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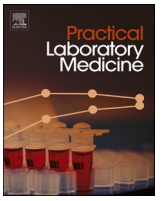

Dopamine infusion at typical infusion rates does not cause interference on plasma creatinine assays

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ABSTRACT

a) Objectives: Dopamine is known to cause negative interference on enzymatic creatinine measurement. However, its effect on the Jaffe reaction, and its concentration required to interfere with enzymatic reactions, remain uncertain. This study was designed to study the interference of stable dopamine infusion on Jaffe and enzymatic creatinine assays, as well as the effect of dopamine infusion drip arm contamination on both creatinine assays.
b) Design and Methods: For the first part of the study, dopamine was spiked into pooled plasma samples at different concentrations to mimic the scenario of patients on dopamine infusion at an infusion rate between 2 and 20 μg/kg/min. For the second part, dopamine preparation of 2 g/L (same as the preparation used clinically) was mixed with pooled plasma samples at different proportions to mimic drip arm contamination. Creatinine concentrations were measured using Jaffe and enzymatic reactions.
c) Results: The first part showed that creatinine measurements were not interfered by dopamine infusion at an infusion rate between 2 and 20 μg/kg/min. The second part showed that dopamine could negatively interfere with enzymatic creatinine assays, even with minute drip arm contamination. The effect on the Jaffe reaction was less significant.
d) Discussion: Creatinine concentration could be reliably measured by Jaffe or enzymatic reactions if samples are from venous access sites other than the site of dopamine infusion. When dopamine interference on enzymatic creatinine assays is suspected, using the Jaffe reaction to cross-check may provide additional useful information.

1. Introduction

Dopamine is commonly used as a vasopressor in critically ill patients for circulatory support [1]. Its half-life is only 2 min [2]. Therefore, it is used as a continuous infusion to maintain its efficacy. The usual range of infusion rate of dopamine is between 2 μg/kg/min and 20 μg/kg/min. It exerts its effects via actions on different receptors when given at different infusion rates. At low doses (0.5–3 μg/kg/min), it promotes vasodilation and improves the coronary, cerebral and renal circulation by acting on dopaminergic

Abbreviations: APS, analytical performance specifications.

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receptors. At intermediate doses (3–10 μg/kg/min), dopamine binds to β1-adrenergic receptors to boost cardiac inotropic and chronotropic effects. At higher infusion rates (10–20 μg/kg/min), dopamine activates α1-adrenergic receptors to cause vasoconstriction [3].

Creatinine is an analyte widely used for assessing glomerular filtration rate and renal function. The mainstream laboratory methods for measuring creatinine concentration are the Jaffe reaction and enzymatic reactions [4]. The Jaffe reaction is based on the reaction between picric acid and creatinine in alkaline solution, which yields a red chromogen for colorimetric measurement. Enzymatic reactions for creatinine rely on the use of a combination of enzymes, with the most common combination being creatininase, creatinase, sarcosine oxidase and peroxidase. The Jaffe reaction is lower in cost, but more prone to interference compared to enzymatic reactions [5].

Dopamine is known to cause interference on enzymatic assays because dopamine can form a quinone-imine dye with a lower absorptivity by reacting with 4-aminophenazone, one of the substrates in the last enzymatic reaction for measuring creatinine, in the presence of peroxidase [6]. The effect of dopamine on the Jaffe reaction is not well studied. The concentration of dopamine that can affect creatinine assays is also not well studied. We presented a study in which we sought to simulate the effect of dopamine infusion (at typical therapeutic concentrations), on creatinine measured by Jaffe and enzymatic reactions.

2. Materials and methods

2.1. Materials

Plasma samples from outpatients who were not on methyldopa or levodopa were pooled, with the target concentration of creatinine being 100, 200, 800 and 1200 μmol/L. Dopamine ampule used for this study was Dopamine Basi 200mg/5 mL obtained from the pharmacy at our hospital. Dopamine is commonly prepared by diluting one ampule with either 100 mL normal saline or dextrose 5 % with the final dopamine concentration being 2 g/L; the former was used in this study to prepare the master dopamine solution of 2 g/L.

