Acta Derm Venereol (Stockh) 1996; 76: 231–235

Cavity Foot Ulcers in Diabetic Patients: A Comparative Study of Cadexomer Iodine Ointment and Standard Treatment

An Economic Analysis alongside a Clinical Trial

J. APELQVIST[1], and G. RAGNARSON TENNVALL[2]

[1]Department of Internal Medicine, University Hospital of Lund and [2]IHE, the Swedish Institute for Health Economics, Lund, Sweden

Diabetic foot ulcers with exposure of tendon, muscle, or bone imply a high probability for deep infections and amputations. Delayed healing times are often described. The aim of this study was to compare the clinical effect and economic cost of cadexomer iodine with standard treatment in diabetic feet with cavity ulcers.

Patients with deep, exudative foot ulcers were included in a 12-week open, randomised, comparative study. When ulcers stopped exudating, vaseline gauze was used in both groups until the end of the study. Costs were estimated for dressing material, staff and transportation.

Clinically relevant improvement was seen in 12 patients treated with cadexomer iodine and in 13 patients treated with standard treatment. The average weekly cost was SEK 903 and SEK 1,421, respectively, of which the major part was costs for staff and transportation related to frequency of dressing changes.

Treatment with cadexomer iodine ointment (Iodosorb®) showed no clinical difference compared to topical treatment consisting of gentamicin solution, streptodornase/ streptokinase, or dry saline gauze but was associated with considerably lower weekly treatment costs. ***Key words: topical treatment; health economic evaluation.***

(Accepted October 31, 1995.)

Acta Derm Venereol (Stockh) 1996; 76: 231–235.

J. Apelqvist, Department of Internal Medicine, University Hospital of Lund, S-221 85 Lund, Sweden.

Ulceration of the foot is a common and devastating complication in patients with diabetes mellitus (1) and causes high costs to both patients and society. Of all hospital admissions in the case of diabetic patients 20–25% are estimated to be caused by foot problems (2), and foot lesions have been found to be the single most costly complication in diabetic patients (3, 4). The ulcers often result in suffering, lifetime disability, a diminished quality of life, risk of limb loss and associated mortality (1, 5). There are few controlled studies on topical strategies (therapy) of foot ulcers in diabetes, especially in those that are deep, moist and necrotic, i.e. cavity ulcers. These ulcers have a high probability for deep infection and subsequent amputation and delayed healing (6–8).

Cadexomer iodine ointment (Iodosorb®, Perstorp Pharma AB) is a product where iodine (0.9%) has been physically incorporated in a modified starch matrix (cadexomer). It has been studied mainly in venous and decubitus ulcers and is described as highly fluid-absorbing, antibacterial and able to dissolve debris and necrotic tissue (9, 10). Cadexomer iodine ointment has been suggested to be a useful addition in the treatment of exudative foot ulcers in diabetic patients according to an open non-comparative study (11).

The costs for treatment of patients with diabetic foot ulcers are high. In a recent study (7), the main cost elements were costs for in-patient care and topical treatment. Costs for topical treatment can be divided into costs for drugs and material and costs for staff and travelling expenses, where the highest costs are those for staff and transportation. An important factor to reduce costs for topical treatment is to choose a treatment strategy where the frequency of the dressing changes can be diminished (12) without inferior quality or prolonged healing time.

The primary aim of the present study was to analyse the potential cost effectiveness of cadexomer iodine ointment versus standard topical treatment in diabetic patients with foot ulcers in a clinical comparative trial. One hypothesis was that if the use of cadexomer iodine produced a healing rate comparative to an alternative treatment with more frequent dressing changes, it would result in reduced staff requirements for ulcer dressing, and travelling, and as a consequence a reduction in total direct costs. A further aim was to analyse and discuss different methodological issues when an economic analysis is performed alongside a clinical trial of this type.

