

REVIEW

Continuous Infusions of Terbutaline in Asthma – A Review

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Background. After the safety issues raised by the Salmeterol Multicenter Asthma Research Trial, concerns persist about the safety of agents that cause prolonged β -adrenoceptor stimulation in asthmatic patients. We therefore decided to revisit and review the use of continuous subcutaneous infusions of terbutaline (CSIT)—a treatment often reserved for those with severe and refractory disease. **Results.** Original studies from the 1980s included 26 patients and showed that CSIT was well tolerated with predominately cutaneous side effects despite maintaining very high serum levels of terbutaline. CSIT led to improved outcomes in approximately 75% of patients which included rises in lowest daily peak expiratory flow rate (PEFR), diminution in diurnal variation, reduction in other medication requirements, and subjective opinion of symptoms. Almost all patients demonstrating an improvement had a wide variation in their pretreatment PEFrs. However, in a retrospective follow-up of 42 patients, the only outcome to be significantly improved by CSIT was that of mean hospital admissions ($p = .031$). CSIT is theorized to stimulate a discrete set of β -receptors not accessible by the inhaled route as further increases in Forced expiratory volume in one second (FEV₁) occur with concurrent nebulized therapy. **Conclusion.** Although some findings are encouraging, they are drawn from small observational studies done at a time when the standard management of asthma was quite different from today. No randomized controlled trials exist for the use of CSIT, which remains off-license for the treatment of asthma in the United Kingdom. Clearly, prospective well-powered studies are required to fully ascertain its potential benefits and safety profile—something that is unlikely to occur given that the use of CSIT remains low and appears to be declining.

Keywords adrenergic beta-agonists, parenteral therapy, subcutaneous, β -adrenoceptor stimulation, severe

INTRODUCTION—CSIT

The very serious safety concerns raised by the Salmeterol Multicenter Asthma Research Trial (1) and substantiated by Salpeter et al.'s (2) meta-analysis have meant that the use of agents that cause prolonged β -adrenoceptor stimulation in the management of asthma has remained a contentious issue. With this in mind, we decided to revisit and review the use of continuous subcutaneous infusions of terbutaline (CSIT), a treatment often reserved for those with severe and refractory disease and one that guarantees near-constant activation of β -receptors.

Over two-and-a-half decades have passed since the use of CSIT was first reported as being potentially beneficial in the management of difficult-to-treat asthma (3). The latest version of the joint BTS/SIGN national guideline on asthma contains reference to the use of CSIT, but also to the fact that there is limited evidence on its efficacy and safety (4). We undertook a review of the available literature to assess the evidence for CSIT (Medline/EMBASE Databases: search terms included asthma, subcutaneous, infusion, β -agonist, and terbutaline; inclusive dates: 1950–to present) with additional articles identified from the references of searched papers as well as from abstracts of recent international meetings and established guidelines. AstraZeneca (London, United Kingdom), who manufacture terbutaline, was also contacted to provide supplementary data but in no way contributed to this review financially or intellectually.

EVIDENCE FOR CSIT

No randomized controlled trials on the use of CSIT exist, which may in part be due to the very low number of patients on this therapy. The two main studies that provide much of the evidence for the potential benefits of CSIT are here reviewed in more depth. The original paper from 1984 (3) was a crossover pilot study involving four patients all of whom had a diurnal variation in peak expiratory flow rate (PEFR) of $\geq 40\%$. It was blinded such that all patients received both a continuous infusion and four subcutaneous injections throughout the day. In the first admission, they received CSIT with placebo (normal saline) injections; in the second they received the opposite regime; and finally they received placebo in both infusion and injections. One patient showed improvement in PEFR from terbutaline administered either way, another only with CSIT, and no objective improvement was recorded in anyone receiving just placebo. Terbutaline was administered at doses of $14 \mu\text{g/kg/day}$, which is significantly lower than in subsequent studies (see below) and indeed the two patients who did not show any response during the trial period were subsequently shown to have improvements in PEFR, as well as being able to reduce other medications, when treated with CSIT at higher doses (12 mg/day).

