12 - 42_Pharmacokinetics

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01 - 1. Principles of pharmacokinetics

1. Principles of pharmacokinetics

02 - A. Absorption

A. Absorption

03 - Oral administration

Oral administration

1. Principles of pharmacokinetics Pharmacokinetics refers to the time course and disposition of drugs in the body (what the body does to the drug). The pharmacokinetics for the same drug will differ to some extent on the basis of the route of administration of the drug. Commonly utilized routes of administration of psychotropic drugs include oral, intramuscular, intravenous and rectal routes. Other possible routes include inhalation, topical, subcutaneous, sublingual and intra-arterial but are not generally used in psychiatric practice Pharmacokinetics involves the processes of (ADME); Absorption, Distribution, Metabolism, and Elimination. We will consider each of the above processes in further detail below. A. Absorption The route of administration and chemical properties of a drug influences its absorption. The various factors that affect rate of absorption include The form of the drug (e.g. enteric coating of a tablet slows down its disintegration in the stomach) The rate of blood flow at the site of administration (higher the blood flow, greater will be the rate of absorption) Solubility of the drug which depends on the pH of the drug, size of particles in the formulation and the pKa of the drug (pKa is the pH at which precisely half of the drug is in its ionized form) Oral administration This is one of the most common routes of drug administration. It leads to a variable plasma concentration, as the absorption may be erratic and subject to metabolism by liver and gut mucosa (first-pass effect). Drugs absorbed from the gut undergo extensive metabolism before entering the systemic circulation. The main mechanisms of absorption of drugs from the GI tract are 1. Active transport 2. Passive diffusion (most common mechanism) 3. Pore filtration Factors influencing absorption of drugs from GI tract include Intestinal motility Gastric emptying Gastric and intestinal pH Intestinal microflora Area available for absorption

  Integrity of blood flow Presence or absence of food Poor oral absorption leads to lower bioavailability of the drug in plasma compared to intravenous administrations. This is mainly due to lack of absorption from the intestine related to the presence of inhibitory factors like food or gastric acid or due to changes in intestinal motility e.g. having diarrhea or vomiting can affect drug absorption. The presence of food delays gastric emptying. The anticholinergic activity of some psychotropic drugs like tricyclic antidepressants, opiates, etc. can lead to delayed gastric emptying. The intestinal flora or intestinal wall enzymes can have drug-metabolizing activity, which could affect the rate of absorption. For e.g. Chlorpromazine is sulfated in the gut; this reduces its absorption. Site of absorption: The small intestine is less acidic than the stomach and most absorption takes place here. This is aided by a large surface area and long transit time via the

small intestine. Although oral administration occurs primarily in the small intestine, the absorption of many ‘slow or sustained release’ drugs occurs in the large bowel. Special preparations: With oral administration, the rate and sometimes the extent, of absorption are largely determined by disintegration and dissolution of the dosage form, both being important for absorption. Tablets and capsules must disintegrate into smaller pieces to expose a greater surface area for absorption. Enteric coating slows down the rate of disintegration. Disintegration is often prolonged by hard compaction or by incorporating wax in a drug matrix. As a result of this, such modified release preparations can prolong the effects of the drugs and reduce peak plasma concentrations and therefore may reduce side effects (E.g. lithium, carbamazepine, sodium valproate, quetiapine XL) Liquids or syrups are more quickly absorbed than tablets because disintegration and dissolution are not required. Dissolution rate is dependent on P-GLYCOPROTEIN

Presence of reverse transporters such as Pglycoprotein can affect drug absorption. P glycoprotein pumps certain drug molecules actively out into gut lumen from the gut cells.

Inhibition of P-glycoprotein (e.g. by grapefruit juice) can increase absorption of certain medications. The “grapefruit juice effect” is due to components of grapefruit juice - bergamottin, 6,7-dihydroxybergamottin, and naringenin – that significantly increase drug oral bioavailability by selectively and rapidly downregulating intestinal (but not liver) CYP3A4 and to a lesser extent, CYP1A2.

This effect is greatest for drugs with high first pass metabolism such as calcium antagonists felodipine and nimodipine, terfenadine, carbamazepine, triazolam and midazolam (to some extent diazepam), simvastatin and methylprednisone. Grapefruit also significantly affects buspirone and pimozide.

04 - Intramuscular administration

Intramuscular administration

05 - Intravenous routes

Intravenous routes

1. Size of drug particle
2. Solubility of the drug
3. Properties of intestinal fluid (e.g. p H)

Intramuscular administration With IM administration, absorption occurs over 10-30 minutes. It avoids most of the first pass metabolism. This route could be used in an emergency (acute disturbance, sedation etc.) or for maintenance medications (depot injections). The rate of absorption of drugs administered intramuscularly is dependent on blood flow and aqueous solubility. Lipid soluble drugs are rapidly absorbed; drugs with a relative low molecular weight are better absorbed. Increased muscle blood flow e.g. after muscular exercise increases the rate of absorption. Depot preparations of solutions of drugs in inert oil allowing delay absorption. Intravenous routes IV administration is the most rapid method of absorption and quickest route for achieving therapeutic concentration. It is used mainly in emergency situations. IV administered drug enters systemic circulation rapidly with no first-pass metabolism (100% bioavailability). IV route also carries the higher risk of sudden and life-threatening adverse effects.

06 - B. Permeation

B. Permeation:

© SPMM Course B. Permeation: Permeation of a drug is defined as the lipid membrane permeability of the drug molecule. After oral administration, a drug may be incompletely absorbed e.g. only 40% of a dose of chlorpromazine reaches the systemic circulation. This is mainly due to lack of absorption from the gut. Lipophilicity: Inherent properties of certain drugs can also affect their absorption e.g. highly hydrophilic drugs cannot cross the lipid cell membrane while highly lipophilic drugs will struggle to cross the water layer in the extracellular space. Drugs such as atenolol are too hydrophilic to be absorbed easily, and have a low bioavailability as a result. Apart from lipid solubility, concentration gradient affects permeation. Only free drug forms contribute to the concentration gradient. Hence, protein binding indirectly affects permeation. Permeation can take place either via simple diffusion i.e. along concentration gradient without any specific transport mechanism or facilitated diffusion i.e. along concentration gradient but ‘facilitated’ by the presence of carrier specific mechanisms. Active transport refers to transport against concentration gradient where ATP dependent energy expenditure takes place. Surface area and vascularity of the gut mucosa are important with regard to absorption of drugs into the systemic circulation. Only the nonionized form of a drug can cross lipid membranes of a cell. Many drugs are either weak acids or weak bases. These substances exist in either nonionized or ionized forms in equilibrium, in relation to the pH of the environment and their pKa (the pH at which the molecule is split into 50% ionized and 50% nonionized forms). The ionized form is more water-soluble than the nonionized form. As a consequence, ionized drug is more or less trapped in the glomerular filtrate and does not get reabsorbed. Hence, renal clearance is higher for ionized drugs. A weak base can be ionized by acidifying urine; a weak acid by alkalinising urine. Hence for salicylate (aspirin) overdose, and barbiturate overdose, alkalinization helps to reduce toxicity. Acidification may help in the elimination of amphetamines and phencyclidine (but often complications associated with this procedure overrides any benefits).

07 - C. Distribution

C. Distribution:

© SPMM Course C. Distribution: Distribution of a drug refers to ‘where’ in the body it can be found. Drugs are not evenly distributed throughout the body. Some drugs are confined to the body fluids only, but others accumulate in particular tissues. Drug distribution is influenced by various factors.

