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Effectiveness of vonoprazan-based regimens compared with proton pump inhibitor-based regimens as first-line *Helicobacter pylori* agents

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In this study, we compared the success rate of eradicating *Helicobacter pylori* (*H. pylori*) in adults and children using vonoprazan (VPZ)-based *H. pylori* regimens to that of proton pump inhibitors (PPIs). In Japan, the success rate of a VPZ-based regimen as first-line therapy was lower in children than in adults. Compared with adults, children around puberty have higher CYP2C19 and CYP3A4 enzymatic activity to metabolize PPIs and VPZ. Further, children generally have shorter intestinal transit times than adults and may absorb antibiotics to a lesser extent. When comparing success rates of pediatric and adult eradication therapy using VPZ, it is very important to maintain a higher intragastric pH with sufficient gastric acid suppression to maintain *H. pylori* in a replicating state and amoxicillin and clarithromycin in the intestinal tract for as long as possible by reducing diarrhea as a side effect. Based on the above, it is reasonable that VPZ, which can suppress stomach acids more strongly than PPI, is a more relevant *H. pylori* eradication therapy.

KEYWORDS

Helicobacter pylori, vonoprazan, proton pump inhibitor, child, adult

1 Introduction

Previous research suggested that vonoprazan (VPZ)-based *Helicobacter pylori* (*H. pylori*) regimens for eradication therapy had a superior eradication efficacy than frequently used proton pump inhibitor (PPI)-based regimens in adults (Murakami et al., 2016; Lyu et al., 2019; Sun et al., 2022). VPZ is a new, potent acid-inhibitory drug, which competitively inhibits potassium binding to the hydrogen-potassium ATPase in gastric parietal cells more efficiently than PPIs (Abdel-Aziz et al., 2021). Therefore, VPZ-based regimens facilitate a shorter eradication therapy and potentially provide significantly higher eradication rates of clarithromycin-resistant strains. To examine why VPZ-based *H. pylori* regimens for eradication therapy were more effective in eradicating *H. pylori* than PPI regimens, we compared its success rate for *H. pylori* eradication in adults and children.

TABLE 1 List of manuscripts on *Helicobacter pylori* eradication therapy success rate using vonoprazan as first-line agent in Japan.

	Authors year	Study design	Number	Regimen	Drug doses VPZ, AMPC, CAM twice for day	Duration (days)	CAM Resistance rate	Success rate
Adult	Murakami et al. (2016)	RCT	329	VPZ + AMPC + CAM	20, 750, 200 or 400 mg	7	38.3%	92.6% (ITT)
	Suzuki et al. (2016)	ROS	181	VPZ + AMPC + CAM	20, 750, 200 mg	7	N/A	91.2% (PP), 89.1% (ITT)
	Tsujimae et al. (2016)	POS	439	VPZ + AMPC + CAM	20, 750, 200 mg	7	N/A	86.3% (PP), 84.6% (ITT)
	Tanabe et al. (2017)	ROS	363	VPZ + AMPC + CAM	20, 750, 200 or 400 mg	7	23.5%	94.4% (PP), 87.2% (ITT)
	Takara et al. (2019)	POS	189	VPZ + AMPC + CAM	20, 750, 200 mg	7	N/A	91.0% (ITT)
	Ozaki et al. (2018)	POS	1,688	VPZ + AMPC + CAM	20, 750, 200 or 400 mg	7	N/A	90.8% (ITT)
	Suzuki et al. (2020)	RCT	167	VPZ + AMPC + CAM	20, 750, 200 mg	7	25.6%	90.2% (PP), 89.2% (ITT)
Child	Kusano et al. (2017)	POS	118	VPZ + AMPC + CAM	20, 750, 200 mg	7	N/A	85.7% (PP), 81.3% (ITT)
	Kakiuchi et al. (2019)	POS	501	VPZ + AMPC + CAM	20, 750, 200 mg	7	N/A	85.1% (PP)
	Kaji et al. (2020)	POS	144	VPZ + AMPC + CAM	20, 750, 200 mg	7	N/A	83.8% (PP), 82.6% (ITT)
	Gotoda et al. (2020)	POS	161	VPZ + AMPC + CAM	20, 750, 200 mg	7	N/A	84.0% (PP), 81.9% (ITT)
	Kakiuchi et al. (2022)	POS	83	VPZ + AMPC + CAM	20, 750, 200 mg	7	57.8%	81.9% (ITT)
	Kakiuchi et al. (2023)	POS	836	VPZ + AMPC + CAM	20, 750, 200 mg	7	N/A	84.0% (PP), 73.6% (ITT)

RCT, randomized controlled trial; ROS, retrospective observational study; POS, prospective observational study; VPZ, vonoprazan; AMPC, amoxicillin; N/A, not applicable; CAM, clarithromycin; ITT, intention-to-treat; PP, per protocol.

2 *Helicobacter pylori* eradication success rate between adults and children

Table 1 shows that the first-line *H. pylori* eradication therapy's success rate by VPZ, amoxicillin (AMPC) and clarithromycin (CAM) for 7 days in Japan, and divided it into adults and children. All these data were previously reported. Considering regional *H. pylori* genotype, I intentionally limited the reports from Japan and omitted the results using second-line *H. pylori* eradication therapy, VPZ dual therapy, and metronidazole. VPZ-based regimen as first-line therapy's success rate in children was lower than those in adults.

3 Discussion

There were three possible reasons why the eradication rate of adults using VPZ was higher than that of children. First, adolescents tend to have a higher rate of *H. pylori* CAM resistance. It has been reported that the *H. pylori* CAM resistance rate is high among young people in Japan (Okamura et al., 2014), which is believed to be a result of the frequent

CAM prescription use for childhood respiratory tract infections in this generation (Tsuboi and Inuma, 2021). Among CAM-resistant strains, VPZ has a significantly higher eradication success rate than PPI (Murakami et al., 2016; Okubo et al., 2020), suggesting that it is important to suppress acid and make AMPC, not CAM, more effective. In addition, sufficient acid suppression is crucial for effectiveness because, bacteria enter their replicative state and become susceptible to AMPC and CAM at high pH. Second, children around puberty have higher CYP2C19 and CYP3A4 enzyme activity to metabolize PPIs and VAP (Anderson and Lynn, 2009). As a result, children metabolize VAP more rapidly than adults and may be attenuated at a higher rate than adults. Third, it has been reported that the ionized agent absorption (many antibacterial agents) that are poorly lipophilic is affected by the small bowel transit time (Martinez and Amidon, 2002). Children generally have shorter intestinal transit times than adults and may absorb less antibiotics than adults. This may be supported by our report (Kakiuchi et al., 2021) that diarrhea during eradication therapy reduces *H. pylori* eradication success rate. The former two suggests that sufficient gastric acid suppression is important for *H. pylori* eradication. The last reason suggests the importance of sufficient antibiotic absorption for *H. pylori*

eradication. Graham (Graham DY, 2023) demonstrated that *H. pylori* eradication was successfully achieved by high intragastric concentrations of antibiotics or an intragastric pH at which amoxicillin is active.

In contrast, the efficacy of a VPZ-based regimen in a Western adult population was not higher compared with that in an Asian population (Chey WD et al., 2022). VPZ is mainly metabolized by CYP3A4 enzyme. Given the lack of clinically significant differences in VPZ pharmacokinetics between Asian and non-Asian populations, the differences between studies conducted among Western adults and Japanese populations are most likely not due to race alone. Different treatment compliance rates may also have contributed to outcome differences. With respect to children, there is no data regarding the eradication of *H. pylori* using VPZ in Western countries; therefore, we could not compare its eradication success rate between populations of Asian, including Japan, and Western countries.

