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[Intervention Review]

Inhaled insulin in diabetes mellitus

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ABSTRACT

Background

Insulin therapy often relies on multiple daily injections of insulin. However this is a considerable burden to many people with diabetes and adherence to such an insulin regimen can be difficult to maintain, hence compromising optimal glycaemic control. Also, short acting injected insulin is absorbed more slowly than insulin released by the normal pancreas in response to a meal. Inhaled insulin has the potential to reduce the number of injections to perhaps one long-acting insulin per day, and provide a closer match to the natural state, by more rapid absorption from the lung.

Objectives

To compare the efficacy, adverse effects and patient acceptability of inhaled versus injected insulin.

Search methods

A sensitive search strategy for randomised controlled or cross-over trials was combined with key terms for inhaled insulins. Databases searched were: The Cochrane Library, MEDLINE, PubMed, EMBASE, Science Citation Index, BIOSIS, Web of Science Proceedings, National Research Register UK, Current Controlled Trials, ClinicalTrials.gov, Conference Papers Index, LexisNexis, and web sites of the ADA and EASD were searched for recent meeting abstracts. Reference lists and journals were handsearched. There were no language restrictions on searching. Manufacturers of inhaled insulin were also contacted. Date of last search October 2002.

Selection criteria

Only randomised controlled trials with parallel groups or controlled cross-over trials, including type 1 or type 2 diabetic patients of any age treated with insulin, were considered eligible. The minimum trial duration considered was 10 weeks, as this is the time taken for glycated haemoglobin to reliably reflect changes in glycaemic control.

Data collection and analysis

Trial selection and evaluation of study quality was performed independently by two reviewers. The quality of reporting of each trial was assessed according to a modification of the criteria outlined in Centre for Reviews and Disssemination (CRD) Report 4, Spitzer; and Jadad.

Main results

Six randomised controlled trials were found and the overall number of participants was 1191. Three trials included patients with type 1 diabetes and three with type 2 diabetes. Three trials had a duration of 24 weeks, and three of 12 weeks. All were open label. There was insufficient information to determine the study quality. Results for HbA1c were similar for all trials, in that all showed comparable glycaemic control for inhaled insulin compared to an entirely subcutaneous regimen. All trials that reported patient satisfaction and quality of life showed that these were signficantly greater in the inhaled insulin group. Overall there was no difference in total hypoglycaemic episodes

between the groups, but one trial showed a statistically significant increase in severe hypoglycaemic episodes for the inhaled insulin group. No adverse pulmonary effects were observed in any of the studies, but longer follow-up will be required to be sure that there are no adverse side-effects. Cavets include: few studies published in full (so quality could not be assessed), and only two studies used the same basal regimen in both the inhaled and injected groups.

Authors' conclusions

Inhaled insulin taken before meals, in conjunction with an injected basal insulin, has been shown to maintain glycaemic control comparable to that of patients taking multiple daily injections. The key benefit appears to be that patient satisfaction and quality of life are significantly improved, presumably due to the reduced number of daily injections required. However, the patient satisfaction data is based on five trials, of which only two have been published in full; also the three trials containing quality of life data are all only published in abstract form at present. In addition, longer term pulmonary safety data are still needed. Also, the lower bioavailability, and hence higher doses of inhaled insulin required, may make it less cost-effective than injected insulin.

PLAIN LANGUAGE SUMMARY

INHALED INSTEAD OF INJECTED SHORT-ACTING INSULIN APPEARS NO MORE EFFECTIVE FOR GLYCAEMIC CONTROL BUT MAY BE PREFERRED BY PEOPLE WITH DIABETES

Six trials have been done on giving short-acting insulin by inhalation instead of injection. Much of the evidence has not yet been published in full. The results so far suggest that inhaled insulin gives similar levels of glycated haemoglobin; overall the incidence of hypoglycaemia also appears similar, but patients prefer inhaled to injected. The quality of evidence is not great - only two studies appeared to use the same basal insulin in the inhaled and injected groups. We need longer studies to see if there are any side-effects in the lung. More insulin has to be given by inhaled than by injection to achieve the same effect, and the cost-effectiveness remains to be assessed.

BACKGROUND

Diabetes mellitus is a chronic metabolic disorder resulting from a defect in insulin production, insulin action, or both. The two main types are type 1 diabetes (formerly known as insulin-dependent diabetes mellitus) and type 2 diabetes (formerly known as non-insulin dependent diabetes). For a detailed overview of diabetes mellitus please see under Additional Information in the information on the Cochrane Metabolic and Endocrine Disorders Group in the Cochrane Library (see "About the Cochrane Collaboration" then "Cochrane review groups").

INSULIN TREATMENT IN DIABETES
In type 1 diabetes, there is an absolute loss of the insulin-producing cells in the pancreas. Insulin treatment is required for survival. In type 2 diabetes, there is a combination of resistance to the effect of insulin in the tissues, and initially over-production (though insufficient relative to the increased needs); over time, insulin production may fall as the pancreas fails to maintain higher than normal production (UKPDS16).

In the non-diabetic person, there is steady production of insulin through 24 hours (known as basal insulin) with sharp peaks of increased production to cover the metabolic needs after meals (sometimes called bolus insulin). For people with diabetes, injected insulin regimens seek to mimic the natural secretion of insulin by the combination of one or more injections of long-acting insulin to provide basal levels, and 2-3 injections of short-acting to provide cover for meals. This form of treatment is known as intensified insulin therapy. Alternatively, continuous subcutaneous insulin infusion (CSII) via an insulin pump may be used.

At present, insulin cannot be given by mouth because it is digested. Research is underway into new forms of insulin which do not need to be injected.

There are two main disadvantages of injected insulin:

- Firstly, it does not mimic the natural state. Short acting insulin is absorbed more slowly than ideal, with a slower rise than insulin released by the normal pancreas in response to a meal. In the case of regular soluble insulins, this is partly because the insulin molecules combine into dimers and hexamers. The newer short-acting analogues reduce this problem through changes in the amino acids in the B chain of human insulin, resulting in them being absorbed more quickly. However although peak action is faster (about 52 minutes compared to 145 minutes with regular soluble insulin; reviewed by Gerich 2002) it cannot match the 10 minute peak of pancreatic insulin.
- Secondly, patients have to perform multiple daily injections. Inhaled insulin has the potential to reduce the number of injections (to perhaps a once daily injection of a long-acting insulin such as glargine). Moreover it may provide a closer match to the natural state, by more rapid absorption from the lung.

Drugs have been given by inhalation in other conditions, most notably asthma. Most corticosteroid and bronchodilator drugs are given by inhalation, and there is a wide variety of devices, recently reviewed (Peters 2002).

Although the concept of giving insulin by the respiratory tract, either nasally or via the lung, is not new, it is only recently that adequate delivery devices have been developed. The two inhaled insulins nearest to marketing are those from Inhale Therapeutic Systems (for powdered insulins, from Pfizer and Aventis) and Aradigm Corporation (which produces a system called AERx, for aerosol insulin from Novo Nordisk). Other devices are being developed (see McAuley 2001 for review).

