Journal of Endocrinology, Metabolism and Diabetes of South Africa 2022; 27(2):75–77
https://doi.org/10.1080/16089677.2021.2018803

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

ARTICLE

The utility of serial prolactin sampling in healthy adult volunteers

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Background: Stress hyperprolactinemia is a common cause of elevated prolactin (PRL) and often leads to additional investigation and radiation exposure. The results of PRL serial sampling in healthy adult volunteers to determine the utility of delayed collection are reported.
Methods: Cannulated serial PRL samples were collected from 30 healthy adult volunteers between April and May 2018 at 20-minute intervals from arrival to 60 minutes (T0, T20, T40 and T60). Exclusion criteria were known risk factors for hyperprolactinemia, and patients fasted for six hours. Cortisol (CORT) was collected as a surrogate marker for stress.
Results: Thirty (30) adult volunteers ($n = 15$ female) had a mean age of 34.7 (+/- 9.5), and mean baseline PRL of 9.7 µg/l in males and 15.8 µg/l females. Elevated PRL-T0 was observed in four volunteers ($n = 3$ male), all of which normalised at different intervals by T60 with serial sampling. The highest PRL was 33.7 µg/ml, normalised at T20, and had concomitant elevated cortisol levels, which remained elevated at T60. The delta decrease (Δ) for PRL was negative for all intervals ($p < 0.05$) and mirrored the delta decrease of cortisol ($p < 0.05$).
Conclusion: In 30 healthy adult volunteers presenting for cannulated serial PRL sampling, four had elevated baseline levels that normalised at different intervals up to T60. The delta decrease (Δ) for PRL was negative for all intervals.

Keywords: cortisol, interval, prolactin, rate of decline, serial sampling

Background

Prolactin (PRL), secreted from the pituitary gland, peaks post-partum to induce lactation and increases in parallel to other stress hormones such as growth hormone and cortisol.[1,2] Normal prolactin levels are < 25 µg/l in females and < 20 µg/l in males.[1]

Pathological hyperprolactinemia includes various drugs, renal failure, pituitary stalk effect, primary hypothyroidism and pituitary tumours. It is important to distinguish these causes from the physiological elevation of PRL, such as exercise, stress and breastfeeding.[1]

The indications for PRL testing include infertility, menstrual irregularities and galactorrhoea in women and hypogonadotropic hypogonadism and/or gynaecomastia in men and the prevalence ranges from 0.4% to 1% in the general population, and up to 17% in fertility services.[3]

The International Society for Endocrinology (ISE) recommends that hyperprolactinaemia can be established on a single measurement of PRL, provided the sample was obtained without excessive venepuncture stress. If the diagnosis is in doubt, the PRL should be repeated. Marginally elevated PRL levels often lead to more investigations including magnetic resonance imaging (MRI) aimed at excluding pituitary tumours.[1,2] Serial PRL sampling has been utilized in prior studies in the evaluation of mild hyperprolactinemia.[4]

The standard operating procedure (SOP) for PRL testing in the private health sector in South Africa is delayed venepuncture by 15–20 minutes, but excludes standard cannulisation. The waiting period is infrequently adhered to, due to discrepant data on ideal waiting period.

Aim of the study

The aim of the study was to examine the utility of cannulated serial PRL sampling in healthy adult volunteers and further support the current practice of delayed sampling.

Methodology

The researchers performed a pilot study at the Endocrine Unit at Tygerberg Hospital, Cape Town, South Africa between April and May 2018. Volunteers were eligible if aged over 18 years and overnight fasting > 6 hours, but were excluded if they were on drugs known to increase PRL, exercised within two hours and post-partum or breastfeeding within 6 weeks.

The researchers collected cannulated PRL samples from 30 healthy adult volunteers ($n = 15$ female) at 20-minute intervals from arrival at T0, T20, T40 and T60. Serum cortisol (CORT) was collected as a surrogate marker for stress at 3 intervals (T0, T20 and T60).

