Nebulised furosemide for the management of dyspnea: does the evidence support its use?

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Abstract

Dyspnea is a common and distressing symptom associated with multiple chronic illnesses and high levels of burden for the individual, their families and health care systems. The subjective nature of the dyspnea symptom and a poor understanding of pathophysiological mechanisms challenge the clinician in developing management plans. Nebulised furosemide has been identified as a novel approach to dyspnea management. This review article summarises published studies, both clinical and experimental, reporting the use of nebulised furosemide. The search criteria yielded 42 articles published in the period 1988 to 2004. Whilst nebulised furosemide appeared to have a positive influence on a person's dyspnea and physiological measurements, caution must be taken with the results primarily coming from small-scale clinical trials or observation trials. Despite the limitations of the studies reported, given the range of conditions reporting effectiveness of nebulised furosemide, further investigation of this potential novel treatment of dyspnea is warranted.

Keywords: Furosemide, Dyspnea, Chronic disease, Acute disease, Drug Administration, Inhalation

Running title: Nebulised furosemide for dyspnea

INTRODUCTION

The burden of dyspnea in chronic illness

Dyspnea, the subjective experience of breathlessness[1] and is a common and distressing symptom in many chronic illnesses, including both malignant and non-malignant conditions. The frequency and intensity of dyspnea can worsen, in both intensity and frequency, as the disease progresses or during periods of exacerbation. This symptom burden often remains despite optimal therapy.[2] A reduction in self-rated quality of life is also seen with dyspnea, due to a reduction in the capacity for physical activity and the potential for adverse psychological symptoms.[1]

In spite of the prevalence of dyspnea, the precise physiological mechanisms remain unclear for symptom aetiology and experience. It is important to consider that dyspnea is a multidimensional symptom, involving not only physiological mechanisms, but also environmental, psychological and social factors. It is the interplay of these multiple factors which are responsible determine the severity and degree of the symptom.[1]

The significant disease burden of dyspnea has led to the exploration of many approaches to relieve this distressing symptom.[1] Nebulised furosemide, a common loop diuretic in the management of oedematous symptoms, has been tested as a treatment option for dyspnea.[3] This treatment option is attractive from both a physiological and management perspective. The potential to achieve adjunctive benefits to symptom management such as ancillary bronchodilator therapy in asthma, chronic obstructive pulmonary disease (COPD) and malignancy is an attractive option as well as the capacity to administer the drug in a non-invasive method, with a low adverse effect profile, and in ambulatory care and home based settings.

The action of furosemide

Furosemide produces increased diuresis through inhibition of the Na^+-K^+-$2Cl^-$ co-transporter in the thick ascending limb of the loop of Henle.[4,5] The reported range of oral availability of furosemide is 10-100% with the mean availability being 60%.[5] Approximately 50-65% of furosemide is excreted in the urine unchanged.[4,5] The plasma half-life of furosemide is approximately 1.5 hours[4,5] in a healthy individual but this figure is nearly double when there is renal, hepatic and cardiac deficiencies.[5]

Despite extensive research into the mechanism of action using in vitro models, the precise mechanism of action of nebulised furosemide is still unknown leading to speculation that more then one mechanism of action is involved.[6,7] Animal and in vitro models suggest that the protective effects of nebulised furosemide are unlikely to be by the same mechanism that it enacts in the kidneys. These models have suggested several mechanism including its protective effect against cholinergic, noncholinergic and nonadreneric contraction of smooth muscle,[8-10] producing an increased vascular response to the tissue,[11] enhancing microvascular leakage to counteract the evaporation of water[12] and vasodilation.[13,14] Recent work in an anesthetised rat model suggested nebulised furosemide could work through the activation of pulmonary stretch receptors and inhibition of vagal irritant receptors.[15] The failure of oral furosemide to protect against exercise induced asthma compared to the protective effect of nebulised furosemide in Bianco's original study, suggests nebulised furosemide has a direct protective effect.[3]

Methods:

The electronic data bases, Medline, Embase, and CINAHL, as well as the World Wide Web were searched for literature in English using key words which included "dyspnea",

"breathless" "inhaled", "nebulised", "furosemide" and "furosemide" from 1988 to 2006. The reference lists of published articles were also examined to find additional references. Articles were considered suitable if they reported findings of clinical or experimental trials of nebulised furosemide for the management of dyspnea in human adults. Both randomized and non-randomized controlled trials were included in this review. The heterogeneity of study design, populations, and endpoints precluded the formal use of metanalysis techniques.

Results:

Initially the search generated 112 citations. In total, 42 articles were retrieved which met the inclusion criteria. The articles retrieved included 39 randomised control trials, 35 studies in asthma, 2 studies in cancer, 8 in healthy participants, 1 in chronic obstructive pulmonary disease, 5 articles measured dyspnea and 40 articles measured changes in physiological outcomes. These are summarised in Table 1. A critical review of the articles was undertaken and the evidence for the use of nebulised furosemide is reported.