MATERIAL AND METHODS

Patients

Forty-one patients with previously known diabetes mellitus were included in the trial because of an exudative foot ulcer. Twenty-two patients were randomised to treatment with cadexomer iodine ointment and 19 to treatment with standard dressings. All patients were investigated and treated as out-patients by a multidisciplinary foot care team consisting of a diabetologist, an orthopaedic surgeon, an orthotist, a podiatrist and a diabetes nurse.

Study design

This was an open controlled trial of 12 weeks' duration with blinded photo-evaluation. The patients were randomly allocated to topical treatment either with cadexomer iodine ointment (Iodosorb®) or standard treatment (gentamicin solution (Garamycin®, Schering-Plough); streptodornase/strepto-kinase (Varidase®, Lederle); dry saline gauze (Mesalt®, Mölnlycke)), according to a computer-generated list of randomly permuted blocks of patients and where the size of the blocks was unknown to the investigator. Stratification was based on size and type of ulcer (Wagner grade I–II) according to Wagner (13): grade I was classified as a superficial ulcer breaking through subcutaneous tissue and grade II as a deep ulcer.

Criteria for inclusion and exclusion

The inclusion criteria were Caucasians >40 years of age with previously known diabetes mellitus, an exudating cavity ulcer below the ankle (Wagner grade I–II) with an ulcer area >1 cm^2 and a systolic toe pressure >30 mm Hg or a systolic ankle pressure >80 mm Hg. The ulcer area was measured by multiplying maximum length and maximum width. Only one ulcer was studied in each patient. If there were several ulcers, the largest fulfilling the inclusion criteria was chosen.

Patients with ulcers >25 cm^2 were excluded, as were patients with

 ISSN 0001-5555

a deep abscess, osteomyelitis or gangrene (Wagner grade III–IV). Subjects undergoing investigations of the thyroid gland or unlikely to adhere to study protocol were not included. Patients were withdrawn from the study in case of hospitalisation, lack of compliance, ulcer deterioration (Wagner grade III–IV), >100 per cent increase in ulcer area, and adverse reactions to the topical treatment.

Treatment

Patients were seen at inclusion and at 1, 4, 8 and 12 weeks. All patients were offered the same basic treatment (7) during the study, and any changes in treatment were documented. Prior to inclusion footwear was corrected or special footwear provided whenever required in order to relieve local pressure.

Oral antibiotics (ciprofloxacine, cephalosporines, metronidazol, clindamycin) were used in case of signs of infection, i.e. cellulitis. A general medical history was established and a standard physical examination was performed prior to inclusion into the study. The ulcers were cleaned with sterile saline and dressed according to the manufacturers' recommendations by regular health care nurses. Frequency of dressing changes, material consumption and time used were documented each time.

Cadexomer iodine was prescribed to be changed once daily during the first week and daily or every second to third day during the following weeks due to degree of exudation. If the ulcer was infected, i.e. cellulitis present, gentamicin solution (80mg/ml) was prescribed twice daily, streptodornase/streptokinase was used for moist necrotic lesions and changed twice daily. Dry saline gauze used as an absorptive dressing was changed once or twice daily according to grade of exudation. In every case when ulcers stopped exudating, vaseline gauze (Jelonet®, Smith & Nephew Medical Ltd) was used. At each visit the patient was asked about possible side-effects.

Wound evaluation

Colour photographs with scales were taken at the visits to the foot care team, and the ulcers were assessed and inspected. The evaluation of the photographs was performed blindly at the end of the study by two separate and independent physicians. A successful result was where the initial ulcer area was reduced by >50 per cent, or an improvement in Wagner grade was seen. Healing was defined as intact skin. In the event of disagreement in the evaluation of the photographs, the measurement from the foot care team was decisive.

Laboratory investigations

The systolic ankle and toe pressure was measured using strain-gauge and Doppler techniques. Blood samples were taken at entry and after 12 weeks. A bacterial culture was obtained at inclusion and during the study if signs of cellulitis occurred.