Samples were collected, transported and processed at the reference laboratory following standard protocols and stored at -20°C (Celsius). Samples were later thawed and analysed by immune-enzymatic ('sandwich') assay, performed on the Beckman Coulter DXI platform (Beckman Coulter Inc, Brea, CA, USA) at Pathcare Laboratories. The reference interval was > 13.1 µg/l (278.7 mIU/l) in males and > 26.7 µg/l (568 mIU/l) in females, respectively. Cortisol was measured by means of a competitive binding immune-enzymatic method on the Beckman Coulter DXI platform with early AM reference interval of 184–618 (nmol/l).

Statistical analysis

The collected data was compiled using Microsoft Excel® (Microsoft Corp, Redmond, WA, USA) and analysed by means of the

Statistical 11 from the Statsoft.com® statistical program (Tibco Data Science, https://www.tibco.com/products/data-science) with the help of the Biostatistics Unit at the University of Stellenbosch. Data were analysed by means of multivariate and univariate logistic regression analysis. Two-sided *p*-values of < 0.05 were considered statistically significant.

Results

Of 30 volunteers ($n = 15$ male), the mean age was 34.7 (9.5) years combined, and 34.5 (9.7) in males and 34.9 (9.5) years in females.

The mean PRL at baseline (T0) was 9.7 µg/l for males and 15.8 µg/l for females. The majority ($n = 26$) of volunteers had a normal PRL level throughout the sampling period to T60. The PRL levels were higher in females compared with males at all intervals ($p < 0.05$).

Demographic and biochemical results are summarised in Table 1.

There was a persistent delta decrease (Δ) in PRL for all time intervals ($p < 0.05$), with the most pronounced decrease observed in the first 20-minute interval and more pronounced in male compared with female volunteers. The delta decrease (Δ) for PRL was negative for all intervals ($p < 0.05$) in males, females and overall, as demonstrated in Figure 1.

The PRL delta decrease also mirrored the CORT delta decrease for all intervals ($p < 0.05$).

Elevated baseline PRL was observed in four volunteers ($n = 3$ male), all of whom achieved normal PRL levels (at different intervals) by T60 with serial sampling. The highest PRL was a female at 33.7 µg/ml that normalised at T20, and had concurrent elevated baseline cortisol levels of 795.1 nmol/l (186–618 nmol/l) that remained elevated at T60.

Table 1: Demographic data and biochemical results

Variable	Cohort, $n = 30$	Male, $n = 15$	Female, $n = 15$
Mean age in years (SD)	34.7 (9.5)	34.5 (9.8)	34.9 (9.5)
Serum prolactin (µg/l):			
Mean PRL-T0 (SD)	12.7 (6.6)	9.7 (4.6)	15.8 (6.9)
Mean PRL-T20 (SD)	10.9 (5.2)	8.5 (4.1)	13.3 (5.1)
	Δ −12.5%	Δ −12.9%	Δ −12.1%
Mean PRL-T40 (SD)	9.7 (4.7)	7.5 (3.4)	12.0 (4.7)
	Δ −9.9%	Δ −9.5%	Δ −10.4%
Mean PRL-T60 (SD)	8.6 (3.8)	6.8 (2.6)	10.5 (3.9)
	Δ −10.1%	Δ −12.2%	Δ −8.1%
PRL > ULN	$n = 4$	$n = 3$	$n = 1$
Serum cortisol (nmol/l):			
Mean CORT-T0 (SD)	399 (22.8)	376.0 (90.0)	423.1 (152.1)
Mean CORT-T20 (SD)	359.4 (20.8)	344.2 (79.2)	374.7 (142.1)
Mean CORT-T60 (SD)	288.7 (16.7)	271.9 (61.1)	305.6 (131.7)

PRL = prolactin; CORT = cortisol (early am; https://www.tibco.com/products/data-science) < 618 nmol/l; SD = standard deviation; ULN = upper limit normal; Δ = delta decrease from previous time interval (% decrease).

