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EDITORIAL

Short acting insulin analogues in intensive care unit patients

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Abstract

Blood glucose control in intensive care unit (ICU) patients, addressed to actively maintain blood glucose concentration within defined thresholds, is based on two major therapeutic interventions: to supply an adequate calories load and, when necessary, to continuously infuse insulin titrated to patients needs: intensive insulin therapy (IIT). Short acting insulin analogues (SAIA) have been synthesized to improve the chronic treatment of patients with diabetes but, because of the pharmacokinetic characteristics that include shorter onset and off-set, they can be effectively used also in ICU patients and have the potential to be associated with a more limited risk of inducing episodes of iatrogenic hypoglycemia. Medical therapies carry an intrinsic risk for collateral effects; this can be more harmful in patients with unstable clinical conditions like ICU patients. To minimize these risks, the use of short acting drugs in ICU patients have gained a progressively larger room in ICU and now pharmaceutical companies and researchers design drugs dedicated to this subset of medical practice. In this article we report the rationale of using short acting drugs in ICU patients (*i.e.*, sedation and treatment of arterial hypertension) and we also describe SAIA and their therapeutic use in ICU with the potential to minimize iatrogenic hypoglycemia related to IIT. The pharmacodynamic and pharmachokinetic characteristics of SAIA will be also discussed.

Key words: Insulin analogues; Short acting drugs; Intensive insulin therapy; Glycemia management; Intensive care

Core tip: In this article we report the rationale of using short acting drugs in intensive care unit (ICU) patients (*i.e.*, sedation and treatment of arterial hypertension) and we also describe short acting insulin analogues (SAIA) and their pharmacokinetic (PK) and pharmacodynamic profile. SAIA have been synthesized to improve the chronic treatment of patients with diabetes but, because of the PK characteristics that include shorter onset and offset, they can be effectively used also in ICU patients and have the potential to be associated with a more limited risk of inducing episodes of iatrogenic hypoglycemia.

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INTRODUCTION

Blood glucose control in intensive care unit (ICU) patients, addressed to actively maintain blood glucose concentration (BGC) within defined thresholds, is based on two major therapeutic interventions: to supply an adequate calories load and, when necessary, to continuously infuse insulin titrated to patients needs: intensive insulin therapy (IIT)[1,2]. Among the most relevant risks related to active management of BGC is the induction of iatrogenic hypoglycemia[1-4]. Endogenous insulin is a 51 amino acids protein formed by 2 chains (A and B chains) linked

by disulphide bridges: "A" chain comprises 21 amino acids and has an N-terminal helix linked to an anti-parallel C-terminal helix with a critical role in the tertiary structure; "B" chain comprises 30 amino acids and has a central helical segment where it joins the N- and C-terminal helices of the A chain[5]. Physiologically, insulin is released by the pancreas with a characteristic biphasic profile as response to BGC increase: a rapid phase, due to exocytosis of "ready pool" granules and associated with the release of 5%-10% of the insulin contained in the beta cells, is activated within few minutes after an increase in BGC and terminates rapidly; a slow phase, due to the release of "reserve pool" granules, and lasts longer. Beside BGC driven insulin release, there is also a continuous insulin secretion throughout the day, not associated with meals that accounts for about 50% of the whole daily endogenous insulin secretion[5].

As underlined by several authors and by the pathophysiology of chetoacidosis in diabetic patients and in ICU patients, to supply an adequate calories load is a preliminary step for optimal management of BGC and should be established before insulin infusion is instituted, even in patients with high BGC values[1,2,6].

Currently the standard of care for the treatment of hyperglycemia in ICU patients is to establish intensive insulin therapy by infusing rapid (R) insulin but-and this is among the most important drawback of this therapeutic approach-it induces some additional risk of iatrogenic hypoglycemia[1]. Various strategies have been used to minimize the risk of inducing hypoglycemia when IIT is instituted, these include: to adopt a tighter BGC monitoring protocol, to target a narrower BGC range, to increase the supplied calories load[1,7-10].

