3. Pharmacokinetic characteristics of drugs regarding skeletal muscles

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Abstract. Drugs may be given by different routes in order to exert systemic or local effect. From the pharmacokinetics point of view, considering muscles as body compartment, it is important to characterize absorption after intramuscular (IM) drug administration, and drug distribution into muscle following drug administration. IM injection is characterized by invasive procedure puncturing the skin with a needle in order to inject the drug directly into a large body muscle for the prophylactic or therapeutic purposes. The rate and extent of drug absorption are determined by formulation, physicochemical properties of drugs, and physiological characteristics of the site of administration. When intravenously or non-IM drug is administered, distribution may occur at various rates and to various extents in different tissues including muscles. Rate of drug distribution depends on vascular membrane permeability, regional blood flow, cardiac output and perfusion rate of the tissue, while extent of distribution is defined by drug’s ability to bind to...
plasma and/or tissue proteins, its liposolubility, and relation of pKa of drug and pH of environment. The article gives an overview of the pharmacokinetic aspects of absorption following IM injection, and distribution of drugs in muscular tissue.

1. Introduction

Drugs may be given by different routes in order to exert systemic or local effect. These routes include: intravenous, *per os*, subcutaneous, sublingual, intramuscular (IM), pulmonary, rectal, vaginal, transdermal, topical, ocular, and other ways of applying drugs into body, and each of them has its specific purposes, advantages, and disadvantages. From the pharmacokinetics point of view, considering muscles as a body compartment, it is important to characterize absorption after IM drug administration, and process of drug distribution into muscles following drug administration (Shargel et al, 2012). Drug metabolism in the muscles does not have high importance as metabolism of endogenous substances (such as formation of creatinine from creatine phosphate during muscle metabolism, glucose, protein metabolism, etc.).

2. Drug absorption after intramuscular administration

IM drug administration is characterized by puncturing the skin with a needle in order to inject the drug directly into a large body muscle for the prophylactic or therapeutic purposes. Drugs are typically given in the deltoid muscle (upper arm), vastus lateralis muscle (thigh), ventrogluteal (hip) and dorsogluteal (buttocks) muscles, usually at a 90 degree angle to the skin. Site selection depends on the patient’s age and muscle development. For IM

![Schematic representation of intramuscular (IM) injection given at 90 degree angle](image)

**Figure 1.** Schematic representation of intramuscular (IM) injection given at 90 degree angle
injection, needle needs to be long enough to ensure drug is injected into muscle (Figure 1). Significant mass of some body muscles enables quantities of up to several milliliters of the fluid to be injected. Therefore, up to 5 milliliters may be given by IM injection in buttocks while up to 1 milliliter can be given in the deltoid muscle due to its limited size (Nicoll and Hesby, 2002).

For certain drugs this is a preferred route of drug administration, while for the others this may be an alternative way of applying drugs when a patient cannot tolerate oral medication, drug is too irritating to be given subcutaneously, when greater volume or faster absorption to subcutaneous application is desired, or when patients' adherence is an issue (Hopkins and Arias, 2013). Various antipsychotic drugs, sex hormones, antimicrobial drugs, analgesics, vaccines are given directly into a muscle mass. They include: haloperidol, chlorpromazine, lorazepam, codeine, morphine, midazolam, methotrexate, metoclopramide, streptomycin, diazepam, prednisone, phenytoin, digoxin, testosterone, risperidone, estradiol valerate, naloxone, quinine gluconate, vitamin B12, etc (Silbergleit et al, 2012; Florence and Attwood, 2006). For most peptides and proteins, due to the lack of absorption after oral administration, administration by injection including IM is the preferred route of delivery, such as for abarelix, alefacept, asparaginase, glucagon, palivizumab, pegaspargase, triptorelin (Tang and Meibohm, 2006).

However, disadvantages of IM injection include: pain and discomfort especially if large volumes are injected (>3 milliliters injected in buttocks can be painful), nerve damage especially if drug injected into gluteus, possibility of sterile abscesses occurrence at the injection site, serum creatine phosphokinase elevation as a result of muscle enzyme release, severe and unexpected adverse drug reactions, haematoma (Ritter et al, 2008). Additionally, with IM administration there is an increased risk of injecting the drug directly into blood vessels.

