

The Influence of Insulin Therapy on the Course of Acute Exacerbation of Bronchial Asthma

K. Wytrychowski, A. Obojski, and A. Hans-Wytrychowska

Abstract

Large doses of systemic corticosteroids are the basis of treatment of acute exacerbation of bronchial asthma. The hyperglycemic activity of systemic corticosteroids often leads to the loss of control of diabetes diagnosed earlier or to its first diagnosis during treatment of the exacerbation of asthma. We conducted a prospective, randomized study in a group of 24 adult patients treated for asthma exacerbation, with the blood glucose level at admission above 8.4 mmol/l. The patients were randomly divided into a group treated with intravenous insulin infusion by an electric syringe pump in doses controlling glycemia at 4.5–7.2 mmol/l (Group A) and a group of patients treated with insulin administered subcutaneously in three doses controlling glycemia at 7.2–10.0 mmol/l (Group B). A control group (Group C) consisted of patients without any disturbances in carbohydrate metabolism, treated for exacerbation of asthma. Asthma exacerbation was treated in all groups in a uniform way. We found that the average hospitalization time was 8.2 ± 2.4 days in Group A, 10.2 ± 5.2 days in Group B, and 5.8 ± 1.9 days in Group C; the last being significantly shorter than those in Groups A and B. We conclude that hyperglycemia is a significant factor increasing the risk of extending hospitalization time due to asthma exacerbation, regardless of the way of insulin therapy.

Keywords

Bronchial asthma • Diabetes mellitus • Exacerbation • Insulin therapy

K. Wytrychowski (✉) and A. Obojski
Department of Internal Medicine, Gerontology and
Allergology, Wrocław Medical University,
66 Skłodowskiej-Curie St., 50-369 Wrocław, Poland
e-mail: anhw@op.pl

A. Hans-Wytrychowska
Department of Family Medicine, Wrocław Medical
University, Wrocław, Poland

1 Introduction

Systemic corticosteroids are the strongest anti-inflammatory drugs. Apart from short-acting β_2 -agonists they are the basic group of drugs applied in exacerbation of bronchial asthma. Serious

shortness of breath, stress and respiratory failure stimulate the secretion of adrenaline, cortisol, growth hormone and glucagon, hormones that operate opposite to insulin. This is the reason of frequent loss of control of early diagnosed diabetes or its diagnosis during treatment of exacerbation of asthma. Insulin affects the tissue metabolism by controlling glycemia, decreasing the concentration of lactates and non-esterified fatty acids in the serum and inhibiting gluconeogenesis. Additionally, insulin exerts numerous non-metabolic actions such as inhibiting the synthesis of free oxygen radicals, nuclear factor κ B, plasminogen activator inhibitor type 1, and the regulation of gene transcription of pro-inflammatory cytokines. Maintaining the proper concentration of insulin also affects the operation of immune system, which particularly concerns the activity of macrophages and neutrophils (Jackson et al. 1999; Dandona et al. 2001). A study by van den Berghe et al. (2001) conducted in a group of 1548 critically ill patients has shown that maintaining glycemia at 4.4–6.1 mmol/l increases the survival rate two-fold compared with patients in whom glycemia was controlled at 10.0–12.1 mmol/l. Most of the patients in that study were after cardio-surgical operations, some had respiratory system diseases, but bronchial asthma was not singled out as a separate disease entity studied.

The aim of the present study was to assess the effect of hyperglycemia on the course of asthma exacerbation. We hypothesized that intensive intravenous insulin therapy in hyperglycemic patients hospitalized due to asthma exacerbation to control the blood glucose at a low level of 4.5–7.2 mmol/l would result in a quicker recovery in terms of hospitalization duration compared with patients in whom hyperglycemia was treated with less effective subcutaneous insulin resulting in the blood glucose level of 7.2–10.0 mmol/l.

