Pharmacology Question Paper Solution

Shaktipal Patil

Assistant Professor

Dept. of Pharmacology

H. R. Patel Institute of Pharmaceutical Education and Research, Shirpur

Que.1. Explain the molecular mechanism of diuretic action of carbonic anhydrase inhibitors.

Ans.- Acetazolamide is a carbonic anhydrase inhibitor. Carbonic anhydrase is an enzyme located in the brush border and cytoplasmof renal proximal convoluted tubule epithelial cells. Inthe proximal tubule, a large amount of H+ is secreted into thelumen via the Na+/H+ exchanger. Most of this H+ combineswith bicarbonate ion in the tubular fluid to form carbonicacid, which is rapidly dehydrated to CO2 and water (this reactionis catalyzed by carbonic anhydrase). The CO2 di uses into the proximal tubular cells, where the opposite react ion takes place to form H+ and HCO3− (this reaction is also catalyzed by carbonic anhydrase). The HCO3− exits the cell on the basolateral side and is reabsorbed as bicarbonate. Hydrogen ion is secreted into the lumen via the Na+/H+ exchanger. By blocking carbonic anhydrase, acetazolamide blocks the reabsorption of bicarbonate and Na+, resulting in increased diuresis. Acetazolamide causes an inhibition, rather than stimulation, of bicarbonate reabsorption. This is the mechanism of action of thiazide diuretics. Hydrogen is not reabsorbed by the kidney. By inhibiting carbonic anhydrase, acetazolamide inhibits the formation of carbonic acid inside the tubular cells, which in turn inhibits the secretion of hydrogen into the lumen.

Que.2. Outline the use of carbonic anhydrase in hibitorsin the prophylaxis of altitude sickness; describe the urine profile of a patient treated with carbonic anhydrase inhibitors.

Ans. -Acetazolamide, a carbonic anhydrase inhibitor, is the only diuretic used to prevent mountain sickness in people who are at risk for this disorder and have to go to a high altitude. The mechanism of this act ion is not clear, but it may be related to the induction of metabolic acidosis. Carbonic anhydrase inhibitors produce urine that is very rich in bicarbonate. Urinary sodium is only slightly increased (the e cacy of the diuretic is low). Urinary K+ excretion is

also increased (all diuretics except potassium-sparing diuretics increase urinary K+ excretion). This urine profile would be caused by osmotic diuretics. This urine profile would be caused by thiazide diuretics. This urine pro le would be caused by loop diuretics. This urine profile would be caused by K+-sparing diuretics.

Que.3. Explain the mechanism of thiazide-induced hypercalcemia.

Ans.-In the kidney, the distal convolute tubule reabsorbs about 8% of the ltered Ca2+ load. This reabsorption occurs through epithelial Ca2+ channels. In the steady state, however, the cell must extrude all the entered Ca2+; this occurs through a plasma membrane Ca2+-ATPase (the Ca2+ pump) and also through the Na+/Ca2+ exchanger located on the basolateral surface of cells of the distal tubule. Thiazides inhibit the Na+/Cl− symporter in the early distal convoluted tubule, thus decreasing the intracellular concentration of Na. This likely enhances the activity of the Na+/Ca2+ exchanger, which in turn creates a greater driving force for reabsorption of Ca2+ through the epithelial Ca2+ channels. The nal e ect is an increased reabsorpt ion of Ca2+ that can cause hypercalcemia or, more often, can unmask hypercalcemia due to other causes, as in this case (malignancy is a common cause of hypercalcemia)

Que.4. Explain the molecular mechanism of furosemide induced metabolic alkalosis.

Ans. -There are three main causes of alkalosis induced by loop diuretics. The most important is increased delivery of Na+to the distal tubule. The consequent increased reabsorption of Na+ creates a lumen-negative potential that favours both H+ and K+ excretion. The second cause is the stimulation of aldosterone release due to volume contract ion and increased renin secret ion. The third cause occurs only when hypokalemiais severe. In this case, K+ tends to leave the cell, and H+ enters to maintain electroneutrality, with the renal result of extracellular alkalosis and intracellular acidosis. These are actions of loop diuretics, but they do not lead to metabolic alkalosis. Loop diuretics actually increase renin secret ion.

Que.5. Describe the therapeutic use of thiazides in diabetes insipidus.

Ans-Polyuria with low urine osmolality suggests the diagnosis of diabetes insipidus. To determine the cause of this syndrome, vasopressin is used. Because nephrogenic diabetes insipidus is vasopressin-resistant, urine osmolality would not change signicantly after vasopressin, as in this case. A common cause of nephrogenic diabetes insipidus is hypercalcemia, which is common in bone metastases of various tumors. Thiazide diuretics can reduce polyuria and polydipsia in diabetes insipidus. The mechanism of this

paradoxical effect is likely related to the extracellular volume reduction, which in turn causes an activation of the renin–angiotensin system. Angiotensin enhances the reabsorption of Na+ and water in the proximal tubule by stimulating the Na+/H+ exchanger. This in turn causes a decreased delivery of uid to the distal tubule. Thus, there is a decrease in the maximum volume of dilute urine that can be produced. Desmopressin is effective in neurogenic diabetes insipidus, but it is ineffective in nephrogenic diabetes insipidus. Neurogenic diabetes insipidus is unlikely in this case, because it is vasopressin sensitive; therefore, urine osmolality would have been increased significantly after vasopressin. Demeclocycline is appropriate for the treatment of syndrome of in appropriate antidiuretic hormone secretion (SIADH). This syndrome leads to hyponatremia (not hypernatremia, as in diabetes insipidus) and low serum osmolality. Amiloride is used e ectively in case of lithium-induced nephrogenic diabetes insipidus because the drug blocks lithium transport into the cells of the collect ing tubule. However, it is not e ective in other forms of diabetes insipidus. Furosemide is not e ective in nephrogenic diabetes insipidus. It can be used in case of chronic renal failure, but this diagnosis is unlikely in this case because urine osmolality is lower than serum osmolality (in chronic renal failure, urine osmolality is usually xed close to that of serum).

Que.6. Outline the actions leading to the therapeutic effect of nitrates in variant angina.

Ans.-Nitrates dilate large epicardial vessels, thus increasing epicardialblood flow. This action is the most important for the therapeutic e ect of these drugs in variant angina, which is characterized by coronary spasm. By causing venous dilat ion, nitrates can cause a decrease, not an increase, of left ventricular end-diastolic volume. Nitrates can cause re ex tachycardia an d re ex increase in cardiac contract ilit y, but these are detrimental, not therapeutic, effects in patients with angina. Nit rates can decrease diastolic perfusion time (as a consequence of re ex tachycardia), but this is a detrimental e ectin pat ients with angina.

Que.7. Explain the site of action of verapamil.

Ans.-Calcium channel blockers with heart act ivit y, such as verapamil and diltiazem, act on voltage-gated channels in cardiac and smooth muscle cell membranes. The blockade of channels in cardiac muscle leads to a reduct ion in cardiac contractilityand rate, whereas the blockade in vascular smooth muscle causes vasodilat ion, which in turn reduces the afterload of the heart . Both act ions are useful for the therapeutic e ectof these drugs in exert ional angina.Thesech an n els are n ot blocked by calcium ch an n el blockers. Calcium is exchanged between cytosol and mitochondria, which are storage sites for calcium,

through speci c mitochondrial store-operated calcium channels, but these channels are not blocked by calcium channel blockers. Calcium channels in the sarcoplasmic reticulum are opened by

depolarization and blocked by ryanodine. Calcium channel blockers aect these channels only at very high concentrat ion.

Que.8. Outline the actions leading to the therapeutic effect of nitrates in pulmonary edema.

Ans.-The signs and symptoms of the pat ient indicate that heis suffering from pulmonary edema. By increasing cyclic guanosine monophosphate product ion, nitrates cause relaxation of both resistance and capacitance vessels, but relaxation of the latter (especially large veins) is more pronounced, with standard therapeutic doses, probably because the enzyme that converts nitrates to nitric oxide is more abundant in veins than in arteries. This venodilation reduces preload to the hear t by pooling blood in the periphery, thus reducing ventricular end

diastolic volume. In this way, pulmonary congestion is reduced, and pulmonary edema is relieved. The nit rate-induced peripheral vasodilation tends to cause re ex tachycardia and re ex increase in cardiac contractility when high doses are given, but this would adversely affect pulmonary edema by increasing the pulmonary pressure. A decreased vent ricular ejection time is usually the consequence of tachycardia, so it would adversely affect pulmonary edema. By causing arteriolar vasodilation, nitrates also decrease afterload, but this action is less pronounced than the venous vasodilat ion. Thus, the decreased afterload is not the main reason for the therapeutic e cacy of nitrates in pulmonary edema. Nitrates decrease platelet aggregat ion, but this is not the reason that they are effective in treating pulmonary edema.

Que.9. Describe the use of nitroglycerin in myocardial infarction.

Ans.-Recent studies have reinvestigated the use of nitrate therapy in myocardial infarction (MI) in the set ting of concomitant thrombolytic therapy and aspirin administration. The pooled e ects from several studies have shown a small but statistically signicant decrease in mortality in patients receiving nitrates. Therefore, intravenous nitroglycerin is currently recommended for rout ine use during the rst 24 to 48 hours in most pat ients with MI, part icularly if they have signs of acute hear t failure (impending pulmonary edema) and are hypertensive, as in this case. Epinephrin e is cont rain dicated in MI because it in - creases cardiac work and oxygen demand. Intravenous β-blockers such as

metoprolol given within the rst few hours after onset of MI improve prognosis by reducing infarct size and incidence of ventricular brillation. In this case, however, they are contraindicated because of bradycardia and the impending pulmonary edema (these patients are dependent on sympathetic activation to increase the heart rate and to maintain blood pressure to vital organs). Verapamil and diltiazem have been shown to reduce the rate of reinfarction and death in patients with preserved left ventricular function, but they are contraindicated in this

case because of bradycardia and signs of cardiac failure. Dihydropyridines such asnefedipine have been uniformly unsuccessful in reducing either mortality or reinfarction in patients with MI.

