Zidovudine for the prevention of hiv transmission

Introduction

Zidovudine is an antiretroviral drug which is a ‘ nucleoside reverse transcriptase inhibitor’; it is used as treatment with other antiretroviral drugs against the Human Immunodeficiency Virus. Additionally, zidovudine can be utilised as a means of reducing the risk of transfer of HIV from a pregnant woman to her child. Furthermore, zidovudine is used in ‘ post exposure prophylaxis’ in order to lower the chance of being infected with HIV in people who have been ‘ exposed’ to the virus. (AHFS Drug Information, n. d.).

Name Of Drug, Structure, Formula and Functional Groups

Zidovudine is also known as ‘ azidothymidine’ and, in short, ‘ AZT’ (Joint Formulary Committee, 2010). The molecular formula of the compound is C10H13N5O4 (The Merck Index, n. d.) and zidovudine has a molecular weight of 267. 25, as calculated using the ISIS ChemDraw package (Cambridge Soft, n. d.). Analysing the compound shows that zidovudine is made up of a thymine group bonded to a 2′, 3′-dideoxyribose group with an attached azide group. Therefore the systematic name of zidovudine is 3′-azido-2′, 3′-dideoxythymidine (The Merck Index, n. d.), as the oxygen of the hydroxyl group on the 3′ carbon of the ribose ring has been removed, giving 3′-deoxyribose, and has been replaced with an azide group and the oxygen on the 2′ carbon has also been removed.

The azide group on the ribose ring is the reason why zidovudine acts as a ‘ nucleoside reverse transcriptase inhibitor’ (AHFS Drug Information, n. d.). In order for zidovudine to carry out its role, it must be ‘ phosphorylated’ by an enzyme called ‘ thymidine kinase’; this is due to the fact that reverse

transcriptase includes the ‘ triphosphates’ produced into the HIV DNA chain being formed during HIV replication. Consequently, after the triphosphate has been included, ‘ 5’, 3′-phosphodiester bonding’ in the DNA chain is not possible, because of azide group in the triphosphate, and therefore DNA formation cannot continue (Foye et al, 2008).

Formulations and Packaging

The generic form of zidovudine is available as ‘ hard capsules’ (Electronic Medicines Compendium, n. d.) in two strengths of 100mg and 250mg (Joint Formulary Committee, 2010). Both strengths are packaged in ‘ foil blister packs’ and plastic bottles and need to be kept in these; they have an expiry date of 2 years from the date of manufacture (Electronic Medicines Compendium, n. d.).

Zidovudine is also available under the brand name of ‘ Retrovir®’ in the form of capsules, oral solution and injection solution (Joint Formulary Committee, 2010). All of the ‘ Retrovir®’ formulations need to be kept below 30 degrees and in their original outer boxes (Electronic Medicines Compendium, n. d.).

The capsules are ‘ hard capsules’ (Electronic Medicines Compendium, n. d.) in strengths of 100mg and 250mg (Joint Formulary Committee, 2010); they have an expiry date of five years from the date of manufacture and are packaged in a ‘ blister pack’ or a bottle (Electronic Medicines Compendium, n. d.).

The oral solution consists of a 50mg in 5ml dose (Joint Formulary Committee, 2010) and is packaged in an ‘ amber bottle’ made of glass. The oral solution has an expiry date of two years from the date of manufacture but should be

disposed of after the bottle has been opened for ‘ one month’ (Electronic Medicines Compendium, n. d.).

The injection solution is available in the dose of 10mg per 1ml and is used for ‘ intravenous infusion’ (Joint Formulary Committee, 2010). It is packaged in a ‘ glass vial’ which is amber or clear in colour. The solution has an expiry date of three years after the date of manufacture however, once opened, it must be used straightaway and any remaining solution disposed of (Electronic Medicines Compendium, n. d.).

According to Martindale: The Complete Drug Reference (n. d.), all the formulations of zidovudine need to be shielded from sources of light and need to be kept in ‘ air tight containers’.

