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Subcutaneous Terbutaline in Children With Chronic Severe Asthma

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Summary. A continuous subcutaneous infusion of terbutaline (CSIT) was used to treat 8 children with chronic severe asthma who continued to experience frequent symptoms, despite treatment with regular oral prednisolone. Five patients experienced a symptomatic improvement from CSIT, leading to a reduction in regular medication. Three patients did not experience any lasting benefit from CSIT. The most common side effects were related to the infusion site (bruising and local infection).

CSIT may lead to an improvement in symptoms and a reduction in oral steroid dose in selected children with chronic severe asthma. These initial findings support the need for further controlled studies to evaluate the use of CSIT in severe childhood asthma. **Pediatr Pulmonol. 2002; 33:356–361.** © 2002 Wiley-Liss, Inc.

Key words: asthma; subcutaneous terbutaline; children.

INTRODUCTION

A small number of children with chronic severe asthma require treatment with regular oral corticosteroids. Long-term use of oral corticosteroids is associated with a number of potential adverse effects,[1] and may occasionally fail to control symptoms adequately.[2] As a result, other treatments are sometimes tried such as cyclosporin, methotrexate, or intravenous immunoglobulin (IVIG),[3] although these may also be associated with serious side effects.

A continuous subcutaneous infusion of terbutaline (CSIT) has been used to treat adult asthmatics, with best results seen in patients with brittle asthma.[4,5] Continuous subcutaneous salbutamol has been used to treat infants with acute asthma.[6] To our knowledge, there are no reports of the long-term use of CSIT in children with asthma. In the last 8 years we have used CSIT to treat a small number of children with severe asthma in whom treatment with regular oral prednisolone had failed to control symptoms, resulting in the development of unacceptable adverse effects in some. A few of the children had previously received trials of other steroid-sparing therapies, such as cyclosporin or methotrexate. In order to evaluate our practice, and to provide pilot data for future controlled studies of CSIT in children, we performed a retrospective review of the use of CSIT in severe childhood asthma.

METHODS

A retrospective review was performed of all children with severe asthma who were treated with regular oral prednisolone, and who had received a trial of CSIT between 1994–2000. Patients were identified by asking each of three consultant pediatric respiratory physicians and the asthma nurse specialist to identify those children whom they had treated with CSIT, and by asking the hospital pharmacy to supply the names of any child who had been prescribed CSIT. Clinical information, spirometry, and peak expiratory flow (PEF) readings were obtained by reviewing the hospital case notes. Information was also obtained from discussions with the children and their families.

Variability in PEF was expressed as the coefficient of variation (CoV) of all recorded values.[7] CoV is the standard deviation of all values divided by their mean.

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RESULTS

Clinical Characteristics

Eight children were identified (Table 1). All had been taking regular oral prednisolone for at least 6 months and continued to experience frequent symptoms. Cushingoid features were present in 5 children. These were most marked in one girl (patient 6), who was subjected to persistent teasing at school because of this. All the children were absent from school for long periods because of the severity of their asthma. Cyclosporin and methotrexate had been tried in selected patients without success (Table 1), but with no significant adverse effects. One boy (patient 7) was also receiving regular IVIG in addition to oral prednisolone.

The diagnosis of asthma was confirmed in all patients according to ATS criteria.[8] Investigations were performed to identify any associated diagnoses.[3] Moderate gastroesophageal reflux disease was diagnosed and treated medically in 2 patients (7 and 8); coexisting mild bronchiectasis was diagnosed in patient 8. The 4 children (patients 5–8) who were treated with CSIT during or after 1998 also underwent fiberoptic bronchoscopy and endobronchial biopsy before starting treatment. This followed the institution in our department of a formal protocol involving bronchoscopy for the assessment of children with severe asthma.[9]

