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RESEARCH ARTICLE

Physiologic kinetic profile of glycemic response in a single dose of clonidine

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ABSTRACT

Background: Clonidine activates peripheral α-2 adrenoreceptors and influences glycemic levels. **Aim and Objective:** The aim and objective of the study was to determine the physiologic kinetic profile of glycemic response in a single dose of clonidine. **Materials and Methods:** Experimental data on fasting glycemic levels of Sprague-Dawley rats in a single dose intraperitoneal administration of clonidine were used to describe the rate mechanisms behind the physiologic response. Parameters of the kinetic models including zero-order, first-order, and second-order were estimated and compared using nonlinear regression analysis. **Results:** Clonidine administration resulted to a dose-dependent fasting glycemic level with maximal cumulative dose effect at 4 μg/kg. The overall physiologic glycemic response behaved under zero-order and first-order kinetic models on the first 3 h, while second-order kinetic model captures the fasting glycemic levels on the 3rd-8th h after drug administration. **Conclusion:** A 4 μg/kg optimal dose accentuates glycemic response behaving under a zero-order or first-order rate mechanism with maximal effect on the first 3 h after clonidine administration.

KEY WORDS: Kinetic Models; Glycemic Level; Clonidine; Zero-order; First-order; Second-order

INTRODUCTION

The release of epinephrine and norepinephrine during stressful conditions stimulates hepatic production of glucose[1] as these catecholamines have significant effects on glycogenolysis and lipolysis[2] which subsequently elevates glycemic level.[3] Clonidine, an α-2 adrenoceptor agonist, decreases norepinephrine release from nerve terminals[4] resulting to a dose-dependent decrease in the concentration of catecholamines in the blood after an oral administration.[5] As such, this justifies the suppressive effects of clonidine in the release of catecholamine and better glucose regulation during stressful conditions. However, clonidine and its derivatives have similar reaction patterns as these substances were found to be sedative and increased blood glucose levels[6] even at low doses,[7] but hyperglycemic responses were suppressed at higher doses.[8] Both intracisternal and intravenous clonidine administrations resulted to hyperglycemia reflecting variations in the mechanisms on its central and peripheral effects.[9] Clonidine mediates direct pancreatic peripheral α-agonist effects resulting to inhibition of secretion[10] and release of insulin[2] which explains clonidine-induced hyperglycemia.

Clonidine decreases blood pressure as it acts on the central α-adrenergic receptors but also influences glucagon, insulin, glucose, and catecholamines in various peripheral adrenergic receptors, as it has been used in the treatment of several medical conditions including diabetic gastroparesis, withdrawal symptoms (nicotine, alcohol, opioid), postmenopausal hotflushes, anesthetic and analgesic in pre- and post-operative procedures,[11] and in the management of painful diabetic

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neuropathy.[12] Hence, there is a need to further investigate and elucidate the kinetics of glycemic effects of clonidine. Although several studies have reported dose-dependent glycemic effects of clonidine in both humans and rats, no kinetic relationship and quantitative characterization of the glycemic effects in relation to experimental conditions applied as previous studies yielded conflicting findings depending on the dose, route, duration, and indication of administration. With these findings and the paucity of information on the kinetics of glycemic response to clonidine, this study investigated and elucidated the physiologic kinetic profile of glycemic response in a single dose administration of clonidine. Understanding the physiologic kinetics of glycemic response will offer a possibly better therapeutic strategy of maintaining, controlling, or improving glycemic levels of patients in clinical setting.

MATERIALS AND METHODS

A completely randomized study design with five treatment groups (subjects assigned to Group I received 1 μg/kg dose; Group II consisted of subjects with 2 μg/kg dose; a dose of 4 μg/kg was given to subjects in Group III; subjects in Group IV received 7 μg/kg dose, and a control group in Group V received 0.9% NaCl) was employed and approved by the Ethics and Review Board. The Philippine Bureau of Food and Drugs provided the 35 adult, 140-330 g in weight, male Sprague-Dawley rats which were placed in individual steel cages, kept in an animal house, maintained at 22-24°C in a 12 h dark and light cycle with unlimited access to standard rat pellets and water, acclimatized for 2 weeks before treatment administration.[13] Seven subjects were assigned in each treatment group 24 h before the treatment administration. These were fasted for an 18-h period and remained fasted, without restriction to water, during the 8-h monitoring period after the intraperitoneal treatment administration.

