mAGiC DRAGONS:
A Protocol for Accurate Glycaemic Control in General Wards

Felicity Thomas,* Hamish Tomlinson,* Angus Waston,* Hamish Borowczyk,* Christopher Pretty,* Liam Fisk,* Jennifer Dickson,* Yeong Shiong Chiew,* Geoffrey Shaw,** J. Geoffrey Chase*

* Department of Mechanical Engineering, University of Canterbury, Christchurch, New Zealand (e-mail: chris.pretty@canterbury.ac.nz).
** Department of Intensive Care, Christchurch Hospital, Christchurch, New Zealand

Abstract: Accurate glycaemic control (AGC) has been shown to be beneficial to the outcomes of critically ill patients. These benefits may also extend to patients in less acute wards, particularly those with existing diabetes. However, the clinical demands of an intensive care glycaemic control protocol are not appropriate for the general wards where the nurse-to-patient ratio is much lower and patients do not typically have an intravenous line available for insulin delivery. Thus, there is a need for a safe, effective glycemic control protocol tailored to the needs of general wards to enable appropriate care for diabetic patients and further testing of the benefits of glycaemic control for this cohort. This paper presents the development and testing of such a protocol for glycaemic control in the general wards.

The DRAGONS protocol (Dynamic Regulation for Accurate Glycaemic-control Optimising iNsulin Subcutaneously) was designed to use subcutaneous insulin and only require blood glucose (BG) measurements every four hours, while maintaining BG concentrations within the range 4.4-8.0 mmol/L. Virtual trial simulation indicated an expected time in the target band of 73.0%, with < 2% risk of BG < 4.0 mmol/L. In the first patient recruited to the pilot trial, the DRAGONS protocol achieved 46% time in band and no severe hypoglycaemic episodes. This trial has also highlighted the need for careful selection of the insulin injection site to prevent excessively rapid transport to plasma.

1. INTRODUCTION

Stress-induced hyperglycaemia is prevalent in critical care, and can occur in patients with no history of diabetes (Capes et al., 2000, van den Berghe et al., 2001, Mizock, 2001, McCowen et al., 2001). Hyperglycaemia worsens outcomes leading to further risk of complication, including sepsis (Bistrian, 2001), myocardial infarction (Capes et al., 2000), polyneuropathy, and multiple organ failure (van den Berghe et al., 2001). Adaptive model-based protocols for accurate glycaemic control (AGC) that modulate insulin and nutrition have shown considerable promise in the intensive care unit (ICU) (Chase et al., 2008b, Chase et al., 2005, Evans et al., 2012, Hovorka et al., 2007, Kulnik et al., 2008), but are not suitable for less acute wards as they can be relatively demanding on clinical staff.

ICU glycaemic control protocols typically rely on intravenous (IV) insulin and require blood glucose measurements every 1-4 hours. This clinical workload, and the need for an indwelling IV line, are generally not feasible in less acute wards. Therefore, to extend safe, effective glycaemic control to the general wards, a simple model-based approach using subcutaneous (SC) insulin delivery and less frequent BG measurement is necessary. However, these changes increase the risk due to variability of the patient and SC insulin appearance. Finally, in addition to safety and efficacy, the protocol must be quick and easy for staff to use.

This paper describes the development and first pilot trial of a simple, table-based protocol for safe and predictable regulation of glucose levels in the general wards. The DRAGONS protocol (Dynamic Regulation for Accurate Glycaemic-control Optimising iNsulin Subcutaneously) was designed to maintain BG concentrations within the range 4.4-8.0 mmol/L. This protocol was developed by adding a detailed model of subcutaneous insulin kinetics (Fisk et al., 2014) to a separate, glucose-insulin system model (Lin et al., 2011) and performing clinically validated virtual trial simulations (Chase et al., 2010). Finally, the results of the first patient recruited to an on-going pilot trial of the protocol are presented as proof-of-concept.