OBJECTIVES

To assess the efficacy, adverse effects and patient acceptability of a combination of short-acting inhaled insulin and long-acting injected insulin versus a combination of short-acting injected and long-acting injected insulin. In practice, this involves assessing combinations of insulin and inhaler devices, because the devices are not transferable amongst insulins.

METHODS

Criteria for considering studies for this review

Types of studies

Only randomised controlled trials with parallel groups and controlled cross-over trials were considered eligible (the latter needed to be in the same patients treated with inhaled and injected insulin by a cross-over trial of satisfactory duration and design). Parallel controlled but non-randomised clinical trials or cohort trials were not included, as they are too prone to bias unless very well matched, and it would not be possible to be sufficiently confident about matching. Simple case series of a before and after nature were not included.

Blinding in trials of this nature would be extremely difficult in practice. As glycated haemoglobin is an objective measure, this outcome should not be affected by blinding; however, outcomes such as patient satisfaction and quality of life could potentially be affected by patients not being blinded to their intervention.

The minimum trial duration considered eligible was 10 weeks, based on the time taken for glycated haemoglobin to reliably reflect changes in glycaemic control (Gonen 1977). For patient acceptability, longer trial duration is desirable - say adherence at 12 months - but results from shorter durations were included (preliminary searches showed that data from longer periods were not available). For long term pulmonary effects an uncertain period of at least several years is required.

Types of participants

People with insulin treated diabetes, whether type 1 or type 2.

Types of interventions

We were interested in comparisons of inhaled short-acting insulin plus long-acting injected insulin, versus injected short-acting insulin plus long-acting injected insulin, or by insulin injected by continuous subcutaneous insulin infusion (CSII). Studies comparing inhaled insulin with oral hypoglycaemic drugs were excluded.

Types of outcome measures

MAIN OUTCOME MEASURES
1. Glycaemic control as measured by glycated haemoglobin. Where the authors did not give the standard deviations of the changes in HbA1c, these were calculated if sufficient data were provided.

2. Patient satisfaction, as reflected in questionnaires or continuation rates.
3. Quality of life, ideally measured with a validated instrument.
4. Frequency and severity of hypoglycaemic episodes.

ADDITIONAL OUTCOME MEASURES
5. Adverse effects, particularly on the respiratory tract.
6. Weight change.
7. Costs.

Search methods for identification of studies

ELECTRONIC SEARCHES:

The following databases were searched:

- The Cochrane Library (all sections) 2002, Issue 4,
- MEDLINE 1993 -June 2002,
- PubMed June - Dec. 2002,
- EMBASE 1993-Sept. 2002,
- Science Citation Index, limited to meeting abstracts only, 1993 - Oct. 2002,
- BIOSIS, limited to meeting abstracts only, 1998-Oct. 2002,
- Web of Science Proceedings, 1990 - Oct. 2002,
- National Research Register UK, 2002 issue 3,
- Current Controlled Trials,
- ClinicalTrials.gov,
- Conference Papers Index 1990 - Oct. 2002,
- LexisNexis 2001-Oct. 2002.

There were no language restrictions on searching.

SEARCH STRATEGIES
Cochrane Library:
(inhal* near insulin*) or (pulmonary near insulin*) or (aerosol* near insulin*)

MEDLINE:
(((aerosol* near insulin*) or (insulin* near inhal*) or (pulmonary near insulin*)) and ((PT=CONTROLLED-CLINICAL-TRIAL) or (PT=RANDOMIZED-CONTROLLED-TRIAL))) or (((aerosol* near insulin*) or (insulin* near inhal*) or (pulmonary near insulin*)) and (phase or random* or trial* or crossover or cross-over or placebo or blind*)) or (((aerosol* near insulin*) or (insulin* near inhal*) or (pulmonary near insulin*)) and (review or systematic or meta-analy* or metaanaly*))

Embase:
((aerosol* near insulin*) or (insulin* near inhal*) or (pulmonary near insulin*)) and ((review or systematic or meta-analys* or metaanaly*) or (phase or random* or trial* or crossover or cross-over or placebo or blind*))

Science Citation Index:
(insulin* same inhal*) or (pulmonary same insulin*) or (aerosol* same insulin*)

Search strategies for other databases were adapted as appropriate.

NOTES: unless stated otherwise, search terms are free text terms; an asterisk (*) stands for 'any character(s)'.

HANDSEARCHES
The last two years of the journals Diabetes, Diabetes Care and Diabetologia were hand-searched for relevant articles and meeting abstracts. The references in the retrieved studies were handchecked.

ADDITIONAL SEARCHES

- Information on unpublished trials was sought from the following pharmaceutical companies which produce inhaled insulin - Aventis, Pfizer and Novo Nordisk.
- The web sites of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) were searched for recent meeting abstracts.

Data collection and analysis

TRIALS SELECTION
All retrieved titles and abstracts were reviewed independently by two researchers. Full papers were retrieved for further assessment if the information given suggested that the study: 1. included diabetic patients treated with insulin (either type 1 or type 2), 2. compared inhaled insulin with insulin injected subcutaneously, 3. assessed one or more relevant clinical outcomes. If there was any doubt regarding these criteria from the information given in the title and abstract, the full article was retrieved for clarification. There was complete agreement between the reviewers on the inclusions.

QUALITY ASSESSMENT OF TRIALS
This was done using the methods described in the manual of the Centre for Reviews and Dissemination (CRD) and Jadad and Spitzer (CRD Report 4 2001; Spitzer 1990; Jadad 1996).

In particular the following factors were studied:
1. Minimisation of selection bias - a) was the randomisation procedure adequate? b) was the allocation concealment adequate?
2. Minimisation of attrition bias - a) were withdrawals and dropouts completely described? b) was analysis by intention-to-treat?
3. Minimisation of detection bias - were outcome assessors blind to the intervention?

Based on these criteria, studies were broadly subdivided into the following three categories (see Cochrane Handbook):
A - all quality criteria met: low risk of bias.
B - one or more of the quality criteria only partly met: moderate risk of bias.
C - one or more criteria not met: high risk of bias.

Trial selection was independently performed by two reviewers.

DATA EXTRACTION
Data extraction was done by three reviewers independently using a predefined data extraction form. This included the following information:
1. General information - author and year, country, setting, published/unpublished, source of funding.
2. Trial characteristics - RCT or CCT, method and security of randomisation, duration.
3. Participants - type of diabetes, age of patients, duration of diabetes, selection method, representativeness, exclusions.
4. Interventions - type of inhaled insulin, inhalation device, comparator regimen.

5. Results - comparability at baseline, losses/drop-outs, glycated haemoglobin, hypoglycaemia, adverse effects, patient preference, quality of life, study duration of 3, 6, 12 months or longer, and whether analysis was by intention to treat.