Clonidine rat doses were extrapolated from absolute human doses based on the surface area relationship.[14] A 7.5 μg/mL (w/v) stock solution was prepared by dissolving 10 75 μg tablets of clonidine hydrochloride (Catapres®) in a 100 mL 0.9% NaCl solution. Subsequently, volume corresponding to the extrapolated dose for each subject was obtained and was intraperitoneally administered using gauge 25 needles in 3 cc syringes (Terumo®). At least 1 μL of whole blood samples were drawn via tail lancing method to quantify glycemic levels using the OneTouch® Ultra™ glucometer (Life Scan, Johnson & Johnson, USA). Baseline glycemic measurements were obtained an hour before treatment administration, and eight subsequent measurements were performed every hour after the treatment administration.

Student's *t*-test was employed to assess changes in the fasting glycemic responses within a specific treatment group. In identifying differences in the means of fasting glycemic levels in the different treatment groups, analysis of variance was utilized. Tukey least significant difference in the *post-hoc* analyses identified which pairs of treatment groups significantly vary. Nonlinear relationships were defined between fasting glycemic level and time. Over the 8-h monitoring period, the cumulative blood glucose levels were calculated in each of the treatment group to establish a possible dose-response relationship using area under the curve (AUC) and nonlinear regression analysis. Zero-order, first-order, and second-order kinetic models were tested to elucidate rate mechanisms behind the glycemic response with parameters estimated employing Gauss-Newton method. All statistical and numerical analyses were performed using Statistical Analysis System software at 5% level of significance.

RESULTS

The hourly fasting glycemic levels increase as the dose increases from 1 to 4 μg/kg (Table 1). However, on the 2nd to the 4th monitoring hours, the mean fasting glycemic levels in the 4 μg/kg are >7 μg/kg treatment group ($P > 0.05$). The average glycemic levels in the control ($P = 0.97$), 1 μg/kg ($P = 0.62$), and 2 μg/kg ($P = 0.06$) treatment groups did not vary across the 8-h monitoring period compared to the 4 μg/kg and the 7 μg/kg treatment groups ($P < 0.01$), where the mean fasting glycemic levels changed over time. Before the single dose intraperitoneal administration of clonidine, the mean baseline fasting glycemic levels among the treatment groups do not differ ($P = 0.91$). On the first to the 4th h after the treatment administration, glycemic responses vary among the treatment groups ($P < 0.05$). An hour after drug administration, differences among the means of treatment groups were observed between 1 and 7 μg/kg (P=0.03), 2 μg/kg and control ($P = 0.01$), 4 μg/kg and control ($P = 0.01$), and 7 μg/kg and control ($P = 0.00$). On the 2nd h after drug administration, the mean fasting glycemic levels in the 1 μg/kg differ with the 2, 4, and 7 μg/kg treatment groups ($P < 0.01$). Likewise, the mean fasting glycemic levels in the control group differ with 2, 4, and 7 μg/kg treatment groups ($P < 0.01$). The mean fasting glycemic levels in the 4 μg/kg vary with the 1, 2 μg/kg, and control groups 3 h after drug administration ($P < 0.01$). Similarly, the mean fasting glycemic levels in the 7 μg/kg treatment group differ with the 1, 2 μg/kg, and control groups ($P < 0.01$). The mean fasting glycemic levels in the 4 μg/kg differ with the 1, 2 μg/kg, and control groups 4 h after clonidine has been administered ($P < 0.05$), and the average glycemic levels in the 7 μg/kg and the control groups vary ($P < 0.05$). The mean fasting glycemic levels did not vary 5-8 h since drug administration ($P > 0.05$).

Over the 8-h monitoring period, the cumulative fasting glycemic levels were computed with relatively higher values of AUC identified in the 4 and 7 μg/kg treatment groups with no significant change in the AUC values from 0 to 1 μg/kg doses of clonidine. However, in 1-4 μg/kg interval, AUC has significantly increased with a possible saturation at 4 μg/kg as no significant change in AUC was observed

Table 1: Comparison of glycemic levels among the different doses of clonidine across time