Cost calculation

Data for the economic evaluation was collected during the clinical trial according to a specially designed protocol. Direct costs were estimated for material and drugs, staff and transportation. When changing dressings, information about type of dressing, quantity of dressing/drug, category who changed the dressing, time consumption, and location for dressing changes were documented. The perspective of the economic evaluation is from a societal point of view. Indirect costs, i.e. costs related to loss of production, were not estimated. All amounts are quoted in SEK in 1993 prices (USD 1 and GBP 1 equalled approximately SEK 8.10, and SEK 12.10, respectively).

Costs of transportation were estimated for the patient to visit an out-patient care unit or for the staff to visit the patient at home. The travelling distance for each visit was assumed to be on average 10 km at a cost of SEK 24.50. If the patient or a relative living in the same household performed the dressing change, no travelling costs and no labour costs were estimated.

Information on price per unit drug and material price was obtained from FASS (14) and current market prices. The average wages for nursing staff 1991 (15), non-wage labour costs added, were adjusted to 1993 prices. Labour costs include time to prepare for the dressing change, to redress the wound and tidying up after the procedure. If someone has been travelling to the patient, an extra 30 min, in addition to the treatment time, have been estimated.

Statistics

Values are given as mean and standard deviation (SD) for clinical data and as mean and range (min-max) for the economic data. Differences between or within groups have been calculated using the Mann-Whitney U-test (two-tailed).

RESULTS

Clinical results

There were no major differences between the two treatment groups, either in clinical characteristics or in healing as measured by size and type of ulcer after 12 weeks' treatment. All patients had signs of severe sensory neuropathy (vibratory, pressure, threshold, VPT >30), and in all cases except 2, a precipitating cause of ulcer was seen, of which mechanical stress was the most common ($n=27$). Surgical revision was performed in 3 patients treated with cadexomer iodine, and in 5 patients treated with standard treatment. Five patients treated with the investigated drug were completely healed during the observation time, compared to 2 patients treated with standard dressings. Total improvement after study termination was 12 and 13 patients, respectively. No adverse reactions related to the topical treatment were documented. Two patients were excluded from the evaluation due to violation of inclusion criteria (size >25 cm^2 and/or type of ulcer, Wagner III) according to the blinded evaluation. Two patients were excluded due to hospitalisation. The reason for in-patient care for the first patient was a myocardial infarction. The other patient became febrile and was treated in hospital for 7 days before death caused by heart failure. This hospitalisation has been classified as probably not associated with study treatment. A special calculation where this patient was included has been performed in the sensitivity analysis. One patient was excluded due to non-compliance to treatment. Thirty-six patients remained for the clinical evaluation.

Economic results

Use of resources. One patient was excluded from the economic evaluation due to insufficient records about resource use at dressing changes, i.e. 35 patients were evaluated (Tables I, II). Most dressing changes were performed by nurses or auxiliary nurses in the patient's home. No patients changed the dressings by themselves during the entire treatment period, but some patients changed dressings occasionally. The average time for the changes was 13 min for cadexomer iodine and 11 min for standard treatment. The average recorded number of weekly dressing changes was 4.7 in the investigated group and 9.9 in the control group. Among patients treated with standard treatment 14 out of 18 patients were treated with gentamicin solution some time during the 12 weeks. Two patients were treated with streptodornase/streptokinase and 9 patients with dry saline gauze (Table I).

Costs. Since no major differences in clinical results regarding size and type of ulcer could be seen between the two treatment groups in this study, a cost minimisation analysis is appropriate and has been applied, i.e. a comparison of weekly costs for the two treatment alternatives. The average weekly cost for topical treatment was SEK 1,169 for all patients evaluable in

Table I. *Use of resources*

Values are given as means (min-max).

