# APPENDICES

## Appendix 1 Solution to Problem Directed Study

### SOLUTION 1.1

a. Since the child is seriously ill, a fast and more predictable action of the antibiotic is needed; a parenteral route of administration is appropriate. Moreover, oral dosing may be difficult in this case as the child is dull and irritable. Entering a vein for i.v. injection is relatively difficult in children, particularly in the presence of dehydration. Therefore, the antibiotic may be injected i.m. However, if an i.v. line is set up for rehydration, the antibiotic may be administered through the i.v. line.
b. In this case the provisionally selected antibiotic should be started as early as possible, because the child is seriously ill. Waiting for the lab. reports to confirm the diagnosis/select the definitive antibiotic may compromise the prognosis.

### SOLUTION 2.1

a. Gastric acid is required for the absorption of oral iron salts. Concurrent ingestion of antacid tablets could have interfered with iron absorption. Hence, the anaemia failed to improve.

### SOLUTION 2.2

a. Aspirin displaces sulfonylureas from plasma protein binding sites. Therefore, plasma concentration of unbound (and active) glibenclamide would have risen after aspirin ingestion causing hypoglycaemia which produced the symptoms. As such, glucose ingestion relieved the symptoms.
b. Paracetamol and ibuprofen are analgesics equally effective in toothache as aspirin, and do not displace or otherwise interact with sulfonylureas. As such, these analgesics are more suitable for the given patient.

## SOLUTION 3.1

a. Rifampin is known to induce the metabolism of contraceptive steroids. Thus, after regular intake of rifampin for more than 2 weeks (needed for enzyme induction) the steady-state blood level of levonorgestrel and ethinylestradiol could have fallen below the threshold for inhibition of ovulation/contraception. As such, fertility was restored and the woman conceived.

b. In view of the essentiality of rifampin (and other antitubercular drugs) in this patient and the likelihood of failure of the oral contraceptive, the couple should have been advised to take additional/alternative contraceptive measure such as condom or intrauterine contraceptive device.

## SOLUTION 3.2

The total volume of distribution and total body clearance for this patients has to be calculated first.

Total V = 1.4 L/kg × 60 kg = 84 L

Total body clearance (CL) = 80 ml/hr/kg × 60 kg

= 4.8 L/hr

Fractional bioavailability (F) $= \frac{70}{100} = 0.7$

Applying the formula:

Loading dose $= \frac{\text{target Cp} \times V}{F}$

Or $\frac{6 \text{ mg/L} \times 84 \text{ L}}{0.7} = 720 \text{ mg}$

Maintenance dose rate $= \frac{\text{Cpss} \times \text{CL}}{F}$

Or $\frac{6 \text{ mg/L} \times 4.8 \text{ L/hr}}{0.7} = 41 \text{ mg/hr}$

Or 41 mg/hr × 24 hr = 984 mg/day

For this patient: Loading dose 720 mg initially; or practically 3½ tablets of 200 mg each.

Maintenance dose: 984 mg/day.

To be practical, the maintenance dose could be one 400 mg tab. in the morning and 1½ tab. (600 mg) in the evening.

## SOLUTION 4.1

a. Since Mtx binds to the same site of DHFRase as the endogenous metabolite DHFA, it will act as a competitive inhibitor. However, because the binding affinity of Mtx for the enzyme is 50,000 times greater, even excess DHFA will not be able to displace it from the enzyme and nonequilibrium type of inhibition will be produced.

b. Folic acid administered as a drug will not be able to counteract Mtx toxicity because it will not be converted to the active coenzyme form THFA. On the other hand, folinic acid will supply readymade active coenzyme THFA and will be able to overcome Mtx toxicity.

## SOLUTION 5.1

a. The most likely pathogenesis of the symptoms on the 3rd day of brisk diuretic therapy in this patient is occurrence of hypokalaemic alkalosis, which precipitated hepatic encephalopathy. In cirrhotics with moderate to severe hepatic dysfunction, ammonia ($NH_3$) produced by gut bacteria is not completely detoxified (by conversion to urea) in the liver. Blood $NH_3$ tends to rise. This ionizes partly to $NH_4^+$ and is excreted in urine as $NH_4Cl$. The $NH_4^+$ ions do not cross the blood-brain barrier. During alkalosis, $NH_3$ ionizes to a lesser extent, raising blood $NH_3$ level which enters brain to cause encephalopathy. Weakness and postural hypotension are the other manifestations of hypokalaemic alkalosis.

b. The diuretic should be withheld till the fluid electrolyte and acid-base balance is restored. Intravenous infusion of KCl along with normal saline can hasten recovery from hypokalaemia and alkalosis. Oral lactulose (a nonabsorbable disaccharide) helps in reducing blood $NH_3$ level by producing acidic degradation products in the gut which convert $NH_3$ into poorly absorbed $NH_4^+$ ions. Moreover, lowering of stool pH by lactulose has a suppressant effect on $NH_3$ producing gut bacteria.

## SOLUTION 6.1

a. The patient has a serious disease for which many effective drugs are available. As such, antitubercular treatment should be continued, albeit with nonhepatotoxic drugs.

b. The criteria for causality assessment, *viz.* temporal relationship, previous knowledge, dechallenge and rechallenge should be applied to identify the causative drug. In this case, the reaction occurred in the 4th week of drug therapy which is consistent with the time-sequencing of drug-induced hepatitis. The reaction can be confirmed and the actual causative drug identified by dechallenge and rechallenge.
   - Stop all suspected drugs (H, R and Z); treat the patient with E and two other nonhepatotoxic drugs, preferably streptomycin (i.m.) and a fluoroquinolone (e.g. levofloxacin). If the jaundice clears in the subsequent weeks, dechallenge is positive (one or more of the 3 stopped drugs had caused hepatitis).
   - Rechallenge by reintroducing the stopped drugs, one at a time, and repeatedly monitor liver function tests.
   - Generally, R is started first followed by H after 7–10 days. If both are tolerated, Z could have been the causative drug. In any case, after completing the intensive phase with H+R+E, the continuation phase with H+R should be extended to 9 months.
   - If R is implicated, it should be stopped as soon as the liver function tests become abnormal. Start H and continue H+E+S for 2 months followed by H+E for 10 months.
   - If H is implicated, it should be stopped immediately, and R+E+Z may be given for 9 months.

In this way, the implicated drug can be identified and antitubercular therapy completed with minimal use of parenteral/2nd line drugs.

## SOLUTION 7.1

a. The diagnosis of myasthenia gravis can be confirmed by the '*edrophonium test*'. Edrophonium is injected i.v. (2 mg initially which if tolerated; followed by 8 mg after 30–60 sec). Reversal of ptosis, diplopia and increase in the strength of affected muscles lasting 5–10 min constitutes a positive result.

   In case edrophonium is not available, the test can be performed with neostigmine 1.5 mg i.v. Atropine 0.6 mg may be given i.m./i.v. to block the muscarinic side effects of edrophonium/ neostigmine.

b. Myasthenia gravis is an autoimmune disorder due to production of antibodies against the nicotinic receptor at the muscle end-plate. No drug is curative. Both anticholinesterases (neostigmine, etc.) and corticosteroids (other immunosuppressants as well) afford only symptomatic relief till administered. The former preserve ACh and improve neuromuscular transmission, while the latter inhibit the immunological reaction, without removing the cause of the illness.

c. In many cases (especially older men), thymus is the source of the nicotinic receptor antigen. As such, thymectomy has been found to lower disease activity and even induce long-lasting remission.

## SOLUTION 8.1

a. Dimenhydrinate is a $H_1$ antihistaminic-antivertigo drug with potent antimuscarinic action. Since muscarinic cholinoceptors mediate neurogenic contraction of the detrusor muscle, antimuscarinic drugs interfere with vesical contractions needed for urination. Elderly men with benign hypertrophy of prostate have bladder neck obstruction and are prone to develop urinary retention as a side effect of antimuscarinic drugs. This patient has history indicative of prostatic hypertrophy. As such, all drugs having antimuscarinic activity must be given cautiously to elderly males.



## SOLUTION 9.1

a. The symptoms and intraocular pressure (i.o.p.) of this patient indicate that she is having gluaucoma in both eyes. Phenylephrine (10%) eyedrop would be the suitable mydriatic for her. Phenylephrine is an $\alpha_1$ adrenergic agonist that dilates the pupil by increasing the tone of radial muscles of iris, which are adrenergically innervated. It does not produce cycloplegia because the ciliary muscles lack adrenergic motor innervation. Cycloplegia causes blurring of near vision and is not required in this patient. Phenylephrine is not likely to raise i.o.p. in glaucoma patients. On the other hand, antimuscarinic mydriatics like tropicamide, cyclopentolate, etc. produce both mydriasis and cycloplegia, and tend to raise i.o.p. in glaucoma patients. Therefore, antimuscarinics are to be avoided in glaucoma patients.

## SOLUTION 10.1

a. The smooth muscles of the bladder neck and prostatic urethra are constricted by sympathetic innervation via $\alpha_1$ adrenergic receptors. Terazosin being $\alpha_1$ receptor blocker reduces the dynamic component of urinary obstruction in benign prostatic hypertrophy, improves urinary flow and affords symptomatic relief.

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b. The $\alpha_1$ adrenergic receptors also mediate reflex vasoconstriction in the lower extremity and trunk which occurs on standing up from a reclining position to maintain cerebral blood flow. Terazosin blocked these $\alpha_1$ receptors as well; reflex vasoconstriction failed to occur when this patient got up from bed to pass urine; blood supply to brain suffered and the patient fainted. That is why he soon regained consciousness on being laid flat on the bed. Such an event is especially likely to occur after the first dose when compensatory haemodynamic adjustments have not taken effect.
c. The patient should have been advised not to spring up from the bed. He should first sit on the bed for few minutes and then slowly assume the erect posture. This would allow time for the reflex adjustments.

The 5 mg terazosin dose is a high starting dose. Therapy should have been initiated at 1 mg daily dose, with upward titration every 1–2 weeks according to the symptomatic relief obtained and the haemodynamic tolerance by the patient.

## SOLUTION 10.2

a. Timolol is a potent lipophilic, nonselective ($\beta_1$ + $\beta_2$) adrenergic blocker. In this patient of mild episodic asthma, the drug in the eyedrops appears to have been absorbed systemically during drainage through the nasolacrimal ducts and precipitated severe bronchospasm by blocking bronchodilator adrenergic $\beta_2$ receptors. Since timolol is a competitive antagonist, its action could be overcome by higher concentration of salbutamol in the nebulized aerosol supplemented with the anticholinergic ipratropium bromide to block the reflex vagal bronchoconstriction.
b. This complication could have been prevented by eliciting the history of episodic asthma and avoiding β-blocker ocular hypotensive drug. Latanoprost (a prostaglandin analogue) would be a more suitable antiglaucoma drug for this patient. In case, it was imperative to use an ocular β-blocker, the $\beta_1$ selective antagonist betaxolol would be a safer alternative. It is also prudent to start with 0.25% timolol drops and change to 0.5% drops only when needed. In any case, the patient should be advised to apply mild pressure by fingertip for few minutes at the inner canthus of the eye after each eyedrop instillation to prevent passage of the drug into the nasolacrimal duct.

## SOLUTION 11.1

a. Since histamine is an important mediator of allergic rhinitis, the $H_1$ antihistaminics afford rapid symptomatic relief. A non-sedating second generation antihistaminic like loratadine, des-loratadine or fexofenadine would be suitable for this patient, who is a taxi driver. These drugs are least likely to impair alertness and driving. The first generation sedating antihistamines like promethazine, hydroxyzine, chlorpheniramine, clemastine, etc. are contraindicated if the recipient has to drive. Even the second generation antihistaminic cetirizine impairs psychomotor performance and should be avoided in this patient.

   However, antihistaminics have no prophylactic effect. Because the patient has recurrent episodes during spring, he should in addition be prescribed a topical corticosteroid like budesonide or fluticasone nasal spray, starting just before and continuing all through the season to prevent further attacks of rhinitis.

## SOLUTION 13.1

a. Prostaglandin $E_2$ (Dinoprostone) has the property to soften the cervix and make it more compliant at term. Applied to the cervix or inserted into vagina, low doses of dinoprostone act within a few hours and help to ripen the cervix so that it is 'taken up' and dilates to allow passage of the presenting part. Side effects are minimal with these routes of administration. The preferred formulation for this purpose is the cervical gel containing 0.5 mg of dinoprostone in 2.5 ml gel. It should be inserted into the cervical canal. Alternatively, the vaginal gel containing 1.0 mg in 2.5 ml should be deposited at the posterior fornix of vagina. These doses of $PGE_2$ only affect the cervix and do not significantly augment uterine contractions.

b. Since the patient has no anaemia or toxaemia of pregnancy or cephalopelvic disproportion, presentation is correct and head is engaged, there are no contraindications to the use of $PGE_2$.

