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Drugs That Must Not Be Present in the Donors's Blood

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SUMMARY

Introduction: Transfusion is probably the most humane area of drug use, as donors freely give a substance that serves as medicine, and even one person can save many lives, especially of newborns. The aim of this work is to single out drugs whose use prevents a voluntary donor from donating blood within a certain period of time. If we talk about blood quality, we must take into account that the presence of metabolites or active substances of certain drugs is a potential cause of adverse reactions in the recipient. Bearing in mind the practical importance of this problem, the authors of this paper make their contribution in order to make transfusion safer.

Topic: The significance of this topic lies in plasma-containing components, where donor-used drugs may be present. The division of drugs potentially harmful to the health of the transfusion recipient is related to the pharmacokinetics, side effects, and drug interactions.

Whole blood is less frequently transfused. In clinical practice, components are applied, such as erythrocytes resuspended in OAS (SAGMANITOL). The drug is present in the whole blood, and by separating the cellular components, it becomes present in the plasma. The concentration of the drug in the stored blood component depends on the pharmacokinetic characteristics (t/2) of the drug, retention of the drug or metabolites in the donor's circulation. In fact, attention should be focused on the components that contain plasma: plasma, cryoprecipitate and platelet concentrates (PC).

Overall, drug use should be divided into groups that temporarily exclude donors and groups that permanently exclude donors. Genetic vaccines are a new form of medicine that alarmingly points to the monitoring of distant side effects due to the presence of spike proteins.

Conclusion: Drugs in transfusion as professional topic must be covered by local guides and SOPs of blood establishments and hospital blood banks. A regulation should be established defining drugs that are contraindications for donating. Modern analytical methods should be used as needed to detect the presence of drugs and their metabolites. Apart from the caution related to the presence of the drug in the blood/components, the biggest harm to the patient can be caused by the ambitious use of mRNA technology drugs and insufficient

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knowledge about this group of drugs. In medically unclear situations, the authors agree with the position of patient blood management that autotransfusion is the solution. The obligation for pharmacovigilance and hemovigilance should be legally regulated.

Keywords: Transfusion, Drugs in Blood, Autotransfusion, mRNA Technology

INTRODUCTION

Blood transfusion is the process of donating blood or blood components from a donor to a recipient of blood or blood components [1]. Transfusion activities in Serbia are regulated by the Law on Transfusion Activities and accompanying regulations [2,3,4,5, 6].

Diseases that are contraindications for voluntary blood donation, according to textbook knowledge, include: Hepatitis A, Hepatitis B, HIV, malignant diseases, chronic diseases, autoimmune diseases, acute infectious diseases, syphilis, etc., clearly defined in the regulations [5, 7]. Serbian legal regulations define these matters in detail. After many years of clinical experience, the authors lean toward the need to revise permanent and temporary contraindications for blood donation [2, 5]. In Serbia, blood and blood components donation according to the Law is voluntary, unpaid, and anonymous [2].

Drugs that contraindicate someone from being a blood donor for transfusion are not defined either by the guidelines or by law in Serbia. According to Serbian law, persons undergoing treatment with cytostatic and immunomodulatory drugs are permanently excluded as blood donors. Serbian regulations align with European Union regulations [8].

Transfusion is probably the most humane area of drug use, as donors freely give a substance that serves as medicine, and even one person can save many lives, especially of newborns [9].

The aim of this work is to single out drugs whose use prevents a voluntary donor from donating blood within a certain period of time. If we talk about blood quality, we must take into account that the presence of metabolites or active substances of certain drugs is a potential cause of adverse reactions in the recipient. Bearing in mind the practical importance of this problem, the authors of this paper make their contribution in order to make transfusion safer.

TOPIC

The Serbian regulations contain diseases as temporary and permanent contraindications for blood donation [2, 5, 10]. Published and professional papers mention both temporary and permanent deferral of donors based on the drugs the donor uses [11,12].In this respect, our regulations need to be supplemented. This area is mostly covered by local guides and SOPs of authorized transfusion institutions (blood establishments). Likewise, it is necessary to strengthen the knowledge of medical teams in hospital transfusion units (Hospital blood bank) [1].