	Cadexomer iodine ($n=17$)	Standard treatment ($n=18$)
Dressing changes/week	4.7 (3.2–6.9)	9.9 (3.1–13.9)
Staff category		
Total number of dressing changes performed by:		
- nurse	210 (27%)	591 (30%)
- auxiliary nurse	350 (45%)	1.095 (56%)
- patient or spouse	113 (14%)	7 (0%)
- other	112 (14%)	276 (14%)
Time consumption/ dressing change (min)	13 (8–24)	11 (5–23)
Type of dressing (no. of patients treated)		
- cadexomer iodine	17	0
- gentamicin solution	0	14
- streptodornase/streptokinase	0	2
- dry saline gauze	1[a]	9
- vaseline gauze	8	6
Treatment weeks	10 (1–12)[b]	11 (5–12)

[a] One patient was changed to dry saline gauze during the last part of the treatment time (week 8–12) as cadexomer iodine could not be used due to the configuration of the ulcer.

[b] For one patient who healed in week 4, only information about treatment during the first week was available in the economic protocol.

Table II. *Economic results and cost effectiveness measured as topical treatment cost in relation to number of patients completely healed*

Costs are in SEK, 1993 prices.
Values are given as means (min-max).
ns = non-significant difference between groups.

	Cadexomer iodine ($n=17$)	Standard treatment ($n=18$)
Weekly cost		
- staff	380 (96–570)	884 (315–1,492)***
- transportation	100 (29–156)	243 (76–341)***
- material and drugs	423 (166–1,113)	294 (37–981) ns
Total weekly cost	903 (524–1,697)	1,421 (428–2,679)**
Number of patients healed	5/17	2/18
Weekly cost related to patients healed	3,070	12,790

*$=p<0.05$, **$=p<0.01$. **$=p<0.001$, between groups.

the economic analysis (min-max 428–2,679). Weekly costs for staff, transportation, material and drugs showed great individual distribution in both treatment groups (Table II).

The number of patients with ulcers that healed completely during the observation time differed between the two groups. This difference was not statistically significant, but a cost effectiveness rate has been calculated as a complement to the cost minimisation analysis and is expressed as weekly cost per patient healed (Table II).

Sensitivity analysis

A sensitivity analysis was performed to investigate how different assumptions about uncertain factors have influenced the economic results. One of these uncertain factors in the study is the estimated costs for travelling expenses. Other factors are which type of staff who perform the dressing, or if patients are able to change their ulcer dressings without help from the health care staff. Another interesting question was whether the cost pattern would be different if patients had been treated exactly according to the prescriptions made by the physician.

If a travelling distance of 5 km instead of 10 km was assumed, this would influence both travelling costs and staff costs. The estimated time for travelling was assumed to be reduced by 15 min. This would result in a reduction of the total weekly cost of 20% for patients treated with cadexomer iodine and 31% for patients in the control group. Travelling costs would be 50% lower in both groups, while staff costs would be 35% and 36% lower, respectively.

If, for example, patients or their relatives living in the same household could perform 50% of the dressing changes, both travelling and staff costs would be reduced with the same percentage. Total weekly costs would decrease by 27% in the investigated group and by 40% in the control group.

The reduction of total weekly costs if all dressing changes were performed by auxiliary nurses compared with if nurses perform all the changes is 7% in the investigated group and 9% in the control group.

If patients were treated according to the frequency of dressing changes prescribed by the physician, the total weekly cost would be SEK 836 for patients treated with cadexomer iodine, and SEK 1,914 for patients treated with standard dressings, provided that the staff proportion and the average treatment time are the same as found in this study.

Total treatment costs of in-patient care for the patient who was hospitalised due to fever was SEK 18,060. If this patient and the costs for in-patient care are included in the economic evaluation the average total and weekly costs for patients treated with cadexomer iodine would be SEK 9,916 and SEK 1,040, compared to SEK 8,910 and SEK 903. The results are therefore sensitive to a possible adverse reaction resulting in hospitalisation.

DISCUSSION

Clinical considerations

Cavity ulcers are related to a high probability of deep infection, subsequent amputation and delayed healing (2, 16, 17). There are, however, no comparative studies published on cavity ulcers in diabetic patients. In the present study the total clinical results in both groups are in agreement (25 out of 36 improved) with previous observations (2, 6–8).

