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Gold as an oral corticosteroid sparing agent in stable asthma (Review)

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[Intervention Review]

Gold as an oral corticosteroid sparing agent in stable asthma

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ABSTRACT

Background

Patients with chronic severe asthma are often dependent on the long term prescription of oral corticosteroids. The use of steroids is associated with serious side effects. Physicians treating such patients continue to search for alternative therapies that reduce the need for chronic dosing with oral steroids. Gold compounds are immunosuppressive agents and have benefits in the treatment of a number of inflammatory disorders. They have therefore been identified as an potentially useful agents in the treatment of chronic severe asthma both in terms of possible efficacy and as steroid sparing agents.

Objectives

The objective of this review was to assess the effects of adding gold to oral steroids in the treatment of chronic steroid dependent asthmatics.

Search methods

The Cochrane Airways Group Specialised Register of trials and reference lists of identified articles were searched. Searches were current as of September 2010.

Selection criteria

Randomised trials looking at the addition of gold compared to placebo in adult steroid dependent asthmatics.

Data collection and analysis

Trial quality was assessed and data extraction was carried out by two reviewers independently. Study authors were contacted for missing information.

Main results

Three trials fulfilled the criteria for inclusion in the review and a total of 376 patients were recruited into these studies. Data from 311 patients could be analysed. There was a small but significant treatment effect for gold in terms of steroid dose reduction (Peto Odds Ratio 0.51, 95% confidence intervals 0.31,0.83). No meta-analysis could be done for measures of lung function although overall there were few changes suggesting a positive benefit for gold. There were trends suggestive of adverse effects but no significant changes for gold treated patients with respect to proteinuria (Peto Odds Ratio 1.4, 95% confidence intervals 0.6, 3.3) dermatitis/eczema Peto Odds Ratio 2.1, 95% confidence intervals 0.9, 4.7). Update searches carried out in September 2007 and 2010 did not yield any new studies.

Authors' conclusions

The changes seen in these trials are small and probably of limited clinical significance. Given the side effects of gold and necessity for monitoring the use of gold as a steroid sparing agent in asthma cannot be recommended.

PLAIN LANGUAGE SUMMARY

Gold may have a small impact on asthma for people dependent on corticosteroids, but adverse effects are serious and a lot of monitoring is needed.

Some people need to rely on corticosteroid drugs to control their asthma. Corticosteroids help reduce the inflammation (swelling) of the airways (passages to the lungs) associated with asthma. Long-term use of these drugs has serious adverse effects, so other ways to try and cut down on the need for corticosteroids are sometimes tried. Gold is used by people with some other kinds of inflammatory problems (such as rheumatoid arthritis). The review of trials found that people with asthma taking gold need careful monitoring as there are harmful effects, and it may only have a very small impact on asthma symptoms.

BACKGROUND

The recognition that asthma is a consequence of airway inflammation has focused treatment objectives towards anti-inflammatory agents. Inhaled and systemic corticosteroids are of proven benefit.

There are, however, a group of asthmatics who continue to have symptoms despite high doses of inhaled steroids and require maintenance treatment with oral corticosteroids. Whilst these patients are in the minority, in the order of 1-2%, this subset constitute a significant number and consume a considerable and disproportionate fraction of the health care resources. Furthermore these patients are at risks from the unwanted effects of long term treatment with systemic corticosteroids. These include osteoporosis, diabetes, hypertension, neuropsychiatric disorders and growth retardation in children.

As a result of this clinical dilemma there have been a number of clinical trials examining the use of 'second-line' immunosuppressive agents. These include agents such as methotrexate, cyclosporin A, azathioprine and gold. The concept that these drugs may be of benefit in asthma has arisen from studies showing there are benefits in inflammatory conditions such as arthritis and psoriasis. To date only methotrexate in asthma has been reviewed.

Elemental gold has been used in the treatment of various ailments for hundreds of years although its use in inflammatory conditions such as rheumatoid arthritis was not fully recognised until 1929.

Gold sodium thiomalate, gold thioglucose and auranofin are the agents used as gold therapy. The latter is a synthetic compound that, unlike the other two parenteral compounds, is lipid soluble and therefore administered by mouth. In addition to its route of administration, there are other pharmacokinetic differences between the formulations that strongly favour auranofin. Not least of these relates to the doses of the various agents required to give the same clinical effect. This is particularly relevant in the context of cumulative toxicity of gold.

The mechanism of action of gold is not well understood, and the mechanism of action for parenteral gold may differ from that of auranofin. Amongst other non-specific actions on immune cells Auranofin has been shown to inhibit the release of cytokines from lymphocytes e.g. IL-1, IL-2 and also inhibit the release of inflammatory mediators from mast calls. Parenteral gold appears to act via the inhibition of lysozyme action and prostaglandin synthesis. Both oral and parenteral gold inhibit lymphocyte responses to mitogen.

Gold is usually prescribed at a dose of 25 - 50 mg a week and taken either orally or by intra-muscular injection.

Auranofin and parenteral gold cause proteinuria and occasionally nephrotic syndrome. Gastrointestinal upset including nausea and vomiting are established side effects and one author has attributed intestinal haemorrhage and perforation to gold in four patients to this treatment. Eczema and blood dyscrasias are also reported.

