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

Sorena Keihani1, James R Craig1, Chong Zhang1, Angela P Presson2, Jeremy B Myers1, William O Brant1, Kenneth I Aston1, Benjamin R Emery3, Timothy G Jenkins3, Douglas T Carrell1,3, James M Hotaling1,3

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; 7,698 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 non-spermatotoxic 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.5 In 2012, a study suggested that seminal Helicobacter pylori treatment, using a PPI regimen, improves sperm motility in infertile men.6 In contrast, however, PPI use was recently linked to lower total motile sperm count (TMSC) in couples planning for pregnancy.7 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 (×10⁹), sperm concentration (×10⁶ 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...
spermatozoa with progressive motility. A TMSC of $\geq 20 \times 10^6$ was considered normal.6

Exclusion criteria included the following: age <18 years, azoosperma, 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.7 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 non-spermatotoxic 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 non-spermatotoxic 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 non-spermatotoxic 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 non-spermatotoxic 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 2016, El-Garem et al.13 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.11,14 In contrast to these findings, in two different reports in 2016, Huijgen et al.15,16 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;5 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, mean with IQR in parentheses) | 70.2 (29.9–129.8) | 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 >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.

---

6. Asian Journal of Andrology

5. Table 2.
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 UL1TR000105 (formerly UL1RR025764).

REFERENCES

1. Rotman SR, Bishop TF. Proton pump inhibitor use in the U.S. ambulatory setting, 2002-2009. PLoS One 2013; 8: e56060.
2. Pallarito K. How Safe are Popular Reflux Drugs? Experts Debate Evidence Linking Acid-Blockers to Possible Bone, Heart Problems. In: US News World Report; 2009. Available from: http://health.usnews.com/health-news/family-health/bones-joints-and-muscles/articles/2009/11/04/how-safe-are-popular-reflux-drugs. [Last accessed on 2016 Nov 29].
3. Practice Committee of the American Society for Reproductive Medicine. Diagnostic evaluation of the infertile male: a committee opinion. Fertil Steril 2015; 103: e18–25.
4. Hirsh A. Male subfertility. BMJ 2003; 327: 669–72.
5. El-Garem Y, El-Sawy M, Mostafa T. Seminal Helicobacter pylori treatment improves sperm motility in infertile azoospermic men. Urology 2014; 84: 1347–50.
6. Huijgen NA, de Ridder MA, Verhamme KM, Dohle GR, Vanrolleghem AM, et al. Are proton-pump inhibitors harmful for the semen quality of men in couples who are planning pregnancy? Fertil Steril 2016; 106: 1666–72.
7. World Health Organization. WHO Laboratory Manual for the Examination of Human Semen and Sperm-Cervical Mucus Interaction. 4th ed. Cambridge: Cambridge University Press; 1999.
8. Hamilton JA, Cissen M, Brandes M, Smeenk JM, de Bruin JP, et al. Total motile sperm count: a better indicator for the severity of male factor infertility than the WHO sperm classification system. Hum Reprod 2015; 30: 1110–21.
9. Sampelski MK, Nangia AK. Adverse effects of common medications on male fertility. Nat Rev Urol 2015; 12: 401–13.
10. Banhiani SA. Omeprazole and semen quality. Basic Clin Pharmacol Toxicol 2016; 118: 181–3.
11. Adler ID, Schmid TE, Baumgartner A. Induction of aneuploidy in male mouse germ cells detected by the sperm-FISH assay: a review of the present data base. Mutat Res 2002; 504: 173–82.
12. Scott D, Reuben M, Zampighi G, Sachs G. Cell isolation and genotoxicity assessment in gastric mucosa. Dig Dis Sci 1990; 35: 1217–25.
13. Moretti E, Figura N, Campagna MS, Iacoponi F, Goinelli S, et al. Infectious burden and semen parameters. Urology 2017; 100: 90–6.

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.,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.16 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.15 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.
Moretti E, Figura N, Collodel G, Ponzetto A. Can *Helicobacter pylori* infection influence human reproduction? *World J Gastroenterol* 2014; 20: 5567–74.

Huijgen NA, Goijen HJ, Twigt JM, Mulders AG, Lindemans J, et al. Effect of medications for gastric acid-related symptoms on total motile sperm count and concentration: a case-control study in men of subfertile couples from the Netherlands. *Drug Saf* 2017; 40: 241–8.

Eusebi LH, Rabitti S, Artesiani ML, Gelli D, Montagnani M, et al. Proton pump inhibitors: risks of long-term use. *J Gastroenterol Hepatol* 2017; 32: 1295–302.

Lam JR, Schneider JL, Zhao W, Corley DA. Proton pump inhibitor and histamine 2 receptor antagonist use and vitamin B12 deficiency. *JAMA* 2013; 310: 2435–42.

Hughes S. Popular Heartburn Medication Linked to Increased Stroke. In: Medscape. Available from: http://www.medscape.com/viewarticle/872483. [Last accessed on 2016 Nov 29].

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

©The Author(s)(2017)