Most dressings are designed to improve healing in different phases of healing (12), especially in complicated wounds such as cavity ulcers. Few dressings with a specified activity in the wound are designed to be used from first occurrence of the ulcer until healing occurs. This was the reason why standard treatment included a preset battery of treatment regimens in different stages of healing, and why vaseline gauze was used when ulcers stopped exudating. In the present study a change of treatment regimens was also performed in a majority of the

patients. This also creates a methodological difficulty in the clinical setting comparing different topical strategies concerning both wound healing and economic analysis.

The average wound healing time for abscess and deep ulcers has in a previous study been found to be 6 months, with a primary healing rate of 68 and 95%, respectively (12). The high risk of amputation for patients with cavity ulcers is in the present study illustrated by the substantial number of previous amputations (approximately 50%), mostly due to deep infection prior to inclusion.

Economic considerations

The results in the present study regarding average weekly cost for treatment with cadexomer iodine or standard treatment, SEK 903 and SEK 1,421, respectively, are in agreement with a previous study (12). In that study a reduction in the frequency of dressing changes was an important factor to decrease total weekly costs.

Staff and transportation

The weekly costs for staff and transportation are high in comparison with costs for material and total weekly cost. This is illustrated by 53% of total costs in patients treated with cadexomer iodine and 79% in patients treated with standard dressings that can be related to staff and transportation. This result is in accordance with the previous study, where the material cost for more frequent dressing changes was proportionally smaller than when less frequent changes were made (12).

As we have seen from the sensitivity analysis the results are sensitive to who performs the change of dressings. However, due to age and multiple disease in these patients, it cannot be assumed that most patients are able to change their ulcer dressings properly. The economic results are less sensitive to a change in staff category between nurses and auxiliary nurses than a change from actual staff to the patient or his/hers relatives. Clinically there is also a quality aspect to consider. More professional staff categories will probably treat the wounds better than less educated persons and that may have implications on the healing rate, too.

The results are also highly sensitive to the assumption about travelling distance and travelling time. These factors may therefore be measured specifically in future studies to gain more valid results.

Frequency of dressing changes

In both treatment groups there is a difference between frequency of dressing changes prescribed and frequency actually performed. The recorded number of dressing changes in the control group, 9.9 per week, is lower than what could be expected, since the frequency of dressing changes prescribed for this group was once or twice daily, and most dressings were expected to be changed twice daily. This lower frequency can result from different causes, e.g. a desire to decrease costs, scarcity of staff, or an expectation of convenience for patients. The average number of dressing changes in the investigated group is somewhat higher, 4.7 per week, than what could be expected. This is in accordance with a previous pilot study of cadexomer iodine treatment. In that study there was a tendency for the nursing staff not to optimise the possibility of a longer interval between dressing changes (11). For an economic evaluation of strategies for topical treatment it is thus important to include a special protocol for collection of information regarding details of dressing changes, since the frequency prescribed by the physician will probably not reflect clinical reality. The sensitivity analysis shows that the results would be different if patients were treated exactly according to the prescriptions made by the physician.

Time

Total observation time in the trial was limited to 12 weeks. During this time few patients were completely healed. In a previous study (12) total time to healing was on average 6 months for deep ulcers. It would be ideal if patients could be followed regarding resource use until final outcome, i.e. complete healing or death. However, as we have found incomplete information about the dressing changes in some of the forms filled in by the staff, it is probably difficult to get correct information about resource use if the information is collected over several months. This is especially a problem when the staff may change from day to day, as happens in the primary or community health care in Sweden.

As we have seen in the present study there was a discrepancy between frequency of dressing changes prescribed and dressing changes actually performed. Therefore it would not be appropriate to produce cost estimations based on calculation of dressing costs over long treatment periods, simply according to treatment prescribed.