2 Methods

2.1 Patients, Clinical Procedures, and Treatment

The study was conducted at the Department of Internal Diseases, Geriatrics and Allergology of

Medical University of Wrocław, Poland, and was accepted by a local Ethics Committee. Out of a total number of 88 patients admitted to the hospital due to acute asthma exacerbation over a 2-year period, 24 patients met the inclusion criteria which were the following:

- history: intensification of shortness of breath and cough which continued despite treatment with β_2 -agonists and oral corticosteroids;
- physical examination: wheezing, frequency of breath above 30/min, pulse rate above 100 beats/min;
- additional tests: hypoxemia (partial pressure of oxygen – $P_{\text{cO}_2} < 70$ mmHg with no oxygen therapy) in arterialized capillary blood, peak expiratory flow (PEF) < 50 % of predicted or forced expiratory volume in one second – $FEV_1 < 50$ % of predicted.
- glycemia > 8.4 mmol/l, irrespective of the presence or no of an earlier diagnosis of diabetes.

Before hospitalization, all patients were chronically treated for asthma with short-acting and long-acting β_2 -agonists (SABA and LABA). Two patients in Group A and three patients in Group B had not been using inhaled corticosteroids (ICS); all patients in Group C used ICS. Diabetes type 2 was diagnosed in 4 patients from Group A, two of them were treated with insulin, one with a sulfonylurea derivative, and one with an α -glucosidase inhibitor. In Group B, diabetes type 2 was diagnosed in five patients, two of them were treated with insulin, one with a sulfonylurea derivative, and two patients remained on a diet.

The exacerbation of asthma had the same treatment pattern in all patients: methylprednisone (MP) 2 mg/kg, i.v. q.i.d.; salbutamol in nebulization 2.5 mg every 4 h, ipratropium bromide 250 μ g every 4 h, oxygen supplementation 3 l/min, potassium supplementation to maintain its serum level at 4.0–5.5 mmol/l. Thiazides were withheld from the treatment regimen. The patients with respiratory tract infection received ceftriaxone 1–2 g i.v. daily, further treatment was conducted according to the result of antibiograms.

The patients were randomly divided into the following two groups of insulin therapy:

- Group A – 11 patients – short-acting insulin (Actrapid HM; Novo Nordisk, Bagsvaerd, Denmark) in solution (50 units in 50 ml 0.9 % NaCl) was given intravenously by an electric syringe pump at the dose required to control glycemia at 4.5–7.2 mmol/l. In patients weighing 50–100 kg, insulin infusion began at 1.0 unit/h during the first hour when glycemia was <10.0 mmol/l or 2.0 units/h when glycemia was >10 mmol/l. In patients over 100 kg of weight, insulin infusion was 1.5 and 3.0 units/h, respectively. When glycemia reached 4.5 mmol/l or less, the supply of insulin was stopped and it was resumed when glycemia reverted to over 6.1 mmol/l.
- Group B – 13 patients – short-acting insulin (Actrapid HM) was given subcutaneously before meals in 3 daily doses (morning 30 %, noon 40 %, and evening 30 %), allowed maintaining glycemia at 7.2–10.0 mmol/l. In patients weighing 50–100 kg, the initial daily dose of insulin was established in the following way: glycemia <10.0 mmol/l – daily dose 0.25 unit/kg, glycemia >10.0 mmol/l – daily dose of 0.5 unit/kg. In patients over 100 kg of weight, doses of insulin were 0.4 and 0.7 unit/kg, respectively. Insulin was given three times a day.
- Group C – 64 patients with no hyperglycemia were included in this control group.

The mean age of the patients in Group C (48.3 ± 14.4 years) was significantly lower than that in Group A ($p = 0.01$). Apart from significantly lower blood glucose level in Group C ($p < 0.001$), clinical condition of patients across the three groups was comparable (Table 1).

The following tests were conducted on all patients on the first day of study: complete blood count, chemistry tests, concentration of glycated hemoglobin (HbA1c), C-reactive protein, general urine test, ECG, chest x-ray, and pulmonary function tests. If an infection of the

respiratory tract was suspected, sputum was taken to grow culture.

