The oral bioavailability of drugs which show pH-dependent dissolution is often significantly affected by gastric fluid acidity. Our previous study in 1984 revealed that the percentage of achlorhydric subjects in Japan increased with age and the percentage exceeded 60% when the age of subjects reached 50 years. Because of the high percentage of achlorhydric elderly, dissolution, bioavailability and bioequivalence studies of new and generic drugs should be performed giving consideration to the effect of gastric acidity on in vivo performance. However, the percentage of achlorhydric subjects in the U.S.A. is very low, and is less than 10% even for the elderly. Concerning gastric acidity, questions arise as to whether there still are many achlorhydric subjects in Japan, especially since daily food consumption patterns and lifestyles have changed. If the number of achlorhydric subjects has significantly decreased, it may be unnecessary to consider the effects of gastric acidity on bioavailability and bioequivalence studies. However, since the current number of achlorhydric subjects was not known, we initiated the present study.

In this study, the percentages of achlorhydric subjects from 1989 to 1999 were determined in different age categories (18—80 years) and compared with the results from 1984. Gastric acidity was estimated using the urinary excretion data of riboflavin after oral administration of GA-Test capsules containing acid-soluble granules of riboflavin to subjects (n=4184).

**MATERIALS AND METHODS**

For measurement of human gastric acidity, GA-Test capsules containing riboflavin (5 mg) granules coated with polyvinylacetal diethylaminoacetate (AEA) in a capsule were used. Drug dissolves out from the granules at acidic pH, but not at pH>5 due to the solubility characteristics of AEA. This dissolving property makes it possible to classify subjects into two groups of low and normal acidity, based on the boundary amount (150 μg) of riboflavin excreted in the urine for 2h after administration of a GA-Test capsule. The GA-test capsules were distributed from our laboratory to clinical research laboratories who needed the capsules to clarify the gastric acidity of human volunteers, mainly for phase I studies. The human volunteers had given informed consent for the experiment at each laboratory. We requested all laboratories to obtain the urinary excretion data of riboflavin after administration of GA-Test capsules. By using the urinary data from 4184 subjects, ranging in age from 18 to 80 years, obtained in 1989—1999, the percentages of achlorhydric subjects were determined according to age and birth year.

**RESULTS**

The gastric acidity of 4184 subjects, ranging in age from 18 to 80 years, were determined in this study. The age range was wider compared with that (from 10 to 50 years) in the previous study in 1984. Figure 1 shows the percentage of subjects having low gastric acidity in each age category for the past 10 years (1989—1999). This increased with age as observed before and reached a plateau of about 70% at 60

---

*To whom correspondence should be addressed. e-mail: morihara@nih.go.jp © 2001 Pharmaceutical Society of Japan*
years. Figure 2 shows the change in percentage of achlorhydric subjects in each age group with the year. The percentage decreased with the year investigated in all age groups, except for that of the 10th year. The decrease was profound for subjects from 40 to 50 years of age, but only slight for 20 year old subjects. Figure 3 shows the chronological change in percentages of achlorhydric subjects determined according to birth year, which did not change significantly in any of the birth groups. These findings suggested that gastric acidity may be more closely related with birth year of subjects rather than age.

**DISCUSSION**

There have been several reports on inter-subject differences in gastric acidity. Our previous study of Japanese subjects revealed that the percentage of achlorhydric subjects increased with age and more than 60% of 50 year olds displayed gastric hypoacidity. On the contrary, a very low percentage (11%) of achlorhydric elderly has been reported for North American subjects. Finholt and Solvang clarified that 20% of patients in a hospital in Norway had gastric pHs higher than 5. Xu reported that the gastric pH of Chinese patients with gastric cancer was much higher than normal controls. These findings indicate that gastric acidity is affected by ethnic, disease and environmental factors, including food.

The present study was undertaken to clarify the current number of achlorhydric subjects in Japan where daily food and lifestyle has changed, and to compare with that in 1984. This study revealed that the trend towards an increase in the percentage of achlorhydric subjects with age did not change this time (Fig. 1), however the percentage is decreasing year by year, especially in the elderly (Fig. 2). The percentage of achlorhydric subjects in the 40 year age group in 1995—1999 was only 12%, which was one third that in 1984. However, such a chronological change was not observed when the number of achlorhydric subjects was determined according to birth year (Fig. 3). This suggests that the birth year of individual subjects should be a key factor in gastric hypoacidity. The reason is unclear but it may be related with infection by *Helicobacter pylori* (*H. pylori*), causing gastritis and gastric pH change, since the number of subjects infected with *H. pylori* is higher for elderly subjects compared with the young who were born and raised in more hygienic conditions. Figure 4 shows the relationship between the percentage of
achlorhydric subjects in different age categories and infection with \textit{H. pylori}, as reported by Fujisawa \textit{et al.}\textsuperscript{7)} The high correlation indicates that the infection is a possible variable for achlorhydria in Japanese. However, foreign subjects showing a low percentage of achlorhydria\textsuperscript{4–6)} are also infected with \textit{H. pylori}, although the number is lower than that in Japan.\textsuperscript{8)} Further studies will be required to clarify the reasons for the large number of achlorhydric elderly in Japan.

From the present study, we conclude that there are still a considerable number of achlorhydric elderly in Japan. Therefore, bioavailability and bioequivalence studies should be performed taking into consideration the effects of gastric acidity on \textit{in vivo} performance of drug products.

REFERENCES