Fourteen asthmatic patients received CSIT in O'Driscoll et al.'s (5) follow-up study in 1988. Patients were differentiated into two distinct groups depending on whether they continued to demonstrate evidence of bronchospasm despite treatment with β -agonists, corticosteroids, and methylxanthines. Thus, patients were considered to have brittle asthma ($n = 10$) if

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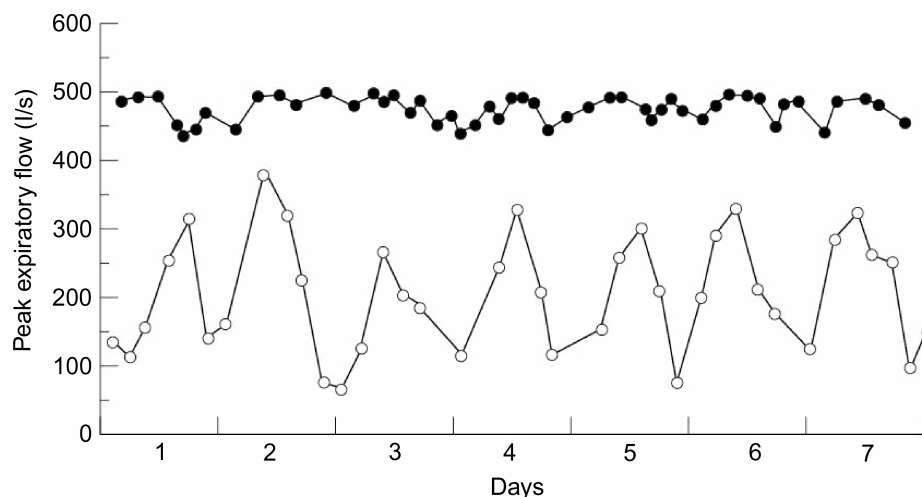


FIGURE 1.—Peak flow chart in a patient with type 1 brittle asthma before (○) and after (●) treatment with continuous subcutaneous terbutaline.

their diurnal PEFR varied by over 50%, on at least 3 days in a week whilst on therapy, and to have chronic disease otherwise ($n = 4$). All patients were admitted to hospital and maintained on their usual therapy to which subcutaneous terbutaline was added. A majority of patients (13/14) initially received a placebo infusion of normal saline, which has alone been reported to induce a positive response very occasionally (6). Mean dose was 10 mg/day (range of 3–12 mg/day) and administration was via a GrasebyTM pump (Smiths Medical Watford, United Kingdom)—the small battery-powered syringe driver that is now commonly used in palliative medicine. Improvements were seen in 80% of the brittle group, which included rises in lowest daily PEFR (mean 142 vs. 297 L/min, $p < .001$), diminution in diurnal variation, reduction in other medication requirements, and subjective opinion of symptoms. The improvement seen in one brittle patient during CSIT therapy is illustrated in Figure 1. Outcomes in the group without large diurnal variation were disappointing, with three out of the four being deemed, on any measure, to have failed to respond. The only individual with chronic asthma who reported a subjective benefit actually had the widest variation in PEFR within that group and just failed to meet the criteria to be included in the brittle group instead. It should be noted that due to the high cost of syringe drivers in the late 1980s, the study included a further eight patients (seven brittle, one chronic) who received subcutaneous terbutaline as injections 4 times a day rather than as a continuous infusion. The results from those receiving a quater die sumendus (QDS) regime were sufficiently similar to the cohort administered CSIT for the study authors to consider the outcomes as a whole in their summary. Although there did not appear to be a significant difference between the routes of administration, the study was not designed or powered to detect one.