The blood glucose level was measured every hour over the initial 4 h of treatment. Further measurements were conducted eight times a day: before breakfast (8:00 a.m.), 11:00 a.m., before lunch (1:00 p.m.), 3:00 p.m., before dinner (6:00 p.m.), 8:00 p.m., before night meal (10:00 p.m.), at night (3:00 a.m.). Blood glucose was measured with an Accu-Check glucometer (Roche Diagnostics, Basel, Switzerland) the result was a mean of two repeat measurements. The diet of patients was established at 25 kcal/kg/day, 30 % of which was fats, 40 % carbohydrates, and 30 % protein.

Every morning, each patient was subjected to pulmonary function tests. PEF was measured before nebulizations at 08:00 a.m. and 8:00 p.m., and gasometry of arterialized blood was performed.

If after the first day of treatment there was no need to supply additional doses of MP or nebulization, PEF or FEV_1 were >59 %, and PcO_2 > 70 mmHg, the daily dose of MP was halved and nebulized budesonide was added in a dose of 1 mg μ g b.i.d (Pulmicort, AstraZeneca; London, UK). Nebulized salbutamol and ipratropium bromide continued at initial doses. Thereafter, it was established at daily intervals whether the patient meets the above outlined criteria of MP dose reduction and inclusion of nebulized budesonide. After MP reduction and addition of budesonide, MP dose was further halved when PEF or FEV_1 increase was greater than 10 % compared with the previous day or reached 80 % of predicted value. The i.v. dose of MP was continually reduced in like manner down to 40 mg/day, after which it was replaced with oral prednisone – 20 mg/day. Then, the patient was discharged the day following that when FEF or FEV_1 remained stable or decreased no more than 10 %. In both groups, in patients with prediagnosed diabetes insulin treatment continued uninterrupted. In patients without the diagnosis of diabetes before inclusion into the study the treatment with insulin was withheld when the required daily dose fell below 12 units

Table 1 General characteristics of patients at hospital admission

	Group A (n = 11)	Group B (n = 13)	Group C (n = 64)
Women/men	6/5	7/6	38/26
Age (year)	61.4 ± 11.0	53.7 ± 12.5	48.3 ± 14.4**
BMI (kg/m ²)	30.6 ± 4.2	31.1 ± 7.2	29.6 ± 6.9
Atopy (n)	6	6	36
Asthma duration (year)	17.7 ± 8.9	17.1 ± 9.2	13.7 ± 7.5
Daily dose of prednisolone (mg)	6.25 ± 7.72	7.69 ± 9.04	5.88 ± 6.11
Daily dose of budesonide (mg)	0.68 ± 0.57	0.65 ± 0.51	0.62 ± 0.44
Patients with diabetes (n)	4	5	0
Diabetes duration (year)	5.5 ± 3.4	2.8 ± 1.3	0
FEV ₁ (%pred.)	45.6 ± 12.9 (26–50)	42.5 ± 14.9 (16–48)	41.8 ± 7.2 (24–49)
PcO ₂ (mmHg)	62.2 ± 5.8 (55–69)	61.2 ± 6.2 (51–70)	63.1 ± 6.0 (52–70)
Glycemia (mmol/l)	10.2 ± 1.8 (8.6–13.4)	10.9 ± 3.0 (8.5–18.1)	5.6 ± 0.9 (4.9–8.2)***
HbA1c (%)	6.1 ± 0.6 (5.3–7.0)	6.9 ± 2.1 (3.5–9.1)	–

Data are means ± SD (range). *BMI* body mass index, *FEV₁* forced expired volume in one second, *PcO₂* partial pressure of oxygen in arterialized capillary blood, *HbA_{1c}* concentration of glycated hemoglobin. ***p* < 0.01 vs. Group A; ****p* < 0.001 vs. Group A and B

and three successive measurements of blood glucose were below 5.8 mmol/l.