Que.10. Explain the molecular mechanism of action of digoxin.

Ans. -At the m olecular level, all cardiac glycosides inhibit Na+/K+ ATPase, the membrane bound transporter called the sodium pump. The increased amount of sodium inside the cell inhibits the Ca2+/Na+ exchanger, an antiporter that uses the electrochemical potential for Na+ to drive Ca2+ extrusion. The consequence of this inhibition is that less Ca2+ is removed from the cell. The increased intracellular calcium is stored in the sarcoplasmic ret iculum during diastole, so a greater amount of Ca2+ is released from the sarcoplasmic reticulum during systole. Digitalis glycosides at high concent ration can open, notclose, cardiac calcium

channels. Digitalis glycosides have no direct e ect on potassium channels. **Que.11. Learning objective: Explain angiotensin-converting enzyme inhibitor (ACE)–induced mortalit y reduction in myocardial infarction.**

Ans.-ACE inhibitors block the vasoconstricting activity of angiotensin-II, thus reducing both preload and afterload, which in turn reduces the workload of the heart. In addition, they reduce the growth e ects of angiotensin II on cardiac myocytes and at tenuate the cardiac fibrosis induced by angiotensin II. These actions lead to reduction of myocardial remodeling.

The initial remodeling phase after a myocardial infarction (repair of the necrotic area and myocardial scarring) may be considered benecial, but over time remodeling causes an increase of vent ricular mass and volume that adversely affects cardiac function. By reducing cardiac remodeling, ACE inhibitors improve eject ion fraction and decrease mortality. ACE inhibitors do not appreciably affect cardiac contractility. By blocking aldosterone formation, ACE inhibitors decrease, not increase, preload. By decreasing the

workload of the heart , ACE inhibitors actually can indirectly cause coronary vasoconstriction. ACE inhibitors have negligible effects on ventricular automaticity.

Que.12. Describe the main action leading to the antihypertensive effect of thiazides. **Ans.-**The initial hypotensive effects of diuretics are associated with a reduction in plasma volume and cardiac output. Peripheral vascular resistance is usually unaffected (or sometimes increased). After 4 to 8 weeks of continuous therapy, blood volume and cardiac output return to normal, and peripheral vascular resistance decreases. Mechanisms underlying this decrease are probably related to a depletion of body Na+ stores. Diuretics cause negligible postural hypotension, because the baroreceptor reflex is not affected. Thiazides tend to decrease, not increase, interstitial fluid volume. Blood flow in any organ is related to perfusion pressure

and vessel resistance. Perfusion pressure in turn is mainly related to cardiac output . After several weeks of treatment with diuretics, cardiac output is normal; therefore, renal blood flow is either normal or increased, not decreased.

Que.13. Describe the antihypertensive uses of calcium channel blockers. Ans.-The patient is sueringfrom stage 2 hypertension, so a combination therapy is advisable. A diuretic (hydrochlorothiazide) and a Ca2+ channel blocker (nifedipine) would be a rational choice because Blacks often have low-renin hypertension and may respond best to diuretics and Ca2+ channel blockers. Moreover, in this patient Captopril is contraindicated because of the renal artery stenosis in a solitary kidney. Propranolol is contraindicated because of chronic obstructive pulmonary disease.

Que.14. Explain the mechanism of antihypertensive action of β-blockers. Ans.-Several mechanisms of the antihypertensive action of β-blockers have been postulated, but the two main mechanisms are most likely the following:

• Reduction of cardiac output due to the decrease in cardiac contractility and rate • Inhibition of the renin–angiotensin system due to inhibition of renin secretion Bet a-blockers have negligible effect on large vein s, but blockade of β2 receptors should constrict, not dilate, the vessels. Beta-blockers have negligible effect on the release of epinephrine from the adrenal medulla. Blockade of β2 receptors should increase, not decrease, blood pressure. In fact, this action of β-blockers is weak under rest ing conditions and is overridden by the effect on cardiac output. This is a postulated mechanism of antihypertensive action of β-blockers but is by no means the main one. In fact, even β blockers that do not cross the blood–brain

barrier, such as atenolol, do have antihypertensive effect. Beta-blockers have negligible effect on blood volume.

Que.15. Learning objective: Describe the electrophysiological actions ofquinidine. Ans.- Blockade of activated sodium channels is the distinctive feature of class Ia antiarrhythmic drugs. The slope of phase 0 of the cardiac act ion potential in normal atrial, Purkinje, and ventricular cells is dependent on sodium current. The higher the number of sodium channels that are in the open state, the higher the sodium current and the steeper the slope of phase 0. By blocking activated sodium channels (the number of channels that are blocked is dose-dependent), the sodium current will be less intense, and the slope of phase 0 decreases. By blocking potassium channels, quinidine slows down repolarization. Therefore, action potential duration is increased, the slope of phase 3 is decreased, and the effective refractory period is increased. The slope of phase 4 is related to automaticity (the steeper the slope, the higher the automaticity). Most antiarrhythmic drugs decrease the slope of phase 4, unless toxic doses are given.

Que.16. Describe the molecular mechanism of action of procainamide. Ans.- Procainamide is a class Ia antiarrhythmic drugs. All drugsof this class block act ivated sodium and potassium channels. Amiodarone and lidocaine are drugs of choice for treatment of vent ricular arrhythmias in the peri-infarction period. Procainamide is an alternative agent when the abovementioned drugs are either not tolerated or ineective. The drug blocks activated Na+ channels, and recovery from blockade is about 1.8 seconds (the fastest of class Ia drugs), so it exerts greater effect in depolarized and/or rapidly driven cardiac myocytes. **Que.17. Describe the lupoid syndrome caused by procainamide.**

Ans.-The patient's signs and symptoms are consistent with drug-induced lupus (also called lupoid syndrome), an autoimmune disorder that is similar to idiopathic systemic lupus erythematosus. The agents most commonly reported to cause the disorder are procainamide (about one third of the patients taking the drug over a 1-year period) and hydralazine.

Other drugs that can cause drug-induced lupus are chlorpromazine, isoniazid, methyldopa, quinidine, sulfonamides,and penicillamine. Onset of the drug-induced lupus syndrome can occur as soon as 1 month after therapy begins, as in this case. Unlike idiopathic lupus, drug induced lupus typically improves rapidly after the discontinuation of the drug. Quinidine can cause lupus but is not used to treat Wol –Parkinson–White syndrome. The risk of drug induced lupus with these drugs is quite low.

Que.18. Explain the molecular mechanism of action of adenosine.

Ans.- Adenosine activates specific A1 adenosine receptors in the heart, which in turn open acetylcholine-sensitive K+ channels, that is, channels normally driven by parasympathetic activity. This leads to hyperpolarizat ion of the sinoatrialand atrioventricular (AV) nodes. Adenosine is considered the agent of choice for the acute conversion of paroxysmal supraventricular tachycardia. Vagotonicmaneuvers (carotid sinus massage, Valsalvamaneuver, etc.), particularly if used early, may terminate the arrhythmia. If these maneuvers are ineffective, adenosine is used. Blocking conduction through the AV node for one beat interrupts the reentrant cycle. On the other hand, adenosine is contraindicated in wide complex supraventricular tachycardias because it can increase conduction through the accessory pathway.

Que.19. Describe the mechanism of action of HMG-CoA (3-hydroxy-3-methylglutaryl–coenzyme A) reductaseinhibitors.

Ans.-HMG-CoA reductase inhibitors inhibit 3-hydroxy-3-methylglutaryl–CoA reductase, which is the enzyme that catalyzesthe synthesis of mevalonic acid from 3-hydroxy-3- methylglutaryl–CoA. The formation of mevalonic acid is the rate-limiting step in cholesterol biosynthesis.The statin -induced inhibition of cholesterol synthesis in the liver results in an upregulation, not down regulation, of hepatic high-affinity low-density lipoprotein (LDL) receptors, which in turn causes an increased removal of LDL from the blood. Statins have no effect on lipoprotein lipase. The LDLs removed from the blood fuse together in the liver, forming larger vesicles called endosomes. Because removal of cholesterol from blood is

increased by stat ins, storage of LDL in hepatic endosomes will also be increased, not decreased. Stat ins can increase the plasma levels of hepatic aminotransferase and creatine phosphokinase, but this is a sign of potential toxicit y, not of therapeutic e cacy of these drugs.

Que.20. Learning objective: Describe the main drug interactions withcholestyramine.

Ans.-Cholestyramine is an anion exchange resin that binds bile acids in the intestinal lumen, thus preventing their reabsorption. In fact, the excretion of bile acid is increased up to 10-fold when the resin is given. This in turn causes an enhanced conversion of cholesterol to bile acids in the liver, an increased uptake of low-density lipoprotein (LDL) and intermediate density lipoprotein from plasma, and an upregulation of high-a nity LDL receptors on cell membranes. Resins can bind many drugs (including β-blockers and thiazides), reducing

their intestinal absorption. Cholestyramine does not affect the distribution or the elimination of drugs given concomitantly. Intestinal absorption of propranolol is actually decreased; therefore, the oral bioavailability is decreased, not increased.

Que.21. Explain the mechanism of action of gembrozil.

Ans.-The prescribed drug was most likely a brate. In fact, -fibrates are the drugs of rst choice when there is a big, isolated increase in t riglyceride level. Moreover, in this patient, niacin is contraindicated because of hyperuricemia, resins can cause an increase in triglyceride level, and statins should be avoided in a woman of reproductive age. The mechanism of action of brates is still uncertain but most likely involves a gene- mediated increase in lipoprotein lipase synthesis. Fibrates cau se lipolysis, not an increase of lipid synthesis.The antihyperlipidemic agents tend to cause an upregulation, not a downregulation, of low

density lipoprotein (LDL) receptors. Statins, not brates, inhibit HMG-CoA (3-hydroxy-3-methylglutaryl–coenzyme A) reductase act ivity in the liver. Fibrates have no effect on absorption of exogenous cholesterol.

Que.22. Explain the molecular mechanism of action of oxytocin.

