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[Intervention Review]

Cyclofenil for Raynaud's phenomenon in progressive systemic sclerosis

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ABSTRACT

Background

Raynaud's is a vasodilatory phenomenon characterised by digital pallor, cyanosis and pain of the extremities. Primary Raynaud's phenomenon has no underlying disease associated with it, while secondary Raynaud's phenomenon is associated with connective tissue disorders such as scleroderma. Scleroderma is a connective tissue disease causing fibrosis and commonly affects the skin and internal organs such as the GI tract, lungs, kidney and heart. Cyclofenil is a drug which is well tolerated and may have efficacy in the treatment of RP secondary to scleroderma.

Objectives

To assess the effects and toxicity of Cyclofenil versus placebo for the treatment of Raynaud's phenomenon (RP) in scleroderma.

Search methods

We searched the Cochrane Central Register of Controlled Trials (*The Cochrane Library* 2007, Issue 3), Medline (January 1966 to August 2007), and Embase (1974 to August 2007) using the Cochrane Collaboration search strategy developed by Dickersin et al.(1994). Current Contents were searched up to and including August 1, 2007. All bibliographies of articles retrieved were searched and key experts in the area were contacted for additional and unpublished data. The initial search strategy included all languages.

Selection criteria

All randomized controlled trials comparing cyclofenil versus placebo were eligible if they reported clinical outcomes of interest. Trials with dropout rates greater than 30% were excluded.

Data collection and analysis

All data were abstracted by two independent and trained reviewers (SH, PT), and verified by a third reviewer (JP). Each trial was assessed independently by the same two reviewers for its quality using a validated quality assessment tool ([Altman 2001](#)).

Peto's odds ratios were calculated for all dichotomous outcomes and a weighted mean difference was carried out on all continuous outcomes. Fixed effects and random effects model were used if the data was homogeneous or heterogeneous, respectively.

Main results

One trial with 38 patients was included. There was a trend for Cyclofenil to demonstrate more improvement [OR 1.26 (95% CI 0.33, 4.73)] and more dropouts [OR 1.58 (95% CI 0.42, 5.91)] compared to placebo, but there were no statistically significant differences. The quality score of the one included study was 4 of 5.

Authors' conclusions

There is insufficient evidence either to support or to refute the use of Cyclofenil in the treatment of Raynaud's phenomenon secondary to scleroderma.

PLAIN LANGUAGE SUMMARY

Cyclofenil is a drug that has been studied in the treatment for Raynaud's phenomenon and associated conditions. It is not used for RP and is an anabolic steroid. See also Cochrane review on Stanzol which is also an anabolic steroid.

Raynaud's phenomenon is a disease that causes decreased blood flow and circulation to patients' extremities. Symptoms include discolouration, pain, and in some severe cases ulceration of the hands and feet. It is most often triggered by cold, stress, and emotional discomfort. Primary Raynaud's phenomenon has no underlying disease associated with it. Secondary Raynaud's phenomenon is most often associated with scleroderma, but may also be related to systemic lupus erythematosus, mixed connective tissue disease, Sjorgen's syndrome, dermatomyositis or rheumatoid arthritis.

Scleroderma is a connective tissue disease causing hardening and commonly affects the skin and internal organs such as the GI tract, lungs, kidney and heart.

One trial which investigated the effect of cyclofenil on 38 patients was included (Blom-Bulow 1981). In general patients treated with Cyclofenil improved more than those treated with placebo, however, these improvements were not statistically significant. Patients treated with cyclofenil reported numerous side effects which in some cases were severe and included an allergic reaction and complications associated with underlying heart conditions.

This review assessed a limited number of studies and therefore the conclusions reached need to be investigated further.

BACKGROUND

Scleroderma is a connective tissue disease causing fibrosis and commonly affects the skin and internal organs such as the GI tract, lungs, kidney and heart (Medsger 1985). Most people with scleroderma also have Raynaud's phenomenon (RP). RP is defined as vasospasm of arteries or arterioles causing pallor and at least one other colour change upon reperfusion such as cyanosis or redness. Primary RP occurs in the absence of causes such as connective tissue disease. Secondary RP occurs in people with underlying diseases that affect blood vessels especially scleroderma and lupus. The RP that occurs in scleroderma is often more severe in that there is not only vasospasm but also a fixed blood vessel defect with intimal proliferation and therefore narrowing of the blood vessels. RP may also be accompanied by digital ulcers which are possibly secondary to ischemia.

There have been many randomized controlled trials of both the treatment of idiopathic or primary RP and secondary RP accompanied by scleroderma and other connective tissue diseases. Over the last two decades better drugs have been developed such as calcium channel blockers, prostacyclin analogues and various other medications compared to treatment years ago where the choices were ganglion blockers and alpha blockers, both of which had many side effects such as postural hypotension and dry mouth.