2.2 Statistical Analysis

The main outcome variable analyzed in the study was the duration of hospitalization of patients with acute asthma exacerbation and hyperglycemia treated with intravenous insulin (Group A) or subcutaneous insulin (Group B) as compared with patients having no disturbance in the blood glucose level (Group C). A single-factor analysis was made using the Kaplan-Meier curves where a chi-squared test or Gehan-Wilcoxon test was applied for comparisons. A multi-factor analysis (combined influence of the kind of treatment, sex, age, and FEV₁) was made using the Cox proportional hazard model where the significance of individual factors was studied with the Wald test. Data were presented as means ± SD or medians. *P* < 0.05 defined the statistical significance of differences.

3 Results

The course of treatment is shown in Table 2. The patients' clinical condition in both groups improved during treatment compared with the

initial condition, which was manifested by increases in FEV₁ and PcO₂. The average daily doses of MP and insulin did not differ in Group A and B. However, the daily dose of MP in Group C was significantly lower than that in Group A or B (*p* < 0.05). Two patients in Group A and 4 patients in Group B required an antibiotic due to respiratory infection. The goal to keep the blood glucose level under the set outpoint was achieved in Group B, where it was, on average, below 11.1 mmol/l, but not in Group A, where it was higher by 0.6 mmol/l than the upper limit of 7.2 mmol/l. Additionally, there were three incidents of hypoglycemia in Group A.

Differences in hospitalization duration among the three groups were studied with the Kaplan-Meier curves. The mean hospitalization durations in Group A, B, and C were 8.2 ± 2.4, 10.2 ± 5.2, and 5.8 ± 1.9 days, respectively (*p* < 0.001; chi-squared test). There was a significant difference between Group A and C as well as Group B and C (*p* < 0.001 for both; the Gehan-Wilcoxon test). No difference was found for hospitalization duration between women and men for all groups combined. The Cox model was used to study the influence of sex, age, coexistence of hyperglycemia (Group A and B), and the level of FEV₁ on hospitalization duration. Only did age (*p* = 0.001) and hyperglycemia in the patients treated with subcutaneous

Table 2 The course of treatment in both groups

	Group A	Group B	Group C
FEV ₁ (%pred.)	60.6 ± 19.5	58.5 ± 25.9	62.2 ± 23.2
Morning PEF (%pred.)	47.9 ± 12.2	45.2 ± 11.7	52.7 ± 16.1
Evening PEF (%pred.)	47.3 ± 12.6	48.0 ± 13.5	56.9 ± 12.4
PcO ₂ (mmHg)	68.0 ± 7.4	66.2 ± 6.2	68.9 ± 5.6
Daily dose of prednisone (mg)	89.3 ± 60.3	80.6 ± 53.4	55.2 ± 36.1*
Blood glucose level (mg/dl)	140.6 ± 40.7	160.5 ± 55.0	–
Daily dose of insulin (unit)	37.9 ± 17.7	37.2 ± 23.6	–
Duration of hospitalization (days)	8.2 ± 2.4	10.2 ± 5.2	5.8 ± 1.9***
No. of hypoglycemic events	3	0	

Data are means ± SD. FEV₁ forced expired volume in one second, PEF peak expired flow, PcO₂ partial pressure of oxygen in arterialized capillary blood. *p < 0.05 vs. Group A or B; ***p < 0.001 vs. Group A or B

Table 3 Analysis of the Cox model

n = 88	Beta	Standard error	Hazard ratio	Wald test	p
Sex	–0.129	0.222	0.878	0.339	0.560
Age	–0.031	0.009	0.969	10.998	0.001 ^a
FEV1	0.015	0.012	1.015	1.509	0.219
Insulin i.v.	–0.539	0.341	0.583	2.488	0.114
Insulin s.c.	–0.944	0.362	0.388	6.817	0.009 ^a

i.v. intravenous, s.c. subcutaneous

^astatistically significant

insulin (Group B) appear of significant relevance (p = 0.01; the Wald test) (Table 3).