In 2001, a large randomized controlled trial in critically ill surgical patients demonstrated that tight glucose control (defined as the restoration and maintenance of BCG at or below 6.1 ± 2.1 mmol/L) by IIT was associated with a decreased mortality and rate of complications[6]. Currently, other authors demonstrated that the incidence of moderate hypoglycemia was significantly increased when target was BGC < 6.7 mmol/L and BGC < 8.3 mmol/L may be a reasonable target for clinical practice[8]. Widening the target-range BGC might reduce the risk of hypoglycemia and hyperglycemia developing, thus limiting neuronal damage[2]. In the subgroup of neurocritical care patients both hypoglycemia and hyperglycemia may cause extended neuronal damage and potentially long-lasting brain injury[1,2]. These patients must therefore undergo strict glycemia monitoring and abnormal blood glucose values should be immediately corrected[1].

In this article we report the rationale of using short acting drugs in ICU patients (*i.e.,* sedation and treatment of arterial hypertension) and we also describe short acting insulin analogues (SAIA) and their therapeutic use in ICU with the potential to minimize iatrogenic hypoglycemia related to IIT. The pharmacodynamic and pharmachokinetic characteristics of SAIA will be discussed.

RATIONALE FOR USING SHORT ACTING DRUGS IN CRITICAL CARE PATIENTS

In pharmaceutical research there is a trend to provide short acting drugs-also called "soft" drugs-to treat critically ill patients and the unstable phase of acute illness and for anesthesia/sedation and perioperative management[11]. The use of short acting vasodilators (*i.e.,* nitroglycerin) in the acute phase of acute myocardial infarction, acute episodes of arterial hypertension in the treatment of the acute phase of heart failure and pulmonary edema is the paradigm of the need for short acting drugs in the treatment of acute illness[12-14]. Recent antihypertensive drugs (as esmolol) and short acting opioids (as remifentanil) are prototypical "soft" drugs designed to fulfill the need for limiting drug-related residual effects when infusion is discontinued[11]. These molecules frequently rely on plasmatic metabolism by non specific bloodstream esterases. A common molecular paradigm to reduce pharmacokinetic (PK) characteristics (including onset and half life) is to modify the parent compound into a "soft" drug by adding an ester linkage, thus, increasing its susceptibility to bloodstream metabolism[11]. In anesthesia new drugs have been developed (midazolam, propofol, desflurane) modifying existing compounds in order to shorten anesthesia induction and awakening times[11,15].

Antihypertensive

Sympathetic stimulation contributes to cerebral hyperemia during emergence from craniotomy. B-blocking drugs may be considered to limit hemodynamic changes of neurosurgical recovery. Esmolol blunted the increase in cerebral blood flow during recovery from neurosurgical anesthesia[16]. Hypertensive emergencies generally require intravenous treatment to achieve a rapid decrease in blood pressure and patients admitted to these care settings may be sicker than patients treated with oral agents. The first choice antihypertensive drug varied by treatment location. In ICU nitroglycerine was by far the most widely used (60%); in the emergency department furosemide was used in 34% of patients and nitroglycerine was used in 27%; perioperatively urapidil was used in 34% of patients and clonidine was used in 28%[12]. While nitroglycerine should be used as an adjunctive therapy, the high rates of use in the European registry for Studying the Treatment of Acute hypertension population likely reflect familiarity with its use, together with its ease of administration, titration and rapid reversibility[12].

Analgesia-sedation

Analgesics and sedatives are commonly prescribed in ICU environment for patient comfort; however, recent studies have shown that these medications can themselves lead to adverse patient outcomes[17]. The use of short acting medications is associated with improved outcomes such as decreased time of mechanical ventilation and ICU length of stay[17]. Using a short-acting opioid

with short context-sensitive half-life in an analgesia based sedation protocol may significantly decrease the duration of mechanical ventilation and the ICU length of stay even though not significantly in long term sedation, while improving the achievement of sedation goals despite a lower requirement for adjunctive hypnotic agents, with no additional costs. The context-sensitive half-life of remifentanil is significantly shorter than those of other opiates. In the remifentanil group, the decreases in need for mechanical ventilation and ICU length of stay were associated with a significant decrease in the use of add-on hypnotics, suggesting that remifentanil was faster adjustable to the required sedation level[18].