In conclusion, a comparison of pediatric and adult eradication therapy success rates using VPZ could reinforce the following conclusions: with regard to *H. pylori* eradication therapy, it is very important to maintain a higher intragastric pH with sufficient gastric acid suppression to keep *H. pylori* in a replicating state and to keep AMPC and CAM in the intestinal tract as long as possible by reducing diarrhea as a side effect. It is reasonable that VPZ, which is more potent in stomach acid suppression than PPI, should gain a dominant position in *H. pylori* eradication therapy.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

References

- Abdel-Aziz, Y., Metz, D. C., and Howden, C. W. (2021). Review article: Potassium-competitive acid blockers for the treatment of acid-related disorders. *Alimentary Pharmacol. Ther.* 53 (7), 794–809. doi:10.1111/apt.16295
- Anderson, G. D., and Lynn, A. M. (2009). Optimizing pediatric dosing: A developmental pharmacologic approach. *Pharmacotherapy* 29 (6), 680–690. doi:10.1592/phco.29.6.680
- Chey, W. D., Mégraud, F., Laine, L., López, L. J., Hunt, B. J., and Howden, C. W. (2022). Vonoprazan triple and dual therapy for helicobacter pylori infection in the United States and europe: Randomized clinical trial. *Gastroenterology* 163 (3), 608–619. doi:10.1053/j.gastro.2022.05.055
- Gotoda, T., Kusano, C., Suzuki, S., Horii, T., Ichijima, R., and Ikehara, H. (2020). Clinical impact of vonoprazan-based dual therapy with amoxicillin for *H. pylori* infection in a treatment-naïve cohort of junior high school students in Japan. *J. gastroenterology* 55 (10), 969–976. doi:10.1007/s00535-020-01709-4
- Graham, D. Y. (2023). Why the vonoprazan helicobacter pylori therapies in the US-European trial produced unacceptable cure rates. *Dig. Dis. Sci.* 68 (5), 1691–1697. doi:10.1007/s10620-023-07886-5
- Kaji, E., Yoden, A., Otani, M., Okuhira, T., Aomatsu, T., Tamai, H., et al. (2020). *Helicobacter pylori* test-and-treat strategy for second-year junior high school students aimed at the prevention of gastric cancer in Takatsuki City. *Helicobacter* 25, e12696. doi:10.1111/hel.12696
- Kakiuchi, T., Matsuo, M., Endo, H., Nakayama, A., Sato, K., Takamori, A., et al. (2019). A *Helicobacter pylori* screening and treatment program to eliminate gastric cancer among junior high school students in saga prefecture: A preliminary report. *J. gastroenterology* 54 (8), 699–707. doi:10.1007/s00535-019-01559-9
- Kakiuchi, T., Matsuo, M., Endo, H., Sakata, Y., Esaki, M., Noda, T., et al. (2023). Efficacy and safety of vonoprazan-based regimen for *Helicobacter pylori* eradication therapy in Japanese adolescents: A prospective multicenter study. *J. gastroenterology* 58 (3), 196–204. doi:10.1007/s00535-022-01942-z
- Kakiuchi, T., Matsuo, M., Endo, H., Sakata, Y., Esaki, M., Noda, T., et al. (2021). Gastrointestinal adverse reactions reduce the success rate of *Helicobacter pylori* eradication therapy: A multicenter prospective cohort study. *Helicobacter* 26 (2), e12776. doi:10.1111/hel.12776
- Kakiuchi, T., Okuda, M., Matsuo, M., and Fujimoto, K. (2022). Smart Gene™ as an effective non-invasive point-of-care test to detect *Helicobacter pylori* clarithromycin-resistant mutation. *J. Gastroenterol. Hepatol.* 37 (9), 1719–1725. doi:10.1111/jgh.15887
- Kusano, C., Gotoda, T., Ishikawa, H., and Moriyama, M. (2017). The administrative project of *Helicobacter pylori* infection screening among junior high school students in an area of Japan with a high incidence of gastric cancer. *Gastric Cancer* 20 (Suppl. 1), 16–19. doi:10.1007/s10120-017-0688-7
- Lyu, Q. J., Pu, Q. H., Zhong, X. F., and Zhang, J. (2019). Efficacy and safety of vonoprazan-based versus proton pump inhibitor-based triple therapy for *Helicobacter pylori* eradication: A meta-analysis of randomized clinical trials. *Biomed. Res. Int.* 2019, 9781212. doi:10.1155/2019/9781212
- Martinez, M. N., and Amidon, G. L. (2002). A mechanistic approach to understanding the factors affecting drug absorption: A review of fundamentals. *J. Clin. Pharmacol.* 42 (6), 620–643. doi:10.1177/00970002042006005
- Murakami, K., Sakurai, Y., Shiino, M., Funao, N., Nishimura, A., and Asaka, M. (2016). Vonoprazan, a novel potassium-competitive acid blocker, as a component of first-line and second-line triple therapy for *Helicobacter pylori* eradication: A phase III, randomised, double-blind study. *Gut* 65 (9), 1439–1446. doi:10.1136/gutjnl-2015-311304
- Okamura, T., Suga, T., Nagaya, T., Arakura, N., Matsumoto, T., Nakayama, Y., et al. (2014). Antimicrobial resistance and characteristics of eradication therapy of *Helicobacter pylori* in Japan: A multi-generational comparison. *Helicobacter* 19 (3), 214–220. doi:10.1111/hel.12124
- Okubo, H., Akiyama, J., Kobayakawa, M., Kawazoe, M., Mishima, S., Takasaki, Y., et al. (2020). Vonoprazan-based triple therapy is effective for *Helicobacter pylori*

