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ORIGINAL ARTICLE

Administration of Proton Pump Inhibitors with and without Inulin and its Effect on Kidney Function: An Experimental Study on Rabbit Model

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ABSTRACT

Aim: To compare the effect of various PPIs (Omeprazole Esomeprazole & Pantoprazole) with and without Inulin on renal functions and serum electrolytes in the rabbit model.

Study Design: An experimental study was conducted by the Department of Pharmacology and Therapeutics, Liaquat University of Medical & Health Sciences, Jamshoro, Sindh.

Place and Duration: This study was completed in a duration of 6 months from 1st February 2021 to 31st July 2021.

Methodology: Male and female rabbits weighting 1 to 3 Kilograms apparently healthy with no known illness were selected for the sample. In total 56 rabbits matching study eligibility criteria were included in the study and randomly divided into seven study groups each comprising of eight rabbits. Three groups were provided with three different PPIs i.e. Omeprazole, Esomeprazole and Pantoprazole while other three groups were provided with three different PPIs as well as inulin. However, the control group was only provided with placebo. Blood samples were collected at day 0 and at the end of 6th week. Serum electrolytes were analyzed for serum Magnesium, Calcium, Urea and Creatinine by using Cobas C-311 analyzer. Data was analyzed using SPSS version 19.

Results: The study found no statistically significant differences in pre and post-intervention weight of rabbit in any of the experimental groups. The serum urea and creatinine levels showed considerable rise following intake of PPI, indicating a somewhat diminished efficiency of the kidneys to get rid of the body from excess urea and creatinine. However, the rise in urea and creatinine was statistically significant for Group A and Group C with rise in creatinine level following use of Omeprazole and Pantoprazole respectively (p-value <0.05).Electrolyte deficiencies were observed among all experimental groups. Groups that were treated with PPIs and inulin both showed much improved results as compared to rabbits which were treated with PPIs only.

Practical Implications: Administration of PPIs along with inulin among human subjects to reduce the adverse effects; specially among critically ill patients or patients with compromised renal function human subject evidence needs to be established by conducting similar trials. This can be breakthrough in treatment protocols for gastritis and patients with renal disease who are also need to take PPIs for any medical indication.

Conclusion: Proton Pump Inhibitors significantly change the normal electrolyte composition by increasing concentration of Serum Urea & Creatinine. However simultaneous inulin administration prevent most imbalances and possibly serves to reduce the adverse events associated with use of PPIs significantly.

Keywords: Proton Pump Inhibitors, Inulin, Electrolytes,

INTRODUCTION

Acid-related disorders (ARDs), which include dyspepsia, gastritis, GERD, and Peptic Ulcer Disease (PUD), are common conditions with a potentially large economic impact on the health care system. Their workup and treatment involve hospitalizations, physician office visits, expensive procedures such as endoscopy, and chronic prescription medication use with H2 receptor antagonists (H2RA), proton pump inhibitors, and pro-motility agents and considerations of cost and cost effectiveness along with safety and efficacy are important for deciding between therapies.[1-4]

Proton Pump Inhibitors are the drug of choice for most acid related disorders such as GERD and GI ulcers of various origins around the globe for many decades. Omeprazole was the first discovered agent of this class in 1989 followed by other drugs like esomeprazole, rabiprazole and pantoprazole etc. The superiority of PPIs over H2 blockers lies in their complete blockage of HCL synthesis by the stomach parietal cells.[5,6] These agents need enteric coating owing to their acid unstable nature to skip the stomach and reach the duodenum to get absorbed with a bioavailability of 30-90%, their metabolism cytochrome P450 dependent specially CYP2C19 and CYP3A4 isozymes. These drugs are prodrugs so must be activated for effectiveness. These agents are available in oral and parenteral form and inhibit >90% acid secretion at standard doses. Their metabolites are excreted through kidneys and feces.[7,8]

Achlorhydria, fracture tendency, B12 deficiency, hypomagnesemia and pneumonia are some well-established side effects of this class of drugs. Recent research work suggests PPIs to be responsible for CKD (chronic kidney disease) in 20%-50% patients. Chronic use of PPIs results in electrolyte imbalance hypocalcemia, hypomagnesemia and hypokalemia but persistent low serum calcium (Ca2+) is of great clinical significance risk of bone fractures.[9, 10]

