Drug interactions associated with distribution biology essay

Science, Biology

Polypharmacy is essential in the treatment of tuberculosis, especially in DR-TB. Several drugs are used in order to prevent resistance to certain susceptible drugs. However with the use of multiple drugs, the risk for potential drug-drug interactions increases. In addition to DR-TB, it is common to treat several other concurrent health conditions such as HIV/AIDS or non-communicable diseases such as diabetes or hypertension increasing the potential for drug interactions. Drug interactions are defined as a modification of the effect of a drug when co-administered with another drug. This effect may enhance or reduce the action of either drug which can result in possible over- or under-dosing and lead to a lack of drug efficacy or toxicity 63. Drug interactions can be divided in three groups: pharmacodynamic, pharmacokinetic or combined interactions 64, 65, 66. Pharmacodynamic interactions occur when the effect of a drug is changed by another drug at the site of actions, without changing the plasma concentrations of either drug. It arises from an antagonistic (drug effect is decreased), additive or synergistic effect (drug effect is increased), and may alter the pharmacological response, such as toxicity and efficacy. Antagonism of antimicrobial agents occurs when the combined killing effect or inhibitory effects of two or more antimicrobial drugs are significantly less than the activity of individual drugs. For example, rifampin can antagonise vancomycin action against staphylococci 67. Additive/synergistic effect occurs when the activity or toxicity of a drug is enhanced due to the presence of another drug with a similar pharmacological action. An example is the great delay in development of resistance to streptomycin when co-administered with PAS 68 .

Pharmacokinetic interactions

Pharmacokinetic interactions are the most common interactions 66. Interactions of this kind may either alter the drug plasma concentration and/or its tissue distribution, consequently affecting the concentration or availability of the drug to the target site. These particular interactions occur when absorption, distribution, metabolism and/or excretion of a drug is altered 63, 64, 69.

Drug interactions associated with absorption

Absorption is the movement of compounds into the circulatory system from site of administration (e. g. gastrointestinal, skin, subcutaneous site, nasal/pulmonary sites, and muscles). The absorption of drugs can be altered by several physiological factors such as intestinal motility, gastric emptying time, gastric pH, transport, intestinal metabolism, and the presence of gastrointestinal disease 69. In addition, concomitant substances such as drugs, can also affect the drug absorption by having a large surface area upon which the drug can be absorbed; alternating the gastric pH; binding or chelating; altering gastrointestinal motility or affecting the transport proteins 61, 63, 65. The most common interaction affecting drug absorption is chelating, which is the binding of metal ions or other substances to the drugs in the gastrointestinal tract 61. For example, PAS absorption is decrease due to the binding of divalent cations (iron, magnesium and calcium) to PAS molecules 70.

Drug interactions associated with distribution

The important mechanisms by which drug interactions can alter drug distribution are the competition for protein binding; displacement from tissue binding sites and alterations of the local tissue barriers 65. The competition of the drugs for protein binding affects the degree of the free drug (pharmacologically active form). Theoretically the plasma concentration of the free drug will increase, but in this case the concentration is maintained due to an increase in free drug elimination 63. Therefore, protein binding displacements are usually considered to be of less clinical significance 69, 71.

Drug interactions associated with drug metabolism

Co-administered drugs may directly or indirectly alter the concentration and activity of another drug by inhibiting or inducing the enzyme activity responsible for the metabolism of the drug. Several clinically important drug interactions have been reported. Some drug interactions can be beneficial, by increasing the activity or bio variability of an effective drug. However, this can also result in high drug levels, which can be toxic and life-threatening 45, 61. For example, co-administration of PAS and INH can be beneficial, but can also result in severe neurotoxicity and/or hepatotoxicity. PAS inhibits the acetylation of INH, consequently increasing the INH levels 72. Both phase I and II enzyme activities can be altered by their substrate or other compounds. Even the transporters such as P-pg are susceptible to drug induction or inhibition 61. The CYP enzyme group consisted out of 12 isoforms and are the major enzyme group involved in the drug metabolism