Treatment With CSIT

CSIT was instituted in hospital (Table 2). For patients 1–4, a 25-gauge butterfly needle was used. For the more recent patients (5–8), a Thalaset® infusion set with a 90° needle was used (Maersk Medical, Lynge, Denmark). The needle was sited in the abdomen and changed at least every 2 days. The starting dose of terbutaline was between 2.5–5 mg/24 hr, increasing to a maximum of 10 mg/24 hr as indicated and tolerated. PEF was measured regularly (at least four times a day) in hospital before and after starting CSIT (Fig. 1). Treatment was given for a minimum of 2 months. After commencing CSIT, all patients with one exception (patient 7) were followed in the outpatient clinic by one of two physicians (A.B. or M.R.). Patient 7 was followed by his local pediatrician, as he lived a long way from London. Attempts were made to wean the dose of prednisolone, depending on the level of asthma control. This was assessed by conventional clinical criteria (reported symptoms and medication use, physical examination, and lung function) according to the British Thoracic Society Asthma Guidelines.[10]

ABBREVIATIONS

CoV	Coefficient of variation
CSIT	Continuous subcutaneous infusion of terbutaline
FEV_1	Forced expiratory volume in 1 sec
IVIG	Intravenous immunoglobulin
PEF	Peak expiratory flow
UK	United Kingdom

Response to CSIT

The response to treatment with CSIT is shown in Table 3. After starting CSIT, 4 patients were able to discontinue treatment with regular oral prednisolone. Three of these 4 have remained off regular prednisolone. Patient 7 has stopped regular IVIG and continues to wean down on the prednisolone dose. Reduction in prednisolone dose was not associated with an increase in frequency of hospital admissions. Three of the 5 patients in whom maintenance treatment was reduced demonstrated an improvement in their best forced expiratory volume in 1 sec (FEV_1) while on CSIT (patients 2, 6, and 8; Table 3).

Three children (patients 1, 3, and 4) did not experience any long-term benefit from CSIT. Of these 3, one subsequently responded to cyclosporin and was able to discontinue prednisolone; one failed a trial of IVIG and remains on oral prednisolone; one failed trials of cyclosporin and IVIG, but has since been well-controlled with monthly intramuscular injections of triamcinolone.[11]

The 5 patients who were able to reduce their prednisolone dose reported a reduction in symptoms and rescue bronchodilator use, and an increase in school attendance and daily activities. One patient remarked that he felt that he could now ''run a mile.'' New activities, which were previously impossible, included cricket and cycling (with the infusion running), and soccer, rugby, and swimming with the infusion stopped and the needle removed for 1–2 hr.

Tachyphylaxis did not appear to be a problem in most of these patients. In 4 of the 5 patients, no further dose escalation was required once a therapeutic dose of terbutaline had been reached; the management of acute attacks using inhaled bronchodilators appeared to be unaffected by CSIT. One child (patient 5) who had initially responded very well became symptomatic after more than a year of CSIT, leading to an increase in CSIT dose and the need to restart regular prednisolone.

All patients experienced adverse effects from the treatment (Table 3). If present, tremor was described in the first few days of starting treatment and was usually transient. The most common physical problem was related to injection sites. Tenderness, bruising, and low-grade infection were reported and treated by avoiding the area of affected skin for at least 2 weeks. Troublesome localized infection (in 2 patients) was treated with antistaphylococcal antibiotics. Hypokalemia has not been reported in adults,[5] and serum potassium was not routinely measured.

TABLE 1— Patient Characteristics

Patient	Age (years)	Gender	Current treatment before starting CSIT	Previously tried therapy	Cushingoid (yes/no)	Best FEV_1 (%) before CSIT[2]	Hospital admissions in previous year
1	8	F	Budesonide 3 mg/day Prednisolone 30 mg 90eod[1]	Methotrexate Salmeterol Theophylline	Yes	101	10
2	14	M	Budesonide 2 mg/day Salmeterol 200 mcg/day Prednisolone 40 mg/day		No	95	3
3	12	F	Budesonide 3 mg/day Salmeterol 200 mcg/day Prednisolone 10 mg 90eod	Theophylline	Yes	68	2
4	12	F	Budesonide 2 mg/day Salmeterol 200 mcg/day Prednisolone 15 mg 90eod	Theophylline Methotrexate	No	86	2
5	11	M	Budesonide 3 mg/day Eformoterol 24 mcg/day Prednisolone 10 mg 90eod	Theophylline Montelukast	Yes	93	1
6	8	F	Budesonide 2 mg/day Eformoterol 24 mcg/day Prednisolone 10 mg daily	Montelukast	Yes	98	1
7	12	M	Fluticasone 2 mg/day Salmeterol 50 mcg/day Prednisolone 10 mg/7.5 mg 90eod IVIG 50 g every 2 weeks	Cyclosporin	No	100	1
8	12	M	Budesonide 1.6 mg/day Salmeterol 200 mcg/day Prednisolone 5 mg/day Montelukast 10 mg/day	Nedocromil	Yes	72	0

[1]CSIT, continuous subcutaneous infusion of terbutaline; 90eod, every other day.
[2]Best FEV_1 in last 12 months.