DATA ANALYSIS
Data on changes in HbA1c from baseline were summarised in a meta-analysis. Continuous data were expressed as weighted mean differences. It was not possible to do a meta-analysis on any other of the main outcome measures as insufficient data were reported.

SUBGROUP ANALYSIS
It was planned to perform a subgroup analysis if the results of at least one of the main outcomes were significant, in order to explore effect size differences between type 1 versus type 2 diabetes.

SENSITIVITY ANALYSIS
We planned to do a sensitivity analysis, if appropriate, in order to explore the influence of the following factors on effect size:
1. Repeating the analysis excluding studies published in abstract form only.
2. Repeating the analysis taking account of study quality, as specified above.
3. Repeating the analysis excluding any very long or large studies to establish how much they dominate the results.
4. Repeating the analysis excluding studies using the following filters: language of publication, source of funding (industry versus other), country.

Cost-effectiveness assessment was not possible because the products have yet to be priced, but it was planned to summarise marginal benefits (if any) as quality adjusted life years (QALYs) if possible, to allow policy-makers to estimate cost per QALY (compared to intensive insulin regimens using injected insulin) once prices are announced (this assumes the inhaled insulins are licensed). It was also planned to check the studies to look for resource requirements, such as educational input or total amount of insulin used.

RESULTS

Description of studies

STUDIES IDENTIFIED
The initial search of MEDLINE, using the search strategy given above, yielded 54 studies. All were downloaded and the titles and abstracts examined; the full versions of 40 articles were requested. To be sure that no studies had been missed, a second more sensitive search of MEDLINE was then done using just the terms (pulmonary or aerosol or inhal*) near insulin*. This retrieved an additional 153 studies which were downloaded and examined. No extra relevant studies were identified. Additional searches of The Cochrane Library and EMBASE yielded an extra 33 and 109 studies respectively, but no additional relevant studies not already identified in MEDLINE were found.

The Science Citation Index (SCI) was next searched, with the search being restricted to meeting abstracts only. (Unlike SCI or BIOSIS, neither MEDLINE or Embase index the individual meeting abstracts published in supplements to journals). This yielded 74 meeting abstracts, of which 26 were requested.

Aventis, Pfizer and Novo Nordisk were contacted for unpublished data. Lists of publications were received from Pfizer and Novo Nordisk, and we ascertained that Aventis were collaborating with Pfizer and had carried out no other trials. Pfizer also provided copies of four posters of studies for which abstracts had been identified from the SCI search. The posters all provided additional data.

Additional searching of the databases listed above, or handsearching, did not yield any additional relevant studies.

The six separate included studies comprised a number of duplicate publications, and several abstracts later published as full journal articles. Four articles were published as full journal papers, one as a letter, nine as meeting abstracts, and four were posters obtained from the manufacturer. Five of the studies used Exubera inhaled insulin (sponsored by Pfizer and Inhale Therapeutic Systems) (Belanger 2002; Cefalu 2001; Quattrin 2002; Skyler 2001; Skyler 2002), and the other study used the AERx insulin diabetes management system (sponsored by Novo Nordisk and Aradigm) (Hermansen 2002).

EXCLUDED STUDIES
Seventeen studies were excluded after further scrutiny. Only one was published in full in a journal, while the remaining 16 were all meeting abstracts only and all published since 1999. Reasons for exclusion are given the 'Table of Excluded Studies'. The major reasons for exclusion were that the studies did not measure outcomes as given in the protocol for this review. Other reasons included the fact that the study was not a controlled trial, that the patients were not previously on insulin or that they did not measure outcomes relevant to this review.

DESIGNS OF INCLUDED STUDIES
Details of the characteristics of the included studies are shown in the 'Table of Included Studies'. All studies were multicentre, parallel-group, randomised controlled trials. All were open label, and appear to have been conducted in North America. Three of the studies (Cefalu 2001; Hermansen 2002), had a duration of 12 weeks. The other three studies (Skyler 2001; Belanger 2002; Quattrin 2002; Skyler 2002), had a duration of 24 weeks.

PARTICIPANTS IN INCLUDED STUDIES
Overall there were 1191 participants in the six trials; 735 had type 1 and 456 had type 2 diabetes. The mean age of the participants with type 1 diabetes was 34 years, and of those with type 2, the mean age was 56 years. Only two trials gave the duration of the diabetes of the participants before the trial i.e. Cefalu 2001 was 11 years (type 2) and Skyler 2001 was 14.5 years (type 1). These were also the only two studies to give the ethnic composition of the participants, and in both cases the majority were white (Cefalu 2001 = 53% and Skyler 2002 = 80%). Four of the studies (Skyler 2001; Belanger 2002; Hermansen 2002; Quattrin 2002) gave the numbers of each gender of the participants, and in all cases there was a slight predominance of males. Participants for both groups in all trials were balanced for baseline characteristics. Skyler 2001 stratified patients on basis of their HbA1c (more than 8.5% vs less than or equal to 8.5%) to help ensure similarity of groups in this key efficacy measure.

INTERVENTIONS IN INCLUDED STUDIES
Table 1 summarises the interventions and comparators used in the six studies. In all trials the intervention was inhaled insulin plus one or two injections of a basal insulin. The control groups all had two or more insulin injections daily of a soluble insulin, in addition to a basal insulin. Only two studies (Hermansen 2002; Skyler 2002)

used the same basal insulin in both groups, and none of the studies used a short acting insulin analogue. The other four studies used a different basal insulin in both groups.

OUTCOME MEASURES OF INCLUDED STUDIES
All studies reported on HbA1c and hypoglycaemic episodes, and all but one (Hermansen 2002) reported on overall patient satisfaction. Four studies reported on pulmonary function (Belanger 2002, Cefalu 2001, Hermansen 2002, Skyler 2001) and weight loss (Belanger 2002,Cefalu 2001, Quattrin 2002,Skyler 2001) and three studies each reported on the outcomes of quality of life (Belanger 2002, Quattrin 2002, Skyler 2002), cough (Belanger 2002; Quattrin 2002; Skyler 2002) and adverse events (Belanger 2002, Quattrin 2002,Skyler 2002). No studies reported costs.

Risk of bias in included studies

The reporting of the methodological quality in all trials was poor, hence it was not possible to adequately assess their quality. This was mainly due to the fact that many studies were published only in abstract form, so not enough space was available to report the details of the methodology.

METHOD OF RANDOMISATION
In only one study (Skyler 2001) was the reported method of randomisation (computer generated) adequate. The method of randomisation in the other five studies was unclear.

ALLOCATION CONCEALMENT
No study reported whether there was concealment of allocation.

BLINDING
All studies were open label. It was not mentioned whether the outcome assessors were aware of the groups to which patients had been assigned.

DESCRIPTION OF WITHDRAWALS AND LOSSES TO FOLLOW-UP AND INTENTION TO TREAT ANALYSIS
Only one study (Skyler 2001) reported that analysis was done by the intention to treat principle, and adequately reported on withdrawals.