Ans.-Oxytocin causes sustained contraction of uterine smooth muscle. Because calcium is needed to contract muscle cells, the activated signaling pathway must lead to increased intracellular calcium. This is brought about by a receptor-mediated activation of phospholipase C that splits by hydrolysis thephosphatidylinositol 4,5-biphosphate into two second messengers, inositol triphosphate (IP3) and diacylglycerol (DAG). IP3 triggers the release of calcium from storage vesicles, whereas DAG activates protein kinase C, an enzyme with a vast array of physiological effects, including smooth muscle contraction. Although the activation of these signalling pathways can in some cases cause increased intracellular calcium, the activation of the phosphoinositide pathway remains the most important trigger for intracellular calcium increase in smooth muscle cells.

Que.23. Identify the enzyme whose synthesis is promoted by follicle-stimulating hormone (FSH).

Ans.-Follitropinalfa is recombinant follicle-stimulating hormone (FSH). It activates specific receptors that act via the adenylyl cyclase pathway to stimulate the granulosa cells of the ovary to produce aromatase. This enzyme (also called estrogensynthase) is a key step in biosynthesis of estrogens. It converts androstenedione to estrone and testosterone to estradiol.

A "step-up" protocol of ovulation inducts ion mimics the natural menstrual cycle. Increasing doses of FSH are given during the rest half of the cycle to promote follicular development. Then an injection of human chorionic gonadotropin is administered to simulate the luteinizing hormone surge that naturally occurs in midcycle and t riggers ovulation.

Que.24. Describe the treatment of thyrotoxicosis during pregnancy. Ans.-The patient's FT4 (free thyroxine) and TSH (thyrotropin) levels indicate that she was suffering from thyrotoxicosis. Either surgery or thioamide is the treatment of choice for hyperthyroidism in a pregnant pat ient. When antithyroiddrug therapy must be used during pregnancy, propylthiouracilis the preferred thioamide during the rst trim ester because it crosses the placenta much less than methimazoledoes, and because a rare embryopathy was associated with methimazole. Subsequently, methimazole should be prescribed to avoid the rare but serious potential hepatic damage associated with propylthiouracil. Radioactive iodine is contraindicated during pregnancy. Octreotide is a somatostatin analogue. It is used only in rare cases of hyperthyroidism due to a pituitary adenoma secreting TSH (thyrotropinoma). This is not the case in this patient, as TSH was very low. Iodine compounds are not used for routine treatment of hyperthyroidism. Low doses of iodine have been used in pregnancy, but only when all other approaches are contraindicated. Methyldopa is used during pregnancy only in hypertensive patients. Beta-blockers are used in hyperthyroidism, but esmololhas a very short half-life and therefore is not suited for chronic use.

Que.25. Explain the mechanism of action of thioamideantithyroid drugs. Ans.- Methimazole and propylthiouracil are thioamides used as antithyroid agents. These drugs inhibit thyroid peroxidase, the enzyme that catalyzes the following three steps in thyroid hormone biosynthesis:

• Oxidation of iodide to iodine

• Iodinat ion of tyrosine residues within thyroglobulin (iodide organi cat ion) • Combination of two diiodotyrosines (DITs), leading to T4, and combination of monoiodotyrosine (MIT) and DIT, which leads to T3. By blocking the enzyme, the synthesis of thyroid hormones is blocked. In addition, propylthiouracil and, to a lesser extent, methimazole inhibit the peripheral deiodinat ion of T4 and T3.

Que.26. Explain why it is essential to maintain maternal euthyroidism during pregnancy.

Ans.- Congenital hypothyroidism, abnormal fetal development, and impaired cognitive development in the newborn have been at tributed to maternal hypothyroidism. A delay in both mental and motor development was observed in children who were born to mothers with low circulating thyroid hormone levels but normal thyroid-stimulating hormone (TSH, thyrotropin) levels during the rst trimester of pregnancy. This is because early development of the fetal brain depends on maternal levothyroxine. Most women with primary hypothyroidism will require about 30 to 50% increment in hormone dosage to maintain euthyroidism during pregnancy. Explanations for this increment include the pregnancy induced increase in thyroid-binding protein s and an in - creased volume of distribut ion during pregnancy. Maternal hypothyroidism can be associated with excessive weight gain, preeclampsia, or even myxedema coma, but these are very rare events, and to avoid these disorders is not the main reason for the increased dosage of thyroid hormone during pregnancy. Human chorionic gonadotropin has signicant TSH activit y, but this has nothing to do with the reason for the increased dosage of thyroid hormone during pregnancy.

Que.27. Describe the effects of glucocorticoids on serum glucose levels. Ans.- Glucocorticoids can lead to hyperglycemia by causing simulation of gluconeogenesis, decreased glucose utilization by cells, and increased glucagon secretion. These e ects are dose dependent, and hyperglycemia can occur even with a low dose of daily prednisone. Glucocorticoids tend to cause effects opposite to those listed. Glucocorticoids can cause hypokalemia, but this is rare with synthetic drugs that have very low mineralocorticoidactivit

y, such as prednisone. Moreover, the pat ient was receiving captopril, which tends to cause hyperkalemia, thus balancing the possible hypokalemic e ect of prednisone.

Que.28. Explain why synthetic glucocorticoids areusually preferred over cortisol in the therapy of nonendocrinedisorders.

Ans.-Synthetic glucocorticoids are usually preferred over natural hormones for the treatment of nonendocrine disorders because they are less prone to induce salt and water retention when given at equivalent antiinammatory doses. All of these e ect s of glucocor t icoids are doserelatedand closely parallel their antiinammatory e ect.

Que.29. Explain the mechanisms of the antiin amatory action of glucocorticoids. Ans.- Acute bursitis results from the in ammation of a fluid led sac, the bursa, which is located between two surfaces that rub together when moving. The in ammation has a rapid onset and can be very uncomfortable. Intra-art icularinject ions of glucocorticoids provide rapid relief

because of their powerful ant iinammatoryactivit y. This e ect is mediated by a vast array of actions, including the induction of the synthesis of lipocortins. These enzymes act as inhibitors of phospholipase A2, the enzyme that catalyzes the release of arachidonic acid from membrane phospholipids. Because arachidonic acid is the precursor of eicosanoids, the corticosteroid- induced induct ion of lipocortins leads to an inhibit ion of phospholipase A2 and, in turn, to an inhibit ion of biosynthesis of all eicosanoids, which are proin amatory compounds. Glucocor t icoids in h ibitadrenocorticotropic h ormon e (ACTH) release, but this has nothing to do with their antiinammatory action. Glucocorticoids do not aect the catabolism of prostaglandins. Glucocorticoids decrease post capillary permeabilit y (due to inhibition of histamine release and kinin activity) and decrease the synthesis of most prion ammatory interleukins, such as IL-6.

Que.30. Outline the pharmacotherapy of Cushing syndrome.

Ans.-In patients with Cushing syndrome, the main goal of pharmacotherapy is to block glucocorticoid secretion. Ketoconazole is an antifungal agent. In doses higher than those employed in antifungal therapy, the drug inhibits cytochrome P-450 enzymes, thus blocking several steps of steroidogenesis. As a result, the drug is the most e ective inhibitor of steroid biosynthesis. Another drug that can be used in Cushing syndrome to inhibit steroid biosynthesis is aminoglutethimide, which inhibits CYP11A, the enzyme that catalyzes the conversion of cholesterol to pregnenolone, the rate-limiting step in steroid biosynthesis. These drugs are useless, or even dangerous, in treating Cushing syndrome.

Que.31. Describe the pharmacological actions of progesterone.

Ans.-Medroxyprogesterone is a synthetic progesterone derivative that is about 15 t imes more potent and has the same pharmacological properties of the parent compound. Progesteroneincreases the sensitivity of the respiratory centerto carbon dioxide, thus leading to an increased ventilator response. This can explain the measurable reduct ion of arterialan d alveolar carbon dioxide th at occurs du ring pregnancy. Progesterone actually exhibits act ions opposite to those listed.

Que.32. Describe the pharmacological effects of vitamin

Ans.- Cholecalciferol (vitamin D3), which is a prodrug, is the most appropriate therapy for vitamin D de ciency in anyone with normal renal function. Cholecalciferol is metabolized to 25(OH) D by the liver and circulates bound to vitamin D–binding protein, making it available for conversion to calcitriol. For the regulation of calcium homeostasis, the renal conversion of calcitriol plays a major role in stimulatingintestinal calcium

absorption, thus adding calcium to the system. Conversion in other tissues contributes to noncalcemic e ects of calcitriol, such as muscle strength and support of the innate immune system. Administ ration of calcitriolas a drug is reserved for cases where the body is unable to make calcitriol, as in renal failure, because of the risk of hypercalcemia. None of these drugs would address vitamin D deciency.

Que.33. Explain the primary mechanism of action of calcitriol.

Ans.-Intestinal calcium absorpt ion is potently augmented by calcitriol, and this is most likely the main action that mediates the therapeutic e cacy of calciferols in osteomalacia. There is lit tle evidence that calcitriol directly promotes bone mineralization. Rather, it is the increased serum calcium level that indirectly promotes bone mineralization by decreasing parathyroid hormone–mediated bone resorption.

Que.34. Outline the therapeutic uses of calcitonin.

Ans.-The patient's signs and symptoms indicate that he was most likely a ected by Paget disease of bone, a chronic disorder of the adult skeleton characterized by uncontrolled osteoclastic bone resorption with secondary increase in poorly organized bone formation. The disease is fairly common, affecting about 3% of adults over age 40. It is often asymptomatic and usually progresses slowly. Pharmacological therapy is indicated (even in the absence of symptoms) when alkaline phosphatase is more than 2 to 3 times the normal levels, as in this case. Bisphosphonates are rst-line agents for this disease. Calcitonin is an alternative to bisphosphonates when these drugs are contraindicated, as in this case. Oral bisphosph on ates are relatively con t rain dicated inpat ients with gastrointestinal reux disease, esophagit is,
gastritis, and peptic ulcer, as they can cause esophageal and gastric irritation. These drugs are useless in Paget disease.

Que.35. Explain the mechanism of action of glyburide.