The use of gold as an adjunct to oral corticosteroids has been reported in both open & blinded randomised controlled studies in asthma. These studies have employed differing methodology and to date the results have been conflicting. Previous narrative reviews give the overall impression that it is of benefit, but this has not been established. A systematic review with meta-analysis may help to synthesize the data.

OBJECTIVES

To conduct a systematic review of the literature concerning the benefit of adding gold to oral corticosteroids in chronic stable adult asthmatics who were dependent on oral corticosteroids

METHODS

Criteria for considering studies for this review

Types of studies

All studies were required to be randomised double blind controlled trials in adult asthmatics. All relevant studies were included.

Inclusion criteria
(i) Gold treatment (either oral or parenteral administration).
(ii) Duration of therapy should have been sufficient to allow for any benefit accruing from gold to appear.

Exclusion Criteria
(i) Inadequate trial duration (less than 12 weeks).

Types of participants

Inclusion criteria

1. All trial patients diagnosed with "asthma" defined in operational terms.
2. Adults, arbitrarily defined as being greater than 16 years old.

Exclusion criteria

1. Subjects who were not on oral steroids before the trial.

Types of interventions

The addition of gold or placebo in a blinded randomised fashion.

Types of outcome measures

Study outcomes reported a wide range of measurements, including at least one of the following:

1. Pulmonary function testing (PEF, FEV1 & any others).
2. Symptoms.
3. Use of rescue medications (e.g. bronchodilators).
4. Frequency of asthma exacerbations.
5. Alterations in steroid dosage.
6. Frequency of use and variation in dosages of other drugs.
7. Side effects & adverse effects.
8. Deaths.
9. Hospital admissions.

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 'asthma' were searched using the following terms:

'Gold OR auranofin'

These searches are current as of September 2010.

Searching other resources

Bibliographies from these primary papers and review articles were surveyed for additional citations & RCTs. Trial authors were contacted for more information.

Studies in languages other than English were to be included.

Data collection and analysis

Selection of studies

The titles and abstracts were reviewed to identify all potential RCTs. Full text versions of these articles were obtained.
Inclusion of studies was decided by two reviewers who independently read the methods section of all identified papers and applied the stated criteria.

Data extraction and management

This was performed by one reviewer and a second reviewer checked the data extraction. Inter-rater reliability was assessed by simple agreement.

Other characteristics of trial validity;

1. "Chronic" & "Stable"
2. Use of inhaled corticosteroids
3. Prior attempts at reduction in oral corticosteroid dose (tapering)

Assessment of risk of bias in included studies

Trials were scored according to the Cochrane assessment of allocation concealment as well as by the 0-5 point scale of Jadad by two reviewers acting independently.

Data synthesis

The planned comparison was a comparison of oral and parenteral gold versus placebo.
Comparisons were performed for each outcome. Outcome data was entered into RevMan 4.1 for statistical analysis. Categorical outcomes were assessed as odds ratios (OR) and 95% confidence intervals. Continuous outcomes were analysed as effect sizes. Fixed effects models were used to obtain summary statistics for the overall efficacy of gold upon specific outcomes.

Subgroup analysis and investigation of heterogeneity

If heterogeneity still existed a sub-group comparison was made on the basis;
A Size of study
B Optimal inhaled corticosteroid use
C Pre trial steroid tapering
D Disease severity

Sensitivity analysis

Heterogeneity was tested for, and if found, a sensitivity analysis done on the basis of methodological quality

RESULTS

Description of studies

Results of the search

The original literature searches identified thirteen trials of which 3 reported data in a form adequate for analysis. Attempts to contact the authors for more detailed information were made. In all instances this was unsuccessful. Updated searches in 2008 and 2010 yielded no further references for consideration.

Included studies

Three studies were identified, all of which were published as full articles. All studies were published in English language publications. Two of the trials were relatively small although all three trials were of adequate quality. In total 311 patients completed the studies suitable for meta-analysis. Given the various possible mechanisms of action and established differences in pharmacological profiles between auranofin and parenteral gold, comparisons of these two agents for steroid sparing effects and efficacy are difficult. Nevertheless for the purpose of this review the studies reported for both oral and parenteral gold will be summarised together. An update search conducted in September 2007 did not identify any additional trials.

Each included trial is presented in detail:

Klaustermeyer 1987 examined 10 steroid dependent asthmatics in 2 phases. The mean prednisolone dose over previous year was 21.15 mg (SD 4.3 mg). No details of attempts to taper steroid doses before the trial are given. Only 5 of the patients were on inhaled steroids. The first period was a double-blind treatment randomising to aurothioglucose or placebo, by injection, over 22 weeks. Thereafter the study was unblinded and placebo patients were swapped over to the gold treatment for a further 22 weeks. Data for the first period alone was used for this meta-analysis. For the initial treatment phase 6 patients were randomised to gold and four to placebo. One patient was withdrawn from the placebo group due to abnormalities in gas transfer on lung function testing. Two patients were withdrawn due to heavy proteinuria after 4 and 15 weeks of gold treatment respectively. Only data from the second individual were included in the paper's analysis. No other adverse events were reported. The data were analysed in terms of individual patient's responses to treatments over time in terms of lung function and steroid dose.