## SOLUTION 14.1

a. Paracetamol taken in adequate doses (upto 2.6 g per day) is the most suitable analgesic for relieving knee pain in the given patient. Unlike many NSAIDs, it does not increase the risk of myocardial infarction/stroke. Paracetamol does not inhibit endothelial $PGI_2$ synthesis, does not affect platelet function and does not nullify the cardioprotective effect of low dose aspirin. Moreover, it is a first-line drug for osteoarthritic pain, and is well tolerated with minimal gastric side effects.

b. The selective COX-2 inhibitors (celecoxib, etoricoxib) are not suitable for this patient, because they increase the risk of heart attack and stroke by inhibiting endothelial $PGI_2$ synthesis. Diclofenac is also not free of such risk. Though propionic acid NSAIDs (ibuprofen, etc.) are nonselective COX inhibitors which do not increase thrombotic risk, they block the cardioprotective effect of low dose aspirin that this patient is taking.

c. Topical NSAIDs, e.g. diclofenac/ketoprofen gel can afford adjuvant symptomatic relief in this patient. Since blood levels of NSAIDs after local application are low, they are well tolerated and do not increase cardiovascular risk.



## SOLUTION 16.1

a. The recently developed symptoms of the patient are indicative of early stage theophylline toxicity. Erythromycin is an inhibitor of several hepatic microsomal enzymes, including those that metabolize theophylline. As such, when the patient took erythromycin, metabolism of theophylline appears to have been retarded, causing rise in its plasma concentration over the next 2 days and producing overdose symptoms.

b. This complication could have been prevented in *two* ways, *viz*—

   i. When erythromycin was prescribed, the daily dose of theophylline should have been reduced from 800 mg to 500 mg, and maintained at this level till the patient was taking erythromycin.

   Or

   ii. An alternative antibiotic (e.g. a β-lactam like amoxicillin or cephalexin) which does not inhibit theophylline metabolism but is effective in sore throat, could have been selected for this patient.

## SOLUTION 18.1

a. Since carbimazole inhibits further synthesis of thyroid hormones ($T_3$, $T_4$) without affecting their release or action, the hormone stored in the gland continues to be released and produce effects. Moreover, thyroxine has a long plasma t½ of 6–7 days. Thus, the effect of carbimazole starts manifesting only after 2–3 weeks and peaks after 2–3 months.
   Many of the symptoms of thyrotoxicosis are due to sympathetic overactivity. Blockade of β adrenergic receptors ($\beta_1$ and $\beta_2$) by propranolol or similar drug affords rapid symptomatic relief, without affecting thyroid status. A nonselective β-blocker given to her along with carbimazole could have controlled palpitation, tremor, etc. within a few days. This drug could be withdrawn when carbimazole had taken effect.
b. The reappearance of neck swelling without any symptom of thyrotoxicosis indicates that it is due to deficient feedback inhibition of TSH by a suboptimal thyroid hormone level as a result of higher maintenance dose of carbimazole. This is supported by the mild hypothyroid symptoms experienced by the patient and the raised TSH level alongwith low normal $FT_4$ level. The raised TSH is stimulating the thyroid so that despite its low functional status, deficiency is not marked. Since the disease activity in Graves' disease may decline after some time, the maintenance dose of carbimazole needs to be adjusted from time-to-time according to the assessed clinical and laboratory thyroid status of the patient. This patient requires temporary discontinuation of carbimazole followed by a lower maintenance dose as assessed later.

## SOLUTION 19.1

a. According to the current recommendation of professional guidelines, the patient should be prescribed metformin therapy concurrently with dietary and lifestyle measures. This is based on the finding that metformin can delay progression of diabetes and prevent microvascular as well as macrovascular (heart attack, stroke) complications. It does not increase circulating insulin, reduces insulin resistance, is unlikely to induce hypoglycaemia and may have a positive influence on pancreatic B cell health. Lack of serious toxicity over several decades of use of metformin is well established. No other antidiabetic drug has all these favourable features, and therefore, it is considered the first-choice drug. Metformin is particularly suitable for this patient who is overweight, because it can aid weight reduction. A combination of antidiabetic drugs is not indicated at this stage. Another drug needs to be added only when the target blood glucose and $HbA_{1c}$ levels are not attained by metformin alone.

## SOLUTION 20.1

a. The patient has received supraphysiological doses of a corticosteroid for more than 3 weeks, and is likely to have developed hypothalamo-pituitary-adrenal (HPA) suppression. The injury and surgery are a stress which need excess corticoid activity. The depressed HRA axis may not be able to cope up with increased demand, and there is risk of developing acute adrenal insufficiency. As such, hydrocortisone hemisuccinate 100 mg should be infused i.v. during surgery and repeated 8 hourly till the patient is stable.
b. Prednisolone therapy must not be stopped in the postoperative period apprehending spread of infection and delayed healing. Effective antibiotic medication to prevent wound infection should be given and prednisolone dose should be increased temporarily (for a week or so) to 20 mg/day, till the stress of the trauma and surgery subsides.

## SOLUTION 21.1

a. This is a case of advanced metastatic prostate carcinoma, for which only palliative therapy with androgen deprivation (tumour cells remain androgen dependent) is possible. When orchidectomy has been refused, the most effective method of androgen deprivation is to give a long acting GnRH agonist. Thus, the choice of triptorelin is correct. The GnRH agonists initially increase LH (also FSH) release for 1–2 weeks, followed by receptor desensitization and nearly total blockade of LH secretion by 3–4 weeks. The raised LH levels in the beginning stimulate testis to secrete more testosterone which activates tumour cells resulting in increased bone pain and bladder obstruction noticed after 1 week of therapy in this patient.

b. The initial flaring of symptoms can be avoided by pretreating with an antiandrogen bicalutamide 50 mg orally daily for 3 days before starting triptorelin injection and then continuing both drugs together. The stimulatory effect of excess testosterone on tumour cells would be blocked by bicalutamide so that no flaring of symptoms would occur. The combined androgen blockade with GnRH agonist + androgen antagonist is the favoured approach.

c. The patient can be given an antiresorptive drug in addition to relieve bone pain. A potent parenteral bisphosphonate like zoledronate infused i.v. over 15 min every 1–4 weeks is the most effective drug for this purpose. It may also retard growth of the bony metastasis for some time.



## SOLUTION 22.1

a. The most likely cause of endometrial thickening in this patient is tamoxifen therapy. Tamoxifen is a selective estrogen receptor modulator (SERM) which has estrogen antagonistic action in the breast (basis of its use in breast carcinoma), but agonistic action on the endometrium which stimulates proliferation. Such unopposed (by progestin) hyperproliferation can produce thickening and predisposes to endometrial carcinoma.

b. For the reason stated above, tamoxifen should not be continued in this patient. Total stoppage of adjuvant therapy is not advisable, because estrogen suppression therapy has been shown to exert protective effect for atleast 5 years. Aromatase inhibitors, which block synthesis of estrogens in the body, have been clearly demonstrated to prevent recurrence of breast cancer, without stimulating endometrial proliferation or predisposing to endometrial carcinoma. Therefore, in this case, tamoxifen should be replaced by letrozole 2.5 mg /day or anastrozole 1.0 mg/day for the next 5 years. Due precautions to prevent osteoporosis and measures to address arthritic symptoms, if they develop, should be taken concurrently.

## SOLUTION 22.2

a. All diseases and conditions which contraindicate use of oral contraceptives or need caution in their use have to be ruled out before prescribing one to this subject. Full medical history, including menstrual history and past pregnancy details should be elicited. Any thromboembolic episode, jaundice or toxaemia of pregnancy should be ascertained. History of smoking, diabetes, hypertension, migraine, tuberculosis and gallbladder disease should be specifically asked. Any medication that she is taking and the reason for it should be taken into account to

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foresee possible interactions with the contraceptive. Whether she is obese or very lean also matters in selecting the contraceptive preparation. General physical examination, including palpation of breast, for any lump and a per vaginum examination for fibroid/other tumour, should be done. Blood pressure should be recorded to rule out hypertension. Fasting and postprandial blood glucose, lipid profile should be ordered to detect diabetes and dyslipidaemia. Ultrasound examination of pelvic organs should be performed for uterus size, fibroid, ovarian cyst or malignancy.

Only after all the above findings are favourable that an oral contraceptive be selected and prescribed.

## SOLUTION 23.1

a. Though the progress of labour in this case is tardy and uterine contractions are relatively weak, there are signs of foetal distress (passage of meconium stained liquor, rapid foetal heart becoming irregular during uterine contraction). Moreover, the mother is dehydrated and exhausted. As such, the best course of action is to deliver the baby by caesarean section.
b. The mother should not be administered an oxytocic drug, because stronger uterine contractions are likely to worsen foetal distress and pose risk to the baby. The mother is also not in a fit condition to endure the stress of a difficult labour.

## SOLUTION 25.1

a. Rocuronium is the preferred muscle relaxant for tracheal intubation and short lasting muscle relaxation in this patient. Succinylcholine (SCh), the fastest and shortest acting muscle relaxant which is most commonly used for aiding tracheal intubation, is not suitable for this patient, because it is a depolarizing blocker and releases $K^+$ from skeletal muscles. Since this patient has extensive burns and tissue injury, which itself causes hyperkalemia due to leakage of $K^+$ from injured cells, the $K^+$ released by SCh will accentuate the hyperkalemia and expose the patient to risk of cardiac arrhythmias and other complications.

   Rocuronium, on the other hand, is a nondepolarizing blocker which does not trigger loss of intracellular $K^+$. It is the fastest acting nondepolarizing blocker with speed of action approaching that of SCh. Intubating conditions can be obtained in 60–90 sec. It also provides surgical grade relaxation for 25–40 min, along with good cardiovascular stability.

## SOLUTION 26.1

a. Labour pain as well as that due to stretching of the birth canal can be largely relieved by spinal as well as epidural anaesthesia. It is desirable, at the same time, not to produce motor block so that the mother can actively participate in the process of labour. Since motor fibres are less sensitive to local anaesthetics (LAs) than sensory fibres, motor block of a lower level is usually produced during spinal anaesthesia. Such separation is more pronounced with epidural anaesthesia. Lidocaine and bupivacaine are the two LAs commonly used for epidural anaesthesia. Out of these, bupivacaine is more suitable for this purpose for the following reasons:

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- It provides greater separation of sensory from motor block. Separation is still larger when lower concentration (0.25% bupivacaine) is used.
- Because of higher lipid solubility, its tissue distribution is large and maternal blood levels are lower. Less drug is likely to cross to the foetus, reducing chances of neonatal depression.
- It is longer acting.

Thus, epidural anaesthesia with 0.25% bupivacaine is most suitable for this patient.

## SOLUTION 28.1

a. Alcohol exerts anticonvulsant action while its concentration in the brain is rising or is maintained. This is followed by lowering of seizure threshold when the concentration falls and becomes zero. Thus, recurrence of seizures in this patient could most likely be due to the temporarily increased susceptibility to seizures caused by withdrawal of alcohol from the brain.

b. Since this lowering of seizure threshold is a short-term problem, no abrupt change in antiepileptic medication or alteration of dose is warranted at this stage. The patient should be kept under observation for few days/weeks and decision about further antiepileptic therapy taken only on the basis of the subsequent course of events. The patient also must be advised to strictly avoid alcoholic drinks in future.



## SOLUTION 29.1

a. Since this patient does not require a hypnotic on regular basis, there is no identifiable cause of occasional sleep onset difficulty and he has tried non-drug measures, he can be prescribed a hypnotic to be kept handy for use when required. Because there is only sleep onset difficulty, and he will take the drug only later at night (after going to bed as usual), he needs a short acting hypnotic which would be free of residual effect next morning. Zaleplon would be suitable for this patient, as it has a short t½ (1 hour), does not cause next morning drowsiness, day time anxiety or rebound insomnia. Tolerance is unlikely to develop, because use is going to be occasional.

## SOLUTION 30.1

a. The husband of the patient should be instructed that at the first sign of a seizure attack the patient should be laid on bed or ground in the prone or lateral position with neck extended to ensure free airway. A wooden/plastic gag should be placed between the teeth to prevent biting of tongue. No emergency medicine is required during or just after the fit. Only reassurance and moral support are needed. These instructions should be shared will other family members, so that anyone who is closeby may do the needful.

b. Because the patient has a history of head trauma and two seizure attacks have occurred within one week, the probability of developing epilepsy is high. As such, antiepileptic medication should be started rightaway without waiting for test reports or further fits to occur.

