Continuous Intravenous Terbutaline in a Brittle Asthmatic

Thomas Hartnett & Nicola Bond
Pharmacy Department, Royal Perth Hospital, Western Australia

Background:

Brittle asthma affects an estimated 10,000 Australians and is notoriously difficult to manage, with patients requiring medical management beyond that of standard asthma. Continuous subcutaneous terbutaline is a last-line option for some treatment-refractory patients however therapy is often complicated by the development of subcutaneous tissue necrosis, abscesses and nodules. These adverse events can limit treatment effectiveness, and may necessitate the transition to intravenous therapy. There is limited evidence guiding transition from subcutaneous to intravenous terbutaline.

Case Description:

A 74-year-old Caucasian male with non-allergic, late-onset asthma, on a background of COPD, ischaemic heart disease and hypertension presented to our respiratory clinic. After failing maximal standard asthma management ten years ago, he commenced continuous subcutaneous terbutaline resulting in a significant reduction in asthma-related hospital admissions. His maintenance dose prior to admission was 2000microg/day with 100-200microg subcutaneous bolus doses when required. He was admitted to our tertiary hospital with significant subcutaneous tissue breakdown following long-term use of subcutaneous terbutaline, requiring transition to intravenous therapy.

Clinical Considerations:

Is there evidence for continuous IV terbutaline in the literature?

1. Continuous infusions used by the Severe Asthma Unit at Birmingham Heartlands Hospital since the 1980s.
   - Mean starting dose across routes 9.5mg per day, mean maintenance dose 11.3mg.
   - Reduced hospital admissions and oral corticosteroid dose.
   - No significant improvement in FEV1.
2. Continuous IV infusions used as an effective tocolytic for up to 8 weeks, maximum rate of 100microg/hr.

› There is evidence to support the appropriate use of continuous IV terbutaline.

Is there any guidance for transitioning from a subcutaneous to an intravenous infusion?

1. When used for tocolysis - maximum subcutaneous infusion rate 100microg/hr, intravenous infusion rate 50-100microg/hr.
2. Mean terminal half-life following a subcutaneous dose = 5.7 hours. Mono-exponential elimination for up to 80 hours post dose.

› Subcutaneous tissue breakdown makes determining current subcutaneous pharmacokinetics difficult. Commence IV infusion at 50% of subcutaneous dose; closely monitor for 28 hours (five times the standard half-life), remain in hospital for duration of subcutaneous dose elimination.

What needs to be monitored during the transition?

1. Efficacy parameters - peak expiratory flow, oximetry, respiratory rate, breakthrough bronchodilator requirements.
2. Adverse effect parameters - heart rate, blood pressure, blood sugar levels, serum potassium, tremor, anxiety.
3. Line-related issues - patency, line site condition, inflammatory markers/temperature.

› Admit with continuous cardiac monitoring for 28 hours after infusion changeover, transfer to respiratory failure unit for remainder of admission.

What are the long term complications of IV administration?

1. Tachyphylaxis - potential development of tolerance with continuous infusions.
2. Line related events –incidence of infection (43%), thrombosis (17%), line blockage (13%).
3. Skeletal myositis – lower rates compared to subcutaneous administration.
4. Psychological effects - anxiety, depression, isolation due to infusion bag changes and requirement of close proximity to a hospital in an emergency.

› Ongoing monitoring by community Silver Chain, Palliative Care Services and Respiratory Physician.

Manufacturing Considerations:

Is there information on terbutaline stability?

1. Information on 3 different concentrations was found in the literature.
   - 100 microg/mL – 23 days at room temperature in normal saline.
   - 30 microg/mL – 7 days at room temperature in normal saline or glucose 5%.
   - 4 microg/mL – 7 days at room temperature in glucose 5%.

What are the tolerances for the continuous infusion pump?

1. Capacity: The CADD®- Legacy pump can accommodate reservoirs as large as 250mL.
2. Flow rate: The CADD®- Legacy pump can accommodate flow rates as low as 0.1mL/hour.

What are the tolerances of the central line?

1. Anecdotal evidence from the manufacturer of the 9mm mini Hickman line suggests that flow rates of 1-2mL/hour are sufficient to maintain line patency.

