Dental Pharmacology 2005
EXAM 2
March 4, 2005
M.E. Maguire

INSTRUCTIONS:

1. There are 40 questions on this exam. Please use pencil on the answer sheet. Including the Bonus Questions, *there are 8 (eight) pages on this exam.* Turn in the answer sheet. KEEP the exam.
2. There are several **BONUS** questions at the end of the exam. You are NOT required to answer these. If you answer them, *nothing* will be deducted for a wrong answer. However, if you answer correctly, I will use that question to replace a question on the regular exam that you answered incorrectly. That is, if you get 30 of the 40 questions correct and answer 3 of the bonus questions correctly, then your score would be 33/40 or 82.5%.

1. The bacterial enzymes that inactivate penicillins and cephalosporins are
   - A. β-lactamases.
   - B. DNA gyrases.
   - C. *erm* methylases.
   - D. *mef* efflux proteins.

2. Among the enzymes responsible for synthesizing bacterial cell walls are
   - A. transpeptidases and carboxypeptidases.
   - B. ligases.
   - C. esterases.
   - D. methyl formylases.

3. Imipenem is a unique β-lactam because it
   - A. has a very short half life.
   - B. serves to inactivate penicillins binding proteins and β-lactamases.
   - C. acts on aminoglycoside transferases.
   - D. interferes with DNA segregation.

4. A known side effect of tetracyclines is that it
   - A. stains the enamel of teeth.
   - B. causes nail discoloration.
   - C. interferes with mental functions by inhibiting GABA transmission.
   - D. causes prolongation of the QT interval.

5. While in general quinolones are safe antibiotics, a recognized side effect is
   - A. prolongation of the QT interval.
   - B. tinnitus.
   - C. ataxia.
   - D. incontinence.

6. Pill dysphagia is seen with
   - A. tetracycline.
   - B. nitrofurantoin.
   - C. trimethoprim.
   - D. sulfamethoxazole.

7. Interference with folate synthesis is seen with
   - A. clindamycin.
   - B. tetracycline.
   - C. chloramphenicol.
   - D. sulfamethoxazole.

8. Which of the following antibiotics interfere with bacterial protein synthesis?
   - A. metronidazole.
   - B. quinolones.
   - C. penicillin.
   - D. macrolides.

9. The most likely antibiotic to cause prolongation of the prothrombin time when patients are taking coumadin are
   - A. tetracycline.
   - B. chloramphenicol.
   - C. trimethoprim.
   - D. rifampin.

10. Which of the following drugs is NOT used to treat *Mycobacterium tuberculosis*?
   - A. Isoniazid
   - B. Rifampin
   - C. Ethambutol
   - D. Streptomycin
   - E. Chloramphenicol

11. A known side effect of isoniazid is
   - A. tinnitus.
   - B. arthralgias.
   - C. hepatitis.
   - D. peripheral neuropathy.

12. Which of the following drugs should NOT be used to treat influenza in the first 36 hours?
   - A. Amantadine
   - B. Rimantadine
   - C. Erythromycin
   - D. Relenza

13. All of the following are drugs used to treat HIV infection EXCEPT
    A. AZT.
    B. DDI.
    C. 3TC.
    → D. amantadine.

14. The cell count (cells/ml) of which one of the following cell types is an important predictor of opportunistic infections in patients with HIV?
    A. Platelets
    B. CD8+ lymphocytes
    C. Neutrophils
    → D. CD4+ lymphocytes
    E. stem cells

15. Using trimethoprim-sulfamethoxazole as prophylaxis in HIV protects against
    → A. PCP.
    B. pneumococcal pneumonia.
    C. influenza.
    D. RSV pneumonia.

16. The mechanism of action of AZT is best described by which of the following?
    A. Molecular rearrangements
    B. DNA translocation
    C. DNA inversion
    → D. Chain termination

17. Which of the following is the drug of first choice in treating trigeminal neuralgia?
    A. Phenobarbital
    B. Buspirone
    C. Disulfiram
    → D. Carbamazepine
    E. Naltrexone

18. All of the following receptors are all ligand-gated ion channels EXCEPT
    A. $GABA_A$ receptor.
    → B. dopamine D2 receptor.
    C. nicotinic acetylcholine receptor.
    D. $5HT_3$ receptor.
    E. NMDA (Glutamate) receptor.

19. Benzodiazepines exert their anxiolytic effects by
    A. enhancing the actions of dopamine.
    B. inhibiting the actions of serotonin.
    C. inhibiting dopamine reuptake.
    → D. enhancing the actions of GABA.
    E. enhancing norepinephrine biosynthesis.

20. Disulfiram, a drug used in treating alcohol abuse, exerts its effects primarily by
A. blocking activation of the $GABA_A$ receptor.
B. inhibiting activation of the NMDA glutamate receptor.
C. blocking serotonin reuptake.
D. inhibiting dopamine reuptake.
→ E. blocking aldehyde dehydrogenase.

21. Anticonvulsants exert their effects by all of the following mechanisms EXCEPT
→ A. depressing the action of dopamine.
B. modifying the activity of voltage-gated Na^+ channels.
C. enhancing the action of γ-aminobutyric acid (GABA).
D. depressing the action of glutamate.
E. inhibiting both voltage-gated Na^+ channels and enhancing $GABA_A$ receptor activity.

22. Gingival hyperplasia is a common side effect of
→ A. phenytoin.
B. tiagabine.
C. morphine.
D. gabapentin.
E. carbamazepine.

23. All of the following statements concerning benzodiazepines are correct EXCEPT
A. The duration of action of a benzodiazepine can be dependent on the half-life of an active metabolite.
→ B. Benzodiazepines inhibit glutamate receptor activation.
C. Benzodiazepines can be sedating.
D. Benzodiazepines cause short-term memory impairment.

24. Which of the following statements about Carbidopa, a drug used to treat Parkinson's disease, is correct?
A. Carbidopa crosses the blood-brain barrier.
B. Carbidopa activates dopamine β-hydroxylase.
→ C. Carbidopa inhibits aromatic L-amino acid decarboxylase.
D. Carbidopa inhibits monoamine oxidase.
E. Carbidopa is converted to the false transmitter carbidopamine.

25. All of the following statements about antipsychotics are correct EXCEPT
A. Most classical antipsychotic drugs block dopamine receptors in the brain.
B. Some of atypical antipsychotics act at serotonin receptors.
→ C. The effects of antipsychotics are immediate.
D. Antipsychotics can cause Parkinsonism-like side effects.
E. Dopamine agonist drugs exacerbate schizophrenia.

26. Bacteria can rapidly evolve to develop resistance to antibiotics by all of the following mechanisms EXCEPT
→ A. Inactivation of enzymes that metabolize antibiotics.
B. Altering (mutating) the target of the antibiotic.
C. Expressing efflux pumps for the antibiotic.
D. Altering expression of porin channels.
E. Secretion of antitoxins.

27. Which of the following drugs is directed against a target in fungal cell walls?
A. Amphotericin A
B. Trimethoprim-sulfamethoxazole
C. Flucytosine
→ D. Caspofungin
E. Voriconazole

28. Which of the following drugs should always be administered with another antifungal agent?
A. Amphotericin A
B. Trimethoprim-sulfamethoxazole
C. Flucytosine
D. Caspofungin
E. Voriconazole

29. All of the following antifungal agents have some efficacy against *Aspergillus* spp. EXCEPT
A. Amphotericin A
→ B. Fluconazole
C. Voriconazole
D. Itraconazole
E. Caspofungin

30. Antacids should NOT be given to patients taking which of the following antifungal drugs?
A. Amphotericin A
B. Fluconazole
C. Voriconazole
→ D. Itraconazole
E. Caspofungin

31 Which of the following antifungal drugs at therapeutic doses is most likely to cause abnormal vision, skin rashes and intrahepatic cholestasis?
A. Amphotericin A
B. Fluconazole
→ C. Voriconazole
D. Itraconazole
E. Caspofungin

32. Benzodiazepines are used primarily to treat which of the following conditions?
   A. Psychosis
   B. Depression
   → C. Anxiety
   D. Parkinson's disease
   E. Trigeminal neuralgia

33. Which of the following drugs or classes of drugs does NOT bind to or interact with $GABA_A$ receptors?
   A. Barbiturates
   B. Benzodiazepines
   C. Ethanol
   → D. Catecholamines

34. Tetracycline antibiotics are considered "broad-spectrum" antibiotics because they are effective against all of the following EXCEPT
   A. most Gram-positive bacteria growing aerobically.
   B. most Gram-negative bacteria growing anaerobically.
   C. *Mycobacteria*.
   → D. fungal pathogens.

