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ffect of cimetidine and ranitidine on absorption of [^{125}I]levothyroxine dministered orally

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STRACT Female patients with a simple goiter re pretreated on 2 occasions (at an interval of 4 wk) h *po* placebo or 400 mg cimetidine (Cim) (Group , $n=10$), or with placebo or 30 mg ranitidine an) (Group B, $n=10$), 90 and 150 min, pectively, proior to the *po* gelatin capsules con- ining [^{125}I]levothyroxine ([^{125}I]LT_4). A double-blind ndomized study protocol was kept. Venous blood mples were taken at 15, 30, 45, 60, 75, 90, 5, 120, 150, 180, 210, and 240 min after *po* I]LT_4 and the radioactivities in serum were count- . Similar [^{125}I]LT_4 radioactivities were found after cebo pretreatment in both groups: AUC 467 ± 82 Group A *vs* 459 ± 109 in Group B. Cimetidine de- sed the serum [^{125}I]LT_4 radioactivities: AUC 371 72 (Cim) *vs* 467 ± 82 (placebo) ($P<0.01$), but Ran not: AUC 477 ± 132 (Ran) *vs* 459 ± 109 (placebo) >0.05).

Y WORDS cimetidine; combination drug rapy; levothyroxine; pharmacokinetics; ranitidine

Histamine H_2 receptor blockers are wide- used and a problem of their interactions h other drugs is becoming increasingly im- tant clinically[1]. In this paper we report influences of cimetidine (Cim) and nitidine (Ran) on the serum concentrations [^{125}I]levothyroxine ([^{125}I]LT_4) administered ly (*po*) to female patients with a simple iter.

TERIALS AND METHODS

This study was approved by the Human Research Ethics Committee of the Silesian School of Medicine, and a written informed consent was obtained from every one of the examined 20 female patients with a simple goiter. They were euthyriod, free from any gastrointestinal complaints, and received no medication at the entry to this study. The patients were randomly allocated to 2 groups of 10 patients each: Group A, age 19-40 a, $\bar{x}$ 26.6 a, wt 55-67 kg, $\bar{x}$ 60 kg, and Group B, age 19-40 a, $\bar{x}$ 28.7 a, wt 50-66 kg, $\bar{x}$ 58.9 kg. At an interval of 4 wk and with accordance with a double-blind randomized study protocol, Group A took *po* placebo ro 400 mg Cim 90 min prior to *po* [^{125}I]LT_4, and Group B took *po* placebo or 300 mg Ran 150 min prior to *po* [^{125}I]LT_4. The 90 and 150 min intervals were needed to reach peak plasma concentrations after *po* 400 mg Cim[2] and 300 mg Ran[3], respectively. [^{125}I]LT_4 was administered in form of a gelatin capsule and its radioactivity ranged between 1.1 and 1.8 MBq (30-50 μCi) and was determined on a weight basis with an accuracy of 0.1 mg by using a stock water solution of [^{125}I]LT_4 with a specific activity of 1.75-1.95 GBq · mg^{-1} (manufacturer: The Reactor and Isotope Production Center, Swierk, Poland). An equal amount of [^{125}I]LT_4 stock solution was put each time to 500 ml redistilled water to get a standard reference.

Blood was taken from the antecubital vein before and at 15, 30, 45, 60, 75, 90, 105, 120, 150, 180, 210, and 240 min after *po* [^{125}I]LT_4. The blood was centrifuged and the serum radioactivity was counted for 10 min twice. After subtraction of background reading, these 2 measurements were averaged. As a measure of [^{125}I]LT_4 absorption, a ratio K between the specific activity of the serum and the total dose of [^{125}I]LT_4 given *po* (the latter was derived from multiplication by 500 of the specific activity

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of the standard reference solution) was taken. This approach allowed correction of the radioactivities measured for the spontaneous disintegration of the radioisotope.

The disintegration time of the gelatin capsules (used for *po* [^{125}I]LT_4) was tested in gastric juice *in vitro* at 37 ℃ by measuring the time period from putting the capsule containing a dye into the medium to a visual staining of the gastric juice. Ten capsules were examined at each of pH 3, 4, 5, 6, and 7. The polyethylene bag containing the juice was gently squeezed thrice per minute to mimic gastric movements. The disintegration time ranged 27–39 s, irrespective of the pH.