Manufacturing Decision Matrix

Concentration	Preparation on Stability	Potential Product	Infusion Rate (mL/hour)	Suitable for CADD® Pump?	Suitable for Central Line?	Practical for Patient and Pharmacy?	Product suitable for manufacture?
100microg/mL	23 days	25mg in 250mL	0.42	Yes	No	Yes	No
4microg/mL	7 days	1mg in 250mL	10.45	Yes	Yes	No	No
30 microg/mL	7 days	7.5mg in 250mL	1.38	Yes	Yes	Yes	Yes

Implementation and Progress:

DAY 1

› Mini Hickman line inserted.
› Subcutaneous infusion still running (83microg/hour).
› Nil reliever medication required.
› Afebrile.

DAY 2

› Intravenous terbutaline (41.6microg/hour) started 0937 hours.
› Subcutaneous terbutaline (83microg/hour) ceased 1044 hours.
› Respiratory function stable; O2 saturation >94% on room air, nil reliever medication required.
› Afebrile.

DAY 3

› Respiratory function stable, nil reliever medication required.
› Afebrile.
› Anxiety regarding daily living and community crisis management.

DAY 4

› 3000microg/100ml CADD® cassette connected and infusion commenced at 1.4ml/hour.
› Palliative care met with family to discuss emergency plans and support services.
› Nil reliever medication required.
› Afebrile.

DAY 5

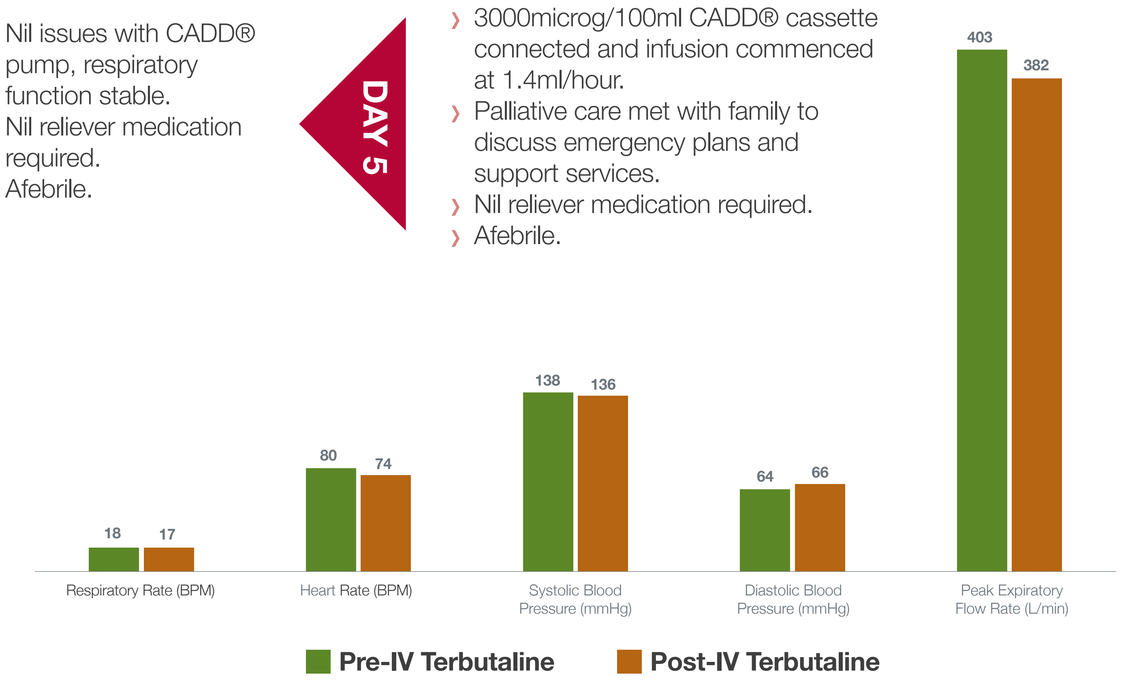
› Nil issues with CADD® pump, respiratory function stable.
› Nil reliever medication required.
› Afebrile.

DAY 6

› Nil issues with CADD® pump, respiratory function stable.
› Nil reliever medication required.
› Afebrile.

DAY 7

› 7500microg in 250ml CADD® cassette connected for discharge.
› Terbutaline 500microg ampoules supplied for oral emergency doses.
› Clinical alert in patient's file with emergency management plan.
› Medic Alert and Ambulance alerts in place.
› Silver Chain visiting twice weekly for CADD® change.
› Palliative care support in community.



Conclusions:

Initial conversion from the subcutaneous to intravenous route was effective and well tolerated. Continuous intravenous terbutaline may offer an alternative option for patients suffering from Brittle Asthma who are unable to tolerate subcutaneous therapy. Dose, infusion stability and psychosocial support are of primary importance in case management.

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