PHARMACOTHERAPEUTIC GUIDE FOR OFF-LABEL USE SUBCUTANEOUSLY IN TRAUMA AND ORTHOPEDICS PATIENTS

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INTRODUCTION

There are different routes of drug administration. Patients with difficulties in venous access and oral intolerance to therapies demand the development of alternative, safe, and effective means of drug administration (Dickman *et al*., 2017; Caccialanza *et al*., 2018;)element.

The subcutaneous approach (CS) has been shown to be of enormous value when favored in elderly, critical, palliative care (PC) patients and/or patients with peripheral venous access failure for hydration, symptomatic control of pain, nausea, vomiting and dyspnea, and even nutrition (Vasconcellos; Milan, 2019; Zaloga *et al.*, 2017).

However, in Brazil, the SC route is still little used in hospital and home clinical practice (Gomes *et al.,* 2017). The main reason for not using the route is the lack of experience of professionals and guidelines that guide its application in relation to which drugs can be used, dilutions, and drug incompatibilities (Forbat *et al.,* 2017; Pontalti *et al*., 2012). In addition, the number of drugs approved by health regulation in this way is scarce (Veras *et al*., 2014; Azevedo, 2016). Thus, the administration of drugs via the CS route is, for the most part, an *off-label* practice, adopted worldwide in PC services, in which there are reports, among other drugs, of successful experiences of using dexamethasone to treat pain in advanced cancer (INCA, 2021; Ministry of Health, 2011).

The *off-label* use of drugs through the SC route is frequent: research points to a high and growing use in PC and intensive care units (ICU), where it can reach a prevalence of use of 73% (Moreira *et al*., 2023). This practice is due, among other factors, to the lack and difficulty of conducting comprehensive clinical trials in these populations, which would come up against obvious ethical and legal issues (Koszma *et al.*, 2021; Lat *et al.,* 2011; Mulac *et al.,* 2021; Vieira *et al.*, 2021). However, regulatory agencies, in Brazil and worldwide, do not

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regulate medical practice or how drugs are prescribed after approval for commercialization, as well as do not provide any guidelines/recommendations related to *off-label* use. (Keys *et al*., 2023; Smithburger *et al*., 2015).

Such an imbroglio threatens, then, the safety of health professionals who use the SC route in this way, due to limited scientific evidence and the lack of complete information, in addition to the lack of familiarity of health professionals with either the correct dosage, appropriate dosage and/or route and specific precautions (Farzi *et al.*, 2017; Mulac *et al*., 2021; Sona Mackova; Karel Urbanek, 2015). Consequently, it is to be expected that such associated factors (lack of experience + absence of institutionalized technical guidelines + scarcity of licensed SC options + *off-label* use + special populations + limited evidence) create obstacles to the prescription, dispensation, and administration of drugs and correct *off-label* use of drugs through the CS route, as it also raises questions related to patient safety (such as avoidable medication errors (EMs) and potential adverse drug reactions (ADRs)) and therapeutic efficacy.

In addition, the manufacturer no longer has any responsibility for any damage that may occur to the patient due to *off-label use*. (Novaes; Nunes; Bezerra; 2020). However, it should be noted that the *off-label* use of medicines is not illegal, nor necessarily incorrect, and can even be predicted and recommended by institutional protocols and international guidelines (Chaves *et al.*, 2023).

In the specific context of traumatology and orthopedics, many pathological conditions are painful, debilitating, and have little potential for cure. The trauma-orthopedics patient is strongly prone to suffer from physical and psychological symptoms that significantly decrease their quality of life (Sagini; Aboulafia, 2005). It is exactly in these circumstances that palliative care (PC) should be remembered and practiced: necessary comprehensive care, promoted by a multidisciplinary team that aims to improve the quality of life of patients and their families, in the face of life-threatening diseases through the prevention and relief of suffering, such as early identification, impeccable evaluation and treatment of pain and other physical symptoms, social, psychological, and spiritual (INCA, 2022). In this study, we considered in such conditions not only cancer patients, but also those with neurological injuries of different traumatic origins, who sometimes end up requiring mechanical ventilation, in ICUs.

In a national reference institute in high-complexity orthopedic surgeries, HPD and SC therapy are especially indicated for pharmacological control of symptoms (pain, nausea, vomiting, and dyspnea) and hydration in patients with advanced chronic diseases in progression, as well as for patients in peripheral venous access failure and on medications

that have an indication for administration by the SC route, with an expected completion within 5 days (except antimicrobials), as recommended by an established routine for the insertion and handling of this practice.

These PC patients are accommodated in the ICU, which observed that since the implementation of the routine (October 2019), it had been little reported. Thus, the research problem arose from the observation that, similarly to what the aforementioned studies suggest, SC therapy, in this IRNTO, is underused due to the absence of a guide that guides professionals on which drugs as well as how (dilutions, forms of infusion and drug incompatibilities) can be safely prescribed by doctors, dispensed by the pharmacy and administered by nursing.

In mid-April 2021, the Clinical Pharmacy Area of the institute was asked to appoint a pharmacist to represent it before the Infusion Therapy Commission. The purpose of this committee is to develop, approve and/or standardize normative and technical-scientific conducts related to infusions, including those related to subcutaneous therapy and HPD. The pharmacist on the commission was tasked with developing a safe and effective guide to drugs and solutions that can be administered *off-label* via SC.

Thus, according to the Patient Safety Plan, which ensures adequate compliance with the Basic Patient Safety Protocols (MS, 2023), especially those related to Safety in the Prescription, Use, and Administration of Medications (ANVISA, 2023), such action aims to safeguard not only the best risk-benefit ratio and ensure patient safety, but also to ensure the safety of all professionals involved.

In view of the advent of PC in orthopedics (within an ICU) in the institution, the elaboration of a validated guide of medications for *off-label* use by the SC route in the referenced hospital is a differential because it will help to meet the International Patient Safety Goals, in addition to providing comfort and a more humanized care to users.

Furthermore, this guide promotes training and best practices, bringing a guideline to all professionals involved in patient care: the physician in the elaboration of a safer drug prescription through this route; the nurse in the safe administration as well as in the training of the nursing team and in the education of the patient and their families/caregivers in this process; and the pharmacist, for quick access to information related to medications, in the guidance of the team on the correct use, adverse effects and possible interactions and drug compatibilities, with the purpose that problems with the prescription, dispensation and/or infusion of drugs through this route can be avoided or significantly minimized (Pontalti *et al.*, 2012). Constituting a recognized strategy for standardization of care and an effective tool to help control unjustified variabilities in the different processes from medication to the patient,

the guide contributes to the excellence of the quality of the services provided at the institution (Cabañero-Martínez *et al*., 2019).

Furthermore, in view of the notorious gap in the university and technical professional training of the professionals involved - whether nurses, pharmacists or physicians (or even nursing technicians) - regarding the use of this pathway, this work contributes to the dissemination of knowledge, in addition to stimulating future discussions on the subject and the development of new research in the area - which may, in the future, to reduce this gap between science and care practice (Quaglio *et al*., 2018).