2. PATIENTS & METHODS

2.1 Virtual trials

The DRAGONS protocol was developed and tested using the validated virtual trial approach (Chase et al., 2010). This approach uses virtual patients, each comprising an insulin sensitivity (SI) profile identified from the clinical data of a real patient using a pharmacokinetic-pharmacodynamic (PK-PD) model of the glucose-insulin system. The SI profile can then be used with the PK-PD model to simulate the glycaemic outcome of different insulin and nutrition interventions.
For this study, the clinically validated Intensive Control Insulin-Nutrition-Glucose (ICING) model of the glucose-insulin system was used (Lin et al., 2011). For forward simulation using monomeric SC insulin (e.g. Actrapid, Novo Nordisk, Denmark), an additional kinetics sub-model was added, modelling transport from the SC layer to the plasma (Fisk et al., 2014).

2.2 Patients

Virtual trials were performed using retrospective data from 63 patients treated by accurate glycaemic control protocols at Christchurch Hospital ICU between 2005 and 2013. Four of the patients were treated exclusively with subcutaneous insulin as part of an on-going trial, 30 patients had been treated by the SPRINT table-based protocol (Specialized Relative Insulin and Nutrition Tables) (Chase et al., 2008b) and the remaining 29 patients were treated with the tablet-based STAR protocol (Stochastic TARGETed) (Evans et al., 2012). Cohort demographics are presented in Table 1.

Table 1. Cohort demographics of the patients used for virtual trial development of the DRAGONS protocol. Data are presented as median [interquartile range] where appropriate.

<table>
<thead>
<tr>
<th>N</th>
<th>63</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>56 [40-70]</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>42/21</td>
</tr>
<tr>
<td>Length of glycaemic control (hrs)</td>
<td>103 [39-158]</td>
</tr>
</tbody>
</table>

The DRAGONS protocol is designed for use in the general wards. However, development was conducted on data from the ICU, as this more controlled environment ensured regular BG measurements and recording of relevant clinical data, enabling reliable virtual patients to be generated. The 63 patients used for virtual trials in this study were specifically selected from a larger cohort of >400 patients as their SI profiles were less variable than that of a typical ICU patient and thus expected to be more representative of patients in general wards.

To provide a benchmark in developing the protocol, results from these trials were compared to the patients’ clinical data and virtual trials using the SPRINT protocol. The SPRINT protocol was a successful table-based, model-derived glycaemic control protocol used in the Christchurch Hospital ICU between August 2005 and November 2011 (Chase et al., 2008b). When comparing these virtual trials, BG results were sampled at 60 min intervals from a linear interpolation between measurements. This resampling enables fair comparison between protocols with different measurement intervals.

2.3 Protocol development

The main requirements for the DRAGONS protocol were low risk of hypoglycaemia and low clinical workload with acceptable time in the target glycaemic band. In consultation with clinical staff from Christchurch Hospital, the specific requirements were determined to be:

- SC insulin dosing
- 4-hourly BG measurement interval
- 4.4-8.0 mmol/L target glycaemic band
- Risk of hypoglycaemia (BG < 4.0 mmol/L) < 5%.

With general wards as the target environment for the DRAGONS protocol, a paper-based implementation is preferable to computerised. Patients in Christchurch hospital general wards do not have bedside computers, so a computerised protocol would require some form of hardware, probably tablets, which would be expensive especially as tablets in the less acute, larger wards could easily be lost, damaged, or stolen. Following in the footsteps of the successful SPRINT protocol, a wheel-based format was selected for simplicity and ergonomics (Chase et al., 2008a). Two independent wheels are used to determine insulin and nutrition doses for the forthcoming period.

2.4 Clinical pilot trials

Following the development of the DRAGONS protocol with virtual patients, a clinical pilot trial was planned. This pilot trial is currently being conducted in the Christchurch Hospital ICU, where the more regulated clinical environment allows the performance and safety of the protocol to be properly evaluated prior to testing in the general wards. Approval for this trial was granted by the Upper South A Regional Ethics Committee (ref: URA/12/06/018).