3. Methods

This study consisted of two parts. The first part simulated the scenario of blood sample collection (from non-infusion site) from patients receiving stable dopamine infusion with infusion rates ranging from 2 to 20 μg/kg/min, and the second part simulated a scenario of drip arm contamination by dopamine infusion. In general, higher concentrations of dopamine were spiked in for the second part of the experiment. This was based on the assumption that higher levels of dopamine are typically found in drip-arm samples than properly collected samples from patients on stable dopamine infusion. Thus, plasma samples with a higher baseline creatinine concentration were used in the second part, in order to better illustrate the effect of dopamine, while still producing clearly measurable creatinine values. Creatinine concentrations, based on Jaffe and enzymatic reactions (a combination of creatininase, creatinase, sarcosine oxidase and peroxidase), were measured by cobas® 8000 modular analyzer series (Roche Diagnostics).

a. Determination of dopamine concentration spiked to simulate stable dopamine infusion with an infusion rate between 2 and 20 μg/kg/min

Dopamine concentration after stable infusion was predicted based on the publication by MacGregor et al. [7]. From the study, steady state plasma concentration of dopamine was in a linear relationship with the infusion rate. In that study, the maximum concentration of dopamine for a healthy male receiving 10 μg/kg/min of dopamine infusion was approximately 200 μg/L; accordingly, we used a coefficient of 20 to roughly estimate the amount of dopamine to be spiked, so as to estimate the effect of dopamine on creatinine assays when dopamine concentrations are at their higher end.

b. Part One: Simulating Blood Sample Collection From Non-Infusion Site From Patients On Stable Dopamine Infusion

Two pooled plasma samples with creatinine concentrations of 100 and 800 μmol/L were used. Each pooled sample was divided into seven 0.8 mL aliquots. Different concentrations (0, 40, 100, 160, 200, 320, 400 μg/L) of dopamine (to simulate an infusion rate of 0, 2, 5, 8, 10, 16 and 20 μg/kg/min, respectively) were spiked to each aliquot. Creatinine concentrations in the aliquots were measured by Jaffe and enzymatic methods.

c. Part Two: Simulating Blood Sample Collection From Patients On Dopamine Infusion with Drip Arm Contamination Dopamine Infusion

Two pooled plasma samples with creatinine concentration of 200 and 1200 μmol/L were used. Each pooled sample was divided into ten aliquots. To simulate drip arm contamination, each aliquot was mixed with different volumes of the master dopamine solution, with the final sample volume being 0.8 mL. Percentage of dopamine by volume in the aliquots were 0 %, 2 %, 4 %, 6 %, 8 %, 10 %, 20 %, 30 %, 40 % and 50 %. Creatinine concentrations in the aliquots were measured by Jaffe and enzymatic methods.

d. Data Analysis

Table 1
Results for Part One, which simulates blood collection from non-infusion site(s) from patients on stable dopamine infusion at a rate ranging from 0 to 20 μg/kg/min. Percentage biases within ±8 % indicate acceptable results.

	Dopamine Infusion Rate To Be Simulated (μg/kg/min)	Dopamine Concentration Spiked Into The Aliquot (μg/L)	Measured Creatinine After Spiking Dopamine (Jaffe) (μmol/L)	Percentage Bias Compared To Baseline Creatinine (Jaffe) (%)	Measured Creatinine After Spiking Dopamine (Enzymatic) (μmol/L)	Percentage Bias Compared To Baseline Creatinine (Enzymatic) (%)
Pooled Sample 1	Baseline (0)	0	131	0.0	127	0.0
	2	40	132	0.8	126	−0.8
	5	100	123	−6.1	125	−1.6
	8	160	127	−3.1	126	−0.8
	10	200	124	−5.3	126	−0.8
	16	320	124	−5.3	125	−1.6
	20	400	127	−3.1	122	−3.9
Pooled Sample 2	Baseline (0)	0	855	0.0	891	0.0
	2	40	885	3.5	892	0.1
	5	100	889	4.0	890	−0.1
	8	160	894	4.6	883	−0.9
	10	200	874	2.2	867	−2.7
	16	320	847	−0.9	869	−2.5
	20	400	856	0.1	873	−2.0

Table 2
Results for Part Two, which simulates drip arm contamination by dopamine infusion. Results with percentage difference > ±8 % were highlighted in bold typeface.

