Asian Journal of Andrology (2018) 20, 290–293
www.asiaandro.com; www.ajandrology.com

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ORIGINAL ARTICLE

Semen Analysis

Proton-pump inhibitor use does not affect semen quality in subfertile men

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Proton-pump inhibitors (PPIs) are among the most widely used drugs worldwide. PPI use has recently been linked to adverse changes in semen quality in healthy men; however, the effects of PPI use on semen parameters remain largely unknown specifically in cases with male factor infertility. We examined whether PPI use was associated with detrimental effects on semen parameters in a large population of subfertile men. We retrospectively reviewed data from 12 257 subfertile men who had visited our fertility clinic from 2003 to 2013. Patients who reported using any PPIs for >3 months before semen sample collection were included; 7698 subfertile men taking no medication served as controls. Data were gathered on patient age, medication use, and conventional semen parameters; patients taking any known spermatotoxic medication were excluded. Linear mixed-effect regression models were used to test the effect of PPI use on semen parameters adjusting for age. A total of 248 patients (258 samples) used PPIs for at least 3 months before semen collection. In regression models, PPI use (either as the only medication or when used in combination with other nonspermatotoxic medications) was not associated with statistically significant changes in semen parameters. To our knowledge, this is the largest study to compare PPI use with semen parameters in subfertile men. Using PPIs was not associated with detrimental effects on semen quality in this retrospective study.

Asian Journal of Andrology (2018) **20**, 290–293; doi: 10.4103/aja.aja_35_17; published online: 5 September 2017

Keywords: infertility; proton-pump inhibitors; semen analysis; sperm quality; spermatozoa

INTRODUCTION

Proton-pump inhibitors (PPIs) remain the most commonly used medication to treat upper gastrointestinal disorders including gastrointestinal reflux disease and peptic ulcer disease. Since their introduction in the 1980s, millions of individuals have been taking this medication with prescription rates increasing during the recent years.[1] With around 113 million prescriptions in 2008, PPIs were the third-highest selling class of drugs in the United States.[2] Although generally considered safe, more recently, concerns have been raised about the possible adverse effects associated with PPI use. Vitamin and mineral malabsorption, increased risk of fractures, increased cardiovascular events, and higher risk of certain infections are some of the proposed adverse effects associated with long-term PPI use. An additional concern is PPI's effects upon fertility and semen parameters.

Subfertility is common in the reproductive-age population; around 15% of couples are not able to conceive after 1 year of unprotected sex.[3] About one out of twenty men is affected by subfertility,[4] and a male factor is responsible or contributes in about half of the couples with infertility.[3] In 2012, a study suggested that seminal *Helicobacter pylori* treatment, using a PPI regimen, improves sperm motility in infertile men.[5] In contrast, however, PPI use was recently linked to lower total motile sperm count (TMSC) in couples planning for pregnancy.[6] Understanding the effects of PPIs on semen is important in counseling subfertile men, considering the high rates of PPI use in the general population. Given the scarcity of evidence and the controversies in the literature, we aimed to assess the effects of PPI use on semen parameters using data from a large population of subfertile men.

PATIENTS AND METHODS

We retrospectively reviewed semen analyses from 10 140 patients (12 182 samples) who visited our Andrology laboratory between 2002 and 2013 and had their medication use information available. The study was conducted in accordance with the Declaration of Helsinki and was approved by the University of Utah Institutional Review Board; informed consent was obtained from all patients prior to their enrollment. When a patient was visited more than once, the inclusion and exclusion criteria were applied to each encounter separately. For each encounter, we extracted the following data: patient age, semen volume (ml), total sperm count ($\times 10^6$), sperm concentration ($\times 10^6$ per ml), total sperm motility (percentage of all progressive and nonprogressive motile spermatozoa), progressive motility (percentage), total motile sperm count (number of spermatozoa with progressive motility in millions), normal head morphology (percentage), and normal tail morphology (percentage). Before 2013, our laboratory measured semen parameters (including sperm morphology) according to the 1999 World Health Organization laboratory manual.[7] TMSC was calculated by multiplying total sperm count by the percentage of

