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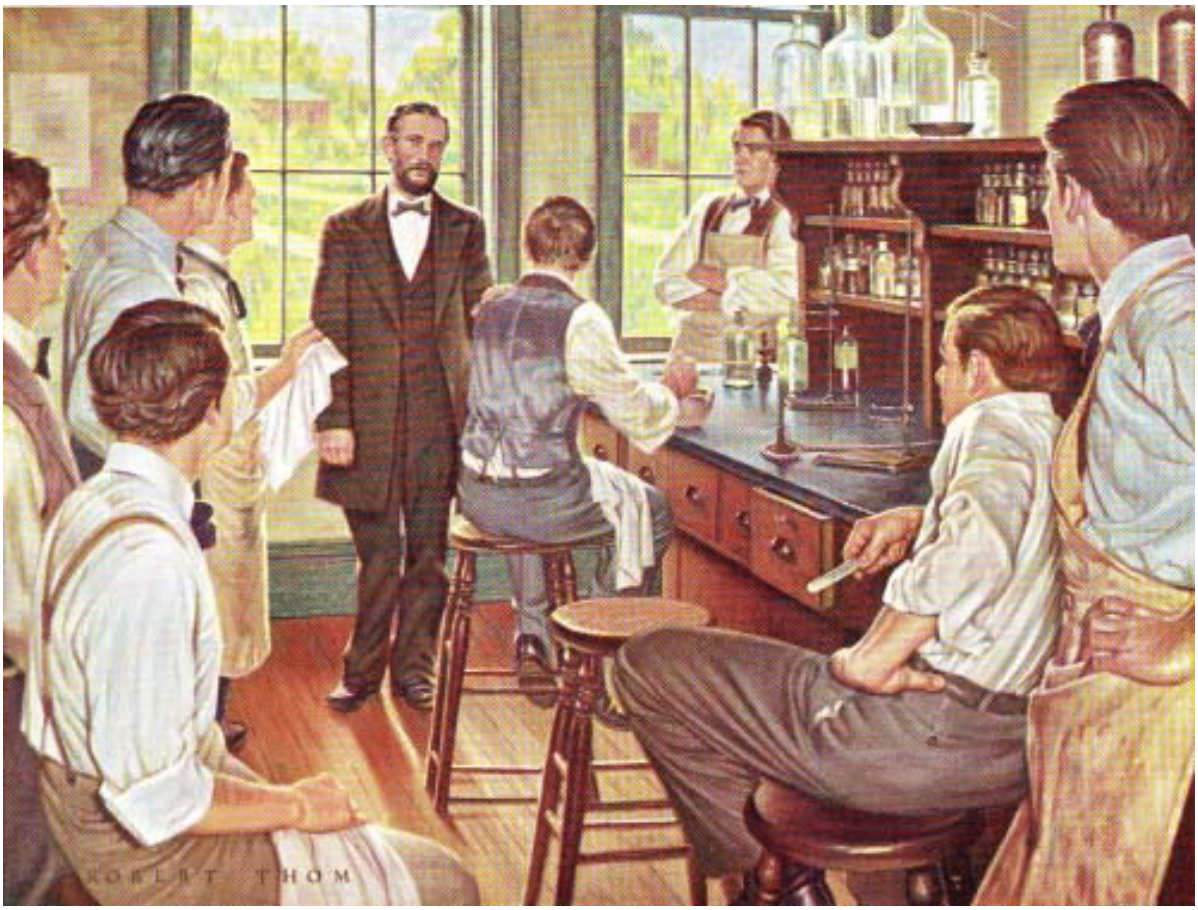

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The Sri Lanka
Prescriber

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Cover picture

A revolution in pharmaceutical education (About 1871)

When Dr. Albert B. Prescott launched the University of Michigan's pharmacy course, he was criticized for abandoning traditional pregraduation apprenticeship. Later, his "revolutionary" innovations were generally accepted by other colleges.

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

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

Results of the *Sri Lanka Prescriber* readers' survey

The *Sri Lanka Prescriber* (*SLP*) commenced publication in its current format in 1993. This independent drug information journal is published jointly by the Department of Pharmacology, Faculty of Medicine, University of Colombo, and the State Pharmaceuticals Corporation (SPC) of Sri Lanka. *SLP* is sponsored by the SPC, which is a government owned Corporation, established to procure pharmaceuticals for the state and private sectors. The editorial board serves in an honorary capacity. The editorial board of *SLP* is a fully independent body regarding all aspects pertaining to its publication. The *SLP* is a quarterly publication, and all doctors employed by the Ministry of Health and Universities are eligible to get a free copy of the journal by sending their permanent address and Sri Lanka Medical Council registration number. The journal has a circulation now of about 5500. The *SLP* became a full member of International Society of Drug Bulletins (ISDB) in 2001.