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c. Therapy should be initiated with a single antiepileptic drug. Antiepileptics with proven efficacy in post-head injury tonic-clonic seizures are phenobarbitone, phenytoin, carbamazepine and valproate. Since the patient is a young active lady, phenobarbitone with sedative/cognitive side effects, phenytoin with gum hyperplasia, hirsutism and other cosmetic side effects, and valproate with tremor and weight gain would be less suitable. Carbamazepine appears to be the most appropriate initial drug in this case.

## SOLUTION 31.1

a. The parkinson's disease of this patient appears to have advanced over the last 5 years and he is now experiencing 'wearing off effect' of levodopa-carbidopa. He is also developing dyskinesia, a late adverse effect of the drug. At this stage, antiparkinsonian medication cannot be withdrawn, because he will develop marked rigidity, immobility and tremor hampering life activities. He is already experiencing an adverse effect of his medication; therefore, the dose should not be increased further.

   Since levodopa-carbidopa is the most efficacious and cheapest medication for parkinsonism, it may be prudent to continue it at a reduced dose and supplement it with another longer acting drug to smoothen the therapeutic effect. The options available as supplementary medication are:

   - A direct dopamine agonist like ropinirole/pramipexole can be gradually added to levodopa-carbidopa whose dose should be reduced in steps. Both drugs can be taken concurrently 3 times a day. Ropinirole/pramipexole being longer acting will smoothen symptom control. They also produce less dyskinesia.
   - A MAO-B inhibitor like selegiline 5 mg twice a day or rasagiline 1 mg once a day in the morning will prevent degradation of dopamine in the brain, prolonging and smoothening effect of levodopa-carbidopa.
   - Entacapone 200 mg with each dose of levodopa-carbidopa can also potentiate and prolong levodopa action by inhibiting another metabolizing enzyme COMT. It can also be an additional third drug to levodopa-carbidopa + selegiline for greater symptomatic relief.



## SOLUTION 32.1

a. The most likely cause of the motor restlessness exhibited by the patient after 4 weeks of haloperidol therapy is appearance of a common extrapyramidal side effect of the antipsychotic drug called 'akathisia'. The symptom does not appear to be due to inadequate dose of haloperidol, because the psychotic symptoms have been relieved and the initial psychomotor restlessness had been controlled. There is no return of anxiety, hallucinations, etc. As such, there is no need to increase the dose of haloperidol. Dose reduction may be tried but return of psychotic symptoms is a risk. One of the atypical antipsychotic drugs may be substituted for haloperidol. Quetiapine with its sleep promoting effect will be more suitable in this case. The atypical antipsychotics have a low propensity to cause extrapyramidal motor side effects, including akathisia.

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b. For early resolution of motor restlessness, a benzodiazepine, e.g. clonazepam 1 mg or diazepam (5 mg) 2–3 times a day may be given. This may be supplemented by trihexyphenidyl 2 mg 3 times/day. In case the akathisia persists, propranolol 40 mg 2–3 times a day may be added.

## SOLUTION 33.1

a. Sertraline is a selective serotonin reuptake inhibitor (SSRI) and a first-line drug for major depression. The choice of drug is correct and the 50 mg twice daily an average dose for initiation of therapy. However, since antidepressant action of any drug (including sertraline) takes 2–4 weeks to manifest, it is too early at 1 week to expect any improvement in depressive symptoms. The dose is not subtherapeutic as indicated by appearance of mild side effects, which nevertheless are quick to appear, but to whom gradual tolerance usually develops. Restlessness, nausea, dyspepsia, epigastric distress, anorexia are expected side effects of SSRIs. The patient and his family members should be counselled to continue the medication for another 3–4 weeks by which time symptoms should start improving. The choice of drug is appropriate, and at this stage, there is no reason to change the medicine or its dose. No additional drug needs to be added at this stage.



## SOLUTION 34.1

a. Symptoms and signs indicate that the patient is going into neurogenic shock due to the excruciating pain of the crush injury. As such, the first priority is to relieve the acute pain. Morphine 5 mg should be injected i.v. immediately. It will not only lessen the pain and suffering of the patient, but also allay apprehension and counteract neurogenic shock. It will facilitate proper examination and first aid measures as well. Supplemental doses may be given every 2–3 hours. An i.v. infusion of saline should be started at the earliest to restore blood pressure and maintain tissue perfusion.

## SOLUTION 35.1

a. The primary reason for no improvement in the state of the patient is that all medicines, including donepezil, take weeks and months before any perceptible improvement in Alzheimer's symptoms become apparent. Moreover, donepezil (or any other drug) is not effective in a significant number of patients. However, one week is too short a time to know whether this patient is going to benefit or not. Since this patient has developed intolerable cholinergic side effects, they are due to donepezil which should be discontinued.

No other anticholinesterase drug is likely to be tolerated by this patient. Therefore, a drug which acts by a different mechanism could be used in this patient. Memantine is the only other drug, with documented efficacy in moderate to severe Alzheimer's disease, which is not a cholinergic drug, and which probably acts by blocking glutamate excitotoxicity. It is better tolerated and does not produce cholinergic side effects. However, improvement in memory and cognitive function is less likely, and it may only serve to slow the functional decline.

## SOLUTION 36.1

a. The weakness, nausea, sweating and fainting suffered by the patient is due to the marked rapid fall in BP caused by captopril (and augmented by furosemide). Congestive heart failure patients have an overactive renin-angiotensin system (RAS) which helps in maintaining haemodynamics in the face of low cardiac output. Captopril is a rapidly acting ACE inhibitor, which, given in doses used for hypertension, removes the RAS support (angiotensin II is not formed) and causes marked fall in BP. This is aggravated by $Na^+$ loss caused by the diuretic.
b. Though, a slower acting ACE inhibitor, e.g. enalapril, would be less likely to cause rapid fall in BP, captopril cannot be considered a wrong choice of drug, provided it is initiated at $1/4^{th}$ dose. In CHF, captopril therapy should be initiated at 6.25 mg dose, which can be gradually increased as haemodynamic adjustments take place.
c. The reaction could have been avoided by initiating captopril at 6.25 mg twice daily dose. A slower acting ACE inhibitor (at low starting dose) could be still less likely to produce acute hypotension.
d. The first measure to be taken in this case is to put the patient in 15° head low position. This could be supplemented by short-term fluid and electrolyte infusion. A pressor agent is rarely needed.

## SOLUTION 37.1

a. This patient of moderate CHF is in a decompensated state with dilated heart. Though, the diuretic (furosemide) and ACE inhibitor (enalapril) will relieve symptoms slowly, they may not be sufficient to restore a compensated cardiac status. Digoxin should be prescribed concurrently as it is the most effective drug for restoring compensation by increasing cardiac contractility. The features of this patient do not indicate any urgency. Therefore, the patient may be started with an average maintenance dose 0.25 mg/day of digoxin. It is expected to produce peak effect after 5–7 days. Dosage adjustment may be done after that depending on the response.
b. Enalapril dose of 5 mg twice a day should be increased by 5 mg/day at 1–2 week intervals till hypotension or other side effects appear or 40 mg/day dose is reached. For maximum prognostic benefit, ACE inhibitors have to be used at or near the highest permissible dosage. Enalapril should not be stopped unless compelled by an adverse effect, because it continues to retard worsening of CHF and avoid complications.
c. Since the patient is in a decompensated state, a β blocker cannot be added at this stage, because chances of deterioration of cardiac status are high. However, after compensation has been restored by digoxin, diuretic and enalapril and the patient is in a stable condition, a suitable β blocker may be started at a very low dose, to be upward titrated later, because β blockers afford further morbidity and mortality benefits.

## SOLUTION 38.1

a. The patient has been having atrial fibrillation (AF) for at least the past one month. He is likely to have developed thrombii in the fibrillating atria, and is at risk of embolic stroke when sinus rhythm (SR) is restored. Therefore, he has been put on anticoagulant medication with warfarin to prevent thromboembolism. *Contd...*

b. His heart (ventricular) rate can be controlled by a drug which depresses A-V conduction. For this purpose verapamil or diltiazem or propranolol should be given orally and dose adjusted to maintain a heart rate between 60–70/min. Digoxin (0.25 mg/day) may be prescribed in addition if the target heart rate is not achieved by monotherapy.
c. If electrical cardioversion does not succeed, amiodarone 200 mg injected i.v. over 60 min may be tried for reversal to SR.
d. After restoration of SR, the same may be maintained by continued treatment with one of the following drugs, *viz.* sotalol/propafenone/amiodarone/dronedarone or disopyramide.

## SOLUTION 39.1

a. This patient is having one or more episodes of angina practically every day; therefore, he should be prescribed regular medication to prevent the episodes. The first line drugs for this purpose which can be given to this patient are:
   1. A long-acting nitrate *viz.* oral sustained release isosorbide mononitrate or similar drug morning and afternoon or transdermal glyceryl trinitrate patch applied in the morning and taken off at night.
   2. A long-acting calcium channel blocker, like amlodipine once a day.

Alternative second line or add-on drugs are:

Nicorandil ($K^+$ channel opener), or ranolazine ($I_{Na}$ current inhibitor), or trimetazidine (LC3-KAT inhibitor) or ivabradine ($I_f$ current inhibitor).

Since he is also suffering from COPD, he cannot be given a β blocker which is likely to precipitate severe breathlessness.

b. This patient is having coronary artery disease (CAD). None of the above drugs can alter the course of CAD or prevent complications like MI or death. He should in addition be put on long-term treatment with the following to arrest/delay the progression of CAD and to afford cardioprotection:
   1. An antiplatelet drug, such as low-dose aspirin or clopidogrel.
   2. A hypolipidaemic statin, such as atorvastatin.
   3. An angiotensin converting enzyme (ACE) inhibitor, such as enalapril.

## SOLUTION 40.1

a. Since the systolic BP is above 140 mm Hg and diastolic BP is below 90 mm Hg, this patient has 'isolated systolic hypertension'. Repeated measurements have confirmed the raised BP, therefore, antihypertensive medication is indicated. Therapy should be initiated with a single drug because he is stage I hypertensive (systolic BP <160, and diastolic BP <100 mm Hg). Considering the age of the patient (>55 years), diagnosis of isolated systolic hypertension, history of stroke in the past, absence of diabetes/heart failure/ischaemic heart disease/chronic kidney disease, the most suitable antihypertensive drug for this patient is a thiazide diuretic (hydrochlorothiazide/chlorthalidone) or a long-acting dihydropyridine calcium channel blocker (like amlodipine).

   Therapy may be initiated with either of these classes of drugs and later modified depending on the response and tolerability.

## SOLUTION 41.1

a. Induction of brisk diuresis with furosemide alone is not the appropriate treatment of cirrhotic edema and ascites. Hepatic cirrhosis is associated with raised aldosterone and low plasma $K^+$ levels. Therefore, the aldosterone antagonist spironolactone is the drug of choice. It can be supplemented by furosemide, because spironolactone alone is a weak diuretic. In this patient, use of furosemide alone resulted in further hypokalaemia and alkalosis. This indirectly raised blood $NH_3$ levels which crosses to the brain resulting in deterioration of mental status and neurological symptoms. Because of secondary hyperaldosteronism, the response to furosemide decreased within few days.

b. At this stage, the patient should be managed by temporarily stopping furosemide and instituting spironolactone (50 mg 6 hourly) therapy along with appropriate i.v. fluid and electrolyte infusion to correct the imbalance, guided by repeated plasma level monitoring. After restoration of the fluid/electrolyte balance and his mental status, the patient should be put on maintenance therapy with spironolactone (100–400 mg/day) and furosemide (40–160 mg/day) with dose adjustment according to response. If hormonal side effects of spironolactone occur, it may be substituted by the other aldosterone antagonist eplerenone. The potassium sparing non-aldosterone antagonist diuretic amiloride is an alternative.

## SOLUTION 43.1

a. There are several reasons which could account for failure of this patient of iron deficiency anaemia to respond to the oral iron medication she has been taking:
   - Taking 160 mg of ferric ammonium citrate (iron content 20%) would provide just 32 mg of elemental iron/day. This is grossly inadequate to treat iron deficiency, for which 200 mg of elemental iron/day is required to yield optimum response.
   - Iron in ferric ammonium citrate needs to be reduced to ferrous form before absorption. Therefore, its bioavailability is lower compared to ferrous salts.
   - Gastric acid is required to reduce ferric iron to ferrous iron and to facilitate iron absorption. This patient is taking acid suppressant medication (rabeprazole, a proton pump inhibitor).