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Received: 25 May 2017; Accepted: 27 June 2017

spermatozoa with progressive motility. A TMSC of ≥20 × 10^6 was considered normal.[8]

Exclusion criteria included the following: age <18 years, azoospermia, missing values for all semen parameters, and consumption of any known spermatotoxic medication during the 3-month period before semen collection. In brief, the list of spermatotoxic medications included the following: testosterone, 5-alpha-reductase inhibitors, alpha-blockers, anticancer medications, anti-hypertensive medications, anti-depressants and psychoactive medications, and selected antibiotics. The full list of medications classified as spermatotoxic is available elsewhere.[9] Patients not taking any medications during this 3-month period served as controls.

We included patients in the PPI group if they had a history of ongoing use of any PPIs for at least 3 months immediately before semen collection. Patients were further categorized into the following two groups: (1) those only using PPIs (PPI-only group) and (2) those using PPIs concurrently with any other nonspermatotoxic medication(s) (PPI + other group).

Data are presented as mean ± standard deviation (s.d.), median (interquartile range [IQR]), and percentages as appropriate. Sperm concentration, count, and TMSC were log-transformed for analyses due to distribution skew and are reported as ratios. Linear mixed-effect regression models, adjusted for age, were used to test the effect of PPI use on semen parameters. A continuous auto-regressive process of order-one correlation structure was used to account for potential correlation within individuals over subsequent encounters. Effect estimates and their 95% confidence intervals (CIs) are reported, and significance was assessed at the 0.05 level.

RESULTS

A total of 248 patients (258 samples) used PPIs for at least 3 months before semen sample collection; ten patients had two encounters while using a PPI. Of the patients taking a PPI, 149 (158 samples) were categorized in PPI-only group and 99 (100 samples) were categorized in PPI + other group. Data from 7698 patients (8760 samples), who were not using any medications, were used as controls. Mean age was 33.3 ± 6.7 years among patients using PPI (PPI ± other nonspermatotoxic medication[s]) and was 32.0 ± 6.3 years among controls. A descriptive summary of age and semen parameters for controls and each category of PPI users is provided in **Table 1**.

In regression models, PPI use (either as the only medication or when used in combination with other nonspermatotoxic drugs) was not associated with any statistically significant change in semen parameters (**Table 2**).

DISCUSSION

To the best of our knowledge, this is the largest study to date assessing the effects of PPI use on semen parameters in subfertile men. Our results suggest that using a PPI with or without other nonspermatotoxic medications is not associated with detrimental effects on semen parameters.

Our findings are consistent with animal studies suggesting that omeprazole and its derivatives are not directly spermatotoxic.[10–12] There have been few human studies focused on the association between PPI use and semen quality. In 2014, El-Garem *et al*.[5] suggested that treating seminal *H. pylori* infection (as measured by *H. pylori* IgA antibodies in semen) improves sperm motility in infertile men. The authors used an oral triple-regimen therapy (including 20 mg omeprazole) to treat these patients and showed that concomitant with a significant decrease in seminal *H. pylori* IgA antibodies, progressive and nonprogressive sperm motility, as well as percentage of spermatozoa with normal morphology significantly increased.[5] This was the first report suggesting that using a regimen that contains a PPI may actually improve semen parameters. Previous studies had suggested that seminal *H. pylori* infection is more common in infertile men, and the presence of seminal *H. pylori* is associated with reduced sperm quality.[13,14] In contrast to these findings, in two different reports in 2016, Huijgen *et al*.[6,15] proposed that PPI use can adversely affect semen quality by decreasing the TMSC. In the first report, the authors used a population-based database of Dutch men who were planning for pregnancy;[6] using data from 129 patients taking PPI, the authors reported that using PPI in a window of 12–6 months before sample collection was associated with a 3-fold risk of having a low TMSC. This association was not present when the time window was set at 6–0 months before semen collection or when the whole time window was considered (i.e., PPI use within 1 year before semen analysis). Additionally, semen parameters other than TMSC were not discussed.[6] Considering the time span of spermatogenesis (around 10 weeks), it is counterintuitive that medication use in a period of 12–6 months before semen collection (and not during the immediate 6-month period) affected semen parameters. Huijgen *et al*.[6] suggested that PPI use does not directly affect spermatogenesis but rather exhausts vitamin resources (e.g., B12 and folate), which will decrease semen quality after 4–6 months. However, this hypothesis is also unlikely considering that only long-term (>2 years) PPI use has been associated with an increased risk of B12 deficiency.[16,17]