Regarding sedation, Clinical Practice Guidelines[19] recommend the use of propofol-rapid onset of sedation (highly lipid soluble and quickly crosses the blood-brain barrier), and rapid offset (quickly redistribution with high hepatic and extrahepatic clearance)-and dexmedetomidine (selective α2-receptor agonist rapidly redistributed into peripheral tissues) over benzodiazepines fot ICU sedation.

Inhaled anesthetics (short acting drugs) may be ideal sedatives for the ICU[20] because of their pulmonary elimination, limited amount of metabolism, bronchodilation and cardioprotective effects[21]. However, inhaled anesthetics are not widely used for sedation in the ICU, since most modern ICU ventilators do not readily accommodate an anesthetic vaporizer. The new anesthetic conserving device, AnaConDa (Sedana Medical™, Sweden) uses a syringe pump to deliver inhaled anesthetic in liquid form into the breathing circuit of a standard ICU ventilator. Belda *et al*[22] adapted a classical PK model to obtain an infusion scheme for the clinical use of the AnaConDa with sevoflurane. Another short acting drug in ICU.

SHORT ACTING INSULIN ANALOGUES

SAIA were developed to improve postprandial glycemic control and to minimize BGC excursions in diabetic patients[23-25]. Due to a PK profile closer to that of endogenous insulin, when physiologically released by the trigger of meals, SAIA have a faster rise in plasma concentration, higher peak concentration and shorter subcutaneous residence time than unmodified human insulin[26]. The clinical use of SAIA is associated with lower postprandial peak BGC as compared with rapid insulin and doesn't increase the incidence of hypoglycemia[23-25].

Currently, 3 SAIA are available for clinical use: lyspro insulin (Humalog®; Eli Lilly, Indianapolis, IN, United States), aspart insulin (Novolog®/NovoRapid®; Novo Nordisk, Bagsvaerd, Denmark) and glulisine insulin (Apidra®; Sanofi, Paris, France).

Lyspro insulin, first SAIA that became available for clinical use in 1996, is characterized by a change in the amino acid sequence of insulin B chain-proline in position 28 and lysine in position 29 are inverted [Lys(B28), Pro(B29)]-that results in a reduced self association[27-29]. These changes result in an insulin molecule with a reduced capacity for self-association[27,28]. Proline at position B28 near the COOH-terminal of the B-chain of human insulin is important for the proper configuration of a p-sheet involving residues B24 through B26. Two insulin molecules align along this surface in an antiparallel orientation to form a nonpolar dimer. At this point, the nonpolar dimer interacts with zinc to form a hexamer, the basis of Regular insulin formulations. The sequence of lysine at B28 and proline at B29 can be found in insulin-like growth factor I (IGF- I) and is thought to be responsible for its lower degree of self-association in comparison to insulin. Accordingly, IGF- I is the model upon which the structure of lyspro is based[27-29]. As a result of these modifications, lyspro exhibits monomeric behavior in solution, binds zinc less avidly, and displays faster pharmacodynamic action than human Regular insulin (Humulin R®). These findings are consistent with the rapid absorption expected from monomeric insulin injected subcutaneously[27,29].

Aspart insulin, second SAIA to achieve regulatory approval in 2000, is characterized by a change in the amino acid sequence of insulin B chain-proline in position 28 is substituted with the charged aspartic acid-this reduces self-association of the molecule, allowing only weak dimeric and hexameric formation and thereby rapid dissociation after subcutaneous injection[27,29,30]. Receptor interaction kinetic studies have shown that aspart insulin behaves essentially like human insulin with regard to both the insulin and IGF- I receptor with a similar potency to that of human insulin[29,30]. Aspart insulin is absorbed twice as fast as regular insulin and reaches a maximum concentration in plasma of approximately twice that of human insulin. Its activity profile is very similar to that of human insulin[29,30].

