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Toxicology Midterm

Question 1) a:doxorubicin
Doxorubicin is an anthracyline and normally this drug used for treatment of different cancers including breast, lung, gastric, ovarian, thyroid, non-Hodgkin's and Hodgkin's lymphoma, multiple myeloma, sarcoma. One very important restriction for this one is for cardiotoxicology. Unfortunately this drug is anti cancer and also has cardiotoxicity as well, if we know better information about the pharmacogenomics of usage of this drug we can use it in lower dose for carditoxicology and better result for anticancer.
"doxorubicin the cancer cell do intercalation into DNA and interference of topoisomerase-II-mediated DNA repair and creation of free radicals and their loss to cellular membranes, DNA and proteins . doxorubicin is oxidized to semi Quinone, an uneven metabolite, which is converted back to doxorubicin in a process that releases reactive oxygen species. Reactive oxygen species can lead to lipid peroxidation and membrane damage, DNA damage, oxidative stress, and triggers apoptotic pathways of cell death."
Doxrubicinol is made when doxorubicin is decreased.Metabolism of doxorubicin inside the mitochondria can interruptand block any respiration that can finally leads to the release of cytochrome-C initiating apoptosis.
impounding of iron blocking free radical formation can affects mechanism of the action of dexrazoxane protection against cardiotoxicity .
the most noticeable result of drug–drug interactions causing to in the cardiotoxicity from cotreatment and coeffection with doxorubicin and trastuzumab or taxanes such as paclitaxel and docetaxel. No using and Without this endogenous cardioprotection, doxorubicin treatment can be more distructed and bad and damaging .The interaction with taxanes is through a different mechanism.the way using and helpful for the taxane-is try to increase in cardiotoxicity is by increased making of doxorubicin, by the changing and making of the catalytic activity of aldehyde reductase.
"doxorubicin mechanism many of the genes that modulate the doxorubicin response. However, PGx studies that implicate variants in these genes are still in their infancy. As with many antineoplastic drugs, the PGx can be complicated by combined treatments. However, there are clear benefits for identifying individuals at risk for toxicity and response".
this drug has a very wide antitumor spectrum, compared with other anticancer drugs; however, just not for Hodgkin's disease, it is not associated and related with therapeutic chemotherapy. Doxorbucin used several years but now and only recently, recognized that the cytotoxic effect and result is produced at the cellular level by multiple mechanisms which have not yet been finally well-known.
Important thing over here are a combination of doxorubicin-induced free radical formation and this is because of metabolic activation, toxic actions at the level of the membrane, and drug-intercalation into DNA.
The problem is clinician found a lot of concentration of doxorubicin in hematopoietic cells and other tissues.

Question 2
Cyp2d6
1)When we want to talk specilally about this one , this is shown in researchers that display genetic polymorphism . metabolization of the substrate in low limit can result for mutation in Cyp2d6.you can find this gene in liver or cns in substansia nigra
" some individual for example obtain no benefit from the opoid analgestic codeine , because they lack cyp2d6 enzyme that o-demethylates and activates the drug"
2) in first step tamoxifen change to cyp3a4 AND cyp3a5 and in other hand tamoxifen change to cyp2d6 to 4-OH-TAMOXIFEN and next step the third step is goes from here and cyp3a4 and cyp3a5 goes to 4-OH-DESMETHYL-TAMOXIFEN and in other hand from step a from cypa4 and cyp3a5 goea to N-desmethyl-tamoxifen and then by step D cyp2d6 goes to 4-oh-n-desmethyl-tamoxifen , we have this one from step c and d together and its both from the affect of cyp2d6 from step b and step d
3) omeperazol , erythromaycine, ketoconazole, ritonavir,
4) This quality encodes an individual from the cytochrome P450 big groups of chemicals enzyme. This one can catalyze a lot of responses and they are monooxygenases and have include in for drug for digestive system and making cholesterol and steroids and some lipids .This protein limits to the endoplasmic reticulum and is referred to metabolize to approximatly of 20% of regularly recommended medications. This gene is really has high number in polymorphic in the world. Some special alles has bad metabolize phenotype and this is their characteristic to reduce the quality of metabolism of the enzyme substrate.