DISCUSSION

There are no evidence-based guidelines for the treatment of children with severe asthma who continue to experience problems due to asthma despite regular oral prednisolone. Previous investigators reported on the use of cyclosporin, IVIG, and methotrexate in this group of children with mixed results.[3] There are no reports on the use of CSIT in children.

This report describes our experience with CSIT over a 7-year period. Patients did not take part in a randomized controlled trial; neither were they enrolled in a formal open study with strict entry criteria. Rather, this report represents a retrospective review of the use of CSIT in

TABLE 2— Instructions for Use of CSIT in Children

Equipment used
Graseby syringe pump, MS 26 (Graseby Medical Ltd., Watford, UK)
10-mL syringe (luer lock)
Thalaset® infusion set with 90° needle, 27-gauge, 8-mm (Maersk Medical, Lynge, Denmark)
Topical anesthetic cream, Tegaderm® dressing, and Mediswab®
Terbutaline (intravenous solution), 0.5 mg/mL; green needles (21-gauge) for drawing up terbutaline
Sharps bin
Making up/changing the infusion
Select area of skin on abdomen to be used. Ensure it is not bruised or hard
Apply anesthetic cream and leave for 1 hr
Wash hands and draw up terbutaline into syringe
Prime Thalaset® infusion set with terbutaline
Remove cream and clean skin with a Mediswab®
Unsheath Thalaset® needle and insert needle into skin
Coil infusion tubing and secure with Tegaderm® dressing
Insert syringe in pump, press start, and check battery working
Needle is changed every 2 days; syringe changed daily