SAMPLE SIZE CALCULATION
Only Skyler 2001 reported details of the sample size calculation to ensure that the trial was adequately powered for the primary outcome measure, HbA1c.

Effects of interventions

Six trials were found. Most had been reported in a number of abstracts, some of which gave little detail of location of the co-authors or study groups, thus making it quite difficult to collate all the reports from all trials. There were also some abstracts which pooled results from more than one trial (Cappelleri 2001; Cefalu 2000). There were three trials in type 1 diabetes (Quattrin 2002; Skyler 2001; Skyler 2002) and three in type 2 (Belanger 2002; Cefalu 2001; Hermansen 2002). These are summarised in the table 'Characteristics of Included Studies'.

Heterogeneity.
Results for HbA1c were similar, in that none of the trials showed significantly better control of blood glucose with inhaled versus short-acting injected insulin. Results for overall patient satisfaction or preference were also similar, in that all showed a significantly greater satisfaction with inhaled insulin.

EFFECTS OF THE INTERVENTION

HbA1c
Only three trials (Cefalu 2001; Skyler 2001; Skyler 2002) provided sufficient data to allow a meta-analysis. This was done on the change from baseline of HbA1c values (see meta-analysis). The results revealed that all three trials showed equivalence in terms of diabetes control, as reflected in glycated haemoglobin.

Patient Satisfaction
Patient satisfaction was measured using the Patient Satisfaction with Insulin Therapy (PSIT) Questionnaire (Cappelleri 2000b). This consisted of a survey of 15 patient administered questions, which covered attributes of satisfaction with both injected and inhaled insulin therapy. The items were derived from five qualitative research studies that consisted of one-to-one interviews conducted in the US. Responses to each item were ranked on a five point Likert scale, ranging from 'strongly agree' to 'strongly disagree'.

All trials, apart from (Hermansen 2002), reported on patient satisfaction, and all five showed significantly greater satisfaction with the inhaled insulins, perhaps because of the reduced number of injections. Three trials (Belanger 2002; Cefalu 2001; Quattrin 2002) also reported significant improvements in all the subscales of treatment satisfaction measured, whereas Skyler 2001 reported a significant difference in the improvement and convenience/ease of use, but no significant difference in social comfort. In three trials (Cefalu 2001; Skyler 2001; Skyler 2002) it was noted that the subcutaneous group also showed an increase in their satisfaction levels.

Results also showed that patients prefered to continue with inhaled insulin (INH) over subcutaneous (SC) insulin. Cefalu 2001 reported that patients in the inhaled insulin group (all with type 2 diabetes) were significantly more likely (71%) to wish to continue their assigned regimen than patients who had to inject short-acting subcutaneous insulin ($P < 0.05$).

Gerber 2000 reported results of a multicentre extension study of 70 type 1 patients who completed a 3 month randomised trial, and were offered a one year treatment extension. Subjects could choose their insulin regimen (INH or SC) for the 1 year extension. Of those on INH in the 3 month trial, 81% chose to stay on INH; of those on SC in the parent study, 79% switched to INH. Subjects switching from SC to INH had significant improvements in overall satisfaction. By contrast, subjects switching from INH to SC showed a trend toward deteriorating satisfaction. However, these results should be treated with caution as the patients were not randomised to their respective groups, and hence the results are potentially subject to bias.

Quality of Life
Three trials reported outcomes for quality of life (Belanger 2002; Quattrin 2002; Skyler 2002), and all showed significant improvements in INH group compared to SC group.

Hypoglycaemic episodes
Overall, there was little or no difference in total hypoglycaemic episodes in any of the trials. Four trials also reported the rates for severe hypoglycaemic episodes. Two found no difference (Skyler

2001; Quattrin 2002); one reported a four-fold risk of severe hypoglycaemic episodes with inhaled insulin (Belanger 2002) but this was not statistically significant (risk ratio 4.07; 95% CI 0.46 to 36.43); the other one (Skyler 2002) showed a risk ratio of 1.97 which was statistically significant (95% CI 1.28 to 3.12). Results did not differ according to type of diabetes.

Insulin antibodies

Three trials (Belanger 2002; Hermansen 2002; Quattrin 2002) reported changes on antibody levels, and all found that INH treated patients developed increased levels of antibody serum binding, but the higher antibody levels did not appear to have any clinical significance.

Weight change

Three trials (Belanger 2002; Cefalu 2001; Skyler 2001) reported that there was no significant difference between the groups in terms of weight change. One trial (Quattrin 2002) reported that there was a slightly significant smaller increase in body weight in the INH group than in the SC group.

Adverse effects

The main concern has been about pulmonary side-effects, but at present there is little or no evidence of harm. Three studies reported a greater incidence of cough in those using inhaled insulin; Belanger 2002 (21% vs 3%); Quattrin 2002 (27% vs 5%); Skyler 2002 (25% vs 7%), but this decreased in incidence and prevalence over the period of the study. There have not yet been any reports of any significant lung disease. This is reassuring but longer-term follow-up will be required, probably for 10 years or more. So far the only long term data on pulmonary safety and efficacy come from a two year cohort study (with no control group). Continued inhaled insulin was offered to type 1 and 2 diabetic subjects who had completed any of three randomised, three month phase two trials (Cefalu 2000). The pooled efficacy (HbA1c) and pulmonary safety data after two years of INH therapy showed that the clinical efficacy and pulmonary safety of INH are sustained for at least that long.

Subgroup analyses

Findings were similar in both type 1 and type 2 diabetes.

DISCUSSION

Summary

The trials show that using inhaled insulin in place of short-acting injected insulin gives similar control of blood glucose but is preferred by patients. Uncontrolled follow-up studies (extension studies and patient preference cross-over, for up to 12 months after the 3-month RCTs) where patients choose which form of therapy to continue with support these findings, but should be interpreted with caution (Gerber 2002).

Patient satisfaction was greater in the inhaled insulin groups, but it should be noted that satisfaction also increased in some control patients, presumably due to the effects of being in a trial. Blinding was not carried out for the different groups, and this could introduce a bias in favour of inhaled insulin for patient satisfaction, which is the key outcome. Patients' views on injections will infuence their satisfaction. Inhaled insulin may be particularly useful in the very small proportion of insulin-treated patients with injection phobia. However there may be a much larger group who has some anxiety about injections. Zambanini 1999 reported that 42% (our calculations give a 95% CI 33 to 51%) of a group of 116 patients had some anxiety about increasing the number of injections. Whether and how much inhaled insulin would help this group is not known, since anxiety about intensification of insulin regimens could be due to other factors such as fear of hypoglycaemia or reluctance to increase blood glucose self-monitoring, rather than the injections themselves.

Limitations

The main concern has been whether there are any pulmonary side-effects. There do not appear to be any short-term ones, but long-term follow-up is needed to provide full reassurance. This concern is partly about pulmonary damage, as yet unspecified, but some have speculated that there could be effects on pulmonary vasculature as well (Chan 2001).