Total weekly cost for topical treatment is lower in the investigated group than in patients treated with standard treatment and will therefore require less resources. This conclusion is valid as long as we have no reason to suspect that the difference in weekly cost will change before the ulcers are completely healed. Another condition for that conclusion is that the healing rate in patients treated with cadexomer iodine will remain at least as good as in patients treated with standard treatment until complete healing is obtained.

If the average time to healing of foot ulcers in patients treated with cadexomer iodine was 15 weeks, the total costs for topical treatment would be SEK 13,545. Patients treated with standard dressings would then have to be completely healed in week 9–10 if total costs were not to exceed this amount. Thus, time to healing would have to be considerably shorter in the control group to compensate for the lower weekly cost in the investigated group.

Methodological aspects related to clinical trials

The perspective of the present study is from a societal point of view. Whether indirect costs should be included or not in an economic analysis has recently been discussed (18, 19). Since most patients in this study are above working age, no indirect costs for lost production have been estimated. It is also difficult to know if a patient has been absent from work due to the foot ulcers or due to the underlying diabetes or intercurrent disease. No time costs have been calculated for patients or relatives who have made dressing changes without help from the health care system. Some authors have, however, argued for an evaluation of costs for such unpaid time that is difficult to value (20, 21).

No further costs, except the costs for topical treatment, have been estimated in the study. In a previous study analysing costs for diabetic foot ulcers (7), costs for out-patient visits were low in relation to total costs, both for patients who healed primarily, and for patients who healed after an amputation. Since an incremental analysis is preferred, and we have no reason to believe that the frequency of out-patient visits should differ between the two patient groups, these costs have been omitted in the analysis.

The present economic analysis was performed alongside a clinical trial. This can, as we have seen, cause some methodological problems. These problems have been discussed by Drummond & Davies (22), who mention that patients in a clinical trial are more closely monitored and that treatment patterns may differ from normal clinical practice. More resources may therefore be consumed only for the purposes of the trial itself. This is a further reason why costs for out-patient visits have not been calculated in this study. Thus, in an economic analysis performed at the same time as a clinical trial, different points have to be considered and weighted regarding their relevance to the clinical or the economic outcome, respectively. It is important that the variables studied in the economic analysis are as equal to clinical reality as possible; otherwise adjustments have to be made to compensate for possible differences. If these differences are difficult to value or to observe it may be wise to consider if performing the economic analysis separately from the clinical trial would be a more appropriate study design. In the present study the design was focused on the economic evaluation.

To solve some of the problems discussed here, a special research nurse can be employed to perform dressing changes and register the resource use in future studies. One disadvantage with such a solution is that the trial will differ more from regular clinical practice than described in the present study. Compliance with therapy is considered to be lower in regular practice than in a clinical trial (23), and adjustments for the economic evaluation then have to be made to reflect clinical practice.

In conclusion, cadexomer iodine ointment is a cost effective and useful addition in the treatment of exudating cavity ulcers in diabetic patients compared with standard treatment, including topical antibiotics.

The present study shows some of the difficulties associated with the design of high-quality clinical trials together with economic evaluations, because of conflicting demands concerning research methodology. These combined studies therefore often require more thorough planning than if each type of study was performed as a single project.

ACKNOWLEDGEMENT

This study was supported by Perstorp Pharma AB, Lund and the Swedish Diabetes Association.