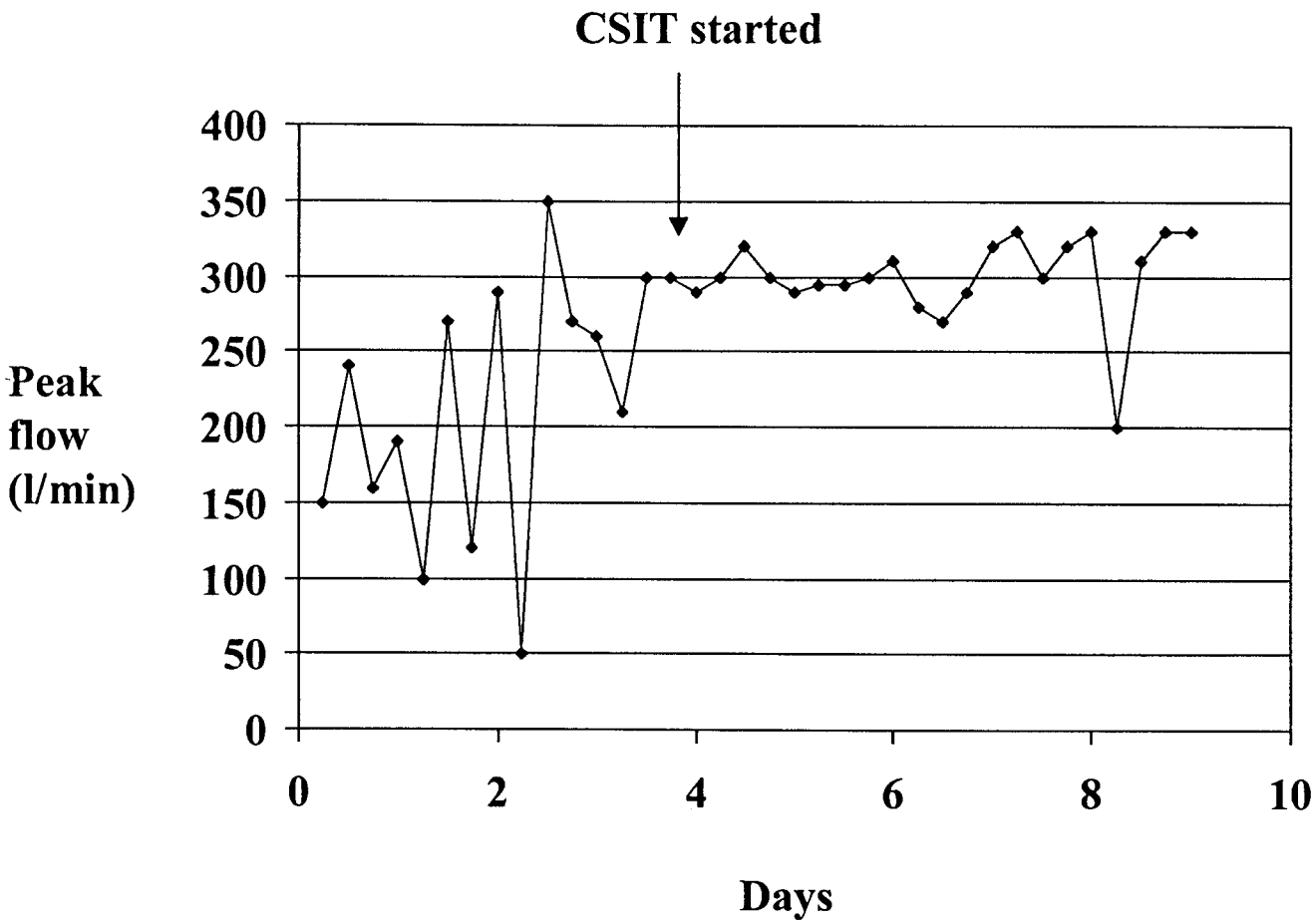

Fig. 1. Peak expiratory flow in a 12-year-old boy before and after starting continuous subcutaneous infusion of terbutaline (CSIT).

those patients in whom a clinical decision had been made to give a trial of therapy because of the severity of their asthma. The aim of this review was to evaluate our practice and provide pilot data to inform future trials of this form of treatment. The positive results seen in the majority of children is encouraging and suggests the need for a formal controlled trial of CSIT in children with severe asthma.

As with any retrospective review, there are a number of weaknesses associated with this report. The patients did not undergo a formal protocol of assessment and monitoring prior to starting CSIT. They were not managed by the same physician; nor were there strict criteria for adjusting other therapy once CSIT had been started. Nevertheless, this report reflects clinical practice in our department. Before starting CSIT, the assessment and management of patients followed accepted current guidelines. The institution of CSIT was the same for all patients, with training in the practical aspects of the treatment given by the same nurse specialist, with one exception.

The evaluation of any form of treatment is improved by the use of objective measures of effectiveness. The change in dose of prednisolone, which was adjusted according to conventional clinical criteria, provided one objective measure of treatment success. Spirometry was performed at each clinic visit. However, this pattern of relatively infrequent monitoring is not particularly useful in assessing the effectiveness of treatment, as patients may have near-normal lung function at a given time, despite frequent symptoms (Table 1). Observed lung function measurements (spirometry or PEF) in hospital are useful in assessing the initial response to treatment. However, CSIT is a long-term treatment. Prolonged home monitoring of PEF is fraught with problems, and the risk of missing or fabricated data increases after a few weeks.[12] This type of home monitoring might be more reliable with electronic PEF meters, although even these may not be totally accurate.[13] In practice, it was not difficult to differentiate patients who responded to CSIT from those who did not. The responders clearly reported a marked and sustained reduction in symptoms and were able to start taking part in activities, particularly sports, which had previously been beyond them. The nonresponders reported no such change and were keen to discontinue treatment when this was suggested. The use of such "real world" measures of effectiveness, in addition