OBJECTIVE

To present a validated pharmacotherapeutic guide, developed for *off-label use* by the SC route with a view to optimizing hydration and control of pain, nausea, vomiting, and dyspnea in palliative trauma and orthopedics patients.

METHODOLOGY

Methodological study developed in two phases: first, a systematic review (published) and elaboration of the guide (SANTOS; PAULA, 2024) Next, an exploratory, quantitative descriptive study was carried out using the content validation index (CVI) in two stages: first by expert judges (in two rounds) and, later, by health professionals from an intensive care unit of a national reference institute in traumatology and orthopedics (SANTOS; PAULA, 2024 – accepted for publication).

This study was approved by the Research Ethics Committees (REC) of the proposing institution and the co-participating institution (CAAE of the proposing institution: 60836122.7.0000.5285 and CAAE of the co-participating institution: 60836122.7.3001.5273, respectively).

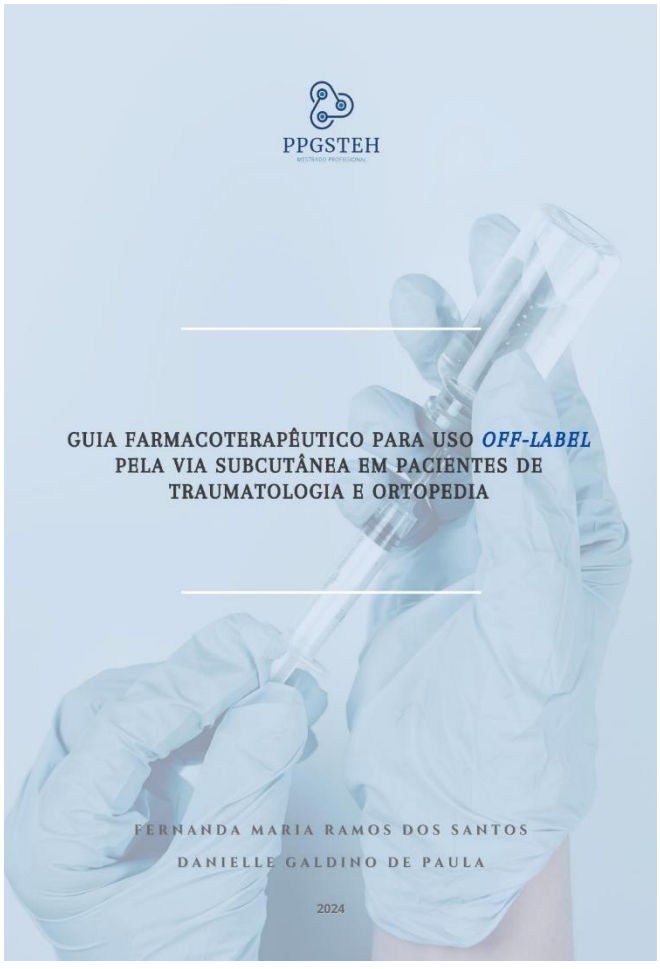
DEVELOPMENT

The systematic review was registered in the *Open Science Framework Registries* (OSFREGISTRIES) platform (DOI: 10.17605/OSF. IO/N67BT). To this end, 22 scientific articles and 2 guides from renowned institutions in Palliative Care were qualitatively analyzed. Subcutaneous *off-label* administration was considered safe and effective in 77.3% of the studies, despite the low robustness of the evidence (data not shown, but already published).

After analyzing the evidence raised by the systematic review, for the construction of the guide, the drugs listed in the selected articles and highly specific and detailed

information from the selected gray literatures (INCA and the Brazilian Society of Geriatrics and Gerontology) were taken into account, according to this methodology. In addition, other evidence from review studies (systematic and integrative), which could not be included in the systematic review, due to the methodological rule for the elaboration of systematic reviews, was also consulted. Once the guide was built, the second phase of the methodology of this study began: the validation of the guide's content in terms of objectivity, content and language.

The final guide was considered reliable and adequate to what is proposed, having been validated with CVI = 0.97 (n = 10) with 90% agreement among the expert judges and legitimized by health professionals (n = 60), with final CVI 0.98 and 90% agreement (data not shown, but accepted for publication). It includes the names and commercial presentations ofthe drugs, therapeutic classes, doses, forms of dilution and infusion, recommendations for exclusive sites, other observations and a table of drugincompatibilities, separately; as well as other information with a view to ensuring the safe *off-label* use of drugs by the subcutaneous route.



LIST OF ACRONYMS USED:

- CCIH: Hospital Infection Control Commission
- CP: Palliative Care
- ICU: Intensive Care Center
- EV: Intravenous
- TAI(s): Prosthetic Joint Infection(s)
- IM: Intramuscular
- INCA: National Cancer Institute
- INTO: National Institute of Traumatology and Orthopedics
- IOA(s): Bone and Joint Infection(s)
- KDa: Kilo Dalton
- ECM: Extracellular matrix
- PPGSTEH: Graduate Program in Health and Technology in the Hospital Space
- ADR(s): Adverse drug reaction(s)
- CS: Subcutaneous
- VO: Oral

PREFACE

This material was developed as a product of the professional master's degree of the Graduate Program in Health and Technology in the Hospital Space (PPGSTEH), of the Federal University of the State of Rio de Janeiro (UNIRIO), in order to meet the demand of the Infusion Therapy Commission of a national reference institute in traumatology and orthopedics (IRNTO): to develop a safe and effective guide to drugs and solutions that can be administered *off-label* subcutaneously (SC) for the proper practice of insertion and handling of SC and hypodermoclysis therapy.

Thus, this guide aims to guide the multidisciplinary team by ensuring correct compliance with the basic patient safety protocols (established by the Ministry of Health) regarding safety in the prescription, use and administration of medications

This work does not intend to mitigate issues related to the technique of insertion and handling of SC and hypodermoclysis therapy (such as the selection of the most suitable sites for subcutaneous puncture in view of the different volumetric capacities that each site has) or to good practices in the handling of injectables. To this end, it is recommended to follow the step-by-step technique described in the institutional routines and/or contact the nurses who are members of the Institute's Infusion Therapy Committee to resolve any doubts.

The drugs selected here were those identified as safe and effective in the national and international literature, through the elaboration of a previous systematic review and subsequent validation by professionals (nurses, pharmacists and physicians) *experts* in palliative care (PC) (from a national reference institute in cancer, in Rio de Janeiro), Intensive Care and Infusion Therapy (from the IRNTO) in 2 (two) stages, in 2023. Therefore, drugs regularly licensed for CS administration, such as insulins, vaccines, antithrombotics (heparins), erythropoietins, among others, are not part of this guide.

However, during the development of this study, a gap in knowledge and concepts was observed, in addition to relative insecurity on the part of some professionals in this area, which led to the addition of some information to the guide in order to better clarify aspects related to patient safety and the safety of the multidisciplinary team in the *off-label* use of drugs for CS therapy.

It is also ratified that this guide is not definitive, and should undergo periodic reviews and updates in order to ensure the safe trajectory of the drug to the patient.

WHAT IS THIS GUIDE FOR?

The use of guides and posters as a strategy for standardizing care in clinical practice has been shown to be a very **EFFECTIVE** tool in reducing ***medication errors1***, helping to control the unjustified variability of different processes2; 3, in particular, those related to the safe *off-label use4* of medicines4.