% Dopamine By Volume		Dopamine Concentration In The Aliquot (g/L (μmol/L))	Expected Creatinine Concentration (μmol/L)*	Expected Dopamine To Creatinine Molar Ratio	Measured Creatinine (μmol/L)	Percentage Bias Compared To Expected Creatinine Concentration (%)
Pooled Sample 1 (Jaffe)	Baseline (0 %)	0 (0)	236	0	236	0
	2 %	0.04 (261)	231	1.1	224	−3.1
	4 %	0.08 (522)	227	2.3	220	−2.9
	6 %	0.12 (783)	222	3.5	202	**−8.9**
	8 %	0.16 (1045)	217	4.8	197	**−9.3**
	10 %	0.2 (1306)	212	6.1	194	**−8.7**
	20 %	0.4 (2611)	189	13.8	159	**−15.8**
	30 %	0.6 (3917)	165	23.7	125	**−24.3**
	40 %	0.8 (5223)	142	36.9	133	−6.1
	50 %	1 (6528)	118	55.3	107	**−9.3**
Pooled Sample 1 (Enzymatic)	Baseline (0 %)	0 (0)	226	0	226	0
	2 %	0.04 (261)	221	1.2	52	**−76.5**
	4 %	0.08 (522)	217	2.4	44	**−79.7**
	6 %	0.12 (783)	212	3.7	39	**−81.6**
	8 %	0.16 (1045)	208	5	39	**−81.2**
	10 %	0.2 (1306)	203	6.4	34	**−83.3**
	20 %	0.4 (2611)	181	14.4	25	**−86.2**
	30 %	0.6 (3917)	158	24.8	21	**−86.7**
	40 %	0.8 (5223)	136	38.5	12	**−91.2**
	50 %	1 (6528)	113	57.8	7	**−93.8**
Pooled Sample 2 (Jaffe)	Baseline (0 %)	0 (0)	1217	0	1217	0
	2 %	0.04 (261)	1193	0.2	1148	−3.7
	4 %	0.08 (522)	1168	0.4	1114	−4.6
	6 %	0.12 (783)	1144	0.7	1114	−2.6
	8 %	0.16 (1045)	1120	0.9	1072	−4.3
	10 %	0.2 (1306)	1095	1.2	1073	−2
	20 %	0.4 (2611)	974	2.7	929	−4.6
	30 %	0.6 (3917)	852	4.6	798	−6.3
	40 %	0.8 (5223)	730	7.2	648	**−11.3**
	50 %	1 (6528)	609	10.7	516	**−15.2**
Pooled Sample 2 (Enzymatic)	Baseline (0 %)	0 (0)	1209	0	1209	0
	2 %	0.04 (261)	1185	0.2	780	**−34.2**
	4 %	0.08 (522)	1161	0.4	338	**−70.9**
	6 %	0.12 (783)	1136	0.7	252	**−77.8**
	8 %	0.16 (1045)	1112	0.9	220	**−80.2**
	10 %	0.2 (1306)	1088	1.2	207	**−81**
	20 %	0.4 (2611)	967	2.7	158	**−83.7**
	30 %	0.6 (3917)	846	4.6	130	**−84.6**
	40 %	0.8 (5223)	725	7.2	103	**−85.8**
	50 %	1 (6528)	605	10.8	71	**−88.3**

*Expected creatinine concentration (after considering dilutional effects) was calculated based on the following equation: expected creatinine concentration = baseline creatinine concentration * (1 - % Dopamine by Volume).

Creatinine concentrations were corrected for the spiked volume. Percentage changes of creatinine in different aliquots compared to that in aliquot without spiking dopamine were calculated. Based on the analytical performance specifications (APS) specified in the Royal College of Pathologists of Australasia Quality Assurance Programs (the external quality assurance program adopted by our laboratory), for a creatinine concentration more than 100 μmol/L, a less than ±8 % difference was deemed acceptable.

4. Results

Tables 1 and 2 summarised the results for Part One and Part Two of the study respectively. For Part One, all the measured creatinine results were within the APS of ±8 % compared to baseline irrespective of methodology, which suggested no significant interference of dopamine on creatinine measurements (Fig. 1). For Part Two, after spiking dopamine, all creatinine results measured by the enzymatic reaction showed a significant drop compared to expected creatinine concentration (after correcting for dilution), even when the molar ratio of dopamine to creatinine was only 0.2. For the Jaffe reaction, dopamine could negatively interfere with creatinine results when the molar ratio was more than 3, but the interference was much less significant compared to the enzymatic reaction (Fig. 2).

5. Discussion

Dopamine is well known to negatively interfere with the enzymatic creatinine assays. However, the concentration of dopamine to cause such interference, and any similar effect on the Jaffe creatinine assay remains uncertain.

The first part of our study has demonstrated that the interferences by therapeutic dopamine infusion on both Jaffe and enzymatic creatinine assays were within APS, thus, creatinine measured by either method was not significantly affected by therapeutic levels of dopamine. This was consistent with some observational studies [8,9] which showed that creatinine measured in samples from venous access sites other than the site of dopamine infusion were not significantly interfered by dopamine, regardless of methodology. However, in those studies, the dopamine infusion rates were not mentioned. Our study could show that even when the dopamine was infused at the upper limit of typical infusion rates, creatinine measurements by either Jaffe or enzymatic reactions were not affected.

The second part of our study has shown that dopamine contamination (when sampling from infusion sites) negatively affects creatinine measurement, with the enzymatic method being affected more significantly than the Jaffe reaction. The samples with a higher creatinine concentration were more resistant to dopamine interference. For example, by using the Jaffe method, a creatinine concentration of around 1200 μmol/L only started to show significant negative interference when 40 % dopamine contamination was present, compared to 6 % dopamine contamination when creatinine concentration was around 200 μmol/L. The extent of contamination was related to the dopamine-creatinine molar ratio in the samples. While creatinine measurement by the enzymatic method showed an increasingly negative interference as the dopamine-to-creatinine molar ratio rose, a more fluctuating degree of interference on creatinine was observed with different dopamine-to-creatinine molar ratio for the Jaffe method. The latter finding was similarly observed in a study by Saenger et al. [9]. Our results showed that the Jaffe method was not completely free of dopamine interference. Nevertheless, only a much higher amount of dopamine contamination would cause a significantly negative impact on creatinine measurement by the Jaffe method compared to the enzymatic method. Therefore, using the Jaffe method to cross-check the enzymatic creatinine results could provide a useful clue in cases in which dopamine interference is suspected.

