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SYMPOSIUM

Risk Factors for Inpatient Hypoglycemia during Subcutaneous Insulin Therapy in Non-Critically Ill Patients with Type 2 Diabetes

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Abstract

Objective:

We aimed to determine risk factors associated with hypoglycemia during subcutaneous insulin therapy in non-critically ill patients with type 2 diabetes.

Methods:

We conducted an analysis of three randomized control trials using basal/bolus regimen and regular sliding scale insulin (SSI) in patients with diabetes admitted to medical and surgical settings.

Results:

We analyzed medical records of 261 general medicine and 211 noncardiac surgery patients treated with basal/bolus regimen with glargine/glulisine (n = 169), detemir/aspart (n = 67), neutral protamine Hagedorn/regular (n = 63), or with SSI (n = 173). The overall frequency of mild and severe hypoglycemia (<70 and <40 mg/dl) was 19% and 2%, respectively. During treatment, medical patients experienced a higher number of hypoglycemia than surgical patients (23% versus 13%; p = .005), but the rate of severe hypoglycemia was similar between groups (1.9% versus 1.9%; p = not significant). Increasing age, impaired kidney function (glomerular filtration rate < 60 ml/min), total daily insulin dose, and type of insulin regimen (basal/bolus versus SSI) during hospitalization were important contributors for hypoglycemia in both medical and surgical patients. Among these variables, increasing age and type of insulin regimen (basal/bolus versus SSI) were found to be independent predictors of hypoglycemic events.

Conclusions:

Mild hypoglycemic events are common during subcutaneous insulin therapy in medical and surgical patients with type 2 diabetes. Increasing age, impaired renal function, daily insulin dose, and insulin regimen (basal/bolus versus SSI) are important predictors of hypoglycemia during insulin therapy in patients with type 2 diabetes mellitus.

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Abbreviations: (BG) blood glucose, (GFR) glomerular filtration rate, (ICU) intensive care unit, (NPH) neutral protamine Hagedorn, (SSI) sliding scale insulin, (TDD) total daily dose

Keywords: basal insulin, detemir, glargine, hospital hyperglycemia, hypoglycemia, neutral protamine Hagedorn, sliding scale insulin

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Introduction

Numerous observational and intervention studies have shown that hyperglycemia in hospitalized patients with and without diabetes is associated with poor outcome[1–3] and that improved glycemic control reduces hospital complications and mortality.[4–6] There is great controversy, however, on the optimal blood glucose (BG) target in hospitalized patients.[7–9] The debate has been fierce, given the risk of hypoglycemia, which is universally present with intensified insulin treatment. The exact prevalence of hospital hypoglycemia is not known, but it varies based on study populations and the definition utilized in the reports. An analysis of point-of-care bedside glucose test results from 575 hospitals using a laboratory information management system from 3,484,795 hospitalized patients [653,359 in the intensive care unit (ICU) and 2,831,436 in non-ICU areas] reported the prevalence of hypoglycemia [<3.9 mmol/liter (70 mg/dl)] as 6.3% of patient days for ICU patients and 5.7% of patient days for non-ICU patients.[10] Data from randomized controlled trials indicate a prevalence of hypoglycemia ranging between 5% to 28.6% in ICU patients treated with intravenous insulin[5,7,11–13] and between 5% and 32% of patients in non-ICU patients treated with subcutaneous insulin.[14–16]

There is substantial observational evidence linking hypoglycemia to higher rates of hospital complications, longer hospital stay, higher health care resource utilization, and hospital mortality.[17–21] In critically ill patients, several studies have shown a strong association between the development of hypoglycemia with an increased risk of cardiovascular events and overall risk of hospital and post-discharge death.[12,18,22,23] In a prospective ICU study, a glucose less than 2.8 mmol/liter (50 mg/dl) was found to be associated with a mortality rate of 22.2% compared with 2.3% in patients without hypoglycemia.[24] Similarly, in non-ICU patients, the development of hypoglycemia has been associated with increased length of hospital stay, ICU admission, and in-hospital mortality.[25,26] Results of several studies, however, have shown that spontaneous (non-insulin-mediated) hypoglycemia rather than insulin-induced hypoglycemia is associated with increased risk of inpatient mortality and complications.[25–27]

Many factors contribute to development of hypoglycemia in the hospital setting. In critically ill patients, major risk factors include poor nutrition intake, underlying illnesses (e.g., renal failure, heart failure, advanced liver disease), advanced age, infections,[19,28] as well as intensity of treatment regimen.[7,8] In the non-critically-ill setting, however, risk factors for hypoglycemia during subcutaneous insulin therapy are not well recognized. To address this important knowledge gap, we conducted an analysis of intervention clinical trials[14,16,29] in order to identify risk factors of hypoglycemia in insulin-treated general medical and surgical patients with type 2 diabetes.