The hazard ratio (HR) for the appearance of hyperglycemia in patients treated with subcutaneous insulin (Group B) was 0.38, meaning that the chance of discharging a patient from group B from the hospital is 2.5 times smaller than that for a patient from Group C. The HR for the appearance of hyperglycemia in patients treated with intravenous insulin was 0.58, meaning that the chance of discharging a patient from Group A from the hospital was 1.7 times smaller than that for a patient from Group C. The results indicate that controlling the level of glucose in the blood within the assumed range of 4.5–7.2 mmol/l in patients receiving large doses of systemic corticosteroids during acute exacerbation of asthma is difficult and causes the risk of hypoglycemia, particularly in older patients. The mean dose of systemic corticosteroids used to treat the exacerbation of asthma was significantly lower in the group of patients with no disturbance of the blood glucose level compared with those having hyperglycemia (Table 2).

The FEV₁ increased at discharge from the hospital to 83.1 ± 11.7, 76.8 ± 15.6, and 79.6 ± 17.3 % pred., in Group A, B, and C, respectively; the increases being of the same magnitude in all three groups. The patients were followed for up to 12 weeks after discharge. The beneficial effect of hospital treatment were sustained regarding both lung function and blood glucose level; the latter amounted to 5.7 ± 1.2 and 6.3 ± 1.2 mmol/l in Group A and B, respectively.

4 Discussion

The major finding of this study was that hyperglycemia accompanying systemic corticosteroid treatment and/or newly diagnosed diabetes hampers recovery from acute exacerbation of asthma requiring hospitalization, which causes an extended hospital stay compared with patients who have no disturbance of carbohydrate metabolism. In addition, the way and intensity of insulin treatment in hyperglycemic patients failed to

have an appreciable effect on the course of exacerbation and duration of hospitalization.

In the past, the adverse influence of hyperglycemia on patients in intensive care units was neglected. In life threatening situations in unconscious patients or patients after operations with parenteral nutrition achieving normoglycemia is difficult and there is a risk of hypoglycemia. Controlling blood glucose level with insulin is greatly beneficial in such patients and results in significant reductions in mortality, fewer, hospital-acquired infections, myocardial and cerebral infarct size, and less frequent blood transfusions (Golden et al. 1999; Malmberg et al. 1999; Capes et al. 2000; Stranders et al. 2004). Initial data on a favorable outcome of glycemia control with intravenous insulin have come from the studies on patients after myocardial infarction and cardio-surgical operations (Malmberg 1997; Dantona et al. 2003). Van den Berghe et al. (2001) have shown in a group of 765 intensive care unit patients that keeping the blood glucose level at around 4.5–6.1 mmol/l results in a two-fold decrease in mortality compared with the glucose level of 10.0–11.1 mmol/l. Another study has demonstrated a significant reduction in hospital mortality in patients whose blood glucose level was kept below 8.1 mmol/l, and an increase in mortality when glucose level is hard to control due to up and down shifts, which requires larger doses of insulin (Finney et al. 2003). The authors have also noted that the actual level of blood glucose is greatly influenced by numerous drugs and the patient condition.

Studies regarding hyperglycemia in the exacerbation of asthma are scarce. However, hyperglycemia in this condition is a serious issue, as about half of such patients manifest disturbed carbohydrate metabolism. The predisposing factors include age and chronic use of systemic corticosteroids. The present study included patients with acute exacerbation of asthma and symptoms of severe respiratory impairment, albeit not requiring mechanical ventilation, and with diagnosed diabetes or temporary glucose intolerance. The strategy of

treatment of asthma exacerbation, applied in the study, complied with the international guidelines (GINA 2015). The incidents of hypoglycemia observed in the group treated with intravenous insulin were mild in form and required administration of glucose *per os* and temporary suspension of insulin supply. That is consistent with the observations made by other authors demonstrating a significant advantage of intravenous supply of insulin in acute medical conditions. The more frequent episodes of hypoglycemia occurring with the subcutaneous supply of insulin are apparently not life threatening to patients (Clement et al. 2004). A shorter hospitalization duration in patients with no disturbance in carbohydrate metabolism (Group C) could also be influenced by a significantly lower age of patients in this group compared with the other two groups. Maintaining the blood glucose level in a range of 4.5–7.2 mmol/l in the group of patients treated with intravenous insulin was difficult, especially at the beginning phase of the study when the doses of systemic corticosteroids were high.