1. Hemodynamic factors like cardiac output, regional blood flow. Organs with the highest blood perfusions such as the brain, kidneys, and liver receive the highest distribution and redistribution is seen in the second distribution phase to tissues such as skeletal muscles, adipose tissues and skin.
2. Plasma protein binding
3. Permeability factors- higher the lipid solubility of the drug, the greater its rate of entry into cells.
4. Blood-brain barrier
5. Blood- CSF barrier Distribution can be viewed as the drug achieving equilibrium between different compartments. An approximation of this property is provided by the two compartment model; body is divided into a central compartment made of the plasma and a peripheral compartment made up of fat and other tissues, which vary with age, sex and weight. Distribution of a drug leads to a fall in the plasma concentration (central to peripheral shift) and is most rapid after intravenous administration. Protein binding: The distribution of a drug depends on how protein bound it is. When in the blood, many drugs are bound to circulating plasma proteins. It is the unbound fraction of the drug (free fraction) that can be active i.e. bind to receptors, pass across blood brain barrier, etc. Generally equilibrium exists between the fraction of bound and unbound molecules. Reduced protein-binding increases the free drug fraction and, therefore, the effect of the drug. Plasma protein binding is usually reversible (not covalent). Therefore, changes in protein binding can have profound effects on the availability of the drugs. Drugs that are highly protein bound (>90%), such as phenytoin, are most prone to interactions mediated by this mechanism. For example, diazepam displaces phenytoin from plasma proteins, resulting in an increased plasma concentration of free phenytoin and an increased risk of adverse effects. The effects of protein displacement are usually not of clinical significance, as the metabolism of the affected drug increases in parallel with the free drug concentration. The result is that, although the plasma level of the free drug rises briefly, the increased metabolism rapidly restores the level to the previous steady state. Therefore, any untoward effects of the interaction are normally short-lived

08 - Blood brain barrier

Blood-brain barrier

© SPMM Course (Chadwick et al., 2005). Protein binding interactions become relevant in a renal disease where proteinuria can occur. The principle plasma protein responsible for binding to acidic drugs is albumin while α1-acid glycoprotein is the primary binding protein for alkaline drugs. Most psychotropic drugs are basic, and they may bind to, for example, alpha-1 acid glycoprotein and lipoproteins. Protein binding is 95-99% for drugs like diazepam, chlorpromazine, amitriptyline and imipramine. Protein binding is 90-95% for phenytoin, valproate, and clomipramine. Volume of distribution: Vd =Q/Cp, where Vd-volume of distribution, Q-quantity of drug and Cp-plasma concentration at the time of administration (‘zero time’). Vd refers to an apparent (not true) volume in which an ingested drug is distributed in the body. The higher the Vd, the lower the plasma concentration. Vd tells us about the characteristics of a drug. When Vd is high, this indicates that the drug has a high affinity for tissues outside body water such as brain and fat. The Vd gives some idea of the whereabouts of the drug in the body. A low value (say 10 or 20 litres) suggests that the drug is concentrated in the blood itself. A high value (say 500 or 1000 litres) indicates that the drug is concentrated in the cells or fatty tissues and not the blood. Increased lipid solubility is associated with increased volume of distribution. This is the case for most psychotropic drugs at physiological pH. If a drug is highly protein bound, its plasma concentration will be high (as proteins exist in plasma), resulting in lower Vd. In other words, Vd is restricted by the total plasma volume for highly protein bound drugs. Tissue binding (e.g. fat or muscle) and accumulation of drugs results in low plasma concentration and, as a result, a high Vd. Hence, competition for protein binding can alter Vd. Blood-brain barrier The distribution of a drug to the brain is governed by 3 factors

1. Brain’s regional blood flow
2. Blood-brain barrier
3. Drug’s affinity for receptors in the brain Blood-brain barrier is a structural and functional barrier comprised of the capillary endothelium of the brain, which possesses tight junctions, acting in unison as a single sheet or membrane.

© SPMM Course This barrier prevents proteins and other molecules such as immunoglobulins from entering or leaving the brain’s blood supply. It also protects the brain from the entry of bacteria, viruses and maintains an osmotic gradient and maintains the cerebral glucose compartment differently from the periphery. Factors that could affect the permeability of the BBB include fever, head injury, hypoxia, hypercapnia, retroviruses, inflammation, vasculitis, hypertension, cerebral irradiation, and aging. The integrity of the BBB can be measured in different ways e.g. by measuring leakiness to labeled IgG molecules or gadolinium. The ability of a drug to pass blood brain barrier depends on its molecular size, lipid solubility and ionic status. Unionized molecules that are freely available and less protein bound are transported across the barrier easily. In general

higher the lipid-water partition coefficient, greater the ability to cross the barrier. Exceptionally there are few molecules that pass the barrier effectively in spite of having a low lipid-water partition coefficient. These have specific carrier mechanisms e.g. aminoacid transport system (this is stereospecific; so l- amino acids not d- amino acids are easily transferred). L-dopa, l-tryptophan and valproate have specific carrier mechanisms. Some small molecules diffuse readily into the brain and CSF from cerebral circulation e.g. lithium ion. Some areas of the brain around the ventricles (circumventricular organs) lack BBB; e.g. subfornical organ, area postrema of the medulla and the median eminence. These circumventricular organs allow the transfer of many compounds from blood to brain. This may have a survival benefit as certain toxic substances stimulate area postrema and induce nausea and vomiting. There is no evidence that inhaled medications bypass the BBB. But to some extent, nasal sprays can reach the brain via olfactory epithelium and bypass the barrier. Anaesthetic agents do not increase the permeability of the blood-brain barrier. In addition to BBB, a blood- cerebrospinal fluid barrier also exists. This is seen in the choroid plexus. Here the tight junctions are located between adjacent epithelial cells, as opposed to adjacent endothelial cells in the case of BBB.

09 - D. Bioavailability

D. Bioavailability:

© SPMM Course D. Bioavailability: Bioavailability refers to how much of an administered drug reaches its target. It is the extent to which the drug reaches the systemic circulation when taken by a patient orally or parenterally, compared with the same quantity of drug given intravenously. In other words, it is the fraction that circumvents the first pass effect and actually reaches the systemic circulation. Plotting plasma concentration against time, for a given dose, provides oral bioavailability. The area under the curve (AUC) after a single dose is proportional to the amount of drug in plasma and allows determination of the fraction of the dose absorbed-the bioavailability. The area under the curve obtained for orally administered drug divided by the area under the curve obtained for intravenous administration of the same dose gives the bioavailability fraction. It is determined by three factors:

1. Absorption
2. Distribution
3. Elimination (metabolism and or excretion). When a drug is administered intravenously, the availability of the drug is 100%. In other words, the amount of drug that enters systemic circulation following IV administration is 100%. This is not the case with extravascular or non-parenteral administrations such as oral, per rectal, inhalational, intramuscular or subcutaneous routes. The reduction in amount reaching circulation is related to the degree of absorption and the effect of ‘first-pass’ metabolism, also called presystemic metabolism. This metabolism is prominent in the gut mucosa, liver and to some extent in the muscle tissue. This explains why higher doses are generally needed orally as compared to intramuscularly. Certain examples of drugs that can undergo a high degree of firstpass metabolism include imipramine (only 30-80% of the oral dose enters systemic circulation) and fluphenazine (only 10% of oral dose enters systemic circulation). Hepatic impairment can reduce first pass metabolism, requiring adjustment of dosages of drugs that are metabolized by the liver. Bioequivalence: It is a measure of comparability of plasma levels of two different formulations of the same active compound when given at same dose and the same route of administration. Two products are said to be bioequivalent when the graphical trace of their plasma level plot against time are superimposable. For this to happen, the two compounds must have the same bioavailability and rate of absorption. Bioequivalence is an important feature to be considered when changing from one brand to another brand of the same compound e.g. camcolit vs. priadel