35. Cephalosporins exert their bacteriocidal effects at the
   A. ribosome.
   B. cell nucleus.
   C. cell membrane.
   → D. cell wall.

36. All of the following can be used to treat depression EXCEPT
   A. SSRI's.
   B. monoamine oxidase inhibitors.
   → C. gabapentin.
   D. tricyclic antidepressants.

37. Which of the following statements concerning cephalosporins is ~~correct~~ incorrect?
   → A. They are effective inhibitors of cell wall synthesis.
   B. Most oral anaerobic bacteria are insensitive to cephalosporins.
   C. They contain a modified β-lactam ring.
   D. They are related to penicillins.

38. Which of the following classes of antibiotics can cause ototoxicity at high doses?
   A. Tetracyclines
   B. Vancomycin
   → C. Aminoglycosides streptomycin
   D. Penicillins
   E. Erythromycin

39. Fungi come in a variety of flavors. All of the following statements about fungi are correct EXCEPT
   A. Yeasts are fungi that are usually round and smooth.
   B. Molds are fungi that form hyphae as part of their life cycle.
   C. Among the groups of fungi, dermatophytes belong the molds.
   D. Dimorphic fungi are rounded when infecting tissues but form hyphae when in culture.
   → E. *Candida* spp. are examples of molds.

40. Among the following receptor types, antipsychotic drugs primarily antagonize
   A. $GABA_A$ receptors.
   B. catecholamine receptors.
   C. glutamate receptors.
   D. acetylcholine receptors.
   → E. dopamine receptors.

IT'S THE BONUS ROUND!!!!!!

41. Hepatic blood flow and intrinsic hepatic clearance are important factors in the clearance of drugs with which of the following characteristics?
    - A. Very water soluble
    - B. Polypeptide structure
    - C. Multiple charges
    - D. Volatile gas
    - → E. Minimal renal excretion

42. Two drugs, A and B, have the same mechanism of action. Drug A in a dose of 5 mg produces the same magnitude of response as Drug B in a dose of 500 mg. Which of the following statements is CORRECT?
    - A. Drug A is less toxic.
    - B. Drug A is more efficacious (greater maximal effect).
    - → C. Drug A is more potent.
    - D. Drug A has a shorter duration of action.
    - E. Drug A is a better drug to use when a maximal response is desired.

43. The rate of absorption of a drug will determine
    - A. steady-state plasma concentration.
    - B. systemic clearance.
    - C. bioavailability.
    - → D. peak plasma concentration.
    - E. intrinsic clearance.

44. Which of the following drugs has NO antiinflammatory properties?
    - A. Aspirin
    - B. Vioxx
    - C. Ibuprofen
    - → D. Acetaminophen
    - E. Prednisone

45. All of the following are correct statements about cells EXCEPT
    - A. bacteria have no nucleus.
    - B. you and I have 46 chromosomes (we hope).
    - → C. bacteria cannot grow in the absence of oxygen.
    - D. most but not all bacteria have a single chromosome.
    - E. bacteria can grow in deep sea vents at temperatures of 90 °C under >200 atmospheres of pressure.

46. The Indians will win the World Series this year because
    - A. the Red Sox finally won, so miracle's really happen.
    - B. George Steinbrenner will sell the Yankees and buy the Indians.
    - C. Which World Series, Little League or Professional Baseball?
    - D. palm trees will suddenly sprout up on our country's "North Shore".
    - E. George Bush drafts all the players on the other teams.

Exam 3 Pharmacology

6. Which of the following statements regarding class III anti-arrhythmia drugs such as Amiodarone is **CORRECT**?

A. May display toxicity to thyroid and lungs
B. Can behave as a partial β-adrenergic antagonist (β-blocker)
C. Attenuate the action potential (phase 0 depolarization)
→ D. Block Na^+ channels to increase repolarization currents

7. Which of the following drugs is a Ca^{2+}-channel blocker used to treat arrhythmias?

A. Lidocaine
B. Flecainide
C. Pindolol
→ D. Diltiazem
E. Midazolam

8. Which effect would be observed if binding of Angiotensin II to the AT_1 receptor were inhibited?

→ A. Decreased vasoconstriction
B. Increased blood pressure
C. Increased Na^+/H_2O retention
D. Increased afterload

9. All of the following statements regarding isoproterenol are correct **EXCEPT** that it

→ A. binds with poor affinity to β-adrenergic receptors.
B. produces peripheral vasodilation.
C. is a good bronchodilator.
D. increases cardiac output.

↓ stroke AP

10. The Ca^{2+}-blocker nifedipine reduces myocardial ischemia/angina by which of the following mechanisms?

A. Reducing activation of α_1-adrenergic receptors
→ B. Decreasing blood pressure and dilating coronary arteries
C. Dilating coronary arteries and increasing myocardial wall tension
D. Enhancing growth of collateral vessels

11. Spironolactone is effective in the treatment of hypertension because it

A. behaves as a β-adrenergic antagonist (β-blocker).
B. blocks Ca^{2+} channels.
→ C. blocks aldosterone effects on the kidney.
D. blocks acetylcholine binding.

12. Losartan™ or Irbesartan™ administration reduces blood pressure by which of the following reasons or mechanisms?

A) They are highly selective angiotensin II receptor antagonists.
B. They are both potent angiotensin-converting enzyme (ACE) inhibitors.
C. They are both Ca^{2+}-channel blockers.
D. They both increase the production of aldosterone.

13 Niacin at high doses can be used as an antihyperlipidemic agent because it

A. inhibits HMG-CoA reductase.
B. acts to inhibit transcription of proteins involved in fatty acid metabolism.
C) inhibits lipolysis in adipose tissue.
D. removes bile acids from the gastrointestinal tract.
E. directly inhibits cholesterol uptake by the liver.

14. Statins like Mevacor™ and Lipitor™ are antihyperlipidemic agents because they

A) inhibit HMG-CoA reductase.
B. act to inhibit transcription of proteins involved in fatty acid metabolism.
C. inhibit lipolysis in adipose tissue.
D. remove bile acids from the gastrointestinal tract.
E. directly inhibit cholesterol uptake by the liver.

15. Which of the following drugs, used as an anti-anginal agent, must be administered sublingually?

A. Captopril
B. Furosemide
C. Isosorbide dinitrate
D) Nitroglycerin
E. Atropine

16. Which of the following drugs used in the treatment of cardiovascular disease would be contraindicated for someone undergoing major oral surgery?

A. Nitroglycerin
B. Captopril
C) Aspirin
D. Furosemide
E. Propranolol

17. Which of the following drugs is used to prevent deep vein thrombosis?

A. Atropine
B. Aspirin
C) Heparin
D. Vitamin K
E. Streptokinase

18. Angiotensin converting enzyme inhibitors are used clinically for all of the following indications **EXCEPT**

A. treatment of cardiac systolic dysfunction.
B. therapy of normal-renin associated hypertension.
C. management of hypokalemia.
D. treatment of acute coronary thrombosis and pulmonary edema.
E. prevention of cardiac remodeling in hypertensive states.