We conducted this first readers' survey covering the total readership of the journal in 2007 after 14 years of continuous publication. Readers may remember that a reward of a *British National Formulary (BNF)* was offered to the winner of a draw of responses. We are happy to inform readers that the winner of the draw was Dr P G A Malani of Pannipitiya.

Responders

Of the 3500 questionnaires sent to readers, 842 (25%) responded. Table 1 gives the categories of responders, and it shows that nearly 50% are non-specialist medical officers and further 20% are registered medical practitioners. Table 2 gives the primary field of practice of the responders. It shows that the speciality was general medicine in 43% and family practice in 14%, but all other specialities are represented.

Table 1. Category of reader

Category	*Number (%)*
Medical officers (non-specialist)	416 (49.4)
Registered medical officer	167 (19.9)
Postgraduate trainee	98 (11.7)
Specialist	92 (10.9)
General practitioner	23 (2.7)
Pharmacist	1
Other	45

Table 2. Primary field of practice of responders

Primary field	*Number (%)*
Anaesthesia	30 (3.6)
Family practice	118 (14.0)
General Medicine	358 (42.5)
Obstetrics and Gynaecology	35 (4.2)
Paediatrics	43 (5.1)
Psychiatry	12 (1.4)
Radiology	3 (0.3)
Sub-specialty in Medicine	9 (1.1)
Sub-specialty in Surgery	23 (2.7)
University academic	6 (0.7)
General Surgery	22 (2.6)
Other	183 (21.7)

Usefulness of the *SLP*

The responses to the question 'Why do you read the *SLP* ?' are given in table 3. We note that readers use the *SLP* for information on their primary field of work, for information on other topics and as a help for managing patients during general practice.

Table 3. Why do readers read the *SLP*

Reasons	*Number (%)*
For information on topics related to my primary field of work	544 (64.6)
For information on topics other than my field	524 (62.2)
As a help for managing patients during general practice	534 (63.4)
For teaching purposes	139 (16.5)

Reader satisfaction

Table 4 provides the responses on reader satisfaction. Reader satisfaction was high (mean scores >3.7, in a scale of 0-5) for usefulness of information in articles, language used, reliability and accuracy of information, length of articles, style and depth of articles. Low satisfaction was noted on the number of issues published annually and the number of pages.

Table 4. Mean scores of satisfaction on various characteristics of *SLP* (scale 0-5)

Characteristic	*Mean score*
Usefulness of information in articles	4.1
Length of articles is convenient	4.0
Depth to which the topic is dealt with	3.7
Level of language appropriate	4.4
Size of each issue (number of pages)	2.8
Format (A4 paper size)	4.2
Number of issues for year	2.7
Reliability/accuracy of information	4.3
Style of articles	3.9

Table 5 gives the opinion of readers on adequacy of areas covered in articles. Readers thought that areas of medicine and related topics, new drugs and adverse drug reactions were adequately covered (mean scores >3.2 in scale of 0-5), whereas surgery, obstetrics and gynaeology, psychiatry and paediatrics were less covered. Readers were satisfied with all types of articles published in the journal with mean scores more than 3.1 (table 6). About 66% of readers identified the need to cover additional areas. The areas suggested were wide and varied and included articles on the main medical specialties surgery, obstetrics and gynaecology, paediatrics, psychiatry, and sub-specialties such as ENT, ophthalmology, dermatology, neurology, anaesthesia, radiology, family medicine, community medicine and forensic medicine. Readers also requested articles on management of medical emergencies, common diseases, and also information about new research, improvements of medicines, vaccines, human genetics, therapeutic hints, new drugs and related topics.

Table 5. Mean score on adequacy of areas covered (scale 0-5)

Area	*Mean score*
Medicine and related topics	4.0
Surgery and related topics	2.6
Obstetrics and gynaecology and related topics	2.5
Paediatrics and related topics	2.9
Psychiatry and related topics	2.4
New drugs	3.2
Adverse drug reactions	3.2

Table 6. Mean scores of satisfaction on areas covered (scale 0-5)

Section	*Mean score*
Articles on therapeutic management	3.7
Articles on new drugs	3.2
Information on newly registered drugs	3.2
MCQs	3.5
Cover page	3.8
Patient information sheets	3.1

About 45% read almost all the *SLP* contents, 34% read 75% of the journal, and 52% of readers say that 1-5 other people also read their copy, indicating that the actual readership is more than the number of copies circulated (tables 7 and 8).

