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(Review)

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[Intervention Review]

Carbonic anhydrase inhibitors for hypercapnic ventilatory failure in chronic obstructive pulmonary disease

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pjones@sgul.ac.uk.**Editorial group:** Cochrane Airways Group.**Publication status and date:** Edited (no change to conclusions), published in Issue 8, 2017.**Citation:** Jones P, Greenstone M. Carbonic anhydrase inhibitors for hypercapnic ventilatory failure in chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews* 2001, Issue 1. Art. No.: CD002881. DOI: [10.1002/14651858.CD002881](https://doi.org/10.1002/14651858.CD002881).

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ABSTRACT

Background

Carbonic anhydrase inhibitors such as acetazolamide cause a mild metabolic acidosis and may stimulate breathing. Some patients with severe chronic obstructive pulmonary disease (COPD) develop chronic hypercapnic ventilatory failure. In theory, they may benefit from use of these drugs with a fall in arterial carbon dioxide level (PCO₂) and a rise in arterial oxygen (PO₂).

Objectives

To determine the effectiveness and safety of acetazolamide in the treatment of hypercapnic ventilatory failure due to COPD.

Search methods

The Cochrane Airways Group Specialised Register was searched with predefined search terms. Searches were current as of October 2010.

Selection criteria

Trials were included in the review provided they were placebo controlled, carried out in patients with stable chronic ventilatory failure due to COPD.

Data collection and analysis

Data were extracted and analysed by two reviewers (PJ and MG) and agreement was reached by consensus. Where data could be aggregated they were analysed using a fixed effects model and reported as a weighted mean difference (MD) and its associated 95% confidence interval (95% CI).

Main results

Four trials were included in the review. Of these, two were randomised parallel studies, one was a crossover study and the other had a sequential design. A total of 84 patients were involved. Study quality was mixed and the studies were short (typically two weeks). All studies showed a similar direction and size of effect. In the randomised parallel studies, acetazolamide caused a metabolic acidosis and produced a non-significant fall in PCO₂ (MD -0.41 kPa; 95% CI -0.91, 0.09; N=2) and a significant rise in PO₂ (MD 1.54 kPa; 95% CI 0.97, 2.11; N=2). One study reported an improvement in sleep but there were no data concerning outcomes such as health status, symptoms, exacerbation rate, hospital admissions or deaths. Side effects were reported infrequently. An update search conducted in October 2005 did not identify any further studies.

Authors' conclusions

Acetazolamide can produce a small increase in arterial PO₂ and fall in PCO₂. These conclusions are drawn from a few small short studies that were not all of high quality. It is not known whether this physiological improvement is associated with clinical benefit.

PLAIN LANGUAGE SUMMARY**Carbonic anhydrase inhibitors for hypercapnic ventilatory failure in chronic obstructive pulmonary disease**

Some people with advanced chronic lung disease (COPD - chronic bronchitis or emphysema) can experience breathing failure. This involves chemical changes which in turn can lower the drive to breathe. The drug acetazolamide is used for mountain sickness, and it can stimulate breathing in some circumstances. The review of trials found that a few days of using acetazolamide can improve the level of oxygen in the blood of people with COPD. It is not clear if this leads to better outcomes, so more research is needed. Not enough data were reported on the safety of the drug.

BACKGROUND

Chronic ventilatory failure leading to chronic hypercapnia occurs in a small number of patients with COPD in the end-stage of their disease. This is associated with high plasma bicarbonate. The raised bicarbonate level buffers the effect of the raised arterial carbon dioxide level (PCO₂) so reducing the drive to breathe associated with the respiratory acidosis. Promotion of renal excretion of bicarbonate by inhibition of carbonic anhydrase produces a mild metabolic acidosis, which can increase lung ventilation. The mild acidosis might also cause favourable shifts in the oxygen (O₂) dissociation curve. The carbonic anhydrase inhibitor acetazolamide is used in the treatment of acute mountain sickness, and in recent years, clinicians have used it as an adjunct to treatment in patients with ventilatory failure due to a variety of causes including chronic obstructive pulmonary disease (COPD). This review examines the clinical trial data for this class of agents in this setting.

OBJECTIVES

To determine whether carbonic anhydrase inhibitors improve patients with ventilatory failure secondary COPD in terms of pulmonary gas exchange and clinical outcomes.