   As such absorption of iron from the medicine that she took could be very low.

b. Since there are obvious factors in this case which can be tackled, it would be inappropriate to abandon oral iron therapy at this stage and jump on to injectable iron. Proper selection of oral iron preparation and its dose, and careful management of therapy may yield a response in this patient. A ferrous salt with high iron content like ferrous sulphate or ferrous fumarate (both having ~33% iron) should be prescribed in a dose of 200 mg 3 times a day (total 600 mg or 200 mg elemental iron/day). However, therapy should be initiated with a low dose to be gradually increased as the gastrointestinal tract adjusts to the medication and tolerance to side effects develops. The doses should preferably be taken in empty stomach, but if gastric discomfort occurs, it may be given with food. Selection of ferrous salt would reduce dependence on gastric acid for absorption of iron. However, if tolerated, an effort should be made to discontinue rabeprazole.

## SOLUTION 44.1

a. Passage of dark urine indicates bleeding in the kidney. This along with blood loss per vaginum has resulted in acute fall in Hb level. The rise in INR value is indicative of excessive deficiency of clotting factors, especially of prothrombin, factor X and factor VII due to relative warfarin overdose. The obvious cause in this patient is the additive hypoprothrombinaemic action of inj ceftriaxone given for treatment of pelvic infection.

   This complication could have been prevented either by selecting an antibiotic that does not cause hypoprothrombinaemia/interact with warfarin or by reducing the dose of warfarin when ceftriaxone was started. The new warfarin dose should have been arrived at by repeated determination of INR value till ceftriaxone was being given.

b. Further warfarin dose must be stopped immediately and vit K 10 mg injected i.m. at the earliest. The patient must be put on bed rest to reduce bleeding. Because Hb level is 9 g/dl, blood transfusion is not required at this stage, but must be kept handy in case she bleeds further. Repeat doses of vit K (5.0 mg i.m.) should be guided by frequent INR measurement and the severity of bleeding, avoiding too much vit K that would interfere with the protective effect of warfarin subsequently. Changing the antibiotic to one which does not cause hypoprothrombinaemia or bleeding may be considered on the basis of bacteriological sensitivity of the organism causing pelvic infection.



## SOLUTION 45.1

a. This subject, though asymptomatic, has four risk factors for coronary artery disease (CAD), *viz*.

   (i) He is a male above 45-year age, (ii) his body mass index (BMI) is >25, (iii) total and LDL-cholesterol (CH) are raised to values that are above the threshold for initiation of hypolipidaemic drug therapy, (iv) the HDL-CH is low (<40 mg/dl). Thus, apart from life-style changes to regulate diet, reduce body weight and increase physical exercise, he requires lipid lowering medication.

b. In view of his lipid profile, he should be treated with a 'statin' drug to lower LDL-CH to below 130 mg/dl. Thus, a 40% reduction in LDL-CH should be aimed. This is likely to be achieved by atorvastatin 20 mg/day or simvastatin 40 mg/day. After treating with either of the above medication for 4–6 weeks, attainment of the goal LDL-CH (<130 mg/dl) should be checked. In case, it is not met, the dose may be doubled. The aim should be to maintain his LDL-CH below 130 mg/dl. With this therapy, the TG level, which is borderline, is also expected to decrease and HDL-CH level to rise above 40 mg/dl.

## SOLUTION 46.1

a. This patient is suffering from recurrent peptic ulcer disease. The earlier episode of similar symptoms had responded to proton pump inhibitor (PPI) therapy. Therefore, it was also due to peptic ulcer. Symptom relief and ulcer healing can be achieved this time as well with the use of a PPI given for 4–8 weeks depending on endoscopic confirmation of ulcer healing. However, it alone cannot prevent recurrences, which most commonly are caused by persistent

*Contd...*

colonization of upper gastrointestinal tract by *H. pylori.* Since the same cannot be confirmed in the absence of testing facility, he should be given the benefit of *H. pylori* eradication therapy which largely prevents ulcer recurrences. A 3 drug, 2 week regimen would be the most effective option. Since he has a history of metronidazole use in the recent past, chances of nitroimidazole resistance are high, and he should be treated with a PPI (omeprazole 20 mg/lansoprazole 30 mg/pantoprazole 40 mg/rabeprazole 20 mg) + amoxicillin 750 mg + clarithromycin 500 mg, all given twice daily. The PPI should then be continued till endoscopic confirmation of healing is obtained, because the ulcer was larger than 10 mm in diameter.

## SOLUTION 47.1

a. This child has developed acute muscular dystonia, an extrapyramidal motor reaction that can be caused by drugs with dopaminergic D2 receptor blocking action. Antiemetics with D2 blocking action are chlorpromazine and related neuroleptics like triflupromazine, prochlorperazine, etc. and prokinetic drug metoclopramide. It is likely that the girl was given injection of one of these drugs by the local doctor, following which the vomiting had subsided and the dystonia had developed within 2–3 hours.
b. Though the dystonic reaction usually passes off within a few hours, it can be rapidly reversed by a parenterally administered centrally acting anticholinergic drug. Since the parents are alarmed and to afford quick relief, she may be given a deep intramuscular injection of 10–15 mg of promethazine or hydroxyzine, which have anticholinergic, antihistaminergic, sedative and antiemetic properties. This can reverse the dystonia within 15–30 min.

## SOLUTION 48.1

a. This patient of diarrhoea seems to have lost only small amount of fluid and there are no signs of dehydration. Moreover, he is a young adult. Thus, there is no need of rehydration therapy, but normal fluid intake and nutrition should be continued.
b. The features of this patient including fever are indicative of moderately severe enteroinvasive infection. As such, antibiotic therapy is indicated. A well absorbed fluoroquinolone like ciprofloxacin or ofloxacin would be suitable first line antibiotic for empiric therapy.
c. Antimotility-antidiarrhoeal drug is contraindicated in this patient, because in all likelyhood there is enteroinvasive infection, so that restriction of bowel clearance can favour further bowel wall invasion and systemic spread of the pathogen.
d. Symptomatic relief of fever can be afforded by paracetamol 500 mg 6 hourly. Abdominal pain can be dampened by an antispasmodic drug like dicyclomine 20 mg 6–8 hourly.

## SOLUTION 49.1

a. Since this is an elective surgery with no indication of any infection in the operative area, but where the biliary tract is going to be cut, with no/minimal spillage or contact with infected material expected, it may be categorized as 'clean-contaminated' surgery. As such, she requires to be given antimicrobial prophylaxis.

*Contd...*

b. The surgery involves cutting the biliary tract. Therefore, prophylaxis covering aerobic as well as anaerobic organisms and both gram-negative as well as gram-positive bacteria would be appropriate. Drugs recommended are:

Cefuroxime 1.5 g i.v. } + metronidazole 0.5 g i.v.
or gentamicin 160 mg i.v. }

Single dose injected i.v. within 30 min before surgery. Normally, there is no need to repeat the injection, but if the surgery lasts more than 2 hours, a repeat injection after surgery may be given.

## SOLUTION 50.1

a. Moxifloxacin is a 2nd generation fluoroquinolone (FQ) antibiotic with high activity against gram positive cocci which are primarily involved in acute sinusitis. Moreover, it has a convenient once a day oral dosing schedule and is generally well tolerated. It has been used in sinusitis with high success rates. These could be the considerations on the basis of which the doctor has decided to use moxifloxacin. However, moxifloxacin is *not* appropirate for this patient because she is receiving amitryptyline, a tricyclic antidepressant which has proarrhythmic potential. Moxifloxacin can prolong Q-T interval and increase the risk of serious cardiac arrhythmias such as *Torsades de pointes* when given along with amitryptyline.

Other antibiotics which are active against gram-positive cocci and suitable for treating sinusitis are amoxicillin alone or with clavulanic acid, a first generation cephalosporin or azithromycin. These antibiotics donot carry the risk of precipitating arrhythmias.



## SOLUTION 51.1

a. In this patient antibiotic therapy should be started on the basis of clinical diagnosis, because the patient is quite sick. Rapid relief of symptoms and cure should be the aim. Moreover, blood culture is not necessarily positive in all cases of typhoid fever. Treatment cannot be withheld for want of confirmation by culture.

b. The most appropriate antibiotic is ceftriaxone (or a similar 3rd generation cephalosporin like cefoperazone, cefotaxime), becuase it produces the fastest and surest response. Moreover, being bactericidal it prevents relapse and the risk of carrier state. Being long acting, ceftriaxone can be given as a once daily injection. The daily dose for this boy would be (75 mg/kg x 25 kg) = 1875 mg or rounded off to 2.0 g per day, given as slow i.v. injection once daily. The dose may be halved after 2 days or when fever subsides. It should be given till 2 days after the fever subsides totally.

c. In case of typhoid fever, a single antibiotic is sufficient, since addition of another antibiotic has not been found to hasten or improve the response.

## SOLUTION 52.1

a. The most appropriate drugs and regimens for treating chlamydial endocervicitis are: Azithromycin 1.0 g (2 tabs of 500 mg) single dose, or Doxycycline 100 mg twice daily for 7 days. Both these regimens are adequate to treat uncomplicated gonococcal infection as well as concurrent chlamydial and gonococcal infection. Both these antibiotics are oral and well tolerated. While azithromycin has the advantage of single dose treatment, doxycycline needs twice daily dosing for one week, but is cheaper.

   Other first choice antibiotics like amoxicillin and ceftriaxone for gonorrhoea are not effective against chlamydia.

b. Both these infections are sexually transmitted diseases. Her husband is also likely to be infected. She must be counselled to get her husband examined and treated concurrently.

## SOLUTION 53.1

a. The recommended dose range of gentamicin for a person with normal renal function is 3–5 mg/kg/day (or 4 mg/kg/day on average). For a patient with creatinine clearance value of 50 ml/min, the dose has to be reduced to 50%, or 2 mg/kg/day. In this patient weighing 60 kg, it would be 120 mg/day. With renal impairment, this patient is not suitable for once daily dosing regimen, and he should be treated with the conventional 8 hourly regimen. As such, he may be injected with gentamicin 40 mg every 8 hours making it 120 mg/24 hours. Since the patient is unconscious and in ICU, an i.v. line must have been maintained. Gentamicin may be injected through the i.v. line taking 30 min to complete the injection. Alternatively, it may be injected i.m.

   The usual dose-range of cefotaxime for an adult is 1–2 g every 6–12 hours (2–8 g/day). This patient has renal impairment, half life of cefotaxime is likely to be prolonged. Therefore, a dose near the lower end the range would be appropriate for him. As such, a dose of 1 g every 8 hours (3 g/day) may be selected. This may be slowly injected in the i.v. line or given by i.m. route.

## SOLUTION 54.1

a. Since the patient has distressing urinary symptoms and is febrile, empirical antimicrobial treatment should be started after urine has been collected for bacteriological testing. Moreover, in a sexually active woman, lower urinary tract infections (UTI) are moslty treated empirically. The first line antimicrobials for this purpose are fluoroquinolones, cotrimoxazole, amoxicillin-clavulanate, an oral 1st or 2nd generation cephalosporin, or nitrofurantoin. Any of these may be selected and prescribed for 3–5 days depending on symptom resolution. She should be avised to abstain from sexual intercouse in this period. Nitrofurantoin is usually not preferred because it needs at least 7 days treatment, and often causes nausea and gastric pain.

b. Phenazopyridine is a urinary analgesic with no antimicrobial activity. It relieves symptoms of bladder and uretheral irritation and can be given with the selected antimicrobial drug.

c. Because this patient has suffered >3 episodes of cystitis within one year, she should be advised long term prophylactic therapy. The suitable prophylactic drug for her is cephalexin 250 mg once daily at bed time, because it is not contraindicated in pregnant women. Though this patient is not presently pregnant, she may conceive during use of the prophylactic drug. The other recommended prophylactic drugs, *viz* cotrimoxazole, nitrofurantoin and norfloxacin are all contraindicated during pregnancy.

## SOLUTION 55.1

a. Since the patient is a previously treated case of TB, it is important to find out the drug resistance status of the bacilli infecting him. Sputum culture for AFB and sensitivity testing should be ordered. However, chemotherapy should be started immediately, because the culture and sensitivity tests take 6 weeks or more and defering treatment for such a long time may jeopardise outcome.

b. Selecting the anti-TB regimen for retreatment patients is guided by assessment of risk of multidrug resistance (MDR) TB. This is a defaulted patient who has taken isoniazid and rifampin only for 3 months. As such, risk of MDR-TB may be categorized as low and he should be treated with the 8 month regimen of 1st line drugs. For the initial 2 months, he should be given all 5 first line drugs, *viz* isoniazid 300 mg + rifampin 600 mg + pyrazinamide 1.5 g + ethambutol 1.0 g all orally and streptomycin 1.0 g i.m. daily. Streptomycin should be stopped after that and the 4 oral drugs given for another 1 month. Pyrazinamide should be discontinued and 3 drugs rifampin, isoniazid and ethambutol should be continued for 5 more months. This is a retreatment case, who should be given drugs daily under supervision. The thrice weekly regimen carries higher risk of drug resistance in his case. The regimen may be modified when the culture and sensitivity report becomes available.

