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Effects of omeprazole and AlOH/MgOH on riociguat absorption

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Background

Riociguat, a soluble guanylate cyclase stimulator, is currently under investigation for the treatment of pulmonary hypertension. The present studies investigated the influence of omeprazole and AlOH/MgOH on riociguat absorption and bioavailability.

Methods

The pharmacokinetics of oral, single-dose, immediate-release riociguat 2.5 mg were characterized in two open-label, randomized, crossover studies in healthy males. In the first study, subjects pretreated for 4 days with once-daily omeprazole 40 mg received co-treatment with omeprazole + riociguat or riociguat alone (no pretreatment) on Day 5 (n = 12). In the second study, subjects received co-treatment with 10 mL AlOH/MgOH + riociguat or riociguat alone (n = 12). Pharmacokinetic characteristics were analyzed assuming log-normally distributed data. Safety and tolerability were also assessed.

Results

Riociguat bioavailability was decreased by pre- and co-treatment with omeprazole, with a mean decrease in C_{max} of 35% and a mean decrease in AUC of 26% (Table 1; Figure 1). Co-treatment with 10 mL AlOH/MgOH resulted in a mean decrease in C_{max} of 56% and a mean decrease in AUC of 34% (Table 1; Figure 2). In the riociguat/omeprazole study, adverse events (AEs) were reported in 4 (33%) subjects receiving riociguat alone and in 5 (42%) subjects receiving riociguat + omeprazole, with no AEs reported during the omeprazole pretreatment phase. The most commonly reported AEs were headache (9 events in 8 subjects; 5 drug-related events) and flushing (3 events in 2 subjects; all drug-related).

Table 1 Riociguat pharmacokinetic parameters (geometric means and coefficients of variation)

Parameter[a]	Riociguat/omeprazole study				Riociguat/AlOH/MgOH study			
	Riociguat 2.5 mg (n=12)		Riociguat 2.5 mg + omeprazole (n=12)		Riociguat 2.5 mg (n=12)		Riociguat 2.5 mg + AlOH/MgOH (n=12)	
	GM	%CV	GM	%CV	GM	%CV	GM	%CV
AUC (µg·h/L)	587.9	71.9	432.8	79.8	465.9	68.2	309.6	87.2
C_{max} (µg/L)	73.8	26.6	48.1	33.8	80.8	38.4	35.5	57.1
t_{max} (h)	3.0	–	3.0	–	1.0	–	2.5	–
$t_{1/2}$ (h)	7.9	46.4	9.0	25.4	5.9	44.4	8.6	53.8
CL/f	4.3	71.9	5.8	79.8	5.4	68.2	8.1	87.2

AUC, area under plasma concentration–time curve; CL/f, total riociguat clearance from plasma; C_{max}, maximum riociguat plasma concentration; CV, coefficient of variation; GM, geometric mean; $t_{1/2}$, elimination half-life; t_{max}, time to reach C_{max}.
[a]Data are mean except t_{max}, which is median.

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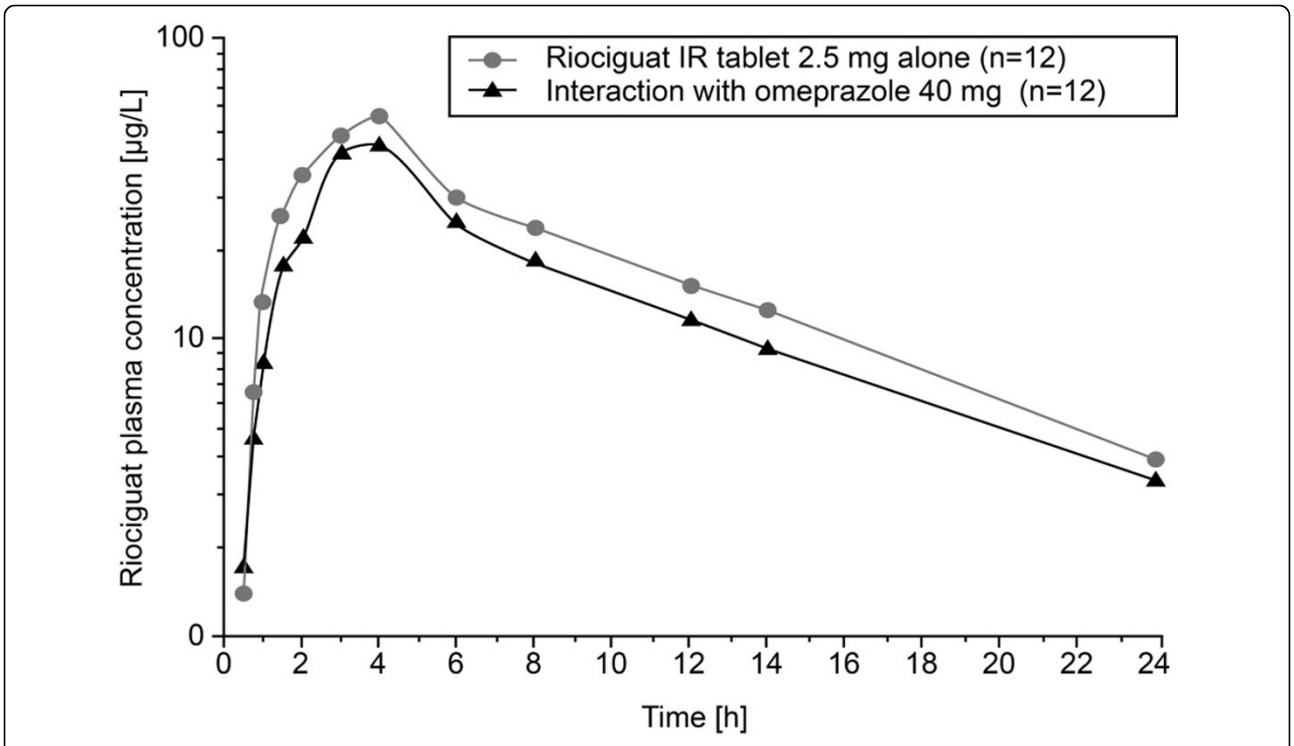