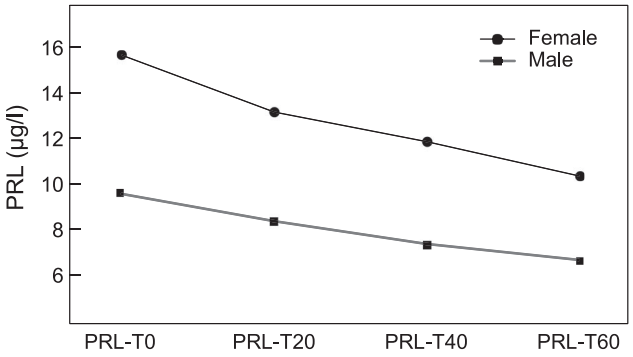

Figure 1: Marginal means of prolactin per interval.

Discussion

We included 30 healthy volunteers with an age distribution reflecting the population that would typically be screened for abnormal PRL levels.

The researchers demonstrated higher baseline PRL levels in females compared with males. The highest PRL was a female volunteer at T0 of 33.7 µg/ml. Four volunteers had marginally elevated PRL levels, with only a single volunteer in the pathological interval (>3 0 µg/ml). All four of these had achieved normal PRL at T60. Considering that these four patients might have been subjected to further investigation based on a single measurement, we demonstrated benefit with delayed serum sampling following a minimum waiting period of 20 minutes before specimen collection in two (of four) patients. This is consistent with previous reported studies on the value of serial sampling.

Research evaluating waiting periods with PRL sampling has marked variation in methodology, thus limiting global consensus recommendations. These periods vary in interval collection and collection period from 30, 60, 90 up to 120 minutes.[4,5] Different studies have, however, confirmed benefit with delayed cannulated sampling with one- and two-hour delayed sampling in patients referred for hyperprolactinaemia.[6,7] This practice of extended sampling in assessing mild hyperprolactinemia further avoids over-diagnosis and unnecessary imaging.[8]

Although a waiting period and serial cannulated sampling involves a prolonged testing protocol with the use of additional resources, the practice involves fewer resources when compared with pituitary imaging and the anxiety associated with investigations.

Limitations of the study

Sample size was limited by availability of PRL test kits. Quantification of stress is subjective and difficult to measure and compare.

Conclusion

In 4 of 30 healthy volunteers with mildly baseline hyperprolactinaemia, normalisation occurred in all 4, at different time intervals from arrival up to T60. In a single patient with elevated PRL and CORT levels at baseline, PRL levels had normalised by T20. This study supports the current practice that delayed PRL sampling of at least 20 minutes is adequate in most patients attending for specimen collection.

Data availability – All data used in this study are publicly available, with the relevant studies cited. Data needed for the primary analyses are shown in Table 1.

Ethical clearance – The investigators obtained ethical approval from HREC at University of Stellenbosch and Tygerberg Academic Hospital (Ref #S17/10/201).

All research was conducted according to the ethical principles of the Declaration of Helsinki (2013) and Good Clinical Practice (GCP) guidelines. Each participant provided written informed consent.

Disclosure statement – No potential conflict of interest was reported by the authors.

Funding – This was a self-funded study by the researchers involved. Sponsorship was received from Beckman Coulter for prolactin and cortisol testing kits. The sponsor had no input other than supply of test kits.

Glossary

PRL-T0	prolactin value at 0 minutes;
PRL-T20	prolactin value at 20 minutes;
PRL-T40	prolactin value at 40 minutes;
PRL-T60	prolactin value at 60 minutes;
CORT-T0	Cortisol value at 0 minutes;
CORT-T20	Cortisol value at 20 minutes;
CORT-T60	Cortisol value at 60 minutes.
SD	standard deviation.
Δ	delta decrease or the change in level compared with previous interval (as %).
ULN	upper limit of normal.

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Received: 30-08-2021 Accepted: 13-12-2021