Glulysin insulin, third SAIA to receive regulatory approval, is characterized by a change in the amino acid sequence of insulin B chain-lysine and glutamic acid are substituted for asparagine and glycine in positions 3 and 29 respectively-it is thought that this latter substitution is predominantly responsible for its PK properties[27,29,31]. Studies indicate that glulisine has a very comparable PK and pharmacodynamic profile to insulin lispro[27,29,31]. Overall, the bioequivalence of glulisine is similar to that of human insulin[27,29,31].

DISCUSSION

In this review article we originally report the use of SAIA in critical care patients. The pharmacodynamic and pharmacokinetic characteristics of SAIA available for clinical use are described and the rationale for using shorter acting insulin is presented.

Altered pharmacology in the intensive care unit

Critically ill patients, not infrequently present alterations of physiological parameters that determine the success/failure of therapeutic interventions as well as the final outcome[32]. Most common and complex syndromes occurring in ICU affect drug absorption, disposition, metabolism and elimination[33]. Pharmacological man-

agement of ICU patients requires consideration of the unique PKs associated with these clinical conditions and the likely occurrence of drug interaction[34]. Rational adjustment in drug choice and dosing contributes to the appropriateness of treatment of those patients[35].

Adverse drug events in intensive care unit

Intensive care medicine provides great benefits to patients with life-threatening acute illness or trauma. These benefits are a consequence of advancements in diagnostic testing, technological interventions and pharmacotherapy. Simultaneously, the complexity and intensity of care required by ICU patients is also associated with greater risks resulting from care[36]. Adverse drug events (ADEs), including adverse reactions and medication errors, are harmful and occur with alarming frequency in critically ill patients[37].

Patients in ICUs may be at especially high risk of an ADE for the following reasons[38,39]: (1) The complexity of diseases; (2) Pathophysiological status characterized by a wide range of changes in organ dysfunction (altering PKs); (3) The high number of medications administered; (4) Administration of complex drug regimens; and (5) Increased length of hospital stay. Hypoglycemia and hyperglycemia are in the 10 top ADE in the ICU[40].

Drug-drug interactions in ICU

Drug-drug interactions (DDIs) in the ICU are associated with longer ICU stays, ADE and end-organ damage[41]. Critically ill patients are at an increased risk of ADE related to DDIs because of the large number of medications that they receive and PK characteristics of the administered medications[42].

The 10 most frequently ocurring DDI in the ICU include insuline/metoprolol (moderate severity rating, β-blockers may enhance the hypoglycemic effects of insulin) and insulin/prednisone (moderate severity rating, corticosteroids may diminish the hypoglycaemic effect of antidiabetic agents)[43].

In this context, medical therapies carry an intrinsic risk for collateral effects; this can be more harmful in patients with unstable clinical conditions like ICU patients[44]. To minimize these risks, the use of short acting drugs in ICU patients have gained a progressively larger room in ICU and now pharmaceutical companies and researchers design drugs dedicated to this subset of medical practice[11]. SAIA have been synthesized to improve the chronic treatment of patients with diabetes but, because of the PK characteristics that include shorter onset and offset, they can be effectively used also in ICU patients and have the potential to be associated with a more limited risk of inducing episodes of iatrogenic hypoglycemia. Clinical studies addressed to assess the dosing profile and the safety of SAIA when used-as intravenous continuous therapy- to accomplish IIT in ICU patients.

REFERENCES

1 **Bilotta F**, Giovannini F, Caramia R, Rosa G. Glycemia management in neurocritical care patients: a review. *J Neurosurg Anesthesiol* 2009; **21**: 2-9 [PMID: 19098617 DOI: 10.1097/ANA.0b013e31818f8a5c]

2 **Bilotta F**, Rosa G. Glycemia management in critical care patients. *World J Diabetes* 2012; **3**: 130-134 [PMID: 22816025 DOI: 10.4239/wjd.v3.i7.130]

3 **Bilotta F**, Caramia R, Paoloni FP, Delfini R, Rosa G. Safety and efficacy of intensive insulin therapy in critical neurosurgical patients. *Anesthesiology* 2009; **110**: 611-619 [PMID: 19237874 DOI: 10.1097/ALN.0b013e318198004b]

4 **Bilotta F**, Rosa G. Glucose management in the neurosurgical patient: are we yet any closer? *Curr Opin Anaesthesiol* 2010; **23**: 539-543 [PMID: 20689410 DOI: 10.1097/ACO.0b013e32833e150a]