It is particularly worrisome since even developed countries have >28 million patients of osteoporosis or low bone mass while 1 out of every 8 citizens above the age of 50 years suffer from the spine fracture. Prolonged use of PPIs will only add to the problem and spell trouble for the individuals and the healthcare system as a whole.[11, 12] Once solution to the problem may have been hiding in plain sight i.e. Inulin. Inulins are naturally occurring polysaccharides also termed as fructans. Dietary supplementations of Inulin are reported to improve these electrolyte abnormalities. Inulin Increases the bioavailability and absorption of calcium making the bones structure healthy both in adolescent and elderly.[13, 14]

This current study is arranged to evaluate the effects of co-administration of PPIs (Omeprazole, Esomeprazole and Pantoprazole) and inulin on the serum electrolytes and renal functions on the rabbit model, this study will further explore the advantages for this drug combination.[15, 16] Hypocalcemia, hypomagnesemia and hypokalemia are problems associated with long term use of PPIs so there is need to find a solution for this issue. The current research may overcome this problem by combined use of the PPIs and Inulin. Nephrotoxic effects of PPIs are also under discussions in research and scientific communities,

this study will also focus to explore any advantage of this combination on renal functions.

This study aimed todetermine the effect of PPIs (Omeprazole Esomeprazole & Pantoprazole) with and without inulin on renal function and serum electrolytes in the rabbit model. This study also compared the effect of various PPIs (Omeprazole Esomeprazole & Pantoprazole) with and without Inulin on renal functions and serum electrolytes in the rabbit model.

METHODS

An experimental study was conducted by the Department of Pharmacology and Therapeutics, Liaquat University of Medical & Health Sciences, Jamshoro. This study was conducted with the collaboration of Animal House of Sindh Agricultural University, Tandojam and Diagnostic & Research Lab, LUMHS Hyderabad. This study was completed in a duration of 6 months from 1st February 2021 to 31st July 2021 after obtaining approval from Male and female rabbits weighting 1 to 3 Kilograms apparently healthy with no known illness were selected for the sample. However, pregnant female rabbits and rabbits already participating or enrolled in another experimental study were excluded from this study. In total 56 rabbits matching study eligibility criteria were included in the study. All the rabbits were randomly divided into seven study groups each comprising of eight rabbits.

Among all the eight groups three groups were provided with three different PPIs i.e. Omeprazole, Esomeprazole and Pantoprazole while other three groups were provided with three different PPIs as well as inulin. However, the control group was only provided with normal saline as placebo. (Figure: 1) All the pharmacological preparations i.e. tablet Omeprazole 20 mg, tablet Esomeprazole 40mg and tablet Pantoprazole 20 mg were obtained from local pharmacy except inulin powder which was purchased online through a local vendor.

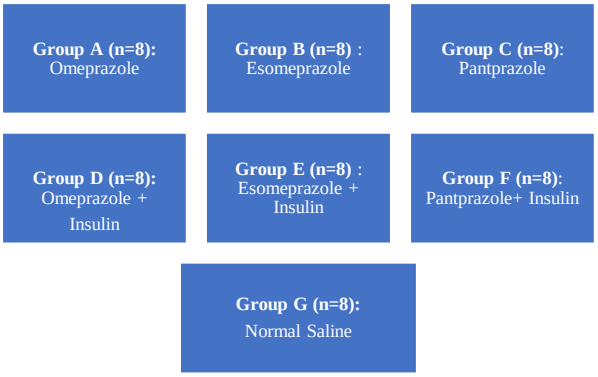

Figure 1: Showing distribution of intervention (PPIs with and without Inulin) to experimental study groups and control (n=56)

Rabbits for each study group were kept in separate cage for acclimatization for one week under temperature and light-controlled conditions with normal diet and drinking water access. PPIs were given to all experimental groups by oral route through proper dose calculation from normal human dose (0.5 mg/kg). Inulin was also be given by oral route through proper dose calculation from normal human dose (210 mg/kg). PPIs and inulin were given daily up to the total experimental period of 6 weeks. However, the control diet consisted of standard pellet chow / fresh grass hays.