Ans.-Sulfonylureas such as glyburide act by binding to a speci creceptor that is closely linked to the adenosine t riphosphate(ATP)–sensitive K+ channels in pancreatic β-cell m embranes. This causes a blockade of the e u x of K+, which in turn leads to membrane depolarizat ion. Voltage-gated Ca2+ channels open in response to depolarizat ion, thus increasing intracellularCa2+ concentrations. This increased concentration ultimately stimulates the release of insulin by exocytosis. Acarbose, metformin, and pioglitazone can be

used in the treatment of type 2 diabetes, but none of them have the described mechanism of action. Insulin and exenatide are not orally active.

Que.36. Explain the molecular mechanism of action of metformin.

Ans.-Biguanides such as m etformincause act ivat ion of adenosine monophosphate (AMP)–activated protein kinase, an enzyme that acts as a sensor of cellular energy status in all eukaryotic cells. The enzyme is activated when cellular energy stores are reduced or when biguanide drugs are administered. Its activat ion in turn causes

- Inhibition of gluconeogenesis and lipogenesis
- Stimulation of glucose uptake and utilization (glycolysis)
- Stimulation of fat ty acid oxidation
- Reduct ion of plasma glucagon levels

The net result is increased glycogen storage in skeletal muscle, decreased glucose production by the liver, and decreased hyperglycemia. All of these actions would decrease hyperglycemia, but they are not elicited by metformin.

Que.37. Describe the insulin resistance in a diabetic patient.

Ans.-The simultaneous elevat ion of blood glucose and insulin levels is strongly suggest iveof in sulin resistance. Insulin resistance can develop especially in diabetics who have a clustering of cardiovascular risk factors, including hypertension, abdominal obesity, and dyslipidemia. The associat ion of insulin resistance with the above-mentioned clustering has been referred to by a variety of names, including insulin resistance syndrome, metabolic syndrome, and dysmetabolicsyndrome. The prevalence of this syndrome is more than 30% in the US populat ion. An estimated 75% of patients with type 2 diabetes have metabolic syndrome, as in this case. The syndrome is strongly associated with an increased risk of cardiovascular diseases. Metformin can cause lactic acidosis, but symptoms of this disorder (vomiting, lethargy, hyperventilation, hypotension) are absent in this patient. Because the

patient has hyperglycemia and insulin resistance, a hypoglycemic reaction is quite unlikely. The pat ient is at increased risk of unstable angina, but symptoms of unstable angina are absent in this patient. The signs and symptoms of ketoacidosis are absent inthis patient.

Que.38. Describe the main contraindications to the use of metformin. Ans.-The pat ient's symptoms and serum values indicate that he was most likely suering from kidney failure (see high creatinine and blood urea nitrogen [BUN] values), a frequent complication of long-standing diabetes and hypertension. Metformin is excreted as such by the kidney and is therefore absolutely contraindicated in a patient with renal failure. These drugs are not contraindicated in renal failure.

Que.39. Explain the molecular mechanism of action of pioglitazone. Ans.-Pioglitazone is a thiazolidinedione derivative. Thiazolidinedionesact by binding to a nuclear receptor called peroxisome proliferator activated receptor gamma (PPAR-γ), which is located mainly in adipose tissue, skeletal muscle, and liver. The receptor regulates the transcript ion of several insulinresponsivegenes. The overall effect is an enhancement of tissue sensitivity to insulin (i.e., a reduction in insulin resistance). Therefore, the need for exogenous insulin is reduced. Because of this, they are called insulin sensitizers.

Que.40. Explain the mechanism of action of acarbose.

Ans.-Acarbose and miglitol are inhibitors of α-glucosidase, an enzyme located on the brush border of intestinal cells that is involved in the breakdown of starches and disaccharides into simple sugars. Inhibition of this enzyme slows the absorption of carbohydrates from the gastrointestinal tract and blunts the rate of rise of postprandial glucose. This is a liver enzyme

that catalyzes the rest step in gluconeogenesis. This is a liver enzyme that phosphorylates glucose to glucose-6-phosphate. These are adipocyte enzymes involved in lipid metabolism.

Que.41. Describe the adverse effects of α-glucosidaseinhibitors.

Ans.-Miglitol is an α-glucosidase inhibitor. These drugs are approved for people with type 2 diabetes as monotherapy and in combination with other oral antidiabetic drugs. The patient's symptoms are classic adverse effects of α-glucosidaseinhibitors, which occur in more than 50% of subjects at the start of the therapy. These drugs decrease the absorption of monosaccharides from the duodenum and upper jejunum by inhibiting the enzyme that is involved in the breakdown of starches into simple sugars. The adverse e ects are due to fermentation of unabsorbed carbohydrates in the small intestine. These drugs do not cause the collection of symptoms reported by the patient.

Que.42. Describe the main therapeutic uses of zafirlukast.

Ans.-Leukotriene inhibitors and antagonists have demonstrated the important role of leukotrienes in aspirin-induced asthma. Some asthmatic patients are very sensitive to aspirin as well as to all nonsteroidalantiinammatory drugs, and even small doses can cause profound bronchoconstriction, flushing, andabdominal cramping. The syndrome is not allergic in nature but seems to be related to the inhibition of cyclooxygenase, which most likely causes

- A shift of arachidonic acid metabolism to the leukotriene pathway; leukotrienes are powerful bronchoconstrictingagents.
- Decreased synthesis of prostaglandin E2 (PGE2), which is an endogenous bronchodilator, very important in maintaining airway patency for most asthmatics

Leukotriene antagonists such as zarlukast and montelukastare the drugs most frequently used for maintenance therapy in pat ients with aspirin -induced asthma. Systemic glucocorticoids and theophylline are used only in case of severe asthma that is resistant to other pharmacotherapies. These drugs are used only by inhalation.

Que.43. Describe the proposed molecular mechanisms of the bronchodilating action of theophylline.

Ans.-The molecular basis for the antiasthmatic action of m ethylxanthinesis still uncertain. Although the primary mechanism of the bronchodilating e ect most likely involves the inhibition of phosphodiesterase enzymes, an additional mechanism seems related to the blockade of adenosine A1 receptors. Adenosine acts as both an autacoid and a transmit ter with myriad biological actions, including bronchoconstriction, mainly in pat ients with bronchospastic disease. Theophylline does not block these receptors.

Que.44. Describe the interaction between β2 adrenoceptoragonists and glucocorticoids in the treatment of asthma.

Ans.-Systemic corticosteroids are given in cases of severe asthma exacerbation for two main reasons:

- They improve the responsiveness of β2 receptors.
- They inhibit many phases of the in ammatory responses.

The antiinammatoryactivit y of corticosteroids is delayed for 4 to 6 hours after administrat ion. However, the restoration of responsiveness to endogenous catecholamines, as well as to exogenous β2 agonists, occurs w ithin 1 hour of glucocorticoidadministrat ion in severe chronic asthmatics. This restoration is therefore the main potential bene t of

intravenous administration of corticosteroids to a patient with severe asthma exacerbation under treatment with β2 agonists. Corticosteroids do not have these e ects.

Que.45. Describe the main adverse effects of β2 agonists.

Ans.-Beta-2 agonists promote the uptake of potassium into the cells, likely by stimulating Na+/K+ ATPase. High doses of these drugs can cause hypokalemia, and these drugs are sometimesused in the therapy of hyperkalemic states. In thiscase, hypokalemia is even more likely because of the earliertreatment with insulin (insulin tends to cause hypokalemia, as it promotes potassium entry into cells). Both hypertension and hypotension can be adverse effects of albuterol, but in this patient , hypotension is more likely due to the hypokalemia. Beta-2 agonists tend to cause e ects opposite to those listed.

Que.46. Explain the molecular mechanism of action of ipratropium. Ans.-Ipratropium is an antimuscarinic drug. By blocking M3 acetylcholine receptors in the bronchial tree, these drugs prevent the increased synthesis of inositol triphosphate, which in turn triggers the release of Ca2+ from storage vesicles. These drugs do not block muscarinic receptors. Like ipratropium, at ropine can block M3 acetylcholine receptors in the bronchial tree, thus counteracting the acetylcholine- mediated increase in Ca2+ availabilit y. However, anticholinergics (except ipratropium and tiotropium) are usually contraindicated in bronchospastic disorders because they decrease bronchial secretion and mucociliaryclearance.

Que.47. Describe the bronchodilating use of ipratropium when β2 adrenoceptor agonists are contraindicated.

Ans.-Accepted guidelines for the treatment of asthma indicate a short-acting β2 agonist as needed in all patients. In this case, however, the patient's atrialbrillation contraindicates the use of β2 agonists. In general, when drugs are given by inhalation, only 10 to 20% of the dose can reach the target site of act ion (lower airways); the rest is swallowed and can be absorbed by the intestine, causing systemic effects. Ipratropium is an e ective bronchodilator agent, and the swallowed dose is not absorbed by the intestine (the drug is a quaternary ammonium compound). Moreover, in this patient

- The bronchospasm was triggered by emotional upset, and it has been shown that inhaled anticholinergic drugs can block this response.
- The nocturnal awakening indicates that the bronchospasm is triggered by a prevalence of the parasympathetic system (which is predominant during the night), so an antimuscarinic drug is appropriate. These drugs are not bronchodilators and cannot be used

for relief of bronchospasm. Oral sustained-release theophylline is an effective bronchodilator, but it has the potential to cause more adverse effects, may interfere with sleep, and is less effective thanipratropium.

Que.48. Outline the use of H2 antagonists in stress induced peptic ulcer.

Ans.-Acute stress-related mucosal bleeding is a type of erosive gastritis that occurs in critically ill patients with severe psychological stress (surgery, trauma, sepsis, etc.). The patientwas in septic shock, and her abdominal pain suggested that stress-related mucosal bleeding was impending. Therefore, she needed aggressive prophylactic treatment. H2 antagonists are the most widely used drugs for prevention of stress ulcer. They must be given intravenously, and infusion is more effective than a single bolus in maintaining the gastric pH above 4. Although proton pump inhibitors (not listed) would appear to be the preferred option because of their greater abilit y to inhibit gastric acid secretion, there is very

little evidence to con rm the clinical superiority to H2 antagonists for stress ulcer prevent ion. These drugs have no antiulcer properties. These ant iulcer drugs are much less e ective than H2-antagonists and are not suited for emergency treatment.

