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A gastrointestinal simulation system for dissolution of oral solid dosage forms before and after Roux-en-Y gastric bypass

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ABSTRACT

Background The Roux-en-Y gastric bypass (RYGB) is a bariatric procedure, greatly reducing the stomach size and bypassing the duodenum and proximal jejunum. Hence, RYGB may reduce the absorption and bioavailability of oral medication. For clinical decisions on the use of medication, knowledge of altered modifications in drug disposition is a prerequisite. An in vitro dissolution method for solid oral medications, simulating conditions before and after RYGB, might be a valuable tool to predict the pharmaceutical availability of medicines frequently used by patients after RYGB.

Objectives To develop a gastrointestinal simulation system (GISS), mimicking conditions before and after RYGB for investigating dissolution characteristics of solid oral medications, and to assess the pharmaceutical availability of metoprolol from immediate-release (IR) and controlled-release (CR) tablets under these conditions.

Methods With an adjusted, pharmacopoeial paddle dissolution apparatus, the GISS enables variation in parameters which are relevant to drug release in vivo: pH, volume, residence time, osmolality and agitation. Metoprolol tartrate 100 mg IR tablets and metoprolol CR tablets were tested. Release profiles were determined by measuring the concentrations of metoprolol spectrophotometrically.

Results From IR tablets, under all conditions applied, >85% of metoprolol was released within 25 min. From all tested CR tablets >90% of metoprolol was released after 22 hours.

Conclusions This GISS is a suitable dissolution system to assess pharmaceutical availability before and after RYGB. In patients who have undergone RYGB, no problems in pharmaceutical availability of metoprolol IR and CR tablets are to be expected. Any changes in response to metoprolol in patients after RYGB should therefore be ascribed to changes in bioavailability.

INTRODUCTION

Worldwide, in 2014 more than 600 million adults were obese, defined as a body mass index (BMI, calculated as weight in kilograms divided by height in metres squared) of ≥30.[1] For morbid obesity (BMI ≥40) bariatric surgery is considered the most effective treatment. Compared with non-surgical options, bariatric surgery results in greater improvement in weight loss and weight-associated comorbidities.[2] Laparoscopic Roux-en-Y gastric bypass (RYGB) is the second most commonly performed bariatric procedure in the world.[3] It greatly reduces the stomach size by approximately 95%, creating a small pouch. This pouch is reattached to the middle of the small intestine, bypassing the duodenum and 50–70 cm of the jejunum. Weight loss is achieved by a combination of restriction of food intake, malabsorption and changes in endocrine response.[4]

After RYGB changes in the anatomy and physiology of the gastrointestinal tract, such as reduced gastric volume, increased gastric pH, decreased surface area available for absorption, altered gastrointestinal transit time, changed intestinal and hepatic first-pass metabolism, and reduced mixing between medicines and biliopancreatic secretions, may all have consequences on the bioavailability of orally administered medications.[4–7] It is likely that medicines with a long absorptive phase and remaining in the intestine for extended periods, will exhibit decreased bioavailability in patients after RYGB. Therefore, although not evidence based, for these patients it is generally recommended that controlled-release (CR) oral medication is replaced by immediate-release (IR) dosage forms.[8]

In optimising pharmacotherapy after bariatric surgery, pharmacists may play a prominent role. For clinical decisions on medication use, knowledge of altered modifications in drug disposition is a prerequisite. However, very few studies on the influence of bariatric surgery on the pharmacokinetics of medicines have been published.[9 10]

For patients who have undergone RYGB it is important to determine whether pharmacotherapeutic management should be different after surgery. Predicting the specific pharmacokinetic changes associated with bariatric surgery and its clinical importance is challenging. Drug solubility, permeability parameters and galenic formulation may be helpful, but not conclusive, for the prediction of oral dug exposure outcome after RYGB.[10]

As yet, modelling in vitro drug dissolution after RYGB has received little attention in the literature.

Seaman *et al*[11] developed an in vitro drug dissolution model to approximate the gastrointestinal environment of the preoperative and post-RYGB states to study dissolution of IR psychiatric medications. This model, not based on a pharmacopoeial dissolution apparatus, uses two different dissolution media in a test tube for a post-RYGB and a control environment. For the post-RYGB model all medications were crushed before studying dissolution. The dissolved portions of medication were determined by weighing the remaining undissolved parts of the tablets. They concluded that 10 of 22

Table 1 Specifications of the five phases of the gastrointestinal simulation system (GISS) before Roux-en-Y gastric bypass

Phase	Simulated GI segment	Volume of simulated GI segment (mL)	Total volume (mL)	Residence time (min)	pH	Osmolality (mosmol/kg)
I	Stomach	500	500	120 (full)/30 (empty)	1.2±0.20	150±25
II	Duodenum	50	550	15	5.5±0.20	250±50
III	Jejunum	80	630	120	6.8±0.20	250±50
IV	Ileum	310	940	30	7.5±0.25	250±50
V	Colon	60	1000	Up to 1440	6.0±0.25	250±60

different psychiatric medications had significantly less dissolution and two had significantly greater dissolution in conditions after RYGB, compared with the preoperative state.[11]

An in vitro dissolution method simulating the conditions before and after RYGB might be a valuable tool to predict the behaviour of drugs with possible bioavailability problems in vivo.