Blood samples were collected at day 0 and at the end of experimental period i.e end of 6th week. At one time a blood sample of 4cc was taken from marginal ear vein under all aseptic measures. The blood samples were analyzed in Diagnostic and Research lab of LUMHS. Serum electrolytes were analyzed by using NOVA-4 analyzer and serum Magnesium, Calcium, Urea and Creatinine were analyzed by using Cobas C-311 analyzer.

Descriptive statistics were calculated for all the study variables. Quantitative continuous variables were calculated as mean and standard deviation while qualitative variables were estimated as frequency and percentage. Wilcoxon signed-rank testwas applied to compare the pre and post treatment serum electrolytes and weight of rabbits in each treatment group. Kruskal-Wallis test was applied to compare the mean weight and mean serum electrolytes among various study groups. P-value of less than 0.05 was considered statistically significant.

RESULTS

The overall pre-intervention mean weight of the rabbits was 1.84 Kgs (IQR = 0.52 Kgs) while the post-intervention mean weight of all rabbits was 1.61 Kgs as recorded at the end of study. However, there were no statistically significant changes inpre and post-intervention weight of rabbit in any of the experimental group (Figure:2).

The serum urea and creatinine levels showed considerable rise following intake of PPI, indicating a somewhat diminished efficiency of the kidneys to get rid of the body from excess urea and creatinine. However, the rise in urea and creatinine was statistically insignificant for all the experiment or intervention group except for Group A and Group C which shows statistically significant rise in creatinine level following use of Omeprazole and Pantoprazole respectively (p-value <0.05)(Figure:3 and Figure 4).

Electrolyte deficiencies were observed among all experimental groups with the most notable findings in Group A (Omeprazole Group).

The mean levels of serum Mg, Na and Ca showed a decline on 42nd dayin the Group A rabbits (given Omeprazole), however this decline was statistically significant only for Mg and Na. Similarly the mean levels of all serum electrolytes showed a decline on 42ndday in the Group B (given Esomeprazole), but this decline was not statistically significant. Meanlevels of Serum Potassium were found to be markedly decreased on 42nd day among the Group C rabbits (treated with Pantoprazole) and this decline was statistically significant (Table:1).

The mean levels of all serum electrolytes were found to be slightly decreased on 42nd dayin Group D, and Group F which were all treated with Omeprazole, Esmoperazole and Pantaprazole respectively in combination with inulin. However, the post-treatment decline in median levels of serum electrolytes of Group D, Group E and Group F was not statistically significant. Moreover, the median levels of serum electrolytes in Group G i.e. Control Group did not show any significant variation after completion of experiment.

Rabbits in Group A and Group C showed major declined in kidney functions as evident by increase urea and creatinine quantity in blood. Rabbit Groups that were treated with PPIs and inulin both showed much improved results as compared to rabbits which were treated with PPIs only.

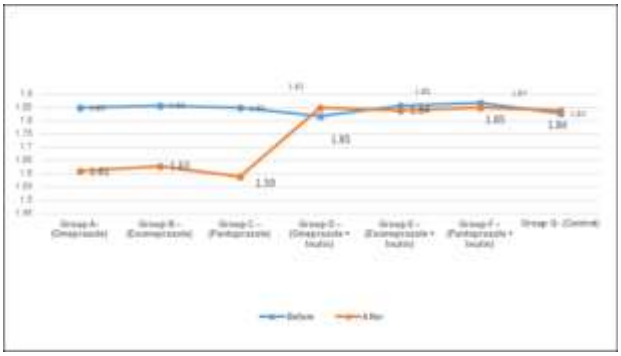

Figure 2: Body weight (In Kilograms) changes observed in Rabbit Model pre and post intervention (PPIs) administeration (n = 56)

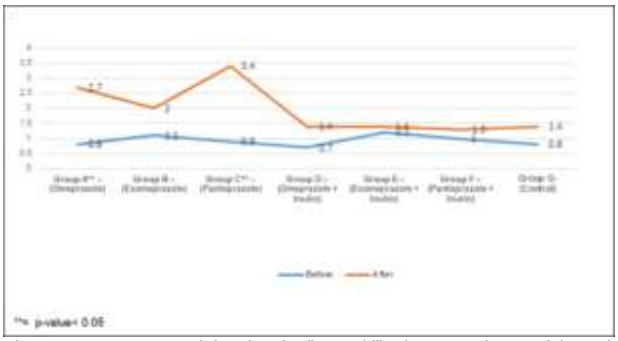

Figure 3: Serum Creatinine levels (in mg/dl) changes observed in Rabbit Model pre and post intervention (PPIs) administeration (n = 56)