Cyclofenil, an anabolic steroid has been studied in RP.

We therefore undertook a Systematic Review to determine the efficacy of Cyclofenil for the treatment of RP in scleroderma versus placebo.

OBJECTIVES

The objectives of this review were to determine the effectiveness and toxicity of : Cyclofenil versus Placebo proposed for the treatment of RP in scleroderma.

The specific hypotheses tested were that Cyclofenil can:

- 1) reduce the frequency of attacks
- 2) reduce the severity of attacks
- 3) increase digital skin temperature
- 4) improve the patient and physician's global assessment of RP
- 5) prevent new ulcers and heal existing ulcers

METHODS

Criteria for considering studies for this review

Types of studies

We aimed to identify all randomized controlled trials (RCTs) in which Cyclofenil was compared to placebo for treatment of idiopathic RP and RP resulting from progressive Systemic Sclerosis.

Types of participants

- 1) The subjects for the trials needed to have a diagnosis of scleroderma as defined by the physician. It was not necessary that such patients satisfy the preliminary American College of Rheumatology (ACR) criteria for scleroderma (ACR criteria 1980).

Trials could include subjects with any subset of scleroderma and at any stage of disease.

- 2) In the absence of an accepted definition for RP, all subjects reported to have RP were accepted, but the diagnostic criteria used were noted.

Mixed Trials: Some trials included RP patients with a number of different diagnoses. Such trials were included if a subset of patients with scleroderma could be separately identified and their outcomes independently assessed.

Design Aspects: Trials must have been truly randomized but, given the nature of some interventions (e.g. infusions), blinding may not have been achieved. Observer or subject blindness was noted. Trials with a drop out rate of greater than 30% were excluded. Both parallel and crossover trials were included.

Types of interventions

Interventions of interest included: Cyclofenil versus Placebo

Types of outcome measures

Outcomes were considered for trials of > or = 1 week duration. Outcome measurements included:

1. Frequency of attacks
2. Severity of attacks
3. Duration of attacks
4. Patient and physician's global assessment
5. Change in digital ulceration
6. Side effects
7. Treatment preference
8. General improvement
9. Signs and Symptoms Likert score
10. Raynaud's condition score
11. Mean functional index

Search methods for identification of studies

The aim was to ascertain all trials since 1966 in all languages, from MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials, using the search strategy developed by Dickersin 1994. Those studies comparing Cyclofenil versus placebo were selected from all articles retrieved.

Along with the Dickersin et al. search strategy, the search strategy developed for the Cochrane Musculoskeletal Group (see review group for details) was carried out including the following key words:

1. Raynauds or Vasospasm
- 2 . Scleroderma or Progressive Systemic Sclerosis or Connective Tissue Disease or Autoimmune Disease.

Data collection and analysis

All data were abstracted by two independent and trained reviewers (SH, PT), and verified by a third reviewer (JP). Each trial was assessed independently by the same two reviewers for its quality using a validated quality assessment tool (Altman 2001).

A fixed effects model approach was used to calculate a weighted estimate appropriate for continuous variables and an odds ratio (Peto) for dichotomous variables (Petitti 1994). A random effects model was used where heterogeneity exists amongst trials. Heterogeneity was tested using a chi square test.

Trials were only included if they were randomized and if the dropout rate did not exceed 30%. The reason for the latter criterion is the fact that the placebo response in RP trials may be quite high and therefore results would be biased to the positive if the dropout rate was > 30% (as subjects often tend to drop out due to inefficacy). Trials that included patients with scleroderma and other causes of RP such as primary or other secondary connective tissue diseases were included if the data were separated so that the scleroderma patients could be determined. We also decided that if a trial contained at least 80% of patients with scleroderma, and the data were not separated, that trial would still be acceptable. Patients with both diffuse and limited scleroderma were included in the trials and the diagnosis was usually stated by the authors' and often the American College of Rheumatology preliminary criteria for the diagnosis of scleroderma were not mentioned.

RESULTS

Description of studies

Two trials were found which compared Cyclofenil in the treatment of scleroderma assessing Raynaud's phenomenon. Other studies were found discussing the possible efficacy of Cyclofenil but they were not randomized controlled trials and therefore were not included. One study (Gibson 1983) was excluded whereby statistical data could not be extracted because only the median and range were available. Another study (Kahaleh 1994) discussed Cyclofenil in Raynaud's phenomenon but was not a randomized controlled trial and was therefore excluded. Therefore only one randomized controlled trial was included in this Systematic Review (Blom-Bulow 1981).

Risk of bias in included studies

The quality assessment was carried out independently by two reviewers (SH, PT).