## SOLUTION 56.1



a. Since the patient had taken the standard multidrug therapy for the prescribed one year, and had responded clinically, the most likely cause of relapse is reactivation of dormant (persister) bacilli. Development of resistance to the multidrug regimen is very rare. The reactivated persisters remain sensitive to the same drugs. As such, he should be treated with the same drugs, *viz* rifampin 600 mg + clofazimine 300 mg once a month alongwith dapsone 100 mg + clofazimine 50 mg daily for one year.

## SOLUTION 57.1

a. The treatment of choice for *Candida* esophagitis is oral fluconazole 100 mg/day for 3 weeks, because it is highly effective and well tolerated. However, some cases do not respond due to fluconazole resistance. These may be treated with itraconazole 200/day or voriconazole 200 mg twice daily.

b. Uncontrolled diabetes is an important predisposing factor in the causation of esophageal candidiasis, and appears to have played a role in this patient. Therefore, measures to achieve quick glycaemia control are needed. Since the patient already had a complication of diabetes (*Candida* infection) it is desirable to shift her to insulin therapy (at least till the esophagitis is fully cured). The dose and frequency of insulin injections should be guided by repeated blood glucose monitoring. Fluconazole (other azoles as well) inhibit CYP450 isoenzymes and raise the blood levels of salfonylureas. The intensity of action of glibenclamide (if continued in this case) is likely to be affected unpredictably. Thus, even if this drug is continued, close monitoring of blood glucose level and dose adjustment of the sulfonylurea is required.

## SOLUTION 58.1

a. Considering the facts of injury and exposure in this case, the risk of contacting HIV infection by the dental surgeon is very low. However, HIV disease can only be prevented, but not cured, and has serious implications. Moreover, even a few virions entering the body can set up an infection. Therefore, it would be prudent to give prophylactic medication to further cut down chances of acquiring the infection.

b. Because the given case is of the low risk category, and the source person is neither symptomatic nor taking any anti-HIV medication, the standard 2 drug prophylaxis would be appropriate. The dental surgeon should be advised to immediately start taking—
Zidovudine 300 mg + Lamivudine 150 mg twice daily for 4 weeks.

## SOLUTION 59.1

a. Recurrence of fever after being afebrile for 7 days indicates 'recrudescence' due to incomplete parasitaemia clearance by the treatment given for the 1st episode of fever. This occurs due to low grade chloroquine-resistance. While majority of asexual schizonts are killed by chloroquine and the fever subsides, some survive and multiply to cause fever again. The second episode of fever is not due to 'relapse' which is caused by *vivax* hypnozoites reinvading RBCs. Relapse generally occurs after 3 weeks to few months. Moreover, the patient is taking primaquine which kills hypnozoites.

b. As broughtout above, recrudescence indicates chloroquine-resistance, which is particularly likely in this case, because the infection appears to be contacted from an area where chloroquine-resistance among *P. vivax* has been detected. As such, she should be treated with an alternative drug effective against chloroquine-resistant *P. vivax*. These are:
   1. Quinine 600 mg three times a day for 7 days along with doxycycline 100 mg once daily for 7 days.
   2. Artesunate 100 mg twice daily for 3 days, along with a single dose of sulfadoxine 1500 mg + pyrimethamine 75 mg.

c. The primaquine therapy should be continued to complete the 14-day course, so as to totally eradicate the *P. vivax* hypnozoites from the liver.

## SOLUTION 60.1

a. Metronidazole is the drug of choice for amoebic liver abscess. Tinidazole is an equivalent, but not necessarily better alternative. Since the patient was seriously ill and was vomiting, the initial choice of i.v. route of administration was appropriate. It was correctly changed to oral route once the patient improved, because oral bioavailability of metronidazole is nearly complete.

b. Experience has shown that a single 10-day course of metronidazole is generally enough to kill all viable amoebae in the liver abscess, though the abscess cavity may persist for few weeks and heal spontaneously. Since the patient has improved clinically, visualization of persisting abscess cavity on ultrasound is not in itself an indication to extend/repeat metronidazole therapy.

*Contd...*

c. Since amoebic liver abscess is always secondary to colonization of colon by amoebae (which may be asymptomatic) and because metronidazole does not effectively eradicate cyst forming trophozoites from the colon (it is completely absorbed in the upper intestine, and very little reaches the colonic lumen), a luminal amoebicide should be given along with or after metronidazole. Absence of cysts in stools does not ruleout colonization of colon by amoebae. The first choice luminal emoebicide that should have been given in addition is:

Diloxanide furoate 500 mg 3 times a day for 5–10 days alongwith or after metronidazole.

## SOLUTION 61.1

a. This patient of neurocysticercosis is suitable for treatment with anthelmintic drug, because there are multiple active parenchymal cysticerci in the cerebral cortex which in addition to seizures can cause other focal reactions in the brain. Planned killing of the cysticerci under corticosteroid cover may prevent future episodes of the reaction and may abolish the cause of seizures, so that long term antiseizure therapy can be avoided.

b. The seizures must be controlled first before starting anthelmintic treatment. The preferred drug is carbamazepine; start with 200 mg 3 times a day, increase by 200 mg/day if the seizures recur till they are fully suppressed or a maximum of 1200 mg/day dose is reached. A second antiseizure drug may be added in nonresponsive cases. However, most cases respond to carbamazepine alone. It should be continued during the course of anthelmintic medication and for about 6 months thereafter, followed by gradual withdrawal over another 2–3 months.

c. Albendazole is the anthelmintic of choice in neurocysticercosis. To this patient, it should be given in a dose of 400 mg twice daily with milk or fat-rich food (to enhance absorption) for 15 days. It is better than the alternative drug praziquantel, because cure rate with albendazole is higher and praziquantel needs to be given for longer period (15–30 days). Carbamazepine induces praziquantel metabolism and lowers its blood level, but not that of albendazole. Dexamethasone (which has to be given) also lowers praziquantel blood levels, but increases albendazole absorption.

d. Dexamethasone in a dose of 8–12 mg once daily in the morning should be started 2 days before initiating albendazole, continued throughout the course and till 15 days thereafter, followed by gradual tapering of dose and final withdrawal. This is essential to suppress the inflammatory reaction to the dying cysticerci killed by albendazole therapy.

# Appendix 2 List of Essential Medicines

(W): Included in WHO Model List of Essential Medicines (17th edition, March 2011)

(I): Included in National List of Essential Medicines (2011), India

## A

| | |
|---|---|
| Abacavir (ABC) | (W) |
| Acenocoumarol | (I) |
| Acetazolamide | (W,I) |
| Acetic acid | (W) |
| Acetylcysteine | (W) |
| Acetyl salicylic acid (Aspirin) | (W,I) |
| Acriflavin + Glycerine | (I) |
| Actinomycin D (Dactinomycin) | (W,I) |
| Activated charcoal | (W,I) |
| Acyclovir | (W,I) |
| Adenosine | (I) |
| Albendazole | (W,I) |
| Albumin | (I) |
| Allopurinol | (W,I) |
| Alpha interferon | (I) |
| Alprazolam | (I) |
| Aluminium hydroxide + Magnesium hydroxide | (I) |
| Amidotrizoate | (W) |
| Amikacin | (W,I) |
| Amiloride | (W) |
| 5-Aminosalicyclic acid (mesalamine) | (I) |
| *p*-Aminosalicylic acid | (W) |
| Amiodarone | (W,I) |
| Amitriptyline | (W,I) |
| Amlodipine | (W,I) |
| Amodiaquine | (W) |
| Amoxicillin | (W,I) |
| Amoxicillin + Clavulanic acid | (W,I) |
| Amphotericin B | (W,I) |
| Ampicillin | (W,I) |
| Anti-snake venom serum (polyvalent/specific) | (W,I) |
| Anti-D immunoglobulin (Human) | (W,I) |
| Anti-Tetanus immunoglobulin (Human) | (W,I) |
| Artemether | (W) |
| Artemether + Lumefantrine | (W) |
| Artesunate | (W,I) |
| Artesunate + amodiaquine | (W,I) |
| Ascorbic acid | (W,I) |
| Asparaginase | (W) |
| Atazanavir | (W) |
| Atenolol | (W,I) |
| Atorvastatin | (I) |
| Atracurium | (W,I) |
| Atropine | (W,I) |
| Azathioprine | (W,I) |
| Azithromycin | (W,I) |

## B

| | |
|---|---|
| B.C.G. vaccine | (W,I) |
| Barium sulfate | (W,I) |
| Beclomethasone dipropionate | (W,I) |
| Benzathine benzylpenicillin | (W,I) |
| Benznidazole | (W) |
| Benzoin compound | (I) |
| Benzoyl peroxide | (W) |
| Benzyl benzoate | (W,I) |
| Benzyl Penicillin | (W) |
| Betamethasone | (W,I) |
| Betamethasone dipropionate | (I) |
| Betaxolol | (I) |
| Biperiden | (W) |
| Bisacodyl | (I) |
| Bisoprolol | (W) |
| Bleaching powder | (I) |
| Bleomycin | (W,I) |
| Bromocriptine | (I) |
| Budesonide | (W) |
| Bupivacaine | (W,I) |
| Busulfan | (I) |

## C

| | |
|---|---|
| Caffeine | (W) |
| Calamine (lotion) | (W,I) |
| Calcium folinate | (W) |
| Calcium salts (gluconate, carbonate) | (W,I) |
| Calcium ipodate | (I) |
| Capreomycin | (W) |
| Carbamazepine | (W,I) |
| Carbimazole | (I) |
| Carboplatin | (W,I) |
| Cefazolin | (W) |
| Cefixime | (W,I) |
| Cefotaxime | (W,I) |
| Ceftazidime | (W,I) |
| Ceftriaxone | (W,I) |
| Cephalexin | (W,I) |
| Cetrimide | (I) |
| Cetrizine | (I) |
| Chlorambucil | (W,I) |
| Chloramphenicol | (W,I) |
| Chlorhexidine | (W,I) |
| Chloroquine | (W,I) |
| Chloroxylenol | (W) |
| Chlorpheniramine | (W,I) |

| | |
|---|---|
| Chlorpromazine | (W,I) |
| Cholera vaccine | (W) |
| Ciprofloxacin | (W,I) |
| Cisplatin | (W,I) |
| Clarithromycin | (W) |
| Clindamycin | (W,I) |
| Clofazimine | (W,I) |
| Clomiphene | (W,I) |
| Clopidogrel | (I) |
| Clomipramine | (W) |
| Clotrimazole | (W,I) |
| Cloxacillin | (W,I) |
| Coal tar | (W,I) |
| Codeine | (W,I) |
| Colchicine | (I) |
| Concentrated vit. A solution (Retinol) | (W,I) |
| Co-trimoxazole (Trimethoprim + Sulphamethoxazole) | (W,I) |
| Cyclizine | (W) |
| Cyclophosphamide | (W,I) |
| Cycloserine | (W) |
| Cyclosporine | (W,I) |
| Cytosine arabinoside (cytarabine) | (W,I) |

## D

| | |
|---|---|
| D.P.T. vaccine | (I) |
| Dacarbazine | (W,I) |
| Danazol | (I) |
| Dapsone | (W,I) |
| Daunorubicin | (W,I) |
| Deferoxamine | (W,I) |
| Dexamethasone | (W,I) |
| Dexchlorpheniramine | (I) |
| Dextran-40 | (I) |
| Dextran 70 | (W,I) |
| Dextromethorphan | (I) |
| Diazepam | (W,I) |
| Diclofenac | (I) |
| Dicyclomine HCl | (I) |
| Didanosine (ddl) | (W,I) |
| Diethylcarbamazine | (W,I) |
| Digoxin | (W,I) |
| Dihydro ergotamine | (I) |
| Diloxanide furoate | (W,I) |
| Diltiazem | (I) |
| Dimercaprol | (W,I) |
| Diphtheria antitoxin | (W,I) |
| Diphtheria vaccine | (W) |
| Dithranol | (W,I) |
| Dobutamine | (I) |
| Docetaxel | (W) |
| Docusate sodium | (W) |
| Domperidone | (I) |
| Dopamine | (W,I) |
| Doxorubicin | (W,I) |
| Doxycycline | (W,I) |

