Advances in Nanomedicine and Nanotechnology Research
ANNR, 1(2): 73-76
www.scitcentral.com

ISSN: 2688-5476

Review Article: Open Access

An Overview on Nanotoxicity

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Received June 24, 2019; Accepted August 30, 2019; Published December 09, 2019

ABSTRACT

Nanotechnology combines the knowledge of pharmaceutical, medicinal, material science, engineering and information technology and has made accurate, precise and rapid diagnosis creating a major development in the field of medicine. The nanoparticle size lies between 1 nm to 100 nm. The main important factor is the size itself. It mainly helps to enter the cell cavity of any small sized microorganisms including bacteria, fungi and even virus. This small size helps nanoparticles to travel through blood stream and ultimately reach the target centers in the human body. Their shape and high surface area to volume ratio make nanoparticles to use in medicine effectively. Nanotechnology aims for the effective drug delivery, better ways of organ regeneration and development of Nano drugs. Techniques used in Nanotechnology include, delivery of Drugs into targeted cells by using Nano particulate carriers. Unfortunately, excess use of Nano drugs has led to toxicity or poisoning due to the Nano medicine carriers. In this paper we would like to highlight the important facts about the toxic side of using Nano drugs in modern medicine. This paper explores the potential and versatile applications of nanoparticles in the field of medicine.

Keywords: Nanotoxicity, Nanomedicines (NMs), PEGylated (Polyethylene glycolated) Nano liposome (SPI-077TM), Respiratory syncytial virus (RSV), Transcriptome analysis console (TAC) software, Targeted drug delivery

INTRODUCTION

Nanomedicine is a relatively new and rapidly evolving field combining nanotechnology with the biomedical and pharmaceutical sciences [1-4]. Nanotechnology has wide applications in medicine in the form of diagnostic imaging, treatment and prevention [5]. Global investment in nanotechnology has been increasing steadily; a significant increase in researches addresses the benefits of nanomedicines over free drugs and presents new opportunities and challenges in all branches of medicine [6]. These medicines are used mainly to overpower diseases like cancer which has proved quite effective, when used in low or trace amounts. Along with such revolutionary advantages, problems and issues like toxic effects of drugs, tissue injury, selective organ toxicity and its carcinogenic effects are to be accounted.

Nanomedicine (NM) is the application of nanotechnology (the engineering of tiny machines) to the prevention and treatment of disease in the human body [7]. This evolving discipline has the potential to dramatically change medical science. The most common application of nanomedicine involves employing nanoparticles to enhance the action of drugs in treatment. NM has potential advantage and less toxic but still one should be very careful while subjecting these interventions in human being. It is important to have a thorough understanding of NMs and their specific properties. Immunotoxic effects, such as complement activation-related pseudo allergy, myelosuppression and hypersensitivity, are not readily detected by using current testing guidelines [8,9].

Cisplatin encapsulated pegylated nanoliposome

Nano particulate carriers deliver nanoparticles without undergoing the normal absorption process and many a times are responsible for toxicity and can also accumulate in organs. Cisplatin encapsulated PEGylated nanoliposome or SPI-077TM, a nanodrug that was experimented to study its effect on tumor growth in mice [10]. Anti-tumor activity and accumulation of cisplatin was observed inside tumor tissues

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Citation: Francis PJJ, Joseph I & Jahan F. (2019) An Overview on Nanotoxicity. Adv Nanomed Nanotechnol Res, 1(2): 73-76.

and blood in large concentrations without any trace of toxicity. Platinum is being tested as a nanoparticle carrier for disease like cancer, clinically it is highly nephrotoxic. It was then used by humans and proved to show low effectiveness due to bioavailability [11-13].

Accumulation of non-biodegradable nanoparticles

Site targeting is a best way to cure diseases, but nonspecific targeting and the accumulation of Nano medicine in the liver, spleen and kidney are unsolved problems [6]. Accumulation of Non-biodegradable nanoparticles can cause cell damage and inflammation, if taken up by macrophages as it would cause free radical release. Similarly if taken up by lysosomes they accumulate and cause toxicity. This is caused due to the absence of a degradation enzyme which results in accumulation of materials in lysosome. The other affected organs due to this accumulation include liver, which is most likely and brain which is the least likely to be affected. These problems can be overcome by coating biodegradable materials on nanomedicines which avoid the accumulation of such particles.

Drug-induced muscle injury

Drug-induced muscle injury is due to exposure of tissue to the slowly releasing drug. 'Application-specific design' methodology requires the accurate identification of the disease, its subtype and target and also needs an in-depth comprehension of the nature and pathogenesis of the disease. Particle-encapsulated cytotoxic drugs are broken down by liver cells and this leads to drug-induced hepatic injury. Increased drug induced toxicity after encapsulation has also been observed recently.

Unfavorable effects on the central nervous system and the immune system

Zinc oxide (ZnO) is termed as a multi-purpose item and is used for manufacturing porcelain, ceramic items etc. ZnO containing creams are used to treat sunburn, insect bites and other skin irritations. Studies prove that these nanomaterials have unfavorable effects on the central nervous system and the immune system. The path for entry and the target organ of the nanoparticles are the lungs.