As an easy-to-access and quick-to-access source of consultation , it provides evidence-based information aligned with the best clinical practices on medications, doses, forms of preparation and administration, and drug compatibilities.

In addition, it was made in proportions that allow it to be printed in A3 format for eventual availability in wards, serving as a visual educational tool through the promotion of communication and training of health professionals in the *off-label use* of medicines through the SC route.

BUT, WHAT IS MEDICATION ERROR, REALLY??

According to the *United States National Coordinating Council for Medication Error Reporting and Prevention*, medication error is:

> "Any preventable **event** that could lead to inappropriate use of medications or harm to the patient while the medication is under the **control of the healthcare provider**, the patient, or the consumer."

Medication errors can occur, therefore, at any stage of care during the use of medications: in the prescription, dispensation and/or administration of medications5.

WHO IS THIS GUIDE FOR?

This guide is intended for **ALL** health professionals in their care practices related to the *off-label use* of medicines through the SC route.

Its elaboration aims to safeguard not only the best risk-benefit and ensure patient safety, but also to ensure the safety of the main actors involved in care:

- ✓ **DOCTORS:** assisting in the preparation of a safer drug prescription through this route;
- ✓ **NURSES:** contributing to the safe administration of medications through this route, as well as in the training of the nursing team and in the education of patients and their families/caregivers in this process;
- ✓ **PHARMACISTS:** providing quick access to information related to medications, guidance on correct use, adverse effects, and possible drug interactions and compatibilities6.

Thus, it is expected that problems with the **prescription**, **dispensation** and/or **administration** of *off-label drugs* through the SC route will be significantly reduced and/or avoided.

BEFORE STARTING IN EARNEST, IT IS IMPORTANT TO "TUNE IN" TO SOME CONCEPTS AND CONTEXTUALIZE SOME INFORMATION!

WHAT IS HYPODERMOCLYSIS OR SC THERAPY?

The term hypodermoclysis or subcutaneous hydration refers to the administration of parenteral rehydration solutions[7]. When the SC route is used for drug/fluid administration, the term "subcutaneous therapy" is considered8; 9 or even "use of the SC route"[10]. However, both terms can be indiscriminately used interchangeably as synonyms for SC11 administration.

This practice has been known for almost two centuries (the first records date back to 1830, their reinforcement from 1860 onwards, gaining notoriety in the hospital environment between 1903 and 1921)[10; 12; 13] and although there are numerous studies evidencing its safety and efficacy, the low robustness of the scientific evidence for most of them suggests caution in the interpretation of the results as well as the need for studies of greater methodological rigor4; 14; 15; 16; 17; 18; 19; 20; 21; 22; 23; 24; 25; 26; 27; 28; 29; 30;31.

WHO IS IT SUITABLE FOR?

This valuable alternative route of medication administration serves as a comfort strategy, reducing stress and pain due to successive (and unsuccessful) punctures, minimizing the occurrence of mechanical and tissue trauma (as well as its consequences), in order to promote a better quality of life32.

Thus, it is especially indicated for patients who present:

- ✓ **Contraindications for oral route (OP),** such as: drowsiness/unconsciousness, obstructions of the gastrointestinal tract, diarrhea, nausea and incoercible vomiting, among others;
- ✓ **Contraindications to intravenous (IV) route**: difficulty and/or impossibility of peripheral venous access
- ✓ **Pharmacologic control of symptoms (pain, nausea, vomiting, dyspnea, and dehydration).**

Thus, through a more holistic view of health, it is widely used in critical patients, PC and geriatrics, not restricted to these clinics only, but also to other patients of any age and diagnosis in all areas of care, including home care[33; 8], in order to promote more humanized care34.

DOES IT HAVE CONTRAINDICATIONS?

Yes! And, for didactic purposes, they were divided into **absolute*** and **relative***[**10; 8; 35; 34]:

Express refusal of the patient and/or caregiver; **Emergencies** (congestive heart failure, marked edema, severe dehydration, shock); **SEVERE bleeding or** coagulation disorders **SEVERE Anasarca**	Cachexia Areas of infection, inflammation, and/or skin ulceration Superior vena cava syndrome Anasarca Ascites Areas of lymphatic circulation impairment (areas near surgical scars, burns, stomata, etc.) Areas of bony prominences and/or joints Peritoneal haemodialysis patients

BUT... *OFF-LABEL* USE OF MEDICATIONS???

It is characterized by the use of registered drugs (in the case of Brazil, with ANVISA) in indications, doses, routes, or populations different from those listed in their registration.

Off-label *use* of drugs through the CS route is frequent: research has shown a high and growing use not only in PC, but also in oncology, pediatrics, and intensive care36; 37; 38; 39;40.

This practice is justified by the small number of pharmaceutical options available through this route10; 41 as well as the lack and difficulty of conducting clinical trials in

certain population groups (PC, geriatrics, neonates, pregnant women, intensive care, etc.), as such trials would run into obvious ethical and legal issues36; 37; 40; 42.

In any case, it should be ratified that such a practice is not illegal, nor necessarily incorrect, and can even be predicted and recommended by institutional protocols and international guidelines42.

BUT... WHAT ABOUT PATIENT SAFETY?

Now, if a drug approved by the regulatory authorities is used outside the standards that attest to its safety and efficacy, concerns naturally arise regarding patient safety and therapeutic efficacy and the manufacturer is no longer responsible for any damage that may occur to the patient due to its use43.

Among the safety and efficacy aspects related to the *off-label* use of medications, the potential medication errors and adverse drug reactions (ADRs) (safety), the observation of the therapeutic results obtained in practice (efficacy or inefficacy); and the number and degree of scientific evidence that support it (safety and efficacy) stand out42.

Thus, the *off-label* use of drugs should **ALWAYS** be based on evidence that supports their use ***in specific clinical scenarios lacking robust data***, where the theoretical benefit would outweigh the potential risks39, as is the case of this specific scenario: PC in ICU! In addition, the *off-label* use of drugs is also justified (and explains) when studies demonstrate an advantage in efficacy and safety or cost-effectiveness over existing alternatives38, as is the case with *off-label use* by the SC route8; 44!

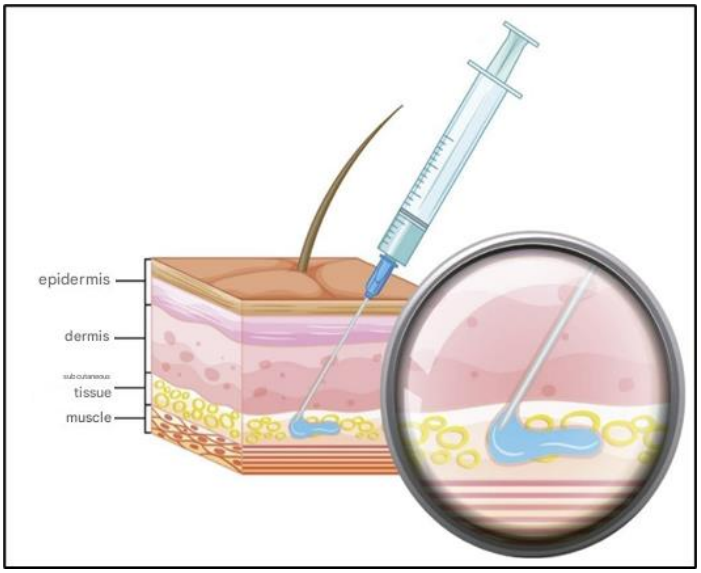
Therefore, the adoption of safe practices related to the *off-label* use of medications (the guide), preventing and/or minimizing possible and avoidable medication errors, as well as being vigilant to the occurrence of ADRs are essential to promote patient safety in this context.