Given the modern lifestyle and voluntary donors in older age groups, drug use is increasingly present among donors, along with an increase in adverse reactions to blood donation, which calls for caution with older donors. In some countries, an increase in the age limit for blood donation is noted. Deferral of donors due to age, drug use, diseases, and personal decisions leads to a reduction in the number of available blood units, becoming a common problem in many countries [13].

In transfusion, the following five basic products from whole blood are used: erythrocyte concentrates, packed red blood cells (pRBC), fresh frozen plasma (FFP), cryoprecipitate, and platelet concentrates (PC) [1]. Components with plasma removed are also used: washed erythrocytes, washed platelets resuspended in optimal additive solutions (OAS), which are used in persons with IgA deficiency. In plasma-containing components it is important that drugs and their metabolites are not present.

The significance of this topic lies in plasma-containing components, where donor-used drugs may be present. The division of drugs potentially harmful to the health of the transfusion recipient is related to the pharmacokinetics, side effects, and drug interactions. This is important because transfusion recipients are often patients already on therapy. Additionally, healthy individuals suffering from traffic or other injuries may receive transfu-

sions. Although of limited clinical importance, academically it should be noted that donors on medication are allowed to donate blood for blood products containing less than 50 ml plasma from a single donor, such as red blood cell concentrates, for use in adults without deferral periods, except for those taking retinoids, thalidomide, lenalidomide, dutasteride, finasteride, or genotoxic drugs [14].

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Donor drug use is common, but there is little information on the impact of use on the safety of transfused blood. According to foreign literature, indications for donor deferral/delay are:

• Factors affecting product quality, testing results for transfusion-transmissible infections (TTI), and infectious disease risks.

• Most transfusion centers defer/delay donors due to use of a small number of highly teratogenic drugs. Deferral due to other pharmacological effects is negligible, and the likelihood of harm to donor or recipient is very low.

Transfusion centers and Red cross develop their own strategy or doctrine based on knowledge of pharmacokinetics and pharmacodynamics of drugs and knowledge of teratogenicity of certain drug groups. It is important to consider the drug elimination half-life, defined as the time needed for the amount of drug in the body to reduce by half [12]. Literature shows that all drugs are completely eliminated after approximately 10 half-lives [15, 16, 17]. For teratogenic drugs, a much lower safety level (<0.000001%) has been proposed [18].

Experimental studies using metabolites as predictors show that some drugs can have a direct and significant impact on erythrocyte metabolism. Researchers affirm that several groups of drugs: calcium channel blockers, alpha and beta-adrenergic blockers, bisphosphonates, anticholinergics, adrenergics, proton pump inhibitors, antimetabolites, selective serotonin reuptake inhibitors, mTOR inhibitors—have a direct, preserving, and significant effect on erythrocyte metabolism. For ranitidine, it has been shown that when introduced into erythrocyte units, it strongly affects RBC markers of storage quality in vitro. Supplementation of blood units stored in bags with ranitidine could through mechanisms involving sphingosine 1–phosphate–dependent modulation of erythrocyte glycolysis and/or direct binding to hemoglobin improve erythrocyte metabolism and storage quality [19].

The presence of drugs in blood during transfusion originates from two sources: the donor's blood and the patient's blood (recipient). Due to frequent transfusion use in surgical procedures, significant study results show no interaction between morphine, pethidine, and ketamine with standard erythrocyte concentrates [20].

Overall, drug use should be divided into groups that temporarily exclude donors and groups that permanently exclude donors.

Individuals receiving antiplatelet therapy are subject to deferral from blood donation due to the inhibitory effects of these agents on platelet function. This applies to medications such as acetylsalicylic acid, clopidogrel, ticlopidine, and ticagrelor. While specific deferral periods are not uniformly defined for antiplatelet agents, blood donation is typically postponed based on clinical assessment of the drug's duration of action and residual anti-platelet effect.

