

Subcutaneous drug supply in the practice of a primary care physician – a literature review

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Summary Subcutaneous administration of drugs can be an important element of a patient's home therapy with proper treatment initiation and continuation rules. Caring for a dying patient requires an interdisciplinary approach and extensive cooperation between many specialists, including palliative care specialists and primary care physicians. The possibility of treating patients from special risk groups (patients requiring palliative care, elderly patients, debilitated patients) and a wide range of drugs which can be safely prescribed make this method appropriate for use in family practice. The most commonly used medications for symptom control in patients at home can be safely used through this method.

There are limitations and even contraindications in the use of high-density and osmolarity drugs, as well as drugs used in chemotherapy. The use of drugs in subcutaneous supply may constitute a smooth transition from the currently used treatment (change of the form of drug administration) or allows for the introduction of new drugs for treatment. It should be noted that for some of the drugs, subcutaneous supply is a supply beyond registration. The most commonly used and recommended puncture at present is a synthetic intravenous puncture of the cannula type.

In order to implement subcutaneous supply, it is necessary to know the rules of this form of treatment and their limitations.

Key words: hypodermoclysis, primary health care, palliative care.

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Background

Caring for a dying patient requires an interdisciplinary approach and extensive cooperation between many specialists [1]. The coverage of palliative care at home by a home palliative care team or a palliative medicine clinic seems to be the best option. However, it is imperative to understand the limitations of this model of care. Territorial differentiation regarding individual palliative care services [2], the small number of palliative medicine specialists, the queue when waiting for care [3] and deterioration of contact between the patient and the family doctor who is currently caring for it are just some of the threats. The implementation of palliative care should take into account the activity of the primary care team, and its members should have the skills necessary to conduct effective medical intervention in patients at the end of life.

One of the elements of health care provided by the primary care physician and the primary healthcare nurse is the effective supply of medicines to the patient at home. For patients with swallowing disorders, in severe condition, debilitated patients and those who do not take meals or drugs orally, this means carrying out parenteral treatment. Such an effective and safe form can be subcutaneous administration at home. Literature on the subject discusses the subcutaneous supply of infusion fluids as a safe form [4, 5]. In this article, literature data on the subcutaneous administration of drugs has been collected.

Methods section

To conduct a literature review for this scientific paper, we follow a systematic approach to ensure comprehensive coverage of relevant literature.

1. The research objective that the literature review aims to address was determined.
2. Appropriate databases were selected: PubMed/MEDLINE and Google Scholar.
3. Search terms and keywords were developed: a list of relevant search terms and keywords related to research objectives were created.
4. Search queries were constructed: search terms were combined by using Boolean operators (“AND,” “OR,” “NOT”) to build search queries. Parentheses were used to group related terms and refine the search. Different combinations were checked to optimise the search results.
5. Filters and limits were applied that included publication date range (1985–2023), language (English, Polish, Portuguese) and specific article types (original research and reviews and recommendations).
6. Search results were reviewed.
7. The search was expanded: reference lists of the articles were examined for additional sources.

The research was based on key words: hypodermoclysis, subcutaneous drug, subcutaneous administration of drugs. For



Identification	Records identified through database searches	PubMed/Medline (<i>n</i> = 1,745) Google Scholar (<i>n</i> = 685) Total number after this step (<i>n</i> = 2,430)
Screening	Duplicates removed	Number of duplicates (<i>n</i> = 662) Total number after this step (<i>n</i> = 1,768)
	Research screened	Wrong outcome (<i>n</i> = 342) Wrong intervention (<i>n</i> = 321) Study not published (<i>n</i> = 3) Recommendation of unknown source (<i>n</i> = 1) Total number after this step (<i>n</i> = 1,101)
Eligibility	Eligibility assessment	No relation to family medicine, palliative medicine or home environment (<i>n</i> = 545) No relation to end of life (<i>n</i> = 511) Total number after this step (<i>n</i> = 45)
		Total number (<i>n</i> = 45)
Included		

Figure 1. Flowchart illustrating the inclusion process

narrowing the results, additional key words were chosen: family medicine, palliative medicine, general practice, end of life, home care. We included 45 articles. We excluded 2,385 articles.

From the 2,430 papers collected during the initial search in databases, 45 publications from the years 1985–2021 in Polish and English and 1 in Portuguese, which met the inclusion criteria, were analysed after translation.

The research was conducted in accordance with the Declaration of Helsinki. The consent of the Bioethical Committee of the Medical University of Wrocław was obtained, decision number KB 472/2020, registration number: CWN UMW: SUB. C290.19.054.