Asthma

Acute Asthma

Several studies and case reports have reported the use of nebulised furosemide as an adjunctive treatment for acute asthma. Two studies reported improvement in pulmonary function when nebulised furosemide (20-100mg) was used after or in conjunction with standard treatment which included sympathomimetics, aminophylline, and steroids.[16,17] These studies showed the addition of nebulised furosemide was able to significantly improve FEV_1 at 60 minutes,[17] and produce a rapid fall in $PaCO_2$ within 20-60 minutes.[16] When compared to salbutamol, nebulised furosemide (100mg) did not increase FEV_1 as much as salbutamol (6.9% compared to 7.9% respectively) at 10 and 30 minutes, however, this difference was not statistically significant.[18]

In contrast, Pendino and colleagues did not show an overall greater protection from nebulised furosemide than normal saline when added to salbutamol (2.5mg). A significant improvement in peak expiratory flow rate (PEFR) was seen on post hoc analysis in the nebulised furosemide group in those patients that had presented to the emergency room within 8 hours of the onset of their symptoms.[19] In a further study, comparing nebulised furosemide with salbutamol in subjects who had not received a nebulised beta agonist in the previous 6 hours, furosemide failed to show a significant improvement in FEV_1. However, the group assigned metaproternol alone did have a significant improvement in their FEV_1.[20]

Experimentally Induced Asthma

Multiple experimental studies have demonstrated the ability to reduce the effects of bronchoconstrictive agents. Adenosine 5'-Monophosphate (AMP) induces bronchoconstriction through the enhancement of mast cell mediated release[21,22] and interference with neural pathways.[22] The protective effects of nebulised furosemide against AMP induced bronchoconstriction can last for up to 120 minutes.[23] Ultrasonically nebulised distilled water (UNDW) likely induces bronchoconstriction through indirectly causing smooth muscle contraction.[24] Nebulised furosemide (28-40 mg) was able to significantly increase the amount of UNDW required to reduce FEV_1 by 20%.[24-26] Nebulised furosemide (30-40mg) successfully increased the amount of sodium metabisulfite (MBS), an indirect stimulant of bronchoconstriction required to produce a 20% fall in FEV_1. This effect was relatively short, with protection lasting between 1.5-3 hours.[27-31]

Bronchoconstriction is directly produced by methacholine through stimulation of muscarinic receptors on airway smooth muscle.[21] There have been different results of the ability of nebulised furosemide to prevent methacholine-induced bronchoconstriction. Nebulised

furosemide (30mg and 28mg) provided no protection against methacholine-induced bronchoconstriction in two studies, while one study showed nebulised furosemide (28mg) was able to increase the amount of methacholine required to produce a 20% fall in FEV_1.

Based upon available data, it is unlikely that nebulised furosemide provides protection against bronchoconstriction by the same mechanism as it exerts diuresis in the kidneys. Nebulised furosemide has been shown to: (1) provide protection against bronchoconstriction when other loop diuretics such as bumetanide, failed to provide protection (2) reduced the amount of experimentally induced bronchoconstriction compared to other loop diuretics (bumetanide, torasemide) (3) provided the same level of protection against MBS induced bronchoconstriction when equivalent doses of ethacrynic acid, a loop diuretic with a different mechanism of action was used.[31]

Nebulised furosemide has been shown to be effective against exercise induced asthma.[3,32] In Bianco's original study, nebulised furosemide was able to protect against exercise induced asthma but oral furosemide was ineffective. This level of protection was also shown to be dose dependent.[3] Furosemide was able to reduce the level of fall of FEV_1 as a result of exercise from 26% with placebo to 14.3%.[32] Another common cause of asthma is allergens. Two studies have examined the efficacy of nebulised furosemide (~28-40mg) to protect against allergen-induced asthma with encouraging results. The protective effects have been seen immediately,[33] and as late as 4-12 hours.[34]

Nebulised furosemide has also proven effective against isocapnic hyperventilation [13,35] and dry air challenges.[36] Gilbert and colleagues found that the protection furosemide provided in

the isocapnic hyperventilation challenge was in conjunction with changes in thermal gradients.[13]

Aspirin can induce asthma in some patients through the inhibition of cyclooxygenase.[37,38] Nebulised furosemide has been shown to provide protection against aspirin induced bronchoconstriction in two randomised controlled studies.[37,38] When patients took indomethacin, a known inhibitor of cyclooxygenase, (50mg,) three times a day for 3 days prior to the test, the effects of nebulised furosemide were significantly reduced.[32] Flurbiprofen, a suspected inhibitor of the synthesis and release of prostaglandins has demonstrated mixed results with nebulised furosemide. Participants that took flurbiprofen 50mg twice daily, for 3 days prior to a methacholine challenge showed flurbiprofen was able to abolish the effects of nebulised furosemide occurred in both asthmatics and healthy subjects.[39] However, a single dose of flurbiprofen (200mg), enhanced the protective effects of nebulised furosemide when taken as a single dose 2 hours prior to a sodium metabisulphite challenge.[30]

The results from these studies highlight the difficulty of finding the mechanism of action of nebulised furosemide. The ability of furosemide to provide protection against a wide of agents with many different mechanisms of action suggests that nebulised furosemide may work at different sites in the respiratory system. The encouraging results from the few clinical trials of furosemide in asthma suggest further examination is warranted.

