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Review article

The benefit/risk balance of subcutaneous injections as used in homeopathy and anthroposophic medicine: A narrative literature review

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ABSTRACT

Introduction: This review explores the benefit/risk balance of using subcutaneous injections. Overall, regulatory authorities regard that the use of injectables are only justified for acute cases and that oral products are better alternatives for both ethical and safety reasons. Conversely, Complementary & Alternative Medicine (CAM) pharmaceutical companies and doctors who prescribe injectables consider them to have additional clinical value compared with the oral route of administration (ROA), and consider the risk of the parenteral ROA as very low.
Methods: A narrative review was conducted. The favourable and unfavourable effects, the uncertainty of the effects and the possible mode of action of the subcutaneous ROA are described and an estimation of the benefit/risk balance is performed.
Results: The review demonstrates a high prescribers demand, and evidence on the existence of several favourable effects of the subcutaneous ROA (e.g., higher clinical efficacy, higher bio-availability, quicker onset of action), some unfavourable low risk effects of the subcutaneous ROA (e.g., risk related to exposure, substance and the needle) and overall a positive benefit/risk balance.
Conclusion: The results justify a more positive attitude from regulatory authorities towards the use of this ROA and towards ampoule prescribing doctors. However, given the small number of good studies on this topic, more research on the favourable and unfavourable effects, the uncertainties of these effects and the conceptualization of the working mechanism of the subcutaneous ROA is indicated.

1. Introduction

Current European standards demand medicinal products of high quality, safety and benefit. Therefore, pharmaceutical companies have to provide evidence of the benefits (e.g., efficacy/effectiveness), risks (e.g., quality, adverse events), and of the benefit/risk balance of their products. Subsequently, the European Medicines Agency (EMA) or national regulatory authorities can recommend the authorization of a medicinal product whose benefits are judged to be larger than its risks. In contrast, a medicine whose risks outweigh its benefits cannot be recommended for marketing [1].

In several pharmaceutical companies producing products used in CAM (Complementary and Alternative Medicine) practice, such as anthroposophic or homeopathic practices, one of the important types of products are the ampoules that are prescribed by doctors for parenteral administration (most often subcutaneous, sometimes intravenous).

Homeopathic and anthroposophic literature documents the use of injectables for over 100 years [2]. Today there are more than 90 million homeopathic/anthroposophic ampoules sold each year, prescribed by doctors for subcutaneous or other parenteral administration [3]. CAM pharmaceutical companies consider the subcutaneous or other parenteral ROA to have a surplus clinical value for clinical practice compared to the oral ROA [4]. In addition they consider the risk of the parenteral ROA in general very low. So overall CAM pharmaceutical companies regard the parenteral ROA to have a positive benefit/risk balance.

However, authorities in several European countries increasingly consider oral products to be better alternatives for ethical and safety reasons. Most important reason for this position is that the oral route of administration (ROA) is not intrusive and therefore has no health related risks associated with injections. In addition, it is claimed that there is currently neither a valid scientific concept of the surplus value of the subcutaneous route of administration, nor is there sufficient empirical evidence that demonstrates its clinical relevance. On the other hand, substantial evidence is also lacking for the position that ampoules prescribing doctors act unethically and expose their patients

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to unacceptable risks.

In order to acquire acceptance from the regulatory authorities for this ROA, scientific evidence has to be provided. This study therefore explores the current scientific evidence with regard to the surplus value, the risks and the benefit/risk balance of the parenteral ROA. Since the subcutaneous ROA is by far the most often used ROA compared to the intravenous ROA, this study is limited to this ROA.

2. Methods

A narrative review of the literature was executed on specific topics concerning the hypothesized surplus value, risks and the benefit/risk balance of this ROA. The following topics were explored:

1. With regard to the preconditions of assessing benefit/risk balances the following topics were studied:
   a. The categories and definitions of benefits and risks.
   b. The procedures to assess benefit/risk balances.
2. With regard to the hypothesized surplus value of the subcutaneous ROA the following topics were studied:
   a. The need/demand of the prescribers regarding the availability of ampoules and the reasons for this need (review of *practice-based evidence/expert knowledge*: clinically perceived surplus value of expert prescribers).
   b. The specific clinical effect of the ROA (review of the *empirical evidence from clinical research* comparing the subcutaneous and oral ROA).
   c. The mechanism of the ROA (review of the *mechanistic evidence/theoretical* added value of the subcutaneous ROA).
3. With regard to the risks and the hypothesized positive benefit/risk balance the following topics were studied:
   a. The risks and the magnitude of the risks of this ROA.
   b. The overall benefit/risk balance of this ROA.
4. With regard to the consequences of removing this ROA on the market the following topics were studied:
   a. The consequences for medicinal products in general.
   b. The consequences for anthroposophic medicinal products and homeopathic medicinal products.