73. Several anti-TB and ARV drugs are metabolised by the CYP group and therefore are susceptible to drug interactions. Some of these drugs are also inducers and inhibitors of the CYP group, which complicates the design of regimens for DR-TB subjects that are also co-infected by HIV/AIDS 61. Alterations in the plasma levels of an antimicrobial or antiretroviral agent can cause sub-therapeutic drug concentrations, which can result in developing of pathogen drug resistance. In risk patients the plasma levels should be monitored to ensure that toxicity is reduced and the MIC is exceeded 45. The Clinical Pharmacology Division of Indiana University summarised the clinically relevant drug interactions of the CYPs. This can be found at: http://medicine. iupui. edu/clinpharm/DDIs/ClinicalTable. aspx.

Combined toxicity

The use of combinations of drugs for a prolonged period, as in TB treatment, often results in drug toxicity 38. Several drugs have similar toxicities which can lead to increased toxicity when co-administered (shared toxicity). In combining these drugs in a regimen, the potential of organ damage is increased. For example, ethionamide and PAS have toxic effects on the thyroid. These drugs are often prescribed in a regimen and long term use can lead to hypothyroidism. In some cases, a drug(s) can enhance the organ toxicity of another drug, even if the enhancing drug has no intrinsic toxicity effect on the organ 65. DR-TB patients often develop hepatotoxicity and renal dysfunction since multiple drugs including more toxic second-line drugs, are prescribed to these patients. These drugs are often metabolised in

the liver and excreted by the kidneys. Therefore, monitoring of liver and kidney functions are important in these patients 10.

Para-aminosalicylic acid (PAS)

Para-aminosalicylic acid (PAS, p-aminosalicylic acid, 4-aminosalicylic acid, 4-ASA), is a second-line anti-TB agent that has been found to be effective in preventing drug-resistance and has formed part of the standard treatment for TB for several decades6. However, due to its significant gastrointestinal intolerance, it was replaced by ethambutol, an equivalent drug in terms of efficacy, but with a better tolerability profile11. Due to the relatively low use of PAS over the last three decades, most isolates of TB remained susceptible to this drug 11; 14. Therefore, PAS was brought back in clinical use for the management of MDR-TB and later XDR-TB. A new granular slow-release PAS formulation (GSR-PAS) with fewer gastrointestinal adverse effects was developed which supported the use of PAS as one of the principal second-line drugs in M/XDR-TB treatments8. Currently, the GSR-PAS (PASER® granules, Para-aminosalicylic Acid Delayed-Release Granules-JACOBUS Pharmaceutical Company Inc., Princeton, NJ 08540) is the only form available in most countries including South Africa.

Indications

GSR-PAS (PASER) is classified as a tuberculostatic agent. It is mainly used to treat drug resistant tuberculosis (M/XDR-TB) or in cases where therapy with INH and rifampicin is not possible due to intolerance and/or a combination of resistance. PAS is prescribed together with other anti-TB agents to which the

specific pathogen strain of the individual patient is expected to be susceptible 12.

Mechanism of action

PAS is a highly specific bacteriostatic agent against M. tuberculosis and valuable in preventing resistance to other drugs such as INH and streptomycin 9, 12. It has a molecular weight (Mw) of 153. 14 (Figure 3) and inhibits the growth of M. tuberculosis in vitro at a concentration of 1-2 µg/ml 2. The mechanism of PAS is still unclear, but it has an influence on the folate pathway of bacteria. Bacteria use folate derivatives as cofactors in the biosynthesis of important molecules such as amino acids, thymidylate, pyrimidines and purines2. Bacteria are unable to use external sources of folic acid; therefore a deficiency in these important molecules inhibits bacterial growth. PAS is structurally similar to sulphonamides, which is an analogue of para-amino benzoic acid (PABA) (Figure 4). PABA is a substrate for dihydropteroate synthase (DHPS), which is an important enzyme in folate biosynthesis of bacteria 8; 74. PAS has therefore been considered to interfere with bacterial DHPS by functioning as a competitive inhibitor (competing with PABA). However, PAS inhibitory activity of folP1 (encodes DHPS) appears to be poor in vitro 75 (Figure 5). A mutation in the thy A gene of clinical PAS-resistant isolates (PASr) was identified and found to be related to a mechanism for drug resistance to PAS 8 (Figure 5). The thy A gene encodes thymidylate synthase A, which is required for thymine biosynthesis in the bacterial folate pathway. This finding implies that PAS acts as a folate antagonist which inhibits folic acid synthesis, but without potentiating anti-