METHODS

Criteria for considering studies for this review

Types of studies

Any RCT or quasi-RCT, comparing blood gases in treated and untreated groups of patients with ventilatory failure due to COPD.

Types of participants

Adults with acute or chronic ventilatory failure (PO₂ less than 8 kPa and PCO₂ greater than 6.5 kPa) due to COPD. Both spontaneously breathing and ventilated patients will be included.

Types of interventions

Any oral or intravenous carbonic anhydrase treatment. Dosing may be single or repeated. Treatment must be compared with a control group (usual care or placebo).

Types of outcome measures

Primary outcomes

Blood gas data

Secondary outcomes

1. Progression to ventilation or speed of weaning if ventilation established. Mortality in hospital and length of stay in intensive care unit or hospital
2. Lung function
3. Side effects

Search methods for identification of studies

Electronic searches

Trials were identified using the Cochrane Airways Group Specialised Register of trials, which is derived from systematic searches of bibliographic databases including the Cochrane Central

Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and CINAHL, and handsearching of respiratory journals and meeting abstracts (please see the [Airways Group Module](#) for further details). All records in the Specialised Register coded as 'COPD' were searched using the following terms:

"carbonic anhydrase*" OR "Carbonate dehydratase*" OR acetazolamide OR Diamox OR dorzolamide OR brinzolamide

The most recent search was conducted in October 2010.

Searching other resources

Following this, the bibliographies of each RCT identified were searched for additional papers that may contain RCTs. The bibliographies of review articles concerning treatment of respiratory failure were also searched. Authors of identified RCTs were contacted for other published and unpublished studies. In addition, the pharmaceutical companies who manufacture carbonic anhydrase inhibitors were contacted.

Data collection and analysis

Both reviewers assessed the full papers of all trials that appeared potentially relevant for inclusion. Agreement was achieved by consensus. Data from the trials were extracted by two reviewers and sent to the authors for verification. If author verification was not possible, the second reviewer assessed the accuracy of data extraction.

Statistical considerations

The analysis compared carbonic anhydrase inhibitor versus placebo (or 'standard treatment' or 'usual care'). Continuous outcome measures were entered as mean differences (MD) or standardised mean differences (SMD) depending upon whether data were measured on the same or different metrics.

Categorical outcomes were analysed as odds ratios.

Pooling Data

Data were only pooled within subgroups - defined as randomised, or non-randomised studies.

Assessment of Methodological Quality

Methodological quality assessment was performed by two reviewers using the Cochrane approach and the method of Jadad.

Inter-rater reliability was measured using kappa, and weighted kappa statistics.

RESULTS

Description of studies

Results of the search

Eight references were identified by searches conducted on the Airways Group register. Of these, five were excluded (see [Characteristics of excluded studies](#) table) and three were included. A further study ([Wagenaar 2003](#)) was identified through correspondence with an author of one of the primary trials (Prof Hans Folgering). An update search was conducted in October 2003 - two references were identified: one study which had been previously included as an unpublished trial ([Wagenaar 2003](#)) and

one study was subsequently excluded ([Wagenaar 2002](#); inadequate control). Update searches conducted in October 2007 and October 2010 did not identify any further studies relevant to the review.

Included studies

[Skatrud 1983](#) involved 15 patients. We excluded the results of two patients who did not have clinically significant COPD. Mean age was 56 years (+/-2), mean FEV1 was 38 L (+/- 6%). Patients with FEV1 less 0.5 L were excluded from this study. The participants were allocated in a quasi-randomised fashion to receive either Acetazolamide or placebo in a single blind manner. The inclusion criteria were chronic CO2 retention. Acetazolamide was administered twice daily in 250 mg BD for 10 days.

The outcome measures were blood gas changes at day 10. Other reported outcomes were lung function, oxygen consumption, mouth occlusion pressure and CO2 responses. PO2 measurements were not given in the paper, but Dr Skatrud was able to provide arterial oxygen levels (PO2) on five patients.

The paper of [Hacki 1983](#) reported results of 14 patients (6 exclusions, no gender breakdown) who were randomised to receive either acetazolamide 250 mg or placebo in a double blind crossover trial. Crossover occurred after 3, 6 and 9 days. The results reported in the review were taken from the longer-term follow-up period. Inclusion criteria were PO2 < 60 mm Hg, CO2 > 45 mm Hg and blood pH > 7.38. Mean FEV1 was 0.89 L (+/- 0.29) at baseline, vital capacity was 2.26 L (+/- 0.78).