Patients were assessed on a weekly basis when spirometry and PEFR were measured and both steroid dose and asthma control were evaluated. The physician made a clinical judgement of the ongoing steroid dose. Overall there were 5 significant and favourable responses in terms of steroid doses to gold treatment with no changes in measures of lung function.

The authors concluded that parenteral gold had a steroid sparing effect in some patients and might therefore have a useful role in severe refractory asthma.

Nierop 1992 was a double-blind, placebo controlled, parallel group study employed a one week run-in period followed by a 26 week treatment phase during which patients were randomised to take either auranofin 3 mg twice daily or matched placebo. 32 patients were enrolled and 28 completed the trial. The mean (SD) dose of prednisolone at entry was 7.9 mg (4.4), with no difference between treatment groups in this regard. No details of attempts to taper steroid doses prior to the trial are given. All but 3 patients were on inhaled steroids. One patient was withdrawn from placebo due to non-compliance, and three (2 in the gold treated group and one in placebo) due to severe eczema resistant to topical treatment.

Patients were assessed every 2 weeks, and steroid tapering was commenced at 12 weeks if asthma control was satisfactory. Spirometry was repeated at 12 and 26 weeks. Changes in the doses of steroid taken by the study patients were derived from the first and last 2 weeks of the treatment phase. The mean (SD) daily dose in the gold treated patients fell from 9.3 mg (6.34) to 5.3 mg (6.19) (p = 0.007), and in placebo treated patients from 11 mg (6.35) to 10.7 mg (7.33) (NS). In parallel there were significant differences between the two groups, in favour of gold, for improvements in symptom scores, FEV1, and courses of added prednisolone for exacerbations.

In addition to eczema in 3 patients there were mild adverse events in 4 other patients on gold (3 nausea, one diarrhoea) necessitating a reduction in the dose for 2 weeks. These settled without further intervention.

The authors concluded that auranofin represented an effective adjunct to the treatment of asthma, leading to a reduction in oral steroid dose.

Bernstein 1996 was a double-blind, placebo controlled, parallel group trial. There was a 4 week baseline period followed by an 8 month treatment phase and a 4 week run-out phase during which patients remained on the same treatment. Patients were randomised to receive auranofin mg twice daily or matched placebo. 334 patients were enrolled and data from 275 patients (136 gold, 139 placebo) were analysed on an intention to treat basis. 157 patients completed the trial. The majority of patients were taking between 10-19 mg of prednisolone a day (gold 68% patients, placebo 66% patients). There were no differences between the study groups for steroid doses or any other demographic variable.

Attempts to taper steroids were made during a 3 month pre-trial screening period. No details about the number of patients on inhaled steroids or the doses used were given. Patients were assessed every 2 weeks and steroid tapering was commenced at 12 weeks if asthma control was satisfactory. Spirometry was re-measured every 4 weeks from week 12 and symptom diaries, home PEFR readings and medication cards were reassessed at these times primary outcome for the study was treatment success, as defined by a 50% reduction in baseline steroid requirements. 41% of the gold treated group achieved therapeutic success as compared to 27% in the placebo group (p = 0.01). The effect was most marked amongst those individuals whose pre-trial steroid dose was between 10 and 19 mg a day. There were no differences between groups for lung function, symptoms or concomitant medication use.

There were significantly more gastrointestinal and dermatological adverse events reported in the gold treated patients.

The authors concluded that auranofin was useful as a steroid agent in the treatment of asthma.

Risk of bias in included studies

Attempts to taper steroid doses before the treatment periods were only explicitly stated in the trial reported by Bernstein 1996 et al. Criteria for steroid dependency was similar in the trials reported by Bernstein 1996 et al and Klaustermeyer 1987 et al (10 mg daily) although in the third trial, Nierop 1992 et al, the patients were only required to take 2.5 mg daily prior to the trial. The actual level of steroid dependency of the patients varied between the trials. Approximately 70% of the patients studied by Bernstein 1996 et al were taking 10-19 mg daily with no specific details given. Furthermore it is not clear how long these patients had been taking steroids, only that a minimum of 3 months was required for trial entry. In the other two studies the mean (SD) duration of steroid dependency was 6.5 (8) years in the trial reported by Nierop 1992 et al and 8.75 (7.5) years amongst the patients studied by Klaustermeyer 1987 et al. The mean baseline steroid doses for these trials 7.9 mg and 21.2 mg respectively. The use of inhaled corticosteroids in these trials was variable.

Effects of interventions

Study design, duration, subjects and outcome measures varied between trials. All patients had demonstrable reversibility of FEV1 following inhalation of beta-agonists (15 - 20% depending on the study). All trials excluded patients with significant co-morbidity.

The three trials included one cross-over and two parallel group trials. Data from the only first limb of the cross-over trial (Klaustermeyer 1987) has been included as the gold patients from the first treatment phase did not cross-over to placebo. The patients in this trial received parenteral gold in the form of aurothioglucose 50 mg I.M. weekly. Patients in the other two trials took oral gold, auranofin 3 mg twice daily.