19. Nearly two-thirds of filtered sodium is reabsorbed in which segment of the nephron?

A. The proximal renal tubules
B. The thin descending limb of the loop of Henle
C. The thick ascending limb of the loop of Henle
D. The distal convoluted tubules
E. The collecting ducts

20. Which portion of the nephron utilizes the greatest amounts of ATP?

A. The proximal renal tubules
B. The thin descending limb of the loop of Henle
C. The thick ascending limb of the loop of Henle
D. The distal convoluted tubules
E. The collecting ducts

21. Which of the following combinations of diuretic drugs is **LEAST** effective?

A. Bumetanide and hydrochlorothiazide
B. Furosemide and triamterene
C. Hydrochlorothiazide and amiloride
D. Spironolactone and triamterene
E. Spironolactone and furosemide

22. Furosemide can produce all of the following effects **EXCEPT**

A. hypokalemia.
B. acute renal failure.
C. toxicity similar to that of sulfonamides.
D. enhanced renin secretion.
E. metabolic alkalosis.

23. All of the following diuretics act at the lumenal side of renal tubules **EXCEPT**

A. hydrochlorothiazide.
B. triamterene.
C. ethacrynic acid.
D. bumetanide.
E. spironolactone.

24. All of the following ions are important in generating currents during each cardiac cycle **EXCEPT**

A. Ca^{2+}.
B. K^{+}.
C. Mg^{2+}.
D. Na^{+}.

25. Which of the following receptors is important for sensing short term changes in blood pressure?

A. β_1-Adrenergic receptors
B. Baroreceptors
C. Chemoreceptors
D. Dopamine receptors
E. Nicotinic cholinergic receptors

26. Which tissue is responsible for the pacemaker potentials that control contraction of the heart?

A. Atrioventricular node
B. Bundle of His
C. Purkinje fibers
D. Sinoatrial node
E. Ventricular myocardium

27. All of the following pairs of agents and actions or agents and receptors occur physiologically in normal individuals **EXCEPT**

A. acetylcholine – muscarinic receptors
B. angiotensin II – vasoconstriction
C. epinephrine – dopamine receptors
D. epinephrine – vasodilation
E. norepinephrine - α-adrenergic receptors

28. All of the following drugs are antiinflammatory **EXCEPT**

A. ibuprofen.
B. naproxen.
C. acetaminophen.
D. aspirin.
E. prednisone.

29. A patient who has been taking large quantities of aspirin might show increased postoperative bleeding because aspirin inhibits

A. synthesis of thromboxane and prevents platelet aggregation.
B. synthesis of prostacyclin and prevents platelet disaggregation.
C. synthesis of prostaglandins and prevents production of blood platelets.
D. thrombin and prevents formation of the fibrin network.
E. intestinal absorption of vitamin K and prevents synthesis of blood clotting factors.

30. Which of the following pharmacologic actions is **NOT** produced by prostaglandins?

A. Pyrexia
B. Uterine contraction
C. Increased gastric acid secretion
D. Increased capillary permeability
E. Increased sensitivity to pain upon intradermal injection

31. Which of the following conditions or effects does **NOT** result from prolonged treatment with corticosteroids?

A. Gastric ulcer
B. Osteoporosis
C. Hyperglycemia
D. Skeletal muscle atrophy
E. Redistribution of body fat

32. All of the following agents useful for treatment of rheumatoid arthritis can be used simultaneously with anakinra **EXCEPT**

A. aspirin.
B. celecoxib. celebrex
C. infliximab.
D. methotrexate.
E. prednisone.

33. The most prominent acute toxic effect associated with acetaminophen use is

A. hemorrhage.
B. renal necrosis.
C. hepatic necrosis.
D. gastric ulceration.
E. respiratory alkalosis.

34. Which of the following drugs is an effective antitussive?

A. Ibuprofen
B. Dextromethorphan
C. Guaifenesin
D. Aspirin
E. Acetaminophen

35. Receptors which mediate the primary effects of opioids are

A. presynaptic transporters of amines.
B. membrane proteins activated by endogenous peptides.
C. enzymes which convert arachidonic acid to prostaglandins.
D. NMDA and glutamate receptors.
E. present in the brain but not the spinal cord.

36. All of the following bind to opioid receptors **EXCEPT**

A. endorphins.
B. enkephalins.
C. naloxone.
D. substance P.
E. dynorphins.

37. All of the following terms have a distinct medical meaning or definition **EXCEPT**

A. opioid.
B. opiate.
C. dependence.
D. addiction.
E. narcotic.

38. All of the following effects are commonly produced by administration of an opioid **EXCEPT**

A. respiratory depression
B. nausea
C. constipation
D. tolerance
E. smooth muscle relaxation

39. Which of the following agents sensitizes peripheral nerve endings to noxious and/or painful stimuli?

A. Bradykinin
B. Serotonin
C. Histamine (itching).
D. H^+ (acid)
E. Prostaglandins

40. All of the following effects can be produced by administration of an opioid **EXCEPT**

A. suppression of the cough reflex (antitussive).
B. elevation of mood.
C. constriction of pupils.
D. inhibition of vomiting (antiemetic).
E. stimulation of release of histamine from mast cells.

41. Which of the following agents is **LEAST** likely to produce either physical dependence or addiction?

A. Codeine
B. Morphine
C. Oxycodone
D. Hydrocodone
E. Tramadol

42. A 57 year old person receiving propranolol (β-blocker) for hypertension presents with an acute allergic asthma attack. Which of the following treatments is specifically *contraindicated*?

A. Ipratropium bromide (anti-cholinergic)
B. Loratadine (anti-histamine)
C. Budenoside (Pulmicort or Rhinocort)
D. Albuterol
E. None of the above

43. Which of the following classes of bronchodilators is **MOST** effective in chronic obstructive pulmonary disease (COPD)?

A. Anticholinergics
B. β-Adrenergic agonists
C. β-Adrenergic receptor antagonists
D. Corticosteroids
E. Methylxanthines

44. Bronchoconstriction in chronic obstructive pulmonary disease (COPD) due to epithelial damage occurs by what mechanism?

A. Loss of endogenous β-agonist release leading to increased smooth muscle contraction
B. Activation of exposed sensory nerve fibers leading to acetylcholine release and cholinergic bronchoconstriction
C. Increased inflammatory mediator release leading to smooth muscle oxidative damage
D. Loss of epithelial derived acetylcholine release leading to increased bronchoconstriction
E. None of the above

45. Anti-leukotrienes and antihistamines are both used as treatments for allergen-induced asthma. These compounds are best used

A. prophylactically to prevent allergen-mediated responses.
B. in response to an acute asthmatic attack due to their fast action.
C. in combination with anti-cholinergic agents.
D. in combination with β-adrenergic antagonists (β-blockers).

46. Which statement accurately describes the mechanisms of action of corticosteroids?

A. Fast-acting anti-inflammatory due to increased calcium release stimulated in inflammatory cells, especially Mast cells
B. Bind selectively to epithelial cells leading to endogenous β-agonist release
C. Slow-acting agents that influence protein expression by binding to nuclear receptors which then bind directly to specific DNA sequences
D. Fast-acting agents that increase chloride secretion across epithelial cells leading to improved airway clearance
E. Fast-acting agents that bind to membrane receptors and elevate Ca^{2+}

47. Which of the following drugs has an antihypertensive effect at low doses and an antidiuretic effect at high doses?

A. Bumetanide
B. Lisinopril
C. Spironolactone
D. Hydrochlorothiazide
E. Losartan

48. Leukotrienes are derived from arachidonic acid and are potent mediators of allergic asthmatic responses. Which of the following therapies would **NOT** ameliorate leukotriene effects?

A. Increased expression lipocortin-1 after corticosteroid treatment
B. Inhibition of cyclooxygenase activity by aspirin or ibuprofen leading to reduced prostaglandin synthesis
C. Inhibition of 5-lipoxygenase activity leading to reduced 5-HPETE formation
D. Receptor blockade using "lukast" drugs

49. Which of the following is a concern with prolonged, repeated use of β-receptor agonists for the treatment of acute asthmatic exacerbations?

A. negative regulation of corticosteroid receptor function resulting in reduced steroid effectiveness
B. Secondary release of acetylcholine leading to cholinergic airway contraction
C. Increased mast cell recruitment leading to more severe allergic responses
D. β-Receptor desensitization *via* β-receptor kinase (βARK) activation
E. None of the above

50. In the electrocardiogram, the QRS complex corresponds to approximately what part of the action potential?

A. Phase 0 to 1
B. Phase 1 to 2
C. Phase 2 to 3
D. Phase 3 to 4
E. Phase 4 to 0

BONUS QUESTIONS

51. While effective in the treatment of congestive heart failure, β-adrenergic antagonists (β-blockers) can also used to treat arrhythmias because they

A. are excreted solely through the kidneys.
B. have no effect on the A-V node.
C. reduce ventricular response to atrial fibrillations.
D. have no effect on mortality.

52. Cholestipol™ is used as an antihyperlipidemic agent because it

A. inhibits HMG-CoA reductase.
B. acts to inhibit transcription of proteins involved in fatty acid metabolism.
C. inhibits lipolysis in adipose tissue.
D. removes bile acids from the gastrointestinal tract.
E. directly inhibits cholesterol uptake by the liver.

53. Which of the following drugs would likely be used to treat sinus tachycardia?

A. Atropine
B. Isoproterenol
C. Propranolol
D. Lidocaine
E. Verapamil

54. All of the following statements describe a known effect of corticosteroid treatment **EXCEPT**

A. decreased recruitment of eosinophils.
B. increased expression of β-receptors on smooth muscle cells.
C. decreased cytokine expression from T-lymphocytes and macrophages.
D. reduced mucous secretion from glands.
E. increased Mast cell recruitment and histamine release.

55. Which of the following sequences correctly describes the order of the conduction pathway for the cardiac action potential?

A. AV node – SA node – internodal pathways – Purkinje fibers – ventricular myocardium
B. AV node – SA node – Purkinje fibers – internodal pathways – ventricular myocardium
C. Internodal pathways – SA node – Purkinje fibers – AV node – ventricular myocardium
D. Purkinje fibers – SA node – internodal pathways – AV node – ventricular myocardium
E. SA node – AV node – Internodal pathways – Purkinje fibers – ventricular myocardium

DENTAL PHARMACOLOGY 2005
EXAM III
April 7, 2005

1. Diuretics such as furosemide are used to treat congestive heart failure because they

   A. increase pulmonary congestion.
   B. decrease plasma volume.
   C. display an "afterload" effect.
   D. increase oxygen demand.

2. Which effect **BEST** describes the mechanism of action of digoxin, a digitalis glycoside used in treatment of congestive heart failure?

   A. Decrease systolic force of contraction
   B. Activates Na^+-K^+ exchange in cardiac muscle
   C. Decreases the influx of Ca^{2+}
   D. Increases cardiac output

3. Angiotensin converting enzyme (ACE) inhibitors such as Captopril are effective in the treatment of congestive heart failure because they are

   A. afterload reducing agents.
   B. preload reducing agents.
   C. direct vasoconstrictors.
   D. direct vasodilators.
   E. effective in increasing sodium and water retention.

4. Which of the following is a β-adrenergic antagonist (β-blocker) used in the treatment of congestive heart failure?

   A. Lidocaine
   B. Propranolol
   C. Verapamil
   D. Enalapril
   E. Digoxin

5. Which of the following reasons **BEST** explains why lidocaine can be used to treat arrhythmias?

   A. Ineffective against atrial flutters and atrial fibrillations
   B. Blocks activated Na^+ channels
   C. Increases conduction velocity
   D. Increases phase 4 depolarization
   E. Blocks closed K^+ channels

[redacted]

Dental Pharmacology 2005
EXAM IV
April 29, 2005

1. Which of the following agents can be administered to *prevent* the adverse effects of high-dose methotrexate?

   A. Methoprim
   B. Leucovorin
   C. EDTA
   D. Cyclophosphamide
   E. 5-Fluorouracil

2. Which of the following is a typical side-effect associated with the administration of Doxorubicin?

   A. Feminization
   B. Hypoglycemia
   C. Myelostimulation
   D. Chronic halitosis
   E. Cardiomyopathies

3. Which of the following agents inhibits dihydrofolate reductase to limit purine biosynthesis?

   A. Doxorubicin
   B. Methotrexate
   C. Bleomycin
   D. 5-Fluorouracil
   E. Cisplatin

4. Which of the following agents directly inhibits dTMP synthesis?

   A. Doxorubicin
   B. Methotrexate
   C. Bleomycin
   D. 5-Fluorouracil
   E. Cisplatin

5. Which of the following agents crosslinks DNA specifically at guanine residues?

   A. Doxorubicin
   B. Methotrexate
   C. Bleomycin
   D. Cyclosporine
   E. Cisplatin

6. Which of the following agents induces DNA damage in a process requiring Fe^{2+} or Cu^{2+}?

A. Mitoxantone
B. Methotrexate
C. Bleomycin
D. Taxol
E. Cyclophosphamide

7. All of the following are major types of anticancer agents **EXCEPT**

A. dealkylating agents.
B. antibiotics.
C. anti-metabolites.
D. microtubule inhibitors.
E. anti-hormones.

8. Tamoxifen is an effective chemotherapeutic agent because it

A. selectively enters cancer cells.
B. crosslinks DNA to inhibit DNA replication.
C. inhibits dihydrofolate reductase.
D. enhances the rate of seminiferous tubule formation.
E. is an antagonist of estrogen.

9. Which of the following agents is a phase *non-specific* drug that covalently modifies DNA?

A. Cyclophosphamide
B. Cyclosporine
C. Hydroxyurea
D. Vincristine
E. 6-mercaptopurine

10. Which of the following is ***not*** a major problem/complication of chemotherapy?

A. Alopecia
B. Acute myelosuppression
C. Weight gain
D. Vomiting
E. Depression

11. Which drug is used to inhibit topoisomerase activity to induce DNA strand breaks?

A. Etoposide
B. Vincristine
C. Taxol
D. Cyclosporine
E. Bleomycin

12. Hydroxyurea is a chemotherapeutic agent that inhibits which of the following metabolic enzymes?

A. Aromatase
B. Cytochrome P450
C. Luteinizing hormone
D. DNA polymerase
E. Ribonucleotide reductase

13. Which of the following statements regarding Rituximab, a monoclonal antibody, i **CORRECT**?

A. Used extensively in the treatment of non-Hodgkin's lymphoma
B. Has no side effects
C. Can be administered orally
D. Penetrates cell to induce cell death
E. Works great with Tums and Rolaids

14. AraC (Cytarabine) is an

A. antagonist of the estrogen receptor.
B. antagonist of the androgen receptor.
C. inhibitor of DNA polymerase.
D. inhibitor of L-asparaginase.
E. inhibitor of thymidylate synthase.

15. Thioguanine acts as a chemotherapeutic agent by inhibiting

A. DNA mutagenesis.
B. the purine salvage pathway.
C. DNA repair.
D. transcription.
E. DNA methylation patterns specifically at GC sites.

16. Which of the following agents inhibits mitosis by promoting tubulin polymerization?

A. Cyclophosphamide
B. Taxol
C. 6-Mercaptopurine
D. Doxorubicin
E. Bleomycin

17. All of the following statements regarding local anesthetics are correct **EXCEPT**

A. amide class local anesthetics are more stable in solution than those of the ester class.
B. ester class local anesthetics have a high risk of allergic reactions, especially when applied topically.
C. both classes act by blocking Ca^{2+} channels.
D. ester class local anesthetics are metabolized predominately by pseudocholinesterases.
E. amide class local anesthetics are metabolized by liver cytochrome P450 enzymes.

18. Local anesthetics produce anesthesia primarily through phasic (or frequency-dependent) blockade of

A. Mg^{2+} channels
B. Na^{+} channels
C. K^{+} channels
D. Ca^{2+} channels
E. Chloride channels

19. All of the following agents can bind to and inactivate Na^{+} channels **EXCEPT**

A. local anesthetics.
B. general anesthetics.
C. dihydropyridine class Ca^{2+} channel antagonists.
D. frog toxins.
E. β-adrenergic antagonists.