Experience

Subcutaneous supply was common in the 1930s and 1940s. It was then superseded by peripheral intravenous supply. This has been experiencing its renaissance since the end of the 1990s. An analysis conducted in 2020 by Wells and MacDougall from the Canadian Agency for Drugs and Technologies in Health in the field of clinical effectiveness, cost and recommendations for the use of subcutaneous drug supply [6] revealed that the available literature data is still modest, and the area of drug supply by subcutaneous route requires further research. One study conducted in 2018 confirming the cost-effectiveness of this method was disclosed [7].

Earlier, in 2015, Bruno conducted a systematic analysis of literature on the safety of the use of subcutaneous administration [8]. The analysis showed that the subcutaneous method is cheaper and simpler than intravenous supply [9]. Its main complication is local oedema, which may undergo self-resorption or can be treated with local massage. Moreover, the method of subcutaneous administration is indicated as safe, both for saline solutions [10] with a concentration of 0.9% and for glucose 5%.

All family doctors should know and use this method of irrigating the patient.

The pharmacokinetics of drugs administered in this way can be compared to peripheral intravenous administration [11] with the proviso that enzymes present in the tissues may lead to a partial decomposition of the active substance already at the site of administration.

Advantages and disadvantages of subcutaneous supply

Literature indicates the significant benefits of subcutaneous drug administration. This method is not free from disadvantages, the existence of which one should be aware of when starting treatment. Key benefits include low cost, improved

patient comfort, ease of relocation of medication, possibility of delivery by trained caregivers, low hardware requirements and ease of access. Key benefits include low cost, improved patient comfort, ease of relocation of medication, possibility of delivery by trained caregivers, low hardware requirements and ease of access. At the same time, significant disadvantages include a typical low rate of supply (1 ml/minute), limitation in the total amount of fluids administered (up to 3,000 ml/day), local tissue swelling, the inability to administer this method of nutrition and hypertonic solutions [8].

Drugs for subcutaneous administration

Analysis of domestic and foreign literature on the possibility of subcutaneous administration of drugs available in solutions was performed. The most commonly used medications for symptom control in patients at home can be safely used by this method. There are limitations and even contraindications in the use of high-density and osmolarity drugs, as well as drugs used in chemotherapy.

The most common active substances, indications for their use and the proposed doses of the drugs administered subcutaneously are summarised in Table 1.

The use of drugs in subcutaneous supply may constitute a smooth transition from the currently used treatment (change of the form of drug administration) or allows for the introduction of new drugs for treatment.

Consideration should be given to the administration of painkillers by the subcutaneous method. In this way, painkillers from the group of non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol, tramadol and morphine, which are available in solutions, can be administered [11, 12]. The European Association for Palliative Care explicitly recommends the use of subcutaneous morphine when oral administration is not possible [13].

It should be noted that for some of the drugs listed here, subcutaneous supply is a supply beyond the registration described in the Summary of Product Characteristics [14].

Antibiotics can also be given by the subcutaneous method [41]. For some of these, literature is very limited (single reports or small groups of respondents). Literature indicates that the subcutaneous method may be a good alternative if it is necessary to use a method other than the oral administration of an antibiotic, subject to caution, especially in the group of patients in palliative care.

Analysis of literature in the field of subcutaneous ceftriaxone supply deserves special attention. Although the peak concentration achieved in the blood was lower for the subcutaneous route of administration than for the peripheral intravenous route, fully satisfactory plasma levels were achieved