folic compounds 8. Description: p-Aminosalicylic-acid--2DFigure Structural formula of PASDescription: sulfaFigure Structural formula of sulphonamides (left) and PABA (right)A recent study 76 investigated the mechanism of action of PAS and reported that PAS, in contrast to the initial speculation, serves as a replacement substrate for DHPS and not as a competitive inhibitor. The PAS metabolites and the subsequent steps in folate metabolism inhibit the enzymes and compete with their substrates. According to the authors, PAS is a pro-drug that blocks the growth of M. tuberculosis when its active forms are generated by enzymes in the pathway, which functions as a poison to the bacteria. PAS is also thought to inhibit the synthesis of the cell wall component, mycobactin, which decreases iron uptake of the bacteria 2, 13. dTMP5, 10 MTHFdUMPDHFTHFDNA SYNTHESIS5, 10 MTHFTHFFADthyXdfrADHPDihydropteridine + PABAfol P1/P2fol CthyAFigure Postulated mechanism of the action of PAS [Modified from Rengarajan8 and Mathys 74

Pharmacokinetics of PAS

With GSR-PAS preparation, the PAS is encapsulated in an acid resistant enteric coating to prevent early breakdown in the stomach. Once the GSR-PAS formulation reaches the more alkaline smaller intestine, it dissolves and is readily absorbed. It is therefore recommended to be taken with an acidic beverage or food, enhancing the delayed-release properties of the GSR-PAS 12. The rate of drug absorption depends on the rate of release from the formulation 35. With the controlled-release formula, the drug is released at a

constant rate over a longer period and fluctuations in the drug plasma concentrations are reduced in comparison to the immediate-release formulations such as the sodium-PAS. PAS is well absorbed from the gastrointestinal tract. A plasma concentration of 2 µg/ml is reached within 2 hours after a 4 g GSR-PAS dose. In a study in healthy volunteers a mean maximum concentration (Cmax) of 20 µg/ml (range: 9-35 µg/ml) with a mean peak time of 6 hours (range: 1. 5-24 hours) was achieved after a single 4 g GSR-PAS dose 12, 77,. In a study in twelve MDR-TB patients a mean Cmax of 51. 3 µg/ml (range: 25. 8-93. 1 µg/ml) and a mean peak time of 5. 2 hours (range: 0-8 hours) was achieved after a 4 g GSR-PAS dose 78. PAS is 50-60% protein bound and is well distributed throughout the body. It is only detected in the cerebrospinal fluid (CSF) if the meninges are inflamed (10-50% of the plasma levels) 2, 12, 77. PAS has a plasma half-life (t½) of 1-2 hours. It is rapidly metabolised in the intestinal mucosa and liver through acetylation by N-acetyltransferase 1 (NAT1), in which more than 50-70% of the drug is acetylated to N-acetyl-para-aminosalicylic acid (APAS) 2, 11, 77, 79. Twenty five present (25%) of the absorbed PAS dose is conjugated to form p-aminosalicyluric acid (PASU) 79. Although PAS is the active form, it is reported that PASU has a 75% inhibitory effect in comparison to APAS which shows little, if any tuberculostatic affect 80. The drug and its metabolites are excreted by tubular secretion and glomerular filtration. Approximately 80% of the drug is excreted in the urine, with about 50% is in the acetylated form. PAS plasma concentrations are not significantly changed by hepatic or renal insufficiency, but with severe renal insufficiency the PAS and its metabolite will accumulate 77.