Using a validated quality assessment tool, we assessed quality defined as "the confidence that the trial design, conduct, and analysis have minimized or avoided biases in its treatment comparisons" (Jadad 1996). One point was given for each of the present following criteria: randomization, statistical methods, double blinding, intent-to-treat, and method of randomization. Consensus was reached on all final scores for each trial. Interobserver agreement was measured using kappa values (> 0.60 indicate substantial strength of agreement) (Cohen 1988).

Effects of interventions

The trial included in this Systematic Review (Blom-Bulow 1981) was a randomized double blinded cross-over study. The quality score was 4. Thirty-eight patients with scleroderma were entered

and 27 completed treatment. The study included six months of treatment with Cyclofenil or a placebo and no wash out period and then six months of the alternative treatment in random order. There were several outcome variables in this study including efficacy of Cyclofenil in scleroderma (skin and joint changes), assessment of pulmonary, cardiac, GI and renal function, and patient and physician assessments. Twenty-five patients who completed the cross-over study were analyzed. The percent improvement was slightly higher in Cyclofenil compared to placebo but was not statistically significant. Drop outs were more common due to side effects in the Cyclofenil group. There was a trend toward more digital ulcer healing in the RP patients when they were treated with Cyclofenil, however none of these data reached statistical significance and the magnitude of improvement with Cyclofenil was relatively small. In summary: The physician global assessment was in favour of Cyclofenil [OR 1.26 (95% CI 0.33, 4.73)]; digital ulcers improved more on Cyclofenil [OR 2.22 (95% CI 0.53, 9.26)]; and there was a trend for Cyclofenil to demonstrate more dropouts compared to placebo: [OR 1.58 (95% CI 0.42, 5.91)].

DISCUSSION

Raynaud's Phenomenon is extremely common in scleroderma and often severe. The literature search for this meta-analysis reveals that many different classes of drugs have been demonstrated to have some degree of efficacy in the treatment of RP with respect to decreasing RP frequency and severity, and preventing and healing digital ulcers. Because RP is variable and many patients are entered into studies when they are having frequent and severe attacks, there is a high placebo response because of the variability of RP with respect to temperature and other emotional factors, and regression to the mean may occur. This placebo response should be taken into consideration when other therapies are investigated in primary and secondary RP and therefore any new drug trials should be randomized, blinded and controlled.

With a long-term study, six months and then crossed over, and no washout period it is difficult to know if a carryover effect occurred and RP on one treatment could be more severe due to the background temperature when comparing active treatment to placebo. The trial that was included analyzed only 25 of the 38 patients who entered the study and no attempt at an intent to treat analysis was performed. No data with respect to RP were statistically significantly different in the Cyclofenil compared to the placebo group. Many of our a priori outcome measurements were not found within the study retrieved for this Systematic Review.

There are several limitations to meta-analyses. Our search from MEDLINE and the references of key review articles may only reveal some of the published articles. Therefore, at this point in time some articles could be missing. There may also have been publication bias where a negative study is less likely to be published. If this is the case with Cyclofenil trials, then further negative studies would not change the results from the reported negative study.

AUTHORS' CONCLUSIONS

Implications for practice

Cyclofenil is not effective in the treatment of Raynaud's Phenomenon secondary to systemic sclerosis.

Implications for research

Cross-over studies of long duration in Raynaud's Phenomenon may not be comparable as an order or carry over effect could occur. Certainly, if a patient were randomized to one treatment for RP in cold months, it could be more frequent than RP in a patient who was then crossed over for six months during warmer seasons. It is

also important to analyze all patients randomized. This study had 38 patients initially, 27 completed the trial and only 25 patients were analyzed. Twenty percent of patients on placebo improved. It is important to realize that in many randomized controlled trials which study RP in scleroderma, the placebo effect may be quite high in the shorter trials and the sample size needs to be adjusted upward.

REFERENCES

References to studies included in this review

Blom-Bulow 1981 {published data only}

Blom-Bulow B, Oberg K, Wollheim FA, Persson B, Jonson B, Malmberg P, Bostrom H, Herbai G. Cyclofenil versus placebo in progressive systemic sclerosis. A one-year double-blind crossover study of 27 patients. *Acta Medica Scandinavica* 1981;**210**(5):419-428.

References to studies excluded from this review

Gibson 1983 {published data only}

Gibson T, Grahame R. Cyclofenil treatment of scleroderma--a controlled study. *British Journal of Rheumatology* 1983;**22**(4):218-223.

Kahaleh 1994 {published data only}

Kahaleh MB. Raynaud's phenomenon and vascular disease in scleroderma. *Current Opinion in Rheumatology* 1994;**6**:621-7.