Stereochemistry and Conformation

As highlighted in the diagram drawn using ISIS ChemDraw (Cambridge Soft, n. d.), zidovudine has a total of three chiral centres and hence zidovudine has eight possible stereoisomers. The 1′ carbon of the ribose ring is of the R configuration whereas the 3′ and 4′ carbons are of the S configuration (Novak et al, 2003). Zidovudine has a specific optical rotation value of +99° in water (Merck, n. d.) and hence rotates the plane of polarized light clockwise; consequently zidovudine is optically active (Freeman, 2010).

Synthesis

Zidovudine was made by Jerome Horwitz in 1964 (Weeks et al, 2010). It can be formed from thymidine, however, this is a costly method and therefore a more cost effective technique is used to make zidovudine on a large scale by

using D-Mannitol as the starting compound (Saunders, 2000). The process has been drawn below using ISIS

ChemDraw (Cambridge Soft, n. d.) with reference to Top Drugs (2000).

In the first stage, a derivative of D-glyceraldehyde is formed from D-mannitol using acetone and a source of protons and refluxing. Lead (IV) acetate is then added. In the second stage a ‘ Wittig reaction’ is carried out and ‘ PH3P= CHCO2Et’ and methanol are added. In the third step hydrochloric acid is added, producing a lactone. In the fourth stage the lactone is ‘ protected’ and the azide group is added on through a ‘ Michael addition’ reaction. The reagents used to protect the lactone are ‘ t-Bu(Me)2SiCl’, imidazole and dimethylformamide. The reagents for the ‘ Michael addition’ reaction are lithium azide, tetrahydrofuran, acetic acid and water. In the fifth stage the lactone is reduced to a lactol at minus 78 degrees using Diisobutylaluminium hydride and dichloromethane. The hydroxyl group is ‘ activated’ to form a ‘ sugar intermediate’ using acetic anhydride and pyridine. In the sixth step, ‘ Vorbruggen conditions’ are adopted and a ‘ condensation reaction’ is performed with the ‘ sugar intermediate’ and ‘ silylated thymine’ which produces ‘ alpha and beta anomers’. The reagents are di-trimethylsilyl-thymine, trimethylsilyl trifluoromethanesulfonate and ‘ EDC’. In the seventh step, the ‘ silyl protecting group’ is taken off and the ‘ anomers’ are uncombined to obtain zidovudine. The reagents used in this step are ‘ n-Bu4N+F-‘ and tetrahydrofuran (Saunders, 2000).

Drug stability: Potential sites of chemical instability and metabolism

Zidovudine decomposes greatly in the presence of light because of the azide group and the product formed from the breakdown is thymine. This is because two nitrogen atoms are removed from the azide group, forming nitrene. An ‘ insertion reaction’ takes place and aziridine is made. Water, as a nucleophile, attacks aziridine. The amide anion formed causes the thymine group to be ‘ nucleophilically displaced’ and hence thymine is produced as the degradation product (Dunge et al, 2004). Therefore as zidovudine is mostly affected by light it is advised that the various formulations of zidovudine are kept away from light sources (British Pharmacopoeia, 2010).

Zidovudine has a ‘ bioavailability’ of 63%. This is due to the fact that zidovudine undergoes ‘ glucuronidation’, giving ‘ zidovudine glucuronide’ which is more water soluble than zidovudine due to a sugar group being added, and is ‘ renally excreted’ (Burton et al, 2006). ‘ UDP-glucuronyl transferease’ is the enzyme which catalyses the reaction (Veal et al, 1995).

Zidovudine can also be converted to 3′-amino-3′-deoxythymidine due to the azide group being reduced (Veal et al, 1995); 3′-amino-3′-deoxythymidine can affect the action of zidovudine against HIV and is possibly toxic (Burton et al, 2006).