Initially a total of 376 patients were enrolled and data was collected from 311 patients across the three trials reviewed. Of these 193 individuals completed the various protocols. The majority of the patients were included in the study by Bernstein 1996 et al (275 analysed on an intention to treat basis). The trials were 22 weeks (Klaustermeyer 1987), 26 weeks (Nierop 1992), and 8 months in duration (Bernstein 1996).

The outcome variable for all trials was a reduction in the dose of steroids. This was assessed differently in each of the three trials. Klaustermeyer 1987 et al reported individual patient responders and non responders who were identified by sorting dose data according to treatment and regressed as a function of time. For the Nierop 1992 study mean daily doses of steroid were calculated for the first and last 2 weeks of treatment and comparisons drawn between groups. A further expression of data was used by Bernstein 1996 et al who compared proportions of each of the treatment groups who fulfilled pre-set criteria for therapeutic response (50% reduction in steroid dose compared to baseline). All three studies found significant reductions in steroid dose amongst the gold treated patients compared to placebo.

The Nierop 1992 data was analysed separately from the other two trials since the Bernstein 1996 and Klaustermeyer 1987 studies both reported results in terms of treatment success rather than in terms of actual steroid doses. For Nierop 1992 et al there was a clear

treatment effect in favour of gold. The dose reduction in the gold treated patients was 4.1 mg (p = 0.007) compared to 0.3 mg in the placebo group (NS). Meta-analysis of the other two trials produced a Peto odds ratio of 0.51 (95% CI 0.31,0.31) supporting a significant treatment effect in favour of gold.

Lung function data from these trials has to be interpreted with caution, because they were designed to test the steroid sparing potential of gold preparations, not as a measure of clinical efficacy. Nevertheless Nierop 1992 et al reported a 6% increase in FEV1 and significant improvements compared to the changes seen in the placebo patients. In addition there were significant differences between the groups for symptoms in favour of the gold group. There were no significant changes in FEV1, PEFR, symptom scores for the patients in the Bernstein 1996 study, nor were any differences reported for FEV1 in the Klaustermeyer 1987 trial.

In the Bernstein 1996 trial 6 patients were withdrawn from the gold group due to uncontrolled asthma as compared to 11 in the placebo group. Nine out of 17 admissions in the gold group were related to asthma exacerbations, compared to 7 out of 19 for placebo. One patient in the gold treated group died of asthma after 13 weeks of treatment. In the study reported by Nierop 1992 et al there were no differences between groups for numbers or duration of asthma exacerbations. No data on exacerbations was presented in the study by Klaustermeyer 1987 et al.

In terms of adverse effects, there was no significant untoward effect of gold with respect to proteinuria (Peto OR 1.4, 95%CI 0.6, 3.3) or dermatitis/eczema (Peto OR 2.1, 95% CI 0.9, 4.7) in the Bernstein 1996 and Klaustermeyer 1987 trials. Nierop 1992 et al reported no changes in urinary parameters in either treatment group.

No heterogeneity was identified amongst the data analysed by meta-analysis.

DISCUSSION

This review has studied three randomised controlled trials looking at the effects of gold amongst a group of oral corticosteroid dependent asthmatics. The authors in each study conclude that this drug has either efficacy or steroid sparing qualities or both. It is not possible to quantify the actual size of the treatment effects measured for steroid sparing qualities in the studies by Bernstein 1996 et al and Klaustermeyer 1987 et al although Nierop 1992 et al report a reduction in steroid dose of 4 mg over the 22 week treatment period. The trials vary in methodology and have some limitations that influence the interpretation of the results of this review.

Whilst oral corticosteroid dependent patients account for approximately 1% of the total with asthma, this group consume a disproportionate amount of available resources. Furthermore these patients are at serious risk of debilitating side effects from chronic steroid dosing, notwithstanding the real risk chronic the asthma poses to their health. It is important to improve the treatment for this group . This underpins the need for trials that assess 'add on' therapies using potent and potentially toxic immunosuppressive agents such as gold.

Given this clinical challenge it becomes obvious that there are two fundamental and separate outcomes to consider in the development of novel treatment strategies, namely efficacy and steroid sparing qualities. The recognition of these outcomes is vital to the whole question of understanding trial design. Studies looking at efficacy should make no attempt to reduce the dose of steroids and simply look at measures of function and asthma control whereas steroid sparing trials should look at doses of steroid in the context of stability. The primary outcome measure of trials therefore defines the type of trial. Extracting functional data from a steroid sparing trial to test efficacy or recording changes in steroid doses in an efficacy trial may be misleading when examining the overall effects of 'add on' drugs. The trials included in this review report both these outcomes, although in fact all three set out to look at reductions in steroid dose.

Efficacy of drugs used to treat asthma should be measured in terms of lung function (PEFR, FEV1, FVC etc) and markers of asthma control (symptom scores, exacerbation rates, quality of life scores etc). The studies reported by Bernstein 1996 and Nierop 1992 looked at markers of function and asthma control. With reference to markers of asthma control no quality of life scores were done and none of the trials included a marker of asthma control amongst the primary outcome variables.

The participants in the trials were similar in terms of baseline lung function. There were inconsistencies in the use of inhaled steroids across these three trials and this is an important limitation in the usefulness of the review given the importance of inhaled corticosteroids as 'oral steroid sparing agents'. Furthermore there were differences in the corticosteroid dependency of the subjects in the included trials. Both this and the lack of tapering in two of the studies creates uncertainty in the interpretation of the results.