Subsequent papers have provided further information on CSIT. A retrospective case note review in 2008 at Heartlands Hospital, Birmingham, the site of much of the earlier work on CSIT, identified a total of 42 patients who had received terbutaline infusions between

1980 and 2008 (7). They included patients who received intermittent as well as continuous infusions and the majority of patients receiving treatment were type 1 brittle asthmatics ($n = 37$, classified as having a diurnal variation $>40\%$ for $>50\%$ of the past 150 days despite high doses of inhaled corticosteroid). Mean duration of CSIT therapy was 86.7 months (range 7–216 months) suggesting that it was well tolerated and used as more than a short-term measure to gain control over difficult-to-treat asthma. Overall, no significant difference could be demonstrated in mean predicted FEV₁, variation in PEFR, or oral corticosteroid maintenance dose during treatment. The only outcome that reached a degree of significance with subcutaneous terbutaline treatment was that of mean hospital admissions, which was decreased by almost half (10.1 ± 13.4 vs. 5.5 ± 10.8 , $p = .031$). The subcutaneous route is a mode of administration of β -agonist especially well suited to very young patients with asthma; Bremont et al.'s (8) study of 11 infants found it particularly useful after the failure of nebulized therapy with no local or general adverse reactions. Subcutaneous β -agonists have also been used in older children where it has improved minimum PEFR and variation, decreased corticosteroid requirements, and caused a subjective improvement in symptoms (this last point, however, was not formally quantified by use of a standardized health questionnaire) (9). Again no controlled trials exist in the pediatric population—data were collected retrospectively from the case notes of just eight patients—half of which had incomplete data sets and only five showed what might be considered a sustained improvement.

OTHER ROLES

It has been suggested that subcutaneous terbutaline may have a wider role beyond maintenance therapy in brittle asthma, specifically in the treatment of acute exacerbations in those not already on CSIT. When terbutaline was given as a bolus, the improvements in FEV₁ achieved parity or exceeded those attained

with adrenaline administered the same way (10, 11). Spiteri et al. (10) envisaged the development of a terbutaline injection prescribed for emergency use on selected brittle asthmatic patients in a pre-hospital setting. Much like an adrenaline autoinjector (e.g., Epi-pen[®] Mylan Inc, Pennsylvania, United States) for patients with severe anaphylaxis, the single use β -agonist could be self-administered or given by a trained carer or relative and perhaps even incorporated into paramedic protocols. Further research into the potential role of such a device is required but encouragingly a subsequent study found that administration by trained healthcare professionals in an out-of-hospital setting was done appropriately and reduced subjective respiratory distress by the time of arrival at hospital (12).

ACTIONS OF CSIT

Bronchodilation resulting from the use of inhaled agents targeting predominantly β_2 -adrenoreceptors is well established, but it has been speculated that CSIT may work by stimulating a separate population of these receptors which are only fully accessible via the systemic route—possibly on smooth muscle and mast cells—Wong et al. (13) have demonstrated such a dichotomy in animals. Lending support to this model is the fact that further improvements in FEV₁ can be demonstrated in patients on CSIT when nebulized therapy is administered, a finding that was unrelated to the type of inhaled β -agonist given (14). Such findings, which support the fact that CSIT targets a discrete set of receptors, would go some way to alleviate fears that a tolerance to constant β_2 stimulation might develop; such concerns have been raised in patients who frequently use high-dose inhaled maintenance therapy (15). Others have anecdotally reported a reduction in symptom control 6–8 weeks into treatment with CSIT (16). The use of “Bricanyl[®] (AstraZeneca, London, United Kingdom) holidays” has been advocated to combat this apparent loss of efficacy with intravenous aminophylline being substituted in during the break off CSIT, a strategy that prevents hospital admissions in this group (16). Certainly, a fall off in apparent effectiveness has been demonstrated in patients receiving regular oral β -agonists (17). Although no head-to-head study exists, the oral route generally compares poorly with subcutaneously administered therapy—despite presumably accessing the same systemic receptors that CSIT targets. CSIT achieves much higher serum concentrations than oral preparations, reported to be up to 20 times greater (18). Despite this fact, it is the oral route which is not well tolerated. Even though CSIT maintains levels of terbutaline in a range comparable to those seen in cases of deliberate oral overdose (19), the side effect profile of CSIT has been predominantly limited to cutaneous reactions local to the infusion site. Skin reactions develop in as many as 50% of patients and range from superficial inflammation and nodules to abscess formation and panniculitis with deep