Cancer

Two studies have examined the efficacy of nebulised furosemide for the alleviation of dyspnea in end stage cancer patients.[40,41] Nebulised furosemide (20mg) three times daily was

able to relieve dyspnea, when standard treatments (morphine, oxygen and orciprenaline) were no longer effective.[41] Interestingly, another group of patients stated nebulised furosemide relieved their dyspnea using the Cancer Dyspnea Scale, particularly in the sense of effort and reduced anxiety items, but there was no significant reduction in the objective measures including arterial blood gases, SaO_2, heart rate and respiratory rate. Whilst these studies were of case study design, they provided encouraging results for the use of nebulised furosemide in this group of patients and further investigation is warranted.[40]

Chronic Obstructive Pulmonary Disease (COPD)

In a study by Ong and co-workers, participants with moderate or severe COPD had dyspnea induced with exercise following administration of either nebulised furosemide or nebulised normal saline in a controlled clinical trial. There was a significant improvement in the patients FEV_1 after nebulised furosemide. The patient's perception of their dyspnea, as measured by a visual analogue scale (VAS), also significantly improved following nebulised furosemide. No significant difference was found with incremental exercise testing.[42]

Healthy subjects

Ventresca et al reported on nebulised furosemide's ability to protect against induced cough in healthy participants.[43] In this study, nebulised furosemide was unable to protect against capsaicin induced cough although it did protect against prostaglandin F2α induced cough.

It is unlikely that nebulised furosemide prevents dyspnea through a decrease of the ventilatory drive of CO_2.[44] Whist nebulised furosemide was able to protect against breath holding and a combination of resistive flow loading and hypercapnia induced bronchoconstriction,[45] there was no effect on the CO_2 slope curve despite an improvement in the dyspnea ratings of the participants.[44]

As was the case with asthmatic subjects,[21] nebulised furosemide was able to protect against methacholine induced bronchoconstriction.[39] The loop diuretic bumetanide was also successful in protecting against methacholine induced bronchoconstriction in this study.

Reported adverse events

Although the therapeutic effects of nebulised furosemide are attractive, it is important to consider potentials for adverse effects, particularly within the context of polypharmacy and co-morbid conditions.

Increased diuresis

Inconsistencies are reported regarding increased diuresis following inhalation of nebulised furosemide. Increased diuresis has only been reported in 4 studies in adults.[18,29,43,46] The effect of the increased diuresis has been reported to last for up to 24 hours.[29] There was a non statistically significant increase in diuresis in the study from Rodriguez et al[18] in the furosemide group compared to placebo. Increased diuresis was reported in 1 of 8 participants in the study from Ventresca et al.[43] Ten studies either specifically reported that there was no increase in diuresis or that no adverse events had occurred following inhalation of nebulised furosemide.[3,16,20,25,27,31,33,40,41,47] No reference to adverse events was made in the remaining articles reviewed.

Discussion

There is some evidence to suggest nebulised furosemide could be an option to use in the management of dyspnea. The case reports of the improvement in dyspnea scores in cancer patients are encouraging; especially given the fact the more traditional dyspnea strategies of opioids were not effective in these patients. Yet in the absence of adequately powered, randomised controlled clinical trials these observations need to be interpreted with appropriate caveats. However, these data generate intriguing hypotheses.

There is further need for studies to evaluate the efficacy of nebulised furosemide on dyspnea management. The majority of studies reported in this review report the effects of nebulised furosemide on pulmonary function and asthma. Whilst there may be some correlation between pulmonary function and dyspnea scores such as lung cancer, there is need to use reliable and valid dyspnea measurement scales with nebulised furosemide use.

The lack of data in the reports surrounding possible diuretic effects of nebulised furosemide is worrisome given the fact that furosemide is a loop diuretic. There is a clear need for pharmacological studies to answer this question if nebulised furosemide is to be used routinely in clinical practice. There is also the potential if nebulised furosemide does have a diuretic effect that this may identify a potential useful vehicle of administration. Both animal and human studies have identified several possible mechanisms for the action of nebulised furosemide including enhanced pulmonary receptor activity, suppression of the pulmonary irritant activity and vasodilation. The complexity of management regimes of the likely populations of nebulised furosemide also demands that the pharmacology be determined so safe, effective prescription is possible.