Question 3 part c)
Aminoglycosides used for along period of time one of the most reason for drug induced nephrotoxicity. Aminoglycosides increased nephrotoxicity but this effects is as nonoliguric renal failure. This is also has an small and slow increase in the serum creatinie and hypoosmolar urinary output developing even after a period of time from treatment.
Aminoglycosides is highly nephrotoxic because a alittle dose of this drug is hold inside of the epithelial cells lining of the S1 and S2 segments of the proximal tubules and then after glomerular filtration. Aminoglycosides gatherd inside of epithelial cells are really in one special places with endosomal and lysosomal vacuoles but they are also located with the Golgi complex .
aminoglycosides has a noticeable changes in lysosomes of proximal tubular cells steady with the buildup of polar lipids .These changes has a result of tubular dysfunction or changes which can decreased reabsorbtion of the protein,k and mg and ca and glucose when these happens in the human body it will result as renal failure mostly because of nonoliguric or deacrese of polyuric hypoosmotic in creatinine clearance.
When we use very high dose in animal very fast affected to inceased cortical necrosis and overt renal dysfunction.one of the most important affect is for the primary steps for uptaking in proximal tubular cells. Although several effects like decreasing of protein synthesis and modulation of gene expression and changing

in mitochondrial .
Reseaches proved that the first and most important cause of functional toxicity is tubular necrosis. aminglycosides toxicity is mostly because of local concentration. This is because of lysosomal change as a most imporatant reason for toxicity. Actually all these are still hypothesis for the cell damage and just some has laboratory result finding but it still strongly mentioned for renal impairment.
While the determinants of cell damage still remain undefined, more knowledge concerning the mechanisms causing the impairment of the renal function is available. It causes the renin angiotensin system to work again and then vasoconstriction comes up for deacreasing in glomerular filtration part.we can understand explanation of when this drug reduced production of vasodilatory prostaglandis pge2 , how does it works for aggravating effect of nonsteroidal anti inflammatory drugs on aminoglycoside nephrotoxicity. An increase in proximal intratubular and some pressure of single nephrons, can be related to necrotic obstruction, reducing of glomerular filtration has a multifactorial origin and involves a mixture of tubular and nontubular mechanisms. The hypo osmotic polyuria, typical of the aminoglycoside toxicity has some result from the reducing fluid reabsorption by proximal tubules, secondary to an impaired solute reabsorption.
Human body kidney has a large capacity to compensate for tubular insults so that an ongoing cell death process may long remain undetected by functional explorations.
“Decreasing or preventing aminoglycoside accumulation by the kidneys would represent one of the most simple and radical approaches to reduce aminoglycoside nephrotoxicity, since it should goes to success whatever the targets of aminoglycosides are in the kidney. Aminoglycoside build up has to decreased either by impairing their uptake or by increasing their release. Reducing and decreasing of uptake has been obtained by two strategies. The first one is goes at complexing the aminoglycosides extracellularly, and the second one is at competing with or decreasing drug binding to the brush-border membrane. An explanation for this unexpected behavior came from the finding that aminoglycoside uptake by kidney tubular cells is saturable ,so that much of the drug that passes in the lumen will not be reabsorbed if the drug is too concentrated. Because saturation was shown to occur at a clinically meaningful range of concentrations, this observation triggered a large number of studies comparing the toxicities of various drug administration schedules.”
between the various approaches applicable to the presently available aminoglycosides, onlyjust one dose a day is good and successfully to the clinic. Other protective approaches such as the coadministration of polyaspartic acid or deferroxamine deserve preclinical and clinical development, and many more could certainly be explored. Recently discover and improvement in molecular modeling and an improved knowledge of the meaningful differences in structure-activity and structure-toxicity relationships for aminoglycosides could also bring us,intrinsically less toxic aminoglycosides.

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