Immunotoxicity and genotoxicity

Oxidative stress is also caused due to NM-induced toxicity and other problems include immunotoxicity and genotoxicity [14]. Genotoxicity testing is important, as it causes mutagenicity and carcinogenicity. Lungs are affected mainly due to burning caused by oxidative stress. Antioxidants reduce the bad effects of oxidative stress. ZnO nano medicines are widely used and show toxic nature on human pulmonary alveolar epithelium and lungs. In order to overcome the problem, studies were conducted on a combination of RSV + ZnO NP. It resulted in showing positive results, cytotoxic and genotoxic toxicity decreased compared to their levels when ZnO was used alone. The reason was that RSV, being a natural antioxidant, avoided genotoxic and cytotoxic damage induced by ZnO nanoparticles on the epithelial cells. They also cause changes in genetic matter that plays a role in the pathogenesis of various diseases. The epigenetic toxicity of NMs is based on *in vitro*. It is not a simple task to find the impact of NMs on genetic material as large number layers of epigenetic control mechanisms and vast variations in individual susceptibility [15].

Different experiments of RSV and ZnO nanoparticles are carried out on the epithelial cells and results are observed using TAC analysis. It was observed that there was decrease in TAC value, on adding ZnO nanoparticles. While increasing amounts of RSV increased TAC on the cells. Thus it was concluded use of antioxidants were beneficial in overcoming oxidative stress problems [15].

Severe combined immunodeficiency disease (SCID)

Targeting of current Nano drugs is based on permeability and retention effect. As a result of binding with many items, increases their chances of accumulation in organs and other tissues. A controlled release of drugs can be brought about by pH, enzymes and temperature. There are several negative effects caused by Nano drugs, given below are some more examples. Severe combined immunodeficiency disease (SCID) was caused by Adagen which was used to improve circulation time and reduce immunogenicity injected Intravenous in 1990 [16]. Mircera, Neulasta and Oncospar causes Anemia, Fibrile neutropenia and leukemia respectively and all these drugs were used to improve stability of proteins. The above include protein based Nano particles. Similarly lipid based Nano particles including DepoCyt and Marqibo cause lymphomatous meningitis and acute lymphoblastoic leukemia, both drugs are used for increased delivery to tumor site through intravenous injection.

Liposomal encapsulated doxorubicin

Generally liposomes are designed to lower their toxicity to healthy tissues as well as to increase their efficacy. A liposomal encapsulation of doxorubicin with surface-bound methoxypolyethylene glycol is known to be less cardiotoxic and nephrotoxic than unbound doxorubicin; however, it produces more dermal lesions primarily on the feet and legs [17]. A liposome-encapsulated doxorubicin–citrate complex shows less cardiotoxicity than unbound doxorubicin; however, it induces increased bone marrow suppression [18].

DNA methylation, acetylation of histones and mRNAs

Production of reactive nitrogen species causes inflammation. NMs cause changes in DNA methylation, acetylation of histones and mRNAs expression also NMs showed that they impair the expression of genes. Nanoparticles coated by gold cause hypermethylation. Gold (Au) nanoparticles are used

widely because they are inert and biocompatible. Chiral Au nanoparticles capped with gold components decrease the catalytic activities of TET proteins. Silver (Ag) nanoparticles induce a reduction in hemoglobin levels in mice erythroleukemia cells. Similarly, titanium dioxide (TiO_2) in nano-form is a substance that causes cancer through inhalation.

Effectiveness and toxicity

Effectiveness and toxicity are two important parameters viewed for medicine development. Free drugs and nanodrugs are compared, effectiveness (E)/toxicity (T) ratios for nanomedicine, (E/T) nanomedicine and a free drug, (E/T) free drug is done as first approach. While the ratio of the toxicity or efficacy of nanomedicine (N) to that of the free drug (F), (N/F) effectiveness and (N/F) toxicity is done as second approach. The E/T ratio for Nano medicines decreases and approaches a ratio value closer to that of the free drug when concentration is increased, suggesting a lowered benefit with an increase in concentration in the first case. While the N/F ratio does not show overall benefit between nanomedicines and free drugs, but it does provide an idea regarding the magnitude of the difference in efficacy or toxicity between a Nano medicine and a free drug [6].

CONCLUSION

Nanomedicines have wide applications and merits in the field of modern medicine, but they have toxic effect also. Cisplatin is a versatile nanomedicine it will collect in the active target tissues and blood resulting less toxic effect. But its effect in human beings is not commendable and it causes nephrotoxicity. Non-biodegradable nanomedicines will lead cell apoptosis and infection inside the body. Particle-encapsulated nanomedicines can cause drug-induced hepatic injury. Versatile nanomedicines like zinc oxide will lead bad impacts on the central nervous system and the immune system. Oxidative stress, immunotoxicity and genotoxicity are the other bad impacts of NM-induced toxicity. Certain nanomedicines cause severe combined immunodeficiency disease and DNA methylation. Using antioxidants and liposomal encapsulation are certain ways of reducing the nanotoxicity. Nanomedicine with lower concentration reduces the toxicity compared to free drug with similar concentration.

Depending on particulate characteristics of their formulations, the toxicokinetic profile or toxicodynamic effects can be stratified. The differences in absorption, distribution, metabolism, excretion, interactions with other chemicals may affect the side effect or toxicity. This may result in altered availability of NM within different tissues leading to toxicity.

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