Limitations of this review

This review has summarised published data to inform future studies and demonstrate potential pharmacological strategies to facilitate symptom management. Therefore only clinical trials of nebulised furosemide in adult humans for the management of dyspnea were reviewed for this manuscript. The heterogeneity of study samples, dosages and methods precludes making firm conclusions regarding the mechanism and efficacy of the action of nebulised furosemide.

This review of nebulised furosemide for managing dyspnea is limited by the lack of studies which measured dyspnea and the heterogeneity of populations and study methods precluding metanalysis technique. Dyspnea was only evaluated in 5 papers.[40-42,44,45] The lack of assessment of dyspnea in the papers is a limitation across many of the studies particularly since there is not always a strong correlation between disease severity and symptom burden.[1,48] Yet the symptom relief of nebulised furosemide in the studies using validated measures of assessing dyspnea suggest nebulised furosemide should continued to be evaluated.[40-42,44,45]

Conclusion

The pathophysiological basis of dyspnea is still not fully understood, limiting appraisal of the mechanistic effects of published studies of nebulised furosemide. Dyspnea research is also problematic due to the subjectivity of this sensation and the complex interplay between physiological and psychological responses that can influence the sensation and manifestation of this symptom. While several studies have examined the effect of nebulised furosemide for the management of dyspnea, methodological limitations make it difficult to derive conclusions regarding efficacy and therapeutic action. Further studies to examine efficacy, indications, and safety profile are necessary before this treatment strategy can be recommended for the management of dyspnea.

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Table 1. Clinical trials using nebulised furosemide

Author (s)	Study Design	n	Disease State	Inducing Agent	Placebo/ Comparator	Furosemide dose (mg)	Intervention	Effect on dyspnea	Adverse Events	Findings
Pendino et al[19]	RCT*	42	Acute asthma	N/A	Saline	40	Study intervention added to 2.5mg nebulised salbutamol in the Emergency department.	Not measured	Not reported	Either 40mg of furosemide or saline was added to 2.5mg salbutamol No difference in PEFR† at 15 or 30 minutes with either furosemide or saline
Rodriguez et al[18]	RCT	80	Acute asthma	N/A	Salbutamol	100	Participants received either nebulised furosemide or placebo.	Not measured	Not reported	Salbutamol group (FEV_1‡ improved 7.9% at 10 min and 30 min, furosemide improved 6.9% ($p > 0.05$).
Ono et al[17]	RCT	40	Acute asthma	N/A	Saline	20	All patients received IV aminophylline 250 mg for 90 min and IV hydrocortisone 100 mg at entry	Not measured	Not reported	Significant increase in mean FEV_1 in furosemide group 28.2 ± 5.9% at 60 min
Tanigaki et al[16]	Case study	7	Acute asthma	N/A	N/A	20	Patients unresponsive to standard treatment (sympathomimetic, aminophylline, cortisone) enrolled	Not measured	No adverse events	Rapid mean fall in $PaCO_2$ from 57.7 mmHg (46.2-66.3 mmHg) to 40.6 mmHg (37.5-46.5 mmHg) within 20-60 minutes.

* Randomised control trial

† Peak expiratory flow rate

‡ Forced expiratory volume in 1 second

							into study			
Karpel et al[20]	RCT	24	Acute asthma	N/A	Metaproterenol and furosemide and metaproterenol	40	Patients in the emergency department for acute asthma. Randomly allocated following spirometry.	Not measured	No significant adverse events	Furosemide alone resulted in 14.9±10.5% improvement in FEV_1 which was not significant and was less then metaproterenol alone 29.2±15.2% which was significant (p=0.0028) No additional improvement with combination therapy
Rodwell et al[49]	RCCT[§]	11	Asthma	4.5% NaCl	pH adjusted saline (Vehicle)	33.2	Patients had dose of 4.5% NaCl required to decrease FEV_1 by 20%. Patients returned at least 3 days later and repeated procedure 10 minutes after inhaling study drug	Not measured	Not reported	The amount of 4.5% NaCl required to produce a 20% fall in FEV_1 was 1.3ml (95% CI 0.7-2.3) with placebo and 8.2 (95% CI 4.7-14.1) with furosemide Increased FEV_1 from baseline after 4.5% NaCl with exposure to furosemide in 5/11 subjects.
Robuschi et al[33]	RCT	10	Asthma	Allergen	Solvent	~28	Amount of allergen required to decrease FEV_1 recorded. On second and third visit, same dose administered immediately after study solution.	Not measured	Did not cause irritation and was well tolerated	Mean maximal fall in FEV_1 with placebo and furosemide was (31.5%; 95%CI 40.2%-22.8% vs 8.4%; 1 1.8%-4.9%) Furosemide provided protection from immediate reaction to inhaled allergen