10 - E. Metabolism of drugs

E. Metabolism of drugs:

© SPMM Course for lithium carbonate or Clozaril vs. zaponex for clozapine. E. Metabolism of drugs: Xenobiotics refer to the mechanism by which a foreign agent such as a drug molecule is metabolized and eliminated from our body. The metabolism or biotransformation of a drug renders it less lipid-soluble and more water-soluble. Therefore, the products of such metabolism are more readily eliminated from the body. The liver is the principal site of metabolism, but metabolism can occur in the gastrointestinal tract, plasma, lungs, kidneys, suprarenal cortex, placenta, skin, and lymphocytes. The four major metabolic routes are oxidation, reduction, hydrolysis, and conjugation. There are 2 phases of drug metabolism. Phase 1 metabolism includes oxidation, reduction and hydrolysis (often mediated by CYP system, see below), as a result of which a molecule (could be active or inactive) suitable for conjugation is produced. It is not essential that a drug undergo phase 1 metabolism in order to undergo phase 2 metabolism e.g. lorazepam, temazepam and oxazepam undergo direct phase 2 reactions. (As a result, in patients with alcoholic liver disease, oxazepam is favoured for alcohol detoxification instead of chlordiazepoxide which requires intact liver enzymes for phase 1 clearance) Phase 2 metabolism involves conjugation reactions such as glucuronidation, as a result of which polar compounds (mostly inactive) that are excretable in bile or urine are formed. A drug or drug metabolite from a phase 1 reaction is conjugated to a polar (water soluble) group by phase 2 metabolism. The result of this would be a water-soluble conjugate that can undergo renal excretion easily if it has a relative molecular mass of less than 300. If the relative molecular mass is more than 300, then the excretion would take place through bile. Metabolism usually yields inactive metabolites that are more polar and are easily excreted. Metabolism could also transfer some inactive pro-drugs into therapeutically active metabolites. Cytochrome P450 enzymes: Most psychotherapeutic drugs are oxidized by the hepatic cytochrome P-450 enzyme system. The human CYP enzymes comprise several distinct families and subfamilies. The most studied is CYP2D6. Together with CYP3A4, this constitutes nearly 90% of all psychotropic metabolism. The CYP enzymes are responsible for the inactivation of most psychotherapeutic drugs. These enzymes act primarily in the endoplasmic reticulum of the hepatocytes and cells of the intestine. Therefore, any cellular pathophysiology caused by viral hepatitis or cirrhosis may affect the

© SPMM Course efficiency of drug metabolism by the CYP enzymes. There are 3 ways in which drug interactions may influence the CYP system. It includes induction, non-competitive inhibition, and competitive inhibition. Genetic variations in the hepatic enzymes affect the rate of metabolism. Between 5 and 10% of Caucasians lack the enzyme CYP2D6 and are poor metabolizers of corresponding substrates. Up to 15-20% of East Asians are poor metabolizers of CYP2C19 substrates. The table below gives the list of some psychotropics with CYP-mediated drug interactions. Some of the important pharmacokinetic drug interactions involving psychotropics

include SSRIs especially fluvoxamine and fluoxetine inhibit CYP system. Fluoxetine increases plasma tricyclic antidepressants via 2D6 and 2C19. Fluvoxamine increases plasma clozapine concentrations. Clozapine levels may be increased 10-fold by the addition of fluvoxamine, which can induce seizures. Carbamazepine decreases the plasma concentration of several drugs including contraceptive pills. Most antidepressants can inhibit the metabolism of warfarin via a complex mechanism resulting in potentially serious bleeding. Tricyclics and haloperidol compete with each other for same metabolic enzymes. Carbamazepine and phenobarbitone can induce their own metabolism. Alcohol, smoking and brussel sprouts are CYP inducers. Grapefruit juice and caffeine inhibit CYP system

CYP enzyme Major psychotropics metabolized Effects of psychotropics CYP2D6 All TCAs, fluoxetine, paroxetine, trazodone, nefazodone, valproate, all neuroleptics, risperidone. Paroxetine, to some extent fluoxetine, neuroleptics, amitriptyline and clomipramine inhibit 2D6. CYP3A4 (Most prominent in gut wall mucosa) Clomipramine, fluvoxamine, mirtazapine, nefazodone, Carbamazepine, most benzodiazepines. Stimulated by carbamazepine and barbiturates. Inhibited by calcium channel blockers, fluoxetine, and nefazodone. Smoking induces CYP1A2 via PAH.

© SPMM Course Autoinduction: Carbamazepine is metabolized by the hepatic CYP2D6, synthesis of which in turn is induced by carbamazepine. As a result of this autoinduction, the rate of metabolism of carbamazepine (and other P450 substrates) gradually increases over the first several weeks of treatment. The initial steady state may be attained within 4 to 5 days, but autoinduction may delay final steady state until 3 to 4 weeks after treatment initiation. Hence, the level of carbamazepine must be monitored, and its dose often needs to be raised during this early phase of treatment. Chlorpromazine can also induce its own metabolism to some extent. Effect of smoking and caffeine: Smoking and caffeine affect glucuronidation reaction via UGT enzyme and CYP1A2. Drugs which are not dependent on CYP1A2 or UGT for their metabolism are unaffected by smoking or caffeine consumption. For example, risperidone and aripiprazole (metabolized by CYP2D6 and CYP3A), quetiapine (mainly metabolized by CYP3A), and ziprasidone (mainly metabolized by an aldehyde oxidase and CYP3A) are unaffected. But the metabolism of clozapine and olanzapine is mainly dependent on CYP1A2 and UGTs. Because caffeine competitively inhibits CYP1A2, it increases the levels of clozapine and olanzapine while Polyaromatic Hydrocarbons (PAH) in cigarettes induce the enzyme. The effects of inhibitors (caffeine) are seen sooner than those of inducers (smoking), which require fresh synthesis of CYP1A2 enzymes to produce an effect (de Leon, 2004).

ALCOHOL BREAKDOWN

Four distinct pathways for ethanol degradation have been described - 3 oxidative pathways and 1 non-oxidative pathway.

Each of the oxidative pathways starts with the oxidation of ethanol to acetaldehyde, which is then oxidized to acetate for subsequent extra-hepatic activation to acetylCoA. The first pathway which contributes for

> 90% breakdown in Caucasians, utilizes cytoplasmic alcohol dehydrogenase, the second oxidative pathway uses the endoplasmic reticulum Microsomal Ethanol Oxidizing System (MEOS or CYP450 2E1) and the third pathway uses peroxisomal catalase.

The nonoxidative pathway for ethanol metabolism is less well characterized but produces fatty acid ethyl esters (FAEEs) as primary end products.

11 - F. Excretion

F. Excretion:

© SPMM Course F. Excretion: The major routes of drug excretion are via urine, faeces and bile. Psychotropic drugs are also excreted in sweat, sebum, tears, saliva and breast milk. Both active forms and inactive metabolites can be excreted. Ionized and non-lipid soluble compounds are the most suited forms for renal excretion. The factors influencing excretion include Increased age (decreases excretion) Reduction in renal blood flow e.g. dehydration Renal impairment leading to decreased renal function Alterations in re-absorption: urine pH. (Changes in the p H of the tubular filtrate can alter the rate of elimination of the drugs. Normally urine is weakly acidic and good for excretion of drugs such as tricyclics and amphetamines. Alkaline diuresis is required to enhance elimination of drugs such as aspirin or phenobarbitone in overdose) and low sodium (Low sodium increases lithium reabsorption and decreases excretion leading to consequent toxicity) Clearance: Clearance is the term used to describe the rate of elimination of a drug. Clearance is defined as the volume of blood cleared of a particular drug in unit time. Total body clearance depends on renal and nonrenal clearance such as sweat, bile, etc. Clearance is directly proportional to the volume of distribution. Cl=k x Vd, Where the constant of proportionality, k, is the first order elimination constant. Clearance is specific for each drug and does not depend on drug concentration in plasma (because if concentration increases, elimination will also increase under first order kinetics). It represents the relationship between the rate of drug elimination (t1/2) and plasma level. For drugs with first order kinetics, clearance is constant irrespective of dose consumed because the rate of elimination is directly proportional to plasma level. Renal elimination without significant liver breakdown is seen for drugs such as lithium, amisulpride, sulpiride, gabapentin, acamprosate and amantadine. Both sulpride and amisulpride have up to 90% elimination via renal route – a minor portion is excreted via the biliary system. Amisulpride produces 2 weak metabolites following limited hepatic breakdown. Half-life: The half-life of a drug refers to the time taken for the plasma concentration of a drug to halve. It is represented by the expression ‘t1/2’. Following intravenous injection, there is a rapid