However, ensuring the safe *off-label* use of drugs for CS therapy is a multi- and interdisciplinary process that requires technical and practical knowledge, for which specific and fundamental knowledge in the areas of Anatomy, Physiology, Pharmacokinetics, and Biochemistry is necessary45; 46; 47; Death 48.

A LITTLE ABOUT SC TISSUE AND DRUG ABSORPTION KINETICS!!

Helping to shape the contours of the body and functioning as a layer of thermal insulation and energy storage and protection against mechanical pressures and trauma, the SC tissue or hypodermis – the third layer of the skin – is located between the dermis and the intramuscular (IM) space, extending over the entire body surface and is primarily

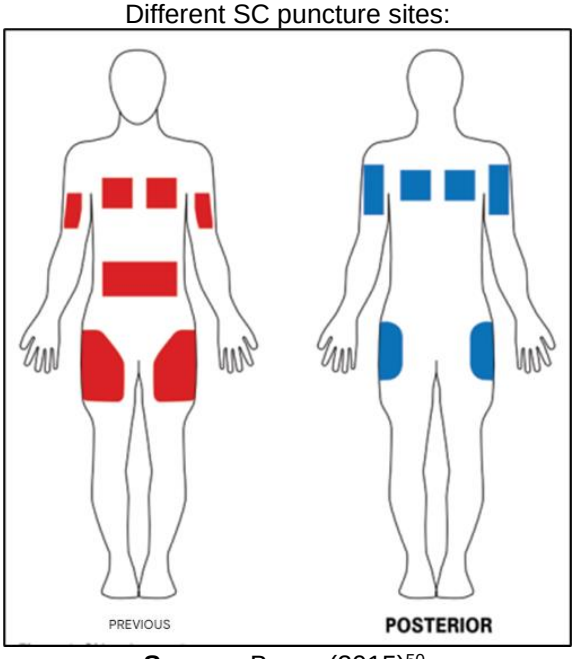
composed of fat cells and connective tissue and transited by nerves. glands, blood and lymphatic capillaries connected to the epidermis by collagen and elastic fibers7; 8;49.



Source: https://eephcfmusp.org.br/portal/online/hipodermoclise-cuidados-prolongados/

Among the main characteristics that favor its use for drug administration are the fact that it has few pain receptors, is well irrigated (which favors absorption) and has low proteolytic activity (with the additional benefit of not undergoing first-pass hepatic metabolism). However, its use inserts other uncertainties in this practice, such as variable bioavailability between different formulations and between different infusion sites. (Different infusion sites, such as thighs, abdomen, and arms, impact absorption kinetics presumably due to local differences in tissue morphology)[7; 8; Death 49].

Different SC puncture sites:



Source: Bruno (2015)[50].

Compared to IV administration, in which the entire administered dose reaches the systemic circulation, SC administration (and IM as well) involves a prior absorption process from the injection site, which leads to a delayed response since the drug molecules must first diffuse through the extracellular matrix (ECM) to achieve circulation. The ECM is an ordered structure with collagen (which confers the mechanical stability of the tissue) and glycosaminoglycans (most commonly hyaluronic acid and chondroitin sulfate), constituting the gelatinous phase of the tissue. Given its composition, it constitutes a significant barrier to the administration of many drugs, limiting both bioavailability and the volume to be injected [7; 49; 51; LIFE 53].

When administered via the CS route, the drugs reach the systemic circulation through both the blood and lymph. Very succinctly, the absorption of subcutaneously administered solutions occurs gradually by diffusion, perfusion, equilibrium between hydrostatic and osmotic pressure, and lymphatic drainage. Thus, absorption is mainly determined by factors, both **physicochemical** (such as the size of the molecule, its electrostatic charge and solubility) and **physiological** factors (those arising from the interaction of the administered drug with endogenous compounds, such as ECM, local blood/lymphatic flow, depth of SC tissue and/or the influence of tissue hydration), but it can also be influenced, to a lesser extent, due to **other factors7; 49; 52** as shown in the table below:

Factors influencing absorption after SC administration:

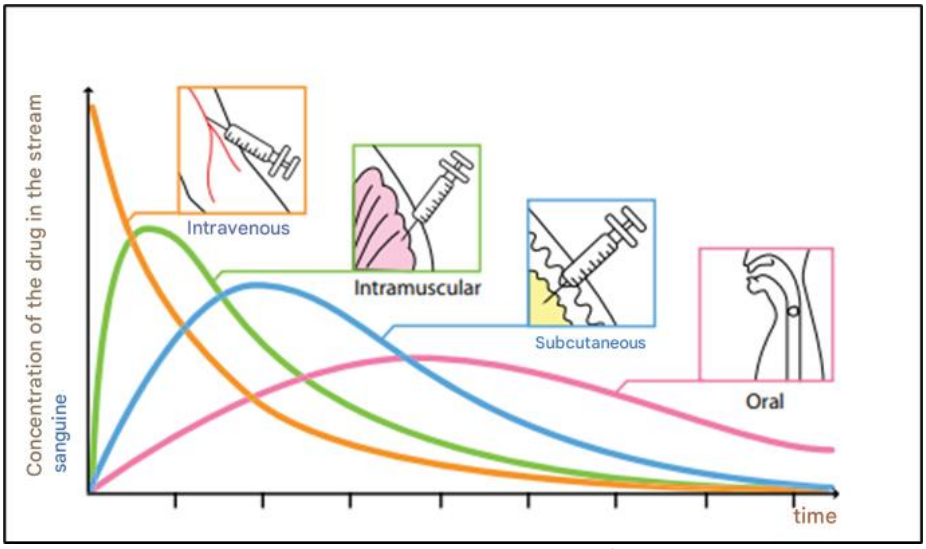
FACTOR	EFFECT ON ABSORPTION	COMMENT
SYSTEMIC:		
Hypoalbuminaemia	Direct	Reduction in oncotic plasma pressure
Hypotension	Direct	Effect on infusion
PLACE: (at the puncture site)		
Connective tissue/puncture site	Indirect	Acts as a barrier to diffusion
Perfusion of the puncture site	Direct	Less vascularity = less absorption
Puncture depth	Direct	The deeper the puncture, the faster the absorption
Frequency of administration	Indirect	The frequency of SC administration at the same site will influence absorption
DRUG:		
Molecular Weight (PM)	Indirect	PM < or = 16 KDa reach the systemic circulation through the blood capillaries PM > 16 KDa reach the bloodstream through the lymphatic vessels with delayed onset of action
Infusion volume	Indirect	Secondary to capillary compression
ph	Direct	Neutral solutions are better absorbed SC Some drugs with acidic pH can be SC infused as long as at a slow speed Buffers used: phosphate, carbonate, citrate or histidine