[§] Randomised control crossover trial

Bianco et al[34]	RCCT	11	Asthma	Allergen	Vehicle	40	Amount of allergen required to decrease FEV_1 recorded on first visit. On second and third visit, same dose administered.	Not measured	Not reported	Mean maximal fall in FEV_1 after 60 min was 35±4% with placebo and 11±2% with furosemide ($p<0.05$) Mean maximal fall in FEV_1 between 4-12 hrs was 35±5% with placebo and 20±4% with furosemide ($p<0.05$)
Polosa et al[23]	2 RCT	12/8	Asthma	AMP **	Study 1: vehicle/ bumetninde Study 2: bumetanide	40	Study 1:Amount of allergen required to decrease FEV_1 recorded. On second and third visit, same dose administered after study solution. Study 2: Time course analysis of bronchial reactivity to study solution.	Not measured	Not reported	Increased AMP concentration required to decrease FEV_1 by 20% from 21.2 mg/ml (2.5-96.9 mg/ml) to 83.4 mg/ml (11.3-345.0 mg/ml; $p<0.01$) after furosemide and 33.8 (4.7-120.9 mg/ml; $p<0.05$) Furosemide was 2.5 more potent then bumetanide ($p<0.01$)
O'Connor et al[28]	RCT	16	Asthma	AMP & MBS ††	Matched placebo	30	Participants underwent a series of bronchial challenges with AMP, MBS and histamine.	Not measured	Not reported	Furosemide attenuated the effects of AMP (log PC_{20} 1.59± 0.24) compared with placebo log PC20 0.98± 0.28, $p<0.01$) No response was seen from furosemide following inhalation of histamine (log PC_{20} 0.09± 0.17) or placebo (log PC_{20} 0.09± 0.20)
Rajakulasinga et	RCT	10	Asthma	AMP and Brady	Matched placeb	40	Following baseline AMP and bradykinin challenges,	Not measured	Not reported	Mean maximal fall in FEV_1 following AMP was 14.86 (2.6-104.6) after placebo and 80.97 (9.97->400.0 mg/ml

** Adenosine 5'-monophosphate

†† Metabisulphite

al[22]				kinin	o		participants were then given study solution 10 minutes before repeat challenges.			after furosemide Mean maximal fall in FEV_1 following bradykinin was 2.52 (0.45-5.61) after placebo and 13.22 (2.53->16.0) mg/ml after furosemide Furosemide provided 5.45 and 5.24 fold protection against AMP and bradykinin
Polosa et al[21]	2-phased, RCT	12	Asthma	AMP and methacholine	Matched vehicle	~28	Baseline provocations studies in phase 1. Phase 2 Study solution given 5 minutes prior to repeat challenge on separate visits.	Not measured.	Not reported	Increased dose required for a 20% fall in FEV_1 with AMP from 30 to 96 mg ml-1 ($p<0.01$) Increased dose required for a 20% fall in FEV_1 with methacholine from 1.1 to 1.8 mg ml-1 ($p<0.01$) Furosemide provided significantly greater protection to AMP induced bronchoconstriction compared to methacholine ($p<0.05$)
Sestini et al[37]	RCCT	16	Asthma	Aspirin	Matched placebo	40	Phase 1: Patients underwent bronchial challenge with Aspirin following study solution Phase 2. The dose of aspiring was delivered in decreasing doses.	Not measured	Not reported	Furosemide provided significant protection against a single aspirin challenge for 120 minutes. Furosemide provided significant protection in the first 90 minutes when multiple doses of aspirin were administered 1 hour apart.
Rodwell [36]	RCCT	15	Asthma	Dry air	Matched placebo/ amilor	38	Phase 1: Baseline challenge. Phase 2: Study solution inhaled 10 minutes before repeat	Not measured	Not reported	The mean difference in PVE_{20} between amiloride and furosemide was 21.5 $l\text{-}min^{-1}$ (95% CI 7.0-36.0; $p<0.01$, n=8)

					ide		challenge			
Pavord et al[32]	RCCT	10	Asthma	Exercise	Matched placebo	40	Took indomethacin or placebo for 3 times a day for 2 days prior to exercise test. 10 minutes before exercise test, study solution given	Not measured.	Not reported	The mean maximal fall in FEV_1 from baseline following furosemide prior to exercise challenge was 14.3% compared to 26% with placebo ($p<0.01$). Three days pre-treatment with indomethacin increased the mean maximal fall to 21.8% in the furosemide group, mean difference 7.5% (95% CI .06, 14.4%:$p<0.05$)
Bianco et al[50]	3-part, RCT	34	Asthma	Exercise	Matched placebo	i) 28 ii)14 and 28 iii)20 oral	Study 1: Participants inhaled study solution before exercise test. Study 2: Study 1 protocol repeated except additional day for extra dose. Study 3. Compared different combination of oral furosemide and placebo.	Not measured	No changes in BP‡‡ or HR§§	Mean maximal fall in FEV_1 was 33.8% (39.1-28.5) with placebo and 11.5% (14.3-8.7) with furosemide The protection is dose-dependent and was not accompanied by any direct bronchodilator effect. Oral furosemide was ineffective.
Feather et al[51]	RCT	10	Asthma	Histamine	Vehicle	30	Participants underwent histamine challenge following inhalation of study solution.	Not measured.	Not reported	The geometric mean (histamine PD_{20}) after inhalation of the solution was 0.6μmumol and after furosemide was 0.45μmumol. The mean difference in PD_{20} between

