Advantage of adjunct metformin and insulin therapy in the management of glycemia in critically ill patients. Evidence for nonoccurrence of lactic acidosis and needing to parenteral metformin

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Abstract

Introduction: Stress-induced hyperglycemia is associated with insulin resistance in critically ill patients. In order to overcome insulin resistance, clinicians increase insulin dose that could result in hypoglycemia, hypokalemia, hypomagnesemia, and other complications.

Material and methods: This randomized clinical study was conducted among thirty-three traumatized adult patients who were admitted to medical-surgical ICU of a reference University hospital. Patients were randomly assigned to receive one of three protocols including intensive insulin monotherapy (A), metformin monotherapy (B), and intensive insulin therapy in combination with metformin (C) to maintain blood glucose level between 80-120 mg/dl. For pharmacokinetic study of metformin a validated ion pair HPLC method was also applied.

Results: Three protocols A, B, and C successfully reduced admission blood glucose levels from 191±28, 189±35, and 192±28 mg/dl to 122±9, 131±17, and 121±7 mg/dl (mean ± SD), as mean weekly values, respectively. These reductions were significant in protocols A (P=0.02) and B (P=0.003). Protocol C showed 34% reduction in mean weekly insulin requirements as compared with protocol A. Although patients in protocols B and C had some fluctuations in their blood lactate levels, lactic acidosis did not occur in any patient. Pharmacokinetic data showed a deficit in oral absorption of metformin in critically ill patients. No direct relationship was observed between pharmacokinetic and pharmacodynamic profile of metformin during the course of critical illness.

Conclusions: It is concluded that metformin reduces insulin requirements in glycemic management of critically ill patients independent of its plasma concentration. Metformin seems to be effective to reverses insulin resistance without induction of lactic acidosis.

Key words: stress-induced hyperglycemia, insulin resistance, critically ill patients, intensive insulin therapy, insulin sensitizing agents, metformin.

Introduction

Critical illness (CI) is associated with alterations in neuroendocrine and immune systems [1, 2]. Disturbances in immunoneuroendocrine axis lead to subsequent alterations in carbohydrate and lipid metabolisms

provoking systemic inflammatory responses [2, 3]. Stress-induced hyperglycemia occurs due to multiple pathogenic mechanisms and associate with development of adverse events and poor prognostic outcomes in severe illness [4]. Today it is well known that glycemic control and intensive insulin therapy decrease morbidity and mortality rates and improve survival of critically ill patients (CIPs) [5-7]. Although several insulin protocols have been designed and applied in different setting of CIPs [5, 6, 8], they have carried the highest risk of hypoglycemia [9]. Intensive insulin therapy promotes entry of potassium and magnesium from the extra-cellular to the intracellular compartment and possibly leading to hypokalemia and hypomagnesaemia [10, 11]. Reductions in potassium and magnesium levels promote insulin resistance [12-14] and higher blood glucose level (BGL). Thus, administration of more insulin is inevitable that initiates the vicious cycle with adverse outcomes. In this regard, blood levels of potassium and magnesium as well as BGL must be closely monitored during insulin therapy [15].

Insulin sensitizing agents are prescribed widely in outpatients for those individual with insulin resistance such as many of the type 2 diabetics [16]. Metformin as an insulin-sensitizing agent may overcome insulin resistance in CI but it has been suspected for lactic acidosis (LA) [17]. Several studies have demonstrated that metformin, *per se*, does not promote LA and this phenomenon is coincidental with other underlying CIs [18, 19]. Except two trials in small population of the burned patients [20, 21], the efficacy of metformin in glycemic control in CIPs has not been studied.

In the present study, we investigated the effectiveness and safety of metformin in the glycemic control of CI traumatized patients by measuring the blood glucose, lactate and pH values of the patients, in addition to their insulin requirements when insulin coadministered with metformin.

Material and methods

Study population

The study has been reviewed and approved by the Institutional Review Board (IRB). A written informed consent was obtained from the closest patient's relative in the hospital.