## E

| | |
|---|---|
| Efavirenz (EFV or EFZ) | (W,I) |
| EMLA cream | (I) |
| Efavirenz + emtricitabine + tenofovir | (W) |
| Eflornithine | (W) |
| Emtricitabine | (W) |
| Emtricitabine + tenofovir | (W) |
| Enalapril | (W,I) |
| Enoxaparin | (I) |
| Ephedrine | (W) |
| Epinephrine (adrenaline) | (W,I) |
| Ergometrine | (W) |
| Erythromycin | (W,I) |
| Estradiol cypionate + medroxyprogesterone acetate | (W) |
| Esmolol | (I) |
| Ethambutol | (W,I) |
| Ether, anaesthetic | (I) |
| Ethinylestradiol | (W,I) |
| Ethinylestradiol + Levonorgestrel | (W,I) |
| Ethinylestradiol + Norethisterone | (W,I) |
| Ethionamide | (W) |
| Ethosuximide | (W) |
| Ethyl alcohol 70%, (Ethanol) | (W,I) |
| Etoposide | (W,I) |

## F

| | |
|---|---|
| Factor IX complex (coagulation factors II,VII,IX,X) | (W,I) |
| Factor VIII concentrate | (W,I) |
| Famotidine | (I) |
| Fentanyl | (I) |
| Ferrous salt | (W,I) |
| Ferrous salt + folic acid | (W) |
| Fluconazole | (W,I) |
| Flucytosine | (W) |
| Flumazenil | (I) |
| Fludrocortisone | (W) |
| Fluorescein | (W,I) |
| 5-Fluorouracil | (W) |
| Fluoxetine | (W,I) |
| Fluphenazine | (W) |
| Flutamide | (I) |
| Folic acid | (W,I) |
| Folinic acid | (I) |
| Formaldehyde IP | (I) |
| Framycetin sulfate | (I) |
| Fresh frozen plasma | (I) |
| Furosemide | (W,I) |

## G

| | |
|---|---|
| Gemcitabine | (I) |
| Gentamicin | (W,I) |
| Gentian violet | (I) |
| Glibenclamide | (W,I) |
| Glucagon | (W,I) |
| Glucose | (W,I) |

| | |
|---|---|
| Glucose with sodium chloride | (W,I) |
| Glutaraldehyde (Glutaral) | (W,I) |
| Glycerine IP | (I) |
| Glyceryl trinitrate | (W,I) |
| Griseofulvin | (W,I) |

## H

| | |
|---|---|
| Haemophilus influenzae (b) vaccine | (W) |
| Haloperidol | (W,I) |
| Halothane | (W,I) |
| Heparin sodium | (W,I) |
| Hepatitis A vaccine | (W) |
| Hepatitis B vaccine | (W,I) |
| Homatropine | (I) |
| Hormone releasing IUD | (I) |
| Hydralazine | (W) |
| Hydrochlorothiazide | (W,I) |
| Hydrocortisone | (W) |
| Hydrocortisone sodium succinate | (I) |
| Hydrogen peroxide | (I) |
| Hydroxocobalamin | (W) |
| Hydroxycarbamide | (W) |
| Hydroxychloroquine $PO_4$ | (W,I) |
| Hydroxyethyl starch (Hetastarch) | (I) |
| Hyoscine HCl | (W) |
| Hyoscine N butylbromide | (I) |

## I

| | |
|---|---|
| Ibuprofen | (W,I) |
| Imipenem + Cilastatin | (W) |
| Ifosphamide | (W,I) |
| Imatinib | (I) |
| Imipramine | (I) |
| Immunoglobulin (human, normal) | (W) |
| Indinavir | (W,I) |
| Influenza vaccine | (W) |
| Insulin injection (soluble) | (W,I) |
| Intermediate acting insulin (Lente/NPH insulin/premix 30:70) | (W,I) |
| Intraperitoneal dialysis solution | (W,I) |
| Iodine | (W,I) |
| Iohexol | (W) |
| Iopanoic acid | (I) |
| Ipratropium bromide | (W,I) |
| Iron dextran | (W,I) |
| Isoflurane | (W,I) |
| Isoniazid | (W,I) |
| Isoniazid + Ethambutol | (W) |
| Isoniazid + Ethambutol + Rifampicin | (W) |
| Isoniazid + Rifampicin | (W) |
| Isoniazid + Rifampicin + Pyrazinamide | (W) |
| Isoniazid + Rifampicin + Pyrazinamide + Ethambutol | (W) |
| Isosorbide dinitrate | (W,I) |
| Isosorbide-5-mononitrate | (I) |
| Isphagula | (I) |
| IUD containing Copper | (W,I) |
| Ivermectin | (W) |

## K

| | |
|---|---|
| Kanamycin | (W) |
| Ketamine | (W,I) |

## L

| | |
|---|---|
| Lactulose | (W) |
| Lamivudine (3TC) | (W,I) |
| Lamivudine + zidovudine | (W,I) |
| Lamivudine + Stavudine | (I) |
| Lamivudine + Nevirapine + Zidovudine | (W) |
| Lamivudine + Nevirapine + Stavudine | (W,I) |
| L-Asparaginase | (W,I) |
| Leflunomide | (I) |
| Levamisol | (W) |
| Levodopa + Carbidopa | (W,I) |
| Levonorgestrel | (W) |
| Levothyroxine | (W,I) |
| Lidocaine (Lignocaine) | (W,I) |
| Lidocaine + Epinephrine | (W,I) |
| Lithium carbonate | (W,I) |
| Lopinavir | (W) |
| Lopinavir + Ritonavir (LPV/r) | (W) |
| Lorazepam | (W,I) |
| Losartan pot. | (I) |
| Lugols solution | (W) |

## M

| | |
|---|---|
| Magnesium sulfate | (W,I) |
| Mannitol | (W,I) |
| Measles vaccine | (W,I) |
| Mebendazole | (W) |
| Medroxy progesterone acetate (depot) | (W,I) |
| Mefloquine | (W,I) |
| Meglumine iothalamate/iotroxate | (W,I) |
| Melarsoprol | (W) |
| Melphalan | (I) |
| Meningococcal vaccine | (W) |
| Mercaptopurine | (W,I) |
| Mesna | (W,I) |
| Metformin | (W,I) |
| Methadone | (W) |
| Methotrexate | (W,I) |
| Methyl cellulose | (I) |
| Methyldopa | (W,I) |
| Methyl ergometrine | (I) |
| Methylprednisolone | (I) |
| Methylrosalinium chloride (Gentian voilet) | (I) |
| Methylthioninium chloride (methylene blue) | (W,I) |
| Metoclopramide | (W,I) |
| Metoprolol | (I) |
| Metronidazole | (W,I) |
| Miconazole | (W,I) |
| Midazolam | (I) |
| Mifepristone | (W,I) |

Miltefosine (W)
Misoprostol (W,I)
Mitomycin-C (I)
Morphine (W,I)
Multivitamins (I)
Mumps vaccine (W)
Mupirocin (W)

## N

N-acetylcysteine (I)
Naloxone (W,I)
Nelfinavir (NFV) (I)
Neomycin + Bacitracin (I)
Neostigmine (I)
Nevirapine (NVP) (W,I)
Niclosamide (W)
Nicotinamide (W,I)
Nicotine replacement therapy (NRT) (W)
Nifedipine (W,I)
Nifurtimox (W)
Nitrofurantoin (W,I)
Nitrous oxide (W,I)
Norethisterone (W,I)
Nystatin (W,I)

## O

Ofloxacin (W,I)
Olanzapine (I)
Omeprazole (W,I)
Ondansetron (W,I)
Oral Poliomyelitis vaccine (live attenuated) (W,I)
Oral rehydration salts (W,I)
Oseltamivir (W)
Oxamniquine (W)
Oxaliplatin (I)
Oxygen (W,I)
Oxytocin (W,I)

## P

Paclitaxel (W,I)
Pancreatic enzymes (W)
Pantoprazole (I)
Paracetamol (W,I)
Paromomycin (W)
Penicillamine (W,I)
Pentamidine isothionate (W,I)
Permethrin (W,I)
Pertussis vaccine (W)
Pheniramine (I)
Phenobarbital (W,I)
Phenylephrine (I)
Phenoxymethyl penicillin (W)
Phenytoin sodium (W,I)
Phytomenadione (W,I)
Pilocarpine (W,I)
Piperazine (I)
Pneumococcal vaccine (W)
Podophyllum resin (W)
Polygeline (I)
Potassium chloride (W,I)
Potassium iodide (W)
Potassium permanganate (W,I)
Povidone iodine (W,I)
Pralidoxime (2-PAM) (I)
Praziquantel (W,I)
Prednisolone (W,I)
Prednisolone acetate/sodium phosphate (I)
Primaquine (W,I)
Procainamide (I)
Procaine benzylpenicillin (W)
Procarbazine (W,I)
Proguanil (W)
Promethazine (I)
Propofol (W,I)
Propranolol (W,I)
Propylthiouracil (W)
Prostaglandin E (W)
Protamine sulfate (W,I)
Prussian blue (W)
Pyrantel pamoate (W)
Pyrazinamide (W,I)
Pyridostigmine (W,I)
Pyridoxine (W,I)
Pyrimethamine + Sulfadoxine (W,I)

## Q

Quinine (W,I)

## R

Rabies immunoglobulin (W,I)
Rabies vaccine (W,I)
Raloxifene (I)
Ranitidine HCl (W,I)
Retinol (Vit A) (W,I)
Ribavirin (W)
Riboflavin (W,I)
Rifabutin (W)
Rifampicin (W,I)
Ringer lactate solution (I)
Ritonavir (r) (W,I)
Rotavirus vaccine (W)
Rubella vaccine (W)

## S

Salbutamol (W,I)
Salicylic acid (I)
Saquinavir (SQV) (W,I)
Selenium sulfide (W)
Senna (W)
Sevoflurane (I)
Silver sulphadiazine (I)
Simvastatin (W)
Sodium calcium edetate (W)

| | |
|---|---|
| Sodium chloride | (W) |
| Sodium fluoride | (W) |
| Sodium bicarbonate | (W,I) |
| Sodium iothalamate | (I) |
| Sodium lactate | (W) |
| Sodium nitrite | (W,I) |
| Sodium nitroprusside | (W,I) |
| Sodium stibogluconate | (W,I) |
| Sodium thiosulfate | (W,I) |
| Sodium valproate (valproic acid) | (W,I) |
| Spectinomycin | (W) |
| Spironolactone | (W,I) |
| Stavudine (d4T) | (W,I) |
| Streptokinase | (W,I) |
| Streptomycin | (W,I) |
| Succinyl choline (Suxamethonium) | (W,I) |
| Sulfacetamide sod. | (I) |
| Sulfadiazine | (W,I) |
| Sulfadoxine + pyrimethamine | (W,I) |
| Sulfasalazine | (W,I) |
| Suramin sod. | (W) |
| Surfactant | (W) |

## T

| | |
|---|---|
| Tamoxifen | (W,I) |
| Tenofovir disoproxil fumarate | (W) |
| Terbinafine | (W) |
| Terbutaline | (I) |
| Testosterone propionate | (W,I) |
| Tetanus toxoid (vaccine) | (W,I) |
| Tetracaine | (W,I) |
| Tetracycline | (W,I) |
| Thiamine | (W,I) |
| Thioguanine | (W) |
| Thiopental sodium | (I) |
| Timolol | (W,I) |
| Tramadol | (I) |
| Tranexamic acid | (W) |
| Triclabendazole | (W) |
| Trihexyphenidyl | (I) |
| Trimethoprim | (W) |
| Tropicamide | (W,I) |
| Tuberculine purified protein derivative | (W,I) |
| Typhoid vaccine | (W) |

## U

| | |
|---|---|
| Urea | (W) |
| Urokinase | (I) |

## V

| | |
|---|---|
| Vancomycin | (W,I) |
| Varicella vaccine | (W) |
| Vecuronium | (W,I) |
| Verapamil | (W,I) |
| Vinblastine | (W,I) |
| Vincristine | (W,I) |
| Vit $B_{12}$ (Cyanocobalamin) | (W,I) |
| Vit D3 (Cholecalciferol) | (W,I) |

## W

| | |
|---|---|
| Warfarin sodium | (W,I) |

## X

| | |
|---|---|
| Xylometazoline | (W) |

## Z

| | |
|---|---|
| Zidovudine | (W,I) |
| Zidovudine + lamivudine + nevirapine | (W,I) |
| Zinc oxide | (I) |
| Zinc sulfate | (W,I) |

# Appendix 3 Prescribing in Pregnancy

There are major concerns of permanent harm (teratogenesis in the 1st trimester [see p. 89] and effect on growth and development of foetus in the 2nd and 3rd trimester) to the baby whenever any drug is administered to pregnant women. Maternal medication can also increase the incidence of abortion, foetal death, premature/ delayed labour or create perinatal problems. Moreover, there are pronounced and progressive physiological changes during pregnancy which can affect drug disposition (*see* p. 65). As such, prescribing for the pregnant woman requires a lot of skill and restraint. Possible harm to the foetus by the administered drug has to be weighed against harm to both mother and the baby due to untreated disease. There is paucity of data about safety of majority of drugs during pregnancy; largely because prospective drug trials in pregnant women are fraught with ethical, legal, emotional and practical difficulties. Information is mostly derived from anecdotal reports and retrospective studies. The US-FDA categorization of drugs into 5 categories (*see* p. 90) according to increasing order of risk documentation during pregnancy is a useful (through in some cases outdated and incorrect) guide to therapeutic decision making during pregnancy.