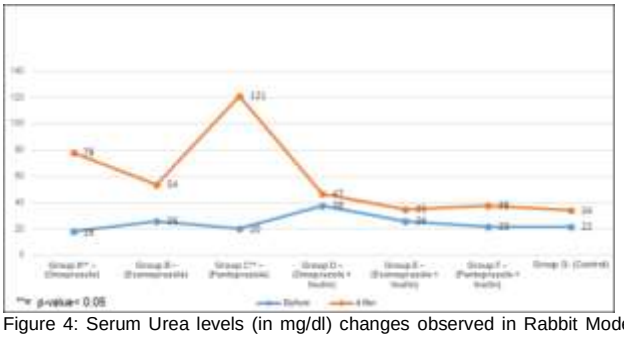

Figure 4: Serum Urea levels (in mg/dl) changes observed in Rabbit Model pre and post intervention (PPIs) administeration (n = 56)

Table 1: Pre and post Intervention (PPI administration) Serum Electrolyte levels measured on Day-0 and Day 42 of Intervention (n =58)

Electrolytes	Serum Sodium		Serum Potassium		Serum Chloride		Serum Magnesium		Serum Calcium	
Experiment Day	Day 0	Day 42	Day 0	Day 42	Day 0	Day 42	Day 0	Day 42	Day 0	Day 42
Group A – (Omeprazole)	139	132**	4.3	4.1	105	102	1.8	0.7**	8.9	7.4
Group B – (Esomeprazole)	140	135	3.9	3.4	100	98	2.0	1.4	9.6	8.4
Group C – (Pantoprazole)	137	131	4.0	2.9**	104	99	2.2	1.7	10.2	8.1
Group D – (Omeprazole + Inulin)	142	139	4.6	4.2	103	101	2.1	1.7	9.4	9.2
Group E – (Esomeprazole + Inulin)	142	138	4.0	3.9	108	98	1.9	1.5	10.4	9.4
9.4Group F – (Pantoprazole + Inulin)	139	133	4.7	4.3	106	103	2.3	1.4	8.9	7.3
Group G- (Control)	140	137	4.3	4.1	105	102	2.1	1.9	9.2	9.4
** = p-vale <0.05										

DISCUSSION

This study is among the few valuable researches intended to explore the effects of PPIs on renal function using rabbit model. This study adapted a novel approach by comparing the effects of PPIs on rabbit model while administrating PPIs with and without inulin. This study found a reduction in weight among rabbits administered with PPIs irrespective of inulin treatment. The study reported an overall pre-intervention median weight of 1.84 KGs (IQR=0.52) which was reduced to a median weight of 1.61 KGs. This decline in weight is suggestive of PPI`s effect on the general health and wellbeing of the animals. However, this finding was not statistically significant which can be explained by the small sample size in each experiment group The finding is contrary to recent research conducted on human subjects which report weight gain as a common side-effect associated with prolong use of PPIs.[17]

Moreover, in this study the serum urea level were found to show a rise following intake of PPI without inulin, indicating depends on the dose and duration of PPIS exposure.[18] Literature suggests that world-wide frequent use of PPIs as an over-the-counter medication can cause reduction in kidney function or capacity to get rid of the body from excess urea. Similarly this study also evident the rise in serum creatinine levels after administration of PPIs without inulin in all the related experiment groups. This finding further supports the hypothesis that PPIs use adversely affect the kidney function. The hazardous role of PPIs use in development of acute and chronic kidney injury is well supported by previous studies.[19, 20] However, the severity of PPIs induced kidney injury can possibly attribute to a large burden of Kidney disease. Hence it is required to monitor the use of PPI to avoid unnecessary long-term exposure or use without appropriate medical indication.[21] However, among all the PPIs the use of Omeprazole was associated with most severe alterations in serum levels of urea and creatinine. This finding warrants about safety and unnecessary use of most commonly used PPI i.e. Omeprazole particularly and needs further exploration.The adverse effect of PPIs on kidney function were also evident by the development of electrolyte imbalances i.e.hypocalcaemia, hyponatremia and hypomagnesaemia which were prevalent among all experimental groups. However, the p-values were not statistically significant for most of the findings which can be explained by small sample size. The role of PPIs on electrolytes is need to be studied in detail as studies conducted among human subjects have already reported decrease in serum magnesium levels as a result of exposure to PPIs.[22, 23]

However, the protective role of inulin on kidney in maintaining electrolyte balance, creatinine and urea can be explained by its complex action on kidney receptors.[24,25] Although the understanding of detailed mechanism of inulin on kidney functioning in presence of PPIs may require further exploration.