5 **Wilcox G**. Insulin and insulin resistance. *Clin Biochem Rev* 2005; **26**: 19-39 [PMID: 16278749]

6 **van den Berghe G**, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R. Intensive insulin therapy in critically ill patients. *N Engl J Med* 2001; **345**: 1359-1367 [PMID: 11794168]

7 **Lena D**, Kalfon P, Preiser JC, Ichai C. Glycemic control in the intensive care unit and during the postoperative period. *Anesthesiology* 2011; **114**: 438-444 [PMID: 21245729 DOI: 10.1097/ALN.0b013e3182078843]

8 **Okawa M**, Kunimoto F, Kanamoto M, Narahara H, Hinohara H, Tobe M, Yanagisawa A, Saito S. Effect of different blood glucose target levels on the incidence of hypoglycemia during insulin therapy in the intensive care unit. *J Diabetes* 2013; **5**: 51-56 [PMID: 23035699 DOI: 10.1111/1753-0407.12010]

9 **Heller S**. Reducing hypoglycaemia with insulin analogues. *Int J Obes Relat Metab Disord* 2002; **26** Suppl 3: S31-S36 [PMID: 12174321]

10 **Derde S**, Vanhorebeek I, Ververs EJ, Vanhees I, Darras VM, Van Herck E, Larsson L, Van den Berghe G. Increasing intravenous glucose load in the presence of normoglycemia: effect on outcome and metabolism in critically ill rabbits. *Crit Care Med* 2010; **38**: 602-611 [PMID: 19851097 DOI: 10.1097/CCM.0b013e3181c03f65]

11 **Chitilian HV**, Eckenhoff RG, Raines DE. Anesthetic drug development: Novel drugs and new approaches. *Surg Neurol Int* 2013; **4**: S2-S10 [PMID: 23653886 DOI: 10.4103/2152-7806.109179]

12 **Vuylsteke A**, Vincent JL, de La Garanderie DP, Anderson FA, Emery L, Wyman A, Rushton-Smith S, Gore JM. Characteristics, practice patterns, and outcomes in patients with acute hypertension: European registry for Studying the Treatment of Acute hyperTension (Euro-STAT). *Crit Care* 2011; **15**: R271 [PMID: 22087790 DOI: 10.1186/cc10551]

13 **Flaherty JT**, Reid PR, Kelly DT, Taylor DR, Weisfeldt ML, Pitt B. Intravenous nitroglycerin in acute myocardial infarction. *Circulation* 1975; **51**: 132-139 [PMID: 803231]

14 **Kaltenbach M**, Bussmann WD, Kober G. [Nitroglycerin in the therapy of coronary insufficiency and heart failure]. *Z Kardiol* 1976; **65**: 424-434 [PMID: 820103]

15 **Bilotta F**, Doronzio A, Cuzzone V, Caramia R, Rosa G. Early postoperative cognitive recovery and gas exchange patterns after balanced anesthesia with sevoflurane or desflurane in overweight and obese patients undergoing craniotomy: a prospective randomized trial. *J Neurosurg Anesthesiol* 2009; **21**: 207-213 [PMID: 19542997 DOI: 10.1097/ANA.0b013e3181a19c52]

16 **Bilotta F**, Lam AM, Doronzio A, Cuzzone V, Delfini R, Rosa G. Esmolol blunts postoperative hemodynamic changes after propofol-remifentanil total intravenous fast-track neuroanesthesia for intracranial surgery. *J Clin Anesth* 2008; **20**: 426-430 [PMID: 18929282 DOI: 10.1016/j.jclinane.2008.04.006]

17 **McGrane S**, Pandharipande PP. Sedation in the intensive care unit. *Minerva Anestesiol* 2012; **78**: 369-380 [PMID: 22240616]

18 **Futier E**, Chanques G, Cayot Constantin S, Vernis L, Barres A,

Guerin R, Chartier C, Perbet S, Petit A, Jabaudon M, Bazin JE, Constantin JM. Influence of opioid choice on mechanical ventilation duration and ICU length of stay. *Minerva Anestesiol* 2012; **78**: 46-53 [PMID: 21971434]

