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Review Article

Inhalational use of antithrombotics in humans: Review of the literature

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ABSTRACT

Introduction: Off label use of anticoagulants is common. The association between fibrin deposition in the lungs and primary lung disease, injury or prematurity affords a strong theoretical basis for the potential benefit of antithrombotic therapies administered directly to the lung tissue. This review offers a critical appraisal of current evidence related to the inhalational administration of antithrombotic therapy in humans.
Materials and methods: An interrogation of 2 databases across a 13 year period of time was undertaken using key words selected a priori. Identified publications were categorized according to the following themes:

1. Inhaled antithrombotic therapy in healthy subjects
2. Inhaled antithrombotic therapy for vascular thromboprophylaxis
3. Inhaled antithrombotic therapy in smoke inhalation and lung injury
4. Inhaled antithrombotic therapy in asthma or allergy
5. Inhaled antithrombotic therapy for plastic bronchitis post-Fontan surgery
6. Inhaled antithrombotic therapy for other indications.

Results: 33 articles were identified consistent with the inclusion criteria developed for this review. Unfractionated heparin, LMWH, activated protein C and thrombolytic agents have been administered via the respiratory track, with asthma and smoke inhalation/lung injury being the most frequently investigated clinical scenarios described. All studies reported had significant methodological limitations.
Conclusions: The safety and clinical utility of inhaled antithrombotic therapies have not been adequately investigated to support the generation of any firm evidence. This review highlights where inhaled antithrombotic therapies have shown promise and importantly, the further research required to confirm mechanism of action and a definitive risk: benefit profile.

Contents

Abbreviations: UFH, unfractionated heparin; LMWH, low molecular weight heparin; APC, activated protein C; DVT, deep vein thrombosis; IU, international units; tPA, tissue plasminogen activator.

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Antithrombotic therapies have been used in clinical practice for nearly a century. In current clinical practice, unfractionated heparin (UFH) and heparin-derivatives remain the most predominant parenterally administered antithrombotic therapies. Early studies investigating parenteral UFH in humans demonstrated its efficacy in both the prevention and treatment of thrombosis across a range of clinical indications [1,2,3]. These early reports of the successful prevention and management of thrombotic disease with UFH produced growing acceptance of the role of anticoagulation in the treatment of arterial and venous thrombotic disease.

Today, the predominant indications for antithrombotic therapies remain the treatment of confirmed thrombosis within a blood vessel or risk of thrombosis within a blood vessel. For such indications, there are evidence-based recommendations regarding the clinical indications, management, monitoring and potential adverse events associated with their use. Despite little published data detailing the safety or efficacy of extravascular uses of antithrombotic therapies, they are increasingly being used in extravascular spaces, including topical application [4] and intra-pulmonary administration. The purpose of this paper is to review the available literature regarding the use of antithrombotic agents administered via the respiratory tract in humans.

1. Materials and Methods

The MEDLINE and Pubmed databases were interrogated in order to identify all publications reporting the use of antithrombotic therapies administered via the respiratory tract between 1990 and December 31st 2013. The following search strategy was employed using "inhalation" and: heparin; warfarin; low molecular weight heparin; tissue plasminogen activator; urokinase; streptokinase; activated protein C.

The literature search inclusion criteria were:

- Any study design, including case reports, trials, cohort studies, retrospective studies and cross over studies examining outcomes from anticoagulants administered via the inhaled route.
- Studies performed in humans of any age.
- Studies published in the "English language".

Articles were excluded if:

- The anticoagulant drug was not inhaled or,
- The article was published prior to 1990, or
- They reported findings from animal studies. Animal studies were excluded from this review they did not support this study's purpose of reviewing the use of antithrombotic agents administered via the respiratory tract in humans.

Review articles were included in the search strategy to enable cross-referencing between original studies identified through the search strategy with references in published reviews. Review articles were subsequently excluded from further analysis. The reference lists of all included papers were subsequently reviewed to identify eligible papers that were not identified in the initial search strategy.

Identified manuscripts were categorized according to the following criteria:

1. Inhaled antithrombotic therapy in healthy subjects
2. Inhaled antithrombotic therapy for vascular thromboprophylaxis
3. Inhaled antithrombotic therapy in smoke inhalation and lung injury
4. Inhaled antithrombotic therapy in asthma or allergy
5. Inhaled antithrombotic therapy for plastic bronchitis post-Fontan surgery
6. Inhaled antithrombotic therapy for other indications.

2. Results

The database interrogation identified a total of 231 publications using various antithrombotic therapies including UFH (167 articles), warfarin (17 articles), low molecular weight heparin (LMWH) (13 articles), tissue plasminogen activator (33 articles), urokinase (20 articles), streptokinase (7 articles) and activated protein C (13 articles). No eligible publications were identified via review of reference lists of publications identified through the database interrogations. After application of exclusion criteria, 41 articles were eligible for inclusion in this review. Table 1 summarizes the results of this search strategy according to the antithrombotic agents included.

2.1. Inhaled Antithrombotic Therapy in Healthy Subjects

Five publications reported the use of inhaled antithrombotic therapy in healthy subjects [5–9]. Markiewicz et al., Bendstrup et al. and Bendstrup et al. all explored the impact of various doses of inhaled UFH within prospective cohort study designs [5,6,8]. Markiewicz determined response to inhaled UFH is circadian, with variation occurring in coagulation and lipid responses triggered by morning versus evening inhalation of UFH [8]. In two studies ranging across three years, Bendstrup and colleagues first determined the pharmacokinetic profile of inhaled UFH [5] and then reported the relative haemostatic and pulmonary function effect of UFH inhaled into the lower respiratory tract [6]. No coagulation-related adverse events were reported in any of these studies, and Bendstrup concluded that inhalation of <32,000 IU of UFH via the lower respiratory tract is safe [6].

Harenberg and Scheuch investigated the safety and efficacy of inhaled LMWH in healthy subjects [7,9]. In a prospective cohort study conducted in young adults, Harenberg determined the inhaled dose of LMWH needed to be 10 times higher than that administered subcutaneously in order to achieve similar levels of anti-factor Xa assay and Heptest prolongation [7]. This conclusion was achieved by administering escalating doses of nebulized LMWH ranging from 9000 IU to 54,000 IU across a 20 minute interval. Scheuch conducted a two-phased study investigating the equivalence between inhaled and subcutaneous administration of LMWH and the haemostatic response to inhaled LMWH [9]. In contrast to Harenberg, Scheuch found a 3-fold

Table 1
Summary of database interrogation.

	Total number of publications	Eligible publications for review
Unfractionated heparin	167	28
Tissue plasminogen activator	33	6
Urokinase	20	1
Warfarin	17	0
Low molecular weight heparin	13	4
Streptokinase	7	0
Activated protein C	13	2