12 - G. Elimination kinetics

G. Elimination kinetics:

© SPMM Course fall in the plasma drug concentration, which is caused by redistribution of the drug from the blood circulation into other tissues. The time taken for this redistribution to halve the initial peak concentration is the distribution half-life. Following this, the process of drug elimination occurs. The time taken by this elimination process to halve the plasma drug concentration is the elimination half-life. Most often, clinicians are interested in the elimination half-life. G. Elimination kinetics: Drugs can undergo two different types of clearance (similar to absorption) when administered. When a constant fraction of drug is cleared per unit time, it is called as first order kinetics. This means that when the amount of drug in plasma or dose of administered drug increases, the clearance proportionately increases as a stable fraction of plasma concentration. In other words, the higher the amounts of a drug present, the faster the elimination. When represented graphically, first-order elimination follows an exponential decay versus time. Using this exponential curve, the time to eliminate 50% of a given amount (or time to achieve a decrease in plasma level to 50% of original) is the elimination half-life (t1/2). For example, if t1/2 is 2 hours for a drug A then the plasma concentration changes as follows 100mg/ml (2hours) □ 50mg/ml (2hours) □ 25mg/ml (2hours) □ 12.5mg/ml Most psychotropic drugs follow first order kinetics. In first order kinetics, the rate depends only on the drug concentration. It is not dependent on any other rate-limiting step. When the system facilitating such clearance of drugs gets saturated, drugs follow zero-order kinetics. Here a constant amount, not a fraction, of the drug is cleared per unit time. This means that irrespective of the amount of drug in plasma or dose of drug administered, the body clears only a fixed unit of the drug. As such, increasing dose might result in serious toxicity in this case. Certain drugs have propensity to undergo zero order kinetics even at therapeutic dose levels. Here the concept of half-life does not hold true as ‘half life’ depends on the dose administered. 100mg (2hours) □ 80mg (2hours) □ 60mg (2hours) □ 40mg In the above example, 20mg of the drug is metabolized in every 2 hours. The apparent ‘half-life’ of 100mg dose is about 5 hours, but the apparent ‘half-life’ of 80mg dose is only 4 hours. Slow release preparations (e.g. lithium MR, depot preparations) follow zero-order absorption kinetics; drugs that rapidly saturate enzymes such as alcohol and phenytoin follow zero-order elimination kinetics. In very high supratherapeutic doses, saturation of enzymes can happen for drugs such as fluoxetine, wherein first order elimination switches to become zero order. Note that in zero order kinetics, the rate does NOT depend on the drug concentration; it depends on some other rate limiting step e.g. availability of enzymes, slow release formula, etc.

© SPMM Course Steady state: When a drug is administered episodically, the plasma values acutely rise immediately after administration and then fall when the continuous input of drug does not take place. But before the fall in levels reaches a flat trough, the next dose gets administered (depending on t ½ of the specific drug, dosing interval varies). Hence, the actual plasma level

starts building up gradually with every subsequent dose. It is estimated that it takes 4-5 t½ for a drug to reach the steady plasma level. When steady state is reached, fluctuations in plasma level do not get eliminated. But the average plasma concentration between 2 successive doses remains the same. Steady state is reached when for a given drug, rate in = rate out. The time to reach steady state is dependent on the elimination t½ of a drug; the actual level of the steady state is independent of the frequency of administration; instead it depends on the actual dose administered. Loading doses can help achieving steady state more rapidly.

13 - 2. Indices of safety and efficacy

2. Indices of safety and efficacy:

© SPMM Course 2. Indices of safety and efficacy: Quantal or dose-response curves: Quantal curves plot the percentage of a population showing a specified, predefined categorical drug effect against the dose or log dose administered. The doseresponse curve plots the drug concentration against the continuous effects of the drug. Using these curves, the median effective dose, or median toxic doses can be determined. The median toxic dose is the dose at which 50% of patients experience a specific toxic effect, and the median effective dose is the dose at which 50% of patients have a specified therapeutic effect. In addition, using these curves the range of intersubject variability in drug response could be studied. Steep D-R curves reflect little variability; flat D-R curves indicate great variability in patient sensitivity to the effects of a drug. The therapeutic index can be determined using these curves. Therapeutic index: It is the relative measure of the toxicity or safety of a drug. It is defined as the ratio of the median toxic dose to median effective dose. In other words, it is the ratio of the minimum plasma concentration causing toxic effects to that causing a therapeutic effect. This can vary according to the toxic symptom specified for a given drug. For example, the gastrointestinal toxicity of lithium can occur at a lower plasma concentration than that for seizures. In the laboratory this is usually determined using the median lethal (LD50) and median toxic dose (TD50) in animal studies. In humans, this is identified using ‘minimal’ effective and ‘minimal’ toxic doses using trial data. Note that the term therapeutic index is only relevant when considering dose-dependent side effects; it is not useful when studying idiosyncratic reactions. Therapeutic index range: Certain drugs such as lithium, carbamazepine and phenytoin have a narrow range of plasma levels within which the efficacy is optimum and toxicity is less evident; crossing this range on higher side will increase toxicity while on the lower range will reduce efficacy. Drugs with the low therapeutic index or narrow therapeutic range will require plasma monitoring. Therapeutic window: This term is often confused with therapeutic safety range. In fact, this term is used to describe a specified plasma concentration value, only within which certain drugs appear to have a therapeutic efficacy. This does not concern the side effects or toxicity. Imipramine, nortriptyline, and desipramine have a curvilinear relationship when plasma levels are plotted against the therapeutic response, i.e. very high or very low levels do not help the patient.

14 - 3. Variables affecting pharmacokinetics

3. Variables affecting pharmacokinetics:

15 - A. Changes in the elderly

A. Changes in the elderly

© SPMM Course 3. Variables affecting pharmacokinetics: A. Changes in the elderly Domains Change Effect Body composition An increase in total body fat. A decrease in total muscle mass (lean body mass). A decrease in total body water. A larger volume of distribution and longer half-life of lipophilic chemicals because of their increased sequestration in fat. e.g. benzodiazepines excretion slower in the elderly Plasma protein Decrease in plasma protein binding capacity in elderly individuals

Nearly 15-25% - due to higher proteinuria and to some extent due to lesser plasma protein synthesis by the liver. Albumin decreased; protein affinity decreased; acid glycoprotein increased. Higher free drug plasma concentration – increased metabolism and clearance of the free drug. More frequent protein binding interactions. Phenytoin is affected Liver Hepatic metabolism not altered much. Decreased hepatic blood flow occurs. Liver withstands aging to considerable extent unless associated physical frailty present. No changes noted up to age 60 - 80. After 80, CYP system declines. Phase 2 (conjugation) metabolism is not affected (Hence lorazepam better than diazepam for elderly). Decreased hepatic first pass effect. Higher oral bioavailability of certain agents. Kidney Decreases in renal blood flow have been approximated at 10% per decade beginning after the fourth decade - leads to reduced creatinine clearance and GFR. More frequent toxicity of renally eliminated agents (e.g. lithium). GI tract Absorption is not greatly affected. GI blood flow is diminished. Gastric pH is increased as acidity drops.