Each DRAGONS pilot trial is 12 hours in duration, requiring three SC insulin doses (Actrapid, Novo Nordisk, Denmark) four hours apart. During the trial, BG measurements were recorded every 30 mins to fully capture the glycaemic trajectory for subsequent evaluation and to ensure patient safety. Plasma insulin concentrations were also measured every 30 mins for the first two hours following an insulin bolus and every 60 mins for the remainder of the trial. BG concentrations were assayed with a clinical blood gas analyser (Radiometer ABL90 Flex, Copenhagen, Denmark), while insulin concentrations were determined by the central laboratory using immunometric assay (Elecsys 2010, Roche Diagnostics, Germany).

3. RESULTS & DISCUSSION

The DRAGONS protocol was iteratively refined using virtual trials until an acceptable trade-off was reached between time in the target band and risk of hypoglycaemia. The inputs to the protocol were limited to ensure ease of use for clinical staff. The finalised protocol requires four pieces of input data:

- Current BG concentration
- Change in BG since the last measurement (ABG)
- Previous SC insulin dose
- Previous nutrition rate

These data are used with the wheels to determine the insulin dose and nutrition rate for the next 4-hour period. Like
SPRINT, the two wheels are essentially independent. The insulin wheel uses the current BG, \( \Delta BG \), and previous insulin dose to select the new insulin dose. Similarly, the nutrition wheel uses the current nutrition rate and \( \Delta BG \). The wheels are presented in Figure A1 of the Appendix.

3.1 Virtual trial performance

During virtual trials, the DRAGONS protocol achieved a median BG of 6.9 mmol/L with 73.0\% time in the desired 4.4-8.0 mmol/L target band. The median SC insulin dose was 5.0 U/hr (20 U SC bolus every 4 hours) and the median nutrition rate was 80\% of patient specific goal feed, based on the ACCP guidelines of 25 kcal/kg per day (Cerra et al., 1997) with approximately 35\% from glucose. More importantly, there were no hypoglycaemic measurements below 2.2 mmol/L and <2\% below 4.0 mmol/L. Table 2 summarises the performance of DRAGONS and for comparison, also shows clinical data and results from virtual trials of the same patients with the SPRINT protocol.

Table 2 illustrates the compromise in target-band performance that was necessary with DRAGONS to meet safety and workload requirements. Compared with SPRINT and STAR, time in the 4.4-8.0 mmol/L band was reduced by approximately 15\%. However, the average measurement interval increased by \( \geq 200\% \) and the use of SC insulin removes the need for an invasive IV line. Importantly, the DRAGONS protocol is one of the safest protocols with the least time below 4.0 mmol/L (142/4170 virtual measurements) while having the longest measurement interval.

<table>
<thead>
<tr>
<th></th>
<th>DRAGONS</th>
<th>SPRINT</th>
<th>Clinical</th>
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<tbody>
<tr>
<td>N</td>
<td>63</td>
<td>63</td>
<td>63</td>
</tr>
<tr>
<td>BG meas/day</td>
<td>6.4</td>
<td>14.6</td>
<td>14.5</td>
</tr>
<tr>
<td>BG (mmol/L)</td>
<td>6.9 [6.0-7.9]</td>
<td>5.6 [4.9-6.5]</td>
<td>5.6 [4.9-6.4]</td>
</tr>
<tr>
<td>% time in 4.4-8.0 mmol/L</td>
<td>73.0</td>
<td>85.6</td>
<td>88.5</td>
</tr>
<tr>
<td>% time &lt; 4.0 mmol/L</td>
<td>1.6</td>
<td>4.4</td>
<td>2.4</td>
</tr>
<tr>
<td>% time &lt; 2.2 mmol/L</td>
<td>0</td>
<td>0.1</td>
<td>0</td>
</tr>
<tr>
<td>Insulin administration (U/hr)</td>
<td>5.0 [4.0-5.5]</td>
<td>3.0 [2.0-3.0]</td>
<td>3.0 [1.0-4.0]</td>
</tr>
<tr>
<td>Glucose administration (g/hr)</td>
<td>5.4 [4.3-6.5]</td>
<td>5.2 [3.8-6.3]</td>
<td>5.4 [3.8-6.5]</td>
</tr>
</tbody>
</table>