Despite a limited scope; this study have few strengths such as; this study is among the only few attempts made at studying the effects of the complete range of common PPI (omeprazole, pantoprazole, esomeprazole) therapy. This study also provides unique opportunity to compare the effects of PPIs when administered in combination with and without inulin. This study also provides insight about the role of inulin in ensuring safety of PPIs and advocates for PPI use in combination with inulin. Nevertheless this study have few inherent limitations such as this study did study the effect of PPIs on rabbit model for a relatively short duration of 6 weeks only. Furthermore this study did not compare the effects of PPIs on non-diabetic rabbits hence cannot provide conclusion about PPIs effects on subjects with diabetes mellitus.

CONCLUSION

Proton Pump Inhibitors significantly change the normal electrolyte composition of the body which may lead to unhealthy consequences as it was evident by increase concentration of Serum Urea & Creatinine ; indicative of reduced kidney functioning. However simultaneous inulin administration prevent most imbalances and possibly serves to reduce the adverse events associated with use of PPIs significantly. Large scale studies with advanced methodology are required to estimate the exact magnitude of risk of Kidney injury due to short-term as well as long-term PPIs use.

REFERENCES

1. Qadir N, Khaliq T, Hussain RA, Shah GA, Asharaf S, Raza A, Noor N. Renal clearance and urinary excretion of omeprazole in healthy female volunteers in Pakistan. Pak. J. Pharm. Sci. 2017:1;30(2).
2. Sarwar MR, Atif M, Scahill S, Saqib A, Qamar-uz-Zaman M, Babar Z. Drug utilization patterns among elderly hospitalized patients on poly-