[Vos 1994](#) reported the effect of acetazolamide on 53 patients (39 male) with a mean age of 65 years (+/- 9) who initially received either room air or oxygen in random order via nasal cannulae. They then received medroxyprogesterone acetate (25 mg), acetazolamide (250 mg) or placebo in random order on a daily basis given in identical capsules.

Inclusion criteria were listed as ATS defined COPD, with FEV1 > 65% predicted value, and daytime arterial PaO2 of > 8.5 kPa.

Patients were excluded from the study who had experienced thromboembolic events in the past, and who had factors suggesting possible obstructive sleep apnoea. Usual medication remained unchanged.

[Wagenaar 2003](#) involved 12 stable COPD patients (no gender ratio given) whose mean age was 68 years (+/- 2). No dropouts were reported. Acetazolamide 250 mg twice daily was administered over two weeks. Inclusion criterion was severe airflow limitation and PaCO2 > 6 kPa. After baseline measurements, all patients received placebo over two weeks. The patients then received acetazolamide or medroxyprogesterone acetate.

Risk of bias in included studies

The [Hacki 1983](#) paper scored three points on the Jadad scale. It was a crossover study; however, we have reported the results of five patients who continued on acetazolamide and eight patients who were followed up after the initial period of treatment. The results from this trial should therefore be treated with caution, since it is not clear whether those who continued the treatment were defined as responsive to acetazolamide.

[Skatrud 1983](#) scored one point on the Jadad scale and was graded C on the Cochrane Collaboration scale of evidence. The study was single blind and there were problems in extracting the data we required due to the failure to report group means but selective presentation of results from ACET responders limit the data which we can use for the review.

[Vos 1994](#) scored three points on the Jadad scale. The paper did not score more than three as there was no description of withdrawals and drop outs from the study. The absence of description of how the study was randomised precluded a higher score. Nevertheless the study was well described and otherwise exhaustive.

[Wagenaar 2003](#) was a crossover trial. The results were reported as an aggregate of the two treatment arms. The patients were randomised to receive acetazolamide and medroxyprogesterone acetate. Methodologically this study was not satisfactory, as patients were not randomised to treatment versus control.

Effects of interventions

Not all of the analyses could be pooled as one was a crossover study ([Wagenaar 2003](#)) and another had a sequential design ([Skatrud 1983](#)) so pooling data from these trials with the papers from [Vos 1994](#); [Hacki 1983](#) was not appropriate.

BLOOD GAS

Acetazolamide led to an improvement in arterial blood gases in all four studies. Arterial pH fell, indicating that the acetazolamide was being taken by the patients and caused a mild metabolic acidosis. This was associated with an overall reduction in PCO2 and a slightly larger improvement in PO2. In the randomised studies ([Hacki 1983](#); [Vos 1994](#)) there was a non-significant fall in PCO2 (MD -0.41 kPa; 95% CI -0.91, 0.09; N=2) and a significant rise in PO2 (MD 1.54 kPa; 95% CI 0.97 to 2.11; N=2).

(NB - the PO2 readings for [Skatrud 1983](#) are incomplete, and correspondence with the author yielded data only for five patients from the study)

The administration of Acetazolamide led to an improvement in arterial blood gases in all four studies that we reviewed. Arterial pH fell and was associated with an overall reduction in PCO2 and an improvement in PO2. In the randomised studies ([Hacki 1983](#); [Vos 1994](#)) PO2 was significantly better for the treatment groups with an improvement ranging from 15 to 27%. The fall in CO2 was between 3 and 12% for all the studies.

LUNG FUNCTION

Lung function data were reported rarely and not in a form that permitted pooling.

PROGRESSION TO VENTILATION OR SPEED OF WEANING IF VENTILATION ESTABLISHED

No paper reported on this outcome. However, given that patients were studied in a stable condition, large numbers of patients were not to be expected.

LENGTH OF HOSPITAL STAY

None of the papers stated whether the patients had been admitted, but it is implicit that the subjects were stable outpatients.

SIDE EFFECTS

The studies suggest that the dose used (250 mg twice daily) was well tolerated. [Hacki 1983](#) reported that no patient had suffered adverse effects. Overall, three patients had parasthesia (one in [Skatrud 1983](#), and two in [Vos 1994](#)). One patient complained of vertigo and one suffered from nausea in [Vos 1994](#). No side-effect data were available from [Wagenaar 2003](#) but no dropouts were reported due to drug side effects.