All adult multiple traumatized patients who were admitted to the intensive care unit (ICU) and diagnosed with both systemic inflammatory response syndrome (SIRS) and hyperglycemia (Table I) were eligible to be enrolled into study.

Eleven patients were included in each therapeutic arm on the basis of a pilot study. Of 33 patients who were enrolled in the study, 4 were excluded due to severe hemodynamic instabilities or developing the excluding criteria (Table I) during the first 12 hours. Baseline characteristics of the patients are demonstrated in Table II.

Study design

Study was carried out between July 2005 and September 2006 in a randomized open label clinical trial fashion, in the medical-surgical ICU of a University hospital. On admission to ICU, those patients who met the inclusion criteria were randomized to receive one of the following protocols for the period of one week. Protocols included intensive insulin therapy (A), metformin monotherapy (B), and intensive insulin therapy in combination with metformin (C). Protocols were instituted to maintain BGL between 80-120 mg/dl as target level.

In protocol A, insulin was administered through continuous intravenous infusion (50 IU insulin regular in 50 ml of 0.9% sodium chloride). The infusion rate was started according to admission BGL and adjusted to a rational algorithm (Table III). BGL was measured at bed every 2 hours. During infusion of insulin with rate of higher than 5 IU/hour, BGL was measured every hour. Whenever BGL reached below 120 mg/dl, the infusion of insulin was stopped.

In protocol B, patients received 1000 mg of metformin every 12 hours. BGL and arterial blood lactate was measured every 6 hours at bed.

In both protocols B and C, metformin was discontinued if lactate level was more than 4.5 mmol/l, or if increased more than 2 mmol/l form the previous lactate level, or if bicarbonate reached lesser than 13 mEq/l, or if pH reached lesser than 7.3, or if two consecutive serum creatinine levels were higher than 1.2 mg/dl, and if maximum arterial pressure reached lesser than 70 mm Hg during the intervention.

In protocol C, similar to protocol A, infusion of insulin started according to admission BGL. Adjustment of insulin dose was done on BGL fluctuations. In addition, patients received 1000 mg metformin orally every 12 hours. Blood glucose and lactate levels were measured every 2 and 6 hours respectively.

Pharmacokinetic study of metformin

A rapid and specific ion pair HPLC method was designed for determination of plasma metformin concentration. A Knauer HPLC system (Germany) was used consisting a pump (K-1001) and a UV detector (K 2600). The analytical column was Teknokroma Lichrospher 100 CN (5 µm 4.6 × 250 mm). The mobile phase consisted of 30% acetonitrile and 70% sodium lauryl sulfate (SLS) 0.1% aqueous solution. The method was validated for selectivity, accuracy,

Table I. Inclusion and exclusion criteria

Included	Excluded
SIRS manifested by two or more of the following demonstrations [3]: • temperature >38°C or <36°C • heart rate >90 • respiratory rate >20 or $PaCO_2$ <32 mm Hg • WBC count >12 000 or <4000, or >10% immature (band) forms Admission hyperglycemia defined as: admission blood glucose level >120 mg/dl	• abdominal trauma • diabetes mellitus • age >75 or <18 • renal failure (serum creatinine >1.2 mg/dl) • hepatic failure (increased hepatic enzymes levels) • blood lactate level >4 mmol/l • pH <7.3 • bicarbonate <13 mEq/l • MAP <70 mm Hg • diarrhea and vomiting

Table II. Baseline demographic data of the patients in protocols A, B, and C

	A	B	C
Age	41.5±19.5	47.5±14	48.5±14.5
BS	191±28	189±35	192±28
APACHE II	15 (13-20)	15 (10-17)	14 (13-17)
pH	7.41±0.06	7.41±0.04	7.41±0.05
Scr	1.07±0.49	0.64±0.19	0.73±0.14
MAP	91±13	93±8	92±7

Data are presented as mean ± SD except APACHE II score which is median (interquartile range). BS is the blood glucose level at admission time. Acute physiological and chronic health evaluation (APACHE) score, pH, and serum creatinine (Scr), and mean arterial pressure (MAP) have been reported for the first day. No significant difference was found in baseline demographic data of three protocols