Slower but nearly equal absorption of oral administered drugs. Decreased gastric first pass metabolism noted. A reduction in the gastric wall content of dopa decarboxylase Leads to a 3-fold increase in the concentration of levodopa in the elderly. Brain receptors Decreased number of brain acetylcholine postsynaptic receptors; choline acetyltransferase is diminished, level of brain acetylcholinesterase also decreased during aging. Some of these counterbalance each other. On the whole anticholinergic side effects more pronounced leading to increased frequency of delirium on polypharmacy. Kidney mass has been reported to be substantially reduced in old age, by approximately 20 to 25% between the age of 30 and 80 years. Renal blood flow reduces with age even in those with normal health. Renal blood flow decreases by about 10% per decade after the age of 20. By age 80, RBF

16 - B. Changes in neonates

B. Changes in neonates:

17 - C. Changes in pregnancy

C. Changes in pregnancy:

18 - D. Changes with renal impairment

D. Changes with renal impairment:

© SPMM Course may be 600ml/min as compared to 1200ml/min in young adults. Creatinine measurements can yield spurious results; hence GFR formulas must be used to correct for age and other variables. Nearly 40% renal function is lost by the age 80. The average decline is around 10mL/min/1.73m2 per decade after age 30. This takes an adult GFR from 130mL/min/1.73m2 to a value of 80mL/min/1.73m2 when the age is 80 (The Baltimore Longitudinal Study). B. Changes in neonates: Neonates have a higher proportion of total body water and extracellular body water Neonates have a lower proportion of adipose tissue. The glomerular filtration rate is lower in those aged less than 3-5 months Neonates have lower gastric acidity and have an increased gastric emptying time Neonates have a more permeable blood—brain barrier The microsomal enzyme activity in the liver is lower in those than 2 months Neonates have a lower plasma concentration of albumin C. Changes in pregnancy: Pregnancy is associated with several pharmacokinetic changes: Delayed gastric emptying, Decreased GIT motility, Increased volume of distribution (5%), Decreased drug-binding capacity, Decreased albumin level Induced liver metabolic pathway, Increased GFR & renal clearance. Psychotropic medication usually passes from the maternal blood to the foetus due to lack of strong barrier, but rate and amount of transfer are variable. Higher doses are associated with higher serum level in the infant. D. Changes with renal impairment: Benzodiazepines should be used with caution The half-life of diazepam remains unchanged in end-stage renal disease, but its metabolite, desmethyldiazepam, may accumulate, causing excessive sedation. The half-life of lorazepam is increased from 8–25 hours in healthy adults to 32–72 hours in end-stage renal disease At a low level of renal function, lorazepam dosage should be reduced by 50% to avoid

© SPMM Course excessive sedation. Imipramine and amitriptyline can be given at their usual dosage as renal impairment does not increase their half-lives Half normal dose is used for citalopram in patients with renal impairment or in elderly The half-life of paroxetine is considerably increased with severe renal impairment, requiring dosage reduction. The dosage of fluoxetine and fluvoxamine does not have to be reduced in the elderly or patients with renal impairment Sertraline manufacturers do not recommend its use in renal impairment Haloperidol does not require a dose reduction in renal impairment unless excessive sedation or

hypotension occurs. Amisulpride is renally excreted almost exclusively. Hence, renal failure will be a relative contraindication to use this drug. Product monograph suggests alternate day dosing or dose reduction if no other alternatives are possible. Risperidone and its active metabolite 9-hydroxy-risperidone are substantially excreted in the urine so that in renal impairment the elimination half-life is prolonged Lithium is best avoided or given at low dosages.

19 - 4. Clinically relevant kinetics and interacti

4. Clinically relevant kinetics and interactions:

20 - A. Tricyclic antidepressants

A. Tricyclic antidepressants:

© SPMM Course 4. Clinically relevant kinetics and interactions: A. Tricyclic antidepressants: The tricyclics are orally well absorbed but have variable time to achieve peak plasma concentration (1 to 12 h). Many of them have active metabolites – see table below. Nearly 7-9% Caucasians are slow metabolizers (measured by debrisoquin hydroxylation) of tricyclics due to CYP2D6 polymorphism (Up to a 40 times difference in plasma TCA concentrations can occur as a result). Children clear more tricyclics from their body whereas the elderly clear less. Most tricyclics have a long half-life (close to 24 h) that allows once-daily dosing. They readily cross lipid barriers such as blood-brain barrier and placenta. They are extensively bound to plasma proteins e.g. Imipramine 80-95%. For TCAs plasma (not serum) levels are measured to assess therapeutic dosing. The levels are determined after 5-7 days when steady state is reached, and 8-12hrs after last dose to avoid false peaks earlier when absorption is occurring. A sigmoidal curve where proportional doseresponse plateaus at a particular dose is noted for imipramine and desipramine. For nortriptyline a clear therapeutic window is seen between 50 to 150ng/ml. This inverted U is not due to decreased responsivity secondary to side-effects.

 Amitriptyline and clomipramine decrease the metabolism of morphine and may contribute to opioid toxicity through UDP glucuronyl transferase interaction. (Chadwick 2005)

Antidepressant Active metabolite Imipramine desipramine Amitriptyline nortriptyline Trazodone, nefazodone mCPP Fluoxetine norfluoxetine Sertraline desmethylsertraline

© SPMM Course Drugs Mechanism Effect Quinidine, cimetidine, fluoxetine, paroxetine, phenothiazines, disulfiram, methylphenidate Inhibit TCA metabolism Increase plasma TCA levels Smoking, phenytoin, carbamazepine, OC pills and barbiturates Induce metabolism Reduce TCA levels Phenothiazines Mutual inhibition of metabolism Both antipsychotic and TCA levels increase Anticoagulants TCAs increase warfarin levels High risk of bleeding Clonidine TCAs reduce clonidine levels Hypertensive crisis MAOIs Synergistic serotonergic enhancement esp. clomipramine TCAs reduce tyramine entry via monoamine reuptake channels Higher risk of serotonin syndrome Lower risk of cheese reaction l-dopa TCAs reduce absorption of l-dopa Lowers l-dopa efficacy in Parkinsonism Morphine Amitriptyline and clomipramine decrease the metabolism through UDP glucuronyl transferase interaction Increased opioid toxicity

21 - B. SSRIs

B. SSRIs

 The SSRIs are rapidly absorbed. Sertraline availability may be increased by the presence of food. Most are highly protein bound except escitalopram which is 56% bound. Fluoxetine is metabolized to norfluoxetine, which has similar activity on 5-HT reuptake as fluoxetine. The half-life of norfluoxetine is 4–16 days while t1/2 of fluoxetine itself is 4–6 days. Similarly, sertraline metabolite has longer half-life but unlike norfluoxetine it is not a potent reuptake inhibitor. Desmethylcitalopram is a potent noradrenaline uptake inhibitor but not produced sufficiently and weakly crosses the blood–brain barrier. Fluvoxamine and paroxetine do not have active metabolites. Both fluoxetine and paroxetine are capable of inhibiting their own clearance at clinically relevant doses. As such, they have nonlinear pharmacokinetics: changes in dose can produce proportionately large plasma levels. The half-life is not related to time to onset of action, but it is relevant for discontinuation reactions. Fluvoxamine Sertraline Escitalopram Citalopram Fluoxetine Paroxetine Lower end: Greatest nonlinearity of kinetics Unpredictable side effects