DISCUSSION

Acetazolamide produced a small fall in arterial PO₂ and rise in arterial PO₂ in all four studies. The study populations were all small and the treatment duration was short. Only that of [Hacki 1983](#) looked beyond an acute effect, although in that study, the criteria for inclusion in the longer-term treatment period were not stated explicitly. None of the studies looked at symptoms other than side effects, although one reported an improvement in the quality of sleep ([Vos 1994](#)). The same study reported an improvement in hypercapnic and hypoxaemic ventilatory responses, but this was not associated with any reported increase in well being. There were approximately equal numbers of patients reporting a favourable judgement as to the treatment effect (7 out of 16 receiving acetazolamide versus 8 out of 18 receiving placebo).

None of the studies were dose ranging, in that all trials used 250 mg twice daily and it is not clear whether greater effects might be obtained with higher doses. Nevertheless the dose used was sufficient to cause a significant change in blood pH. From the available data, the drug appeared to be well tolerated in this dose. One striking finding is the absence of even medium term data in the studies with only five patients having received the drug for more than two weeks ([Hacki 1983](#)). It is possible that side effects would be more likely with longer-term administration.

Ventilatory failure usually occurs late in the natural history of COPD. It is not unusual for patients with an acute exacerbation to require admission to hospital with acute respiratory acidosis. These patients are managed with increased doses of bronchodilators, corticosteroids and non-invasive ventilation. Usually the hypercapnia resolves with treatment. Patients who are chronically hypercapnic usually have more severe disease and a worse prognosis. They also require long term oxygen therapy (LTOT) at home for > 15 hours per day. One intriguing possibility is that long term treatment with acetazolamide might improve the arterial PO₂ sufficiently to delay the point at which patients may need LTOT, or

improve the PO₂ above the level at which LTOT is required (7.5 kPa when breathing room air in a clinically stable state). It seems likely; however, those patients with the worst FEV₁ are those least likely to respond. Indeed [Skatrud 1983](#) noted that patients with the worst spirometry were the least likely to respond. The patient groups in these studies were relatively mild in terms of hypercapnia and clinicians will want to know whether the drug is equally effective in patients with more severe hypercapnia, many of whom may be very symptomatic and in whom chronic ventilatory support might be considered.

In conclusion, whilst the studies were small, short and often of poor design, it does appear that acetazolamide reduces arterial PCO₂ and increases arterial PO₂ over the short term with few reported side-effects. There is no evidence as to whether this physiological improvement translates into improved symptoms (with the sole exception of a single report of improved sleep by [Vos 1994](#)), a reduction in exacerbations, hospital admissions or mortality or an improvement in health status (health-related quality of life).

AUTHORS' CONCLUSIONS

Implications for practice

Short-term clinical trial data suggest that acetazolamide has a small beneficial effect on arterial PCO₂ and PO₂. There is no evidence of other clinical benefits. The drug appears to be well tolerated, with few side-effects over two weeks in a dose of 250 mg twice daily, so may be considered in patients with chronic hypercapnic ventilatory failure.

Implications for research

Well-controlled randomised longer-term studies are required. Such studies should measure symptoms, sleep, health status, need for LTOT, exacerbation frequency, hospitals admissions and deaths. They would need to be multi-centred and have adequate power to detect a difference between the two treatments and sufficiently resourced to accommodate the lengthy follow-up period (between three and five years).

ACKNOWLEDGEMENTS

The authors of this review would like to thank the following people: Jane Dennis, Stephen Milan, Anna Bara and Karen Blackhall (members of the Cochrane Airways Group) for their continued support. A note of thanks should also be made for the Cupertino of Prof. Hans Folgering and Dr James Skatrud who very kindly supplied us with unpublished data.

REFERENCES

References to studies included in this review

Hacki 1983 {published data only}

Hacki M, Waldbeck G, Brandli O. Acetazolamide in hypercapnic chronic obstructive lung disease - a renaissance? [Acetazolamide bei hyperkapnischer chronischer obstruktiver Lungenkrankheit - eine Renaissance?]. *Schweizerische medizinische Wochenschrift* 1983;**113**(3):110-4.

Skatrud 1983 {published data only}

Skatrud J, Dempsey J. Relative effectiveness of Acetazolamide versus medroxyprogesterone acetate in correction of chronic carbon dioxide retention. *American Review of Respiratory Disease* 1983;**127**(4):405-12.