Table III. Intensive insulin therapy protocol

Admision blood glucose level [mg/dl]	Insulin infusion rate [IU/hour]
120–140	1
141–160	2
161–180	3
181–200	4
201–220	5
221–240	6

For every 20 mg/dl increase in blood glucose, rate of insulin infusion increased by 1 IU/hour

precision, and calibration curve on the basis of FDA guideline for validation of bioanalytical method [22]. Blood samples were obtained at 7 time points: before administration of the drug, and at 24, 26, 28, 30, 33, 36 hours after the first dose. Patients' blood samples were collected in heparinized glass tubes and centrifuged. Subsequently, separated plasmas were frozen at –20°C until analysis [23, 24].

Calculation of pharmacokinetic parameters of metformin

The pharmacokinetics of metformin was determined by noncompartmental analysis. The maximum plasma concentrations (C_{max}) was recorded as observed. The elimination rate constant (K_e) was estimated as the absolute value of the slope of a least-square linear regression of the terminal phase of the logarithmic plasma concentration-time curve. The plasma elimination half-life ($t_{1/2e}$) was calculated as 0.693/Ke. The area under the plasma concentration-time curves (AUC) from time zero to the infinite time $AUC_{(0\text{-}12)}$ was calculated by trapezoidal rule during the dosing interval. Apparent volume of distribution and total clearance were calculated as

$$Vd/F = \frac{D_o}{Ke.[AUC]}, \quad Cl/F = \frac{D_o}{[AUC]}, \text{ respectively.}$$

Data collection

For calculating acute physiology and chronic health evaluation II (APACHE II) score [25], arterial blood gases, electrolytes, and complete blood counts were determined daily, and blood pressure, heart rate, respiratory rate, body temperature, pulmonary indices, and hemodynamic profiles were checked and recorded every 2 hours and mean daily values were calculated.

Statistical analysis

Daily outcome variables were compared between each pair of groups. Each group was compared with two others by use of independent samples t-test. The normality of distribution of variables was examined with Kolmogrov-Smirnov test. Comparisons between admission values of BGL, blood lactate level and first day APACHE II score and mean values in the course of the study in each group were performed by paired sample t-test. Chi-square test was performed for analysis of mortality. Data are mean ± SD unless otherwise stated. Significant level was defined as $P<0.05$.

Results

Mortality

Four patients in group A, 2 in group B, and 3 in group C died during the intensive care. Difference in the mortality rate of these groups was not statistically significant (P>0.05).

Glycemic control by protocols A, B, and C

By applying of all protocols, the initial BGL decreased. Admission time BGL in protocol A, B, and C were 191±28, 189±35, and 192±28 mg/dl respectively. Following institution of protocols (A, B, and C), these values reduced and mean weekly BGL reached 122±9, 131±17, and 121±7 mg/dl, respectively (Figure 1). No significant difference in the control of glycemia was observed between three protocols. Comparison of initial BGL and mean weekly values showed a significant reduction in group A (P=0.02) and B (P=0.003) but the 36% reduction in admission BGL of group C was not statistically significant (P=0.17).

Insulin requirement

During the course of the study, mean daily insulin requirements of patients in the protocols A and C were 19.5 and 12.7 IU/day. A 34% reduction in mean daily insulin infusion dose was observed in protocol C as compared to protocol A but it was not statistically significant (Figure 2).

Lactate monitoring

Although patients had some fluctuations in their blood lactate levels, there was no severe hyperlactatemia (blood lactate level >5 mmol/l). The admission lactate values were 2.7±0.4 and 2.6±1.2 mmol/l in groups B and C that reached to 2.4±0.5 and 2.3±0.15 mmol/l, respectively. These fluctuations in blood lactate levels were not significant within each groups [P(B)=0.45 and P(C)=0.79] and there was no significant difference between two groups (P=0.66) (Figure 3).

Acid base balance in protocols A, B, and C

No significant difference was observed between mean daily pH values of the patients in protocols A, B, and C. All the calculated comparison P values were >0.9. There was no pH <7.3. pH values had tiny fluctuations in normal range.

