispensing of drugs has to be done by the pharmacist or by an apprentice pharmacist, under the direct supervision of a pharmacist.

Prescriptions shall be written in the generic name of the medicine. If the prescriber wishes, he may, in addition to the generic name write a particular brand name, for the medicine prescribed. Where the brand of the medicine in the prescription is not available in the pharmacy, or is not affordable to the customer, the pharmacist may dispense any other generic medicine with the consent of the customer. The

pharmacist shall inform the range of products available in the pharmacy of the generic medicine and their prices, enabling the customer to buy the medicines according to his choice.

Pricing

A Pricing Committee will be established in the Authority. The Authority will decide on the introductory price based on the submission by the applicant and other relevant factors such as the prevailing market prices for similar products within the same therapeutic class, a pricing formula, the international reference prices and other factors. Price revisions, which were previously under the Consumer Affairs Authority will also come now under the NMRA.

Local manufacture

Promoting local manufacture is specifically mentioned in a separate section and clauses, to provide technical assistance and other necessary assistance to prospective manufacturers. There is provision to restrict import of products which are manufactured locally.

Appeals committee

Parties whose applications for registration have been turned down can initially appeal to the Authority for reconsideration. After this step they could appeal to a 3-member Appeals Committee.

Miscellaneous areas

Clauses to regulate advertising and promotion of products and giving samples is included. Provision is made to import unregistered medicines in limited quantities for personal use. Such medicines should not be sold. As in most Acts, the NMRA also has sections on prohibitions, offences and punishments.

Definitions

Definitions for various terms such as medicines, medical devices and borderline products and other terms used in this Act are provided. Ayurveda and Homeopathic products do not come under the purview of the NMRA.

Comments and conclusions

This NMRA Authority will function outside the Department of Health Services. With appropriate funding it will be able to establish itself and work independently. According to the repealed CDD Act one person functioned as the Authority. In the NMRA a 13-member Authority will hold responsibility. As there is independence from the Department of Health Services, it is hoped that decision making and operation will be less bureaucratic. Up to now, in Sri Lanka the Authorities did not have provision to regulate the initial price of medicines, medical devices and borderline products. With the provisions of the NMRA the Authority will be able to have an influence on the prices of medicines. For effective implementation of the provisions of this Act, regulations have to be drafted in several areas. The impact of the new Act will be felt only after establishment of the NMRA and implementation of its activities effectively. It is our belief that people will be served better with the new NMRA Act, with quality products being made available in the market at affordable prices.

Further reading

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Self-assessment questions

Select the **best** response in each question

Question 1

A 70-year old man who had a brief loss of consciousness at a bus halt was brought by ambulance to the ETU of a General Hospital. He was conscious but confused, and the only medical history he gave was that he had taken treatment for several years from a District Hospital for chronic abdominal pain. His BP was 105/72 mmHg. The pulse was regular at 110 bpm and a 12-lead ECG was unremarkable. Initial biochemical results were.

Glucose	4.0 mmol/l (3.5 – 6.0 fasting)
Urea	22.0 mmo/l (2.5 – 6.5)
Na	122 mmol/l (135 – 145)
K	2.9 mmol/l (3.5 – 5.0)
Cl	85 mmol/l (95 – 105)
HCO_3	42 mmol/l (22 – 30)

What is your interpretation of the initial biochemical data?

Question 2

A 62-year old woman stabilised on thyroxine 150 µg/day for hypothyroidism for 3 years, was seen at a routine clinic visit with the following biochemical results.

Hb 11.0g/dl (12.4 – 15.2)

WBC, DC, and platelets normal

TSH 21 mU/l (0.4 – 4.0)

Free T_4 16 pmol/l (12.0 – 22)

She had no specific complaints. What is your interpretation of her thyroid status?

Question 3

A 69-year old woman taking hydrochlorothiazide 25 mg and losartan potassium 50 mg daily for hypertension is admitted to the ETU, breathless at rest. Arterial blood gases on air and other biochemical results are as follows

pH	7.48 (7.35 – 7.45)	Na	136 mmol/l (135 – 145)
Pa O_2	8.2 kPa (10 – 13)	K	3.3 mmol/l (3.5 – 5.0)
Pa CO_2	5.3 kPa (4.5 – 6)	Urea	4.6 mmol/l (2.5 – 6.7)
HCO_3	32 mmol/l (22 – 30)	Creatinine	84 µmol/l (60 – 120)
Base excess + 7.2		Glucose	8 mmol/l (3.5 – 6.0 fasting)

Oxgen saturation 93%

What is your interpretation of these data?

Answers to self-assessment questions

Question 1 This man has hyponatraemia and hypokalaemia. The high urea is consistent with dehydration (water deficiency), and the low chloride and high bicarbonate are compatible with metabolic alkalosis produced by copious vomiting. Full investigation showed later that he had a non-malignant pyloric stenosis, with episodic bouts of profuse vomiting.

Question 2 A high TSH with a normal free T_4 in a hypothyroid patient on thyroxine treatment is indicative of non-adherence to the regular daily replacement regimen. Commencing regular thyroxine again will normalise free T_4 level in a few weeks, but the raised TSH will take much longer to adjust to the normal free T_4 level.

Question 3 This woman may have metabolic alkalosis consequent to hypokalaemia due to the diuretic, or a Type 1 respiratory failure (eg. pneumonia, pulmonary embolism).

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