Fig 1. Measured patient data from the first DRAGONS trial patient. The top panel shows the glucose profile with half hourly measurements, and the target band coloured green. The bottom panel shows the measured plasma insulin profile. Subcutaneous insulin interventions were given at t = 0, 240 and 480 mins.
The noticeably higher insulin and lower glucose rate of DRAGONS compared with the other protocols is a result of SC insulin kinetics. Several clearance pathways remove a significant and variable proportion of SC insulin before it appears in plasma (Wong et al., 2008), necessitating larger doses than IV bolus insulin for a similar effect. The SPRINT and STAR protocols exclusively used IV insulin, resulting in the overall differences observed in Table 2. Additionally, the reduced and variable effect of SC insulin, coupled with the long measurement interval required the DRAGONS protocol reduce glucose administration to control BG concentrations, rather than risk larger insulin doses. With long measurement intervals and patient variability, reducing the insulin administration reduces the risk that an unexpected change in patient insulin sensitivity will cause a hypoglycaemic episode.

3.2 Clinical pilot trials

At the time of writing, only one patient had been recruited to the DRAGONS pilot trial. The results from this patient are presented to illustrate the performance of the protocol. Prior to commencing the trial, the patient’s glycaemia had been managed by the STAR protocol using IV insulin. The patient was a 57 year old female.

BG and insulin concentrations measured during the trial are shown in Figure 1. The patient received three SC insulin doses of 10 U, 14 U and 18 U at t = 0, 240 and 480 mins, respectively. The patient was also receiving enteral nutrition with the glucose component administered at a rate of 4.9 g/hr for 0-240 mins, and 6.3 g/hr for 240-720 mins. It is interesting to note that following the bolus at 240 mins, BG continued to rise for 60 mins before starting to fall. This is likely the combined result of the slow release of SC insulin to plasma and an increase in enteral glucose rate. The nutrition rate was increased by ~30% at the discretion of the clinical staff, in contradiction to the recommendation of the protocol, which would have maintained the previous rate of 4.9 g/hr.

This apparent unresponsiveness in BG to the previous insulin dose resulted in the protocol recommending a larger bolus at 480 mins. It should be reiterated that although BG concentrations were measured every 30 mins for analysis, the protocol only had access to the measurements at t = 0, 240 and 480 mins. Thus, the protocol saw little change in BG between 240 mins and 480 mins following a 14 U bolus, and with BG above the target band, recommended an 18 U bolus. This bolus of insulin resulted in BG falling to 3.3 mmol/L before clinical staff intervened with an IV dextrose bolus at t = 660 mins.

Just prior to the insulin bolus at 480 mins, the patient was turned and the insulin was delivered to an area that had been under pressure. This factor may explain the more rapid appearance of insulin in plasma (Fig 1, bottom panel) and the associated reduction in BG following this injection, as reduced oedema at the injection site would result in increased concentration and consequently, faster transport kinetics.

Despite this low BG event, the protocol performed well and no severe hypoglycaemic events occurred. However, this trial highlighted an important aspect of patient management that must be taken into account in future trials. Care must be taken in selecting the SC insulin injection site, so as not to cause too rapid transport to plasma.

REFERENCES


APPENDIX: The DRAGONS protocol.

Fig A1. The DRAGONS protocol wheels. The top panels show the insulin wheel with (right) and without (left) the rotatable selection disk. Similarly, the bottom panels show the nutrition wheel. Goal feed is related to the ACCP guidelines of 25 kcal/kg per day.