20. All of the following agents or conditions can affect local anesthetic potency and/or efficacy **EXCEPT**

A. vasoconstrictors.
B. alkalinization of blood or tissue.
C. pregnancy.
D. site of injection.
E. protein binding.

21. All of the following are signs of *CNS toxicity* from local anesthetics **EXCEPT**

A. vertigo.
B. flushing (of the skin).
C. tinnitus.
D. circum-oral numbness.
E. garrulousness.

22. *Compared to local anesthesia*, general anesthesia has all of the following advantages **EXCEPT**

A. patient cooperation is not completely essential.
B. the patient is unconscious.
C. the patient has amnesia regarding the surgery/trauma.
D. titration of the level of anesthesia is easier.
E. cardiovascular toxicity is more easily avoided.

23. For volatile anesthetics, the rapidity of onset of anesthesia is determined primarily by

A. lipid solubility.
B. the rate of liver metabolism.
C. the blood:gas partition coefficient.
D. solubility in muscle.
E. metabolism by blood pseudocholinesterases.

24. All of the following are potential adverse effects of general anesthetics **EXCEPT**

A. pneumothorax with nitrous oxide.
B. malignant hyperthermia.
C. fulminant hepatic necrosis with halothane.
D. coma.
E. peripheral pain sensitization with volatile anesthetics.

25. Compared to most other agents used parenterally, midazolam has the desirable property of producing

A. loss of consciousness.
B. analgesia.
C. decreased salivation.
D. amnesia.
E. lack of hallucination upon recovery.

26. Which of the following agents must be taken immediately *before* meals to be most effective?

A. Misoprostol
B. Cimetidine
C. Sucralfate
D. Omeprazole prilosec
E. Aspirin

27. Which of the following ions secondarily stimulates acid secretion in the stomach and thus is not a preferred component of antacids?

A. Magnesium
B. Calcium
C. Aluminum
D. Sodium
E. Potassium

28. Of the following classes of agents, which is most effective at blocking all routes of *hormonal* stimulation of acid secretion in the stomach?

A. H_1-receptor agonists
B. H_1-Receptor antagonists
C. H_2-receptor antagonists
D. Prostaglandin E receptor agonists
E. Prostaglandin E receptor antagonists

29. Pseudoephedrine and oxymetazoline are marketed as nasal decongestants. They are α-adrenergic agonists. Which of the following effects is likely from oral administration of pseudoephedrine but not after intranasal administration of oxymetazoline?

A. bradycardia
B. increased blood pressure
C. decreased blood pressure
D. tachycardia
E. bronchoconstriction

30. Which of the following drugs is highly likely to cause skin rash and allergic reactions when applied topically?

A. antibiotic ointments
B. benzocaine
C. Lubriderm
D. selenium sulfide
E. hydrocortisone

31. All of the following statements about drugs sold over-the-counter (OTC) are correct **EXCEPT**

A. previously prescription-only drugs now available OTC are often sold in sub-optimal dosing forms.
B. OTC drug formulations often contain agents that have no therapeutic effect.
C. OTC drugs must meet the same safety and effectiveness standards as prescription drugs.
D. generic forms of OTC drugs are generally as effective as the original name-branded drugs.
E. drug formulations often contain one or more agents is sub-optimal doses compared to other drugs in the formulation.

32. The mechanism of action of omeprazole and other drugs of this class is to

A. block muscarinic cholinergic receptors.
B. stimulate prostaglandin E receptors.
C. inhibit Na^+,K^+-ATPase in the stomach.
D. inhibit H^+,K^+-ATPase in the stomach.
E. block histamine H_2 receptors.

33. Which of the following agents should not be prescribed for women of child-bearing age?

A. Misoprostol
B. Cimetidine
C. Vioxx
D. Omeprazole
E. Aspirin

34. All of the following are classes of endocrine hormones **EXCEPT**

A. polypeptides.
B. proteins.
C. amino acid derivatives.
D. complex carbohydrates.
E. steroids derived from cholesterol.

35. Symptoms of hyperthyroidism include all of the following **EXCEPT**

A. poor cold resistance.
B. nervousness.
C. tremor.
D. tachycardia.
E. muscle wasting.

36. All of the following statements concerning glucocorticoids are correct **EXCEPT**

A. suppresses immune response.
B. decreases blood pressure.
C. causes body fat redistribution.
D. enhances cataract formation.
E. blocks arachidonic acid release from membranes.

37. Addison's disease is due to primary adrenocortical insufficiency and is diagnosed by lack of patient response to ACTH. Which of the following drugs can be used to treat this disease?

A. Tamoxifen
B. Estrogen
C. Testosterone
D. Hydrocortisone
E. Gonadotropin releasing hormone (GnRH)

38. Although androgens have therapeutic utility in the treatment of hypogonadism, they may have all of the following adverse effects **EXCEPT**

A. increased fertility.
B. liver damage.
C. prostate enlargement.
D. priapism.
E. impotence.

39. The major clinical use of progestins (progesterone derivatives) is

A. stimulation of ovulation.
B. treatment of polycystic ovarian disease.
C. contraception.
D. pattern baldness.
E. halitosis.

40. Which of the following is NOT a typical characteristic of cancer cells?

A. Limitless replicative potential
B. Sustained angiogenesis
C. Metastasis
D. Sensitivity to growth/cell cycle checkpoints

41. Tamoxifen

A. blocks androgen receptors.
B. stimulates prolactin receptors.
C. antagonizes estrogen receptors.
D. inhibits dihydrofolate reductase.
E. stimulates thromboxane receptors.

42. Prednisone is an effective chemotherapeutic agent for which of the following conditions?

A. Bone resorption
B. Diabetes mellitus
C. Leukemias
D. Androgen insufficiency
E. Infertility

43. All of the following are correct statements **EXCEPT**

A. unmanaged hypothyroid patients generally have low blood pressure.
B. patients being treated with iodide may have gum soreness and increased salivation.
C. prophylaxis with antibiotics is contraindicated in patients on glucocorticoids.
D. diabetic patients may exhibit increased incidence of oral infections.
E. poor control of blood sugar is associated with increased caries.

44. Over-the-Counter (OTC) drugs are significantly different than prescription drugs?

A. True
B. False

45. While he was enjoying a siesta in his back yard, the wife of a 60 year-old pharmacology professor "accidentally" sprayed him in the face with a pesticide. In the emergency room, he exhibited tachycardia, lachrymation, increased salivation, and increased anxiety. Which of the following agents is most likely to be an effective antidote?

A. N-acetycysteine
B. Naloxone
C. Morphine
D. Ethanol
E. Pralidoxime

46. The following week, the same pharmacology professor had a root canal performed by student dentists. To alleviate the extreme pain caused by the several hour procedure, he washed down 25 tablets of Tylenol™ with half a bottle of Johnny Walker Black Label. Which of the following agents should be administered as a (hopefully effective) antidote?

A. N-acetycysteine
B. Naloxone
C. Morphine
D. Ethanol
E. Pralidoxime

47. 50. A deficiency of which of the following vitamins can cause gingivitis?

A. Vitamin A
B. Vitamin C
C. Vitamin D
D. Vitamin E
E. Vitamin K

48. Administration of syrup of ipecac would produce all of the following effects **EXCEPT**

A. removal of all toxins from GI tract.
B. stimulation of chemoreceptor trigger zone.
C. vomiting within 20 minutes.
D. potential induction of asphyxiation.

49. Which of the following drugs or groups of drugs are responsible for the most accidental overdoses?

A. Heroin and similar "narcotics"
B. Prescription drugs
C. OTC drugs such as analgesics and antihistamines

50. Which of the following age groups exhibits the highest frequency of accidental overdose with OTC drugs?

A. Young children (5-9 years old)
B. Adolescents (10-19 yo)
C. Young adults (20-50 yo)
D. Older adults (50-70 yo)
E. Geriatric patients (>70 yo)

BONUS QUESTIONS

51. Phase I drug metabolic reactions include all of the following **EXCEPT**

A. drug reduction reactions.
B. drug hydrolysis reactions.
C. cytochrome P450-catalyzed oxidations.
D. acetylation reactions.
E. non cytochrome P450-catalyzed oxidations.