Que.49. Identify the site of antiemetic action of ondansetron.

Ans.-Serotonergic antagonists such as ondansetron are currently considered to be rst-line agents for prevent ion of chemotherapy-induced nausea and vomiting. Ondansetronand congeners block 5-HT3 serotonin receptors located in the nucleus tractussolitarius (likely the main site of act ion), chemoreceptor t rigger zone, and visceral aerent nerves. In this way, it is thought that they can prevent both peripheral and central stimulation of the vomiting center.

Que.50. Explain the mechanism of action of methylcellulose.

Ans.-Methylcellulose is an indigestible hydrophilic polysaccharide polymer that absorbs water, forming a bulky gel that distends the intestine, thus stimulating peristaltic act ivit y. It acts mainly in the colon and takes 1 or 2 days to work. The laxative effect is mild. All of these laxatives act mainly in the small intestine.

Que.51. Outline the use of lactulose in portal-systemic encephalopathy. Ans.- Eliminating toxic enteric products (mainly fecal ammonia) is a therapeutic goal in portal-systemic encephalopathy. Patients with severe liver disease have an impaired capacity to detoxify ammonia coming from the colon, where it is produced by bacterial metabolism of fecal urea. Ammonia is an important cause of brain toxicit y. Lactulose, in high doses,

can lower colonic pH, which results in "trapping" of the ammonia by its conversion to polar ammonium ion, which is poorly absorbed.

Que.52. Describe the e ects of aluminum hydroxide on serum ions.

Ans.- Aluminum salts bind phosphate in the gut, preventing phosphate absorption. Moreover, they can induce a blood to gut phosphorus gradient that favors the eliminat ion of circulating phosphate. In fact , chronic use of high doses of aluminum salts is one of the common causes of hypophosphatemia. The disorder is usually asymptomatic, but severe phosphorus depletion

can cause anorexia, muscle weakness, and osteomalacia. Aluminum salts usually do not cause this effect .

Que.53. Explain the molecular mechanism of the antidiarrheal action of loperamide.

Ans.- Loperamide is an opioid agonist that directly activates m u (μ) receptors in the enteric nervous system. This activation of enteric neurons and smooth muscle ultimately causes a decrease in contraction of intestinal longitudinal muscle and a marked increase in contract ion of circular muscle. Therefore, propulsive perist alt ic waves are diminished, and tone is increased, thus relieving diarrhea. Loperamide cannot bind these receptors. **Que.54. Explain why the dose of H2 histamine antagonists must be reduced in patients with renal insuciency**

Ans. The high creatinine level indicates that the patient was suffering from chronic renal insufficiency. Famotidine is an H2 histamine antagonist. All drugs of this class are cleared mainly by the kidney. Although the overdose toxicity of H2 antagonists is quite low, the dosage should be reduced in elderly patients with renal insuciency, as in this case.

Que.55. Outline the therapeutic uses of bismuth subsalicylate.

Ans.- The patient is most likely a ected by travelers'diarrhea, which typically begins within 24 to 48 hours after eating fecally contaminated food. Several enterobacteriaceae can cause t ravelers' diarrhea, varying according to the area of travel. *Escherichia coli* is the most common in Central America. Bismuth subsalicylate is e ective in patients with diarrheacaused by *E. coli, Helicobacter pylori, Campylobacter jejuni,* and *Salmonella* species and also inhibits enteric secretions.Magnesium sulfate is an osmotic laxative and therefore is contraindicated in the t reatment of diarrhea. These antibiotics are not e ective against enterobacteriaceae. These drugs have no antidiarrheal properties.

Que.56. Outline the therapeutic use of iniximab in Crohn disease.

Ans.- Treatment of m ild colonic Crohn disease can start w ith sulfasalazine or glucocorticoids. If remission is not achieved, in iximab, azathioprine, or methotrexate is added. An important proinammatory cytokine in Crohn disease is tumornecrosis factor (TNF). In iximab is a monoclonal ant ibodythat binds to soluble and membrane-bound TNF with high a nit y, thus preventing the binding of the cytokine to its receptors.To add these drugs is irrational, as prednisone and sulfasalazine were not effective. Daclizumab is a monoclonal antibody used only for treatment of acute organ rejection.

Que.57. Outline the therapy for ulcerative colitis.

Ans.- The patient's symptoms, together with macroscopic and microscopic endings, suggest that he was most likely affected by ulcerative colit is. The limitation of the lesions to the

superficial mucosa and crypt abscesses con rm the diagnosis (Crohn disease involves all layers of the bowel frommucosa to serosa). Remission induct ion in ulcerative colitisis usually accomplished with glucocorticoids. Their effects on in ammatory bowel disease are well documented, but the response in individual patients is variable. About 40% of patients are responsive, 40% have only partial response, and 20% are resistant. An t ibiotics such as met ronidazole and clarithromycin are used only as adjunctive t reatment along with other medications. These drugs are not effective and may be dangerous in inflammatory bowel disease.

Que.58. Identify the receptors that can be blocked by metoclopramide. Ans.- Metoclopramide is a dopamine D2 receptor antagonist , a serotonin 5-HT3 receptor antagonist, and a serotonin 5-HT4 receptor agonist. In the enteric nervous system, all of these molecular actions seem to contribute to the final e ect that is related to an increased activity of cholinergic motor neurons. In this way, the drug exerts a prokinetic e ect; that is, it increases the lower esophageal sphincter tone and enhances transit in the upper digest ivetract . It has negligible e ects on gastric secretion or motility of the large intestine. In addition, the blockade of D2 receptors and 5-HT3 receptors in the chemoreceptor t rigger zone can explain the antiemetic activity of the drug.

Que.59. Outline the therapeutic uses of proton pump inhibitors.

Ans.- The patient is m ost likely suering from Zollinger–Ellison syndrome, a rare condition characterized by a t riad of clinical findings, including severe recurrent peptic ulcer disease, signicanthypersecretion of gastric acid, and a tumor of the pancreas (gastrinoma) that funct ions as an ectopic source of gastrin. This tumor is usually located in

the pancreas but can be found in other regions, part icularly the duodenum. Currently, most patients with gastrinomascan be e ectivelyt reated with high doses of a drug such as omeprazole that inhibits H+/K+ ATPase in gastric parietal cells. These are the mechanisms of action of H2- receptor antagonists (A), misoprostol (B), sucralfate (C), and antacids (D). All of these antiulcer drugs are less e ective than proton pump inhibitors in reducing gastric acid secretion and therefore are not rst-line agents in Zollinger–Ellison syndrome.

Que.60. Describe the drug classes used to treat chemotherapy-induced nausea and vomiting.

Ans.- Serotonergic antagonists are currently considered rstlineagent s to prevent chemotherapy-induced nausea and vomit ing. Ondansetron and congeners block 5-HT3 receptors located in the nucleus of the t ractussolitarius (likely the main site of act ion), chemo receptor trigger zone, and visceral a erent nerves. In this way, it is thought that they

can prevent both peripheral and cent ralstimulat ion of the vomiting center. These drugs can cause, not prevent , nausea andvomiting. These drugs have ant iemetic properties but are muchless e ective than serotonergic antagonists in chemotherapy induced nausea and vomiting.

Que.61. Describe the antiemetic activity of dronabinol.

Ans.- Dronabinol is a Δ9-tetrahydrocannabinol, the most active cannabinoid from cannabis. Its mechanism of ant iemeticaction is still uncertain, but the drug likely activates speci c cannabinoid receptors in the vomiting center. Because of the availability of more e ective agents, dronabinol is uncommonly used in patients receiving cancer chemotherapy, but can be a useful addit ion when other antiemeticmedicat ions are not e ective, as in this case. These drugs are devoid of antiemetic properties. It would be illogical to add a glucocorticoid drug when dexamethasone was not e ective. Meclizine is an antihistamine agent useful in prevention of motion sickness–induced vomiting. Antihistamines are not effective in chemotherapy-induced vomiting.

Que.62. Outline the therapeutic use of H2 blockers in gastroesophageal reflux disease (GERD).

Ans.- The patient was most likely suering from GERD. Because the patient requested a medication to specically prevent meal-related symptoms, H2 antagonists such as famotidine are appropriate. Their onset of symptom relief occurs within 30 to 45 minutes and persists up to 10 hours. They also have a benecial e ect of reducing nocturnal acid

secretion, which is mainly histamine-dependent. Proton pump inhibitors (not listed) have an e cacy higher than that of H2 antagonists with regard to symptom relief and duration of suppression, but their onset of activity is slower (2 to 3 hours), and complete relief may take up to 4 days of therapy. At rop in e is act u ally con t rain dicated, as it may favour re u x by relaxing the lower esophageal sphincter.These drug are of no value in GERD. This drug would be indicated only in case of peptic ulcer, which is unlikely in this pat ient.

Que.63. Identify the best laxative for a patient with renal insufficiency. Ans.- Lactulose is a nonabsorbable sugar that is hydrolyzed in the colon to organic acids. These acids draw water into the lumen by osmotic forces, stimulating colonic propulsive motility by stretching the colonic wall. The laxative e ect is mild. Castor oil is too strong a cathartic to be used regularly. Magnesium and phosphate preparations are contraindicated in renal insuciency because the small amount of absorbed salt cannot be readily excreted, thus causing systemic toxicity (hypermagnesemia or hyperphosphatemia). Mineral oil has several
adverse e ects (interference with absorption of fat-soluble substances, elicitation of foreign body react ion) that preclude its regular use.

Que.64. Describe the best treatment in case of laxativeinduceddiarrhea. Ans.- When diarrhea is experienced with the use of laxatives, the laxative should be discontinued until resolution of the diarrhea. A diet rich in berand abundant uid intake usually helps to normalize the intestine. The sit uation is not self-limiting. Tolerance to bisacodyl is negligible. These opt ion s would main t ain th e drug-in du ced
diarrhea. Castor oil is too strong a cathartic to be used regularly.

Que.65. Explain the molecular mechanism of action of aprepitant.