  Selectivity: Citalopram is the most selective (and escitalopram) while paroxetine is the most potent. Fluoxetine weakly inhibits noradrenaline reuptake and binds to 5-HT2C receptors; sertraline weakly inhibits noradrenaline and dopamine reuptake. Paroxetine has significant anticholinergic activity at higher dosages and binds to nitric oxide synthase. Fluoxetine & olanzapine when taken together increase brain concentrations of noradrenaline. Dosing: Apart from depression and GAD, panic disorder, OCD, OCD spectrum disorders and bulimia respond to SSRIs. OCD may need a higher dose for several months for the effects to become evident. Fluoxetine treatment of bulimia is best given together with psychotherapy. Again higher dosages are required. SSRIs are useful in premenstrual dysphoria (PMDD) where sertraline or paroxetine used either daily or only during luteal phase produces a positive effect. Intermittent dosing is usually as effective as continuous administration. Beneficial effects are seen very quickly in one to two days, but proof of efficacy is lacking. Fluvoxamine reduces the clearance of both diazepam and its active metabolite, Ndesmethyldiazepam, there is a strong likelihood of substantial accumulation of both. Accordingly, diazepam and fluvoxamine should not ordinarily be co-administered. Citalopram is metabolized by CYP2C19 initially and then by CYP2D6. CYP3A3 and CYP3A4 are responsible for demethylation of sertraline. Drug CYP450 Profile Interacting psychotropic drug Effect Clinical notes Fluoxetine Inhibits 2C19, 2D6. Partially metabolized by 2D6.

All TCAs especially Clomipramine Imipramine (both 2C19 & 2D6), Citalopram, Sertraline, Moclobemide, Duloxetine, Mirtazapine Venlafaxine. Levels of these drugs increase in plasma.

Potential TCA toxicity. Associated with therapeutic benefit? Effect may last up to 2 weeks after stopping fluoxetine. Paroxetine Predominantly metabolized by 2D6. Inhibits 2D6 All TCAs Citalopram, Fluoxetine, Fluvoxamine, Duloxetine, Mirtazapine, Venlafaxine. Levels of these drugs increase in plasma. Potential TCA toxicity, may be associated with therapeutic benefit when combined. May have non-competitive inhibition resulting in unpredictable effect in combinations.

© SPMM Course The autoinhibition of CYP2D6 is responsible for nonlinear pharmacokinetics of paroxetine and at least partially for the nonlinear pharmacokinetics of fluoxetine. Fluvoxamine reduces the clearance of theophylline approximately 3-fold via CYP1A2 inhibition. Therefore, if theophylline is co-administered with fluvoxamine, its dose should be reduced to one-third of the usual daily maintenance dose and plasma concentrations of theophylline should be monitored. No dosage adjustment is required for fluvoxamine. When fluvoxamine is administered with warfarin, warfarin plasma concentrations increases by 98% and prothrombin times are prolonged. Hence, anticoagulant dose must be adjusted accordingly. Fluvoxamine Inhibits 1A2, 2C19, 3A4 Clomipramine, Doxepine, Trimipramine Duloxetine, Mirtazapine Citalopram, Escitalopram, Sertraline Trazodone. Levels of these drugs increase in plasma. Potential TCA toxicity. Duloxetine

Inhibits 2D6, similar to SSRIs. All TCAs Citalopram, Fluoxetine, Paroxetine, Fluvoxamine, Mirtazapine, Venlafaxine. Levels of these drugs increase in plasma. Potential TCA toxicity especially at higher dose - may not be clinically meaningful at lower doses. Desipramine, Clomipramine Inhibits 2D6 All TCAs Citalopram, Fluoxetine Fluvoxamine, Duloxetine, Mirtazapine Venlafaxine. Can increase levels of these drugs Potential serotonin toxicity. SSRI Plasma elimination half-life Linearity of pharmacokinetics

Single dose Multiple dose [active metabolite]

Paroxetine 10h. 21h. Nonlinear Fluvoxamine 11h. 14h. Nonlinear Sertraline 26h. 26h. [36h.] Linear Citalopram 33h. 33h. Linear Fluoxetine 1.9 days 5.6 days [7-15 days] Nonlinear

22 - C. Other antidepressants

C. Other antidepressants

© SPMM Course C. Other antidepressants The MAOIs are all rapidly absorbed. For the irreversible MAOIs the half-life does not correlate with duration of action as the effects on the MAO enzyme are irreversible and new enzyme needs to be synthesized for restoration of normal activity - a minimum of 5 to 7 days. Hence, it is recommended that for drugs that can interact fatally with MAOIs (irreversible) - the safest recommendation is to wait 2 weeks before starting. The combination of MAOIs and pethidine (meperidine) can produce either a depressive (pronounced sedation due to opioid toxicity) or excitatory reaction (related to serotonin excess: agitation, hyperpyrexia and cardiovascular collapse, coma, and death). Pethidine, in particular, has a serotonin releasing property and some reuptake inhibition property. Pethidine must never be used in the presence of MAOIs because of the risk of this fatal excitatory interaction. Morphine has fewer propensities to cause this interaction. Amphetamine also induces serotonin release, while methylphenidate does not. The latter is relatively safe in terms of serotonin toxicity with MAOIs. Venlafaxine has low protein binding; it has t1/2 around 3.5 hours. Venlafaxine is well absorbed per orally. An extended-release formulation of venlafaxine is available, facilitating once daily administration. The metabolite O-desmethyl venlafaxine (ODV) has a half-life of 9 hours. It is metabolized by hepatic cytochrome P450 (CYP) 2D6. Venlafaxine has no enzyme-inducing properties. Duloxetine has t1/2 of about 12 hours – it is extensively metabolized by hepatic enzymes CYP450 and highly protein bound. Trazodone and nefazodone undergo extensive hepatic metabolism, and one major metabolite is m-chlorophenylpiperazine which stimulates 5-HT receptors. Trazodone is readily absorbed and has a half-life of 5 to 9 hours. Trazodone is a weak inhibitor of serotonin reuptake and antagonist of serotonin 5-HT2A and 5-HT2C receptors. The active metabolite of trazodone is mchlorophenylpiperazine (mCPP) is 5-HT2C agonist with t1/2 around 14 hrs. mCPP can cause migraine, anxiety, and weight loss. Trazodone has an acute sedative effect, which is useful in the treatment of agitation, anxiety, and insomnia. Antianxiety effects of trazodone appear earlier than antidepressant effects. Trazodone can increase levels of digoxin and phenytoin and warfarin. CYP 3A4 inhibitors can increase mCPP by reducing its breakdown leading to an increase in side effects. Buspirone has a short half-life of 2-11 hours. Hence it is given three times daily. Buspirone has an active metabolite called 1-pyrimidinylpiperazine (1-PP) – which has some degree of activity

23 - Terms used to describe therapeutic effects of

Terms used to describe therapeutic effects of antidepressants

 compared to buspirone but achieves higher brain concentration in the brain. Buspirone acts as a partial agonist on serotonin 5-HT1A receptors – presynaptic agonism leads to inhibition of release of serotonin, with consequent antianxiety effects. Postsynaptic agonism leads to antidepressant activity. St John's wort: It acts via multiple monoamine reuptake inhibition. It is a CYP inducer and can interact with warfarin, OCPs and antiepileptics, decreasing their efficacy. Terms used to describe therapeutic effects of antidepressants

Mirtazapine reaches peak plasma concentrations within 2 hours; it binds to plasma proteins (85%) and has a bioavailability is approximately 50%, owing to extant first-pass metabolism. It follows first-order linear elimination kinetics over a dose range of 15 to 80mg. The elimination t ½ ranges from 20 to 40 hours. Metabolism is mediated by the CYP2D6 and CYP3A4; thus paroxetine and fluoxetine, which inhibit the CYP system, can increase plasma concentrations of mirtazapine by 1/5th to 1/3rd but usually there are no clinical consequences. Carbamazepine causes a 60% decrease in plasma concentrations. Mirtazapine has no inhibitory effects on CYP isoenzymes. Agomelatine undergoes extensive first-pass metabolism with a low bioavailability. It is extensively protein bound (95%) and has a half-life of 2.3 hours. It is mostly metabolized by CYP1A2 (90%) and CYP2C9 (10%).