The trials reported by Klaustermeyer 1987 and Nierop 1992 were small and the majority of patients included in this review are derived from the study by Bernstein 1996 et al. Clearly this is relevant to the interpretation of the data arising from any meta-analysis. No significant heterogeneity was identified for any outcome measure used in the meta-analysis. Only Nierop et al showed power calculations for their study and these were based on changes in steroid dose. Klaustermeyer et al did not stipulate any primary outcome variables. Clearly this may be of importance given the negative results included in the papers. Bernstein et al presented non-significant results for measures of lung function, and asthma control (notwithstanding the design of the trial as a steroid sparing study). Similarly Nierop et al (who did not identify markers of asthma control as a primary outcome) failed to show significance for PEFR and exacerbations (although did find significant differences for symptom scores). This issue is important as Type 2 statistical errors cannot be excluded and firm conclusions about these negative results should not be drawn.

The duration of the Klaustermeyer 1987 and Nierop 1992 studies was brief when considering the context of chronic asthma and the assumptions made about mechanisms of action for disease modifying immunosuppression. The longest treatment period was 6 months (Bernstein 1996 et al). These attempts to show conclusive effects for gold may have been hindered by short treatment trial duration.

Only Bernstein 1996 et al stated that tapering of steroids was carried out during the run in to the study. This process is important to minimise error arising from falsely positive benefits arising from excessive steroid doses amongst the study subjects. As a result, the benefits seen in the Klaustermeyer 1987 and Nierop 1992

trials needs to be interpreted with caution. The trial reported by Klaustermeyer et al was a cross-over design. Patients who received gold during the first phase did not cross over to placebo due to concerns about carry-over effects and therefore the need for long washout times i.e. the code was broken after completion of the first treatment period. Data from the double blind phase has been used in this review. The other two trials were both parallel group design.

A further difference between the trials relates to the use of both parenteral gold and auranofin. These compounds may exert their immunomodulatory actions in different ways. Given the lack of randomised controlled trials it was decided to pool what little evidence there is and review the potential class effect of this treatment. There are similarities in the profile of untoward effects and this aspect of the review is probably justified.

As stated there are considerable differences in the way that data for steroid doses were expressed in all the trials. Therefore the meta-analysis for this comparison was divided between the data of Bernstein 1996 et al and Klaustermeyer 1987 et and that from the study by Nierop 1992 et al. For the former meta-analysis there were significant treatment effects seen as measured by 'therapeutic successes' (Peto OR 0.5 95% CI 0.3, 0.8) and for the latter analysis Nierop 1992 showed significant benefits in favour of auranofin. It should be reiterated that the majority of the patients in the meta-analysis were derived from the study reported by Bernstein 1996. Furthermore the authors of this trial comment on marked benefits for auranofin amongst those patients taking between 10-19 mg of steroid although no explanation for this has been proposed.

There was so little extractable data on measures of lung function that no meaningful analyses could be done. Data from the individual papers, as already mentioned, shows mixed results. Overall the results fail to provide evidence of efficacy or steroid sparing effect.

None of the trials examined possible mechanisms of action for gold such as measures of airways inflammation. Gold compounds are known to have inhibitory effects on a number of inflammatory pathways inclusive of lymphocytic expression of a cytokines that may be relevant to the immunopathology of asthma. Clearly an interpretation of the results would be more easier if mechanistic data supporting the clinical findings had been available.

With reference to safety, there was a shortage of data for analysis. As with the outcome measures, there were differences in the ways these parameters were measured further complicating comparisons. Interestingly the important side effect of gold, namely proteinuria did not emerge as a major problem from the two studies that presented adequate data for extraction (Peto OR 1.4 ;95%CI 0.6, 3.3). Whilst no data was presented in the study reported by Klaustermeyer 1987 et al the authors discuss two patients who were withdrawn due to proteinuria. This side effect resolved on discontinuation of the drug. There were excess reports of dermatological reactions and two patients were withdrawn from the Nierop 1992 study due to this.

In summary, the three trials included in this review amount to a relatively small body of evidence. There are flaws in each that limit the conclusions to be drawn from their results. Nevertheless, the combined data shows that the addition of gold has resulted in modest reductions in steroid dose. The clinical relevance of these changes, even if the assumption is made that they represent real effects of the drug alone, is debatable. From the perspective of safety there are established serious side effects of this treatment although this review has not been able to demonstrate significant untoward changes in parameters such as renal function that would countenance against the use of gold. The potential benefits in terms of reduced steroid risk cannot be quantified but it seems unlikely that significant clinical gain would be forthcoming.

AUTHORS' CONCLUSIONS

Implications for practice

The changes seen for both markers of efficacy and steroid sparing qualities are small and probably clinically insignificant. Given the side effect profile for this agent, the routine use of gold in the treatment of steroid dependent asthma cannot be recommended. If prescribed, it should only be prescribed by physicians experienced in its use.