Drug concentration	Indirect	Improved tolerance by dilution with isotonic solutions or by decreasing the infusion rate
Water solubility	Direct	Water-soluble: better absorbed by connective and adipose tissue; Less irritating, less risk of build-up
Oily medications or excipients	Indirect	Fat-soluble: irritant, with a higher risk of precipitation and accumulation, correlated with abscesses and edema
Molecule/Drug Charge	Indirect	The charge of the ECM favors the transport of negative molecules
Viscosity	Indirect	High viscosity represents an obstacle to absorption
Temperature	Direct	The closer to physiological temperature, the faster absorption
ADDITIVES:		
Local anesthetic	Indirect	Causes vasoconstriction
Local cold	Indirect	Causes vasoconstriction
Local massage	Direct	Increase in local vascularity
Hyaluronidase	Direct	Mucolytic enzyme used as a factor that increases local absorption

Source: Adapted/translated Duems-Noriega and Ariño-Blasco (2015)[7].

COMPARED TO OTHER ROUTES OF ADMINISTRATION, WE HAVE:

Variation in the concentration of the drug in the bloodstream over time:



Source: Azevedo (2016)[10].

- ✓ **The SC and IV routes are NOT equivalent**: although the doses used are similar to those of the IV route, the drugs administered by the SC route are absorbed more slowly, but in some cases they can reach the same plasma concentration as if administered EV10; 24;53.
- ✓ **The SC and IM routes have similar kinetics**, however, drugs administered by the SC route tend to reach lower serum concentrations, but for a longer time50 (similar to an extended-release system)[24; 33].

- ✓ **SC absorption tends to be slower than IM,** consequently, irritants can cause greater inflammatory reactions via SC than via IM10.
- ✓ Its **kinetics**, with longer absorption time, can provide **more stable serum concentrations of the drugs**, avoiding undesirable side effects as a result of plasma peaks: **optimal for pain control with opioids50; 8**.
- ✓ A consensus is that the **dose administered by the SC route should be lower than the oral dose,** since the use of the subcutaneous route implies greater bioavailability of the drugs10.

Summing up

Advantages*	Disadvantages*
▪ More **affordable** and **comfortable** than the EV route with **range gain**; ▪ **Easy** catheter insertion and maintenance technique (can even be used at **home and/or outpatient**) ▪ **Low cost** (of material involved, as it facilitates/promotes deinstitutionalization of the patient, and for the shorter time spent by nursing professionals); ▪ It is **safe**: reduced local complications; low risk of systemic adverse effects; and low rates of infectious complications. ▪ It is **effective:** it provides better symptomatological control, with fewer side effects due to the reduction of fluctuation in plasma concentrations of drugs, especially pain control with opioids.	▪ **Restriction of medications and electrolytes** that can be infused. ▪ **Limited infusion volume and speed** (up to 1500 ml/24h per puncture site, at a rate of 1 ml/minute). ▪ **Not feasible for rapid adjustment of doses.** ▪ **Variable absorption** (depends on perfusion, diffusion, balance between hydrostatic and osmotic pressure, and lymphatic drainage, which, in turn, vary according to the patient's clinical conditions). ▪ Skin reactions at the infusion site **(erythema, oedema, cellulitis, bruising, pain, infections and/or abscesses) may occur (< 5%).**
**10; 22; 12; 27; 8; 29; 35	

OFF-LABEL USE OF DRUGS BY SC ROUTE: GENERAL PRINCIPLES!

The safe *off-label* use of drugs by the CS route is a complex multidisciplinary process that requires, in addition to the specific technical knowledge briefly mentioned above, certain precautions in order to avoid adverse events before, during or after administration, as well as problems of incompatibilities54.

However, when it comes to *off-label* use, information about it, in addition to being scarce, is also often conflicting and divergent and, therefore, a standardization of conducts (through a guide) is so important and necessary[4; 10; 23; 50; LIFE 53].

In **general,** it is stated that:

- ✓ It is a consensus that medicines must be in liquid form.

- ✓ To optimize the effects and minimize pain, irritation and tissue damage, the ideal drug for SC administration should be **water-soluble**, with neutral **pH (or close to neutrality: 7.38 – 7.45),** low **viscosity and low molecular weight**.
- ✓ Medications with extreme pH values (<2 or >11) should be avoided, as they present a higher risk of precipitation or local irritation35.
- ✓ **Hypertonic, hypotonic and fat-soluble** solutions may not **be infused.**
- ✓ Drugs with low water solubility require dilution in oil solutions, which increases the likelihood of pain and edema after subcutaneous infusion.
- ✓ As for fluid infusion, it is known that isotonic solutions are considered safe for subcutaneous use.
- ✓ Regarding the dilution of medications, there is also no clear consensus in the literature (and the routines adopted by each service differ greatly from each other). In any case, **dilution is always recommended** to minimize irritation at the puncture site.
- ✓ The administration of more than one drug at the same site requires caution: parenteral administration of drugs is a recognized cause of medication error, and the incompatibilities and stability of drug combinations is a matter of patient safety.
- ✓ Although many **mixtures appear physically compatible** (clear, colorless, and free of precipitates), **the risk of chemical incompatibility cannot be ignored.**

In any case, drugs such as **N-butylscopolamine bromide** or **hyoscine** (pH:3.7-5.5), **haloperidol** (pH: 3-.0-3.8), **metoclopramide** (pH: 3.0-5.0), and **ondansetron** (pH: 3.5), despite the **acidic pH**, can be administered via CS, as long as it is **SLOW** and in **proper dilution10; 33; LIFE 35**.

SC infusions can be bolus, intermittent or continuous, according to need10;22. The different puncture sites have different volumetric capacities. But, in practice, do not forget: the tolerance of each site varies according to the patient's conditions and the volume to be infused10.

As for solutions, **sodium chloride (NaCl) or 0.9% saline (SF), glycophysiological solution and 5% glucose solution or glucose serum (5% SG)** are considered **safe and well tolerated.** However, **electrolyte** administration can be done **as long as DILUÍDOS10; Death 30**.

For prescribed volumes greater than 1500 ml per day, a second access is recommended on the opposite side of the first installation50;53.

Such volumes of infusion by the SC route can be explained by the fact that the lymphatic system returns to the systemic circulation between 2 and 4 liters of lymph every day and this volume represents about 6% of the cardiac output, contrary to the generalized information in undergraduate and professional training courses, that the maximum volume for infusion by the SC route described is between 0.5 and 1.5 ml[33].

In addition, there are numerous express recommendations to **DO NOT INFUSE**: **phenytoin**, **diazepam**, **diclofenac**, **chlorpromazine**, glucose solutions **greater than 5%, colloidal solutions**, **total parenteral nutrition**, **blood** and **blood products10; LIFE 34**.