Time (h)	Glycemic level (mean ± standard deviation, mg/dL)				
	1 µg/kg	2 µg/kg	4 µg/kg	7 µg/kg	0.9% NaCl
Baseline	62.714±13.162	58.714±6.157	62.500±9.439	59.429±12.501	62.143±7.105
1	74.000±11.518	83.000±16.176	83.833±14.811	90.571±17.831	60.857±4.598
2	71.143±11.950	87.429±9.693	97.667±10.893	89.000±7.371	61.286±12.606
3	67.429±13.151	75.857±11.852	102.833±11.514	92.714±1.543	66.714±6.488
4	69.143±14.758	71.857±18.916	89.833±8.472	83.857±7.267	65.000±13.540
5	60.857±9.388	70.429±22.941	75.500±14.110	86.286±14.523	67.286±12.932
6	61.429±11.297	66.571±25.396	68.667±12.485	72.714±13.238	78.429±31.696
7	66.429±14.581	62.571±18.293	69.500±16.404	71.571±6.949	68.286±9.912
8	68.286±18.400	64.857±20.440	63.000±7.483	71.429±11.886	69.857±14.218

from 4 to 7 µg/kg doses. Since an optimal dose of 4 µg/kg clonidine has been identified to have a maximal effect on the glycemic response on the first 3 h after the intraperitoneal administration, further elucidation on the physiologic kinetics of the glycemic response in a 4 µg/kg clonidine dose revealed that on the first 3 h after intraperitoneal drug administration, the fasting blood glucose levels behave in accordance to zero-order (R^2 = 0.9329) and first-order (R^2 = 0.9020) kinetic models (Table 2). These models offer adequate fit of the observed experimental values (Figure 1a). From the 3rd to 8th h after clonidine administration, the kinetic behavior of the fasting glycemic levels of a 4 µg/kg clonidine dose obey the second-order kinetic model (R^2 = 0.9341) (Table 2). The graph of the second-order kinetic model offers a reasonable fit of the observed experimental values in the 3rd to 8th-h monitoring period (Figure 1b).

Table 2: Parameter estimates of the different physiologic kinetic models in the 4 µg/kg dose

Model	Equation	Parameter	Time interval	
			0-3 h	3-8 h
Zero-order	$G = c_o t + G_o$	C_0	13.483	−7.629
		G_0	66.483	120.180
		R^2	0.9329	0.8879
First-order	$G = G_o e^{c_1 t}$	c_1	0.165	−0.095
		G_0	66.527	129.748
		R^2	0.9020	0.9140
Second-order	$G = \frac{G_o}{1 - c_2 G_o t}$	c_2	0.002	−0.001
		G_0	66.225	151.515
		R^2	0.8667	0.9341

G: Fasting glycemic level (mg/dL), t: Time (h), G_o: Initial fasting glycemic level (mg/dL), c_0: Zero-order rate constant (mg/dL/min), c_1: First-order rate constant (min^{-1}), c_2: Second-order rate constant (dL/mg/min), R^2: Coefficient of determination

DISCUSSION

In animal studies, clonidine has been observed to have a nonlinear pharmacokinetic behavior[15] with its sympathomimetic effects described as a steady rise in the glycemic levels in response to a single dose administration. In this study, the dose-dependent response identified on the first 4 monitoring hours is a similar phenomenon described among patients with essential hypertension.[16] A possible saturation kinetics was attained when at least 4 µg/kg dose was administered and AUC linearly increased with dose.[16] Stimulation of postsynaptic α-2 adrenoceptor inhibits insulin release while stimulation of the presynaptic α-2 adrenoceptor inhibits release of norepinephrine describing clonidine's sympathomimetic and sympatholytic actions.[17]

Fasting glycemic levels were not affected when a 1 µg/kg clonidine dose was administered contrary to the hyperglycemic responses during surgery when a similar dose was administered.[14] A 1 µg/kg clonidine premedication accentuated hyperglycemic responses to lower abdominal surgery caused by significant reduction in insulin plasma concentrations,[14] while an administration of 0.4 mg/kg clonidine significantly decreased glucose level.[18] The disagreement in the findings might be possibly due to the variations in the mode of administration (intraperitoneal vs. intravenous) and differences in stress conditions (surgery vs. no surgery). In this study, 1 µg/kg clonidine did not inhibit sympathoadrenergic stimulation suggesting changes in hypothalamic pituitary adrenal axis mainly regulate the serum glucose levels.[14]

The hyperglycemic responses observed in the 2, 4, and 7 µg/kg clonidine doses differ from the decreased glycemic response at 3-6 µg/kg due to variations in study populations and experimental conditions.[8,19] Subarachnoid clonidine reduced glucose utilization[20] while intrathecal clonidine administration significantly elevated the level of plasma corticosterone.[21] On the first 4 h of monitoring, 4 and 7 µg/kg doses accentuated glycemic response possibly due to the activation of the pancreatic postsynaptic α-2 adrenoreceptors as these doses have maximal glycemic values observed 3 h