Implications for research

Further randomised controlled trials with sufficient power to conclusively evaluate gold in terms of efficacy and steroid sparing effects (i.e. separate trial designs) are required to clarify whether the small effects demonstrated by this meta-analysis represent clinically significant changes. It will then be possible to assess whether benefits, if any, can be applied to clinical practice.

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Okatani 1970 *{published data only}*

Okatani Y. Gold salt therapy in bronchial asthma. *Japanese Medical Journal* 1970;**2432**:17-21.

Von Lebinski 1936 *{published data only}*

Von Lebinski. Contribution of gold therapy [Beitrag zur goldtherapie]. *Therapie der Gegenwart* 1936;**77**:564-7.

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bernstein 1996

Methods	Randomised, double blind, placebo controlled study. 12 week screening period when tapering of steroid dose was undertaken, 4 week baseline period, 24 week treatment phase, and 4 week run out period.
Participants	334 patients screened, 140 randomised to gold, 139 to placebo. 146 men,133 women. Mean age (SD); gold, 52.9y(13.5): placebo, 50.5y(12.8). Variable ICS, no nos. or dose details given. Mean prednisolone dose not given, 66% gold patients and 68% placebo maintained on 10-19mg steroid per day. FEV1 %predicted; gold 64%: placebo 63%.
Interventions	Randomised to auranofin 3mg twice daily or placebo. Primary outcome - therapeutic success, defined as 50% reduction in steroid dose cf baseline Secondary outcomes - spirometry, PEFR, symptoms, beta agonist use, global assessments of asthma control. First 12 weeks of treatment no change to steroid dose attempted. Second 12 week period of treatment, steroids reduced as per pre-set protocol.

Bernstein 1996 *(Continued)*

	Symptom cards, daily PEFR and clinic visits every 4 weeks.
Outcomes	Therapeutic success achieved in 41% gold patients and 27% placebo (p = 0.01). Lung function maintained. No difference between groups with respect to other parameters.
Notes	Inadequate information regarding allocation concealment. Senior author kindly responded to enquiries seeking clarification but did not have access to study file and subsequent efforts to access this have been unsuccessful.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Described as randomised; other information not available

Klaustermeyer 1987

Methods	Randomised , double blind, placebo controlled, parallel group study. 10 month run-in, 22 week treatment phase.
Participants	10 patients enrolled, evaluable data from 8. All males. Mean age, 56y. Mean (SD) prednisolone dose 21.25mg (4.3). 5/8 ICS, no dose details Mean FEV1, 2.15L
Interventions	Randomised to gold or placebo. Clinic visits every week. Clinic measurements of PEFR,FEV1,FVC. Steroid dose revised at each visit as clinically indicated, details not given.
Outcomes	5/8 responded to gold, no significant differences for steroid dose or lung function between groups.
Notes	Inadequate information regarding allocation concealment. Authors did not respond to correspondence seeking clarification.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Described as randomised; other information not available

Nierop 1992

Methods	Randomised, double blind, placebo controlled, parallel group study. One week run-in, 26 week treatment phase.
Participants	32 patients enrolled, data evaluated from 28 patients who completed the study. 17 men,15 women. Mean age (range), 52.4y (28-72). 3 patients not using ICS (not tolerated), remainder treated with a minimum of 800micograms daily. Mean dose (SD) prednisolone (mg); gold, 7.6(5.31): placebo, 9.4(4.47).

Nierop 1992 *(Continued)*

	Mean % predicted FEV1 (range); gold, 59.8 (14-100): placebo, 59.7 (33-97). 2 smokers
Interventions	Randomised to Auranofin 3mg twice daily or placebo. Visits to clinic every 2 weeks. If stable after 12 weeks treatment, taper steroids by 2.5mg per week. Diary cards and spirometry.
Outcomes	Mean (SD) prednisolone dose (mg) for fist 2 weeks and last 2 weeks of treatment; gold 9.3(6.34) and 5.3(6.19) respectively (p = 0.007):placebo 11.0(6.35) and 10.0(7.33) respectively (p = 0.48). Between group comparison p = 0.056. Mean % predicted (SE) FEV1 at baseline and end of treatment; gold 59.8%(26.8) and 66.2%(29.6) respectively: placebo 59.7%(19.45) and 50.2%(14) respectively. Differences between groups for FEV1 significant. Significant differences for symptoms in favour of gold.
Notes	Inadequate information regarding allocation concealment. Authors did not respond to correspondence seeking clarification.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Described as randomised; other information not available

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Araki 1969	Uncontrolled trial
Bernstein 1988	Open trial. 18 patients treated with auranofin over 24 weeks. Significant protection afforded against methacholine challenge but no changes in lung function. Reductions in steroid dose recorded.
Dudan 1932	Uncontrolled trial. Parenteral gold, some benefits for reduction in bronchodilators and lung function
Honma 1994	Double blind trial amongst 19 patients treated over 12 weeks. Excluded as group were not steroid dependent asthmatics. Reductions in airway responsiveness to methacholine noted in gold treated patients.
Ishizaki 1965	Uncontrolled trial.
McNeil 1989	Open trial. 8 patients treated for 7-17 months with oral gold. Global improvements in asthma control but no change in lung function. Reductions in steroid doses recorded.
Montagna 1936	Uncontrolled trial
Muranaka 1978	Double blind trial amongst 79 patients treated with gold or placebo over 8 weeks. Excluded on the basis that the trial subjects were not all steroid dependent asthmatics. Of the subjects completing the trial, physician assessment of asthma control showed significant improvements in 20/28 gold treated patients and 16/36 placebo treated patients.
Okatani 1970	Uncontrolled trial. Derived from data from over 1000 asthmatics treated over 14 years.