Effects of protocols on APACHE II scoring

No significant difference was observed in weekly APACHE II score between the protocols A, B, and C and within the patients (Table IV) but the reduction in basal APACHE II score in group B was significant (P=0.005).

Pharmacokinetic profile

Pharmacokinetic parameters of metformin including C_{max}, K_e, $T_{1/2e}$, $AUC_{(0-12)}$, Vd/F, and Cl/F are shown in Table V. The K_e and $T_{1/2e}$ values were in the range of normal values of healthy or outpatient diabetic subjects. C_{max} and $AUC_{(0-12)}$ levels were lower than normal values. The Vd/F and Cl/F values were higher than normal ranges.

Correlation between pharmacokinetic and clinical parameters

No significant correlation was observed between plasma drug concentration and reduction of blood glucose or blood lactate levels, or blood pH values (Table VI).

Discussion

Major clinical outcomes of the present study

Results of the present study indicate that three protocols successfully reduce initial BGL. Although the present mean plasma metformin level was lesser than its reported therapeutic levels in outpatients (0.5-1 mg/l in the fasting state and 1-2 mg/l after meals) [26], the patients' BGL reduced and their insulin requirements decreased.

Despite a few mild increase in BGL of some patients that might be related to medical interventions or instability of patients in acute and catabolic phase of critical illness, both protocols of A and C reduced BGL to the target points (80-120 mg/dl) during the first 48 hours. Nevertheless, temporal reduction of BGL in group C was not statistically significant possibly due to scarce number of the patients. Comparison of insulin requirements between protocols A and C show a 34% reduction in average daily insulin dose in protocol C; although this reduction was not statistically significant (P=0.21), the insulin requirement reduced in combination with metformin indicating potential of metformin to overcome insulin resistance. Metformin monotherapy controlled hyperglycemia and improved APACHE II that adequately confirm its benefit in CIPs. Nevertheless, it is suggested to conduct such investigations in larger population to reach more extendable and reliable results.

Current insights in glycemic control of CIPs

It has been demonstrated that intensive insulin therapy in the absence of euglycemia has no significant effect on improvement of the patients' outcome [27, 28]. Likewise, it has been strongly suggested that metabolic control as a result of normoglycemia rather than insulin infused dose is related to beneficial effects of intensive insulin therapy. Thus, although insulin itself has plenty of

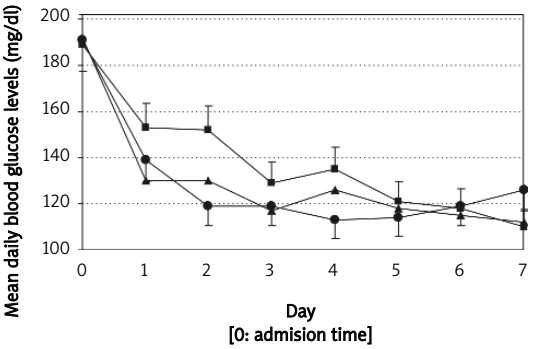

Figure 1. Temporal trend of blood glucose levels in protocols A (●), B (■), and C (▲) during the period of study. Values at the time (0) shows admission time blood glucose level. Data are mean ±SEM

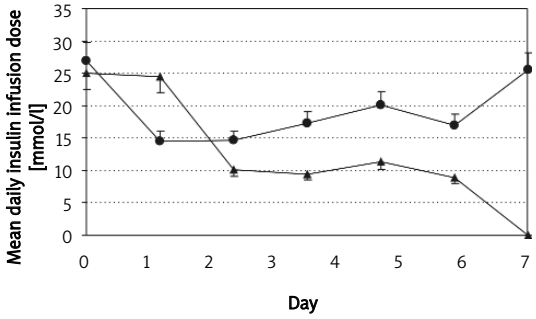

Figure 2. Temporal trend of daily insulin administered dose in protocols A (●) and C (▲). Data are mean ±SEM