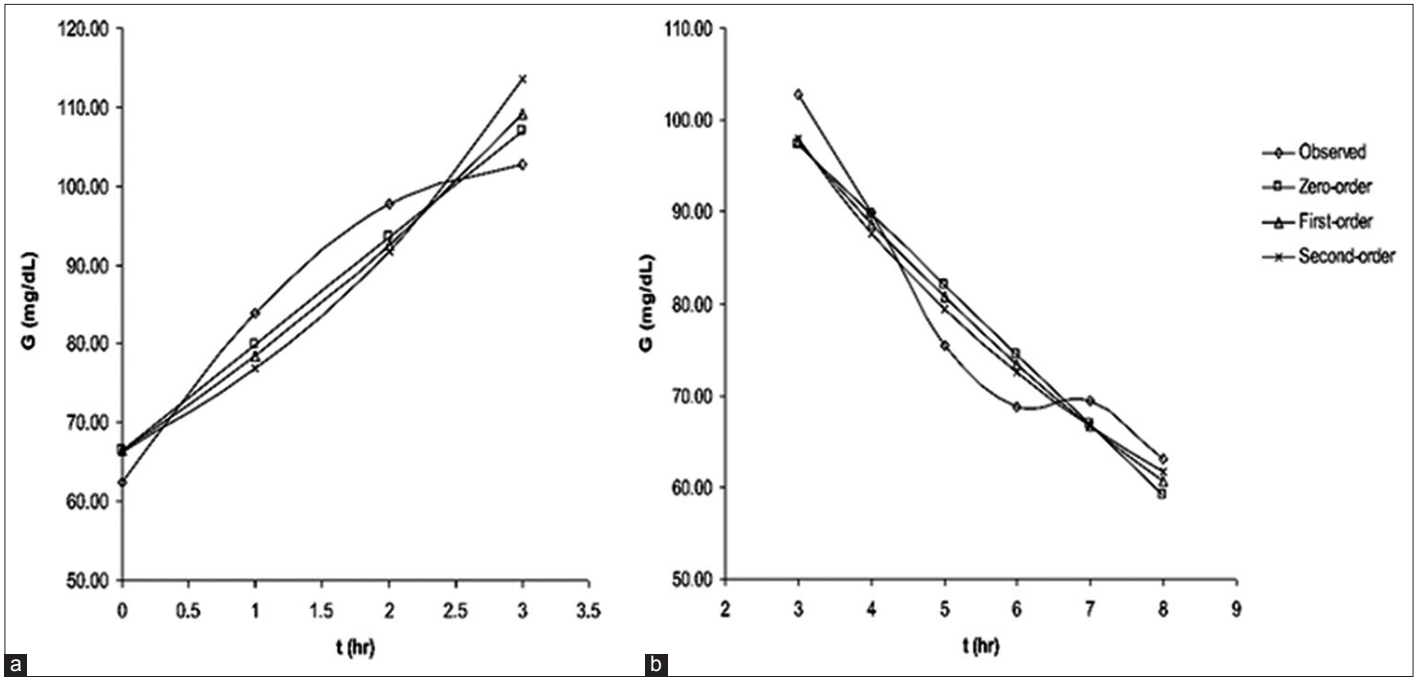

Figure 1: (a and b) physiologic kinetic profile of glycemic response in a 4 μg/kg clonidine dose

since drug administration compared to the 2 μg/kg noted to peak 2 h after drug administration. These maximal effects are within the specified range of 1.5-2.5 h for clonidine to reach its maximal plasma concentration after a single dose.[16] Half-lives vary depending on the dose, as single oral doses of clonidine (1.77 and 2.33 μg/kg) have a half-life of 0.5 h, higher dose (3.36 μg/kg) has a half-life of 12.8±2 h, and low doses have a half-life of 6.2±2.3 h.[16] For epidural clonidine, administration of a 150 μg yields elimination half-life of 66±2 min with an absorption half-life of 31±7 min and T_{max} of 60±7 min.[22] The observed effects of 2, 4, and 7 μg/kg doses may reflect the relationship between the plasma concentration and time when plotted for an intraperitoneal administration of clonidine. However, no published studies are currently available involving intraperitoneal administration of clonidine to describe plasma concentration across time which will define its half-life and T_{max} values. As an oral monotherapy, in increasing doses (3.1-25.7 μg/kg), among patients with essential hypertension, no change in plasma clonidine was observed which clearly suggests the need for close monitoring of clonidine therapy.[23]