Research Methods

We combined the data from three randomized controlled multicenter trials that compared the efficacy and safety of different insulin regimens in patients with diabetes admitted to general services.[14,16,29] The methodology and results of these studies have been previously reported in detail.[14,16,29] These three studies included patients with known history of type 2 diabetes for >3 months who had an admission BG level between 140 and 400 mg/dl. Oral antidiabetic drugs were discontinued at randomization, and subjects were treated with subcutaneous insulin therapy to achieve a target fasting and premeal glucose <140 mg/dl. Blood glucose was measured at the bedside by a glucose meter before meals and at bedtime, and daily insulin dose was adjusted following a similar insulin algorithm increasing basal insulin by 10% for BG between 140 and 180 mg/dl and by 20% for glucose > 180 mg/dl. If a patient developed hypoglycemia, the dose of insulin was decreased by 20% to 40% for glucose <70 and <40 mg/dl, respectively. In addition, critically ill patients admitted to the ICU or with anticipated ICU admission, clinically relevant hepatic disease or impaired renal function (creatinine ≥ 3.0 mg/dl), glucocorticoid use, and pregnancy were excluded.

In the RABBIT 2 trial,[14] a total of 131 insulin-naïve medical patients were randomized to receive glargine and glulisine or a standard regular sliding scale insulin (SSI) protocol. Glargine was given once daily and glulisine before meals at a starting total daily dose (TDD) of 0.4 U/kg/day for BG 140–200 mg/dl or 0.5 U/kg/day for BG 201–400 mg/dl. A SSI was given four times per day for BG >140 mg/dl. In the DEAN trial,[29] 130 patients admitted to general medicine wards were assigned to receive either a basal/bolus regimen with detemir and aspart or a split-mixed regimen with neutral protamine

Hagedorn (NPH) and regular insulin. Patients treated with detemir/aspart received 50% of TDD as detemir and 50% as aspart insulin given before meals. Patients treated with NPH/regular insulin received two-thirds of TDD before breakfast and one-third before dinner. The insulin dose was given as two-thirds NPH and one-third regular insulin before breakfast and dinner. The RABBIT Surgery trial[16] included 211 patients with type 2 diabetes who underwent noncardiac general surgery. Patients were treated with a basal/bolus insulin regimen with glargine and glulisine or with regular SSI. Patients in the basal/bolus arm received half of their TDD as insulin glargine once daily before or after surgery and the other half as insulin glulisine before meals for BG >140 mg/dl. To prevent hypoglycemia in the three trials, the full basal insulin was administered, but the dose of prandial insulin was held in patients who were not able to eat.

Hypoglycemia was defined as a BG level <70 mg/dl (<3.9 mmol/liter), and severe hypoglycemia was defined as a BG value <40 mg/dl (<2.2 mmol/liter) according to the definition provided by the American Diabetes Association.[30]

Insulin dose defined as TDD per body weight (U/kg) over a 24 h period was further stratified to TDD ≥ 0.5 U/kg and TDD < 0.5 U/kg. Type of insulin patients received was classified into four categories: those who received basal/bolus regimen with glargine and glulisine, detemir and aspart, and NPH and regular insulin and those who were treated with regular SSI.

To assess the effect of renal function on hypoglycemia, serum creatinine measured at admission was used and categorized to serum creatinine ≤ 2 versus >2 and <3.0 mg/dl. Glomerular filtration rate (GFR) was calculated using the Modification of Diet in Renal Disease study equation[16] using standardized serum creatinine, age, race, and gender. The calculated GFR was then stratified into GFR < 60 versus ≥60 ml/min/1.73 m^2).