Lipinski’s Rules For Orally Active Drugs

According to Clarke’s Analysis Of Drugs And Poisons (n. d.) the Log P value of Zidovudine is 0. 05 and the molecular weight is 267. 25 as calculated on ISIS ChemDraw (Cambridge Soft, n. d.). Zidovudine has a total of two hydrogen bond donor sites and a total of nine hydrogen bond acceptor sites (Lipinski et

al, 1997). As a result, zidovudine follows ‘ Lipinski’s Rules of Five’ as it has a molecular weight of less than 500, a Log P value of less than 5, there are less than five hydrogen bond donor sites and there are less than ten hydrogen bond acceptor sites (Lipinski et al, 1997).

As the Log P value of zidovudine is 0. 05 (Clarke’s Analysis Of Drugs And Poisons, n. d.) it can be seen that the drug is slightly polar. Zidovudine contains aromatic and large aliphatic regions which are hydrophobic; the polar character arises from the hydroxyl group, an amide region, an ether link and azide group, which are all hydrophilic regions. Therefore as there is a slight imbalance of more hydrophilic groups to hydrophobic groups, zidovudine is slightly hydrophilic and slightly polar and therefore is water soluble and has less affinity to cross the lipid membranes (Bichenkova, 2010).

pKa and Ionization State At pH 2, 7. 4 and 10 and Solubility

According to the International Agency for Research on Cancer (n. d.), the pKa value of Zidovudine is 9. 68 and hence it is weakly acidic. Using the equation for the percentage of ionization, which has been derived from the Henderson-Hasselbalch equation, I am able to calculate the percentage amount of ionization of zidovudine at various pH values.

The equation used consists of: % ionization of an acid = 100/ 1 + antilog(pKa – pH) (Freeman, 2010).

At pH2, the equation will read % ionization = 100/ 1 + antilog (9. 68 – 2). This gives the value 2. 09×10^-6 %. Hence it can be seen that in the stomach only a very small amount of zidovudine will be ionized and

generally it will be largely unionized. The percentage of zidovudine unionized at pH2 is 99. 99% and hence as zidovudine is highly unionized at pH 2, it will be absorbed from the stomach. At pH2 2. 09×10^-6% of zidovudine is ionized as the azide group can be protonated (Chemicalize, n. d.).

At pH 7. 4 the calculation gives a value of 0. 52%. Hence in the blood stream zidovudine will be largely unionized as the percentage of zidovudine that is unionized in the blood stream is 99. 8%. In the bloodstream 0. 52% of Zidovudine will be ionized as the azide group can deprotonate (Chemicalize, n. d.). As zidovudine is largely unionized at pH 7. 4, it can be absorbed from the bloodstream into the CD4 cells where it carries out its role as an antiretroviral (Foye et al, 2008).

At pH 10 a value of 67. 63% is obtained. Therefore in basic conditions, zidovudine is largely ionized as the azide group is deprotonated and the amide group of thymine is deprotonated (Chemicalize, n. d.). The percentage of zidovudine unionized in the blood is 32. 37%.

Zidovudine is absorbed very quickly in the body (Burton et al, 2006) and this can be seen through the fact that zidovudine is greatly unionised in the stomach and blood stream and hence can quickly enter the CD4 cells in the blood (Foye et al, 2008).

Conclusion

As zidovudine has an azide group it is able to stop HIV replication (Foye, 2008). Zidovudine follows ‘ Lipinski’s Rules’ and hence is well absorbed in the body (Lipinski et al, 1997). As zidovudine has a pKa of 9. 68, the drug can be absorbed from the stomach as it will be largely unionised in the

stomach. This is also the case for the drug in the bloodstream and hence zidovudine can be taken up quickly by the cells and carry out its role as an antiretroviral despite being slightly polar. The bioavailability of zidovdine is limited however by the fact that some zidovudine is glucuronidated and hence is lost; some zidovudine is also affected by the azide group being reduced as the product formed can affect zidovudine’s role as an antiretroviral and could be toxic (Burton et al, 2006). As zidovudine degrades in the presence of light, the drug is packaged in ‘ blister packs’ or ‘ plastic bottles’ and all formulations of the drug need to be kept out of light and in the packaging they came in (Electronic Medicines Compendium, n. d.).