‡‡ Blood pressure

§§ Heart rate

										control and furosemide was -0.50 µmol (furosemide test more reactive) but this change was not statistically significant.
Gilbert et al[13]	2 phased RCT	8	Asthma	Iscaponic hyperventilation	Saline	45±3 (SE)	Phase 1: Participants inahled frigid air at baseline. Phase 2: Protocol repeated after study solution on separate days.	Not measured	Not reported	Mean maximal fall in FEV_1 occurred after 10 minutes in both groups. Significantly greater decrement in lung function after saline compared to furosemide up to 45 minutes ($p<0.006$). FEV_1 returned to baseline after 45 minutes with saline and 30 minutes with furosemide. Furosemide significantly attenuated airstream cooling at 3 ($p<0.04$) and 4 minutes ($p<0.01$) and absolute end-inspiratory airstream temperature was warmer in furosemide then saline group (27.0±0.9 vs 26.0±0.08^oC , respectively; $p<0.01$)
Vargas et al[38]	RCCT	6	Asthma	Lysine-aspirin	Saline	20	Participants inhaled saline on day 1 and furosemide on day 2. Following inhalation patients underwent challenge with lysine aspirin	Not measured	Not reported	Mean dose causing 20% fall in FEV_1 with placebo was 30.4 mg/ml None of the participants FEV_1 fell by 20% when pre-treated with furosemide even when aspirin dose was 360mg/ml
Pye et al[31]	RCCT	8	Asthma	MBS	Placebo / Ethacrynic	20 and 40	Participants received study solutions on separate days,10 minutes prior to	Not measured	No adverse effects	Compared furosemide, ethacrynic acid and placebo (saline) Furosemide (20 and 40mg) increased the amount of UNDW*** required to

*** Ultrasonically nebulised distilled water

					acid		undergoing MBS bronchial challenge.		with furosemide, ethacrynic acid caused cough and upper airway irritation	produce a 20% fall in FEV_1 (mean 1.1; 95CI;0.-2.4; p>0.05) and (mean1.6;0.4-2.9;p<0.05) doubling doses respectively Ethacrynic acid (25 and 50mg) increased the amount of UNDW required to produce a 20% fall in FEV_1 (0.9;-0.4-2.2;p>0.05) and (1.5;0.2-2.8;p<0.05) doubling doses respectively
O'Connor et al[30]	RCCT	12	Asthma	MBS	Matched placebo	40	Participants underwent a series of bronchial challenges with MBS over 4 study days.	Not measured	Not reported	Furosemide shifted response curve to right by 1.9 (p<0.01) doubling doses immediately and 0.7 doubling doses at 3 hours (p<0.05) Furosemide and flurbiprofen (200 mg) shifted response curve to right by 2.7 (p<0.001) doubling doses immediately and 1.9 doubling doses at 3 hours (p<0.001). Significantly greater then either agent alone (p<0.01)
Yeo et al[29]	2 RCCT	16	Asthma	MBS	Saline	40	Study 1. Baseline MBS challenge performed 1 hour prior to inhalation of test solution. MBS challenge repeated at 5 minutes, 1.5, 3, 6 and 24 hours. Study 2. Single MBS	Not measured	Significant diuresis lasting 24 hours with both	Furosemide caused a 3.8 fold (95% CI 2.3-6.3) piretanide 2.5 (1.8-3.4) and placebo 1.7 (1.5-1.9) increase in PC_{20}MBS. Furosemide and piretanide significantly greater then placebo. 2nd Study: No significant difference in dose of MBS at 90 between any of the groups

							challenge performed 90 minutes after inhalation of test solution		piretanide and furosemide	
Yates et al[46]	2 RCCT	12 and 12	Asthma	MBS and methacholine	Placebo not defined	i) 10 or 20 ii) 10	Study 1: Inhaled 10 or 20mg furosemide 15 minutes before MBS bronchial challenge. Study 2: 2 week run in phase then participants inhaled study solution 4 times a day for 4 weeks separated by 2 week washout period. MBS challenges repeated	Not measured	1 patient in experiment 2 complained of increased diuresis	Experiment 1: After inhalation of furosemide (10mg or 20mg, mean log PC_{20} increased significantly (0.89 ± 0.08; $p<0.02$ and 1.10 ± 0.09; $p<0.001$) respectively. Experiment 2: No significant difference between placebo and furosemide when compared to baseline, however there was a significant difference between furosemide and placebo at the last visit ($p<0.05$)
Nichol et al[27]	RCCT	7	Asthma	MBS and methacholine	Saline	30	MBS challenge. After determining dose of MBS required to decrease FEV_1 by 20% over 3 test days, subjects inhaled test solution. Methacholine challenge. Repeated procedure of MBS challenge.	Not measured	No increased diuresis	The level of MBS required to cause 20% fall in FEV_1 were 15.1 mg/ml ±1.6 after placebo and 40.7 mg/ml ± 1.7 mg/ml after furosemide ($p<0.001$)
Rodriguez	RCT	50	Asthma	N/A	Salbutamol	50	Groups received either nebulised	Not measu	Non statisti	Furosemide and placebo given every 12 hours over 5 days