dermal necrosis. Cutaneous side effects may only become apparent after concurrent steroid therapy is reduced or withdrawn and can be severe enough to warrant discontinuation of CSIT. Unidentified impurities and constituents of the syringe bungs have been implicated in their pathogenesis (20, 21). Systemic side effects have not been shown to be a major issue—none of the 26 patients from the case reports in the 1980s developed hypokalemia, only 2 reported significant tremor, and a subsequent study confirmed that rises in serum creatine kinase levels are attributable to skeletal and not cardiac release (22). Even where the use of CSIT does not allow the reduction or withdrawal of other asthma treatments (see above) it does not significantly interfere with the pharmacokinetics of concurrently administered oral theophyllines (23). When used in combination with more modern asthma therapies such as intravenous magnesium sulfate—which appears to potentiate the action of terbutaline—serious adverse effects are still unlikely (24). Other reported side effects have included muscle cramps and menorrhagia (5). Subcutaneous terbutaline has been used safely for many years as a tocolytic, with obstetricians often prescribing much higher doses than that used in asthma—albeit for much shorter periods of time. In the pediatric population studied, CSIT administration seemed to be well tolerated with a similar adverse effects profile to that commonly seen in adults, mainly limited to injection site problems and tremor (8).

As mentioned previously, positive responses have been very occasionally noted during the run-in periods of studies, prior to terbutaline commencing, whilst only saline was being administered subcutaneously. What element of any benefits attributed to CSIT may in fact be placebo in nature is difficult to estimate without blinded randomized controlled trials. The psychological impact of CSIT has also not been studied, although it has been shown to be significant in similarly delivered treatments for other chronic conditions, such as insulin pumps in diabetes (25), where it has been shown that a patient's attitude toward the driver influenced underlying glycemic control.

SUMMARY

No unequivocal benefit can be demonstrated for the use of CSIT from such small studies. The use of terbutaline as a subcutaneous infusion for the management of asthma remains off-license in the United Kingdom. The available data would seem to support the theory that those most likely to benefit from CSIT have large variations in their peak flow throughout the day, what Ayres et al. termed type 1 brittle asthma (26) and where other therapies have failed to provide adequate symptomatic control.

The evidence reviewed suggests that the treatment is acceptable to the majority of patients and delivers consistently high serum levels by circumventing issues with absorption and first-pass metabolism. CSIT has a side effect profile mainly limited to cutaneous problems local to the site of infusion, and no life-threatening side effects could be attributed to CSIT. However,

concerns surrounding the apparent loss of exacerbation awareness during CSIT therapy (6) need addressing—as there is widespread speculation that this phenomenon is responsible for the increased morbidity and mortality seen with inhaled long-acting β -agonists (2).

It should also be borne in mind that the majority of data collected comes from a time when the standard management of asthma was quite different from that used today. What impact the use of newer therapies such as regular inhaled long-acting β -agonists, which none of the patients from the original studies took in any form, might have on the efficacy of CSIT is unclear. However, it seems likely that CSIT achieves at least part of its effect by accessing a discrete population of β -receptors to that of the inhaled route and therefore further benefit might reasonably be expected even in those on long-acting β -agonist inhalers. Other modern asthma concepts such as phenotyping patients have also not been addressed in the context of CSIT. It might be useful for future studies to clarify exactly which, if any, group of asthmatics is most likely to benefit from parental therapy. Further investigations with well-powered prospective randomized controlled trials are required—something that is likely to prove very difficult with so few patients receiving the treatment. From our own survey (unpublished data), it would seem that the use of CSIT remains low and seems to be declining.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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