Table 7. How much of the *SLP* is read?

Response	*Number (%)*
Almost all	380 (45.1)
About 75%	281 (33.4)
About 50%	119 (14.1)
About 25%	17 (2.0)
< 25%	19 (2.3)

Table 8. Number of people reading a single copy of the *SLP*

Response	*Number (%)*
Only myself	322 (38.2)
1-5 people	438 (52.0)
More than 5 people	53 (6.3)

Suggestions for improvement and other comments

The most common suggestion was to increase the number of pages and issues. Readers also suggested providing more information in brief and increasing the number of topics covered. There were also requests to send *SLP* to all college and hospital libraries. We are pleased to learn that readers find *SLP* a useful resource, especially in the outstations, by the encouraging and supportive comments of readers.

What we have already done and hope to do

Based on the results of the survey we have already increased the number of pages by 4 with support from the SPC. From 2008 we have been able also to increase the number of articles.

We have also included several areas such as surgery, paediatrics, obstetrics, and sub-specialties such as ophthalmology, and anaesthesia. More articles on inadequately covered areas are planned for the coming issues. We have increased the length of articles from about 1200 to about 1500 words to provide more information. We have discussed about the size of the *SLP*, and the editorial board wishes to keep it at A4 size, as the *SLP* is meant to be read at leisure, and not carried in the pocket.

Publishing a journal regularly in the Sri Lankan context is not easy. The journal does not have any full-time staff, and all editorial board members work in an honorary capacity. *SLP* articles are available via the SPC website (www.spc.lk) or Colombo Medical Faculty website under the Department of Pharmacology (www.cmb.ac.lk/academic/medicine)

Although we have concluded the readers' survey, we welcome your suggestions and feedback on the *SLP*. Write to us on any aspect of the journal addressed to the editorial secretary in the Department of Pharmacology, Faculty of Medicine through normal mail or via email. We thank you for responding to the readers' survey, and for your ideas and encouragement.

Dr. Priyadarshani Galappatthy, MBBS, MD, MRCP, *Honorary Editorial Secretary* and **Professor Colvin Goonaratna,** MBBS, FRCP, PhD, *Chief Editor, Sri Lanka Prescriber*.

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Management of irritable bowel syndrome

Irritable bowel syndrome (IBS) is a functional bowel disorder characterised by abdominal pain, bloating and altered bowel habits (change in stool frequency and consistency) in the absence of a specific organic pathology. IBS is more commonly diagnosed in patients younger than 50 years of age but no age is immune [1]. In the western countries women are more likely to be diagnosed with IBS although males represent about 70% of patients with IBS in the Indian subcontinent [5].

IBS is a chronic relapsing condition. It does not increase mortality, the risk of inflammatory bowel disease, or of cancer. Traditionally, IBS is a diagnosis of exclusion although positive diagnosis can be made using various criteria. The 2006 Rome 111 criteria [2] for the diagnosis of IBS require that patients must have recurrent abdominal pain or discomfort at least 3 days a month during the past 3 months, that is associated with 2 or more of the following: relieved by defecation, onset associated with a change in stool frequency, and onset associated with a change in stool form or appearance.

There are several hypotheses about how and why IBS develops. Despite intensive research the cause is not yet clear, and some of the current therapies are based on these hypotheses.

1. Food intolerance is common in patients with IBS. A number of foods are known to cause symptoms that mimic or aggravate IBS, including milk products which contain lactose, legumes (eg beans), Jack fruit, apples and cruciferous vegetables (eg cabbage). These foods increase intestinal gas, which often causes bloating and abdominal cramp.

2. People with IBS who seek medical help are more likely to suffer from anxiety and stress. It is likely that anxiety and stress worsen symptoms, although according to available evidence they are not the cause of IBS.

3. Some people develop IBS after a severe gastro-intestinal infection (eg *Salmonella*). It is not clear how the infection triggers IBS. This subgroup of patients is known as post-infectious IBS [3]. However, most people with IBS do not have a history of such infection.

4. Many researchers believe that IBS is caused by increased sensitivity of the intestine to normal sensation (so called visceral hyperalgesia). This theory proposes that nerves in the bowel are overactive in people with IBS and normal amounts of gas or peristalsis are perceived as excessive and painful.