The area under the curves of the *K* ratio by time (AUC) was computed by a trapezium method. Statistical analysis involved a two-way ANOVA and *t* test (individual comparison for paired data and group comparison for unmatched probes) of Welch test[4]. All the results are expressed as a mean ± standard deviation ($\bar{x} \pm s$).

RESULTS

The time to reach a peak *K* ratio for [^{125}I]LT_4 was 111 ± 35 min (placebo) *vs* 135 ± 31 min (Cim) in Group A, and 104 ± 35 min (placebo) *vs* 92 ± 29 min (Ran) in Group B—the differences between an H_2-receptor blocker and placebo were statistically non-significant. A significant decrease in [^{125}I]LT_4 absorption from the gut was brought about by Cim (ANOVA: $F_{1;108} = 56.479$, $P < 0.01$) but not by Ran (ANOVA: $F_{1;108} = 2.569$, $P > 0.05$) pretreatment (Tab 1).

The comparison of the AUC of the *K* ratio by time indicated an identical [^{125}I]LT_4 absorption following a placebo pretreatment in the 2 groups (Tab 2). Cim reduced the [^{125}I]LT_4 absorption by 20.6%, when referred to the situation with placebo; this decrease was more pronounced during the first 2 h than during the next (Tab 2). On the other hand, no significant effect on the [^{125}I]LT_4 absorption was elicited by Ran pretreatment.

DISCUSSION

It should be pionted out that the 2 groups of patients were well matched not only in terms of their ages and weights, but also in

Tab 1. Effect of free cimetidine and ranitidine pretreatment on absorption of *po* [^{125}I]levothyroxine, as reflected by *K* ratio ($\times 10^{-6}$) between serum specific activity and total [^{125}I]LT_4 activity given *po*.

Time after *po* [^{125}I]LT_4, min	Group A ($n = 10$)		Group B ($n = 10$)	
	Placebo	Cimetidine[a)]	Placebo	Ranitidine[b)]
15	2.4 ± 3.3	2.1 ± 2.5	2.4 ± 1.9	7.2 ± 8.0
30	26.5 ± 26.5	18.0 ± 16.3	35.9 ± 32.4	53.9 ± 54.5
45	73.5 ± 42.2	44.8 ± 29.2	84.8 ± 56.7	100.0 ± 64.1
60	110.8 ± 39.1	69.9 ± 36.8	120.2 ± 42.3	132.1 ± 49.4
75	135.7 ± 38.0	92.8 ± 32.3	140.9 ± 37.9	148.1 ± 47.8
90	147.1 ± 29.6	111.3 ± 31.0	151.1 ± 47.7	151.6 ± 46.6
105	153.2 ± 26.0	124.1 ± 35.7	149.4 ± 35.0	153.6 ± 47.4
120	152.6 ± 24.6	127.4 ± 37.1	147.4 ± 37.2	151.0 ± 45.5
150	151.4 ± 25.6	129.6 ± 32.1	145.9 ± 37.6	143.3 ± 42.3
180	143.2 ± 25.9	124.3 ± 30.7	132.8 ± 34.7	134.7 ± 40.0
210	136.0 ± 26.3	119.6 ± 30.4	125.5 ± 34.0	127.1 ± 39.9
240	130.5 ± 25.0	115.6 ± 27.5	120.4 ± 32.1	124.4 ± 23.0

a) placebo or 400 mg cimetidine was given *po* 90 min before [^{125}I]LT_4.
b) placebo or 300 mg cimetidine was given *po* 150 min before [^{125}I]LT_4.

Tab 2. Area under the curves of *K* ratio (ratio between specific activity of serum and total [^{125}I]LT_4 activity given *po*) by time after a placebo or H_2–receptor blocker pretreatment.