PAS dosing regimens

The current prescription for GSR-PAS is 8-12 g in divided doses10. Since PAS is bacteriostatic, several daily doses are recommended in order to maintain the concentration of PAS above the MIC of 1 µg/ml 76, 81. It was noted that divided doses reduce the intolerance to PAS 81. However, it has been reported in several early studies that once-daily dosing of PAS was better tolerated than multiple dosing 80, 82, 83. Early studies experimented with various doses of PAS in combination with other drugs such as INH. A study 84 in 1957 found that dosage of 10-12 mg/kg PAS in divided doses accompanied by INH provided better results than 5-6 mg/kg PAS which was also accompanied by INH, implying that higher concentrations of PAS will enhance the drug activity. Clinical 82 and animal 85 studies have investigated the possibility of decreasing the frequency of PAS administration to a single daily dose. Karlson and Carr 85 experimented with a 125 mg single daily sodium PAS dose in guinea pigs and reported that the once-daily dose was as effective as the twice-daily dose, despite the fact that PAS is rapidly absorbed and excreted. Bridge and Carr 82 investigated the effect of a single 5 g dose of PAS combined with 150 mg of INH given twice-daily to 70 subjects. They compared these results to 192 subjects that followed a regimen of 3 g PAS three times a day. In the 5 g daily group negative sputum cultures were reported in nine subjects (12. 9%) after two months and in five subjects (7. 1%) after four months. Thirty one patients (16. 1%) of the 3 g PAS three times daily group discontinued the PAS treatment due to intolerance, while only three subjects (4%) who used the single 5 g dose developed intolerance. According to Bridge and Carr 82, the

once-daily dosing was not only better tolerated as multiple doses, but equally effective. Bang et al. 86 investigated various PAS preparations in single and divided doses and concluded that divided doses of PAS give lower PAS concentrations. Although multiple doses still maintain the PAS concentration above the MIC, a single daily dose is considered to be a more rational treatment because it increases the free PAS levels in the plasma. PAS was previously available as potassium, sodium or calcium salts and as an acid preparation. Sodium salt preparations, which are still marketed, are completely and rapidly absorbed, and a peak is seen within 90-120 minutes after drug administration 13, 79. Since PAS has a short half-life, more frequent dosing is required, especially when using the salt formulations. The salt formulations are not as well tolerated as the GSR-PAS preparation. Not only is the GSR-PAS preparation better tolerated, but maximum concentrations of PAS are seen after 4-6 hours 12, 13. Therefore, the drug is longer present in the systemic circulation, and less frequent dosing is needed to maintain the PAS concentration above the MIC. Only one study 81 investigated different dosing strategies with the GSR-PAS preparation. The investigators compared a single 4 g once-daily and 4 g twice-daily GSR-PAS dose to determine if a once-daily dosing regimen will be sufficient. PAS concentrations were maintained above the MIC throughout the twice-daily dosing interval, but not with the once-daily regimen. The granules were generally well tolerated in this study; however a few subjects reported nausea and gastrointestinal discomfort.

Resistance

M. tuberculosis isolates have developed resistance to various antibiotics and antimicrobial chemotherapy agents, including PAS 8. However, resistance to PAS has been reported to be less common than to other antibiotics. Since PAS is a bacteriostatic agent, it is important to maintain the plasma concentration above the minimum inhibitory concentration (MIC) in order to inhibit bacteria growth and the development of resistance as discussed above. The MIC of PAS is different among the various multi-drug resistant strains. The MIC for M. tuberculosis in 7H11 agar was less than 1. 0 µg/ml for nine strains including three multidrug resistant strains tested, but 4 and 8 µg/ml was measured for two other multidrug resistant strains. Little dose response was seen with the 90% inhibition in 7H12 broth (Bactec), but the MIC was interpreted as being less than or equal to 0. 12-0. 25 µg/ml for eight strains12. Therefore, a MIC of 1 µg/ml can be seen as the natural MIC of M. tuberculosis for PAS.