Symptoms and subgroups of IBS [5]

1. **Abdominal pain.** Typically crampy, varying in intensity, and located in the left lower abdomen. The nature, severity and location of pain can vary considerably from person to person. Some people notice that emotional stress and eating worsen the pain. If pain is the main symptom, the term "pain predominant IBS" is used to describe them.

2. **Altered bowel habits.** This can include diarrhoea, constipation, passage of mucus, alternating with diarrhoea and constipation. Depending on the more common symptom the condition is called either "diarrhoea predominant IBS", "constipation predominant IBS", or "alternating type IBS".

3. **Other symptoms.** These include bloating of the abdomen, gas, flatulence and belching.

4. **Non-gastrointestinal symptoms.** Such as urinary symptoms and painful menstrual periods may be associated with IBS, but they need to be evaluated carefully before labelling them as IBS associated.

5. **Alarm features.** Rectal bleeding, weight loss, iron deficiency anaemia, nocturnal symptoms, diagnosis after 50 years of age and short history are not features of IBS. The presence of one or more of these alarm features increases the chance of underlying organic pathology.

Panel 1. Alarm features

Rectal bleeding

Weight loss

Nocturnal symptoms

Age of diagnosis > 50 years

Short history of illness

Family history of colonic tumours or inflammatory bowel disease

Panel 2. Disorders that may mimic IBS

Malabsorption (eg lactose or fructose intolerance, gluten sensitivity), inflammatory bowel disease (eg ulcerative colitis)

Hyper- or hypothyroidism

Autonomic neuropathy

Bowel disorders in diabetes

Small bowel bacterial overgrowth

The diagnosis of IBS begins with a detailed medical history. The diagnostic criteria (eg. Rome criteria) may help the diagnosis but these are not useful in distinguishing it from other conditions that may mimic IBS.

There are no diagnostic tests for IBS. Most clinicians request routine blood tests to exclude underlying medical conditions, although these tests are not recommended by international guidelines. They include, ESR or CRP, thyroid function tests, and examination of stools.

These tests are normal in IBS and may help to reassure both patient and clinician that the diagnosis of IBS is correct. Routine colonoscopy / flexible sigmoidoscopy and imaging (barium studies) are not recommended in patients younger than 50 years with typical IBS symptoms with no alarm features, but they are mandatory in atypical IBS patients with alarm features, those over the age of 50 years.

Treatment

Since IBS is a chronic condition with no known cure, the aim of treatment should be on relief of symptoms and addressing the patient's concerns. (Panel 3).

Panel 3. Treatment options

Explanation / education / reassurance

Diet and non-pharmacological measures

Non-specific bowel directed therapy

Specific therapy

Stress relieving medication / hypnotherapy / cognitive behavioural therapy

Alternative medicine

1. It is necessary to give a clear explanation of what IBS is, and that there is no miracle cure. People with IBS have concerns of serious illness such as cancer, and its effects on job, marriage and married life. Patients should be informed of the benign but chronic nature of the condition.

2. A careful dietary history may reveal patterns of symptoms related to milk or gas producing foods. An empirical trial of lactose free diet should be considered in patients suspected of having IBS. Data regarding the effectiveness of fibre are controversial because 40 – 70% of patients improve with placebo. Fibre supplementation may improve symptoms of constipation, but some patients experience bloating and distension with a high fibre diet. Avoidance of caffeine may help to reduce anxiety and symptom exacerbation. Benefits of probiotic supplementation in patients with IBS are unproven.

3. Initial therapy for IBS should include measures to reduce specific symptoms such as diarrhoea, constipation and pain.

Anti-diarrhoeal drugs

Loperamide or diphenoxylate may be used in diarrhoea predominant IBS. They should only be used as required and not on a continuous basis.

Treatment for constipation

Fibre supplementation, magnesium salts, phosphate salts and polyethylene glycol based laxatives may be taken on a scheduled basis or as needed. Lactulose is also effective but expensive and produces intestinal gas, which many patients find difficult to tolerate. Stimulant laxatives such as bisacodyl and senna can cause abdominal cramps and are associated with dependency. Long term use of stimulant laxatives should be avoided.

Antispasmodics and anticholinergic medications

Hyoscine and mebeverine may provide short term relief of abdominal pain and discomfort in IBS. Evidence of long term efficacy is not available.