Statistical Analysis

We compared baseline and outcome variables by hospital service type (medicine versus surgery), type of insulin regimen, and occurrence of hypoglycemia. The comparisons were made with the use of Wilcoxon tests (or Kruskal–Wallis tests) and Chi-square tests (or Fisher's exact test) as appropriate. Logistic regression was adopted in the multivariate analysis of predictors of hypoglycemia, producing odds ratio estimates and the corresponding confidence intervals for the predictors considered. Statistical analysis was performed using SAS (version 9.2; SAS Institute, Cary, NC). A p value of <0.05 was considered significant. The data are presented as means ± standard deviation for continuous variables and count (percentage) for discrete variables.

Results

A total of 472 patients with type 2 diabetes mellitus admitted to general medicine (n = 261) and surgery (n = 211) services were included in the three trials. Of them, 130 patients were enrolled in the DEAN trial, where 67 patients received detemir and aspart and 63 patients NPH and regular insulin. RABBIT Medicine and Surgery enrolled 131 and 211 patients, respectively, with 169 patients randomized to basal/bolus insulin regimen with glargine and glulisine and 173 patients treated with regular SSI. Clinical characteristics of patients are shown in **Table 1**. There were no differences in mean age, gender, body mass index, or mean hospital length of stay between medicine and surgery patients. Medical patients had significantly worse kidney function on admission, with higher serum creatinine and lower GFR (both $p \leq .01$). Medicine patients had higher hemoglobin A1c (8.6% ± 2.3 versus 7.7% ± 2.2) and higher admission BG than surgery patients (222 ± 65 versus 198 ± 54; $p < .001$). In addition, medicine patients had higher mean daily glucose during the hospital stay (173 ± 44 versus 159 ± 423 mg/dl; $p < .001$) compared with surgery patients. The overall mortality during the hospital stay in the three studies was low, with only one death reported in medicine and two in surgical patients.

Medicine and surgery patients treated with a basal/bolus regimen with glargine and glulisine experienced significantly greater improvement in glycemic control compared with patients treated with SSI. The overall inpatient BG difference between patients treated with basal/bolus versus SSI was 24 mg/dl ($p < .01$) in medical patients and 27 mg/dl in surgical patients ($p < .01$). Compared with NPH and regular insulin therapy, the use of basal/bolus with detemir and aspart resulted in similar reduction in mean daily BG level after the first day of therapy and in no difference in the percentage of the BG readings within the target of <140 mg/dl before meals (p = not significant).

Among patients treated with insulin prior to admission, medicine patients were treated with higher doses compared with surgical patients (0.6 ± 1.0 versus 0.1 ± 0.1 U/kg/day; $p < .0001$; **Table 1**). Similarly, they required higher doses of insulin during the hospital stay (0.4 ± 0.3 and

Table 1.
Clinical Characteristics of Insulin-Treated Patients with Type 2 Diabetes Admitted to Medical and Surgical Services

	All	Medical patients	Surgical patients	*P* value
Number of patients, *n*	472	261	211	
Age, years	57 ± 11	57 ± 10	57 ± 11	0.5
Gender, m/f (%)	51/49	51/49	51/49	1
Body mass index, kg/m^2	32 ± 8	32 ± 9	31 ± 7	0.2
Diabetic treatment on admission *P* = .001				
Diet alone, *n* (%)	67 (14)	30 (11)	37 (18)	
Oral agents, *n* (%)	291 (62)	160 (62)	131 (62)	
Insulin alone, *n* (%)	79 (17)	57 (22)	22 (10)	
Insulin + oral agents, *n* (%)	33 (7)	13 (5)	20 (10)	
Glycemic values				
Admission hemoglobin A1c, %	8.2 ± 2	8.5 ± 2	7.7 ± 2	<0.001
BG on admission, mg/dl	211 ± 61	221 ± 64	198 ± 53	<0.001
Renal function				
Admission creatinine, mg/dl	1.0 ± 0.4	1.1 ± 0.4	0.9 ± 0.3	0.0001
GFR, ml/s	88 ± 37	85 ± 39	93 ± 33	0.002
Insulin treatment				
Home (preadmission) insulin dose, U/kg/day	0.3 ± 0.2	0.6 ± 1.0	0.1 ± 0.1	<0.0001
Hospital insulin dose, U/kg/day	0.3 ± 0.3	0.4 ± 0.3	0.3 ± 0.2	<0.0001
Hypoglycemic events				
# patients < 40 mg/dl, %	9 (2)	5 (2)	4 (2)	1.0
Average # of BG readings < 40 mg/dl, *n* ± standard deviation	0.01 ± 0.2	0.1 ± 0.4	0.01 ± 0.1	0.01
# patients < 70 mg/dl, %	89 (19)	61 (23)	28 (13)	0.005
Average # of BG readings < 70 mg/dl, *n* ± standard deviation	0.5 ± 0.9	1.6 ± 0.9	0.2 ± 0.7	<0.001