2.1. Databases and other sources

We searched the website of EMA to study topic 1 and the databases PubMed, Google Scholar, and the Internet for topics 2–4, from the dates of their inception to May 2016. Combinations of the following search terms were used related to routes of administration (oral vs. subcutaneous), effects, safety, and two CAM specific medical systems: efficacy, effectiveness, route of administration, safety, vaccinations, oral, subcutaneous, parenteral, benefits, risks, acupuncture, immunotherapy, adverse reactions, adverse events, anthroposophy, homeopathy. Since this was a narrative review with an expected small number of relevant publications, all publications relevant for topics 1 to 4 were included in the analyses.

2.2. Analyses

The favourable and unfavourable effects and the uncertainty of the effects of the subcutaneous ROA are described and quantified, using the quantative results from the studies reviewed. An estimation of the absolute benefit/risk balance was performed, based on the input from the publications.

3. Results

3.1. Selection of studies

For choosing the *categories and definitions of benefits and risks and the procedures to assess benefit/risk balances*, we used the documents from the working group of the Committee for Medicinal Products for Human Use (CMPH) of EMA, that had worked on this topic. As a result two documents were used in this review.

Table 1
Overview of databases, search terms, numbers of hits and selected studies.

Database	Search terms	Number of hits
PubMed	oral AND subcutaneous/injection	47,110/11,559
	oral AND subcutaneous/injection AND anthroposophic/anthroposophy	0
	oral AND subcutaneous AND homeopathic/homeopathy	6
	oral AND injection AND homeopathic/homeopathy	9
Google Scholar	oral AND subcutaneous/injection	655,000/2.380,000
	oral AND subcutaneous AND anthroposophic	265
	oral AND subcutaneous AND homeopathic/homeopathy	3,880/3,870
	oral AND injection AND anthroposophic/anthroposophy	693/397
	oral AND injection AND homeopathic/homeopathy	10,900

The rest of the search strategy involved the use of multiple search terms with 'oral, subcutaneous or injection' as the basic search term. Other search terms were added alone or in combinations during the selection process: 'effects', 'safety', 'efficacy', 'effectiveness','route of administration', 'safety', 'vaccinations', 'benefits', 'risks', 'acupuncture', 'immunotherapy', 'adverse reactions', 'adverse events', 'anthroposophy or anthroposopic', 'homeopathy or homeopathic'. The search was limited by language (English).

The initial search ('oral AND subcutaneous OR injection') resulted in 11,559–2,380,000 hits in PubMed and Google Scholar (Table 1). In order to narrow down the numbers of results, one or more combinations of other search terms were used in addition. During the review process, based on the first results, it was decided to search for reviews on safety of acupuncture ("risk of the needle") and on the relationship between the extracellular matrix and subcutaneous injections ('location effects').

Then the abstracts and/or title of each publication were scanned to determine relevance to the research questions and publications and were included if they were able to provide an answer to one of the research questions. Papers retained at this stage were then read in more detail to determine their relevance to the research questions. The majority of papers were excluded at this stage as they were descriptive on use of oral and subcutaneous injections providing no answers on benefits or risks.

Finally forty-two articles were included that provided information on: practice-based evidence (4), empirical evidence from clinical studies comparing the subcutaneous and the oral routes of administration (8), working mechanisms of the subcutaneous ROA (20), risks of the subcutaneous ROA (10) (Fig. 1).

3.2. Categories and definitions of benefits and risks

Between 2006 and 2008 a working group of the Committee for Medicinal Products for Human Use (CMPH) of EMA worked on the topic of benefit/risk assessment aiming to improve the transparency, consistency and communication of benefit and risk assessment in CHMP reports. Based on the literature that demonstrated several different categories and definitions of benefits and risks, EMA decided to avoid the terms *benefit* and *risk*. Instead they adopted the EMA's four-fold model: