


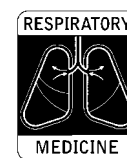
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Short Report

Inhaled heparin is effective in exacerbations of asthma

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Introduction

Despite advances in anti-asthmatic therapy, new antiasthmatic agents are still needed. Inhaled heparin may be such an agent due to its often over-looked anti-inflammatory properties. We have previously characterized heparin aerosols and determined the dose administered to the lower respiratory tract by inhalation in normal subjects (1,2). We used this knowledge in two patients who did not respond to systemic corticosteroids during exacerbations. This is the report of the outcome.

Patient 1

Patient 1 is a 57-year old female who had had progressive, allergic asthma for 6 years. Inhaled steroids and long-acting β_2 -agonists had maintained spirometry at normal levels: forced expiratory volume in 1 sec (FEV_1) 3.00 l (pred. 3.10), forced vital capacity (FVC) 3.80 l (4.00). Over 6 months her clinical condition had deteriorated despite courses of systemic steroid (prednisolone, 30 mg for 1 week tapered by 5 mg every third day) and ampicillin (750 mg t.i.d. for 10 days) as sputum cultures yielded monocultures of *H. Influenzae* twice.

On the 16th day of another steroid course, at 15 mg daily, she was admitted due to increased dyspnoea and no regular sleep for several nights. FEV_1 was 1.53 l and FVC 2.30 l. Chest X-ray and a ventilation-perfusion ratio (V/Q) scan were normal, leucocytes were 11.2 (pred $2.9-10.4 \times 10^9 l^{-1}$), and *H. Influenzae* sensitive to ampicillin was again cultured from sputum. Prednisolone was increased to 30 mg and another course of ampicillin begun. As no improvement had occurred after days, the patient agreed to try inhaled heparin.

One hundred thousand IU of unfractionated sodium heparin (Leo Pharmaceutical Ltd.) was nebulized in a Sidestream jet nebulizer (Medic-Aid, Bognor Regis, England) at a flow rate of $10 l min^{-1}$; thereby 7000 IU of heparin was administered to the lower respiratory tract daily for 5 days (2). Spirometry and symptoms improved immediately; on the third day FEV_1 was 2.55 l, FVC 3.55 l

and sleep was uninterrupted. The patient was discharged on the 5th day, with steroids tapered as usual. Inhaled heparin was administered once weekly for 3 weeks; on the first visit there were no symptoms and spirometry had normalized (FEV_1 3.08 l, FVC 3.92 l) and remained so beyond the discontinuation of steroids (4 weeks). Daily/weekly counts of platelets, activated partial thromboplastin time and prothrombin time remained normal.

Patient 2

Patient 2 is a 67-year old female with allergic asthma since childhood. Her asthma had remained well-controlled on inhaled steroids and long-acting β_2 -agonists. Her optimal spirometry was FEV_1 1.53 l (pred. 1.96 l), and FVC 2.00 (pred. 2.06 l).

Four weeks prior to admission, an exacerbation was treated in another hospital ward with prednisolone 30 mg for 14 days, with increase up to 50 mg daily for 3 days without effect. The patient was readmitted due to further deterioration with difficulties performing activities of daily living and difficulty sleeping. Spirometry on admission was: FEV_1 0.98 l and FVC 1.40 l. Chest X-ray and V/Q scans were normal. Leucocytes were $9.4 \times 10^9 l^{-1}$, and there were neither fever nor sputum. The usual inhaled medication was maintained. Conjunctivitis and rhinitis appeared on the 5th day of admission. The patient was reluctant to accept another course of systemic steroids and instead agreed to try inhaled heparin. Heparin administration and dosage was similar to that of patient 1. Symptoms improved immediately, the conjunctivitis and rhinitis disappearing within the hour after the first inhalation, and sleep was only interrupted once the following night. Spirometry improved significantly to a maximum FEV_1 of 1.24 l and FVC of 1.84 l after 5 days when she was discharged free of symptoms. One week after discharge, FEV_1 had improved to 1.30 l, and FVC to 1.93 l, remaining unchanged for the following 4 weeks. The eosinophil count remained elevated ($1840-1650 \times 10^9 l^{-1}$), while platelets, APTT and prothrombin time remained unchanged.

Discussion

The lower respiratory tract dose delivered to normal subjects by nebulization of 100 000 IU in the Sidestream

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jet nebulizer is 7000 IU, but may be somewhat larger in asthmatic subjects (3). We have studied single lower respiratory tract doses of up to 28 000 IU (nebulizer charge 400 000 IU) and found very small and clinically irrelevant changes in coagulation variables, but the effects of repeated daily doses are unknown; in these two patients no untoward effects were observed during 5 days.

Heparin inhibits mast cell activation and mast cell mediators, possibly through inhibition of 1,4,5-triphosphate receptors (4). Heparin also inhibits eosinophil cell migration and eosinophil cationic proteins (5). Such effects may be the mechanism behind the attenuation of exercise-, histamine- and allergen-induced bronchoconstriction (6,7).

Not only may the effects of inhaled heparin in asthma differ from those of steroids, but the side effects are highly likely to be fewer and milder than those needed for anti-coagulation and thrombotic therapy. Therefore, when the lower respiratory tract doses and their distribution in asthmatic subjects and the effects of repeated dosing of aerosolized heparin have been determined, clinical trials of heparin against steroids and leukotriene antagonists are desirable in order to determine the potential place of aerosolized heparin in the treatment of asthma.

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