Regarding the infusion rate, the ***bolus speed*** should always be **SLOW.** The use of microdroplet sets is generally recommended in the literature for continuous gravitational infusions. However, the use of Infusion Pumps (IB) ensures the constant and more precise administration of the drug, being especially useful for the administration of analgesics and sedatives, not only because it avoids rapid and inadvertent infusions, but also because it prevents the plasma concentration from decreasing below the therapeutic level, which can favor the reappearance of symptoms10;33. The recommended infusion rate is from 60 ml/h to a maximum of 125 ml/h. At an average infusion rate of **1 ml/min (i.e., 60 ml/h**), the absorption of solutions occurs without significant edema even in patients with scarcer CS tissue24;33.

Thus, it is recommended that the forms of drug administration, volumes, infusion times and speeds, and types of diluents be carefully observed in order to avoid compromising patient safety, therapeutic failure and/or ADRs.

DRUGS SELECTED FOR *OFF-LABEL USE* BY THE SC ROUTE AT THIS INSTITUTION:

GUIA DE MEDICAMENTOS PARA TERAPIA SUBCUTÂNEA (USO *OFF-LABEL*)

MEDICAMENTO E APRESENTAÇÃO	CLASSE TERAPÊUTICA	DOSE*	DILUIÇÃO	INFUSÃO	SÍTIO EXCLUSIVO	OBSERVAÇÃO
BUTILBROMETO DE ESCOPOLAMINA (HIOSCINA) 20mg/ml - ampola de 1ml	ANTIESPASMÓDICO E ANTICOLINÉRGICO	20 a 120mg / 24h	1ml de SF para cada 1ml da solução medicamentosa	Bólus	Não	
BROMOPRIDA** 5 mg/ml - ampola de 2ml	PROPULSIVO	**	1ml de SF para cada 1ml da solução medicamentosa	Bólus	Sim	
DEXAMETASONA 4 mg/ml - F/A de 2,5 ml	GLICOCORTICÓIDE	2 a 16mg / 24h	1ml de SF para cada 1ml da solução medicamentosa	Bólus (até 4ml) ou Infusão gravitacional a 1ml/minuto	Não	Risco de irritação local
DIPIRONA 500 mg/ml - ampola de 2ml	ANALGÉSICO E ANTIPIRÉTICO	até 8g /24h	20ml de SF para cada 2ml da solução medicamentosa	Infusão em BI: 20 a 30 minutos	Sim	
FENTANIL*** 0,05 mg/ml - ampola de 2ml 0,05 mg/ml - ampola de 5ml 0,05 mg/ml - ampola de 10ml	ANALGÉSICO OPIÓIDE	A critério médico (ACM)	50ml de SF para cada 2ml da solução medicamentosa	Infusão em BI: 20 a 60 minutos ou ACM	Sim	
FUROSEMIDA 10 mg/ml - ampola de 2ml	DIURÉTICO	20 a 140mg / 24h	1ml de SF para cada 1ml da solução medicamentosa	Bólus (até 4ml) ou Infusão contínua	Sim	
HALOPERIDOL 5 mg/1ml - ampola de 1ml	ANTIPSICÓTICO	0,5 a 30mg / 24h	SF* 5ml	Infusão lenta	Não	*Se a solução preparada tiver concentração > ou = 1mg/ml, recomenda-se usar água destilada como diluente (risco de precipitação com SF) Risco de prolongamento do intervalo QT
METOCLOPRAMIDA 5mg/ml - ampola de 2ml	PROPULSIVO	30 a 120mg / 24h	50ml de SF para cada 2ml da solução medicamentos	Infusão em BI: 30 minutos	Não	Risco de irritação
MIDAZOLAM 5mg/ml - ampola de 3 ml 5mg/ml - ampola de 10ml	HIPNÓTICO E SEDATIVO	1 a 5mg (bólus) 10 a 120mg /24h (infusão)	1ml de SF para cada 1 ml da solução medicamentosa (até dose de 5 mg) ou 50 a 100ml de SF	Bólus (até 4ml) ou Infusão gravitacional a 1ml/minuto ou Infusão contínua	Não	Risco de irritação local
MORFINA 10mg/ml - ampola de 1 ml	ANALGÉSICO OPIÓIDE	2 a 3 mg 4/4h (Bólus) ou 10 a 20mg /24h (Infusão) (não existe dose "teto")	Bólus: não requer diluição Infusão gravitacional: 1 ml de SF para cada 1 ml da solução medicamentosa ou Infusão contínua: 100ml de SF	Bólus (até 4ml) ou Infusão gravitacional a 1ml/minuto ou Infusão contínua	Não	Iniciar com a menor dose possível em pacientes muito idosos, frágeis ou com doença renal crônica Pode-se aumentar o intervalo das aplicações em casos de insuficiência hepática ou renal
ONDANSETRONA 4 mg (2 mg/ml) - ampola de 2ml 8mg (2 mg/ml) - ampola de 4ml****	ANTIEMÉTICO E ANTINAUSEANTE	4 a 24mg / 24h	30 ml de SF	Infusão em BI: 30 minutos	Não	Risco de prolongamento do intervalo QT
TRAMADOL 50mg/ml - ampola de 1ml 50mg/ml - ampola de 2ml	ANALGÉSICO OPIÓIDE	100 a 400mg /24h	50 ml de SF para cada 1ml da solução medicamentosa ou 100 ml de SF	Infusão gravitacional a 1ml/minuto ou Infusão contínua	Não	

SF = Soro Fisiológico 0,9% e BI = Bomba Infusora Adaptado do Guia da SBGG e ANCP, 2a edição, 2017 e INCA, MS, 2021

* As doses sugeridas podem ser alteradas pelo prescritor conforme necessidade.

** Medicamento apresentado como opção terapêutica apenas no manual do INCA, o qual não sugere dose.

*** No INCA seu uso é restrito a casos excepcionais por considerarem os estudos frágeis e/ou pouco robustos.

**** Apresentação não padrão na Instituição, porém pode ser utilizada em substituição à apresentação padrão, se necessário. (Mesma concentração que a apresentação padronizada.)

LEMBRETES:

As infusões em "bólus" devem ser sempre LENTAS.

O uso de antimicrobianos por esta via (SC) é PROSCRITO nesta Instituição de acordo com a Rotina de Interface das Áreas do Instituto n128.

GUIA DE MEDICAMENTOS PARA SOROTERAPIA / FLUIDOTERAPIA SUBCUTÂNEA (USO *OFF-LABEL*)					
MEDICAMENTO	**APRESENTAÇÃO**	**DOSE**	**DILUIÇÃO**	**INFUSÃO**	**SÍTIO EXCLUSIVO**
SORO FISIOLÓGICO 0,9% (SF) (CLORETO DE SÓDIO 0,9%)	Solução injetável - sistema fechado - frascos de 100, 250, 500 e 1000 ml	Máximo de 1500ml/24h por sítio		Veloc. Máxima de infusão = 62,5 ml/h	Coxa é preferencial para volumes maiores
SORO GLICOFISIOLÓGICO		Máximo 1500ml/24h por sítio	2/3 SG 5% + 1/3 SF	Veloc. Máxima de infusão = 62,5 ml/h	Coxa é preferencial para volumes maiores
SORO GLICOSADO 5% (SG) (GLICOSE 5%)	Solução injetável - sistema fechado - frascos de 100, 250 e 500 ml	Máximo de 1000ml/24h por sítio		Veloc. Máxima de infusão = 62,5 ml/h	Coxa é preferencial para volumes maiores
CLORETO DE SÓDIO 20% (NaCl 20%)	Ampola de 10 ml	10 a 20ml / 24h	SF ou SG 5% > 100ml	**SEMPRE** diluído em SF ou SG 5%, em volume superior a 100ml Veloc. de infusão = 62,5 ml/h	Sim

Adaptado do Manual da SBGG, 2a edição, 2017 e INCA, MS, 2021

SF = soro fisiológico 0,9%
SG 5% = soro glicosado 5%
Veloc. = Velocidade

For a better understanding of this picture, take into account the rules of traffic lights!