In terms of evidence, the main limitations are: firstly that evidence is still sparse (four out of the six included studies were available only as abstracts/posters; one published as a 'brief communication'); secondy, that only two studies used the same basal comparator (see below and table); thirdly, that short-acting analogue injected insulins were not used.

Generalisability

It is difficult to comment on generalisability because several of the studies give little or no details of the patients recruited. The average ages of the type 2 patients in the studies was 56, which may be representative of type 2 patients who are treated with insulin.The generalisability of the results is reduced by the large number of exclusion criteria. It should be noted that one of the main reasons for exclusion is asthma, which has been reported in Europe to be less common in people with type 1 diabetes than in the general population (EURODIAB Substudy 2). There does not appear to be any evidence of increased risk of harm in people with both diabetes and asthma, and their exclusion is presumably only on the grounds of caution. However the bioavailability of inhaled insulin might well be affected if asthma led to bronchoconstriction, and this would need to be assessed. Smokers have also been excluded; it has been shown that smokers show a greater absorption of inhaled insulin (Heinemann 1997), and once patients had worked out the appropriate dosage at meal-times, it might be necessary to ensure people did not vary their smoking habits around the time of inhaling insulin. As always, one cannot say how typical patients who participate in trials are of all insulin-treated patients.

Comparators

Ideally, the regimens used would have varied only in the meal-time insulins, with basal being kept standard between inhaled and control groups. This was the case with only two of the studies, Hermansen 2002 (NPH at bedtime, in type 2 diabetes) and Skyler 2002 (NHP twice daily, in type 1) (see Table 1).

Variability of absorption

Variability from day to day of absorption of inhaled insulin has been reported to be similar to (Heinemann 1999), or less than subcutaneous insulin (Mellen 2001; Pfuetzner 2002). Unpublished data provided by Novo Nordisk, admittedly from a small study with only 17 participants with type 1 diabetes, suggests that there is less variation in the bioavailability of inhaled insulin than there is with short-acting subcutaneous insulin. In a recent study of 15 patients with type 2 diabetes, Perera 2002 found no greater intra-patient variability of effect between inhaled and subcutaneous administration. A review by Heinemann 2002 of the

literature on comparative bioavailability concluded that the intra-individual variability remained a problem irrespective of route of administration.

None of the trials so far seem to have used short-acting analogues such as lispro and aspart. These would give some advantages over regular soluble insulins in terms of hypoglycaemic episodes, though would still have the disadvantage of needles. Nor have any trials yet used glargine as basal insulin, though that would not affect the comparison if it was used as basal for both groups. Similarly no trials have used continuous subcutaneous insulin infusion (CSII).

This review is concerned only with the replacement of short-acting injected insulin by inhaled insulin. A recent trial has found that in patients with type 2 diabetes who are poorly controlled on oral agents, control can be improved either by adding inhaled insulin to oral agents, or by stopping the oral hypoglycaemic agents and replacing them with inhaled insulin (Cefalu 2002).

Costs and cost-effectiveness
The bioavailablity of inhaled insulin is less than with injected, but there are varying figures quoted. Skyler 2001 quotes studies giving a range of 10-30% of the inhaled dose being absorbed into the bloodstream. Gerich 2002 quotes other studies suggesting 15% bioavailability for inhaled versus 19% for subcutaneous, presumably for powder forms, but a 10-fold difference for aerosol forms. With the powder form, most (White 2001 reports 95%) of what is inhaled is drug, whereas with the aerosol forms, 98% is water.

The simplest way to assess comparative bioavailability of inhaled and injected short-acting insulins would be from the doses used in the trials. However only two studies gave details of dose (Cefalu 2001; Skyler 2001), and they used different basal insulins, which introduces a confounding factor into comparisons of doses of short-acting insulins. With that caveat, we note that about two to three times as many units had to be inhaled as were injected.

Some trials admitted patients to hospital for conversion to inhaled insulin, including training. This will increase costs but is unlikely to be needed in routine practice.

It is not possible to estimate cost-effectiveness until the prices of inhaled insulins are known. The prices will reflect not just the insulin cost but also the delivery inhaler, but there will be a reduction in syringe/needle or pen use. The gain in quality adjusted life years (QALYs), required for economic analysis, will depend on quality of life and patient preference, since in terms of control of blood glucose as reflected in HbA1c, the results so far show equivalence. The marginal cost will depend on price and dosage needed.

Licensing
Neither of the two inhaled insulins has yet been licensed in any country, as far as we know (as of December 2002).

Insulin antibodies
Inhaled insulins have been reported to cause higher levels of insulin antibodies than subcutaneous, but this may be more to the frequency of dosing, rather than the pulmonary route itself. Increased frequency of injections also increases antibody levels (see Stoever 2002 for review). The higher antibody levels observed in the inhaled insulin groups in the trials did not result in any apparent clinical change.

Ongoing trials
It was recently reported (Anonymous 2002) that Novo Nordisk and Aradigm have announced the initiation of the phase III clinical program for NN1998 - the AERx insulin diabetes management system (iDMS). The first phase III study, in people with type 1 diabetes, is designed to show that the long-term safety and efficacy profile of inhaled human insulin is comparable to that of subcutaneous injections. This 24-month study is a multicentre, open-label study with patients receiving either inhaled insulin via the AERx system or subcutaneous injections of NovoRapid (NovoLog in the US) three times daily before meals. Additionally, both groups are receiving basal insulin once or twice daily. In addition to investigating long-term pulmonary safety, the study will also look at the incidence of hypoglycaemic events, insulin antibody formation, glycaemic control (blood glucose profiles) and overall treatment satisfaction.

Other developments
A new form of insulin production may enhance its potency by up to threefold. A recent news report (O'Neill 2002) suggested that "nanomised" insulin (formulation of insulin in tiny particles under 100 nanometres in diameter) may have improved bioavailability and produce a more sustained effect, meaning that diabetic patients may be able to reduce their number of daily injections.

Other delivery routes are being tested. The development of an effective oral insulin has proved a significant challenge in the past due to relatively poor absorption from the gastrointestinal tract and substantial variability in the amounts absorbed within and among subjects. However, recent research has been directed to overcoming these problems (see Modi 2002; Still 2002 for reviews). Also Cavallo 2001 reports preliminary experience with an oral spray in three patients.

AUTHORS' CONCLUSIONS

Implications for practice

Inhaled insulin may provide a practical, non-invasive alternative to injections, while achieving comparable glycaemic control and increased patient satisfaction and quality of life. However, it will still not completely eliminate the need for injections, as although inhaled insulin can potentially be substituted for soluble pre-prandial insulins, the longer-acting preparations still require subcutaneous injections. If inhaled insulin is to become a viable clinical option, longer term data on pulmonary safety and efficacy will be needed. Also, the marginal price and dosage required compared to subcutaneous insulin will be critical in determining whether it will be an economically viable alternative.