We conclude that the control of glycemia in patients with asthma exacerbation is a serious challenge. Frequently, application of large doses of systemic corticosteroids results in the loss of control of diabetes. This control may be restored with intravenous insulin, which acts faster and requires smaller doses than subcutaneous insulin therapy (Kitabchi et al. 2001; Metchick et al. 2002). Nonetheless, a better control of hyperglycemia does not necessarily translate into more effective therapy of asthma exacerbation, which would end up with a shorter duration of hospitalization.

Conflict of Interest The authors declare no conflict of interest in relation to this article.

References

- Capes SE, Hunt D, Malmberg K, Gerstein HC (2000) Stress hyperglycemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. *Lancet* 355:773–778

- Clement S, Braithwaite SS, Magee MF, Ahmann A, Smith EP, Schafer RG, Hirsch IB, American Diabetes Association Diabetes in Hospitals Writing Committee (2004) Management of diabetes and hyperglycemia in hospitals. *Diabetes Care* 27:553–591
- Dantona P, Aljada A, Bandyopadhyay A (2003) The potential therapeutic role of insulin in acute myocardial infarction in patients admitted to intensive care and in those with unspecified hyperglycemia. *Diabetes Care* 26:516–519
- Dandona P, Aljada A, Mohanty P, Ghanim H, Hamouda W, Assian E, Ahmad S (2001) Insulin inhibits intranuclear nuclear factor kappaB and stimulates IkappaB in mononuclear cells in obese subjects: evidence for an anti-inflammatory effect? *J Clin Endocrinol Metab* 86:3257–3265
- Finney SJ, Zekveld C, Elia A, Evans T (2003) Glucose control and mortality in critically ill patients. *JAMA* 290:2041–2047
- GINA Report – Global Strategy for Asthma Management and Prevention (2015) <http://www.ginasthma.org/documents/4>. Updated April 2015. Accessed on 20 May 2015
- Golden SH, Peart-Vigilance C, Kao WH, Brancati FL (1999) Perioperative glycemic control and the risk of infectious complication in cohort of adults with diabetes. *Diabetes Care* 22:1408–1414
- Jackson NC, Carroll PV, Russel-Jones PH, Sönksen PH, Treacher DF, Umpleby AM (1999) The metabolic consequences of critical illness: acute effects on glutamine and protein metabolism. *Am J Physiol* 276:E163–E170
- Kitabchi AE, Umpierrez GE, Murphy MB, Barrett EJ, Kreisberg RA, Malone JI, Wall BM (2001) Hyperglycemic crisis in patients with diabetes mellitus. *Diabetes Care* 24:131–153
- Malmberg K (1997) Prospective randomized study of intensive insulin treatment on long term survival after acute myocardial infarction in patients with diabetes mellitus. DIGAMI Study group. *BMJ* 314:1512–1515
- Malmberg K, Norhammar A, Wedel H, Rydén L (1999) Glycometabolic state at admission: important risk marker of mortality in conventionally treated patients with diabetes mellitus and acute myocardial infarction: long-term results from the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study. *Circulation* 99:2626–2632
- Metchick LN, Petit WA, Inzucchi SE (2002) Inpatient management of diabetes mellitus. *Am J Med* 113:317–323
- Stranders I, Diamant M, van Gelder RE (2004) Admission blood glucose level as risk indicator of death after myocardial infarction in patients with and without diabetes mellitus. *Arch Intern Med* 164:982–988
- Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R (2001) Intensive insulin therapy in critically ill patients. *N Engl J Med* 345:1359–1367