While insufficient data are available to make definitive recommendations regarding choice of drugs for treating common problems likely to be encountered during pregnancy, the table on the succeeding pages attempts to delineate the relatively/probably safer alternatives. The list is not exhaustive and manufacturers literature/ package inserts or other authoritative texts should be consulted. Drugs marked (X) are contra-indicated during pregnancy.

**Principles of prescribing during pregnancy**

- Where possible use nondrug therapy.
- Prescribe drugs only when definitely needed.
- Choose the drug having the best safety record over time.
- Avoid newer drugs, unless safety is clearly established.
- Over-the-counter drugs cannot be assumed to be safe.
- As far as possible, avoid medication in the initial 10 weeks of gestation.
- Use the lowest effective dose.
- Use drugs for the shortest period necessary.
- If possible, give drugs intermittently.

## Choice of drugs for common problems during pregnancy

| Drug class (condition) | Safety uncertain/unsafe | Safer alternative |
|---|---|---|
| 1. Antiemetics (morning sickness, other types of vomiting) | Domperidone (X) Ondansetron | Promethazine, Doxylamine Dicyclomine, Prochlorperazine Metoclopramide |
| 2. Drugs for peptic ulcer and GERD | Cimetidine, Lansoprazole Cisapride (X), Mosapride | Ranitidine, Famotidine Omeprazole Pantoprazole, |
| 3. Laxatives (constipation) | Senna, Bisacodyl, Docusates Saline purgatives | Dietary fibre, Ispaghula Lactulose |
| 4. Antidiarrhoeals | Diphenoxylate-atropine, Loperamide | Oral rehydration salts |
| 5. Analgesics (headache, bodyache, joint pain, visceral pain) | Aspirin, Metamizol, NSAIDs COX-2 inhibitors, Codeine Dextropropoxyphene, Morphine (X) Pethidine, Tramadol | Paracetamol Ibuprofen (low dose) |
| 6. Cold-cough remedies | Codeine, Dextromethorphan Bromhexine, Expectorants | Xylometazoline, Oxymetazoline, Budesonide } Nasal drops |
| 7. Antiallergics | Cetirizine, Loratadine Fexofenadine, Astemizole (X) | Chlorpheniramine Promethazine |
| 8. Antibacterials (systemic bacterial infections) | Cotrimoxazole, Fluoroquinolones (X), Tetracycline (X), Doxycycline (X), Chloramphenicol (X), Gentamicin, Streptomycin (X), Kanamycin (X), Tobramycin (X), Clarithromycin, Azithromycin, Clindamycin, Vancomycin, Nitrofurantoin | Penicillin G, Ampicillin Amoxicillin-clavulanate Cloxacillin, Piperacillin Cephalosporins Erythromycin |
| 9. Antitubercular | Pyrazinamide, Streptomycin (X) | Isoniazid, Rifampicin, Ethambutol |
| 10. Antiamoebic | Metronidazole, Tinidazole Quiniodochlor | Diloxanide furoate, Paromomycin |
| 11. Antimalarial | Artemether, Artesunate Primaquine (X) | Chloroquine, Mefloquine, Proguanil Quinine (only in 1st trimester), Pyrimethamine + Sulfadoxine (only single dose) |
| 12. Anthelmintic | Albendazole (X), Mebendazole (X) Ivermectin, Pyrantel pamoate, Diethylcarbamazine (X) | Piperazine Niclosamide Praziquantel |
| 13. Antifungal (superficial and deep mycosis) | Amphotericin B (X), Fluconazole Itraconazole (X), Ketoconazole (X) Griseofulvin (X), Terbinafine | Clotrimazole, Nystatin, Tolnaftate } Topical |

*Contd...*

*Contd...*

| Drug class (condition) | Safety uncertain/unsafe | Safer alternative |
|---|---|---|
| 14. Antiretroviral (HIV-AIDS) | Didanosine, Abacavir, Indinavir Ritonavir, Efavirenz | Zidovudine, Lamivudine, Nevirapine, Nelfinavir, Saquinavir |
| 15. Antiviral (other than HIV) | Acyclovir, Ganciclovir (X) Foscarnet (X), Amantadine (X) Vidarabine (X), $\alpha$-interferon (X) | — |
| 16. Antihypertensives | ACE inhibitors (X), Angiotensin antagonists (X), Thiazide diuretics Furosemide, Propranolol Nitroprusside | Methyldopa, Hydralazine, Atenolol Metoprolol, Pindolol, Nifedipine Prazosin, Clonidine |
| 17. Antianaemic | — | Iron salts (oral), Iron dextran (i.m.) Folic acid, Vit $B_{12}$ |
| 18. Antidiabetics | Sulfonylureas (X), Metformin (X) Pioglitazone, Repaglinide, Nateglinide, Acarbose (X) | Insulin (preferably human insulin) |
| 19. Corticosteroids | Betamethasone, Dexamethasone (high dose and prolonged use) | Inhaled corticosteroids Topical corticosteroids Prednisolone oral (low dose) |
| 20. Thyroid hormone (hypothyroidism) | — | Thyroxine |
| 21. Antithyroid drugs (thyrotoxicosis) | Carbimazole, Radioactive iodine (X), Iodide | Propylthiouracil |
| 22. Antipsychotic (schizophrenia) | Chlorpromazine, Fluphenazine (X) Clozapine, Olanzapine, Risperidone | Haloperidol Trifluoperazine |
| 23. Antimanic (bipolar illness) | Lithium carbonate, Valproate Carbamazepine | — |
| 24. Antidepressants | Trimipramine (X), Dothiepin (X) Sertraline, Paroxetine, Citalopram Trazodone, Venlafaxine Moclobemide | Amitriptyline, Imipramine, Fluoxetine |
| 25. Anticoagulants (thromboembolism) | Warfarin (X), Acenocoumarol Phenindione (X) | Heparin (unfractionated) Heparin (LMW) |
| 26. Antiasthmatic | Theophylline, Ketotifen (X) Montelukast, Zafirlukast Systemic corticosteroids | Salbutamol/Salmeterol Ipratropium bromide Beclomethasone/ Budesonide Sod. cromoglycate } Inhaled |

# Appendix 4 Drugs in Breastfeeding

Administration of drugs to women who are breastfeeding may have ill effects on the suckling infant, and/or affect lactation. Estrogens (in oral contraceptives) and bromocriptine (D2 agonist) decrease milk production. Toxic effects on the infant are largely dependent on entry of the drug in milk in pharmacologically significant amounts. In the case of large number of drugs (except those acting on CNS and few others), the concentration in milk is low, and the breastfed infant receives insufficient quantity to produce adverse effects. Maternal medication or breastfeeding should not be interfered in case of such drugs. However, currently available data are insufficient to make specific recommendations in the case of many drugs and the list given below is not exhaustive. Manufacturer's recommendations/package inserts should be consulted.

### A. Drugs whose amount in milk is too small to be harmful to the infant, or those found to be safe in ordinary doses

| | |
|---|---|
| Acetazolamide | Insulins |
| Albendazole | Ipratropium Br. (inhalation) |
| Antacids | Iron dextran (i.m.) |
| Antifungal drugs (topical) | Iron salts (oral) |
| Aspirin (low dose) | Ketoprofen |
| Baclofen | Lidocaine |
| Beclomethasone (Inhaled) | Loperamide |
| Benzyl benzoate (topical) | Mebendazole |
| Bupivacaine | Methyldopa |
| Buprenorphine | Naproxen |
| Cephalosporins | Nefopam |
| Cloxacillin | Niclosamide |
| Codeine | Paracetamol |
| Cromoglycate sod. | Permethrin (topical) |
| Dextropropoxyphene | Piperacillin |
| Diclofenac | Piperazine |
| Digoxin | Piroxicam |
| Domperidone | Praziquantel |
| Ergometrine | Pyrantel |
| Erythromycin | Pyrazinamide |
| Ethambutol | Salbutamol (inhalation) |
| Folic acid | Sucralfate |
| Gentamicin | Terbutaline (inhalation) |
| Heparin | Valproate sod. |
| Hydralazine | Vitamins (maintenance dose) |
| Ibuprofen | Warfarin |

## B. Drugs to be used with special precaution in breastfeeding women or drugs contraindicated

| Drug | Comment / possible adverse effect on breast-fed infant |
|---|---|
| ACE inhibitors (Enalapril, Lisinopril) | : S/P amount in milk small, magnitude of risk not known, watch for hypotension |
| Acenocumarol | : S/P; give prophylactic vit K to infant |
| Acyclovir | : S/P; significant amount in milk |
| Alcohol | : Intoxication, reduced suckling |
| Allopurinol | : S/P; secreted in milk; no data on risk to infant |
| Amiloride | : C/I; no information on risk to infant; may reduce lactation |
| Aminoglycosides | : S/P; risk not known, most manufacturers advise caution |
| Amiodarone | : C/I; risk of hypothyroidism from released iodine |
| Amlodipine | : S/P; no data on risk to infant |
| Amphetamines | : C/I; significant amount in milk |
| Ampicillin/Amoxicillin | : S/P; diarrhoea, candidiasis in the infant |
| Androgens | : C/I; masculinization of female infant, precocious development of male infant, reduced lactation |
| Anthraquinones (senna, etc.) | : C/I; diarrhoea in the infant |
| Anticancer drugs | : C/I; anaemia, diarrhoea, immunosuppression |
| Anticonvulsants | : S/P; monitor infant for side effects |
| Antidepressants (tricyclic) | : S/P; use doses < 150 mg amitriptyline per day or equivalent; monitor infant for side effects, sedation, respiratory depression |
| Antihistamines ($H_1$) | : S/P; significant amount in milk, watch for drowsiness, respiratory depression |
| Antihistamines (2nd generation) | : No data on risk to infant; manufacturers advise avoid |
| Antipsychotics | : S/P; drowsiness, muscle dystonia; avoid chlorpromazine, haloperidol, clozapine; amount in milk small, but long-term effect on developing nervous system not known |
| Aspirin | : S/P; Avoid high doses, bleeding, Reye's syndrome |
| Atorvastatin | : Avoid; no data on risk to infant |
| Atropine | : S/P; monitor for anti-muscarinic effects |
| Azathioprine | : C/I; immunosuppression |
| Azithromycin | : Avoid; no information on risk to infant |
| Barbiturates | : S/P; drowsiness, lethargy, withdrawal symptoms |
| Benzodiazepines | : S/P; compatible in single dose; avoid repeated doses; lethargy, hypotonia, reduced suckling, weight loss |
| Beta blockers | : S/P; amount in milk generally small; bradycardia, hypotension, cyanosis |
| Bromocriptine | : Suppresses lactation |
| Buspirone | : Avoid; no information on risk to infant |
| Caffeine | : Avoid regular consumption of large amounts; irritability, CNS effects |
| Carbamazepine | : S/P; amount in milk small but monitor infant |
| Carbimazole | : S/P; hypothyroidism, use lowest effective dose, or suspend breastfeeding |
| Carisoprodol | : S/P; concentrated in milk; avoid |
| Chloral hydrate | : C/I; sedation |
| Chloramphenicol | : C/I; diarrhoea, bone marrow depression |
| Chloroquine | : S/P; amount in milk small; haemolysis in <1 month old infant and in G-6-PD deficient |
| Cimetidine | : S/P; significant amount in milk, but no harmful effect reported |
| Ciprofloxacin | : C/I; high concentration in milk, theoretical risk of arthropathy |
| Clindamycin | : S/P; amount in milk small, but risk of diarrhoea, watch for blood in stools |