REFERENCES

1. Reiber GE. Diabetic foot care. Diabetes Care 1992; 15, Suppl 1: 29–31.
2. Sims DS, Cavanagh PR, Ulbrecht JS. Risk factors in the diabetic foot. Recognition and management. Phys Ther 1988; 68: 1887–1902.
3. Jönsson B, Persson U. A study in health economics. The Swedish Institute for Health Economics. IHE report, Lund 1981:7.
4. Lithner F. Epidemiology and economic impact of diabetic foot—a major health problem. In: Bakker K, Nieuwenhuijzen Kruseman AC, eds. The diabetic foot. Amsterdam: Excerpta Medica, 1991: 9–17.
5. Pecoraro RE. The nonhealing diabetic ulcer—a major cause of limb loss. In: Barbul A, Caldwell MD, Eaglstein WH, Hunt TK, Marshall D, Pines E, et al., eds. Clinical and experimental., approaches to dermal and epidermal repair: normal and chronic wounds. New York: Wiley-Liss, Inc. 1991: 27-43.
6. Apelqvist J, Castenfors J, Stenström A, Agardh C-D. Wound classification is more important than site of ulceration in the outcome of diabetic foot ulcers. Diabetic Med 1989; 6: 526–530.
7. Apelqvist J, Ragnarson Tennvall G, Persson U, Larsson J. Diabetic foot ulcers in a multidisciplinary setting. An economic analysis of primary healing and healing with amputation. J Int Med 1994; 235: 463–471.
8. Sage R, Doyle D. Surgical treatment of diabetic foot ulcers: a review of forty-eight cases. J Foot Surg 1994; 23:102–111.
9. Ormiston MC, Seymor MTJ, Venn GE, Cohen RI, Fox JA. Controlled trial of Iodosorb in chronic venous ulcers. BMJ 1985; 291: 308–310.
10. Skog E, Arnesjö B, Troëng T, Gjöres JE, Bergljung L, Gundersen J, et al. A randomized trial comparing cadexomer iodine and standard treatment in the out-patient management of chronic venous ulcers. Br J Dermatol 1983; 109: 77–83.
11. Apelqvist J, Larsson J, Stenström A. Cadexomer iodine gel in the treatment of deep diabetic foot ulcers. In: Harding KG, Leaper DL, Turner T D, eds. Proceedings of the first European conference on advances in wound management, Cardiff, September 1991. London, Macmillan Magazines, 1992; 18: 43–55.
12. Apelqvist J, Ragnarson Tennvall G, Larsson J. Topical treatment of diabetic foot ulcers: an economic analysis of treatment alternatives and strategies. Diabetic Med 1995; 12: 123–128.
13. Wagner FW. The dysvascular foot: a system for diagnosis and treatment. Foot Ankle 1981; 2: 64–122.
14. FASS 1995. Pharmaceutical Specialties in Sweden. Stockholm: LINFO, Läkemedelsinformation AB, 1995.
15. Statistics Sweden. Statistical Yearbook of Sweden 1994. Stockholm: Statistics Sweden 1993.
16. Frykberg RG, ed. The high risk foot in diabetes mellitus. London: Churchill Livingstone, 1991.
17. Levin ME, O'Neal LW, eds. The diabetic foot. 5th edn. St Louis, MO: Mosby, 1993.
18. Koopmanschap MA, Rutten FFH. Indirect costs in economic studies. Confronting the confusion. PharmacoEconomics 1993; 4: 446–454.
19. Drummond M, Brandt A, Luce B, Rovira J. Standardizing methodologies for economic evaluation in health care. Practice, problems, and potential. International Journal of Technology Assessment in Health Care 1993; 9:1: 26–36.
20. Guyatt G, Drummond M, Feeny D, Tugwell P, Stoddart G, Haynes RB, et al. Guidelines for the clinical and economic evaluation of health care technologies. Soc Sci Med 1986; 22: 393–408.
21. Torgerson DJ, Donaldson C, Reid DM. Private versus social opportunity cost of time: valuing time in the demand for health care. Health Economics 1994; 3: 149–155.
22. Drummond MF, Davies L. Economic analysis alongside clinical trials. Revisiting the methodological issues. International Journal of Technology Assessments in Health Care 1991; 7:4: 561–573.
23. Drummond MF, Bloom BS, Carrin G, Hillman AL, Knill-Jones RP, de Pouvourville G, et al. Issues in the cross-national assessment of health technology. International Journal of Technology Assessment in Health Care 1992; 8:4: 671–682.