Figure 1 Riociguat plasma concentrations after a single oral dose of riociguat 2.5 mg with and without pre- and co-treatment with once-daily omeprazole 40 mg (geometric means, semilogarithmic scale; all subjects valid for pharmacokinetics; n=12). IR, immediate release.

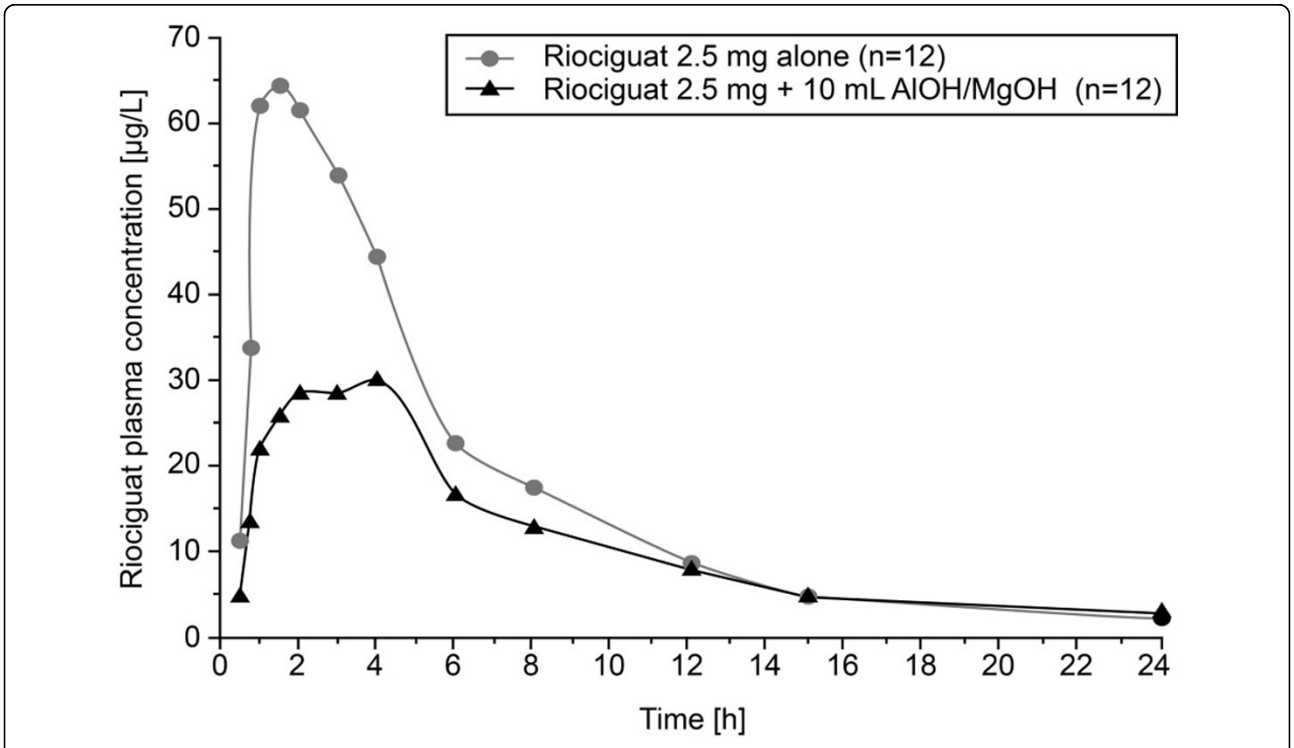

Figure 2 Riociguat plasma concentrations after a single oral dose of riociguat 2.5 mg with and without co-administration of 10 mL AlOH/MgOH (geometric means, semilogarithmic scale; all subjects valid for pharmacokinetics; n=12).

In the riociguat/AlOH/MgOH study, AEs were reported in 9 (75%) subjects receiving riociguat alone and in 8 (67%) subjects receiving riociguat + AlOH/MgOH. The most commonly reported AEs were headache (12 events in 7 subjects; all drug-related), rhinitis (3 events in 3 subjects; no drug-related events), nasal congestion (3 events in 2 subjects; 2 drug-related events), and upper abdominal pain (3 events in 2 subjects; no drug-related events). No serious AEs were reported in either study and all AEs resolved by the end of the observation period.

Conclusion

Treatment with riociguat, with or without omeprazole or AlOH/MgOH, was well tolerated, with a good safety profile. The results confirm the lower bioavailability of riociguat in neutral versus acidic medium as expected from in vitro data. For co-medication of antacids like AlOH/MgOH, staggered intake between riociguat and antacid is practically possible and may be advisable. A general dose adaptation for patients with co-medication acting on gastric acidity, beyond the dose titration concept for riociguat, is not recommended.

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