Ans.- NK1 neurokinin receptors are located in the nucleus of the tractussolitarius in the brainstem. Act ivat ion of these receptors by substance P and related substances causes an increase in ring to the vomiting center. Aprepitant is an NK1-receptor antagonist that is able to cross the blood–brain barrier. It has ant iemetic e ects, especially in cases of delayed emesis, and it improves the e cacy of standard antiemetic regimens in pat ients receiving multiple cycles of chemotherapy.

Que.66. Explain the efficacy of a triple-drug regimen in the therapy of Helicobacter pylori–associated ulcers.

Ans.- For *H. pylori*–associated ulcers, there are two therapeuticgoals: eradicate the *H. pylori* and heal the ulcer. The rst goal is important because it has been shown that eradication of *H. pylori* almost completely eliminates the risk of ulcer recurrence. The most e

ectiveregimens for *H. pylori* eradication are combinations of two antibiotics and a proton pump inhibitor. After complet ion of triple-drug therapy, the proton pump inhibitor should be continued for 3 to 6 weeks to ensure complete ulcer healing. Omeprazole has no bactericidal activit y against *H. pylori*. It only creates a hostile environment for *H. pylori* by increasing gastric pH. The triple-drug regimen can cure the ulcer in more than 90%, not up to 70%, of cases.

Que.67. Describe the adverse e ects of metoclopramide.

Ans.- The patient's symptoms suggest that he is suering from acute dystonia, an extrapyramidal syndrome that can occur after treatment with neuroleptics and other drugs that block D2 receptors in the basal ganglia. Young pat ients, especially males who receive these drugs intravenously, are at greater risk of this adverse e ect, as in this case. Metoclopramide is a drug with antiemetic properties, probably due to its blocking act ivit y on both D2 and 5- HT3 receptors located in the chemoreceptor t rigger zone and the nucleus of the tractussolitarius. It is often used to treat postoperative nausea and vomiting. These antiemetic drugs do not cause acute dystonias.

Que.68. Explain the mechanism of action of saline laxatives.

Ans.- Saline laxatives such as m agnesium salts (citrate and hydroxide)and phosphate salts are poorly absorbed and holdwater in the intestine by osmotic forces. The increased volume of intestinal content stretches the intestinal wall, thus stimulating peristalsis. Magnesium salts stimulate, not inhibit , cholecystokinin release. The drug causes water retent ion in th e intestinal lumen, not in the vessels. This is the mechanism of action of mineral oil. This is the mechanism of act ion of dietary bers.

Que.69. Describe the therapeutic uses of loperamide.

Ans.- The patient's symptoms suggest that she was most likely suering from irritable bowel syndrome, a condition that affects 10 to 15% of the population in the United States. Many patients with this syndrome can be managed sat isfactorilywith simple medical counseling and supportive measures, including dietary rest riction and ber supplementation. The pharmacological t reatment of bowel symptoms (either diarrheaor constipat ion) is symptomatic. In this case, an ant idiarrhealdrug is needed. Opioid agonists such as loperamideand diphenoxylate are commonly used. They have the advantage of negligible cent ral nervous system (CNS) activity because penetration into the CNS is poor.

Other drugs used for this purpose are muscarinic and 5-HT3 antagonists. Drugs from these classes would increase, not decrease, bowel movements.

Que.70. Explain the mechanism of action of sucralfate.

Ans.- Sucralfate is a mucosal protective agent. In a strong acid environment (pH < 4), the negatively charged sucrose sulphate undergoes extensive cross-linking to positively charged proteinsto produce a viscous, st icky polymer that adheres toepithelial cells and ulcer craters for up to 6 hours after a single dose. Sucralfate does not have these e ects. Sucralfate may have cytoprotective e ects, including stimulation of local production of prostaglandins, which in turn can inhibit acid secret ion and stimulate bicarbonate secret ion, but this is not the main mechanism of action of the drug.

Que.71. Identify the most appropriate laxative used during pregnancy Ans.- Up to 30% of women experience constipation during pregnancy. Laxatives must be used cautiously because they can increase motility and blood ow in the lower abdomen, and mild agents are preferred. A stool softener such as docusate or a bulk-producing product such as psyllium is commonly used. Stimulant cathartics (castor oil, bisacodyl, and senna) and saline cathartics (magnesium hydroxide and sodium sulfate) are not recommended during pregnancy.

Que.72. Identify the drug used to treat gastroesophagealre ux disease (GERD) in a patient with concomitant disorders.

Ans.- The substernal pain and re ux of gastric contents into the esophagus are classic symptoms of GERD, a disorder that affects 7% of the population in the United States. Proton pump inhibitors such as omeprazole are e ective in the treatment of GERD, and a once-daily dose for 4 weeks will heal 60 to 80% of patients with severe esophagitis. Atropin e is contraindicated, because it may favor re u x by relaxing the lower esophageal sphincter. These drugs are not e ective in treat ing GERD. Metoclopramide is used in the treatment of GERD becauseit promotes gastric peristalsis and also increases thelower esophageal sphincter resting tone. However, it is contraindicated in pat ient s with Parkinson disease because it is a D2 antagonist. H2 antagonists are currently used in GERD, but cimetidineis not appropriate in a patient taking other drugs because it can inhibit the metabolism of most drugs, including selegiline.

Que.73. Identify the best drug regimen to prevent chemotherapy-induced nausea and vomiting.

Ans.- According to the guidelines for the use of ant iemetics in oncology from the American Society of Clinical Oncology, the best regimen to prevent nausea and vomiting in

pat ientsundergoing chemotherapy is a three-drug combinat ion of a 5-HT3 receptor antagonist , a glucocorticoid, and aprepitant. This combinat ion prevent s acute emesis in 80 to 90% of p atien t s an d p reven t s delayed emesis in m oreth an 70% of patients. Ben zodiazepines have no direct antiemetic e ect . They are sometimes added to the main regimen because the antianxiety e ect could reduce the ant icipatory component of nausea and vomiting. Ranitidine has no antiemetic e ect. Anticholinergic drugs such as scopolamine are not e ective in chemotherapy-induced nausea and vomiting.Loperamide is not an antiemetic drug. These drugs are used in chemotherapy-induced nausea and vomit ing only when other ant iemetic drugs are not e ective.

Que.74. Describe the use of dronabinol as an appetitestimulant in treating AIDS. Ans.- Appetite-enhancing (also called orexigenic) drugs are a vast array of medications used to prevent undesired weight loss in the elderly and in patients suering from such diseases as AIDS and cancer, which often result in wasting of the body's muscle tissue, as well as overall weight loss. Agents with orexigenic e ects include 5-HT2C serotonin receptor antagonists (cyproheptadine), adrenergic antagonists (carvediloland mirtazapine), anabolic steroids (oxandrolone and nandrolone), glucocorticoids (cortisol, prednisone, and dexamethasone), antidiabetic drugs (Insulin and glibenclamide),and cannabinoids. Dronabinol, the most active

cannabinoid of cannabis, has been shown to stimulate appetite in patients with AIDS and is often used for this purpose.These drugs are devoid of orexigenicproperties. **Que.75. Identify the prokinetic drug that acts by opening type 2 chloride channels in the small intestine.**

Ans.- Lubiprostone is a prokinetic drug that acts in the small intestine. Several agents, commonly called laxatives, can stimulate intestinal motility in nonspeci c or indirect ways, but the term *prokinetic*generally is reserved for agent s that enhance intestinal t ransitthrough interact ion with speci c receptors. Lubiprostone is a prostaglandin E1 derivative that appears to bind to prostaglandin E4 receptors linked to activation of adenylyl cyclase. This in turn can open specific type2 chloride channels in the luminal cells of the intestinal epithelium,

increasing chloride-rich fluid secretion into the intestine. Clinically, lubiprostone alters stool consistency and promotes regular bowel movements. Signs and symptoms related to constipat ion, including abdominal bloat ing, abdominal discomfort , stool consistency, and

st raining, are im proved, and long-term data suggest a sustained response over a 6- to 12-month treatment period. These drugs do not a ect intestinal t ype 2 chloride channels.

Que.76. Explain the mechanism of antimigraine action of ergot alkaloids. Ans.- The e ectiveness of ergot alkaloids in migraine seems to be primarily related to their cerebral vasoconstricting e ects, which are apparently due to activation of both α adrenoceptors and serotonin (5-HT) receptors. The pathophysiology of migraine seems to include a vasomotor component , because the onset of headache is sometimes associated with increased amplitude of temporal artery pulsations; ergotamine can diminish these pulsations. Other mechanisms are probably also operat ive. For example, ergotamine blocks in ammation of the t rigeminal neurovascular system. This act ion, possibly mediated by activation of 5 HT receptors, may be responsible for both the pain-relieving and the vasoconstricting e ects of ergot alkaloids. Ergotamine does not cause these e ects. Moreover, these e ects would increase, not decrease, the risk of a migraine attack.

Que.77. Explain the mechanism of action of histamine H1-receptor antagonists. Ans.- Diphenhydramine is a rst-generation histamine H1- receptor antagonist . Most drugs of this class can also block muscarinic receptors. The drug easily crosses the blood– brain barrier and can block H1 receptors and muscarinic receptors located in vestibular nuclei and in the nucleus of the t ractus solitarius, thus decreasing the ring from these nuclei to the vomiting center. All of these options have at least on e receptor that is not involved in the mechanism of nausea and vomiting.

Que.78. Identify the central site of action of sumatriptan.

Ans.- Sumatriptan and its congeners are currently rst-line agents for the abort ive therapy of acute, severe migraine attacks. The pathophysiology of migraine remains unknown, but the current view is that a complex series of neural and vascular events initiates migraine (the so called neurovascular theory). The theory states that activation of the nucleus caudalis of the trigeminal nerve leads to the release of several potent vasodilating neuropeptides, which in turn causes dilat ion of cerebral blood vessels. This vasodilation seems to be a major cause of the throbbing headache of the migraine at tack. By activating presynapt ic serotonin 5-HT1D receptors on trigeminal nerve endings, triptans can prevent the release of vasodilating neuropeptides.