Study	Reason for exclusion
Von Lebinski 1936	Uncontrolled trial.

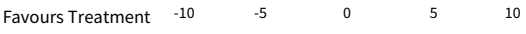
DATA AND ANALYSES

Comparison 1. Gold versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Steroid dose reduction	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Treatment success (significant steroid reduction)	2	283	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.51 [0.31, 0.83]
3 FEV1	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4 Exacerbations	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5 Exacerbations (hospital episodes)	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
6 Haematology	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
7 Proteinuria	2	285	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.42 [0.61, 3.27]
8 Dermatitis/eczema	2	303	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.05 [0.89, 4.71]

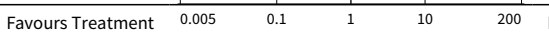
Analysis 1.1. Comparison 1 Gold versus placebo, Outcome 1 Steroid dose reduction.

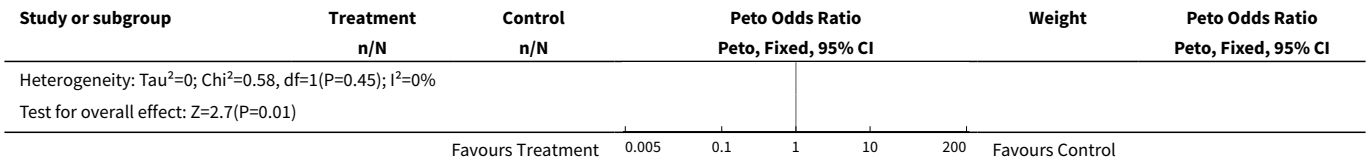
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Nierop 1992	15	-4.1 (5.3)	13	-0.4 (3.9)		-3.74[-7.18,-0.3]



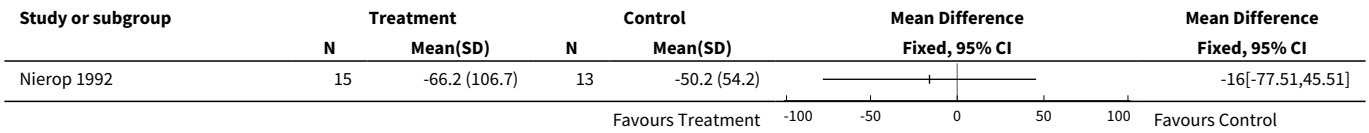
Analysis 1.2. Comparison 1 Gold versus placebo, Outcome 2 Treatment success (significant steroid reduction).

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Bernstein 1996	80/136	102/139		97.46%	0.52[0.32,0.86]
Klaustermeyer 1987	3/5	3/3		2.54%	0.15[0.01,3.41]
Total (95% CI)	**141**	**142**		**100%**	**0.51[0.31,0.83]**
Total events: 83 (Treatment), 105 (Control)					

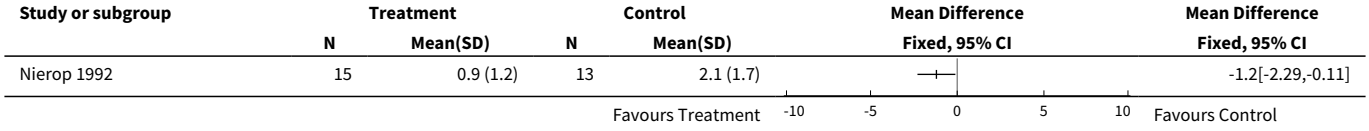




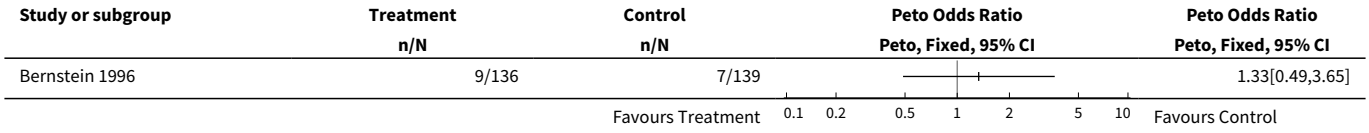
Analysis 1.3. Comparison 1 Gold versus placebo, Outcome 3 FEV1.



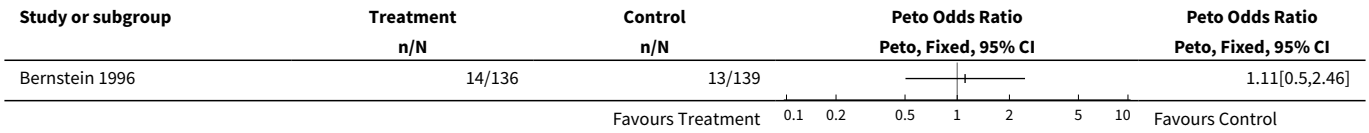
Analysis 1.4. Comparison 1 Gold versus placebo, Outcome 4 Exacerbations.