- ✓ **GREEN =** Move on or... You can match!
- ✓ **YELLOW =** Attention!! Untested compatibility! Administer the drugs separately: preferably in different sites and far from each other.
- ✓ **RED =** Stop! Do not mix these medicines! Administration **should be** carried out **in different and distant sites**!

QUADRO DE INCOMPATIBILIDADES DE MEDICAMENTOS PARA TERAPIA SUBCUTÂNEA

MEDICAMENTO		1 BUTILBROMETO DE ESCOPOLAMINA (HIOSCINA)	2 BROMOPRIDA	4 CLORETO DE SÓDIO 20% (NaCl 20%)	5 DEXAMETASONA	6 DIPIRONA	7 FENTANIL	8 FUROSEMIDA	9 HALOPERIDOL	10 INSULINA	11 METOCLOPRAMIDA	12 MIDAZOLAM	13 MORFINA	14 NALOXONA	15 ONDANSETRONA	16 TRAMADOL	MEDICAMENTO	
1	BUTILBROMETO DE ESCOPOLAMINA (HIOSCINA)	*			C		C	I	C		C	C	C		C	C	BUTILBROMETO DE ESCOPOLAMINA (HIOSCINA)	1
2	BROMOPRIDA		*					I									BROMOPRIDA	2
4	CLORETO DE SÓDIO 20% (NaCl 20%)			*				I									CLORETO DE SÓDIO 20% (NaCl 20%)	4
5	DEXAMETASONA	C			*		I	I	I	C	C	I	C		I	C	DEXAMETASONA	5
6	DIPIRONA					*		I									DIPIRONA	6
7	FENTANIL	C			I		*	I	C		C	C			C		FENTANIL	7
8	FUROSEMIDA	I	I	I	I	I	I	*	I	I	I	I	I	I	I	I	FUROSEMIDA	8
9	HALOPERIDOL	C			I		C	I	*		C	C	C		C	C	HALOPERIDOL	9
10	INSULINA				C			I		*	C	C	C				INSULINA	10
11	METOCLOPRAMIDA	C			C		C	I	C	C	*	C	C		C	C	METOCLOPRAMIDA	11
12	MIDAZOLAM	C			I		C	I	C	C	C	*	C		C	C	MIDAZOLAM	12
13	MORFINA	C			C			I	C	C	C	C	*		C	I	MORFINA	13
14	NALOXONA							I						*			NALOXONA	14
15	ONDANSETRONA	C			I		C	I	C		C	C	C		*		ONDANSETRONA	15
16	TRAMADOL	C			C			I	C		C	C	I			*	TRAMADOL	16
MEDICAMENTO		BUTILBROMETO DE ESCOPOLAMINA (HIOSCINA)	BROMOPRIDA	CLORETO DE SÓDIO 20% (NaCl 20%)	DEXAMETASONA	DIPIRONA	FENTANIL	FUROSEMIDA	HALOPERIDOL	INSULINA	METOCLOPRAMIDA	MIDAZOLAM	MORFINA	NALOXONA	ONDANSETRONA	TRAMADOL	MEDICAMENTO	
		1	2	4	5	6	7	8	9	10	11	12	13	14	15	16		

Adaptado do Guia da SBGG e ANCP, 2a edição, 2017 e INCA, MS, 2021

LEGENDA: C COMPATÍVEL | I INCOMPATÍVEL | NÃO TESTADO | * NÃO CONSTITUI MISTURA

ATENÇÃO: Em casos de incompatibilidades ou compatibilidades não testadas, a administração deve ocorrer em sítios distintos

*Attention! Remember to also check the compatibility of intermittent and *bolus infusions* with continuous infusions still in progress!! Thus, it is possible to optimize puncture sites and administration volumes, providing greater comfort to the patient!

CAN I MIX THE MEDICATIONS OR "SAVE" THEM FOR LATER USE?

Ideally, parenteral medications should always be infused in an exclusive route for each medication55. However, in clinical practice, the occurrence of (1) polypharmacy (common in PC and ICU) is frequent, associated with (2) a limited number of puncture sites/access routes. Together, these factors hinder the safe administration of medications, especially those of continuous infusions3; 56, which may favor the occurrence of medication errors (avoidable events) due to medication incompatibilities during infusion therapy.

Thus, the continuous administration of medications concomitantly with intermittent medication corroborates the occurrence of medication incompatibilities, especially when care regarding compatibility and scheduling of administration times are not considered3;57.

Drug incompatibilities are pharmaceutical interactions that occur outside the patient, i.e., when different drugs are mixed in the same syringe, serum, sets (via Y) or other devices3;58.

These drug reactions may result in changes in **the PHYSICAL characteristics** in the final solution (such as **color changes, turbidity, opalescence, crystal formation, flocculation, release of gases in the form of bubbles**, etc.) that may or may not be associated with **CHEMICAL changes** in the final solution (**not always visually observable**):

- **changes in pharmacological activity,**
- **decreased activity and/or inactivation of one or both drugs,**
- **formation of new compounds (unknown by-products and equally unknown/unpredictable pharmacological activities)**
- **poisoning by one or both drugs and/or their by-products**.

Incompatibilities result, therefore, in drug solutions that are no longer ideal for the patient, with well-documented consequences, such as **therapeutic inefficacy** (increasing hospitalization time and costs), **catheter occlusion** (which can cause infections) or **thromboembolic events** (such as embolism)[58; LIFE 59].

On the other hand, **pharmaceutical stability**, according to the World Health Organization (WHO), is the ability of the drug to maintain its chemical, physical and microbiological properties within the specified limits throughout its shelf life. Different factors, such as **temperature, humidity, light, pH**, **microbial contamination**, among others, compromise the stability of the drugs and, therefore, strictly controlled environmental conditions associated with good handling practices with aseptic techniques

is a *sine qua non* condition for **maintaining the quality of the drugs** (**and consequent expected efficacy and safety**) and the care provided60.

Thus, quite succinctly, the incompatibilities and stabilities of drug solutions used *off-label* via SC are important issues to be considered during drug preparation, and should not be overlooked in order to ensure not only patient safety, but also the efficacy of the therapy. Therefore, according to the SAFETY PROTOCOL IN THE PRESCRIPTION, USE AND ADMINISTRATION OF MEDICINES (GOV/MS/ANVISA), quick and accurate information must be available for consultation at the place of preparation or a pharmacist can be consulted.