0.3 ± 0.2 U/kg/day for medicine and surgery, respectively ($p < .001$).

Patients treated with basal/bolus regimen received significantly higher insulin TDD than those treated with SSI. In the RABBIT Medicine trial, the mean daily dose of insulin glargine was 22 ± 2 U, and the daily dose of insulin glulisine was 20 ±1 U.[14] In the DEAN trial,[29] the mean total daily insulin dose was 57 ± 45 U in the detemir/aspart group and 45 ± 32 U in the NPH/regular group. In the RABBIT Surgery trial,[31] the average total insulin in the basal/bolus group was 33.4 U/day compared with 12.3 U/day in the SSI group ($p < .001$). Of interest, in both medicine and surgery patients treated with SSI, the mean daily insulin dose averaged 12.5 ± 2 U/day, with more than half of patients receiving less than 10 U/day.[14,16]

The overall frequency of mild and severe hypoglycemia (<70 and <40 mg/dl, respectively) in the three trials was 19% and 2%, respectively. During treatment, medical patients experienced higher number of BG <70 mg/dl than surgical patients (23% versus 13%; $p = .005$), but the rate of severe hypoglycemia (BG <40 mg/dl) was similar between the two groups (1.9% versus 1.9%; p = not significant; **Table 1**). Of the 4137 BG readings in the medical group, 97 glucose values were <70 mg/dl and 6 glucose values were <40 mg/dl. Of the 2834 glucose readings in the surgical group, 41 glucose values were <70 mg/dl and 4 glucose values were <40 mg/dl.

We observed, however, differences in the frequency of hypoglycemic events among the type of insulin used in the different trials. In the RABBIT Medicine trial (**Table 2**), BG <70 mg/dl occurred in 5 patients (7.7%)

treated with glargine/glulisine and in 8 patients (12.1%) treated with SSI (p = .56), and there were no episodes of BG <40 mg/dl in either group. In the DEAN trial, 25 patients (37.3%) treated with detemir/aspart and 23 patients (36.5%) patients in the NPH/regular group had BG <70 mg/dl (p = .92) and 3 patients (4.5%) in the detemir/aspart group and 2 patients (3.2%) in the NPH/regular group had BG <40 mg/dl (p > .99).[29] In the RABBIT Surgery trial (**Table 3**), BG <70 mg/dl occurred in 23.1% of patients treated with glargine/glulisine and 4.7% of patients treated with SSI, p < .001; however, there were no differences in the frequency of severe hypoglycemia (p = .057).

In medicine and surgery patients, risk factors for hypoglycemia (<70 mg/dl) in univariate analysis included

Table 2.
Factors Associated with Hypoglycemia in Medical Patients[a]

	BG < 70 mg/dl		BG < 40 mg/dl	
	No hypoglycemia	Hypoglycemia	No hypoglycemia	Hypoglycemia
# of patients	200	61	256	5
Age, years	56 ± 11	61 ± 10[b]	57 ± 11	58 ± 11
Body mass index, kg/m^2	33 ± 10	30.3 ± 7	33 ± 9	27 ± 4
GFR, ml/min	89 ± 40	75 ± 35[c]	86 ± 39	73 ± 36
GFR < 60 ml/min, *n* (%)	48 (24)	23 (38)	69 (27)	2 (40)
Type of insulin regimen in the hospital[b]				
	Patients with BG < 70 mg/dl		Patients with BG < 40 mg/dl	
Detemir/aspart, *n* (%)	25 (37.3)		3 (4.5)	
NPH/regular, *n* (%)	23 (36.5)		2 (3.2)	
Glargine/glulisine, *n* (%)	5 (7.7)		0 (0)	
SSI, *n* (%)	8 (12.1)		0(0)	

[a] Data are reported as mean ± standard deviation or percentage.
[b] P < .001 compared with patients without hypoglycemia.
[c] p < .05 compared with patients without hypoglycemia.