•minimal or <25% decrease in baseline severity of sx non-response non-response •25-50% reduction in baseline severity (sx still evident) partial response partial response •>50% reduction, but still some sx evident partial remission partial remission

•no sx; returning to normal function (<6months from last episode) remission remission •return to fully sx state when in remission relapse relapse

•extended remission sustained for longer than 6-12 months recovery recovery

•onset of a new episode of depression when in recovery recurrence recurrence

24 - D. Mood stabilisers

D. Mood stabilisers

© SPMM Course D. Mood stabilisers Lithium is orally well absorbed but not metabolized in the liver; it is renally excreted. Lithium carbonate and citrate are not bioequivalent preparations; hence the careful prescribing practice is required. Lithium is rapidly and completely absorbed after oral administration. Lithium takes 45 days to achieve a steady state in healthy young males. It is not protein bound. Lithium's plasma half-life is around 18 hours initially but later after 1 year of chronic use increases to 36 hours. Lithium is excreted via the proximal tubules where sodium is also filtered. Hence, any loss of body sodium can increase lithium reabsorption as compensation in error leading to toxicity. Hence maintaining sodium homeostasis is important in patients on lithium therapy.

Agents increasing lithium levels Agents decreasing lithium levels Toxicity with normal levels ACE inhibitors Osmotic diuretics Carbamazepine – increased antithyroid effect and neurotoxicity Loop diuretics Caffeine Atracurium – increased neuromuscular blockade Fluoxetine Aminophylline Haloperidol, clozapine – increased neurotoxic effects NSAIDs Theobromine, Theophylline Calcium channel blockers – increased neurotoxicity Thiazides Carbonic anhydrase inhibitors Metronidazole – increased neurotoxicity Valproate is available as semisodium compound (divalproex) and as sodium salt of the valproic acid. Divalproex consists of half valproic acid and half sodium valproate. Semisodium compound is somewhat better tolerated. Valproate is well absorbed, with a bioavailability close to 100%. It is quite hydrophilic, with a low volume of distribution. Valproate has t1/2 of 9 to 16 hours and is highly (90%) protein bound. This binding is saturable so that at higher doses a greater percentage of the drug may be in the free form. At higher doses, the increased free fraction may remain in the plasma compartment (rather than escaping into the tissues) and thus be cleared by the liver. This may yield ‘‘sublinear’’ kinetics so that with higher plasma concentrations, greater increases in dose may be required to yield the desired increase in plasma level (Graves, 1995). Binding interactions occur so that VPA can increase free diazepam. Carbamazepine has a tricyclic structure and undergoes hepatic metabolism. It has an erratic absorption and a bioavailability of about 80%. It is about 75% bound to plasma proteins. Carbamazepine induces its own breakdown. Before autoinduction of the epoxide pathway (via induction of CYP3A3/4), the half-life of CBZ is about 24 hr, and the clearance is about 25 mL/ min. After autoinduction (2 to 4 weeks into therapy), the half-life falls to about 8 hr, and clearance rises

25 - E. Typical antipsychotics

E. Typical antipsychotics:

© SPMM Course to about 75mL/min. The active CBZ-10,11-epoxide (CBZ-E) metabolite has a half-life of about 6 hr. The conventional form needs to be given in multiple divided doses while extended release can be given twice a day. A steady-state plasma concentration of 4 to 12 ng/ml is therapeutic. Verapamil and diltiazem can increase carbamazepine levels and cause clinical toxicity, but this does not occur with other calcium channel blockers nifedipine and nimodipine. Also, carbamazepine decreases nimodipine and felodipine levels. Valproate inhibits epoxide hydrolase, increasing the plasma carbamazepine-epoxide levels, often without altering total plasma carbamazepine levels. Valproate also displaces carbamazepine from plasma proteins, increasing free carbamazepine. Patients can have neurotoxicity due to elevated plasma carbamazepine - epoxide levels in spite of normal plasma total carbamazepine levels. Carbamazepine reduces warfarin efficacy. Erythromycin can produce carbamazepine toxicity. Gabapentin has no significant mood stabilizing effects though it is useful to treat anxiety in bipolar patients. It is not bound to plasma proteins, is not metabolized and is 100% excreted in the urine. Gabapentin has a half-life of about 6 hrs (4 to 9) and a clearance similar to that of creatinine (120 ml/min, similar to the glomerular filtration rate), so that increased physical activity may increase GBP clearance. The bioavailability of gabapentin is not dose-proportional; it decreases as the dose increases. When gabapentin is given in 3 divided doses, at 900 mg per day the bioavailability is approximately 60%, but at 2400 mg per day it drops to 34% and at 4800 mg per day it is only 27%. Gabapentin does not induce or inhibit hepatic metabolism. It is not bound to plasma proteins and displays linear pharmacokinetics at usual dosages. Consequently, drugdrug interactions are not an issue with gabapentin. It is usually given three times a day. In patients with normal renal function, steady state is reached after 1 to 2 days of taking a stable dose of gabapentin. The dose that a patient takes should not be increased until steady state has been reached (or some time later) so that the effects of the previous dosage can be assessed.

Lamotrigine achieves peak concentrations within about 3 hours postdose with an oral bioavailability of about 98%. It is 56% plasma protein bound with t½ of 24 to 36 hours. Enzymeinducing drugs (phenytoin, phenobarbital or carbamazepine) reduce the half-life of lamotrigine whereas valproate increases the half-life. Lamotrigine itself does not affect CYP450 in most cases but increases levels of carbamazepine-10,11-epoxide, the metabolite of carbamazepine. E. Typical antipsychotics: Typical antipsychotics are well absorbed when administered both orally or parenterally. Peak plasma levels are reached in 30 min after intramuscular injection and 1 to 4 h after oral injection. Steady state is achieved in 3 to 5 days. The half-life for elimination is in the range of 10 to 30 h.

26 - Depot atypicals

Depot atypicals

© SPMM Course Lipid storage and brain retention are significant; depot forms of haloperidol or fluphenazine may persist for 1 to 3 months. Thioridazine has an active metabolite mesoridazine, and loxapine produces 7hydroxyloxapine. Typical antipsychotics are mainly substrates of CYP1A or CYP2D6, or both and can inhibit 2D6. Chlorpromazine has highly variable absorption rate (around 37% bioavailability) for different persons and has nearly 100s of metabolites. Antacids can decrease absorption of phenothiazines; this leads to reduced plasma concentration and therapeutic effect of phenothiazines Interactions: Enzyme inducers Carbamazepine, phenytoin, ethambutol, barbiturates - reduce antipsychotic levels. Clearance inhibitors SSRIs, TCAs, cimetidine, erythromycin, ciprofloxacin, and ketoconazole can inhibit metabolism – increase antipsychotic levels. Depot atypicals Depot drug Preparation Kinetics Flupenthixol decanoate Esterified in coconut oil Peak levels 3–7 days post IM. Apparent half-life of 17 days Fluphenazine decanoate Esterified in sesame oil Peak levels are 24h post-IM. The apparent half-life of 7-14 days. Smoking reduces levels Haloperidol decanoate Esterified in sesame oil Peak levels 7 days post IM. The apparent half-life of 3 weeks. Smoking reduces levels Perphenazine decanoate Esterified in sesame oil Peak levels 1-7 days post IM. Apparent half-life of 2 weeks Pipotiazine palmitate Esterified in coconut oil Peak levels 1-2 weeks post IM. Apparent half-life of 2 weeks Zuclopenthixol decanoate Esterified in coconut oil. Contrast this depot from zuclopenthixol acetate preparation used for rapid tranquillisation Peak levels 1 week post IM. The apparent half-life of 7-20 days.