Table 1. List of drugs for subcutaneous supply with their dosing		
Recommendations	Active substance	Dosing
Mild to moderate pain (NRS 1–3)	Paracetamol [15, 16] (rarely used in this method of administration in Poland) Selected NSAIDs Ketoprofen [17] Diclofenac [18]	15 mg/kg body weight up to 4 x/day, in total up to 4 g/day, and in malnourished patients with liver diseases, in dehydration, up to 2 g/day in total Usually 50–100 mg/dose up to 2 x/day, briefly (local reactions possible) 50 mg every 8–12 hours
Moderate pain (NRS 4–6)	Tramadol [19] or morphine sulphate (see below)	50–100 mg/dose, every 4–6 hours, in total not more than 400 mg/day
Severe pain (NRS 7–10)	Morphine sulphate [20, 21]	According to the conversion of the equivalent dose from the treatment used so far (converting the daily dose of oral morphine to parenteral morphine, we use a ratio of 3:1 or 2:1), in addition, if the patient's condition worsens, it is recommended to reduce the dose by 20–60% or titration by subcutaneous method 2.5–5 mg of morphine sulphate every 15–20 minutes until satisfactory analgesia/side effects are achieved, then administration every 4–6 hours 1/2 of the total dose administered short-term administration of 1/6 of the daily dose
Dyspnoea	Morphine sulphate [22, 23]	2.5–5 mg/dose, every 4 hours
Vomiting	Ondansetron [24] Metoclopramide [25] Haloperidol [26–28] Chlorpromazine (Fenactil) [29] Levomepromazine (Tisercin) [30, 31]	8 mg 2–3 x/day 10 mg/dose up to 3 x/day 1–2 mg/dose, typically up to 10 mg/day 25–50 mg/dose 25 mg every 12 hours (higher doses may be recommended), dilute with physiological saline as skin reactions are possible
Hiccups	Haloperidol [26–28] Metoclopramide [32]	1–2 mg/dose, typically up to 10 mg/day 10 mg/dose up to 3 x/day
Gastroduodenal Ulcer	Ranitidine [33]	50–75 mg/dose, every 8–12 hours
Contraction of the respiratory, digestive and urinary tracts and the reduction of secretions in the respiratory tracts or in the digestive tracts	Hyoscine butylbromide [34, 35]	20 mg/dose, should not exceed 100 mg/day
Bleeding	Tranexamic acid (Exacyl) [36]	500–1,000 mg 2–3 times/day, and in case of renal failure – reduced doses
Arousal	Haloperidol [26–28] Midazolam [23] Levomepromazine (Tisercin) [31, 37]	0.5–2 mg/dose, typically up to 10 mg/day 2 mg every 4–6 hours (higher doses or more frequent doses may be recommended) 25 mg, every 12 hours (higher doses may be recommended) Dilute in saline as skin reactions are possible
Oedema, congestive heart failure, high blood pressure	Furosemide [38]	20–40 mg/day under blood pressure and diuresis control (1–2 ampoules/day)
Pain, swelling, breathlessness, vomiting, cachexia	Dexamethasone [39, 40]	Depending on indications, usually 2–8 mg/day, also in divided doses; at elevated intracranial pressure, metastases to the CNS, spinal compression, gastrointestinal obstruction: 12–16 mg/day in divided doses

with a prolonged duration of action and a very similar rate of absorption to that of the intravenous and intramuscular route [41–43]. Studies were also conducted for antibiotics from other groups, including amikacin, teicoplanin or gentamicin, but due to the lack of their availability in open health care in Poland, the above-mentioned items are not discussed in this study.

Rationale for administering drugs subcutaneously

There are certain situations when subcutaneous drug administration should be considered. The use of subcutaneous supply

in the case of patients at home for the situations discussed in the article primarily includes:

1. Self-administration: Subcutaneous injections are frequently chosen when patients can administer medications at home on his/her own or by the caregivers. It provides convenience and reduces the need for medical assistance.
2. Prolonged drug release: Some medications, especially those used to treat pain, need to be released slowly and steadily over time to achieve the desired therapeutic effect.
3. Patient compliance: If patients have difficulty adhering to medication regimens, subcutaneous delivery can be an effective approach. By reducing the frequency of dosing, it can improve patient compliance and medication adherence.
4. Difficulties in providing a different form of drug supply: When oral or intravenous access is not available or feasible.
5. Emergency situations: In certain emergency scenarios, subcutaneous administration may be used.

Technique of inserting a puncture

The most commonly used and recommended puncture at present is a synthetic intravenous puncture of the cannula type (most often “blue”). The small diameter protects against too rapid administration (especially of liquids), and the Teflon tip does not irritate the tissues. Metal needles (so-called “butterfly”) are now recommended less frequently.

The puncture should be placed on the skin in the upper half of the body (front or back wall of the chest, shoulder area), possibly in the area of the skin of the abdomen or lower limbs (thighs).

1. Before inserting the puncture, prepare all of the necessary medical equipment (gloves (non-sterile), cannula, veneer, skin disinfectant, sterile gauze, syringe with drug prepared for administration).
2. The skin in the chosen area has to be disinfected. Choose an area of skin free from hair; alternatively, you can also (in advance) shave the area.
3. The cannula should be deeply inserted subcutaneously (lifting the skin fold by about 2–3 cm), at an angle of about 45 degrees to the surface of the skin; after insertion, remove the needle from the cannula.
4. The cannula should be glued to the skin using a veneer (preferably transparent).
5. The prepared medicine can be administered. Using the cap, plug the cannula.