Tolerability and safety

The most common side effects of PAS are hypothyroidism and gastrointestinal intolerance which includes nausea, vomiting, abdominal pain, diarrhoea and anorexia 12, 13, 77. Prolong administration of PAS often results in hypothyroidism and is increased with the co-administration of ethionamide. Hepatitis has been reported in 0. 3-0. 5% of patients receiving PAS. In a review of 7, 492 patients treated with PAS, 0. 5% developed hepatitis12. This condition emerges within three months of therapy, is often associated with rash and fever, and less frequently with anorexia, nausea or

diarrhoea12. In a few days or weeks, 90% of the patients show symptoms of jaundice. Hepatitis is usually accompanied by hepatomegaly, and often by leucocytosis, lymphadenopathy, and eosinophilia 87Other rare side effects include leukopenia, hypoprothrombinemia, agranulocytosis, goitre, thrombocytopenia, Coomb's positive haemolytic anaemia, and lupus-like syndrome. The side effects of PAS are summarised in Table 212, 87. More information regarding the side effects is available in Appendix A: PASER package insert. Table Reported side effects of PAS

Disorder

Side effects

Blood dyscrasias and lymphatic systems disordersLeucopoenia, agranulocytosis, thrombocytopenia, eosinophilia, Coombs positive haemolytic anaemia may develop in patients with G6PD deficiencyCardiovascularPericarditisCoagulopathyHypoprothrombinaemia has been reported. Dermatological side effectsSkin rash, erythematousmaculopapular and pruritic lesionsExfoliative dermatitisDysglycaemiaHypoglycaemia has been reportedTable 2 Reported side effects of PASDisorderSide effectsEndocrine effectsHypothyroidism and goitre relatively common' Flu-like' syndromeLöffler's syndrome, an infectious mononucleosis-or lymphoma-like syndrome, has been reportedGastrointestinal disordersNausea, vomiting, abdominal painDiarrhoeaRarely, associated with peptic ulcers gastric haemorrhageGeneral disordersFever; thrombocytopeniaHepatobiliary disordersJaundice, hepatitisHypersensitivityLymphadenopathy, leucocytosis,

conjunctivitis, headache, joint pain, vasculitis, Metabolism and nutrition disordersMalabsorption syndrome, including: steatorrhea, an abnormal small bowel pattern on X-ray, villus atrophy, reduced cholesterol, D-xylose and iron absorption. Malabsorption of vitamin B12, folate, iron and lipids may results in clinically important erythrocyte abnormalitiesNervous system disordersOptic neuritis, encephalopathy, psychosisRenal and urinary disordersHypocalcaemiaRespiratory, thoracic andmediastinal disordersEosinophilic pneumoniaVascular disordersVasculitis

Pharmacogenetics of PAS

The N-acetyltransferase 1 (NAT1) is the only gene that has been studied in the pharmacogenetics of PAS, since it is predominantly involved in PAS metabolism. 2, 79, 88. N-acetyltransferase (NAT) enzymes are involved in the metabolism of various drugs such as PAS, INH and dapsone. Belonging to the phase II enzymes, they are important in the detoxification of harmful chemicals and in deactivation and elimination of certain drugs. This group of enzymes catalyse the N-acetylation and O-acetylation of heterocyclic amine, aromatic amine and various aryl amine and hydrazine drugs15, 89. Both genes of the isoforms (NAT1 and NAT2) are located on the short arm of chromosome 8 (NAT18p21. 3-23. 1 and NAT2 8p21. 3-23. 1 and 8p22). These genes are 87% similar on the nucleotide level, which translates to an 81% homology at an amino acid level 90. Both NAT1 and NAT2 are known to be polymorphic. NAT2 is more extensively studied than NAT1, due to its clinical relevance in the metabolism of INH 15. Initially it has been believed that NAT1 is monomorphic, with no distinct differences in its phenotype or