Table 3.
Factors Associated with Hypoglycemia in Surgical Patients[a]

	BG < 70 mg/dl		BG < 40 mg/dl	
Group	No hypoglycemia	Hypoglycemia	No hypoglycemia	Hypoglycemia
# of patients	183	28	207	4
Age, years	57 ± 11	64 ± 10[b]	57 ± 11	67 ± 6
Male/female, %	51/49	46/54	50/50	100/0
Body mass index, kg/m^2	32 ± 8	30 ± 8	31 ± 8	26 ± 8
GFR, ml/min	95 ± 33	80 ± 34[c]	93 ± 34	80 ± 11
GFR < 60 ml/min, *n* (%)	32 (17)	9 (32)	41 (20)	0 (0)
Type of insulin regimen in the hospital				
	Patients with BG < 70 mg/dl		Patients with BG < 40 mg/dl	
Glargine/glulisine, *n* (%)	24 (23.1)[b]		4 (4)[c]	
SSI, *n* (%)	4 (4.7)		0 (0)	

[a] Data are reported as mean ± standard deviation or percentage.
[b] P < .001 compared with patients without hypoglycemia.
[c] p < .05 compared with patients without hypoglycemia.

increasing age, GFR < 60 ml/s, insulin use prior to admission, a daily insulin dose ≥ 0.5 U/kg/day, and the type of insulin regimen used during the hospital stay. However, in multivariate analysis adjusted for age, GFR < 60 ml/s, previous insulin use, study type (medicine versus surgery), TDD, and insulin regimen (basal/bolus versus SSI), only increasing age and type of insulin regimen during the hospital stay were independent predictors of hypoglycemia. Odds ratio for hypoglycemia (95% confidence interval) are shown in **Table 4**. Compared with treatment with SSI, the use of basal/bolus with glargine and glulisine resulted in increased odds ratio for hypoglycemia in surgical but not in medical patients. In contrast, treatment with detemir and aspart combination or with NPH and regular insulin were both associated with increased risk of hypoglycemia compared with SSI regimen in medical patients (**Table 4**).

Discussion

This study aimed to analyze the results of intervention clinical trials[14,16,29] in order to identify risk factors of hypoglycemia in insulin-treated general medical and surgical patients with type 2 diabetes. We found that the overall frequency of mild and severe hypoglycemia (<70 and <40 mg/dl) was 19% and 2%, respectively. During treatment, medical patients experienced higher numbers of hypoglycemia than surgical patients (23% versus 13%; p = .005), but the rate of severe hypoglycemia was similar between groups (1.9% versus 1.9%; p = not significant). Increasing age, impaired kidney function (GFR <60 ml/min/1.73 m^2), total daily insulin dose, and type of insulin therapy (basal/bolus versus SSI) during hospitalization are important contributors for hypoglycemia in both medical and surgical patients. Among these variables, increasing age and type of insulin regimen (basal/bolus versus SSI) were found to be independent predictors of hypoglycemic events in medicine and surgical patients with type 2 diabetes.

Hypoglycemia in hospitalized patients is a common and serious complication of intensified insulin treatment. The overall rate of severe hypoglycemia in previous ICU trials have ranged between 5% and 28.6%.[5,8,11–13,32] A similar prevalence has been reported in the non-ICU setting, where 5% to 32% of patients treated with subcutaneous insulin develop hypoglycemia (<3.9 mmol/liter [70 mg/dl]).[14–16] Minimizing the rate of hypoglycemia events is of major importance in ICU patients, because it has been shown that hypoglycemia may be an independent risk factor of poor clinical outcome and mortality.[24,33,34] In contrast to ICU patients and in agreement with retrospective studies,[26,27] we observed no increased mortality in insulin-treated patients. These studies have clearly shown that greater in-hospital mortality associated with hypoglycemia appears to be limited to patients with spontaneous hypoglycemia and not to patients with insulin-associated hypoglycemia. This suggests that spontaneous hypoglycemia may be a marker of disease burden, but it might not be a direct cause of mortality.