et al[18]							salbutamol, followed by nebulised placebo 12 hours later or nebulised furosemide followed by nebulised furosemide 12 hours later for 5 days.	red	cally signifi cant increas e in diuresi s	FEV_1 improved 15.22% in salbutamol group and 12.7% in the furosemide group ($p>0.05$). Peak flow in the evening showed no sizeable differences.
Bianc o et al[47]	RC CT	9	Asth ma	N/A	Saline	40	Chronic asthma patients on high dose beclomethasone (2mg/day) took a combination of furosemide (40mg) and lysine aspirin (720mg) twice daily. Steroid dose was halved every 15 days and eventually suspended unless subject deteriorated	Not measu red	No advers e effects	During placebo phase, all subjects had worsening of symptoms During combination phase, 2 subjects ceased steroid completely, all other subjects reduced steroid to 0.5-0.25mg/day. Mean reduction 71%±7% FEV_1, weekly PEFR, symptom score and bronchodilator were significantly better with combination
Crimi et al[52]	RC T	1 1	Asth ma	NKA †††	Saline	40	Phase 1. Undertook concentration response studies. Phase 2. Test solution given 10 minutes prior to NKA and histamine challenge.	Not measu red	Not reporte d	Increased the amount of NKA required to produce a 20% fall in FEV_1 from 130.3 (35.8-378.8) after placebo to 419.9(126.5-1000) µg/ml after furosemide Small increase in the amount of histamine required to produce a 20% fall in FEV_1 from 0.58(0.12-3.80) after placebo and 1.04(0.28-4.33) after

††† Neurokinin A

										furosemide
Echazarreta et al[53]	RCCT	11	Asthma	PAF ‡‡‡	Not defined	40	All subjects underwent 2 bronchial challenges at least 1 week apart. PAF challenge administered 15 minutes after inhalation of study solution.	Not measured	Not reported	Pre-treatment with furosemide did not abolish PAF induced systemic effects, or cellular and lung function. Furosemide did inhibit the urinary excretion of leukotriene (LT)E_4 : $p<0.04$
Foresi et al[25]	RCT	12	Asthma	UNDW	Polyethylene glycol, and trometamol	28	Baseline response to UNDW challenge. 3 minutes after inhalation of study solution, UNDW challenge performed.	Not measured	Remarkable increase in diuresis only in torasemide group	Mean dose causing 20% fall in FEV_1 with placebo was 1.73 ml/min, with furosemide 4.25 ml/min ($p<0.025$), and torasemide 3.05 ml/min ($p=0.07$)
Moscato et al[24]	RCT	10	Asthma	UNDW	Saline	40	Baseline FEV_1 measured before, 5, 15, 30 min after UNDW challenge. Procedure repeated day 2 and 3 after inhalation of study	Not measured	Not reported	Furosemide prevented bronchoconstriction in 9 participants 7.5% decrease in FEV_1 following furosemide after UNDW compared with 31.1% with placebo ($p<0.001$) Maximal increase in NCA§§§ after UNDW with placebo was 52.9%, SEM

‡‡‡ Platelet activating factor

§§§ Neutrophil chemotactic activity

							drug.			9.2: furosemide 3.8% SEM 3.1 (p=0.001)
Robuschi et al[26]	RCT	16	Asthma	UNDW	Diluent solution without furosemide	~28	Baseline UNDW challenge performed. Test solution administered followed by UNDW challenge.	Not measured	Not reported	Mean maximal fall in FEV_1 was 26% (20-32) with placebo and 6% (-1-12) with furosemide
Daviskas et al[35]	RCT	22	Asthma & healthy	Isocapnic hyperventilation	pH adjusted saline	35.7 ±0.44	Baseline lung function measured with dry air challenge. Visit 2 and 3. Spirometry, study solution, radioaerosol inhalation, emission gamma images, ISH, emission gamma images.	Not measured	Not reported	Furosemide delayed the onset of mucociliary clearance for approximately 10 minutes in the whole right lung ($p<0.002$) and central lung ($p<0.01$) in asthmatics but not healthy subjects
Bellingan et al[54]	RCT	10	Asthma & healthy	MBS	Saline	40	MBS challenge carried out 10 minutes after inhalation of study solution.	Not measured	Not reported	Compared the effects of nebulised furosemide, ipratropium bromide and saline against MBS challenge Furosemide ($p<0.005$) and Ipratropium bromide ($p<0.05$) significantly inhibited MBS induced bronchoconstriction compared to placebo but the response was more variable with Ipratropium bromide. .
Hasani et	RCT	11	Asthma	N/A	N/A	40	Study solution inhaled 30 minutes	Not measu	Not reporte	Furosemide had no effect on lung mucociliary clearance in asthmatics