genetics91. However, it was soon discovered that this assumption is incorrect. Studies have identified NAT1 allelic variants that are associated with increased enzyme activity92. Several oncology studies 89, 93 have also reported the association of NAT1 polymorphisms with cancer development, especially bladder and breast cancers. It seems that NAT1 and NAT2 polymorphisms can interact with each other and increase or decrease the risk for cancer development 93. Several distinct allelic polymorphisms at the NAT1 locus cause a large variability in the human population 58. So far, 26 alleles have been described 94. The NAT1*3, NAT1*4, NAT1*5, NAT1*10 and NAT1*11 are the most common alleles. The allelic variations are single polymorphisms or a combination of a number of nucleotide substitutions and insertions/deletions, which will increase (e. g. NAT1*10, NAT1*21, NAT1*24 and NAT1*25) or decrease (NAT1*14, NAT1*15, NAT1*17, NAT1*19 and NAT1*22) or have no effect (e. g. NAT1*11, NAT1*20 and NAT1*23) on acetylation activity with respect to enzyme encoded by the NAT1*4 (wild type[a]) 20, 94, 95. The NAT1*11 allele has been considered as a rapid allele in Caucasians and Black South Africans 96. NAT1*4 has been found in higher frequency among Caucasian populations than in Asian and African populations, whilst the opposite may be true for the NAT1*10 15, 95. The NAT1*3 allele is found in a higher frequency among Chinese than in Caucasian or African Americans 97.

Drug interactions of PAS

Only a few drug interactions with PAS have been described. One of the most important interactions is the decrease in INH acetylation. PAS administered

as a 12 g dose has been reported to reduce the acetylation of INH by 20%, especially in rapid acetylators in the population 98. PAS reduces the absorption of vitamin B12, folate, lipids, rifampicin, digoxin and iron. PAS (5 g) can reduce the absorption of vitamin B12 by 55%, which can lead to erythrocyte abnormalities 12, 87,. So far no interactions have been described between PAS and any of ARVs14. Table 3 summarises the known drug-drug interactions between PAS and other medications. Table Drug-drug interactions between PAS and other medications

Concomitant drugs

Effect

Angiotensin convertingenzyme inhibitorsPAS may reduce the antihypertensive effectAzathioprinePAS may increase the toxicityCarbonic anhydrase inhibitorsPotentiate adverse events of both PAS and the inhibitorsCorticosteroidsIncrease the adverse events of corticosteroidsDigoxinPAS decreases absorption with 20%Table 3 Drug-drug interactions between PAS and other medications

Concomitant drugs

Effect

DiphenhydramineImpaired absorption of PASEthionamidePotentially increased risk of hepatotoxicityFolate, lipids, iron. PAS reduces the absorption of folate, lipids, ironINHInhibited acetylation of INH and may lead or increase concentrationsLoop diureticsPAS may reduce the effect of loop diuretics, and the loop diuretics can increase the serum levels of PASMercaptopurinePAS may increase the toxicityMethotrexatePAS may

increase toxicityNon-selective NSAIDS (except diclofenac)Increase adverse effects of PASOral anticoagulants, thrombolytics or salicylatesPAS may increase the risk of bleedingProbenecidCompetitive excretion: increased PAS levelsRifampicinPAS reduces the absorption of rifampicinSulfonylureaPAS may increase the hypoglycaemic effectSulindacPAS may decrease the serum concentrationVitamin B12PAS decrease absorption of vitamin B12Systemic corticosteroidsIncrease the number and severity of adverse effects, especially gastrointestinalThioguaninePAS may increase the toxicityTolmetinPAS may increase the risk of GI bleedingTreprostinilPAS may increase the risk of bleedingAdapted from http://www. drugbank. ca/drugs/DB00233, Mllleron 87, Arbex et al. 13