Mini Review
Volume 6:4, 2022

Journal of Clinical Anesthesiology: Open Access

ISSN: 2684-6004 Open Access

Spleen Function in the Drug metabolism of Monoclonal Antibodies and Nanoparticles

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Abstract

Drugs distribute in the body after absorption, in part to reach target tissues and in part to be disposed of in tissues where they have no clinically relevant effects. Drug metabolism and/or elimination usually end therapeutically relevant effects. The spleen's traditionally attributed role in these fundamental pharmacokinetic processes was clearly marginal. However, due to its high blood flow and microcirculation characteristics, this organ is expected to be significantly exposed to large, new generation drugs that cannot penetrate other tissues with tight endothelial barriers.

The spleen is barely mentioned in pharmacology textbooks and among its physiological roles, such as immunological surveillance, removal of aged blood cells, hematopoiesis and blood volume regulation, neither drug disposition nor involvement in pharmacological drug action are ever mentioned. The spleen received little attention in pharmacology due to a lack of evidence that it could play a significant role in the disposition of "classical" drugs. However, just as when a new character appears in a novel and our perspective on the story changes dramatically, our perspective on the relationship between drugs and the spleen is changing as a result of the development of "new-generation" drugs.

Keywords: Liposomes • Endothelial barriers • Monoclonal antibodies

Introduction

However, just as when a new character appears in a novel and our perspective on the story changes dramatically, our perspective on the relationship between drugs and the spleen is changing as a result of the development of "new-generation" drugs. We intend to use the generic term "new-generation" drugs to refer not only to truly novel drugs, such as nanoparticle drugs (e.g., liposomes or nanotubes), but also to drugs that are no longer novel, such as biotechnological drugs (e.g., recombinant proteins and monoclonal antibodies). "New" generation drugs differ from "classical" drugs in that their chemical structure is much more complex and their size is larger, making them more similar to the antigen particles to which the spleen physiologically responds. The spleen has a unique microanatomy that makes it very interesting from a pharmacological standpoint. A systematic analysis of splenic structures [1-3] beyond the scope of this paper and interested readers can find more information on this topic in textbooks and several excellent reviews. Here, we will look at the more notable aspects that give this organ very specific properties in terms of drug diffusion and, possibly, metabolism and action. We will begin by analysing how the vasculature distributes within the spleen because this is the simplest way to describe the microanatomy of this complex organ.

They then develop into central arteries surrounded by sheaths of lymphatic tissue, often enlarging to form splenic follicles, which comprise the so-called white pulp. The central arteries branch further after leaving the white pulp to form the penicillar arteries, which enter the red pulp of the spleen. Whereas the white pulp of the spleen is essentially made of lymphatic tissue, there are two main kinds of structures in the red pulp: the sinuses and the splenic cords. Splenic sinuses are distinct structures that differ from traditional capillaries. They are basically cavities that have been lined up by a discontinuous endothelium. Splenic cords are cavities within the red pulp's stroma that are filled with red and white cells. Splenic cords are not lined by endothelium, but are a stromal specialisation delimited by fibroblasts and extracellular matrix. To return to the general circulation, red blood cells in splenic cords must squeeze across the splits of the splenic sinusoids. Erythrocytes that are too old or diseased to cross these slits are trapped in the red pulp and destroyed. This is also a mechanism involved in nanoparticle sequestration by the spleen, as we will see later. There has long been debate about how the penicillary arteries in humans feed the splenic sinuses and cords.

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Date of Submission: 02 August 2022, Manuscript No. jcao-22-77607; **Editor assigned:** 04 August 2022, Pre QC No. P-77607; **Reviewed:** 16 August 2022, QC No.77607; **Revised:** 21 August 2022, Manuscript No. R-77607; **Published:** 28 August 2022, DOI: 10.37421/2684-6004.2022.6.146

Literature Review

For a long time, it was assumed that penicillary arteries opened in the red pulp with no direct continuity with the sinus wall, resulting in an open circulatory system in which blood could freely exit the arterial compartment. Further research suggested that penicillary arteries continue directly in sinuses (closed circulation models) and combined models in which both open and closed circulation coexisted were also proposed. In 2011, Steiniger published a detailed 3D reconstruction of red pulp vessels in the human spleen, revealing that almost all of the circulation was open. Further research suggested that penicillary arteries continue directly in sinuses (closed circulation models) and combined models in which both open and closed circulation coexisted were also proposed. Published a detailed 3D reconstruction of red pulp vessels [4,5] in the human spleen in 2011, revealing that nearly all of the circulation was of the open type. Furthermore, 3D reconstruction studies have recently addressed another area of contention concerning the blood supply of the white pulp.