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Cohen J. Statistical Power Analysis for the Behavioural Sciences. Lawrence Erlbaum Associates, Inc., 1988:21-34.

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Freedman RR, Ianni P, Wenig P. Behavioral treatment of Raynaud's phenomenon in scleroderma. *Journal of Behavioral Medicine* 1984;**7**(4):343-53.

Jadad 1996

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LeRoy 1992

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Medsger 1985

Medsger TA Jr. Systemic sclerosis (scleroderma), eosinophilic fasciitis, and calcinosis. In: McCarty DJ editor(s). *Arthritis and Allied Conditions*. 10th Edition. Philadelphia: Lea and Febiger, 1985:944-1036.

Petitti 1994

Petitti D. Meta-analysis, decision analysis, and cost-effectiveness analysis: methods for quantitative synthesis in medicine. New York: Oxford University Press, 1994:90-114.

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Blom-Bulow 1981

Methods	Randomized Double-blind Crossover design Efficacy Placebo controlled
Participants	N=38 initial progressive systemic sclerosis patients, N=27 completed trial. Pts from clinics and others who had been referred. Typical sclerodermatous skin changes, Raynaud's phenomenon or sensitivity to cold and at least one definite site of visceral involvement. Females=14 completed study (6 dropped out), Males = 13 completed study (5 dropped out). Mean age (yrs)=52+/-13 completed study (59+/-9 dropped out) Duration of disease (yrs)=6.3+/-5.7 completed study (6.9+/-4.5 dropped out) Country: Sweden
Interventions	Each patient was treated for 6 months with Cyclofenil and for six months with Placebo tablets. Continued low doses of cortisone were permitted, but the dose had to be kept constant throughout the study Duration: 2x6 months

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Blom-Bulow 1981 *(Continued)*

Outcomes	Full clinical and lab evaluation at entry, 6, and 12 months. Skin and joint function assessed. RP variables: peripheral circulation, hand thermography, resting blood flow. Peripheral circulation assessed. Also pulmonary and cardiac assessment: PFTs, spirometer testing, pulmonary resistance, ECG, BP, CXR. GI function assessed. Renal function assessed. Subjective assessments made, also physician overall assessment. Bloodwork completed.
Notes	Quality Score = 4

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

Study	Reason for exclusion
Gibson 1983	Greater than 30% dropout rate.
Kahaleh 1994	No statistical data available; for discussion only

DATA AND ANALYSES
Comparison 1. Cyclofenil vs. Placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 % improvement (physician global)	1	50	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.26 [0.33, 4.73]
2 dropouts (because of side effects)	1	76	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.88 [0.53, 6.68]
3 Improvement (ulcers)	1	50	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.22 [0.53, 9.26]

Analysis 1.1. Comparison 1 Cyclofenil vs. Placebo, Outcome 1 % improvement (physician global).

Study or subgroup	Cyclofenil n/N	Placebo n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Blom-Bulow 1981	6/25	5/25		100%	1.26[0.33,4.73]
Total (95% CI)	25	25		100%	1.26[0.33,4.73]
Total events: 6 (Cyclofenil), 5 (Placebo)					
Heterogeneity: Not applicable					
			Favours placebo 0.1 0.2 0.5 1 2 5 10 Favours cyclofenil

Analysis 1.2. Comparison 1 Cyclofenil vs. Placebo, Outcome 2 dropouts (because of side effects).

Analysis 1.3. Comparison 1 Cyclofenil vs. Placebo, Outcome 3 Improvement (ulcers).

WHAT'S NEW

Date	Event	Description
29 August 2008	Amended	Converted to new review format.
		CMSG ID: C022-R

CONTRIBUTIONS OF AUTHORS

Pope J - Guarantor, Coordinator, Conceiving the review, Designing search strategies, Screening search results, Obtaining and screening data on unpublished studies, Providing general advice on the review, Securing funding for the review

Tingey P - Data collection, Designing the review, Undertaking searches, Organized retrieval of papers, Screening retrieved papers against inclusion criteria, Appraising quality of papers, Extracting data from papers, Obtaining and screening data on unpublished studies, Data management, Entering data into Revman, Analysis of data, Interpretation of data, Writing the review

Harding S - Data collection, Designing the review, Undertaking searches, Organized retrieval of papers, Screening retrieved papers against inclusion criteria, Appraising quality of papers, Extracting data from papers, Obtaining and screening data on unpublished studies, Data management, Entering data into Revman, Analysis of data, Interpretation of data, Writing the review

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- University of Western Ontario, London, Canada.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Cyclofenil [*therapeutic use]; Raynaud Disease [*drug therapy] [*etiology]; Scleroderma, Systemic [*complications]

MeSH check words

Humans