4. **Antidepressants**

Tricyclic antidepressants (TCAs) are more effective than placebo at relieving global IBS symptoms. Many TCAs have pain relieving effects and are also helpful in diarrhoea predominant IBS. The dose of TCAs is typically much lower in IBS than that used for treating depression (eg. amitriptyline 10 mg nocte). Selective serotonin reuptake inhibitors are recommended for people with IBS and depression (eg. Fluoxetine).

5HT3 receptor antagonists

Alosetron is effective in diarrhoea predominant IBS. Although this drug is FDA approved, prescribing guidelines must be followed. Side-effects are constipation and colonic ischaemia.

5HT4 receptor agonists

Tegaserod. This drug is effective in women with constipation predominant IBS.

Selective C2 chloride channel activators

Lubiprostone. This is effective in women with constipation predominant IBS. Long term safety is unknown. Most of these receptor agonists and antagonists are not registered in Sri Lanka.

5. Some patients benefit from formal counselling with or without anxiolytics. Other therapies such as cognitive behavioural therapy and dynamic psychotherapy are more effective than drugs in relieving global symptoms of IBS.

6. Herbal, natural therapies and acupuncture. There is no evidence for benefits of these therapies in carefully conducted studies.

Conclusion

Irritable bowel syndrome is a common gastrointestinal disorder affecting a significant segment of the population. Although the condition cannot be cured, treatments are available to alleviate symptoms. The management of IBS includes positive diagnosis of the illness, exclusion of alarm symptoms, avoidance of unnecessary tests, a clear explanation about the condition and symptom directed therapy.

Further reading

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Conflicts of interests: none declared.

Management of dental caries

Dental caries is a complex and multifactorial disease. It is modified by dietary components in which saliva plays a critical role. The dietary component responsible for dental caries is fermentable carbohydrate including various sugars. Sucrose has been implicated more than any other carbohydrate in the development of caries. Cariogenic bacteria metabolise sugar and produce organic acids, mainly lactic acid, which causes demineralisation of dental hard tissue. Frequency of refined carbohydrate intake is more important than the total carbohydrate intake. Salivary calcium and phosphate help in maturation of enamel and in remineralisation of decalcified enamel. Salivary bicarbonate has a buffering action to neutralise bacterial acids, and saliva also has antibacterial substances. It also contains fluoride which helps remineralisation.

Dental caries is a process where initially enamel and later dentine is demineralised by the acids produced by bacterial fermentation of carbohydrates. This is followed by breakdown of the organic part of dental hard tissue. The main indicator bacteria in this process are *Streptococcus viridians* group of "mutans streptococci", *Lactobacillus acidophillus* and *Lactobacillus casei*. Initiation of the carious lesion is by mutans streptococci and progression is mainly by *Lactobacillus*. The two species responsible for initiation of dental caries in man are *S. mutans* and *S. sobrinus*. *Streptococcus mutans* will reflect the difficultly in maintaining oral hygine whereas *Lactobacillus* is more relevant to misuse of carbohydrates. Some strains of *Actinomyces* also have cariogenic potential.

Cariogenic bacteria adhere to tooth surface and are acidogenic and aciduric. The mutans streptococci require a hard non-desquamative surface for colonisation. Hence they are not found in infants till the later stages of eruption of deciduous teeth. Dental caries is a transmissible disease. Mouth to mouth transmission from mother to children, or in a nursery child to child, is also possible. Transmission could be delayed or prevented by reducing the mutans streptococci in mothers. Increased sugar intake will favour colonisation and brushing of teeth will promote non-colonisation. The colonised bacteria on tooth surfaces are called bacterial plaque. Formation of extracellular polymer chains of glucans and fructans via breakdown of sucrose will enhance colonisation and restrict the salivary buffering effect. Intracellular metabolism of carbohydrates produces acids, mainly lactic, and reduces the resting pH within minutes. Without any further carbohydrate challenge the resting pH will be achieved in another 15 minutes.

Caries is a dynamic process involving both the loss of enamel minerals and its replacement. The balance can be disturbed by factors in oral cavity such as plaque, pH and presence or absence of fluorides. Presence of fluorides favours remineralisation and facilitates diffusion of calcium ions and phosphate ions back into the lesion, forming fluoridated hydroxyapatite crystals, which are more resistant to acids, producing true repair of initial carious lesions. As long as the surface layer of enamel is intact remineralisation takes place, and restorative treatment of teeth could be avoided.