Vos 1994 {published data only}

Vos P, Folgering H, de Boo T, Lemmens W, van Herwaarden C. Effects of chloromadione acetate and oxygen on awake and asleep gas exchange in patients with chronic obstructive pulmonary disease. *European Respiratory Journal* 1994;**7**(5):850-5.

Wagenaar 2003 {published and unpublished data}

* Wagenaar M, Vos P, Heijdra Y, Teppema L, Folgering H. Comparison of acetazolamide and medroxyprogesterone as respiratory stimulants in hypercapnic patients with COPD. *Chest* 2003;**123**(5):1450-9.

Wagenaar M, Vos P, Heijdra Y, van Herwaarden C, Folgering H. The effects of Medroxyprogesterone acetate and acetazolamide on the nocturnal oxygen saturation in COPD patients. [unpublished] 1999.

References to studies excluded from this review

Chin 1983 {published data only}

Chin R, Pesce R. Practical aspects in management of respiratory failure in chronic obstructive pulmonary disease. *Critical Care Quarterly* 1983;**6**(2):1-21.

DeBacker 1995 {published data only}

DeBacker W, Verbraecken J, Willemen M, Wittsaele W, DeCock W, van de Hayning P. Central apnea index decreases after prolonged treatment with acetazolamide. *American Journal of Respiratory and Critical Care Medicine* 1995;**151**(1):87-91.

Izquierdo 1994 {published data only}

Izquierdo J, Morera J. Respiratory stimulants and COPD [Estimulantes respiratorios y EPOC]. *Revista Clinica Espanola* 1994;**194**(12):1003-5.

Noone 1994 {published data only}

Noone P, Olivier K, Knowles M. Modulation of the ionic milieu of the airway in health and disease. *Annual Review of Medicine* 1994;**45**:421-34.

Vos 1995 {published data only}

Vos P, Folgering H, van Herwaarden C. Visual attention in patients with chronic obstructive pulmonary disease. *Biological Psychology* 1995;**41**(3):295-305.

Wagenaar 2002 {published data only}

* Wagenaar M, Vos PJ, Heijdra YF, Teppema LJ, Folgering HT. Combined treatment with acetazolamide and medroxyprogesterone in chronic obstructive pulmonary disease patients. *European Respiratory Journal* 2002;**20**(5):1130-7.

References to studies awaiting assessment

Faisy 2016 {published data only}

Faisy C, Meziani F, Planquette B, Clavel M, Gacouin A, Bornstain C, et al. Effect of acetazolamide vs placebo on duration of invasive mechanical ventilation among patients with chronic obstructive pulmonary disease: a randomized clinical trial. *JAMA. United States: American Medical Association* (E-mail: smcleod@itsa.ucsf.edu), 2016; Vol. 315, issue 5:480-8.

Fontana 2016 {published data only}

Fontana V, Santinelli S, Internullo M, Marinelli P, Sardo L, Alessandrini G, et al. Effect of acetazolamide on post-niv metabolic alkalosis in acute exacerbated COPD patients. *European review for medical and pharmacological sciences. Italy*, 2016; Vol. 20, issue 1:37-43.

Rialp 2017 {published data only}

Rialp Cervera G, Raurich Puigdevall JM, Moran Chorro I, Martin Delgado MC, Heras la Calle G, Mas Serra A, et al. Effects of early administration of acetazolamide on the duration of mechanical ventilation in patients with chronic obstructive pulmonary disease or obesity-hypoventilation syndrome with metabolic alkalosis. A randomized trial. *Pulmonary pharmacology & therapeutics. England: Academic Press*, 2017; Vol. 44:30-7.

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Hacki 1983

Methods	RCT, single blind, parallel group study
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Hacki 1983 (Continued)

Participants	N = 13. Inclusion criteria: Patients with COPD, pO ₂ <60mm Hg, pCO ₂ > 45mm Hg, pH > 7.38
Interventions	Diamox and placebo
Outcomes	Blood gases, Lung function
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Skatrud 1983

Methods	Sequential single blind, placebo controlled crossover trial.
Participants	N = 13. Inclusion criteria: Patients mean age was 56 years (+/- 2). Mean weight was 90 kg (+/- 7). Patients with FEV ₁ < 0.5 L were excluded.
Interventions	Placebo was administered before both ACET and MPA
Outcomes	Blood gases, Lung function, Response to exercise, mouth occlusion pressure, CO ₂ response.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Vos 1994