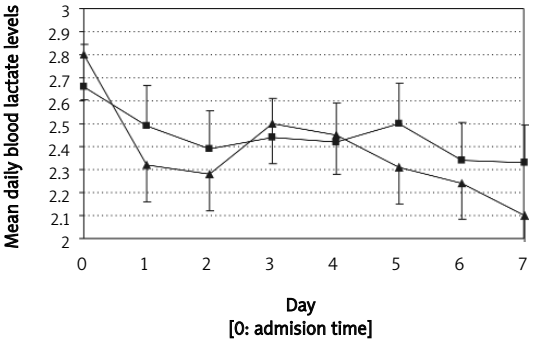

Figure 3. Temporal trend of blood lactate levels in protocols B (■) and C (▲). Values at the time (0) shows admission time blood lactate level. Data are mean ±SEM

Table V. Pharmacokinetic parameters of metformin

Parameter		Mean ± SD
$(K_e)^a$	[1/hour]	0.17±0.06
$(t_{1/2e})^b$	[hour]	4.52±1.81
$(C_{max})^c$	[ng/ml]	970±185
$(AUC)^d$	[ng × hour/ml]	6710±1056
$(CL/F)^e$	[l/hour]	153±28
$(Vd/F)^f$	[l]	1042±570

[a] – elimination rate constant, [b] – plasma elimination half-life, [c] – maximum plasma concentrations, [d] – area under the curve, [e] – apparent total clearance, [f] – apparent volume of distribution

Table IV. APACHE II scores of the patients throughout the first week after admission

Day	APACHE II score					
	protocol A		protocol B		protocol C	
	score	number	score	number	score	number
1	15 (13-20)	10	15 (10-17)	11	14 (13-17)	8
2	15 (10-19)	10	14 (8-17)	11	14 (14-17)	8
3	14 (11-22)	9	15 (9-17)	11	14 (13-17)	8
4	14 (11-22)	7	13 (7-16)	10	15 (12-16)	8
5	15 (11-22)	7	13 (7-14)	9	12 (7-17)	6
6	15 (12-21)	7	12 (5-13)	9	12 (8-17)	6
7	17 (12-24)	5	10 (5-17)	6	14 (13-17)	2

Data are presented as median (interquartile range). No significant difference was found in the temporal trends of APACHE II scores between three protocols (P=0.18). Comparison between the basal and weekly trends of APACHE II scores within each protocol's patients shows a significant difference in protocol B (P=0.005) but the variation was not significant in protocols A (P=0.172) and C (P=0.345)

Table VI. Correlations between AUC and acute physiopharmacologic effects of metformin

	$BG_0 - BG_1$	$BG_1 - BG_2$	$LAC_0 - LAC_1$	$LAC_1 - LAC_2$	pH
r	–0.111	0.239	–0.213	0.206	–0.029
P	0.732	0.454	0.506	0.52	0.928

BG – blood glucose at 0 (admission time), and days 1 and 2 post admission, LAC – blood lactate at 0 (admission time), and days 1 and 2 post admission

beneficial metabolic and non-metabolic effects in CIPs [4, 7, 29, 30], it seems intensive glycemic control has a pivotal role in improvement of outcomes rather than intensive insulin therapy alone [31]. Insulin resistance and inflammatory processes that are characterized by increased proinflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) [32, 33], have crucial roles in the pathogenesis of stress-induced hyperglycemia [4, 34, 35]. Current approach to control this metabolic disorder is intensive insulin therapy that associates with some complications. Insulin is one of the five highest risk medications in the inpatient setting. To avoid insulin adverse effects, tight glycemic control, and monitoring of potassium and magnesium levels is inevitable that accompany with higher nursing workload [15].

The current approach to manage metabolic syndrome and type 2 diabetes mellitus in outpatients with insulin resistance is administration of insulin sensitizing agents like metformin [16]. This medication enhances insulin's actions [36] and has anti inflammatory properties which prevent initiation and progression of inflammatory processes [4, 26, 37, 38]. Thus, regarding the significant role of proinflammatory cytokines and oxidative stress mediators in pathogenesis and prognosis of many chronic and acute diseases [39-43], administration of such medications could be a novel therapeutic approach to prevent and control hyperglycemia in CIPs. However, safety, efficacy, and pharmacokinetic of these medication are the matter of concerns in ICU patients.