52. Which of the following statements concerning a drug's properties is **CORRECT**?

A. An antagonist can block the action of a partial agonist but not the action of a full agonist.
B. A partial agonist has greater potency than an antagonist.
C. An antagonist has less potency than an agonist.
D. The effects of a competitive antagonist are reversible.
E. The effects of a non-competitive antagonist are reversible.

53. Which of the following statements concerning pharmacokinetics is **CORRECT**?

A. Elimination of most drugs follows first order kinetics.
B. Steady state drug concentration is dependent on V_D.
C. Loading dose is dependent primarily on Cl.
D. The rate of absorption of a drug is dependent on its Cl.
E. The $T_{1/2}$ for elimination of a drug is directly dependent on Cl.

54. The rate of gastrointestinal absorption of a drug is generally dependent on all of the following factors **EXCEPT**

A. Intestinal surface area.
B. the oil:water partition coefficient of the drug.
C. the pK_a of the drug.
D. the rate of stomach emptying.
E. stomach surface area.

55. Which statement accurately describes the mechanisms of action of corticosteroids?

A. Fast-acting anti-inflammatory due to increased calcium release stimulated in inflammatory cells, especially Mast cells
B. Bind selectively to epithelial cells leading to endogenous β-agonist release
C. Slow-acting agents that influence protein expression by binding to nuclear receptors which then bind directly to specific DNA sequences
D. Fast-acting agents that increase chloride secretion across epithelial cells leading to improved airway clearance
E. Fast-acting agents that bind to membrane receptors and elevate Ca^{2+}

56. All of the following terms have a distinct medical/pharmacological meaning or definition **EXCEPT**

A. opioid.
B. opiate.
C. dependence.
D. addiction.
E. narcotic.

57. Which of the following drugs used in the treatment of cardiovascular disease would be contraindicated for someone undergoing major oral surgery?

A. Nitroglycerin
B. Captopril
C. Aspirin
D. Furosemide
E. Propranolol

58. A known side effect of tetracyclines is that it

A. stains the enamel of teeth.
B. causes nail discoloration.
C. interferes with mental functions by inhibiting GABA transmission.
D. causes prolongation of the QT interval.

59. Benzodiazepines exert their anxiolytic effects by

A. enhancing the actions of dopamine.
B. inhibiting the actions of serotonin.
C. inhibiting dopamine reuptake.
D. enhancing the actions of GABA.
E. enhancing norepinephrine biosynthesis.

60. All of the following statements about antipsychotics are correct **EXCEPT**

A. Most classical antipsychotic drugs block dopamine receptors in the brain.
B. Some of atypical antipsychotics act at serotonin receptors.
C. The effects of antipsychotics are immediate.
D. Antipsychotics can cause Parkinsonism-like side effects.
E. Dopamine agonist drugs exacerbate schizophrenia.

Lidocaine Pharmacokinetics
ANSWERS

There are 4 key pharmacokinetic parameters that are useful in predicting the plasma concentration **(C)** that develops on a particular dosage regimen **(D/T)**. These parameters are clearance **(Cl)**, volume of distribution **(V_D)**, half-life **($T_{1/2}$)**, and, for orally administered drugs, the fraction of the orally administered dose that enters the systemic circulation **(F_{oral})**. In the exercise on lidocaine the 3 fundamental equations relating these parameters must be applied. The general form of these simple expressions is reviewed before applying them specifically to answer the individual questions.

After administration of a single dose of drug, the peak concentration is given by:

$$C = (F_{oral}) \times (D) / V_D$$

This equation assumes that *measurement of C is made after distribution is complete and that all drug is absorbed before any appreciable amount of drug is eliminated.* This expression is very useful, but it can be quite incorrect when the assumptions on which it is based are erroneous. You should know, for example, that this equation will not correctly predict the peak concentration that occurs when a single dose of acetaminophen is given on a full stomach. In this case absorption is slow and appreciable elimination occurs before absorption is complete.

The half life of a drug depends both on the Cl and on the V_D:

$$T_{1/2} = (0.693) \times (V_D) / (Cl)$$

Obviously a small clearance will favor a long half-life so clearance and half-life will be inversely related, but a large volume of distribution will also favor a long half-life (it takes longer to clear a large volume than it does to clear a small one) so half-life and volume of distribution are directly related.

On a fixed dosage oral regimen of an IV infusion *at steady state* the rate at which drug is being given must equal the rate at which it is being eliminated:

$$(F_{oral} \times D) / (T) = (C_{av}) \times (Cl)$$

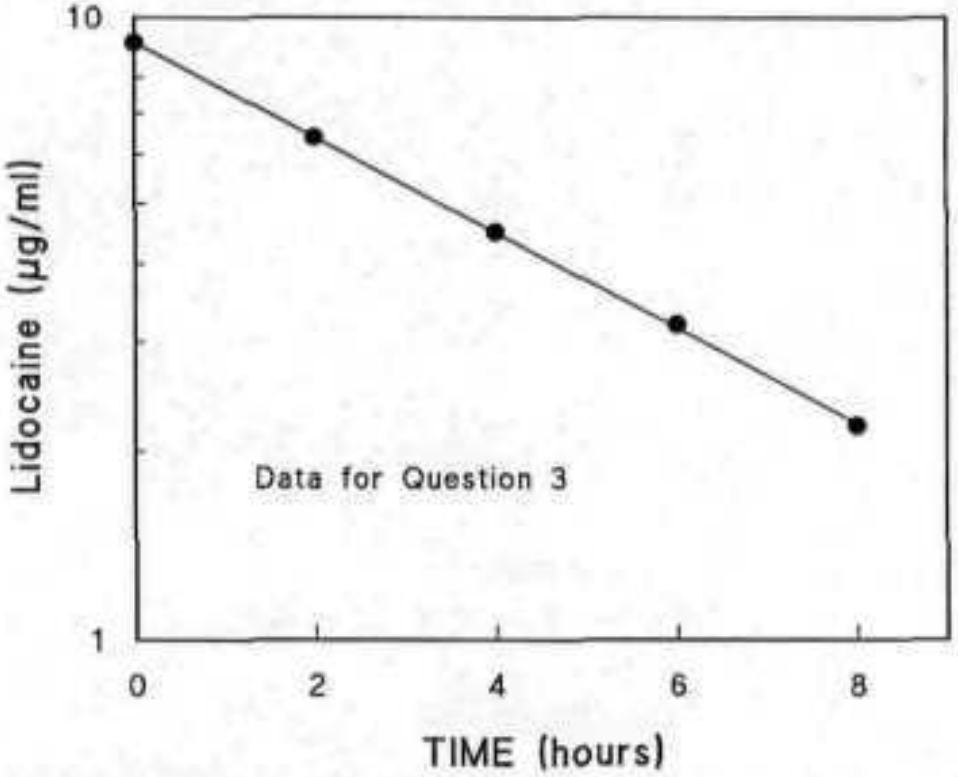
Note that the concentration here is the *average concentration at steady state.* With an IV infusion this will be the concentration measured, but *with oral doses the concentration will vary between doses*; that is, *there will be a peak after each dose and the plasma level will then decline to a trough just before the next dose.* The amount that the plasma level will vary between doses will depend on the half life of the drug and the interval between doses. In cases where there is little change between doses a good estimate of the average concentration is easily obtained but there can be considerable change in plasma level between doses on some oral dosage regimens.

the systemic circulation. Poor availability generally means variable availability so the relationship between oral doses and plasma concentration will be considerably more variable than the relationship between IV doses and plasma concentration and it will be more difficult to predict the response to oral drug. In the case of lidocaine the poor oral availability of the drug is largely due to first pass elimination in the liver. If the liver of a particular patient clears lidocaine especially rapidly, it will not only cause drug in the systemic circulation to be removed more rapidly but will also, through first pass elimination, cause less lidocaine to enter the systemic circulation. The first pass elimination of drugs like lidocaine which are rapidly metabolized in the liver magnifies the interindividual variation in plasma level on a fixed oral dosage regimen.