Table 1: Descriptive summary of age and semen parameters by proton-pump inhibitor use

Variable	*Control (n=8760)*	*PPI only (n=158)*	*PPI + other drugs (n=100)*	*PPI ± other drugs (n=258)*
Age (year, mean±s.d.)	32.0±6.3	31.8±6.4	35.7±6.5	33.3±6.7
Ejaculate volume (ml, mean±s.d.)	3.2±1.6	3.2±1.5	2.9±1.4	3.1±1.5
Concentration (×10^6 per ml, median with IQR in parentheses)	70.2 (29.9–126)	76.4 (24.5–129.8)	64.4 (27.9–129.8)	75.2 (24.8–129.8)
Total count (×10^6, median with IQR in parentheses)	197.2 (75.3–373.6)	215.1 (59.2–407.5)	189.8 (45.1–374.4)	204.3 (53.6–402.5)
TMSC (×10^6, median with IQR in parentheses)	94.6 (26.3–204.1)	111.4 (23.9–236.1)	94.4 (17.2–208.5)	108.8 (21.6–225.1)
TMSC >20 ×10^6, *n* (%)	6795 (77.6)	122 (77.2)	70 (70.0)	192 (74.4)
Progressive motility (%, mean±s.d.)	46.8±20.8	49.5±20.7	46.9±20.9	48.5±20.8
Total motility (%, mean±s.d.)	56.2±19.5	58.2±19.2	55.9±20.0	57.3±19.5
Vitality (%, mean±s.d.)	52.7±16.0	53.5±15.7	53.1±18.0	53.3±16.6
Head morphology normal (%, mean±s.d.)	28.7±15.1	30.7±15.1	29.8±15.4	30.4±15.2
Tail morphology normal (%, mean±s.d.)	56.2±19.5	58.2±19.2	55.9±20.0	57.3±19.5

Number of missing values for each variable: age 11; total sperm count 24; vitality 345; motility 101; head morphology 350; tail morphology 350. IQR: interquartile range; PPI: proton-pump inhibitor; s.d.: standard deviation; TMSC: total motile sperm count

Table 2: Regression models testing effects of proton-pump inhibitor use on semen parameters

Outcome measures	*Coefficient (95% CI)*	*P*
PPI only *vs* control		
Ejaculate volume (ml)	–0.05 (–0.24–0.14)	0.58
Concentration ($\times 10^6$ per ml)	0.97 (0.80–1.17)[a]	0.73
Total count ($\times 10^6$)	0.96 (0.80–1.14)[a]	0.62
TMSC ($\times 10^6$)	0.97 (0.80–1.18)[a]	0.79
Progressive motility (%)	1.41 (–1.14–3.96)	0.28
Total motility (%)	1.08 (–1.31–3.47)	0.38
Viability (%)	0.82 (–1.17–2.81)	0.42
Head morphology normal (%)	1.49 (–0.41–3.39)	0.13
Tail morphology normal (%)	0.66 (–0.86–2.17)	0.40
PPI ± other nonspermatotoxic *vs* control		
Ejaculate volume (ml)	–0.03 (–0.28–0.21)	0.78
Concentration ($\times 10^6$ per ml)	0.96 (0.75–1.23)[a]	0.74
Total count ($\times 10^6$)	0.99 (0.79–1.24)[a]	0.94
TMSC ($\times 10^6$)	1.06 (0.83–1.36)[a]	0.65
Progressive motility (%)	2.52 (–0.75–5.79)	0.13
Total motility (%)	1.89 (–1.18–4.95)	0.23
Viability (%)	0.42 (–2.11–2.95)	0.74
Head morphology normal (%)	1.93 (–0.50–4.35)	0.12
Tail morphology normal (%)	0.90 (–1.03–2.83)	0.36