TABLE 3— Response to Continuous Subcutaneous Infusion of Terbutaline

Patient	Maximum dose (mg/day)	Best FEV_1 (%) on CSIT	Peak flow in hospital (L/min)[1]						Hospital admissions on CSIT[2]	Changes to therapy on CSIT	Subjective response	Adverse effects	Long-term outcome
			Pre-CSIT			On CSIT							
			Max	Min	CoV (%)	Max	Min	CoV (%)					
1	5	No change	390	340	5.1	400	350	4.4	1 in 2 months	No change	Symptoms improved in first week only. No prolonged benefit	Tremor. Irritation and infection at injection sites	CSIT stopped after 2 months. Failed trials of cyclosporin and IVIG. Subsequently well-controlled on intramuscular triamcinolone
2	10	108	No data			No data			1 in first 12 months	Prednisolone stopped after 3 months	Improvement in symptoms Increased school attendance. Able to play soccer	Transient tremor Discomfort and bruising at injection sites	CSIT continued for 3 years. Off regular prednisolone
3	5	73	No data			No data			1 in 2 months	Prednisolone increased to 20 mg/day	Some improvement in symptoms for 2 weeks only. No prolonged benefit	Transient tremor	CSIT stopped after 2 months. Failed a trial of IVIG. Responded well to cyclosporin
4	5	98	220	100	27.6	280	100	24.9	None in 6 months	No change	Initial symptomatic improvement, but no reduction in prednisolone possible	Transient tachycardia Bleeding and infection at injection sites	Commenced on IVIG after 6 months of CSIT, with little success. Continues on regular prednisolone
5	7	No change	290	180	15.6	310	240	8.4	None in first 12 months	Prednisolone stopped after 3 months. Restarted after 2 years of CSIT	Marked improvement in symptoms in first year. Increase in activities. Able to play cricket	Transient tremor. Mild discomfort at injection sites	On CSIT for 2 years (continuing), but back on prednisolone
6	4	114	No data			No data			1 in first 12 months	Prednisolone stopped after 4 months	Improvement in symptoms and activities. Able to play rugby	Mild discomfort at injection sites	CSIT for 2 years (continuing). Remains off regular prednisolone
7	5	No change	No data			390	330	4.7	None in 10 months	IVIG stopped after 4 months. Prednisolone down to 7.5 mg/2.5 mg 90eod[3]	Marked symptomatic improvement. Feel, like ''I can run a mile''	Transient tremor	CSIT for 10 months (continuing). Weaning prednisolone
8	5	76	350	100	32.6	330	200	10.3	None in 11 months	Prednisolone stopped after 4 months	Dramatic improvement in symptoms. Able to ride a bike. Attending school for first time for over a year	Bruising and infection at injection sites	CSIT for 11 months (continuing). Remains off regular prednisolone

[1]Max, maximum; Min, minimum; CoV, coefficient of variation; CSIT, continuous subcutaneous infusion of terbutaline.
[2]Up to and including first 12 months of treatment.
[3]90eod, every other day.

to objective measures, can provide useful information in this context.[14]

Allowing for these weaknesses, this report has two major strengths. First, it provides useful practical information about the use of CSIT in children. Even in the absence of evidence to support its use in children with severe asthma, CSIT has been used in a number of other pediatric centers in the United Kingdom (UK). Collaboration between centers using CSIT is important, as this may allow for sufficient numbers of patients to take part in a controlled trial of this treatment. Until such a trial is underway, centers will require access to practical information regarding the use of CSIT. This report is the first of its kind to provide this information in children.

The second strength of this report is that it documents in a small number of children the profile of adverse effects associated with CSIT. Tremor was common, but transient. More troublesome was the development of bruising and local infection at injection sites. In the light of adult experience with this treatment, patients were not monitored for hypokalemia. Although there were no reported adverse effects to suggest hypokalemia, we cannot state that it did not occur. With this proviso, there were no serious documented adverse events, unlike those described with cyclosporin or methotrexate. We also demonstrated that some children were willing and able to tolerate the treatment, providing they experienced some benefit. This information is important when considering a future controlled trial.

This report does not provide enough evidence to recommend the use of CSIT in children with severe asthma. However, in view of the significant improvement in the clinical condition of some of the children, we feel that further evaluation of CSIT in the management of severe childhood asthma is warranted in the form of a randomized controlled trial[15] or else a series of $n = 1$ trials. Patients would need to undergo a strict protocol of assessment, including bronchoscopy and measurement of markers of airway inflammation, with monitoring of symptoms, bronchodilator use, and PEF, possibly using electronic monitors, before and after starting treatment. Alteration of other therapies would need to be according to agreed criteria. We soon hope to develop a database of children with severe asthma in the UK which should help to identify a sufficient number of patients to allow us to proceed with such a study.

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