C/I=Contraindicated or suspend breastfeeding
S/P = Use with special precaution while breastfeeding and monitor infant

*Contd...*

| Drug | Comment / possible adverse effect on breast-fed infant |
|---|---|
| Clofazimine | : S/P; skin discolouration |
| Clonidine | : S/P; sedation, hypotension |
| Corticosteroids | : S/P; compatible in single doses; pituitary-adrenal suppression possible with >10 mg prednisolone daily to mother, impaired growth |
| Cotrimoxazole | : S/P; folate deficiency, risk of kernicterus, haemolysis in G-6-PD deficient; safe for healthy older infants |
| Cyclosporine | : C/I; significant amount in milk |
| Dapsone | : S/P; haemolytic anaemia, jaundice |
| Depot medroxyprogesteron acetate (i.m.) | : Compatible with breastfeeding from 6 weeks postpartum |
| Diltiazem | : S/P; significant amount in milk |
| Disopyramide | : S/P; small amount in milk, antimuscarinic effects |
| Doxepin | : S/P; sedation, respiratory depression |
| Ephedrine | : S/P; irritability, sleep disturbance |
| Ergotamine | : C/I; ergotism in the infant; may suppress lactation |
| Estrogens | : C/I; gynaecomastia in male infant, may suppress lactation |
| Ethosuccimide | : C/I; hyperexcitability, poor suckling |
| Famotidine | : S/P; present in milk, but harm to infant not known |
| Fluconazole | : C/I; secreted in milk, but harm to infant not known |
| Fluoxetine | : S/P; small amount in milk, but can accumulate in infant; avoid if possible |
| Furosemide | : S/P; small amount in milk, electrolyte disturbances in the infant |
| Gemfibrozil | : Avoid; no information on risk to infant |
| Indomethacin | : C/I; CNS effects, convulsions |
| Iodine/Iodides | : C/I; concentrated in milk, hypothyroidism and goiter in the infant |
| Iodine radioactive | : C/I; suspend breastfeeding for 24 hr after diagnostic dose and for long-term after therapeutic dose |
| Isoniazid | : S/P; neuropathy, convulsions, jaundice, give prophylactic pyridoxine |
| Itraconazole | : Avoid unless essential; amount in milk small |
| Ketoconazole | : C/I; secreted in milk but harm to infant not known. |
| Ketorolac | : Avoid as no data on safety |
| Lansoprazole | : Avoid unless essential; no data on safety |
| Levodopa/Carbidopa | : S/P; no data on safety |
| Lithium carbonate | : C/I; intoxication in the infant, cardiac arrhythmias |
| Losartan | : S/P; magnitude of risk not known; avoid if possible |
| Mefloquine | : S/P; secreted in milk, but harm to infant unlikely |
| Metformin | : C/I; secreted in milk; hypoglycaemia, lactic acidosis |
| Mesalazine | : S/P; amount in milk small; watch for diarrhoea |
| Methotrexate | : C/I; toxicity in infant |
| Metoclopramide | : S/P; watch for diarrhoea, dystonia in infant |
| Metronidazole | : Significant amount in milk: avoid high doses; suspend breastfeeding for 12 hr after single dose therapy |
| Montelukast | : Avoid; no data on risk to infant |
| Morphine (and other opioids) | : S/P; usual doses unlikely to affect infant; lethargy, poor growth, withdrawal symptoms in infants of dependent mothers |
| Nalidixic acid | : S/P; small risk of haemolytic anaemia; avoid if possible |
| Neostigmine | : S/P; small amount in milk but monitor infant |
| Nifedipine | : S/P; small amount in milk but monitor infant |
| Nitrofurantoin | : S/P; small amount in milk, haemolysis in G-6-PD deficient infant |
| Norfloxacin | : Avoid; no information on risk to infant |
| Omeprazole | : Not known to be harmful, manufacturer advises 'avoid' |
| Oral contraceptives | : Avoid until 6 month after birth, *see* estrogens |
| Penicillins | : Toxicity unlikely but risk of allergy |
| Phenolphthalein | : C/I; diarrhoea, rashes |

*Contd...*

| Drug | Comment / possible adverse effect on breast-fed infant |
|---|---|
| Phenytoin | : S/P; small amount in milk, but monitor infant |
| Progestins | : Low doses safe, may suppress lactation at high doses |
| Propylthiouracil | : S/P; hypothyroidism with high doses only |
| Pyrimethamine-sulfadoxine | : S/P; significant amount in milk; appears safe if infant is older |
| Quinidine | : S/P; significant amount in milk but harm to infant not known |
| Ranitidine | : S/P; significant amount in milk but harm to infant not known |
| Rifampin | : S/P; amount in milk small, but monitor infant for jaundice |
| Sertraline | : S/P; present in milk but no harm reported in short-term |
| Spironolactone | : S/P; drowsiness, hirsutism, gynaecomastia |
| Streptomycin | : Compatible with breastfeeding; monitor infant for diarrhoea and thrush |
| Sulfonamides | : S/P; rashes, small risk of kernicterus in neonate, haemolysis in G-6-PD deficient; safer for older infants |
| Sulfonylureas | : S/P; no adverse effect reported, but watch for hypoglycaemia |
| Tetracyclines | : C/I; growth retardation, candidiasis, tooth discolouration |
| Theophylline | : S/P; irritability, CNS effects |
| Thiazide diuretics | : S/P; amount in milk small; may reduce lactation |
| Thyroxine | : S/P; monitor for hyperthyroidism |
| Tinidazole | : S/P; present in milk; suspend breastfeeding till 3 days after stopping |
| Vancomycin | : S/P; present in milk, but absorption from infant's gut unlikely |
| Verapamil | : S/P; small amount in milk, but monitor infant |
| Vigabatrin | : C/I; present in milk, no data on risk to infant |
| Vitamin A and D | : Avoid high doses, risk of hypervitaminosis |
| Zolpidem | : Avoid unless essential; amount in milk small, but watch for sedation in infant |

# Appendix 5 Drugs and Fixed Dose Combinations Banned in India[$]

(updated till Dec. 2012)

## A. Single drug preparations (or combinations of)

1. Amidopyrine.
2. Phenacetin.
3. Nialamide.
4. Methaqualone.
5. Methapyriline (and its salts).
6. Practolol.
7. Penicillin skin/eye ointment.
8. Tetracycline/Oxytetracycline/Demeclocycline liquid oral preparations.
9. Chloral hydrate.
10. Dover's powder and Dover's powder tablets I.P.
11. Chloroform exceeding 0.5% w/w or v/v in pharmaceutical preparations.
12. Mepacrine HCl (Quinacrine and its salts) in any dosage form for use for female sterilization or contraception.
13. Fenfluramine
14. Dexfenfluramine
15. Terfenadine
16. Astemizole
17. Phenformin
18. Rofecoxib
19. Valdecoxib
20. Rimonabant
21. Rosiglitazone
22. Nimesulide formulations for children below 12 years age
23. Cisapride
24. Phenylpropanolamine*
25. Sibutramine and R-Sibutramine
26. Gatifloxacin
27. Tegaserod
28. Human placental extract formulations, except for:
    i. topical application for wound healing
    ii. injection for pelvic inflammatory disease
29. Halogenated hydroxyquinolines in liquid oral antidiarrhoeals or any other dosage form for pediatric use.
30. Letrozole for induction of ovulation in anovulatory infertility.

## B. Fixed dose combination with any other drug

1. Corticosteroids with any other drug for internal use, except for metered dose inhalers and dry powder inhalers.
2. Chloramphenicol with any other drug for internal use.
3. Sodium bromide/chloral hydrate with other drugs.
4. Crude ergot with any drug except preparations containing ergotamine, caffeine, analgesics, antihistamines for treatment of migraine, headache.
5. Anabolic steroids with other drugs.
6. Metoclopramide with other drugs (except with aspirin/paracetamol).
7. Pectin and/or kaolin with any drug which is systemically absorbed from g.i. tract, except for combination of pectin and/or kaolin with drugs not systemically absorbed.
8. Hydroxyquinolines with any other drug except in preparations for external use.
9. Oxyphenbutazone or phenylbutazone with any other drug.
10. Dextropropoxyphene with any other drug except antispasmodics and/or NSAIDs.
11. Analgin (metamizol) with any other drug.
12. Fixed dose combination of haemoglobin in any form.

## C. Fixed dose drug combinations of

1. Penicillins with sulfonamides.
2. Tetracyclines with vitamin C.

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* Presently stayed by Highcourt.

$ Drugs Control Organisation, Govt. of India; http//www.drugscontrol.org/ban_drugs.htm

3. Antitubercular drugs with Vitamins (except Isoniazid with Pyridoxine HCl).
4. Vitamins with Analgesics/Antiinflammatory drugs.
5. Vitamins with Tranquillisers.
6. Atropine and Analgesic-antipyretics.
7. Yohimbine and Strychnine with Testosterone and Vitamins.
8. Strychnine and Caffeine in tonics.
9. Iron with Strychnine, Arsenic and Yohimbine.
10. Antihistaminics with Antidiarrhoeals.
11. More than one Antihistamine in the same preparation.
12. Sedatives/Hypnotics/Anxiolytics with Analgesic-antipyretics.
13. $H_2$ receptor antagonists with Antacids (except those combinations approved by Drugs Controller, India).
14. Anthelmintics (except Piperazine) with a Cathartic/Purgative.
15. Salbutamol (or any other bronchodilator) with centrally acting Antitussive and/or an Antihistamine.
16. Centrally acting Antitussives with Antihistamines having atropine like activity in expectorants.
17. Centrally acting Antitussive and/or Antihistamine in preparations for cough associated with asthma.
18. Laxatives and/or antispasmodic drugs in enzyme preparations.
19. Glycerophosphates and/or other phosphates, and/or CNS stimulant in liquid oral tonics.
20. Estrogen and Progestin (other than oral contraceptives) containing per tablet estrogen more than 50 µg ethinylestradiol (or equivalent) and progestin more than 3 mg of norethisterone acetate (or equivalent), and all fixed dose combination injectable preparations containing synthetic estrogen and progesterone.
21. Ethambutol with Isoniazid, except in the following daily doses:
    Isoniazid 200 mg + Ethambutol 600 mg or
    Isoniazid 300 mg + Ethambutol 800 mg.
22. Pyrazinamide with other antitubercular drugs, except that which provide the following daily doses:

| | |
|---|---|
| Rifampicin | 450 to 600 mg |
| Isoniazid | 300 to 400 mg |
| Pyrazinamide | 1000 to 1500 mg |

23. Essential oils with Alcohol having percentage higher than 20% proof (except preparations given in the I.P.).
24. Liquid oral tonic preparations containing alcohol more than 20% proof.
25. Streptomycin with penicillin in parenteral preparation.
26. Antidiarrhoeals containing adsorbants like kalolin, pectin, attapulgite, activated charcoal etc.
27. Antidiarrhoeals containing phthalylsulfathiazole, succinyl sulfathiazole, sulfaguanidine, neomycin, streptomycin, dihydrostreptomycin.
28. Antidiarrhoeal formulations for pediatric use containing diphenoxylate, loperamide, atropine, hyoscyamine.
29. Antidiarrhoeals with electrolytes.
30. Pancreatine or pancrelipase containing amylase, protease and lipase with any other enzyme.
31. Oral rehydration salts other than those conforming to the following parameters:
    (a) Oral rehydration salts on reconstitution to one litre shall contain: sodium–50 to 90 mM; total osmolarity–240 to 290 mOsm; dextrose: sodium molar ratio–not less than 1:1 and not more than 3:1.
    (b) Cereal based ORS on reconstitution to one litre shall contain: total osmolarity not more than 2900 mOsm. Precooked rice equivalent to not less than 50 g and not more than 80 g as total replacement of dextrose.
    (c) ORS may contain amino acids in addition to ORS conforming to the parameters specified above and labelled with the indication for "Adult Choleratic Diarrhoea" only.
    (d) ORS shall not contain mono or polysaccharides or saccharin sweetening agent.
32. A drug, standards of which are prescribed in the 2nd schedule to Drugs and Cosmetics Act with an Ayurvedic, Siddha or Unani drug.
33. Vitamin $B_1$, vit $B_6$, and vit $B_{12}$ for human use.
34. Diazepam with diphenhydramine HCl.
35. Nitrofurantoin with trimethoprim.
36. Phenobarbitone with any antiasthmatic drug, or with hyoscine and/or hyoscyamine, or ergotamine and/or belladonna.
37. Haloperidol with any anticholinergic agent including propantheline Br.
38. Nalidixic acid with any antiamoebic including metronidazole.
39. Loperamide with furazolidone.
40. Cyproheptadine with lysine or peptone.