Evaluation of key pharmacokinetic indices of metformin in CIPs

Previous studies in healthy volunteers and diabetic outpatients demonstrated that there is a proportional relationship between plasma maximum metformin concentration and administered dose [44]. Our study showed that despite the higher administered dose (1000 mg BD), C_{max} levels were lower than C_{max} levels in other single oral dose studies with lesser dosage size [44], and the AUC is small indicating a defect in the absorption of drug. This defect might back to existence of gastrointestinal (GI) abnormalities such as organ hypoperfusion and hypomotility during CIs [45, 46].

The apparent volume of distribution and total clearance of metformin in the present study were higher than reported values for healthy subjects or diabetic patients [44]. As a matter of fact, fluids shift to interstitium and thus administration of crystalloids or colloids fluids and alteration in plasma proteins could not be suspected. In addition, metformin per se has a large volume of distribution and its protein binding is negligible [44, 47]. Therefore, the most probable reason for these high volumes of distribution and total clearance values is low F value (F is the fraction of drug absorbed) which is mainly related to the considerable GI abnormalities. Potential alterations in oral bioavailability makes the intravenous rout of administration as a generally preference in CIPs [38]. With due attention to low bioavailability of metformin in healthy subjects or outpatients (40 to 60%) [44, 47] and lower bioavailability in CIPs, the intravenous administration should be tried to evaluate exact effects of drug in higher plasma concentration.

Some investigations concluded that circulating metformin concentration correlates with plasma glucose levels in outpatients [44] that is not supported by the present findings since no significant association between AUC and reduction of BGL was observed. The explanation is that pharmacodynamic profile of the drug may differ in CI and some unproven subcellular mechanisms may orchestrate its pharmacologic effects in stressful situations.

Safety of metformin in CIPs

Except nausea and vomiting, other adverse effects of metformin such as vitamin B_{12} deficiency are not matter of concern in CIPs because they do not occur in a short period of time [48]. The present data did not show even GI nausea or vomiting.

Despite the probable differences between the rate and extent of absorption of the drug in different days, no correlation was observed among AUC and intraday degree of difference values of lactate. The present data indicated no correlation between plasma metformin concentration and blood lactate or pH levels. Although hyperlactatemia (>2 mmol/l) was frequently seen in the study patients [median (interquartile range) was 2.4 (2.1-2.7)], metformin did not induce lactic acidosis (>5 mmol/l and pH <7.3).

Lactic acidosis is claimed as a limitation in the use of metformin in CIPs [49, 50] but it is too difficult to differentiate hyperlactatemia as a common sequel of metabolic alterations in severe illness [51] with that of metformin. Some investigations confirmed coincidental rather than causal association between metformin and lactic acidosis in outpatients [19, 52]. On the other hand, other investigations found no obvious relationship between metformin accumulation and rate of lactic acidosis or the associated mortality in patients with precipitating conditions who received therapeutic doses of the drug [53]. Likewise, some studies have shown that underlying hemodynamic conditions are the main determinant of hyperlactatemia and there is no association between metformin accumulation and blood lactate levels [18, 54].

Since the incidence of lactic acidosis is rare in metformin therapy [17-19], to attain more convincing results, more studies should be conducted in larger number of patients.

Efficacy of metformin in acute care medicine

Some investigators have reported no acute effect of metformin on production of hepatic glucose or peripheral glucose disposal [55]. In contrast, there are reports indicating benefit of acute metformin in insulin resistant patients [56-59] that is supported by the present study. Fortunately, no complications such as hypoglycemia, hypokalemia, and hypomagnesaemia that commonly happen in insulin therapy [36], were observed in the present study.

Taking collectively, this preliminary study suggests the benefit of combination therapy of hyperglycemic CIPs with metformin and insulin but remains to be confirmed by more experimental and clinical investigations with larger sample number in different types of CIPs. Of course, it should not be forgotten that CIPs are under influence of various stresses that can disturb both kinetic and dynamic of drugs used in ICU [60, 61] seeming the source of controversies among different reports.

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