Unless steps are taken to arrest or reverse the process it will advance towards the dentine enamel junction and spread laterally undermining the enamel, causing breakdown and cavity formation. Cavitated lesions may also reminerialise but restoration of teeth cannot be avoided. The formation of cavities on smooth surfaces of teeth could be prevented by fluorides, improvement of oral hygiene and dietary control, whereas in pits and fissures on biting surfaces of a tooth, pits and fissure sealant materials are helpful.

Chlorhexidine in an antiplaque agent. It is absorbed onto tooth surface and salivary mucins, later to be released slowly in an active form.

Early childhood caries (E.C.C.) or "nursing bottle caries" is a specific form of severe dental caries affecting infants and young children. E.C.C. is a result of interaction of the factors involved in other types of dental caries. However, the dietary factors also include frequent consumption of liquids containing fermentable carbohydrates, especially through a bottle at sleep times. Juices, infant formulas and sodas have been implicated in E.C.C. Laboratory studies have shown that milk without sugar is not cariogenic, and may even protect tooth surfaces because of its calcium content.

Assessment of caries risk is an important part in the management of dental caries. Factors relevant to assessment of caries risk factors are the social history, medical history, dietary habits, plaque control, use of fluorides, saliva and clinical evidence.

Numerous studies have suggested that salivary counts of mutans streptococci and *lactobacilli* are predictors of caries risk. Chairside diagnostic tests for rapid detection of high level of *S. mutans* are available without the need for incubation. Once it is decided that the patient is a high risk for dental caries, involvement of the patient in the management is essential, as it is the patient who will control caries. When the reasons for the caries have been found, the dental surgeon and patient are in a position to start to modify risk factors so that lesion progression can be arrested. In the management of dental caries preventive measures must always go hand in hand with operative techniques. To do otherwise may be likened to repairing a building that is still on fire.

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To mix or not to mix – compatibilities of parenteral drug solutions

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Summary

Many injectable drugs cannot be mixed together in syringes or infusions. Some cannot be safely diluted in infusion bags. Incompatibility can involve precipitation, ionic reactions, evolution of gas and denaturation of biological molecules. Knowledge of drug compatibility is needed before mixing drugs. Reference texts can provide information, but data are often unavailable for new drugs. If drugs are mixed together, the mixture should be inspected for precipitates, turbidity or changes in colour, however not all incompatibilities are visible.

Key words: diazepam, injections, phenytoin, precipitation.

(Aust Prescr 2008; 31: 98-101)

Introduction

Mixing solutions of parenteral drugs is generally not recommended because of the potential for incompatibility and consequent loss of activity of one or both drugs. However, in some circumstances there may be compelling reasons for mixing two or more parenteral drug solutions in the same infusion bag, in the same syringe or at a Y-site junction where two or more intravenous lines meet. Such circumstances include:

- difficulties with venous access limiting the number of intravenous lines available for continuous administration of multiple drugs
- multiple drugs requiring parenteral administration within a short time frame such as in a home visit by a general practitioner
- patients at home requiring many drugs by simultaneous continuous infusion where multiple intravenous lines are not feasible, for example, use of a syringe driver during palliative care.

The decision to mix drugs should not be made without knowledge of their compatibility. If intravenous drugs are not mixed but are given consecutively, the infusion line should be flushed through with compatible fluid between each administration.

Mechanisms of incompatibility

Incompatibility problems are more likely to arise when small concentrated volumes are mixed in a syringe rather than in the larger volume of an infusion bag. This is because of higher mutual drug concentrations and potentially greater pH changes in the more concentrated solution. The absence of any visible change to a solution upon mixing does not automatically exclude degradation of either or both components.

Drugs that precipitate upon dilution

Precipitation of a drug from its concentrated injection solution when it is diluted with water or saline is counter-intuitive. However, a small number of injection solutions are formulated in non-aqueous solvents to allow dissolution of a poorly water soluble substance in a small volume. In these formulations, dilution of the non-aqueous injection vehicle with water or saline may precipitate the drug.

The problem is frequently observed when diazepam injection is diluted. Diazepam is very poorly water soluble so it is formulated as an injection solution in a vehicle comprising 50% propylene glycol and 10% ethanol. At first, dilution produces a slight turbidity which clears upon mixing, but dilution beyond fourfold produces an opaque white precipitate which does not clear until substantial further dilution.