More clearly defined are the deferral intervals for individuals using anticoagulant therap.Those treated with low-molecular-weight heparins such as nadroparin, dalteparin, reviparin, or enoxaparin, as well as with fondaparinux, are deferred from donation for a minimum of twodays following the last dose. This same two-day deferral applies to direct oral anticoagulants, including dabigatran, apixaban, rivaroxaban, and edoxaban. In contrast, treatment with vitamin K antagonists such as warfarin and acenocoumarol necessitates a longer deferral of seven days due to their extended anticoagulant effect. Individuals treated with unfractionated heparin are similarly deferred for seven days.

Donors who have recently taken isotretinoin, used primarily in the management of severe acne, must be deferred from donation for one month due to its teratogenic

risk and tissue persistence. Patients undergoing oncologic treatment for multiple myeloma with thalidomide or lenalidomide are not eligible for donation during treatment, with deferral determined by risk evaluation and treatment duration. The same applies to individuals treated with immunomodulatory drugs such as upadacitinib and finasteride, where donor eligibility is assessed individually based on potential hormonal or immunological effects.

Those receiving dutasteride, typically for prostatic hyperplasia, are deferred for six months due to its long biological half-life and reproductive risks. Individuals taking immunosuppressive agents such as mycophenolate mofetil are deferred for at least six weeks following the last dose. These medications may alter immune cell populations and pose risks to immunocompromised transfusion recipients.

For persons on therapy or prophylaxis for hepatitis or HIV, the deferral period ranges from three months to permanent, depending on the indication, drug type, and risk of transmissible infections [12]. Finally, individuals undergoing treatment for autoimmune diseases, particularly those on cytotoxic or biologic agents, are generally subject to permanent deferral due to the long-term immunosuppressive nature of these therapies and the potential impact on blood safety (Table 1).

One of the most commonly used groups of drugs, benzodiazepines with long action, depending on Body mass index (BMI), can remain in the blood for up to 7 days, while cannabis remains in the blood for about 2 weeks. Following our concept, all donors on medication (except for retinoids, thalidomide, lenalidomide, dutasteride, finasteride, or genotoxic/cytostatic drugs) may be accepted if

Table 1. Recommended Medication deferral list for Serbia

	Brand name of the drug	Generic name of the drug	Time since last drug intake
Antiplatelet drugs	Aspirin, Anbol, Cardiopirine	Acetil salicilna kiselina	3 days
	Plavix	Clopidogrel	14 days
	Ticlodix	Ticlodipin	14 days
	Brilique, Ecugra, Gartyz, Tikagrelor	Ticagrelor	7 days
Anticoagulant drugs	Fraxiparine	Nadroparin	2 days
	Fragmin	Dalteparin	2 days
	Clivarin	Reviparin	2 days
	Clexane	Enoksaparin	2 days
	Arixtra	Fondaparinoux	2 days
	Farin	Varfarin	7 days
	Sintrom 4	Acenokumarol	7 days
	Pradaxa	Dabigatran	2 days
	Eliquis	Apixaban	2 days
	Rivaroks Rivaroksaban, Xarelto, Trombocen	Rivaroxaban	2 days
	Roteas	Edoxaban	2 days
	Heparin	Heparin	7 days
Acne therapy	Roaccutan, Aknova	Isotretinoin	1 month
Multiple myeloma	Thalidomid	Thakidomide	1 month
	Revlimid	Lenalidomide	
Rheumatoid arthritis	Rinvoq	Upadacitinib	1 month
Hair loss remedy	Finasterid, Proscar	Finasteride	1 month
Prostate therapy	Dutasterid	Dutasteride	6 months
Immunosuppressants	CellCept, Micolat, Trixin	Mikofenolat mofetil	6 weeks
Hepatitis and HIV therapy and prevention			3 months or permanently
Autoimmune disease therapy			permanently

blood banks separate donor blood for distinct purposes, i.e., newborns and children under 12 years only [14].

Genetic vaccines are a new form of medicine that alarmingly points to the monitoring of distant side effects due to the presence of spike proteins. Serious side effects include agglutination of RBCs and platelets, whereby leukodepletion alone will not resolve the issue. A wide variety of health injuries include thrombocytopenia, thrombotic disorders with thrombocytopenia, deep vein thrombosis, thrombocytopenic purpura, cutaneous vasculitis, sinus thrombosis, infertility, cancers. Microscopic observation has revealed that in addition to abnormally shaped red blood cells, amorphous material has been found floating in the blood of mRNA-vaccinated individuals, some of which has shown grossly abnormal findings. Potentially, spike protein is neurotoxic and can cross the blood–brain barrier which suggests that the spike protein used as an antigen in genetic vaccines might itself be toxic [21]. In medically unclear situations, the authors agree with the position of patient blood management that autotransfusion is the solution [1].