[a]Ratio in the outcome measure between PPI users and controls. All other coefficients are interpreted as units of increase or decrease in the outcome measure due to PPI use. CI: confidence interval; TMSC: total motile sperm count; PPI: proton-pump inhibitor

Additionally, this is more common in women and those who are at a risk of nutritional deficiencies, and it would be highly unlikely to happen in young men who are having a regular diet after just 6–12 months of using a PPI. In another study by the same group, the investigators included forty subfertile men taking a medication for gastric acid-related symptoms (including 34 men using a PPI) and compared the semen parameters to 843 subfertile controls taking no medications.[15] No significant difference was found in semen parameters between cases and controls (except semen volume being significantly higher in those taking the medications). However, in regression models, use of these medications was associated with decreased sperm concentration and a 2-fold higher risk of low TMSC (unadjusted odds ratio: 2.16, 95% CI: 1.05–4.43). Our findings contradict the conclusions made by Huijgen *et al.*[6,15] and suggest that using a PPI is not detrimental to semen parameters in subfertile patients. Differences in sample size, statistical models, and classification of medication users may be partly responsible for the observed differences in these studies. This, however, calls for larger and prospective studies to provide more robust evidence on the effects of PPI on semen quality.

The evidence on long-term risks of PPI use is mainly from observational and retrospective studies. Hence, selection bias and different baseline characteristics of the patients are important factors to consider in concluding whether the observed effects are real or just a marker of the risk.[18] In other words, patients are using PPIs to address an underlying condition and usually represent an overall less healthy population. Hence, the adverse effects of PPI use on semen parameters, if any, may be more attributable to the underlying conditions and not the medication itself. For example, a re-infection or partially treated *H. pylori* infection might explain the lower TMSC reported by Huijgen *et al.*[6] that was only observed in patients using PPI from 12 to 6 months before semen analysis. The information on safety of PPIs in subfertile men would be even more valuable when plausible evidence is available for treating seminal *H. pylori* infections in subfertile patients and when a PPI-containing regimen is to be used for *H. pylori* eradication.

Our study has a number of limitations. First, the semen parameters are based on a single semen sample for the majority of the patients and might not reflect the intra-individual variations in semen parameters. Information on body mass index, smoking, and alcohol use was not available in our database and might be a source of bias in our study. Additionally, the sample size was not large enough to assess the effect of each type of PPI medications or different doses and durations of treatment in subgroup analyses.

CONCLUSIONS

PPI use (alone or in combination with other nonspermatotoxic medications) was not associated with detrimental effects on conventional semen parameters in subfertile patients. Our findings, from this retrospective large single-center study on infertile men, are inconsistent with previous reports suggesting lower sperm motility in PPI users.

AUTHOR CONTRIBUTIONS

SK and JMH designed the study. KIA, BRE, and TGJ participated in data preparation and acquisition. CZ and APP analyzed the data. All authors interpreted the data. SK and JRC drafted the manuscript. JMH, JBM, WOB, and DTC provided critical revisions to the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

ACKNOWLEDGMENTS

This investigation was supported by the University of Utah Study Design and Biostatistics Center, with funding in part from the National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health, through Grant 8UL1TR000105 (formerly UL1RR025764).

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