19 **Barr J**, Fraser GL, Puntillo K, Ely EW, Gélinas C, Dasta JF, Davidson JE, Devlin JW, Kress JP, Joffe AM, Coursin DB, Herr DL, Tung A, Robinson BR, Fontaine DK, Ramsay MA, Riker RR, Sessler CN, Pun B, Skrobik Y, Jaeschke R. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med* 2013; **41**: 263-306 [PMID: 23269131 DOI: 10.1097/CCM.0b013e3182783b72]

20 **Kong KL**, Bion JF. Sedating patients undergoing mechanical ventilation in the intensive care unit--winds of change? *Br J Anaesth* 2003; **90**: 267-269 [PMID: 12594134]

21 **De Hert SG**, Van der Linden PJ, Cromheecke S, Meeus R, Nelis A, Van Reeth V, ten Broecke PW, De Blier IG, Stockman BA, Rodrigus IE. Cardioprotective properties of sevoflurane in patients undergoing coronary surgery with cardiopulmonary bypass are related to the modalities of its administration. *Anesthesiology* 2004; **101**: 299-310 [PMID: 15277911]

22 **Belda JF**, Soro M, Badenes R, Meiser A, García ML, Aguilar G, Martí FJ. The predictive performance of a pharmacokinetic model for manually adjusted infusion of liquid sevofluorane for use with the Anesthetic-Conserving Device (AnaConDa): a clinical study. *Anesth Analg* 2008; **106**: 1207-1214, table of contents [PMID: 18349194 DOI: 10.1213/ane.0b013e31816782ff]

23 **Lindholm A**, McEwen J, Riis AP. Improved postprandial glycemic control with insulin aspart. A randomized double-blind cross-over trial in type 1 diabetes. *Diabetes Care* 1999; **22**: 801-805 [PMID: 10332685]

24 **Heinemann L**, Hompesch M, Flacke F, Simms P, Pohl R, Albus K, Pfützner A, Steiner S. Reduction of postprandial glycemic excursions in patients with type 1 diabetes: a novel human insulin formulation versus a rapid-acting insulin analog and regular human insulin. *J Diabetes Sci Technol* 2011; **5**: 681-686 [PMID: 21722583]

25 **Luijf YM**, van Bon AC, Hoekstra JB, Devries JH. Premeal injection of rapid-acting insulin reduces postprandial glycemic excursions in type 1 diabetes. *Diabetes Care* 2010; **33**: 2152-2155 [PMID: 20693354 DOI: 10.2337/dc10-0692]

26 **Home PD**. The pharmacokinetics and pharmacodynamics of rapid-acting insulin analogues and their clinical consequences. *Diabetes Obes Metab* 2012; **14**: 780-788 [PMID: 22321739 DOI: 10.1111/j.1463-1326.2012.01580.x]

27 **Howey DC**, Bowsher RR, Brunelle RL, Rowe HM, Santa PF, Downing-Shelton J, Woodworth JR. [Lys(B28), Pro(B29)]-human insulin: effect of injection time on postprandial glycemia. *Clin Pharmacol Ther* 1995; **58**: 459-469 [PMID: 7586939]

28 **DiMarchi RD**, Mayer JP, Fan L, Brems DN, Frank BH, Green LK, Hoffman JA, Howey DC, Long HB, Shaw WN, Shields JE, Slieker LJ, Su KSE, Sundell KL, Chance RE. Synthesis of a fast-acting insulin based on structural homology with insulin-like growth factor 1. In Peptides: chemistry and biology, proceedings of the twelfth american peptide symposium. Smith JA, Rivier JE, Eds. Leiden, Netherlands, ESCOM, 1992: 26-28

29 **Sheldon B**, Russell-Jones D, Wright J. Insulin analogues: an example of applied medical science. *Diabetes Obes Metab* 2009; **11**: 5-19 [PMID: 19120431 DOI: 10.1111/j.1463-1326.2008.01015.x]