Methods	RCT, double blind, parallel study
Participants	N = 53. Inclusion criteria: FEV ₁ < 65% predicted. Daytime PaO ₂ < 8.5 kPa.
Interventions	ACET, Chlormadinone or placebo.
Outcomes	Blood gases, Lung function, ventilatory responses, end tidal CO ₂ , sleep quality, nocturnal oxygen saturations.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
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Vos 1994 (Continued)

Allocation concealment (selection bias)	Unclear risk	B - Unclear
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Wagenaar 2003

Methods	Crossover double blind, placebo controlled trial
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Participants	N = 12
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Interventions	
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Outcomes	
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Notes	
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Risk of bias

Bias	Authors' judgement	Support for judgement
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Allocation concealment (selection bias)	Unclear risk	D - Not used
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Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Chin 1983	Review article
DeBacker 1995	Not COPD
Izquierdo 1994	Review article
Noone 1994	Review article
Vos 1995	Healthy controls
Wagenaar 2002	RCT assessing the effects of combination therapy. Inadequate control group.

DATA AND ANALYSES
Comparison 1. Diamox versus control

Outcome or sub-group title	No. of studies	No. of participants	Statistical method	Effect size
1 PCO ₂ (kPa)	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

Outcome or sub-group title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Randomised Studies	2	48	Mean Difference (IV, Fixed, 95% CI)	-0.41 [-0.91, 0.09]
1.2 Crossover studies	1	24	Mean Difference (IV, Fixed, 95% CI)	-0.70 [-1.22, -0.18]
1.3 Sequential studies	1	26	Mean Difference (IV, Fixed, 95% CI)	-0.73 [-1.56, 0.10]
2 PO ₂ (kPa)	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 Randomised Studies	2	48	Mean Difference (IV, Fixed, 95% CI)	-1.54 [-2.11, -0.97]
2.2 Crossover studies	1	24	Mean Difference (IV, Fixed, 95% CI)	-1.20 [-2.25, -0.15]
2.3 Sequential Studies	1	10	Mean Difference (IV, Fixed, 95% CI)	-1.15 [-2.89, 0.59]
3 pH	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 Randomised Studies	2	48	Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.07, -0.03]
3.2 Crossover studies	1	24	Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.07, -0.03]
3.3 Sequential Studies	1	26	Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.08, -0.04]
4 HCO ₃	4		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 Random studies	2	48	Std. Mean Difference (IV, Fixed, 95% CI)	-1.60 [-2.29, -0.91]
4.2 Crossover studies	1	24	Std. Mean Difference (IV, Fixed, 95% CI)	-2.60 [-3.74, -1.47]
4.3 Sequential studies	1	26	Std. Mean Difference (IV, Fixed, 95% CI)	-1.74 [-2.67, -0.82]

Analysis 1.1. Comparison 1 Diamox versus control, Outcome 1 PCO₂ (kPa).

Analysis 1.2. Comparison 1 Diamox versus control, Outcome 2 PO₂ (kPa).

Analysis 1.3. Comparison 1 Diamox versus control, Outcome 3 pH.

Analysis 1.4. Comparison 1 Diamox versus control, Outcome 4 HCO3.

WHAT'S NEW

Date	Event	Description
21 August 2017	Amended	New literature search run to assess the need to update this review. Three potentially eligible studies identified and added to Studies awaiting classification .

HISTORY

Protocol first published: Issue 1, 1998

Review first published: Issue 1, 2001

Date	Event	Description
28 October 2010	New search has been performed	New literature search run. No new studies found. Minor copy edits made.
21 July 2008	Amended	Converted to new review format.
19 September 2000	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Paul Jones - conceived the protocol, assessed search results, entered data and interpreted the results.

Mike Greenstone - assisted with protocol conception, assessment of search results, and overall interpretation.

DECLARATIONS OF INTEREST

There are no known conflicts of interest. There are no external sources of support.

SOURCES OF SUPPORT

Internal sources

- NHS Research and Development, UK.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Acetazolamide [*therapeutic use]; Carbonic Anhydrase Inhibitors [*therapeutic use]; Clinical Trials as Topic; Hypercapnia [*drug therapy] [etiology]; Pulmonary Disease, Chronic Obstructive [*complications]; Respiratory Insufficiency [*drug therapy]

MeSH check words

Female; Humans; Male