Discussion

Spleen function in monoclonal antibody disposition

Monoclonal antibodies are immunoglobulins produced from a single cell clone and, as a result, have a high specificity against a single epitope. Monoclonal antibodies are created using various technologies and share varying degrees of similarity with human immunoglobulins. Aside from

highly specific antigen recognition based on their variable regions, these molecules have additional pharmacological properties such as opsonization or complement fixation based on the IgG class to which they belong. Monoclonal antibodies are an important tool in the clinic because of their selectivity and specificity in neutralising and/or inducing immune destruction of very specific antigen targets. More than sixty monoclonal antibodies were marketed for human use at the start of 2017.

Monoclonal antibodies are highly polar molecules with molecular weights in the 150 kDa range. Because of these characteristics, they differ significantly from "classical" drugs in terms of pharmacokinetics and their distribution behaviour is thought to be more similar to that of bacterial antigens or nanoparticles. More specifically, while in the case of "classical" drugs, simple diffusion accounts for a large portion of drug distribution across endothelial barriers, this process is considered negligible in the case of monoclonal antibodies, which enter peripheral tissues primarily through convection. As a result of the differences in hydrostatic pressure between the capillary lumen and the interstitium, this process is dependent on lymph efflux from the interstitium itself. Convection bypasses the plasma membranes of endothelial cells as it moves through the intercellular space and as the intercellular junctions become looser and looser, it becomes more and more favoured. Monoclonal antibodies, like any other protein, filter as they move through the intercellular space via convection. This sieving is accomplished by the connective tissue of the lamina basalis and the deeper layers of the capillary wall, as well as the glycocalyx, which opposes protein transfer through the capillary wall.

The classical Starling equation or its more recent revisions can be used to mathematically model the process of convective filtration through the capillary wall. The reflective coefficient is a specific parameter in this equation that accounts for the different leakiness of the intercellular sieve in the different capillary beds. While capillary barriers in most tissues have reflective coefficients around 0.950.98 and are almost impermeable to plasma proteins [6-8] spleen capillaries are much looser and their reflective coefficients have been estimated to be around 0.85. This finding is consistent with evidence that the splenic circulation is permeable to plasma proteins. As a result, more monoclonal antibodies are expected to enter the splenic parenchyma than any other organ. This raises the question of what might happen to them after that. Simply put, part of them will pass through the parenchyma and be removed by lymph, while the rest will be captured by the spleen and processed or returned unaltered to the blood. To gain a better understanding of the role of the spleen in the pharmacokinetics of monoclonal antibodies, these various processes must be better characterised and quantified in the context of these drugs' whole-body disposition.

Unfortunately, there is still a scarcity of data to address this issue. What is clear is that a fundamental distinction must be made between monoclonal antibodies that can bind specifically to antigens expressed in splenic cells and monoclonal antibodies that are directed against targets that are not present in significant quantities in this organ. The monoclonal antibody will bind to its target in the first case and the spleen will be a preferential site of accumulation and pharmacological action, whereas in the second case, less specific antibody capture mechanisms will be involved. Immunoglobulin recycling via FcRn receptors opposes this clearance mechanism. Because immunoglobulin binding to these receptors is reversible upon acidification, antibodies are released from FcRn in the acidic endosomal compartment and recycled to plasma after being internalised. As a result, FcRns play a critical role in controlling the circulating half-life of immunoglobulins, which can be increased through targeted mutations of the FcRn interaction site. FcRn receptors are also found in the spleen, where they may limit immunoglobulin degradation by splenic macrophages.

Conclusion

The advancement of nanotechnology has paved the way for the development of new generation drugs that differ from traditional drugs due to their nanoscale dimensions. Although still very small, these particles are several orders of magnitude larger than traditional drugs and represent a significant advance in drug therapy because they can be assembled as multimolecular complexes that include not only pharmacologically active molecules, but also molecules for selective targeting to specific tissues. As a result, conventional drugs, biotechnological drugs and nucleic acid drugs can be incorporated into nanoparticles for selective targeting to specific tissues and increased half-life. The term "nanoparticles" refers to particles with a size in the nanometer range, according to the International Union of Pure and Applied Chemistry (IUPAC). The acquired immunodeficiency syndrome (AIDS) caused by HIV-1 infection has piqued the interest of researchers looking into splenic macrophage targeting. Indeed, in this disease, viral accumulation and replication occur in macrophages and macrophage-like cells, which serve as a reservoir for the virus and, in some cases, the primary infected cell type, such as microglia in the brain. As a result, targeting macrophages may be beneficial in the treatment of this disease.

Acknowledgement

None.

Conflict of Interest

There are no conflicts of interest by author.

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How to cite this article: Myles, Jessica. "Spleen Function in the Drug metabolism of Monoclonal Antibodies and Nanoparticles." J Clin Anesthesiol 6 (2022):146.