Our study has some limitations. First, use of normal saline as a diluent might cause matrix effect on the measurement of creatinine, especially when the spiked dopamine volume was significantly large compared to the plasma volume. However, according to

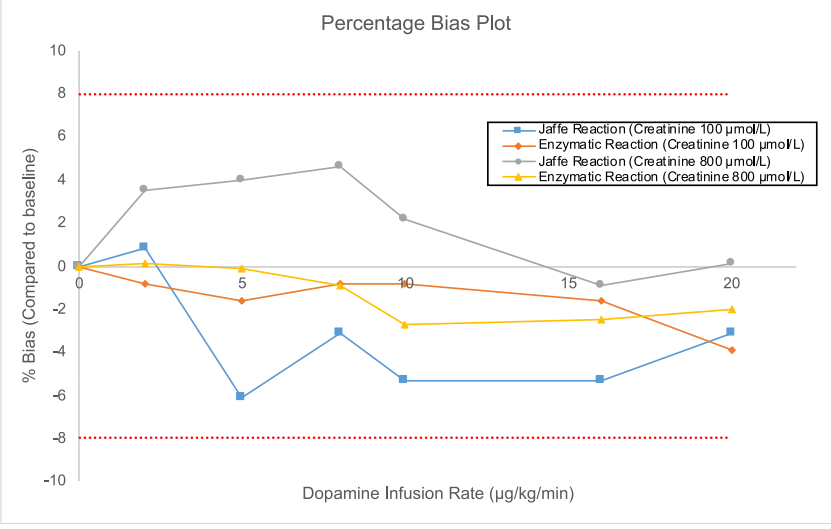

Fig. 1. Percentage bias plot for Part One, which simulates blood collection avoiding infusion site(s) from patients on stable dopamine infusion at a rate ranging from 0 to 20 μg/kg/min. Percentage bias within ±8 % (indicated by dotted lines) indicate acceptable results.

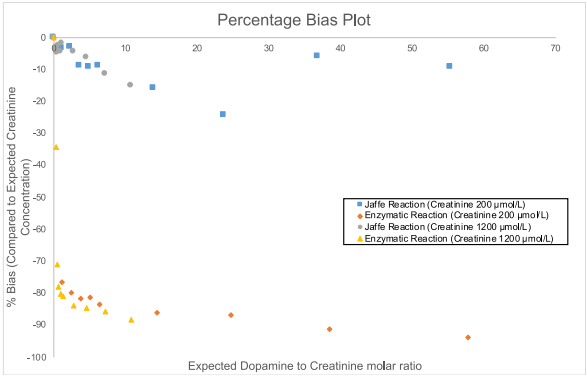

Fig. 2. Percentage bias plot for Part Two, which simulates drip arm contamination by dopamine infusion.

manufacturer kit inserts of Roche creatinine assays, normal saline is a recommended diluent. The effect posed on our results due to matrix effect was thus thought to be minimal. Second, the effect of dopamine metabolites (e.g. epinephrine and 3-methoxytyramine) on creatinine assays could not be assessed in this study. However, it has previously been reported that dopamine would pose a more significant interference on creatinine assays compared to epinephrine [8]. This is hence thought to have a minimal effect on the results of the first part of our study.

In conclusion, this study showed that creatinine results are unlikely to be significantly affected in patients on dopamine infusion at typical infusion rates, irrespective of methodology used for creatinine measurement (Jaffe or enzymatic). However, samples collected from the infusion site should be avoided for measuring creatinine, as significant negative interference was demonstrated when this scenario was simulated, particularly for enzymatic methods. Indeed, for samples collected from infusion sites, even if creatinine is measured by the Jaffe reaction, it may also pose a smaller negative interference, especially when the dopamine-to-creatinine molar ratio is high. Laboratorians and healthcare professionals should thus be cautious when interpreting results in such cases.

CRediT authorship contribution statement

Jenny Yeuk Ki Cheng: Writing – original draft, Investigation, Conceptualization. **Shreenidhi Ranganatha Subramaniam:** Writing – review & editing, Formal analysis. **Stephanie C.Y. Yu:** Writing – review & editing, Formal analysis. **L.Y. Lois Choy:** Writing – review & editing, Formal analysis. **Jeffrey Sung Shing Kwok:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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