As an extra vascular route of administration with the purpose to reach the systemic circulation, IM given drugs have to undergo the absorption phase, and the problems encountered in the stomach and intestine (such as drug instability in acid pH, enzyme and microbial flora inactivation, first pass effect, P-glycoprotein efflux) are bypassed. Skeletal muscles are highly vascular and its capillaries have pores that facilitate small molecular weight substances to pass via passive diffusion into the bloodstream. The rate and extent of drug absorption depend on formulation, physicochemical properties of drugs, and physiological characteristics of the site of administration (Florence and Attwood, 2006). In order to pass capillary walls, the drug has to stay in solution at pH of muscle. Otherwise, microcrystallization will occur, and redissolution of a drug may be unpredictable affecting drug absorption (Brown and Tomlin, 2010).
Absorption rate explains how fast the drug appears in the bloodstream, and it is quantified with absorption rate constant ($k_a$) in compartment (model-dependent), or maximal (peak) blood level ($C_{\text{max}}$) and time needed to achieve $C_{\text{max}}$ ($t_{\text{max}}$) in non-compartment (model-independent) pharmacokinetic analysis (Shargel et al, 2012). IM administration usually shows faster drug absorption than per os or subcutaneous given drug. Hence, greater $k_a$, and shorter $t_{\text{max}}$ are observed after IM to absorption from subcutaneous tissue or gastrointestinal tract (Figure 3). When IM drug solution is injected, absorption is often perfusion-limited (Rowland and Tozer, 2010). Thus, differences may be observed in $C_{\text{max}}$ according to injection site as epinephrine concentrations were significantly higher after IM injection into the thigh than after IM or subcutaneously into the upper arm (Simons et al, 2001). In certain conditions, such as administration of aqueous solution, rate of drug absorption after IM injection may be as fast as if drug was given intravenously (Shargel et al, 2012).

As drug solution distributes throughout a large muscle volume, absorption rate increases. Hence, by massaging the injection site, increasing local temperature, absorption rate may be enhanced. Additionally, the local muscle blood flow, and consequently injection site, determine absorption rate. As the blood supply is greater, the drug faster appears in bloodstream (Rowland and Tozer, 2010). Therefore, as the deltoid muscle has rich blood supply, it is considered optimal for rapid absorption while it takes more time for a drug to be absorbed from gluteus muscles. During exercise (in acute exercise blood is shunted primarily to the muscles at the expense of other organs, while in chronic exercise, cardiac output is relatively high, so perfusion of all tissues is increased.), the increase in blood circulation improves.
A balance between hydrophilic and lipophilic drug characteristics is important for a passive diffusion through biological phospholipids’ membranes. Thus, hydrophilicity is required in order to maintain drug in solution at the injection site until absorption occurs, while drugs’ lipophilicity is essential for passive penetration all the way through lipid bilayer interdispersed with carbohydrates and protein groups (Shargel et al, 2012). Passive diffusion process follows first-order kinetics that explains proportionality of absorption rate to drug concentration remaining at the site if injection. Hydrosoluble structure of midazolam at pH<4 allows drug formulation in aqueous solution. At injected site of muscle, midazolam undergoes structural changes in order to enhance its liposolubility and allows absorption from IM site (Brown and Tomlin, 2010). Some data indicate that pH value at the different sites of IM injection may be variable. Accordingly, it determines if a drug will dissolve or precipitate from given formulation (Florence and Attwood, 2006). Precipitation can result in prolonged absorption of drug over up to even several days. Since capillary walls are discontinued with pores filled with water, it allows some hydrosoluble molecules such as mannitol, inulin, dextran to diffuse through pores as they can not pass lipid barrier. However, the molecular size may limit the transport if molecular weight exceeds 5000.

As already mentioned, if drug is in aqueous solution, the absorption is rather fast with t_{max} ranging from 10 to 60 minutes. However, IM injections may be given for slower absorption if the drug is mixed with a non-aqueous
(sesame, vegetable or mineral oil) solution or suspension (encapsulation of drug in liposomes, niosomes, biodegradable spheres)– depot formulation. In these preparations drug is usually in a form of ester (fluphenazine decanoate ester) or salt (microcrystalline salts of penicillin G) which releases active free drug slowly, and provides a sustained drug concentration for a prolonged period of time, so the absorption rate is slower than following per os administration. Rate-limited absorption of fluphenazine decanoate is hydrolysis of the drug at the surface of the oil droplets (Florence and Attwood, 2006). Depot formulation may allow as rare as once-monthly dosing as aripiprazole is given as maintenance treatment in adults with schizophrenia (Kane et al, 2012). Depot formulations are used when steady drug level are to be maintained, in patients who are suspected of non-adherence (psychiatric patients). In these situations, flip-flop phenomena may occur which is observed as several times greater value of the elimination than the absorption rate constant because at the beginning all drug dose is in muscles and none in plasma. When the plasma concentration increases the elimination rate becomes greater than the absorption (Curry and Whelpton, 2011).