pharmacy in Punjab, Pakistan. J. Pharm. Policy Pract. 2017 1;10(1):23.
3. Sarwar N, Ahmed R, Saadullah M, ullah Khan K, Kamran S, Baig FA, Mansoor MK, Aqib AI, Prince K, Saleem MZ, Manzoor AW. Prevalence of Helicobacter pylori infection and its associated diseases in low socio-economic workers in tertiary care hospital of Lahore, Pakistan. Biomed. Lett. 2019;5(1):1-6.
4. Kamran Q, Mund MD, Ali HA, Qasim M. Pathophysiology and Clinical Applications of Gastro-Esophageal Reflux Disease. Arch. clin. biomed. res.2017:17;1(5):242-54.
5. Burdsall D, Flores HC, Krueger J, Garretson S, Gorbien MJ, Iacch A, et al. Use of proton pump inhibitors with lack of diagnostic indications in 22 Patterson Midwestern US skilled nursing facilities. J Am Med Dir Assoc. 2013; 14(6):429–32.
6. Farley A, Wruble LD, Humphries TJ. Rabeprazole versus ranitidine for thetreatment of erosive gastroesophageal reflux disease: a double-blind, randomized clinical trial: Raberprazole Study Group. Am J Gastroenterol 2000;95:1894-1899
7. Tjon JA, Pe M, Soscia J, Mahant S. Efficacy and safety of proton pump inhibitors in the management of pediatric gastroesophageal reflux disease. Pharmacotherapy. 2013; 33(9):956-71.
8. Hess MW, Hoenderop JG, Bindels RJ, Drenth JP. Systematic review: hypomagnesaemia induced by proton pump inhibition. Aliment PharmacolTher. 2012; 36(5):405–413.
9. Pradeep Arora, Anu Gupta, MojganGolzy, Nilang Patel, Randolph L Carter, Kabir Jalal. Proton Pump Inhibitors are associated with increased risk of development of Chronic Kidney Disease. BMC Nephrol. 2016; 17:112. Xie Y, Bowe B, Li T, Xian H, Balasubramanian S, Al-Aly Z. Proton pump inhibitors and risk of incident CKD and progression to ESRD. J. Am. Soc. Nephrol. 2016 Oct 1;27(10):3153-63.
10. Deroux A, Khouri C, Chabre O, Bouillet L, Casez O. Severe acute neurological symptoms related to proton pump inhibitors induced hypomagnesemia responsible for profound hypoparathyroidism with hypocalcemia. Clin Res HepatolGastroenterol. 2014; 38(5):e103–105.
11. Leontiadis GI, Moayyedi P. Proton pump inhibitors and risk of bone fractures. Curr Treat Options Gastroenterol. 2014; 12(4):414–23.
12. Justin L Carlson, Jennifer M Erickson, Beate B Lloyd, Joanne L Slavin. Health Effects and Sources of Prebiotic Dietary Fiber. CurrDevNutr 2018;2:nzy005 doi: https://doi.org/10.1093/cdn/nzy005
13. Hess MW, de Baaij JHF, Gommers LMM, Hoenderop JGJ, Bindels RJM. Dietary Inulin Fibers Prevent Proton-Pump Inhibitor (PPI)-Induced Hypocalcemia in Mice. PLoS ONE 2015;10(9): e0138881.
14. Whisner CM, Martin BR, SchotermanMHC, Nakatsu CH, McCabe LD, McCabe GP et al. Galacto-oligosaccharides increase calcium absorption and gut bifidobacteria in young girls: a double-blind cross-over trial. Br J Nutr 2013;110(7):1292–303.
15. Arashdeep Singh et al Inulin fiber dose-dependently modulates energy balance, glucose tolerance, gut microbiota,hormones and diet preference in high fat-fed male rats. J Nutr Bio. 2018; 59:142-152.
16. Czwornog JL, Austin GL. Association of proton pump inhibitor (PPI) use with energy intake, physical activity, and weight gain. Nutrients. 2015 Oct;7(10):8592-601.
17. Hart E, Dunn TE, Feuerstein S, Jacobs DM. Proton pump inhibitors and risk of acute and chronic kidney disease: a retrospective cohort study. Pharmacotherapy. 2019 Apr;39(4):443-53.
18. Rodriguez-Poncelas A, Barcelo MA, Saez M, Coll-de-Tuero G. Duration and dosing of proton pump inhibitors associated with high incidence of chronic kidney disease in population-based cohort. PLoS One. 2018 Oct 17;13(10):e0204231.
19. Moledina DG, Perazella MA. PPIs and kidney disease: from AIN to CKD. J. Nephrol. 2016: 1;29(5):611-6.
20. Lee HJ, Lee H, Oh SH, Park J, Park S, Jeon JS, Noh H, Han DC, Kwon SH. Chronic kidney disease (CKD) patients are exposed to more proton pump inhibitor (PPI) s compared to non-CKD patients. PloS one. 2018;13(9).
21. Toth-Manikowski SM, Grams ME. Proton pump inhibitors and kidney disease—GI upset for the nephrologist?Kidney Int. Rep. 2017 May 1;2(3):297-301.
22. Cheungpasitporn W, Thongprayoon C, Kittanamongkolchai W, Srivali N, Edmonds PJ, Ungprasert P, O'Corragain OA, Korpaisarn S, Erickson SB. Proton pump inhibitors linked to hypomagnesemia: a systematic review and meta-analysis of observational studies. Ren Fail. 2015 Aug 9;37(7):1237-41.
23. Danziger J, William JH, Scott DJ, Lee J, Lehman LW, Mark RG, Howell MD, Celi LA, Mukamal KJ. Proton-pump inhibitor use is associated with low serum magnesium concentrations. Kidney Int. 2013 Apr 1;83(4):692-9.
24. Li L, Garikepati RM, Tsukerman S, Kohan D, Wade JB, Tiwari S, Ecelbarger CM. Reduced ENaC activity and blood pressure in mice with genetic knockout of the inulin receptor in the renal collecting duct. Am. J. Physiol. Renal Physiol. 2013 Feb 1;304(3):F279-88.
25. Pina AF, Borges DO, Meneses MJ, Branco P, Birne R, Vilasi A, Macedo MP. Inulin: trigger and target of renal functions. Front. Cell Dev. Biol. 2020 Jul 29;8:519.