Implications for research

Research needs could be divided into safety, efficacy and economics.

- For safety purposes, we need long-term follow-up (i.e. years, not months) of large numbers of patients who use inhaled insulins. Large observational cohort studies would suffice. Because of fears of pulmonary side-effects, most studies to date have excluded all people with diseases such as asthma or chronic bronchitis, and most have excluded smokers. There is no

evidence of an increased risk of harm in these patients, though smokers may absorb inhaled insulin more rapidly.

- For efficacy purposes, we need more studies which have the same basal insulin in both the inhaled and control groups; it would be useful to use both short-acting and long-acting analogues in these. A trial compared to CSII would also be useful. Studies in children and adolescents are needed. Greater caution may be required in young children where the lung is still growing, and perhaps trials should be done first in the adolescent age group, where we know that many have poor control, which may cause long-lasting damage. Half the studies of inhaled insulin are in type 2 diabetes. In many of these patients, poor control is associated with overweight or obesity, and trials of intensified dietary advice and exercise are also required.
- For economic analysis, we need to include collection of cost and quality of life data in future RCTs. The main gain from inhaled insulins is in quality of life. In future trials, the optimum injection methods should be used, including CSII.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Belanger 2002

Methods	Trial design: parallel group RCT Randomisation prodedure: unclear Blinding: open Setting: 50 centres Country: USA and Canada ITT analysis: ?
Participants	Inclusion criteria: Type 2 diabetes diagnosed for at least one year; to have been participating in a stable sc insulin regimen of at least 2 injections daily for 2 months prior to study; BMI<=35; fasting plasma c-peptide >=0.2 pmol/l; HbA1c between 6%-11.0%; Exclusion criteria: patients with poorly controlled asthma, significant COPD, other significant respiratory disease, or had smoked in last 6 months Type of diabetes: 2 Numbers: 298 (INH=149; SC=149) Age: mean 57.5 (SD 10.4) years; range 35-80 years Duration of diabetes: ? Gender: 66% male Ethnic Groups: ?
Interventions	Intervention: INH before meals plus single bedtime ultralente insulin injection Control: continue on current regimen of 2 mixed regular /NPH insulin injections/ day Duration of trial: 6 months
Outcomes	1) HbA1c: * mean Hb1c decreased similarly in the two groups INH: -0.7%, SC:-0.6% *target HbA1c <8.0% was achieved by 76.2% in INH (n=109) and 69.0%% in the SC group (n=100) * further improvements in glycaemic control (HbA1c <7.0%) was observed in signficantly more patients receiving INH (46.9%, n=67) than SC (31.7%, n=46) 2) Treatment Satisfaction and Quality of Life: * Overall Patient Satisfaction: INH: 59.3 (SD 1.2) to 76.3 (SD 1.1). signficant increase (p = 0.0001) and SC: 60.1(SD 1.3) to 58.8 (SD 1.4) decrease NS (p=0.08) * Significant improvements in all treatment satisfaction subscales (11 items) all p<000.1 * The analogue health rating, quality-of-life total scale and sub-scales of health perceptions, symptom interface and cognitive function - also showed more favourable improvements for INH vs SC(all p< 0.05). 3) Hypoglycaemia * Overall hypoglycaemia (events per subject-month) statisitically significantly lower in INH group (1.4) than in SC group (1.6); risk ratio 0.89; 95% CI [0.82, 0.97] * Severe hypoglycaemia (events per 100 subject-months) was not statistically signficantly different between the INH (0.5; 4 events) and SC (0.1; 1 event) groups (INH-SC risk ratio 4.07; 95% CI [0.46, 36.43]) 4) Weight gain: greater increase in SC group but NS 5) Pulmonary function: no significant differences between the groups 6) Adverse effects: The frequency and nature of adverse events were comparable between the groups. *Two patients in INH group and no patients in SC group discontinued due to a treatment emergent adverse event judged to be related to the study drug. *Cough more frequent in INH group 21% vs 3% - judged 'mild to moderate'.

Belanger 2002 *(Continued)*

	* There were no treatment related serious adverse events in INH group and one in SC group. 7) Losses to follow up: ?
Notes	Poster Sponsored by Pfizer, Aventis, Inhale Therapeutics

Risk of bias

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

Cefalu 2001

Methods	Trial design: RCT Randomisation prodedure: unclear Blinding: open Setting: multicentre (clinical and outpatient research clinics) Country: USA ITT analysis: not done for patient satisfaction, no details for HbA1c
Participants	Inclusion criteria: HbA1c 7% -11.9%; age 35-65 yrs; stable insulin regimen (2-3 injections/day); weight 100-175% ideal; normal chest and pulmonary function Exclusion criteria: creatinine >265 umol/L; major organ disease; smokers; insulin regimen >=4 daily doses or 150 units insulin daily, oral hypo drugs, on insulin pumps Type of diabetes: 2 Numbers: 51 (INH=26; SC=25) Mean ages: INH: 51.1; SC: 53.6 Duration of diabetes (mean years): 11 (INH 11.2, SC 11.5) Gender: INH=16M/10F: SC=15M/10F Ethnic Groups: white 53%; black 12% hispanic (35%)
Interventions	Intervention: INH before meals (dry powder aerosol delivery - Inhale Therapeutics via Exubera device) plus single Ultralente SC insulin injection at bedtime Control: sc insulin- usual regimen of split/mixed insulin 2 to 3 injections/day Both groups: 4 week lead in phase; prior to randomisation, instructed on weight maintenance, diet, blood glucose monitoring. Weekly adjusted of insulin dose. Pts hospitalised for 2 days for instruction in self-administering INH Duration of trial (weeks): 12
Outcomes	Primary: 1) HbA1c: difference between groups. INH ˜ 0.7% (SD 0.7); SC: ˜ 0.7% (SD 0.7) after adjustment for baseline HbA1c and centre the 95% CI for difference = -0.2% to 0.6% Secondary: 2) Overall Patient Satisfaction: INH 31% (CI 14-50%); SC 13% (CI 7-19%). Geometric mean % improvement statistically signficantly greater in INH group p<0.05 3) Mild to moderate hypos: INH=0.83 episodes/month: SC=1.1 (NS) 4) Severe hypos: none in either group 5) Average Weight Loss: no significant difference 6) Adverse effects: none reported for the pulmonary function tests. 7) Losses to follow up: 9% for patient satisfaction
Notes	Sponsored by Pfizer Trial powered prospectively for HbA1c values (the primary end point) and not patient satisfaction.