Clearly IV infusion is the way to administer lidocaine, but this means that the drug is only useful in the acute in-hospital situation and cannot be used to control chronic ventricular arrhythmias in patients outside the hospital.

Question 3

Since no lidocaine is being given and none is being absorbed during the time over which concentrations are being measured, the half-life of lidocaine is given by the time it takes for the plasma level to be halved. The original lidocaine concentration is 9.1 μg/ml. The time it takes to fall to half of this concentration (4.55 μg/ml) can be read off the appropriate semilog plot (**Figure 1**) and is 3.9 hours. You should verify that if you pick any other concentration the time to fall to half of that concentration is also 3.9 hours. Look, for example, at the time it takes to fall from 8 to 4 and from 6 to 3 μg/ml.



With maintenance dosing, whether by IV infusion or repeated oral dosing, it takes 3 half-lives to achieve 7/8 of the final average steady state concentration and 4 half-lives to achieve 15/16 of the final average steady state concentration of a drug *regardless of the initial*

loading dose. Since the half-life of lidocaine in this patient is long it has taken 16 hours (about 4 half-lives) for the lidocaine concentration to reach a toxic level.

Question 4

The clearance of lidocaine can be calculated from the average steady state concentration and the rate of infusion. In this case one can be confident that the first plasma level measured is very close to a steady state level because the drug has been infused for 16 hours which is about 4 half-lives. At steady state:

$$D/T = (C) \times (Cl)$$

Rearranging and substituting:

$$Cl = (2.8mg/min)/9.1\mu g/ml)$$
$$Cl = (2800\mu g/min)/9.1\mu g/ml) = 308ml/min$$

With a clearance of 308 m1/min the infusion rate needed to achieve 3.5 μg/ml is given by:

$$D/T = (C) \times (Cl)$$
$$D/T = (3.5\mu g/ml) \times (308ml/min)$$
$$D/T = 1078\mu g/min = 1.08mg/min$$

It will take about 4 half-lives or about 16 hours to achieve steady state concentration when infusion is reinitiated.

Question 5

The half-life ($T_{½}$) of a drug depends both on its volume of distribution and on its clearance. The expression relating these variables is:

$$T_{1/2} = (0.693) \times (V_D)/(Cl)$$

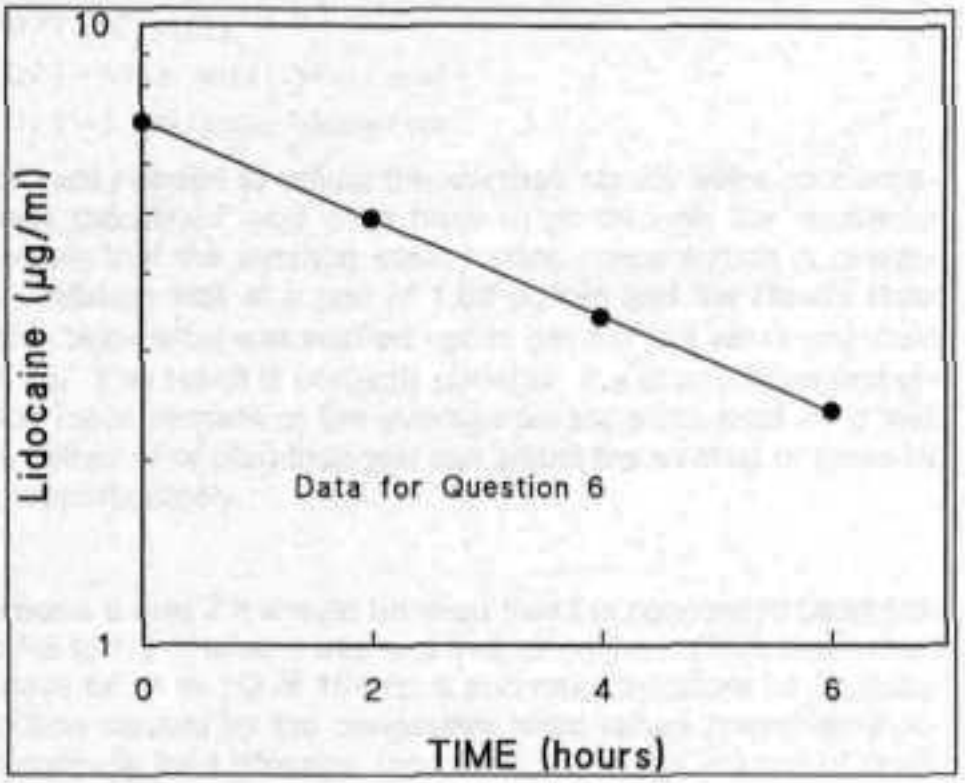
This equation expresses what should be intuitively obvious. If there is a larger volume of distribution to clear it is going to take longer to clear half of it. If clearance is smaller the volume of distribution will be cleared less rapidly and it will take longer to clear half of it.

Substituting and rearranging:

$$V_D = (308ml/min) \times (3.9hr)/0.693$$
$$V_D = (308ml/min) \times (234min)/0.693$$
$$V_D = 104{,}000ml = 104 \text{ liters}$$

If one assumes that the initial bolus of 105 mg distributes immediately into this 104 liters, then the concentration obtained would be 1.0 μg/ml. It takes time, however, for lidocaine to distribute into its entire volume of distribution. Initially, lidocaine distributes into an "apparent central volume" of 0.5 liters/kg which in a 70 kg man would be a volume of about 35 liters. The 105 mg distributes initially in this volume giving a concentration of 105 mg/35 liters = 3.0 μg/ml which is well within the therapeutic range. The half-life for distribution into the "true" volume of distribution is 8-10 minutes so in 3 half-lives (24-30 minutes) the concentration will be very close to 1.0 μg/ml and out of the therapeutic range. This explains the early therapeutic effect of lidocaine and its rapid loss. The key point is that when lidocaine is given by IV bolus there is a short period of very high concentration before distribution is complete.

Question 6



The half-life is determined as described in the answer to **Question 3** (see **Figure 2**, next page), and it is unchanged at 3.9 hours. The steady state concentration is twice that predicted.

Steady state concentration at a given rate of infusion depends only on clearance:

$$C = (D / T) / (Cl)$$

so the two fold increase in concentration implies only that the Cl has become 1/2 of the value that was determined earlier in **Question 4** and then used to calculate the infusion rate. Half-life, which is given by:

$$T_{1/2} = (0.693) \times (V_D) / (Cl)$$

would be expected to change when clearance changes *unless there is a corresponding change in the volume of distribution.* In congestive heart failure both the volume of distribution and the clearance decrease so there is no change in half-life. Clearance decreases because of poor kidney perfusion. V_D decreases for two reasons. First, in congestive heart failure there is poor perfusion of the peripheral tissues. Secondly, α_1-acid-glycoprotein ("acute phase reactant) increases substantially after a myocardial infarction and the subsequent congestive failure. This serum protein binds lidocaine and thus restricts a large amount of the drug to the plasma, which will obviously decrease V_D. *The point is that constancy of half-life does not guarantee constancy of pharmacokinetic parameters*

Question 7

The clearance calculated from the steady state concentration is:

$$Cl = (D / T) / (C)$$

Substituting:

$$Cl = (1.08 mg / min) / (7.0 \mu g / ml)$$

$$Cl = (1080 \mu g / min) / (7.0 \mu g / ml)$$

$$Cl = 154 ml / min$$

Clearance is now 1/2 of what it was previously. In congestive heart failure the rate of blood flow to the liver is decreased. Since *the metabolic elimination of lidocaine is limited only by blood flow (virtually all blood that flows through the liver is cleared of lidocaine)*, lidocaine clearance and hepatic blood flow decrease proportionately. The adjusted infusion rate now required is given by:

elevated and caused the convulsion. Oxidative N-dealkylation is the major route of lidocaine metabolism in the liver. The initial metabolite formed is monoethylglycinexylidide (MEGX) and MEGX is itself further metabolized in the liver. MEGX is known to have convulsant activity and there is evidence that it is, in fact, elevated in congestive heart failure. It may be that the elimination of MEGX is also influenced by hepatic blood flow.