Glycemic responses across varying doses of clonidine revealed a consistent dose-dependent relationship. This clonidine-induced hyperglycemia is mediated by the glucocorticoid system via spinal nerves or peripheral sympathetic nervous system activation[21] as clonidine specifically acts on α-2 pancreatic receptors.[24] The cumulative dose effect of 4 and 7 μg/kg doses did not vary indicating a possible saturation of receptors at a 4 μg/kg dose, saturation was identified on the 3rd h which is possibly explained by the expected completion of clonidine absorption within 2.5 h.[16] Subsequently, glycemic responses start to decrease possibly because of the clonidine-induced hyperglycemia stimulating insulin release via a different mechanism. The glycemic response in a 4 μg/kg dose described a slower rise to maximal fasting glycemic level and a smoother decline. However, among children receiving clonidine, 2% glucose infusion maintained the glycemic concentrations within physiologic ranges[8] since clonidine alone resulted to significant drowsiness which may mask early sign of severe hypoglycemia.[25]

Acute clonidine administration has been identified to induce a significant elevation in human glycemic levels as a significant reduction in concentrations of immunoreactive serum insulin and elevation in serum glucose were noted 5 min after either 2 or 20 μg/kg of clonidine were administered for 10 min.[26] However, prolonged clonidine administration among hypertensive patients did not affect their basal plasma glucose and glucose tolerance, serum insulin concentration and insulin response to oral glucose suggesting some counter-regulatory homeostatic mechanisms in glucose metabolism on the acute effect of clonidine administration.[27] Fifteen to 18 h after cessation of a continuous subcutaneous clonidine infusion 10 μg/kg/h for 10 days, glycemic levels significantly decreased while the insulin levels remained suppressed which suggests that the hypoglycemia is a result of an increased metabolic needs along with the post-infusion withdrawal syndrome.[28] As a premedication of type 2 diabetes mellitus patients before surgery, clonidine significantly improved glycemic levels with a reduction in insulin requirements during the ophthalmic procedure[19] while a 4-week treatment with 2.5 mg/week transdermal patch clonidine showed a significant reduction in the fasting glucose levels.[29] Transdermal clonidine decreased norepinephrine and epinephrine

responses, but did not alter cortisol response or extent of glucose recovery from hypoglycemia[30] while subcutaneous administration of clonidine in fasted mice slightly increased glycemic levels in a dose-dependent manner[31] and daily administration of 25 μg/kg clonidine for 6 weeks has several favorable metabolic and endocrine effects.[32]

Regardless of the dose, 5 h after intraperitoneal administration of clonidine, glycemic levels did not vary suggesting that clonidine has possibly reached its maximal plasma concentration within the first 5 h after a single dose when administered intraperitoneally. In this study, detailed assessment of the physiologic kinetic profile of the glycemic response in a single dose administration of clonidine revealed that the optimum dose is at 4 μg/kg, and the glycemic response reflects a linear increase of 13.48 mg/dL in the mean glycemic level given that the physiologic response behaved under a zero-order rate mechanism within the time interval when clonidine approaches its maximal effect. Glycemic level elevation is slightly lower when compared to the 20 mg/dL elevation in the fasting glycemic level consistently observed in monotherapy transdermal clonidine (Catapres-TTS) among mild hypertensives.[33] Beyond the time of maximal effect, physiologic kinetics of glycemic response changes into a second-order rate mechanism. Therefore, it is necessary to design a better therapeutic strategy which closely simulates physiologic metabolism such as insulin therapy to suppress endogenous glucose production and to stimulate glucose utilization. However, attempts to administer exogenous insulin, regardless of the regimen, expose patients to 5-10% risk of hypoglycemia.[34] Hence, better understanding of the physiologic kinetics and temporal profile of glycemic response to clonidine administration during these stressful conditions allows the clinician to consider an optimum therapeutic strategy without exposing patients to a possible risk of hypoglycemia.

CONCLUSION

Intraperitoneal administration of clonidine influences glycemic response at varying doses and exhibits a similar time distribution pattern regardless of dose. The maximal effect was observed within the first 3 h after drug administration at an optimal dose of 4 μg/kg. The physiologic kinetic profile of glycemic response behaves under either a zero-order or a first-order rate mechanism. However, beyond the maximal effect, glycemic response kinetic profile shifts to a second-order rate mechanism as the glycemic levels diminished possibly because clonidine-induced hyperglycemia stimulated pancreatic beta cells to secrete insulin.

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