However, given the scarcity of research in the area, evidence on the physical, chemical, and microbiological compatibilities and stability of solutions for continuous subcutaneous infusions is still very limited due to 2 main reasons: (1) laboratory analyses are expensive and laborious and (2) the number of potentially possible combinations is extremely variable and high16; 61;62.

Thus, it is also emphasized that although many combinations may **seem physically compatible** (e.g., clear, colorless, and free of precipitates), **the risk of chemical incompatibility cannot be ignored62**. Thus, **under no circumstances should you consider administering a mixture of medications based solely on the clarity and/or clarity of the resulting drug solution. Remember: chemical reactions are not always visible** and **can compromise the safety and effectiveness of the therapy**.

OPTIMIZING THE USE OF THE GUIDE!!

1. Whenever possible, mixing of medications should be avoided;
2. If mixing cannot be avoided, refer to the guide to check the compatibility between the drugs;
3. It is also recommended that each puncture site receives, **AT MOST, 03 (three)** drugs compatible with each other;
4. Even if the guide attests to compatibility between the drugs, **ALWAYS** observe the **final appearance of the mixture** (clarity, absence of turbidity, precipitates, flocculation, crystals, etc.) before administering;
5. In case of incompatibilities or lack of knowledge about it (untested compatibilities), it is recommended to administer the drugs at different puncture sites and distant from each other;
6. For incompatible medications administered in **Y equipment,** be sure **to salinize the route with 0.9% saline between each medication**.

7. Given the lack of information on the stability of mixtures for *off-label* SC use, drugs should only be prepared **immediately BEFORE** use;

RATIFYING!!

- ✓ Storage of the drug solution prepared for *off-label* administration by SC route is not recommended and should be discarded if not immediately used.
- ✓ **Do not administer** mixtures classified as **untested** or **incompatible** even if the final solution is clear, clear, free of precipitates, flakes, crystals, bubbles, etc.!!
- ✓ If any information contained in this guide differs from the information provided by the manufacturer, it is recommended, for legal support, to follow the manufacturer's recommendations.

WHAT ABOUT ANTIBIOTICS??

Recent scientific evidence has shown success in the use of antibiotics by the CS route, however the levels of evidence vary from moderate to weak, demonstrating the need for further research in this area63;64.

Comparative studies have shown that the SC and IV routes have similar efficacy for ceftriaxone, teicoplanin, and ertapenem (in patients with NON-severe infections). And the SC use of other antibiotics such as ampicillin, ceftazidime, cefepime, piperacillin/tazobactam, metronidazole and fosfomycin have also been described in the scientific literature. The results have shown ample corroboration by pharmacokinetic/pharmacodynamic analyses, especially for time-dependent antibiotics, as well as pointing out that complications of SC therapy are rarely severe, with no reports of bacteremia or other invasive infection related to this route of administration, although they ratify the importance of adequate therapeutic monitoring of drugs by this route in order to better adjust the dose and avoid toxicity[64]element.

On the other hand, **bone and joint infections (IOAs)** are among the **most difficult infectious diseases to treat** and have complex management, which requires a multidisciplinary approach, from diagnosis to the choice of the best medical-surgical strategy, given that there are different types of IOAs. The administration of antibiotics for long periods of time during the treatment of IOA is complex, with loss of venous accesses, contraindication of the IM route due to the use of anticoagulants, and pain and poor adherence to the oral procedure. Recent research has demonstrated the *off-label use* of beta-lactam antibiotics and teicoplanin by the SC route, presenting themselves as safe and interesting alternatives for cases in which a **surgical strategy or oral procedure are not**

feasible in IOAs65; 66; 67;68. However, some authors even emphasize that **the IV route should continue to be the preferred route for administering the loading dose in the acute phase of a SEVERE infection,** and administration by the SC route would act as part of a change once the infection is under control66.

Thus, it is ratified that an appropriate antimicrobial therapy is essential to ensure a positive outcome, as therapeutic failure can be devastating and is usually related to factors such as: subtherapeutic serum concentration, inadequate administration time, as well as lack of adjustments according to the patient's kinetic changes[69]. Thus, in the context of *off-label* antibiotic therapy by SC route, studies propose an original approach to drug dosage, based on **therapeutic drug monitoring**, **determination of the Minimum Inhibitory Concentration**, and **individualized pharmacokinetic/pharmacodynamic goals**, facilitating and optimizing antibiotic therapy by SC route in Prosthetic Joint Infections (PAIs)[70].

Thus, given the information previously exposed about the variability in the absorption kinetics of *off-label* drugs by this route, added to the difficulties in carrying out and scarcity of large randomized and controlled studies in vulnerable populations, and also considering the highly specific characteristics of certain infectious conditions, especially IOAs (with prolonged treatment time, in general) and, consequently, **in order to prevent microbial resistance**, **the *off-label* use of antibiotics by the SC route is not provided for in the routines of this institution,** and it is therefore recommended that **any possible need for their use be previously discussed with the Hospital Infection Control Committee (HICC) and communicated to the Infusion** Therapy Committee to regulate the necessary adjustments (such as forms of dilution and infusions, for example), according to the hospital routine.

MONITORING AND FOLLOW-UP

But what if reactions occur?

Reactions can occur even when the drug is administered correctly. Thus, it is important to confirm that ADRs are not necessarily related to medication errors (and vice versa).

Since the drug is used *off-label*, more rigorous monitoring is necessary in order to better evaluate the efficacy and safety of the therapy35.

Complications related to the use of the CS route are rare, usually local and easily avoidable and avoidable, especially when both dilution and infusion rates are respected (as well as when the technique is used correctly)[4; 10; 18; 22; 12; 29].

Therefore, be aware if local ADRs, such as **erythema, edema, extravasation, hematomas, bleeding, burns, abscesses, cellulitis or pain**, are detected:

1. Follow the conducts provided for in the institutional routine, regarding puncture and site change
2. Communicate the doctor and/or nurse responsible for the patient for better evaluation
3. Notify Risk Management (GRISC)

The occasional and rare risks of systemic complications (such as overhydration and cardiac overload) are minimal, since their first signs can be monitored during the (long) infusion period and, as soon as detected, the infusion is immediately interrupted8.

And always remember: effective communication between the healthcare team and the patient is essential to report any suspected ADRs or adverse events related to medications.

ATTENTION!!! In cases of SEVERE ADRs, do not forget to also notify the Infusion Therapy Committee so that more urgent measures or conducts can be quickly taken.

FINAL CONSIDERATIONS

It is an economical, sustainable and highly complex technical production (demands synergy and association of different areas of knowledge and the interaction of multiple actors - doctors, pharmacists and nurses). It also has high applicability and impact because it has been validated and adapted to the clinical reality and needs of palliative trauma and orthopedics patients, increasing its acceptance and confidence, and stimulating its use in practice. The guide contributes to patient and professional safety by reducing the occurrence of potential medication errors and helping to control unjustified variability in the different processes (whether in prescribing, dispensing and/or administering medications) related to *off-label* use of medicines. Finally, the guide will provide comfort and humanized care to patients, contributing to the excellence of the quality of services provided to patients in palliative care of traumatology and orthopedics.

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