Question 10

Two things cause lidocaine to work poorly in this situation: *i)* Blood flow is increased in an inflamed region like this so lidocaine will be removed from its site of action more rapidly than normal; *ii)* Local anesthetics like lidocaine exist in a charged and an uncharged form.

In an inflamed region pH is low favoring the charged form. This form is probably the form that actually interferes with the voltage-dependent sodium conductance in excitable membranes thereby blocking action potentials in pain afferents and providing local anesthesia, but it does not penetrate as well as the uncharged form. Reduction of the amount of uncharged form may contribute to the poor result with lidocaine by reducing the amount of drug which penetrates to the appropriate site.

It would be unwise to push lidocaine in this patient because accelerated entry of drug into the circulation and the likelihood that lidocaine metabolism may be impaired (congestive heart failure and probable cirrhosis of the liver) combine to favor toxic effects from the lidocaine. The best approach would be to block the nerve supplying the finger. The nerve can be blocked by administering a small amount of lidocaine outside the inflamed region and excellent anesthesia can be obtained.

Class Exercise: Lidocaine Pharmacokinetics

INTRODUCTION

Lidocaine (xylocaine) is a local anesthetic that has two important clinical uses: 1) It is frequently infiltrated to provide local anesthesia for minor surgical procedures, and 2) It is the drug of choice for the management of *ventricular* arrhythmias occurring in the setting of a myocardial infarction.

The key pharmacokinetic data for lidocaine (taken from Goodman and Gilman *Pharmacological Basis of Therapeutics* which is the ONLY text that has this type of information tabulated) are listed below. With this data you should be able to answer the questions listed below by applying the basic principles presented in lecture. *Please try to work out the answers to these questions before class.*

Pharmacokinetic data for lidocaine

For these reasons not given orally	Oral availability (%)	35 ± 11 high variation means large first pass effect
	Urinary excretion (%)	2 ± 1 very little gets unchanged via urine, so highly metabolized
	Bound in plasma (%)	70 ± 5
	Clearance (ml min^{-1} kg^{-1})	9.2 ± 2.4 (90% by liver) = for 70 kg = 644 ml/min
	V_D (liters/kg)	1.1 ± 0.4 × 70 kg = 77 L
	$T_{1/2}$ (hours)	1.8 ± 0.4
Therapeutic Window	Effective concentration	1.5-6 µg/ml
	Toxic concentrations	
	Occasional	6-10 µg/ml
	Frequent	> 10 µg/ml

QUESTIONS

$T_{1/2} = .693\left(\frac{V_D}{CL}\right) = 15$ min select target concentration $D = 3.5\frac{\mu g}{ml}\left(\frac{9.2 ml}{min\ kg}\right)(70 kg)$

1. How would you administer lidocaine to achieve and maintain a therapeutic concentration of 3.5 µg/ml rapidly (within 15 minutes) in a 70 kg man with the pharmacokinetic parameters shown above?

$3.5\frac{\mu g}{ml} = \frac{(1)D}{77{,}000\ ml}$ $D = 270$ mg

2. Lidocaine is not given orally to control ventricular arrhythmia. Why do you suppose that this is the case?

CASE HISTORY

A 55 year old man who weighs 70 kg develops severe crushing substernal pain which radiates into his left shoulder. He is taken by ambulance to the emergency room where he is diagnosed as having a myocardial infarction. An EKG taken in the emergency room reveals 8-10 ventricular premature contractions (VPC's) per minute. To treat the VPC's, a bolus of 105 mg of lidocaine is administered IV. Initially, this treatment is effective - the VPC's stop. The patient is then transferred to the coronary care unit (CCU), but, on arrival in the CCU 25 minutes after the lidocaine injection, the VPC's have reappeared at a rate of 8-10 per minute.

A second bolus of 70 mg of lidocaine is administered IV, and an infusion of 2.8 mg/min is begun. Eight hours later the patient's condition is stable, and the VPC's are controlled. Sixteen hours later the patient has a convulsion. At this point, lidocaine infusion is stopped, and there are no additional convulsions. Blood is drawn periodically for lidocaine analysis. The results of the lidocaine assays are shown below.

Time after convulsion (hours)	Lidocaine Concentration (μg/ml)
0	9.1
2	6.4
4	4.5
6	3.2
8	2.2

toxic concentration

QUESTIONS

$t_{1/2} = 4$ hrs

3. Determine the half-life for lidocaine in this patient from the data given above. Why has it taken so long for toxicity to develop in this patient? 4 half lives required, so 4 hrs × 4 = 16 h

4. Determine the clearance for lidocaine in this patient from the data given above. What rate of lidocaine infusion is necessary to maintain a steady state plasma level of 3.5 μg/ml? How long will it take to achieve this concentration once infusion is reinitiated.

5. Determine the volume of distribution of lidocaine in this patient from the data given above. What concentration of lidocaine would have been present in the plasma of this patient immediately after the initial 105 mg bolus of lidocaine? Would you expect this concentration to be effective in controlling VPC's? Why was the therapeutic effect lost 25 minutes after the first bolus of lidocaine?

The patient is controlled without toxicity when lidocaine is infused at the rate calculated in QUESTION 4, but on the third day in the CCU the patient has a second myocardial infarction that is complicated by congestive heart failure. Sixteen hours after the second infarction, the patient has a second convulsion. Lidocaine infusion, which has been maintained at the rate calculated in QUESTION 4, is stopped, and blood is drawn periodically to determine the plasma levels of lidocaine. The results of this analysis are shown below:

Time after second convulsion (hours)	Lidocaine Concentration (μg/ml)
0	7.0
2	4.9
4	3.4
6	2.4

Pharmacology Case 1
March 2005

Mrs. Henrietta Sloan is a 78 year old female widow of 19 years. She lives alone in her own home on the east side of Cleveland. She comes to the School of Dental Medicine for care in the general clinics. She lives in a third floor 2 bedroom apartment in a building that has an elevator. Upon admission at the School, a review of her medical history indicates medical diagnoses of severe Chronic Obstructive Pulmonary Disease (COPD), arthritis, and constipation. She has a 45 year habit of smoking (1 pack per day) and was diagnosed 15 years ago with COPD which is now worsening. She is fairly debilitated from her disease and has difficulty in catching her breath with normal activities that require small levels of exertion.

Medications: Oxygen: 2 Liters/min.; Ipratropium 18 microgram/spray MDI 2-3 p tid-qid with valved holding device; Colace

Physical Limitation: has difficulty walking long distances or walking up stairs. Although she lives alone, she is assisted by her daughter who does her weekly grocery shopping for her.

Dental Status: Mrs. Sloan is partially edentulous with 5 teeth remaining in the maxilla (# 3,4 and 13,14,15) and a 25 year old partial denture. In the mandible, she has the following teeth: #s 19 20, 21, 22, 28, 29. There is a lower partial denture which is also about 25 years old and in ill-repair. Most remaining teeth have 3 mm of horizontal bone loss with 3-5 mm of pocketing. All mandibular teeth demonstrate mobility (1+ - 2+).

1. What are the physiologic mechanisms for maintaining respiratory function?
2. What are important issues highlighted in this case?
3. How would you address these issues?
4. What actions do her medications have on her medical disease?
5. What oral side-effects would you expect to see in a patient taking these medications?
6. What would the consequences of sedation be in a patient like this?
7. What dental considerations must you be concerned with in treating a patient like this?