Que.79. Describe the action that mediates the therapeutic use of misoprostol. Ans.- The patient's history and symptoms suggest that she was at risk of nonsteroidal antiin ammatory drug (NSAID)–induced ulcer. The prevalence of endoscopically con rmed peptic ulcer in

NSAID users is 15 to 30% in the United States. When pept ic ulcers develop in patients taking NSAIDs, the preferred approach is to stop the NSAID and to give an antiulcer drug, usually a proton pump inhibitor or a histamine H2 antagonist. Prophylactic therapy should be considered for patients who are unable to discont inue NSAID therapy, as in this case. Misoprostol, a synthetic analogue of prostaglandin-E1, is the drug most often prescribed, as it is able to prevent (but not to treat) NSAID-induced ulcers. This preventive effect is most likely due to the following mechanisms:

• At low doses, misoprostol activates prostaglandin receptors on supercial epithelial cells of the stomach, increasing bicarbonate and mucus secret ion (the so-called cytoprotective e ect). • At higher doses, it activates prostaglandin receptors on parietal cells of the stomach, decreasing gast ric acid secretion (most likely the main mechanism).

These are the mechanisms of action of sucralfate or of bismuth compounds. These drugs are much less e ect ive than misoprostol when the ulcer is secondary to chronic ingestion of NSAIDs. This is the mechanism of action of antimuscarinic drugs. These drugs are no longer used as antiulcer agents. Gastrin receptor blockers are not yet available. Antibiotic drugs are

not used in NSAID-induced peptic ulcer unless there is evidence of *Helicobacter pylori* infection.

Que.80. Explain the mechanism of antipyretic action of nonsteroidal antiin ammatory drugs (NSAIDs).

Ans.- Ibuprofen is an NSAID of the propionic acid derivat ive class that is approved for children younger than 2 years. All NSAIDs inhibit prostaglandin biosynthesis by blocking cyclooxygenase both in the peripheral tissues and in the central nervous system. The release

of prostaglandins (PGE1, PGE2) in the hypothalamus seems to be the ult imate factor that adjusts the hypothalamic thermoregulatory mechanism to maintain body temperature at a higher than normal level. By inhibiting prostaglandin synthesis, NSAIDs promote the return of the hypothalamic thermostat to the normal set point. Once the normal set point is restored, the temperature-regulating mechanisms operate (by dilation of superficial blood vessels, sweating, etc.) to reduce temperature. All of th ese act ion s can lead to an an t ipyret ic e ect ,

but NSAIDs do not have these actions. The in h ibit ion of cyclooxygen ase in periph eral t issues can lead to an antiin ammatory e ect that can reduce fever. However, the

main mechanism of the antipyretic e ect of NSAIDs is central rather than peripheral. Blockade of oxidat ive phosphorylat ion in skeletal muscle leads to hyperthermia, not to an antipyretic effect.

Que.81. Outline the therapeutic uses of celecoxib in a patient with a relevant past medical history.

Ans.- Celecoxib is a selective inhibitor of cyclooxygenase-2. Drugs of this class (sometimes called coxibs) have analgesic, antipyret ic, and antiin ammatory act ions. However, they lack action on platelet aggregat ion and have lower adverse e ects on the gastric mucosa than nonselective inhibitors of cyclooxygenases. These drugs are therefore preferred in patients at risk of peptic ulcer disease, as in this case.

Que.82. Identify the immunosuppressive mechanisms of prednisone. Ans.- An immunosuppressive drug therapy must be given to all patients undergoing organ transplant. No consensus exists on the best induction and maintenance immunosuppressive regimen, but most regimens rely on three or four agents, and one of these is almost always a glucocort icoid, such as prednisone. Glucocorticoids suppress primarily cellular immunity because of their ability to modify cellular funct ion. In addition, they can inhibit phospholipase A2, blocking both prostaglandin and leukotriene synthesis, and they increase the fractional catabolic rate of immunoglobulin G (IgG), the major class of antibody immunoglobulins, thus lowering the concent ration of specific antibodies. All of these immunosuppressive drugs can suppress cellular immunit y, but they do not a ect eicosanoid synthesis or the catabolism of IgG ant ibodies.

Que.83. Describe the mechanism of glucocorticoids in autoimmune diseases. Ans.- Myasthenia gravis is an acquired autoimmune disease characterized by exercise induced muscle fatigue that resolves after rest. The pathogenesis is due to antibody-mediated destruction of cholinergic Nm receptor sites. The initiating event leading to ant ibody product ion is unknown. This patient most likely developed a myasthenic crisis (edrophonium

improved muscle strength), which may be precipitated by infect ion but also can occur without apparent cause. Myasthenic crisis requires intensive management that includes selected anticholinesterase drugs such as neostigmine and immunosuppressive treatment with glucocort icoids and cyclosporine. The immunosuppressive e ect of glucocorticoids is likely due to multiple mechanisms of action. Especially important in this regard is the inhibition of T-cell activation (due to inhibition of synthesis of interleukin-1)

and T-cell proliferat ion (due to inhibition of synthesis of interleukin-2). Glucocorticoids have no e ect on plasma cholinesterase or nicotinic receptors. Glucocorticoids actually decrease the synthesis of these interleukins.

Que.84. Explain the mechanism of action of sirolimus.

Ans.- Sirolimus (formerly called rapamycin) resembles tacrolimus and binds to the same intracellular FK-binding proteins. However, whereas tacrolimus and cyclosporine block gene transcript ion, sirolimus acts later to block interleukin-2- dependent lymphocyte proliferation. This blockade is likely due to the inhibit ion of mammalian kinase (called mammalian target of rapamycin), an enzyme that is essential for cell-cycle progression. Therefore, the drug substant ially inhibits T- and B-cell proliferat ion.

Que.85. Explain the molecular mechanism of action of tacrolimus.

Ans.- Ant ibiotics endowed w ith immunosuppressant propert ies include cyclosporine, tacrolim us, and sirolim us. They interfere with T-cell function by binding to immunophilins, small in tracellular proteins that play a key role in T-cell response to cytokines. Cyclosporine binds to cyclophilin; tacrolimus and sirolimus bind to FK-binding proteins. The tacrolimus–

protein complex binds to calcineurin, a cytoplasmic phosphatase, thus inhibit ing calcineurin mediated expression for production of several cytokines. Azithromycin is a macrolide antibiotic with an tibacterial act ivit y. It is devoid of immunosuppressive properties. Azathioprine is a cytotoxic drug with immunosuppressive properties, but it does not bind to an FK-binding protein. Cyclosporine also inhibits calcineurin actions, but it binds to cyclophilin, not to an FK-binding protein. Tobramycin is an amin oglycoside an t ibiot ic devoid of immunosuppressive properties.

Que.86. Explain the molecular mechanism of action of muromonab-CD3. Ans.- Muromonab-CD3 is a monoclonal ant ibody against CD3 molecules present on the surface of human thymocytes and mature T cells. CD3 molecules are necessary for a signal to be transduced to the cytoplasm after the T-cell receptor binds to the antigen. The drug binds and neut ralizes the CD3 protein receptor complex, causing the death of T cells. Muromonab CD3 has negligible e ects on B cells. Stimulation of the synthesis of interleukin-1 would cause an immunostimulant, not an immunosuppressive, effect.

Que.87. Explain the molecular mechanism of action of aldesleukin.

Ans.- Aldesleukin is recombinant interleukin-2 (IL-2) with a mechanism of action essentially identical to that of IL-2. Aldesleukin activates IL-2 receptors expressed on T-helper cells and stimulates a cytokine cascade involving various interferons, interleukins, and tumor necrosis factors. In this way, it induces proliferation of B and T cells (including cytotoxic T cells) and activation of natural killer cells and lymphokine- activated killer cells. The drug is approved for the adjunctive t reatment of renal cell carcinoma and malignant melanoma. The mechanism of ant itumor act ivity is unknown but is probably related to the act ivation of cytotoxic T cells. Aldesleukin is associated with serious cardiovascular, renal, and central nervous system toxicit y, so extensive monitoring is required during therapy.

Que.88. Explain the mechanism of action of Rho(D) immune globulin. Ans.- Because the woman was Rho(D) negat ive, and her husband was Rho(D) posit ive, the baby had a 100% chance (if the father was homozygous) or a 50% chance (if the father was heterozygous) of being Rho(D) positive. When a Rho(D)- negative mother carries a Rho(D)- posit ive fetus, she will produce antibodies against Rho(D)-positive erythrocytes if these erythrocytes leak into the maternal circulat ion. This can occur during pregnancy, and the risk of this fetomaternal transfer increases as the pregnancy progresses. The risk is the highest during delivery. In subsequent pregnancies, these maternal ant ibodies are t ransferred to the fetus, leading to the development of hemolyt ic disease in the newborn (called erythroblastosis fetalis). If Rho(D) immune globulin is administered just after delivery, it destroys the Rho(D)-posit ive fetal cells in the maternal bloodstream before she has an opportunity to make her own antibodies, thus preventing erythroblastosis fetalisin subsequent pregnancies. This is an example of passive immunization.

Que.89. Explain the mechanism of action of colchicine.

Ans.- Colchicine can be used to stop an acute gout at tack or, most often, for the prevent ion of further at tacks, as in this case. The drug binds to the int racellular protein, tubulin, thereby preventing its polymerization into microtubules and thus blocking mitosis in metaphase. Cells with the highest rate of division are a ected early. Granulocyte migration into the inamed area and phagocytosis of urate crystals by macrophages are inhibited, thus relieving the pain and inammation of gouty arthritis. These actions are speci c, and the drug is devoid of general analgesic or antiin amatory e ects. These drugs are effective in gout y arthrit is but have

different mechanisms of actions. These drugs can decrease the risk of gout at tacks by decreasing the urate pool, not by inhibiting tubulin polymerization.

Que.90. Outline the use of methotrexate in rheumatoid arthritis.