Drug administration

In palliative medicine, a continuous subcutaneous infusion of certain drugs is practiced with the use of battery-powered portable syringe pumps for subcutaneous administration of drugs (in Polish conditions, it is possible for the home palliative care team to lend such a pump to a patient). The Scottish Palliative Care Guidelines also include guidelines on the use of a syringe pump for subcutaneous administration [44]. They are recommended as a useful means of drug delivery when the oral route cannot be used in a patient. According to the cited document, the recommended subcutaneous infusion is:

- pain medications (diamorphine, morphine, alfentanil or oxycodone),
- anti-sickness drugs (metoclopramide, cyclizine, haloperidol, levomepromazine),
- tranquilizers (midazolam),
- anti-secretory drugs (hyoscine butylbromide, glycopyrronium).

Regular subcutaneous bolus administration of a single drug or combination of drugs is recommended when a syringe pump is not available or there are not enough personnel trained to operate such a pump.

Patient caregivers can independently administer medications and fluids with subcutaneous access. There is no risk of bleeding, even if the cannula is ripped out. In practice, the inserted puncture is changed about every 2 weeks. The injection site should be changed if a skin reaction appears.

Caregivers should note that the drug is deposited in the subcutaneous tissue before absorption; hence, the appearance of slight swelling after drug administration is normal (the administered drug temporarily accumulates in the subcutaneous tissue). Each time, the drug should be “pushed” using a saline solution or injection liquid (the cannula has its own volume, usually about 0.5 ml).

The prepared syringes with drugs (including diluted drugs) can most often be stored for up to 24 hours, preferably without exposure to sunlight, at a temperature indicated by the manufacturer. The optimal volume for single administration is 1.5–2 ml, and saline may be added to complete the volume.

One puncture should be used to administer one drug.

Significant errors in the administration of subcutaneous drugs include:

- unclear instructions too superficially given to patient caregivers,
- lack of sufficiently well-trained staff to continue drugs administration,
- no plan for continuing treatment,
- insertion of one subcutaneous puncture (optimally, two should be inserted),
- no recommendation to “push” the dose of the administered medication,
- too rapid fluid supply or over-administration.

Alternatives

There are alternatives for subcutaneous administration: rectal suppositories, sublingual preparations, nasogastric tube, peripheral intravenous access, central access through the vascular port, and for patients under the care of a nutritional treatment clinic, the administration of drugs for PEG (Percutaneous Endoscopic Gastrostomy) or specialist tubes (intestinal, including in the form of an emerging stoma). All of these have their limitations. For the nasogastric tube, this is primarily the patient’s discomfort and the risk of retention of food in the stomach, vomiting and choking. For peripheral venous access, there is the risk of local and generalised infection and great difficulty in conducting such treatment at home (access service requires professional medical personnel). The central vascular port is a significant facilitation, but its insertion is possible only in hospital conditions, and the operation (due to rare use) is problematic for medical personnel. The simplest method seems to be the administration of drugs through PEG-type access or an intestinal tube.

Refund

Among the limitations in the use of subcutaneous drugs, in addition to those indicated earlier in the text, their reimbursement should be mentioned. There is a reimbursement for most drugs in the oral supply used in palliative medicine in Poland. This includes painkillers, glucocorticosteroids, antispasmodics and loop diuretics, among others. Their forms available in ampoules (for subcutaneous administration), with the exception of tramadol and morphine, are not refundable.

For example, the daily cost of treating a patient with dexamethasone (a glucocorticosteroid commonly used in palliative medicine) at a dose of 4 mg/day for oral administration is PLN 0.39–0.43, and subcutaneously, this is PLN 4.50– 7.10 [45]. This

can constitute a significant economic barrier for the patient and his caregivers to access this form of treatment. Hence, it is important to ensure that the patient is financially able to cope with treatment with the use of subcutaneous drugs.

Conclusions

The subcutaneous route is a safe and effective method of securing a drug supply to the patient during home care. Basic trained medical personnel (doctor and nurse) can successfully conduct such treatment, monitor its effectiveness and educate patients and their caregivers. This is a method that builds fam-

ily trust and creates security in terms of securing the changing health needs of the patient at the end of life. The use of subcutaneous access is a practice frequently used in palliative medicine. Therefore, this use by a general practitioner may be an important element in the treatment process.

The wide spectrum of subcutaneously administered drugs makes it possible to meet the patient's various health needs. However, it is important to be aware of the limitations on reimbursement of drugs in subcutaneous supply, which may have a negative impact on the choice of these drugs by the patient or their caregivers. This route is also underestimated in the case of the need for parenteral irrigation of the patient at home.

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