al[55]			& healthy				after inhalation of radioaerosol solution.	red	d	
Stone et al[56]	2 RCT	19	Asthma and healthy	Chloride deficient solution	Matched placebo	40	Baseline cough challenge performed. 2 hours later, study solution inhaled followed by repeat cough challenge at 30 min, 2,4,6 hours	Not measured	Not reported	Furosemide caused a sustained inhibition of cough in normal subjects ($p<0.05$ at 2hr, $p<0.01$ at 4hr) but only small, not significant effect at 30min with asthma participants No significant fall in FEV_1 in asthma group from chloride deficient solution and didn't correlate with number of coughs
Kohara et al[40]	Open clinical trial	15	Cancer	N/A	N/A	20	Assessment occurred before and 60 minutes after furosemide.	Significantly reduced dyspnea	No severe adverse effects. Cough, sputum production, and nausea were the most comm	CDS scores were significantly decreased ($p=0.007$) in 12/15 patients with the biggest reduction in sense of effort ($p=0.013$) and reduced anxiety ($p=0.04$) No significant changes were observed in PaO_2, $PaCO_2$, SpO_2, HR, RR****

**** Respiratory rate

									on toxicities	
Shimoyama, & Shimoyama [57]	Case study	3	Cancer	N/A	N/A	20	Furosemide was inhaled 4 times a day.	Furosemide was effective in reducing dyspnea	No adverse events	Nebulised furosemide provided these three patients with effective relief of their dyspnea in the end stages of their disease. No titration from the original 20mg was required to provide continual relief
Ong et al[42]	RCCT	19	COPD††††	Exercise	Saline	40	Study solution inhaled followed by incremental exercise testing. 1 hour later another dose of study solution followed by constant work exercise test.	Significantly reduced dyspnea during constant work exercise test	Not reported	Significant improvement in mean FEV_1 and FVC‡‡‡‡ following furosemide (p=0.038 and 0.005) but not placebo Mean VAS§§§§ lower after furosemide but not placebo (33.7±25.2 vs 42.4 ± 24.0 mm, p=0.014) Significant bronchodilation after furosemide but not placebo
Minowa et	RCCT	10	Healthy	CO_2	Saline	40	Following CO_2 steady state test,	Increase in	Not-reporte	Inhaled furosemide doesn't effect breathing patterns of resting breathing

†††† Chronic obstructive pulmonary disease

‡‡‡‡ Forced vital capacity

§§§§ Visual Analogue Scale

al[44]							subjects inhaled study solution followed by CO_2 rebreathing test.	dyspnea score less after furosemide then placebo	d	Inhaled furosemide does not affect the slope and intercept of the CO_2 response curve. Inhaled furosemide improves the dyspnoeic sensation produced during hypercapnic hyperpnoea.
Nishino et al[45]	RCCT	12	Healthy	i) breath holding ii) resistive loading and hypercapnia	Diluent without furosemide	40	Subjects breathed 100% O_2 for 5 mins. Breath held for as long as possible. 5 mins later loaded breathholding test performed for 7 minutes. 15 mins later study solution given.	Furosemide scores increased slower during loaded breathing.	Not reported	Total breathholding time after furosemide (median 93[78-112]sec) and placebo (67 [47-74] sec) $p<0.05$ Respiratory discomfort with loaded breathing developed more slowly after furosemide
Ventresca et al[43]	RCCT	8	Healthy	low chloride content solutions and capsaicin	Saline	30	Study 1 part 1. Study solution inhaled immediately prior to low chloride challenge. Study 1 part 2. Chloride solution causing biggest response administered 20 minutes before study	Not measured	1 participant reported increased diuresis within 4h of	Chloride free solutions induced 13.1± 1.6 coughs after placebo and 8.4 ± 1.9 coughs after furosemide ($p<0.005$) Capsaicin induced 20.8± 1.8 coughs after placebo and 21.5 ± 2.7 coughs after furosemide ($p<0.005$)

							solution. Study 2. Capsaicin challenge performed after inhalation of study solution.		furosemide administration.	
Polosa et al[39]	RCT	22	Healthy	methacholine	Matched placebo	40	Phase 1. Subjects underwent concentration response studies. Phase 2 and 3. Subjects took 3 days of flurbiprofen twice daily. or placebo. 10 minutes before challenge subjects took study solution.	Not measured	Not reported	Both by furosemide and bumetanide inhibited methacholine-induced bronchoconstriction The protective effect of furosemide is reversed by cyclo-oxygenase blockade