Ans.- Methotrexate is currently a rst-line treatment for most patients with rheumatoid arthritis because of its high rate of response, relatively rapid onset of action (1 to 2 months), and long sustained e cacy. Moreover, it has been shown that the drug can enhance the action of some other disease-modifying antirheumatic drugs (DMARDs), including hydroxychloroquine, so it would be an appropriate drug to add to the ongoing therapy in this case. The patient was already receiving a nonsteroidal antiinammatory drug, so the addition of another drug of the

same class would be of little value. Fentanyl is a powerful opioid drug. Opioid analgesics are used in rheumatoid arthritis only exceptionally, on an as-needed basis, when the pain is excruciating. Some antidepressants, such as amitript yline, and some anticonvulsants, such as carbamazepine, are often effective in cases of neuropathic pain, but not for treatment of nociceptive pain such as occur in rheumatoid arthritis.

Que.91. Explain the mechanism of action of β-lactam and identify the drug contraindicated in a patient with previous allergic reaction to β-lactam drugs. antibiotics.

Ans. Cephalosporins are β-lactam antibiotics. The mechanism of action of all β-lactam antibiot ics involves the inhibition of transpeptidase, the enzyme that catalyzes the nal connection (cross-link) of two amino sugar chains by peptide bridges. In this way, the synthesis of peptidoglycans is inhibited.

The signs of the patient and the lab results strongly suggest the diagnosis of gonorrhea. Ceft riaxone would be the rstline agent for gonorrhea, but a previous anaphylactic reaction to penicillin contraindicates the use of most β-lactam drugs. All of th ese an t ibiotics are e ect ive again st *Neisseria gonorrhoeae*; they are not rst-line agents, but none of them are contraindicated in this case.

Que.92. Describe the renal elimination of cephalosporins.

Ans.- Most community-acquired urinary tract infect ions are due to *Escherichia coli.* First-, second-, and third-generation cephalosporin, fluoroquinolones, and trimethoprim sulfametoxazole are first-line agents for these infections. Most cephalosporins are eliminated by the kidney, mainly by active secretion in the proximal tubule (two notable except ions are ceftriaxone and cefoperazone, which are excreted mainly through the biliary tract). In most cases, concentrations in urine are higher than those in plasma. Macrolides are

mainly eliminated by biliary excret ion. Metronidazole is mainly eliminated by liver metabolism.

Aminoglycosides are excreted almost entirely by glomerular filtration only. Renal excretion of tetracyclines occurs by glomerular ltration and tubular reabsorption.

Que.93. Identify the drug used to treat chancroid.

Ans.- The history of the patient and the site of the ulcer suggest a sexually transmit ted disease. Among these diseases, those characterized by ulcer on the penis include chancroid (caused by *Haemophilus ducreyi*), lymphogranuloma venereum (caused by *Chlamydia trachomatis*), granuloma inguinale (caused by *Donovania granulomat is*), syphilis (caused by

Treponem a pallidum), and genital herpes (caused by herpes simplex virus). The presence of gram-negat ive bacilli excludes viral infections such as genital herpes, as well as chlamydia and donovania infections (chlamydia and donovania are intracellular bacteria). Syphilis is unlikely because of the negative dark eld microscopy and FTA-ABS (uorescent treponemal

ant ibody absorpt ion) test . Therefore, the patient 's disease is most likely caused by *H. ducreyi,* a gram-negat ive bacterium that is sensitive to second- and third-generation cephalosporins, trimethoprim-sulfametoxazole, quinolones, and tet racyclines. Ceftriaxone is most often used because it has a long half-life (about 7 hours) and therefore can provide a

long minimum bactericidal concent ration (most β-lactam antibiotics exhibit time-dependent killing). These an t ibiot ics are not e ect ive against gramnegative bacteria. Metronidazole is not e ective against *H. ducreyi.*

Que.94. Describe the mechanisms of bacterial resistance to β-lactam drugs. Ans.- Resistance to β-lactam antibiotics is due to four main mechanisms: • Product ion of β-lactamase enzymes (by far the most im por t an t m ech an ism). Beta lactamases hydrolyze the β-lactam ring, thus producing penicilloic acids that are devoid of antibacterial act ivit y.

• Development of penicillin-binding proteins that have decreased a nity for the antibiotic (the mechanism for penicillin resistance in pneumococci)

• Decreased permeability of the cell membrane to the drug (the mechanism for resistance in many gram-negat ive bacteria)

• Development of an active e ux pump (the mechanism for resistance in some gram-negative bacteria)

These mechanisms would increase, not decrease, the sensitivity of bacteria to β lactam antibiotics. This is a mechanism of resistance to antibiotics that inhibit protein synthesis.

Que.95. Explain the main reason for antibiotic-induced superinfections.

Ans.- Superinfections are new infections that occur during antibacterial therapy of a primary infection. Superinfection is due to removal of the inhibitory influence of the micro flora that normally inhabits certain parts of the body (oropharynx, in testine, vagina, etc.). In fact, many members of the normal micro ora appear to produce ant ibacterial substances, and they also presumably compete for essential nut rients. The broader the spectrum of an antibiotic, the greater the alteration of the normal micro flora. When the normal micro flora is altered, a single microorganism can become predominant, invade the host, and cause infection.

Que.96. Explain the mechanism of action of potassium clavulanate. Ans.- The patient's symptoms and physical examination suggest the diagnosis of acute otit is media, one of the most common infectious diseases a icting infants and children. The main bacteria causing otit is media in children are *Streptococcus pneumoniae*, *Haemophilus in uenzae,* and *Moraxella catarrhalis*. Most clinicians advocate a stepped approach to the antimicrobial therapy, which involves initial treatment with amoxicillin or t rimethoprim sulfamethoxazole. If this regimen does not reduce symptoms within 3 days, amoxicillin/ clavulanate or cefuroxime or ceftriaxone should be substituted for the initial therapy, as was done in this case. Potassium clavulanate is a β-lactamase inhibitor that blocks many, but not all, β-lactamase enzymes, protecting amoxicillin from inact ivation by β-lactamase-producing bacteria. Beta-lactamase inhibitors extend the antibacterial spectrum of amoxicillin, but *Pseudomonas aeruginosa* remains resistant. Beta-lactamase inhibitors do not signi cantly affect the kinet ics of penicillins. Beta-lactamase inhibitors do not a ect the allergenicit y of β lactam antibiotics.

Que.97. Explain the mechanism of action of β-lactam antibiotics.

Ans.- The m echanism of action of β-lactam antibiotics includes the following two actions: • They bind to speci c β-lactam receptors called penicillinbinding proteins located on the cytoplasmic membrane. These proteins are en zymes endowed with various catalytic functions that are inhibited by binding to the ant ibiotic. The most impor tant enzymes inhibited are t ranspeptidases, which catalyze the nal cross-link step in the synthesis of murein (also called peptidoglycan). Because peptidoglycan layers are constituents of bacterial cell walls, the synthesis of the cell wall is blocked.

• Autolytic enzymes (called autolysins or murein hydrolases) are present in the cell wall and degrade the peptidoglycan. Beta-lactam antibiot ics can act ivate these autolysins (apparently by blocking an autolysin inhibitor), thus promoting the lysis of bacteria. **Que.98. Explain the mechanism of the antimicrobial action of vancomycin.**

Ans.- The patient's signs, symptoms, and lab tests indicate that she was most likely suffering from pneumonia due to methicillin resistant (MR) *Staphylococcus aureus*. The patient infections. Vancomycin binds to the terminus of nascent peptidoglycan pentapeptides. The binding inhibits transglycosylase, the enzyme that catalyzes the elongation of pept idoglycan

chains, preventing formation of linear peptidoglycan chains. The binding also inhibits t ranspeptidase, but because t ransglycosylat ion precedes transpeptidation, inhibition of t ransglycosylase is the primary mechanism of action of the drug. These act ions are not inhibited by vancomycin.

Que.99. Explain the action of penicillin-binding proteins.

Ans.- Penicillin-binding proteins are speci c targets for β-lactam antibiotics. They are located in the bacterial cytoplasmic membrane, and some of them are transpept idases that catalyze the cross-linking of the peptidoglycan amino sugar chain by peptide bridges. This gives the cell wall its st ructural rigidity. By binding to these transpeptidase enzymes, β-lactam

antibiotics block the t ranspeptidat ion reaction and therefore the synthesis of peptidoglycan. A Porin ch an n els are aqueou s ch an n els presen t on th e outer membrane of gram-negat ive bacteria. Beta-lactam antibiotics enter the cell through these channels. Penicillinbinding proteins do not a ect this process. Th e breakdown of th e β-lact am ring is cat alyzed by β-lactamases, not by transpeptidases. Beta-lactam ant ibiotics can activate, not inhibit, murein hydrolases, which are enzymes able to destroy the cell wall. Beta-lactam ant ibiotics bind to penicillin-binding proteins. not to the peptidoglycan layer.

Que. 100. Explain the mechanism of action of gentamicin.

Ans.- Gentamicin is an aminoglycoside antibiotic. These drugs bind irreversibly to specific 30S ribosomal subunits and inhibit bacterial protein synthesis in at least three ways:
• Blockade of the "initiation complex," the complex formed for initiation of translation that consist s of the 30S microsomal subunit, messenger RNA (mRNA), transfer RNA (tRNA), and some initiation factors. This blockade leads to an mRNA chain with only a single ribosome on it, the so called monosome.

• Misreading of mRNA templates, which leads to the product ion of aberrant proteins. These proteins may be inserted in to cell membranes, altering permeability and further stimulating aminoglycoside transport (energy-dependent phase II transport).

• Blockade of translocation (i.e., the ribosome advancement of three nucleotides is blocked) For extern al ot it is, th e drug would be given topically as ear drops. Gentamicin can be ototoxic, especially if given systemically. All of these antibiotics are act ive against *Pseudomonas aeruginosa*, but they do not cause misreading of the bacterial mRNA template.

Que.101. Explain the mechanism of action of fluoroquinolones.

Ans.- Ciprooxacin is a fluoroquinolone antibiotic. Fluoroquinolones inhibit bacterial DNA synthesis by blocking the following enzymes:

• Topoisomerase II (also called DNA gyrase). The blockade prevents the relaxation of supercoiled DNA, which is required for normal transcription (prevalent mechanism in gram negative bacteria).

• Topoisomerase IV. The blockade interferes with separation of replicated chromosomal DNA during cell division (prevalent mechanism in gram-positive bacteria).