Other drugs which demonstrate solubility problems and which are formulated in injection vehicles other than simple aqueous solutions include digoxin, clonazepam, phenytoin, amiodarone and phytomenadione. In some cases, the manufacturer recommends administration of the undiluted drug. In other cases, care needs to be taken to ensure that if the injection solution is diluted, the dilution is adequate to ensure continuing solubility over the duration of the infusion.

Precipitation of drugs due to pH change upon mixing

The water solubility of any drug is enhanced by ionisation of the molecule. For a drug molecule which acts as a proton acceptor (a Lowry-Bronsted base), ionisation is achieved by formulation in a low pH solution usually as a hydrochloride or hydrogen sulfate salt (for example, amiodarone hydrochloride or adrenaline acid tartrate). Conversely, for a drug molecule which can lose a proton or hydrogen ion (a Lowry-Bronsted acid – usually a weak organic acid), ionisation is achieved

Table 1. Examples of drug compatibilities

Drug	*Compatible in syringe*	*Incompatible in syringe*	*Comments*
Benzylpenicillin 600 mg powder for reconstitution	No common drugs listed in published data	Prochlorperazine, promethazine, chlorpromazine, sodium bicarbonate	
Dexamethasone sodium phosphate 4 mg/1 mL	Metoclopramide, ondansetron, ranitidine	Glycopyrrolate, midazolam, prochlorperazine, promethazine	
Diazepam 10 mg/2 mL	Nil	Widely incompatible – do not mix with other drug solutions	Poorly water soluble drug marketed in a complex solvent system
Frusemide 20 mg/2 mL	No common drugs listed in published data	Buprenorphine, chlorpromazine, droperidol, metoclopramide, midazolam, morphine sulfate, prochlorperazine, promethazine	pH of solution is 8.0 – 9.3. Frusemide is unstable in acidic media which may include glucose 5% solution.
Haloperidol 10 mg/2 mL	Hydromorphine	Benztropine, ketorolac	

Drug	*Compatible in syringe*	*Incompatible in syringe*	*Comments*
Hydrocortisone sodium succinate 100 mg powder for reconstitution	Metoclopramide	Prochlorperazine, promethazine, midazolam	
Lignocaine hydrochloride 2% in 5 mL	Glycopyrrolate, metoclopramide	Ampicillin, sodium bicarbonate solution	
Metoclopramide hydrochloride 10 mg/2 mL	Chlorpromazine, dexamethasone, droperidol, fentanyl, hydrocortisone sodium succinate, lignocaine, midazolam, morphine, pethidine, promethazine	Ampicillin, frusemide, sodium bicarbonate	
Morphine sulfate, morphine tartrate (various strengths)	Stability of at least 15 minutes published for atropine, bupivacaine, droperidol, fentanyl, glycopyrrolate, hyoscine butylbromide, ketamine, prochlorperazine, and up to 24 hours for metoclopramide	Aminophylline, flucloxacillin, frusemide, phenytoin, promethazine, sodium bicarbonate	Is less soluble in alkaline conditions
Prochlorperazine edisylate	Atropine, hydromorphone, hyoscine hydrobromide, morphine sulfate (may vary with brand), pethidine	Aminophylline, amphotericin, ampicillin, benzylpenicillin, calcium gluconate, cephalothin, dexamethasone sodium phosphate, frusemide, heparin, hydrocortisone sodium succinate, midazolam	The bulk of the published data refer to the edisylate salt which is marketed overseas. The salt marketed in Australia is mesylate which is similar, and for which extrapolation of data is considered reasonable.
Promethazine hydrochloride 50 mg/2 mL	Atropine, droperidol, fentanyl, glycopyrrolate, metoclopramide, midazolam, pethidine	Aminophylline, benzylpenicillin, dexamethasone sodium phosphate, frusemide, hydrocortisone sodium succinate, morphine, phenytoin, sodium bicarbonate	Locally irritant and unsuitable for subcutaneous injection. Avoid extravasation in intravascular injection.
Tramadol hydrochloride 100 mg/2 mL	No common drugs listed in published data	Diazepam, midazolam	This is a relatively recently marketed drug on which there is a paucity of published compatibility data

by formulation in a high pH solution, usually as a sodium or potassium salt (for example, benzylpenicillin sodium). Any change in pH towards the other end of the pH scale will reduce the proportion of ionised to un-ionised drug in solution and will therefore reduce the water solubility of the drug.