CONCLUSION

OTransfusion centers and Red cross have to develop their own strategy or doctrine based on knowledge of pharmacokinetics and pharmacodynamics of drugs and knowledge of teratogenicity of certain drug groups.

Drugs in transfusion as professional topic must be covered by local guides and SOPs of blood establishments and hospital blood banks. A regulation should be established defining drugs that are contraindications for donating and receiving blood. The obligation for pharmacovigilance and hemovigilance should be legally regulated.

Modern analytical methods should be used as needed to detect the presence of drugs and their metabolites. Keep in mind, do not discontinue prescribed medications due to the intention to donate blood. In medically unclear situations, the authors agree with the position of patient blood management that autotransfusion is the solution.

CONFLICT OF INTEREST

All authors declare no conflict of interest.

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Lekovi koji ne smeju biti prisutni u krvi davaoca

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KRATAK SADRŽAJ

Uvod: Transfuzija je verovatno najhumanija oblast primene lekova jer donori besplatno daju supstancu za lek pa čak jedan čovek može da spasi veliki broj života posebno novorođenčadi. Cilj ovog rada je da izdvoji lekove čija primena onemogućava dobrovoljnom davaocu da da krv u određenom vremenskom periodu. Ako govorimo o kvalitetu krvi moramo uzeti u obzir da je prisustvo metabolita ili aktivne supstance određenih lekova potencijalni izazivač neželjenih reakcija kod primaoca. Imajući u vidu fuziji i farmakologijitransfuziju bezbednijom.

Tema: Značajnost za ovu temu imaju komponente koje sadrže plazmu u kojoj mogu biti prisutni lekovi koje koristi donor. Podela na lekove koji su potencijalno oštećujući po zdravlje pacijenta primaoca transfuzije vezana je za farmakokinetiku leka i neželjena dejstva, i interakciju lekova. Cela krv se sve ređe daje. Daju se komponente i pri tome eritrociti se resuspenduju u OAS (SAGMANITOL). a lek prisutan u celoj krvi biva prisutan u plazmi u zavisnosti od svojih farmakokinetskih karakteristika (t/2) i koncentracije kao i zadržavanja leka ili metabolita u skladištenoj krvnoj komponenti. Zapravo, pažnju pri primeni treba fokusirati na komponente koje sadrže plazmu a to su sam plazma, krioprecipitat i koncentrati trombocita. Generalno, upotreba lekova treba da se podeli na grupe koje privremeno isključuju davaoce i grupe koje trajno isključuju davaoce. Genetske vakcine su novi oblik lekova koji alarmantno ukazuje na bavezu praćenja udaljenih neželjenih efekata zbog prisustva spike proteina. U medicinski nejasnim situacijama, autori podržavaju stručni stav transfuzije da je autotransfuzija rešenje.

Zaključak: Lekovi u transfuziji kao stručna tema moraju biti obuhvaćeni lokalnim vodičima i standardnim operativnim postupcima (SOP) ovlašćenih transfuzioloških ustanova i bolničkih banaka krvi. Trebalo bi da se uspostavi propis kojim se definišu lekovi koji su kontraindikacije za doniranje. Trebalo bi da se koriste savremene analitičke metode po potrebi za detekciju prisustva lekova i njihovih metabolita. Pored opreza vezanog za prisustvo leka u krvi/komponentama, najveću štetu pacijentu mogu prouzrokovati ambiciozna upotreba lekova mRNK tehnologije i nedovoljno znanje o ovoj grupi lekova. Autori podržavaju stručni stav transfuzije da se prema inikacijama primenjuje autologna transfuzija. Farmakovigilanca i hemovigilanca treba da budu puna zakonska obaveza zdravstvenog osoblja.

Ključne reči: transfuzija, lekovi u krvi, autotransfuzija, mRNK tehnologija

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