Extent of absorption (absolute bioavailability, F) is defined as fraction of the administered drug dose that reaches the systemic circulation. This is quantified by dose-corrected area under the concentration-time curve (AUC) for IM injection divided by AUC after intravenous drug administration (Figure 4). Drugs with incomplete absorption after IM injection include: ampicillin, diazepam, dicloxacillin, phenylbutazone, quinidine (Florence and Attwood, 2006). Due to possibility of incomplete absorption, extent of absorption

![Pharmacokinetic parameters of rate and extent of bioavailability](image)

**Figure 4.** Pharmacokinetic parameters of rate and extent of bioavailability (\(C_{\text{max}}\), maximal drug concentration, \(t_{\text{max}}\), time needed to achieve \(C_{\text{max}}\), AUC-area under the curve) after intramuscular injection.
following IM injection is usually in range from 75 to less than 100%. Bioavailability has to be carefully considered when switching patients from IM to per os (F=5 to <100%), intravenous (F=100%) formulations (Rowland and Tozer, 2010).

3. Drug distribution into muscle tissue

Drug distribution occurs at various rates and to various extents in different tissues. Therefore, apart from direct injection into a muscle, drug may be distributed to muscles (mainly skeletal and cardiac) from a circulation following intravenous or other extravascular route of administration. Rate of drug distribution depends on vascular membrane permeability, regional blood flow, cardiac output and perfusion rate of the tissue, while extent of distribution is defined by drug’s ability to bind to plasma and/or tissue proteins, its liposolubility, and relation of pKa of drug and pH of environment (Rowland and Tozer, 2010). Adult male has in average up to 42% of skeletal muscle mass, while female up to 36% of body weight. When inactive, perfusion rate of muscles is approximately 0.025 milliliters/minute/gram (Rowland and Tozer, 2010). Hence, due to intermediate blood flow in muscles, time needed to achieve equilibration with blood is possible to quantify (2-4 h) (Shargel et al, 2012). Consequently, pharmacokinetics of a drug that distributes to muscles is commonly described by two- or three-compartment model, depending on the rate of distribution (Figure 5). After absorption, drug passes from central (includes plasma and highlyperfused organs) to the peripheral (tissue including muscle) compartment at the rate described by corresponding constants till equilibrium is achieved.

**Figure 5.** Schema of two compartment pharmacokinetic model for a drug given intravenously. $k_{12}$, $k_{21}$- distribution rate constants between compartments, $k_{10}$-elimination rate constant from central compartment.
Extent of drug distribution is quantified by volume of distribution (Vd), and for some drugs Vd is high. For digoxin Vd is 500 liters due to its extensive affinity to bind to heart and skeletal muscles, which can also act as drug reservoirs, storing considerable quantities of drug. Drugs that accumulate outside the plasma compartment, by binding to target tissues, may have apparent Vd exceeding total body weight. However, Vd value does not tell us where is the locus of pharmacological effect or as for insulin (Vd=0.085 liters/kilogram) does not suggests extent of distribution even it is known that it exerts its effects in the muscle, fat, and liver cells via receptors exposed to interstitial fluid (Brown and Tomlin, 2010). Great interindividual variability in the bound fraction of drugs to muscle tissue was observed, and it ranged from 13% for aminophenazone to 98% for desipramine (Fichtl and Kurz, 1978).

Certain transporters are expressed on the membrane of human skeletal muscle, and play vital role in drugs’ safety profile. Thus, Knauer and colleagues (Knauer et al, 2010) identified the molecular determinants of statins’ (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) distribution into human skeletal muscle. Atorvastatin and rosuvastatin are identified in vitro as substrates to uptake transporter OATP2B1 (human organic anion transporting polypeptide 2B1) and the efflux transporters, multidrug resistance-associated protein (MRP)1, MRP4, and MRP5 (Knauer et al, 2010). These, sarcolemmal skeletal muscle membrane transporters play role in statins exposure in muscles, and hence toxicity related to muscles (e.g. myopathy, rhabdomyolysis).

Physiologically based pharmacokinetic models are based on compartments representing anatomical and physiological structures of the body. If a drug primarily distributes to the muscle, then it would be included as a tissue compartment connected to other rapid or slowly equilibrium compartments by arterial and venous blood supplies. Therefore, the rate of pharmacokinetic processes within muscle, in physiologically based pharmacokinetic models, is dependent on blood flow, drug concentration in arterial and venous blood, and muscle mass (Riviere, 2011; Rowland and Tozer, 2010).

4. Conclusion

Intramuscular route of drug administration is preferred route of administration for many drugs due to limitations observed after per os dosing. Fast absorption after intramuscular injection is achieved from aqueous solution, whereas controlled drug delivery by dissolving drug in oil or aqueous suspension. Hence, rate and extent of absorption may vary
depending on formulation characteristics, vehicles, site of injection, blood flow. Furthermore, if drug administered via non intramuscular route it may distribute from a circulation to muscles at various rates and to various extents. In order to provide optimal drug therapy, pharmacokinetic aspect of drugs at the skeletal muscles level has to be considered.

References