Group	$AUC_{0-120\ min}$		$AUC_{120-240\ min}$		$AUC_{0-240\ min}$	
Group A ($n=10$)	Placebo 181 ± 48	Cimetidine $124 \pm 25^{***}$	Placebo 286 ± 49	Cimetidine $248 \pm 61^{**}$	Placebo 467 ± 82	Cimetidine $371 \pm 72^{***}$
Group B ($n=10$)	Placebo 189 ± 57	Ranitidine 206 ± 69	Placebo 269 ± 70	Ranitidine 271 ± 81	Placebo 459 ± 109	Ranitidine 477 ± 132
P values	>0.05	<0.01	>0.05	>0.05	>0.05	<0.01

In Group A placebo or 400 mg cimetidine, and in Group B placebo or 300 mg ranitidine was given *po* 90 min and 150 min before [^{125}I]LT_4, respectively; $^{**}P<0.05$, and $^{***}P<0.01$ *vs* placebo.

the absorption of [^{125}I]LT_4 after a placebo pretreatment. This observation validated a direct comparison (on the basis of unmatched probes) of the effect of Cim *vs* that Ran on [^{125}I]LT_4 absorption from the gut. The present study showed that Cim but not Ran may decrease [^{125}I]LT_4 absorption after *po* in humans. Obviously, a full proof of a decreased [^{125}I]LT_4 absorption from the gut would be obtained if concentrations of this compound were measured in portal blood and / or if a lack of a significant conversion to inactive iodothyronines or even radiolysis of [^{125}I]LT_4 after the hepatic passage was assured. In the light of the existing published data the latter qualification can be ruled out. Rudolph *et al*[5] demonstrated that serum concentrations of ^{125}I–labelled: triiodothyronine (T_3), reverse–triiodothyronine (rT_3), diiodothyronins, and iodoproteins were negligible up to 10 d after *po* [^{125}I]LT_4 in humans. Moreover, it was revealed that stable *L*–thyroxine given *po* did not significantly increase the serum total or free T_3 at a time interval corresponding to that during which we examined the effect of H_2–receptor blockers on [^{125}I]LT_4 absorption[6]. Snarski *et al*[7] who examined [^{125}I]LT_4 from the same manufacturer as we used in the present study, did not find a significant radiolysis even 48 h after administration of this compound. Thus the reports cited speak in favor of the contention that a diminished absorption from the gut may accunt for the decreased [^{125}I]LT_4 bioavailability after Cim pretreatment.

The mechanism of the phenomenon observed remains yet obscure. Obviously, such factors as physical interaction between Cim and [^{125}I]LT_4 resulting in complexation or chelation, as well as changes of the gastrointestinal milieu evoked by altered gut motility, intestinal blood flow, or luminal pH should be taken into consideration. There is no sufficient evidence, however, however, that H_2–receptor blockers could decrease absorption of other drugs due to a physical interaction[1]. Previously we found that 300 mg Ran *po* evoked a significant delay in gastric emptying of a radiolabeled solid meal, whereas 400 mg Cim *po* under identical conditions did not exert any significant effect on gastric evacuation in either healthy subjects or patients with an active duodenal ulcer[8]. Moreover, 300 mg Ran *po* would be expected to elicit a more pronounced reduction in gastric acid output and an increase in the luminal pH within the stomach than after 400 mg Cim *po*[9]. Therefore, the factors mentioned above cannot be responsible for the decreased absorption of *po* [^{125}I]LT_4 after Cim but not Ran pretreatment. Also, there is no sufficient evidence that either Cim or Ran would diminish the hepatic blood flow in man[10,11].

Assuming that a chronic Cim treatment

involved a similar reduction of levothyroxine absorption as we found in this work on the basis of a single study, it would be necessary to adjust the levothyroxine dosage upwards in patients requiring this treatment and taking at the same time Cim. However, exact recommendations in this respect cannot be delineated yet. Firstly, a certain limitation of the present study is the relatively short observation period during which the [^{125}I]LT_4 absorption was examined. Although we found that with every treatment variant examined, the Cim pretreatment inclusive, the *K* ratio achieved a peak within some 2 h after *po* [^{125}I]LT_4 administration, and that thereafter the *K* ratio decreased, a possibility cannot be excluded that a later second *K* ratio peak might have occurred. Secondly, apart from a decreased [^{125}I]LT_4 absorption, an increased conversion of thyroxine to biologically inactive rT_3 may occur under Cim treatment[12]. Taking into account the standard dosage regimens of Cim: 3 × 200 mg + 400 mg *po* nocte, or 2 × 400 mg *po*, as well as the pharmacokinetic data concerning this drug, such as the half elimination time[2,9], an interaction between Cim and levothyroxine seems to be highly probable in patients taking both the drugs and thus warrants further research on the interference of Cim treatment with LT_4 bioavailability.

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