27 - F. Atypical antipsychotics

F. Atypical antipsychotics:

© SPMM Course F. Atypical antipsychotics: All atypicals are orally well absorbed. Drug Half life Chlorpromazine equivalents (100mg/day CPZ or 2mg Haloperidol) Risperidone 15hrs 2 mg/day Clozapine 16hrs 50 mg/day Quetiapine 6hrs 75 mg/day Olanzapine 30 hrs 5mg/day Aripiprazole 90hrs 7.5 mg/day From Woods SW. J Clin Psychiatry. 2003 Jun;64(6):663-7. Risperidone undergoes extensive first-pass hepatic metabolism to 9-hydroxyrisperidone, an active metabolite. CYP 2D6 catalyzes hydroxylation of risperidone to 9-hydroxyrisperidone. Risperidone is 90% protein bound; its metabolite is 77% bound. Paliperidone is the major active metabolite of risperidone (9-OH). It is a potent 5HT2 blocker apart from partially blocking D2 receptors. Its efficacy and side effects are the same as risperidone. It comes in a sustained release preparation similar to methylphenidate XL wherein gradual water absorption delivers the drug molecules slowly. Once daily administration is sufficient; there is no need to titrate the dose. Quetiapine has a shorter half-life of 6 to 12 hours, and multiple daily dosing is required; though with longer use, as pharmacodynamic receptor action has longer duration once daily dosing may be sufficient. Aripiprazole and its active metabolite dihydro aripiprazole have exceptionally long half-lives of 75 (nearly 3 days) and 94 hours respectively, and steady state concentrations are achieved after 14 days. Aripiprazole is metabolized by CYP 3A4 and CYP 2D6 enzymes. It is highly (99%) protein bound. Atypical depots o Aripiprazole depot: no need to refrigerate; once monthly; gluteal administration only; only 2 weeks oral dose tapering needed. o Paliperidone depot does not need oral tapering; once monthly; no need to refrigerate; primarily renal excretion. o Risperidone microspheres are used in depot preparations; they release the active drug at therapeutic levels only 3 weeks after gluteal or deltoid injection. Long-acting risperidone should DEPOT KINETICS

Some long-acting injections (such as risperidone, pipotiazine) show delayed as well as prolonged release. These require adeqaute cover with oral antipsychotics after first dose is administered.

Steady-state plasma levels are often delayed for 2–3 months. During this time, plasma levels are likely to rise substantially even when dosages are not increased, thus producing dose-dependent side effects.

Dose–response relationships are not clearly understood for most LAIs. Test doses are often used but may not be sufficient to assess tolerability in longer-term use.

28 - G. Antidementia drugs

G. Antidementia drugs:

29 - H. Other drugs

H. Other drugs:

© SPMM Course be supplemented with oral risperidone for 3 weeks. Requires refrigeration as it is granular, not ester-based. o Olanzapine depot is a crystalline salt composed of olanzapine and pamoic acid with a half-life of 30 days and steady state reached at 12 weeks. Oral supplementation of olanzapine is not required.

G. Antidementia drugs: Tacrine is poorly absorbed with short t1/2. It is metabolized by CYP 1A2 hepatic enzymes. Donepezil has an oral bioavailability around 100%, with linear pharmacokinetics. The drug reaches steady state in about two weeks. Its t1/2 is long - 70 hours, enabling once-daily dosing. Donepezil is extensively bound to plasma proteins, and while a part is excreted unchanged the other is extensively metabolized by CYP 2D6 and 3A4 hepatic enzymes to active and inactive metabolites. The oral bioavailability of rivastigmine is about 40% up to a dose of 3 mg, after which this increases non-linearly. The t1/2 of rivastigmine is just 1.5 hours. The drug undergoes hydrolysis by cholinesterase itself, with minimal hepatic involvement. It is excreted almost entirely in the urine as the sulfate of the decarbamylated metabolite. The oral bioavailability of galantamine is about 90%; it has low protein binding (18%). It undergoes metabolism by CYP2D6 and CYP3A4 enzymes while one-third is excreted unchanged in the urine. Memantine has low protein binding (45%) and a long half-life of 60–80 hours. Approximately half the dose of memantine is excreted unchanged in the urine; the remainder undergoes hepatic conversion to inactive metabolites. Drugs that alkalinize the urine (e.g., carbonic anhydrase inhibitors) reduce the clearance of memantine.

H. Other drugs: Methylphenidate is absorbed well orally and achieves peak plasma levels in 1-2hrs with t1/2 2-3 hrs necessitating multiple daily dosing. This is obviated by sustained release preparation that can be given once daily. Modafinil reaches peak plasma concentrations in 2 to 4 hours and has a half-life of 15 hours. Atomoxetine has a t1/2 5 hours and is metabolized by the CYP 2D6 pathway. SSRIs may raise atomoxetine levels.

30 - Benzodiazepines

Benzodiazepines:

© SPMM Course Benzodiazepines: Drug Duration of action Effect Diazepam, chlordiazepoxide, clonazepam, flurazepam Long-acting Can have more than 200hrs t1/2 in genetically slow metabolizers. Also, toxicity can take 1 – 2 weeks to be evident when higher doses are given. Lorazepam, oxazepam, temazepam, Alprazolam Intermediate or short acting Severe withdrawal phenomena but the lesser risk of daytime impairment and daytime sedation. Rebound insomnia and anterograde amnesia more often seen in short t1/2. Lorazepam t1/2 15 hours; temazepam somewhat shorter – 10 hours. Triazolam Very short acting Used in anaesthesia Diazepam is well absorbed orally - oral bioavailability nearly 100%. Peak plasma concentration is reached in 15 - 90 minutes after oral administration; has a second peak at 6 - 12 hours due to enterohepatic recirculation. Diazepam is widely distributed - highly lipophilic (so CSF concentration more or less equals plasma concentration) with 95-99% plasma protein binding. It has a slow elimination t½ 30 h (ranges between 20 - 100 h). It also takes a long time to reach steady state (5 -6 days). It gets extensively metabolized in the liver with 3 active metabolites: Nordiazepam or desmethyldiazepam (principal metabolite – could accumulate due to long t1/2), Oxazepam and Temazepam. “Z”-hypnotics Zolpidem, zaleplon, and eszopiclone are quickly and completely absorbed when given orally. Food may delay absorption by an hour. Lack of active metabolites of zolpidem, zaleplon, and eszopiclone avoid the accumulation and hang over effects. NICE's appraisal committee concluded that no compelling evidence of a clinically useful difference exists between the Z-drugs and short-acting benzodiazepines in terms of effectiveness, adverse effects, or potential for misuse or dependence. But this is controversial. Z HYPNOTICS

Zopiclone / Eszopiclone (enantiaomer) Onset within 45 mins; half-life 4 to 5 hours (acts up to 8 hours) Benzodiazepine receptor selective for alpha 1 subunit; eszopiclone is the only Z-hypnotic indicated for sleep maintenance therapy (US FDA) – others are used for initiation problems. Zaleplon Onset within 30 mins; half-life 1 to 2 hours (acts up to 4 hours). Shorter half-life and quick onset – makes it suitable for those with sleep initiation problems; not so helpful for the maintenance of sleep. Zolpidem Onset within 30 mins; half-life 1 to 4 hours (acts up to 6 hours). Shorter half-life and quick onset – makes it suitable for those with sleep initiation problems; not so helpful for the maintenance of sleep. Less hangover effect.

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