Cefalu 2001 *(Continued)*

Risk of bias

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

Hermansen 2002

Methods	Trial design: RCT Randomisation prodedure: unclear Blinding: open Setting: multicentre Country: USA ITT analysis: ?
Participants	Inclusion criteria: non-smoking, type 2 diabetics, of both sexes on any pre-trial insulin Exclusion criteria: not given Type of diabetes: 2 Numbers: 107 (INH=54; SC=53) Mean age: 59 years Duration of diabetes: ? Gender: ? Ethnic Groups: ?
Interventions	Intervention: pre-prandial inhaled insulin via AERx insulin Diabetic Management System plus NPH bed-time insulin Control: pre-prandial sc injections of human insulin plus NPH bedtime insulin Duration of trial (weeks): 12
Outcomes	Primary: 1) HbA1c: mean decrease - INH = 0.8%, SC=0.7%. P=0.60 Secondary: 2) Hypos: AERx=151; s.c.group=211. No significant difference in frequency, nature, and severity of episodes 3) Adverse effects: no major pulmonary safety issues 4) Losses to follow up: 9 [98 pts (92%) completed trial]
Notes	Meeting abstract Bioeffectivenss: Based on the amount of insulin actually delivered by AERx iDMS at the selected doses, an overall bioeffectiveness for inhaled insulin was 16% relative to s.c. injection

Risk of bias

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

Quattrin 2002

Methods	Trial design: RCT phase III Randomisation prodedure: unclear

Quattrin 2002 *(Continued)*

	Blinding: open Setting: 41 centres Country: USA and Canada ITT analysis: ?
Participants	Inclusion criteria: Diagnosed with type 1 diabetes for at least a year; to have been participating in a stable sc insulin regimen of at least 2 injections daily for 2 months prior to study; BMI<=30; fasting plasma c-peptide >=0.2 pmol/mL; HbA1c between 6% and 11.0%; Exclusion criteria: patients with poorly controlled asthma, significant COPD, other significant respiratory disease, or had smoked in last 6 months Type of diabetes: 1 Numbers: 335 (INH=170; SC=164) Age: 34 (SD 13); range 12-65 years Duration of diabetes: ? Gender: 54% male Ethnic Groups: ?
Interventions	Intervention: Inhaled insulin (dry powder Exubera: INH) plus a single injection of Ultralente long acting subcutaneous insulin at bedtime. Control: conventional SC insulin regimen with 2-3 daily injections (regular insulin BID; NPH insulin BID) Duration of trial: 6 months
Outcomes	1)HbA1c: * Mean HbA1c decreased similarly in two groups (from 8.1% to 7.9% in INH group; from 8.1% to 7.7% in SC group. (adjusted difference: 0.16%; 95% [CI -0.01,0.32]) * Target HbA1c <8.0% was achieved by 58.0% in INH (n=91) and 61.9% in the SC group (n=96) * further improvements in glycaemic control (HbA1c <7.0%) was achieved by 15.9% in INH group (n=25) and 15.5% in sc group (n=24) 2) Hypoglycaemia * Overall hypoglycaemia (episodes per subject-month) was lower in the INH group (8.6) than SC group (9.0). risk ratio 0.96; 95% CI [0.93, 0.99] * Severe hypoglycaemia (episodes per 100 subject-months) was not statistically significantly between the INH (5.5) and SC groups (4.7) (INH/SC risk ratio 1.16; 95% CI [0.76, 1.76]) 3) Treatment Satisfaction and Quality of Life: * Overall Satisfaction Summary score significantly improved for the INH group (p<0.0001) and decreased signficantly for the SC insulin group (p=0.03) * Significant improvement in all treatment satisfaction subscales in INH group (p<0.01) * Signficant quality of life treatment differences in mental health, depression and mental acuity (p<0.03), positive affect and well-being (p<0.01) and in adjustment of both general and diabetes-specific symptoms (p<0.02) for INH group cf SC group. 4) Weight gain: Trend towards a smaller increase in body weight in INH group = 0.9kg and SC=1.5kg - adjusted mean difference between groups 0.55 kg; 95% CI [-1.26, 0.16] 5) Adverse effects: The frequency and nature of adverse events were comparable between the groups. * Number of discontinuations due to treatment related adverse events: INH = 3 (1.8%) [1 mild cough; 1 hypo]; SC=0 * Mild to moderate cough more frequent in INH group (27% vs 5%) - decreased in prevalence and incidence over the study period 6) Losses to follow up: ?
Notes	Poster Sponsored by Pfizer and Aventis

Risk of bias

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

Skyler 2001

Methods	Trial design: RCT Randomisation prodedure: unclear Blinding: open Setting: 10 academic centres Country: USA ITT analysis: HbA1c reported as ITT; but no ITT for patient satisfaction.
Participants	Inclusion criteria: Type 1 diabetes, age 18-55; 80%-130% ideal weight, stable insulin schedule for >2 months involving 2-3 injections/day, HbA1c 7-11.9%, fasting C-peptide ?0.2pmol/mL; normal on chest radiography and pulmonary function tests; normal ECG; willing to monitor blood glucose at home 4 times/day Exclusion criteria: asthma/ other suspected or actual respiratory disease; cardiac, cerebrovascular, liver disease or renal insufficiency; history of allergies, epilepsy, drug or alcohol abuse, systemic steroid use; pregnancy either actual or planned within 6 months; diabetic autonomic neuropathy; ? 2 serious hypoglycaemic episodes in previous year; hospital or emergency room admission with poor diabetic control in previous 6 months; use of insulin-pump or regimen with ? 4 daily dose or total daily insulin > 150 units. Type of diabetes: 1 Numbers: 72 (INH=35.4; SC=37) Mean ages: INH: 35.4; SC: 39.7 Duration of diabetes (mean years): INH 14.6, SC 14.4 Gender: INH: 19M/16F; SC: 18M/16F Ethnic Groups: white 80%; black 3%; other 16%
Interventions	Intervention: rapid onset INH 3 times/day. Dry powder aerosol (Inhale Therapeutics) plus single dose sc ultralente at bedtime Control: sc injections 2-3 times/day. (No rapid acting analogs) and human isophane insulin before breakfast and bedtime] Both groups: had insulin adjusted weekly to achieve pre-prandial target of 5.6 to 8.9 mmol/l. 4 week lead in phase before randomisation - all received advice from dietician and 2 day admission to hospital for instruction on dosing and experience with preprandial INH. Duration of trial (weeks): 12
Outcomes	Primary: 1) HbA1c: Adjusted mean difference between groups: INH =-0.64 (0.98); SC= -0.83 (0.92) (both n=35) 95%CI -0.2% to 0.5% Secondary: 2) Overall Patient Satisfaction: increase in satisfaction from baseline significantly greater in INH versus SC. Diff in improvement =24.5% (95% CI 6.6% - 42.5%) p<0.01 3) Convenience/ease of use : increase from baseline significantly greater in INH cf SC.Diff in improvement =30.1% (95% CI 10.7% - 49.5% p<0.01 4)Social comfort: No statistically significant difference between treatment groups 95% CI -14.6% to 34.6%, p=0.42 5) Hypos: Total INH=35, sc=37: Severe: INH=5, sc=5. No significant difference between groups. 6) Body weight. No significant difference between groups. 7) Insulin used: INH group: mean daily dose=12.2 mg (4.9) inhaled insulin (equivalent to about 36.6 [14.7] units sc insulin, assuming 10% bioavailability) and 24.8 units (9.3) of long-acting SC insulin at end of 12 weeks. SC group: mean daily dose=15.9 units (9.8) of short acting regular insulin and 31.0 units (13.2) of long-acting insulin at end of 12 weeks. 8) Adverse effects: no serious or major adverse effects on pulmonary function reported 9) Losses to follow up: For HbA1: 1 on SC insulin; For patient satisfacation: INH=2 (8%); SC 4(11%)
Notes	Support: Pfizer assuming 10% bioavailability,