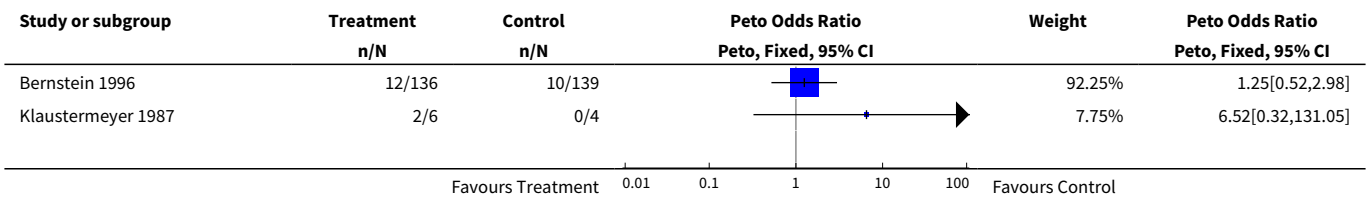
Analysis 1.5. Comparison 1 Gold versus placebo, Outcome 5 Exacerbations (hospital episodes).

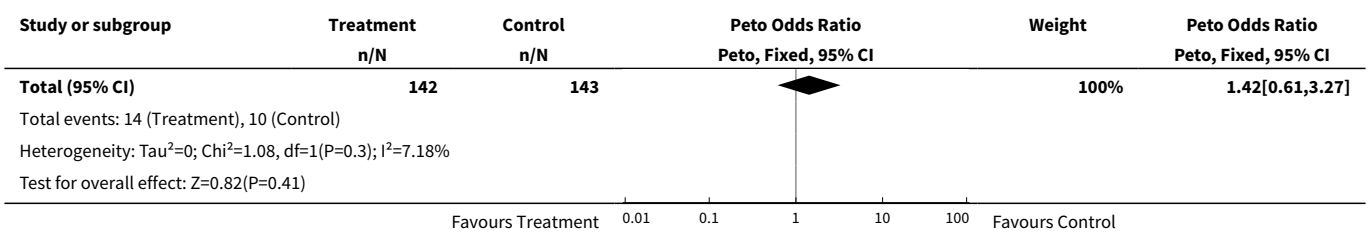


Analysis 1.6. Comparison 1 Gold versus placebo, Outcome 6 Haematology.

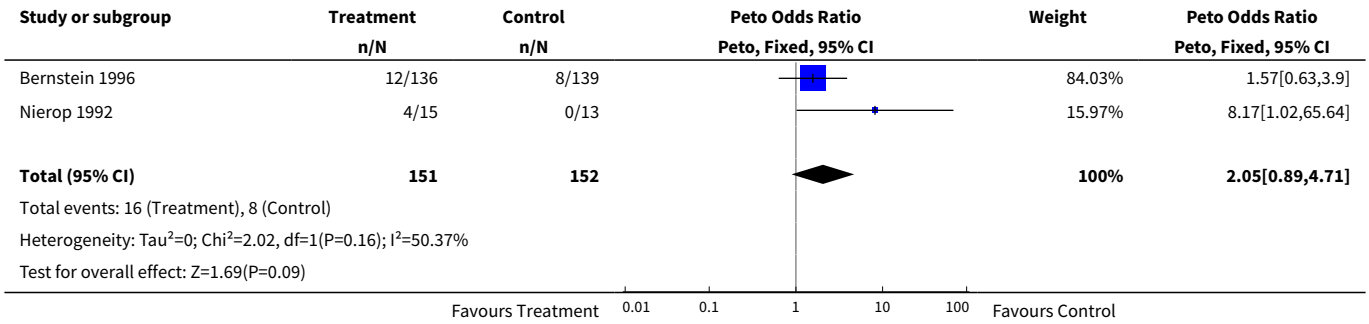


Analysis 1.7. Comparison 1 Gold versus placebo, Outcome 7 Proteinuria.





Analysis 1.8. Comparison 1 Gold versus placebo, Outcome 8 Dermatitis/eczema.



WHAT'S NEW

Date	Event	Description
3 September 2010	New search has been performed	Literature search re-run. No new studies found.

HISTORY

Protocol first published: Issue 2, 2000
Review first published: Issue 3, 2001

Date	Event	Description
25 September 2008	Amended	Search update. No new trials were found.
25 July 2008	Amended	Converted to new review format.
4 August 2000	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Evans DJ - Inclusion/exclusion criteria, quality assessment, data extraction/entry, data analysis, preparation of text, interpretation and conclusions
Cullinan P - Inclusion/exclusion criteria, quality assessment, data extraction/entry, data analysis, preparation of text, interpretation and conclusions

Geddes DM - Intellectual direction/supervision, interpretation and conclusion
Jones PW - Intellectual direction/supervision, interpretation and conclusion

DECLARATIONS OF INTEREST

None

SOURCES OF SUPPORT

Internal sources

- NHS Research and Development, UK.

External sources

- NHS Executive South East, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenal Cortex Hormones [*administration & dosage]; Anti-Asthmatic Agents [*therapeutic use]; Asthma [*drug therapy]; Auranofin [*therapeutic use]; Aurothioglucose [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Humans