30 **Mudaliar SR**, Lindberg FA, Joyce M, Beerdsen P, Strange P, Lin A, Henry RR. Insulin aspart (B28 asp-insulin): a fast-acting analog of human insulin: absorption kinetics and action profile compared with regular human insulin in healthy nondiabetic subjects. *Diabetes Care* 1999; **22**: 1501-1506 [PMID: 10480516]

31 **Becker RH**, Frick AD, Burger F, Scholtz H, Potgieter JH. A comparison of the steady-state pharmacokinetics and pharmacodynamics of a novel rapid-acting insulin analog, insulin glulisine, and regular human insulin in healthy volunteers using the euglycemic clamp technique. *Exp Clin Endocrinol Diabetes* 2005; **113**: 292-297 [PMID: 15926116]

32 **Rivera-Fernández R**, Nap R, Vázquez-Mata G, Reis Miranda D. Analysis of physiologic alterations in intensive care unit patients and their relationship with mortality. *J Crit Care* 2007; **22**: 120-128 [PMID: 17548023]

33 **Boucher BA**, Wood GC, Swanson JM. Pharmacokinetic changes in critical illness. *Crit Care Clin* 2006; **22**: 255-271, vi [PMID: 16677999]

34 **Roberts JA**, Lipman J. Antibacterial dosing in intensive care: pharmacokinetics, degree of disease and pharmacodynamics of sepsis. *Clin Pharmacokinet* 2006; **45**: 755-773 [PMID: 16884316]

35 **Zagli G**, Tarantini F, Bonizzoli M, Di Filippo A, Peris A, De Gaudio AR, Geppetti P. Altered pharmacology in the Intensive Care Unit patient. *Fundam Clin Pharmacol* 2008; **22**: 493-501 [PMID: 18684127 DOI: 10.1111/j.1472-8206.2008.00623.x]

36 **George EL**, Henneman EA, Tasota FJ. Nursing implications for prevention of adverse drug events in the intensive care unit. *Crit Care Med* 2010; **38**: S136-S144 [PMID: 20502167 DOI: 10.1097/CCM.0b013e3181de0b23]

37 **Kane-Gill S**, Rea RS, Verrico MM, Weber RJ. Adverse-drug-event rates for high-cost and high-use drugs in the intensive care unit. *Am J Health Syst Pharm* 2006; **63**: 1876-1881 [PMID: 16990635]

38 **Kane-Gill SL**, Jacobi J, Rothschild JM. Adverse drug events in intensive care units: risk factors, impact, and the role of team care. *Crit Care Med* 2010; **38**: S83-S89 [PMID: 20502179 DOI: 10.1097/CCM.0b013e3181dd8364]

39 **Joshua L**, Devi P, Guido S. Adverse drug reactions in medical intensive care unit of a tertiary care hospital. *Pharmacoepidemiol Drug Saf* 2009; **18**: 639-645 [PMID: 19421963 DOI: 10.1002/pds.1761]

40 **Reis AM**, Cassiani SH. Adverse drug events in an intensive care unit of a university hospital. *Eur J Clin Pharmacol* 2011; **67**: 625-632 [PMID: 21246350]

41 **Moura C**, Prado N, Acurcio F. Potential drug-drug interactions associated with prolonged stays in the intensive care unit: a retrospective cohort study. *Clin Drug Investig* 2011; **31**: 309-316 [PMID: 21344954 DOI: 10.2165/11586200-000000000-00000]

42 **Reis AM**, Cassiani SH. Prevalence of potential drug interactions in patients in an intensive care unit of a university hospital in Brazil. *Clinics* (Sao Paulo) 2011; **66**: 9-15 [PMID: 21437429]

43 **Smithburger PL**, Kane-Gill SL, Seybert AL. Drug-drug interactions in the medical intensive care unit: an assessment of frequency, severity and the medications involved. *Int J Pharm Pract* 2012; **20**: 402-408 [PMID: 23134100 DOI: 10.1111/j.2042-7174.2012.00221.x]

44 **Van den Berghe G**. What's new in glucose control in the ICU? *Intensive Care Med* 2013; **39**: 823-825 [PMID: 23460140 DOI: 10.1007/s00134-013-2874-3]

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