The most prominent example of a pH-related reduction in solubility is dilution of phenytoin sodium injection.The drug is formulated with non-aqueous solubilising agents and the solution is adjusted to a pH of 12. Dilution of injectable phenytoin by adding it to an infusion bag lowers its pH and therefore reduces its solubility resulting in precipitation of the drug. Glucose 5% infusion solution, which has a pH of 4.3 – 4.5, will precipitate phenytoin almost immediately. Indeed, phenytoin injection is so incompatible that it should generally not be mixed with any other solution.

Ionic reactions forming insoluble substances

The salts of monovalent cations, such as sodium and potassium, are generally more soluble than those of divalent cations, such as calcium and magnesium. Mixing solutions containing calcium or magnesium ions has a substantial risk of forming an insoluble calcium or magnesium salt. Mixing magnesium sulfate 50% and calcium chloride 10% results in precipitation of insoluble calcium sulfate. The mixing of drug salts of calcium, and to a lesser extent magnesium, with phosphates, carbonates, bicarbonates, tartrates or sulfates should also be avoided. A recent warning has been issued about mixing calcium-containing solutions, including Hartmann's solution, with ceftriaxone causing the formation of the insoluble ceftriaxone calcium salt.[1]

Denaturation of biological molecules

Biological substances including blood products and insulin are prone to denaturation when exposed to variations in pH and osmolality. While published compatibility data exist for insulins and some of the blood products, most recently marketed biological drugs such as infliximab, interferons and recombinant coagulation factors have no such data available and mixing with other drugs is not recommended.

Evolution of gas

Addition of an acidic drug solution to a solution containing a carbonate or bicarbonate may result in production of carbon dioxide gas. However, the evolution of gas is a normal part of the reconstitution of some drugs, notably ceftazidime.

Use reliable reference material

Some incompatibilities are eminently predictable from simple chemical knowledge, but most compatibilities and incompatibilities are not so easily predicted. For this reason, the decision to mix any two injection solutions whether in a syringe, in an infusion bag or at a Y-site should be based on a reliable reference. However, published data are specific to the concentration, solvent, ambient temperature and sometimes the composition of the syringe or infusion bag. A number of references, in addition to the manufacturer's product information, are available. These include the Australian Injectable Drugs Handbook.[2] Table 1 shows some of the compatibility and incompatibility data currently available.

Palliative care

There are a number of drugs that are commonly delivered via syringe driver to patients having palliative care in the community (see box). Combinations of two, three or more of these drugs occasionally need to be co-administered via syringe driver. Specialist references dealing with their mutual compatibilities need to be consulted.[3,4]

Combinations of drugs commonly used in palliative care *

Haloperidol and midazolam

Hydromorphine and clonidine

Metoclopramide and atropine

Metoclopramide and midazolam (and morphine)

Metoclopramide and morphine

Morphine and clonidine

Morphine and glycopyrrolate

Morphine and midazolam

* In palliative care settings and in chronic pain control, combinations of as many as four of these drugs may be mixed in the same syringe for use in a syringe driver over 24 hours.

Conclusion

While some general principles can be applied to the mixing of injection solutions, they are fraught with exception and applicability varies with circumstance. Mixing is best avoided. If circumstances are so compelling as to warrant mixing any two or more solutions, there should be

support from published compatibility data. A visual check for precipitation, turbidity or colour change should be carried out before administering the mixture, but does not guarantee compatibility.

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Further reading

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Conflict of interest: none declared.

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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)**
Pregabalin	Pregab	Capsule, 150mg	Madras, India	Pharma Associates	Antiepileptic
Lapatinib	Tykerb	Tablet, 250mg	Glaxo, UK	GSK	Breast cancer
Calcium polystyrene sulfonate	Kreduce	Oral powder, 15g /sachet	SG Pharma, India	Lifeserv	Hyperkalaemia
Ciclesonide	Osonide	Inhaler, 80mcg and 160mcg/dose	Ranbaxy, India	Hemas	Asthma
Tiotropium bromide	Tiova	Inhaler, 9mcg/dose	Cipla, India	Citihealth	Bronchodilator
Escitalopram	Nexito 20	Tablet, 20mg	Sun, India	Harcourts	SSRI
Risedronate	Oseorise	Tablet, 5mg	CCL, Pakistan	Hemas	Bisphosphonate
Nimotuzumab	BIOMab EGFR	Injection, 50mg/10ml	Biocon, India	ABC Pharma Services	Monoclonal antibody
Metolazone	Metoz	Tablet, 5mg	Centaur, India	Harcourts	Diuretic
Telbivudine	Sebivo	Tablet, 600mg	Novartis, Switzerland	Baurs	Antiviral

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