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

TK searched the literature. TK conceived and wrote the manuscript. TK contributed to the manuscript and approved the submitted version.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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- eradication irrespective of clarithromycin susceptibility. *J. gastroenterology* 55 (11), 1054–1061. doi:10.1007/s00535-020-01723-6
- Ozaki, H., Harada, S., Takeuchi, T., Kawaguchi, S., Takahashi, Y., Kojima, Y., et al. (2018). Vonoprazan, a novel potassium-competitive acid blocker, should be used for the helicobacter pylori eradication therapy as first choice: A large sample study of vonoprazan in real world compared with our randomized control trial using second-generation proton pump inhibitors for helicobacter pylori eradication therapy. *Digestion* 97 (3), 212–218. doi:10.1159/000485097
- Sun, Y., Yue, L., and Hu, W. (2022). Effectiveness and safety of vonoprazan-based regimens compared with those of proton pump inhibitor (PPI)-based regimens as first-line agents for *Helicobacter pylori*: A meta-analysis of randomized clinical trials. *Eur. J. Clin. Pharmacol.* 79 (2), 279–288. doi:10.1007/s00228-022-03430-y
- Suzuki, S., Gotoda, T., Kusano, C., Ikehara, H., Ichijima, R., Ohyauchi, M., et al. (2020). Seven-day vonoprazan and low-dose amoxicillin dual therapy as first-line *Helicobacter pylori* treatment: A multicentre randomised trial in Japan. *Gut* 69 (6), 1019–1026. doi:10.1136/gutjnl-2019-319954
- Suzuki, S., Gotoda, T., Kusano, C., Iwatsuka, K., and Moriyama, M. (2016). The efficacy and tolerability of a triple therapy containing a potassium-competitive acid blocker compared with a 7-day PPI-based low-dose clarithromycin triple therapy. *Am. J. gastroenterology* 111 (7), 949–956. doi:10.1038/ajg.2016.182
- Takara, Y., Endo, H., Nakano, R., Kawachi, K., Hidaka, H., Matsunaga, T., et al. (2019). Smoking and drinking did not increase the failure of therapeutic helicobacter pylori eradication by vonoprazan, clarithromycin, and amoxicillin. *Digestion* 99 (2), 172–178. doi:10.1159/000490889
- Tanabe, H., Ando, K., Sato, K., Ito, T., Goto, M., Sato, T., et al. (2017). Efficacy of vonoprazan-based triple therapy for helicobacter pylori eradication: A multicenter study and a review of the literature. *Dig. Dis. Sci.* 62 (11), 3069–3076. doi:10.1007/s10620-017-4664-1
- Tsuboi, I., and Inuma, K. (2021). Immunochromatography-application example and POCT type genetic testing. *Chem. Pharm. Bull.* 69 (10), 984–988. doi:10.1248/cpb.c21-00164
- Tsujimae, M., Yamashita, H., Hashimura, H., Kano, C., Shimoyama, K., Kanamori, A., et al. (2016). A comparative study of a new class of gastric acid suppressant agent named vonoprazan versus esomeprazole for the eradication of helicobacter pylori. *Digestion* 94 (4), 240–246. doi:10.1159/000454762