Table 4.
Multivariate Analysis of Predictors of Hypoglycemia

		Odds ratio, 95% confidence interval p value		
		All, medicine and surgery patients	Medicine	Surgery
Age, years		1.04, (1.02–1.08) p < .001	1.04, (1.01–1.07) p = .01	1.06, (1.01–1.10) p = .01
GFR < 60 ml/min/1.73 m^2		1.5, (0.9–2.7) p = .1	1.4, (0.7–2.9) p = .3	1.8, (0.7–4.8) p = .2
Total daily insulin dose ≥ 0.5 U/kg		1.3, (0.7–2.6) p = .4	1.5, (0.7–3.4) p = .3	0.8, (0.2–3.0) p = .8
Home insulin treatment		1.4, (0.7–2.5) p = .3	1.2, (0.5–2.6) p = .7	1.7, (0.6–4.7) p = .3
Insulin regimen in the hospital	Glargine/glulisine versus SSI	2.5, (1.1–5.1) p = .015	0.6, (0.2–1.9) p = .343	7.2, (2.3–22.4) p < .001
	Detemir/aspart versus SSI	6.5, (2.4–17.9) p < .001	3.1, (1.1–8.7) p = .030	Not applicable
	NPH/regular versus SSI	7.4, (2.7–20.0) p < .001	3.5, (1.3–9.6) p = .016	Not applicable

The majority of hospitalized patients with diabetes are treated non-ICU settings, thus it is important to identify risk factors associated with hypoglycemia in patients admitted to general wards. We found that increasing age, impaired kidney function, total daily insulin dose, and type of insulin therapy (basal/bolus versus SSI) are important risk factors for hypoglycemia in general medicine and surgery patients. These results are in agreement with Rubin and colleagues,[35] who highlighted the relationship between total daily insulin doses and the use of basal/bolus over SSI and hypoglycemia risk in the general medicine setting. In a study of 1990 hospital-ward patients with diabetes, the higher weight-based insulin doses (>0.6 U/kg/day) were associated with greater odds of hypoglycemia, independent of the types of insulin used. In addition, Boucai and associates[26] reported that increasing age and impaired renal function are associated with higher rates of hypoglycemia.

The frequency of mild hypoglycemia (<70 mg/dl) in medicine patients was twice as common as that observed in surgery patients (23% versus 13%; $p = .005$). Several factors may explain differences in hypoglycemia, including a worse kidney function, higher admission glucose and hemoglobin A1c levels, higher home insulin dose prior to admission, and higher daily insulin dosage during the hospital stay in medicine compared with surgical patients. The higher insulin requirement in the hospital could be explained by better oral intake and differences in insulin sensitivity in medicine compared with surgery patients. In addition, the use of insulin prior to admission also appears to increase the risk of hypoglycemic events during the hospital stay. Insulin naïve patients in the RABBIT Medicine trial had a rate of hypoglycemia <10% compared with ~20% in medicine and surgery patients treated with insulin prior to admission.

We acknowledge several limitations in our study, including a relative small number of patients and the fact that we excluded patients without a known history of diabetes prior to admission. Patients meeting these criteria make up a substantial percentage of hospitalized patients. We reported that hyperglycemia was present in 38% of patients admitted to the hospital and that one-third of these patients had no history of diabetes prior to the admission.[3] We also excluded patients treated with high-dose insulin and patients with hepatic and renal insufficiency who have been shown to have a higher risk of hypoglycemia during the hospital stay.[36] Large, randomized clinical trials are needed to determine the safety and efficacy of the three basal insulins (NPH, glargine, and detemir) in improving glycemic control and in reducing hypoglycemic events in general medicine and surgery patients in non-ICU settings.

In summary, hypoglycemia is common during subcutaneous insulin therapy in medical and surgical patients with type 2 diabetes. In the non-ICU setting, medical patients experience higher numbers of mild-to-moderate hypoglycemia than surgical patients. Factors associated with increased risk of hypoglycemia in general medicine and surgery patients treated with subcutaneous insulin include increasing age, impaired renal function, use of basal/bolus insulin over SSI regimen, and a total daily insulin dose > 0.5 U/kg.

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