Skyler 2001 *(Continued)*

Risk of bias

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

Skyler 2002

Methods	Trial design: RCT phase III Randomisation prodedure: unclear Blinding: open Setting: multicentre Country: USA? ITT analysis: ?
Participants	Inclusion criteria: Type 1 diabetes Exclusion criteria: Type of diabetes: 1 Numbers: 328 (INH=163; SC=165) Mean ages: 29.5 (14.6); range 12-65 years Duration of diabetes: Gender: ? Ethnic Groups: ?
Interventions	Intervention: INH prior to meals plus, a morning and bedtime dose of NPH insulin. (INH inhalations delivered as 1-2 inhalations of 1 or 3 mg) Control: Pre-meal regular SC insulin, plus a morning and bedtime dose of NPH insulin Duration of trial: 24 weeks
Outcomes	1) HbA1c: * Decreased similarly in both groups: INH =-0.3% (SE 0.06%); SC=-0.1% (SE =0.07%) p=0.08 * A comparable percentage of patients in both groups achieved either an HbA1c <8% or <7% vs SC [INH vs SC=64.2% vs 60.4% and 23.3% vs 22.0% respectively] 2) Patient Satisfaction and Quality of Life: * Overall Patient Satisfaction: subjects had greater improvement with INH cf SC (p<0.0001) * Overall quality of life scale and subscales of behavioural and emotional control, general and hyperglycaemic sympton distress, overall cognition, mental acuity and awareness also improved more favorably for INH cf SC (all p<0.01 to 0.05) 3) Hypoglycaemia: * Overall hypos (events/subject-month): INH=9.3; SC=9.9 (95% CI: 0.91, 0.97) * Severe hypos (events/100 subject-months): INH=6.5, SC=3.3 (95% CI: 1.28, 3.12) 4) Adverse effects: The frequency and nature of adverse events were comparable between the groups. * Cough more frequent in INH group (25% vs 7%) [judged mild to moderate, decreased in incidence and prevalence over study period] 5) Losses to follow up: ?
Notes	

Risk of bias

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

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

Study	Reason for exclusion
Brunner 2001	Did not measure outcomes of interest to this review
Cappelleri 2001	No new data reported
Cefalu 2000	Not a randomised study
Dennis 2002	Did not measure outcomes of interest to this review
Gelfand 2000	Patients were non insulin treated diabetics
Gerber 2000	Patient preference study
Harrison 2002	Study was not in humans
Heinemann 1999	Healthy volunteeers
Heinemann 2001	Healthy volunteeers
Henry 2001	Healthy volunteeers and asthmatic patients
Kipnes 1999	Did not measure outcomes of interest to this review
Pfuetzner 2002	Did not measure outcomes of interest to this review
Pfutzner 2001	Did not measure outcomes of interest to this review
Pozzilli 2002	Not inhaled insulin
Rosenstock 2002	Patients were not previously on insulin
Simonson 2001	Patients were not previously on insulin
Weiss 1999	Patients were not previously on insulin

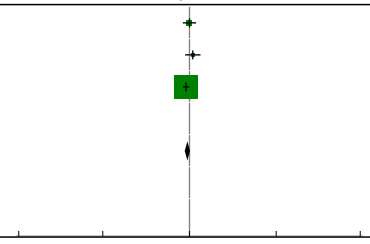
DATA AND ANALYSES

Comparison 1. Inhaled insulin versus subcutaneous injections

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 HbA1c (change from baseline)	3	448	Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.28, 0.03]

Analysis 1.1. Comparison 1 Inhaled insulin versus subcutaneous injections, Outcome 1 HbA1c (change from baseline).

Study or subgroup	Inhaled insulin N	Inhaled insulin Mean(SD)	s.c. insulin N	s.c. insulin Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Cefalu 2001	26	-0.7 (0.7)	25	-0.7 (0.7)		15.92%	0[-0.38,0.38]
Skyler 2001	35	-0.6 (1)	35	-0.8 (0.9)		11.86%	0.19[-0.26,0.64]
Skyler 2002	162	-0.3 (0.8)	165	-0.1 (0.9)		72.22%	-0.2[-0.38,-0.02]
Total ***	**223**		**225**			**100%**	**-0.12[-0.28,0.03]**
Heterogeneity: Tau^2=0; Chi^2=2.99, df=2(P=0.22); I^2=33.13%							
Test for overall effect: Z=1.56(P=0.12)							



ADDITIONAL TABLES

Table 1. Table of intervention and comparators used in inhaled insulin studies

Study	Type of diabetes	Basal used with INH	Daily dosage (basal)	Comparator	Daily dosage (comp)	Comments	Analogue used?
Belanger 2002	T2	Ultralente bedtime	no details	twice daily soluble and NPH	no details	different basal	no
Cefalu 2001	T2	Ultralente bedtime	15 mg = 45u inh + 36 ult 15 mg = 45u inh + 36 ult 15 mg =45 u INH + 36 ult	unclear ? - ultralente and mixed/split 2-3 injections a day	19 sol 51 ult (before, not controls)	unclear	no
Hermansen 2002	T2	NPH bedtime	no details	mealtime soluble and bedtime NPH	no details	same basal	no
Quattrin 2002	T1	Ultralente bedtime	no details	twice daily soluble and NPH	no details	different basal	no
Skyler 2001	T1	Ultralente bedtime	inh 12 mg = 37u + ult 25u	soluble 2-3 times daily and NPH twice daily	sol 16 NPH 31	different basal	no
Skyler 2002	T1	twice daily NPH	no details	soluble 2-3 times daily and NPH twice daily	no details	same basal	no

WHAT'S NEW

Date	Event	Description
10 May 2017	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 4, 2002
Review first published: Issue 3, 2003

Date	Event	Description
23 August 2003	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

NORMAN WAUGH: protocol development, selection of studies, data analysis, development of final review.

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LAURA McAULEY: quality assessment, data extraction, data analysis, development of final review.

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DECLARATIONS OF INTEREST

NW has received funds for small epidemiological studies and hospitality from Novo Nordisk

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INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Inhalation; Diabetes Mellitus, Type 1 [*drug therapy]; Diabetes Mellitus, Type 2 [*drug therapy]; Hypoglycemic Agents [*administration & dosage]; Insulin [*administration & dosage]; Randomized Controlled Trials as Topic

MeSH check words

Humans