Influence of clarithromycin on the bactericidal effect of amoxicillin in patients infected with clarithromycin-resistant strains of *H. pylori*

We read the manuscript written by Suzuki *et al*[1] with interest. They reported that the eradication rate of *Helicobacter pylori* attained by the dual therapy with vonoprazan and amoxicillin (VA-Dual) was almost the same as that attained by the triple therapy with vonoprazan, amoxicillin and clarithromycin (VAC-Triple), as previously reported by us.[2] The most interesting point in this paper was that the VA-Dual therapy was superior to the VAC-Triple therapy in eradicating the clarithromycin-resistant strains of *H. pylori*. In this regard, the authors consider the possibilities of a type I error, the difference in the proportion of amoxicillin-resistant strains, and the excessive inhibition of gastric acid secretion caused by the interaction between clarithromycin and vonoprazan. We have another opinion on this phenomenon. We infer that the pharmacodynamic antagonism between clarithromycin and amoxicillin underlies this phenomenon. In other bacteria, the combination of amoxicillin and clarithromycin has been reported antagonistic.[3 4] The target of amoxicillin is the penicillin-binding protein (PBP), which is the enzyme involved in the biosynthesis of the bacterial cell wall. When *H. pylori* grows, the expression of PBP is enhanced, which means that the expression of target of amoxicillin is increased, resulting in the bactericidal effect of amoxicillin being enhanced. On the contrary, when the growth of *H. pylori* is inhibited, the expression of PBP is decreased. In this situation, the bactericidal effect of amoxicillin is decreased because the expression of target of amoxicillin is decreased. Clarithromycin is known as the inhibitor of ribosomal RNA (rRNA), indicating that clarithromycin inhibits protein synthesis including PBP. Then, the sensitivity to amoxicillin is decreased by clarithromycin.

However, if the patient is infected with clarithromycin-sensitive strains, there is no problem because these strains can be killed by clarithromycin. However, in cases infected with clarithromycin-resistant strains of *H. pylori*, there might be some problems. The minimum inhibitory concentration ranges of clarithromycin-resistant strains of *H. pylori* are very wide (eg, from 1 µg/mL to >32 µg/mL). In cases infected with clarithromycin-weakly resistant strains of *H. pylori*, clarithromycin will work halfway. Although *H. pylori* strains cannot be killed by clarithromycin, the inhibitory effect of clarithromycin on rRNA may affect the subsequent protein synthesis including PBP, leading to reduced sensitivity to amoxicillin.

The eradication rates attained by a proton pump inhibitor (PPI), amoxicillin and clarithromycin were reportedly very low in patients infected with clarithromycin-resistant strains of *H. pylori*,[5 6] although amoxicillin-resistant strains of *H. pylori* are rare in Japan. The present study by Suzuki *et al*[1] accounts for the poor eradication rates by the triple therapy with a PPI, amoxicillin and clarithromycin in patients infected with clarithromycin-resistant strains of *H. pylori*. These clinical studies have suggested that clarithromycin not only does not work as antibiotics, but also has an adverse effect on the action of other antibiotics in cases infected with clarithromycin-resistant strains of *H. pylori*. This paper has suggested the importance of selecting appropriate antibiotics according to susceptibility, again from another point of view.

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