Patients undergoing RYGB may use various medicines for multiple comorbidities, such as cardiovascular diseases, type 2 diabetes mellitus, obstructive sleep apnoea and depression.[12] After bariatric surgery, comorbidities may resolve or improve. Although after surgery a significant reduction in use of β blockers has been reported, many patients still use them.[12] Metoprolol is a widely used cardioselective β blocker available as an IR and CR tablet. According to the Biopharmaceutics Classification System, metoprolol is a class I substance with a high solubility and a high intestinal permeability and therefore a useful model substance.[13]

The objectives of this study were to develop a gastrointestinal simulation system (GISS) mimicking conditions before and after RYGB for investigating dissolution characteristics of solid oral medications, and to assess the pharmaceutical availability of metoprolol from IR and CR tablets under these conditions. The GISS enables the variation in parameters which are relevant to drug release in vivo: pH, volume, transit time, osmolality and agitation. During the test a solid oral medication is exposed to solutions simulating stomach (duodenum), jejunum, ileum and colon in fasted and non-fasted conditions (as reflected in the residence time in the stomach (pouch)) before and after RYGB.

MATERIALS AND METHODS

Reagents and materials

All chemicals used were reagent grade and obtained from commercial suppliers. Demineralised water was used. In this study the dissolution of metoprolol from two different oral tablet formulations in simulated conditions before and after RYGB was investigated. Metoprolol tartrate 100 mg IR tablet (Pharmachemie, Haarlem, The Netherlands; (metoprolol IR)), and metoprolol succinate 95 mg CR tablet, equivalent to 100 mg of metoprolol tartrate (Pharmachemie, Haarlem, The Netherlands; (metoprolol CR)) were used.

Instrumentation and equipment

A Prolabo Dissolutest (Rowa Techniek BV, Leiderdorp, The Netherlands) coupled to a UV-visible spectrophotometer (UV1601, Shimadzu, Duisburg, Germany) with a Watson-Marlow 202S peristaltic pump (Watson-Marlow Pumps Group, Falmouth, UK) was used for dissolution testing of the oral formulations. A JPS-8 Ismatec peristaltic pump (Cole-Parmer, Wertheim, Switzerland) was used for pumping switch solutions into the dissolution vessels. The pH testing of the several dissolution solutions was performed using a R735 Consort pH metre (Consort, Turnhout, Belgium). The osmolality of the solutions was measured on an Osmomat 030 osmometer (Gonotec, Essen, Germany). An Eppendorf centrifuge 1–14 (Sigma, Osterode am Harz, Germany) was used for centrifuging samples manually taken from the dissolution vessels. A Unicam UV-500 UV-visible spectrophotometer (Thermo Spectronic, Cambridge, UK) was used for analysing samples manually taken, and for the calibration curves.

Dissolution testing

The GISS is a dissolution method which is based on a design by Schellekens *et al*.[14] It consists of a paddle apparatus, as described in the USP 39 and the European Pharmacopoeia 9.0, to simulate conditions in consecutive sections of the gastrointestinal tract. Tables 1 and 2 show details of the phases and the biorelevant media which were applied to simulate conditions before and after RYGB, respectively.

At the end of each phase a switch solution was added with a peristaltic pump in 5–10 min to obtain the required composition of the next phase. Tables 3 and 4 show the composition of these switch solutions.

The paddle was operated at 50 rpm and the system was kept at a temperature of 37°C. Before testing, the dissolution media were preheated. For fasted and non-fasted conditions before RYGB, the residence times in the stomach were 30 and 120 min, respectively. For fasted and non-fasted conditions after RYGB the residence times in the stomach pouch were 15 and 120 min, respectively. Because of the smaller volume of the stomach pouch after RYGB, the length and diameter of the paddle were adjusted when simulating conditions after RYGB. Evaporation

Table 2 Specifications of the four phases of the gastrointestinal simulation system (GISS) after Roux-en-Y gastric bypass

Phase	Simulated GI segment	Volume of simulated GI segment (mL)	Total volume (mL)	Residence time (min)	pH	Osmolality (mosmol/kg)
I	Stomach (pouch)	50	50	120 (full)/15 (empty)	5.0±0.20	150±25
II	Jejunum	80	130	70	6.8±0.20	250±50
III	Ileum	310	440	30	7.5±0.25	250±50
IV	Colon	60	500	up to 1440	6.0±0.25	250±60

Table 3 Composition of the switch solutions gastrointestinal simulation system (GISS) before Roux-en-Y gastric bypass

	From	To	Composition
At start			1.0 g sodium chloride, 3.5 mL hydrogen chloride 37%, demineralised water q.s. 500.0 mL
Switch solution I	Phase I	Phase II	3.14 g potassium dihydrogen phosphate, 21.7 mL sodium hydroxide 2.0 M, demineralised water q.s. 50.0 mL
Switch solution II	Phase II	Phase III	0.94 g potassium dihydrogen phosphate, 8.2 mL sodium hydroxide 2.0 M, demineralised water q.s. 80.0 mL
Switch solution III	Phase III	Phase IV	2.04 g potassium dihydrogen phosphate, 10.8 mL sodium hydroxide 2.0 M, demineralised water q.s. 310.0 mL
Switch solution IV	Phase IV	Phase V	10.0 mL hydrogen chloride 3.0 M, demineralised water q.s. 60.0 mL

from the dissolution vessels was minimised by applying tight-fitting covers. Metoprolol IR and CR tablets were tested in triplicate for each condition.

When simulating conditions before RYGB, by the automated system continuous UV measurement of the solution was performed by sampling through a cannula with a filter immersed in the dissolution medium. Release profiles were determined by measuring the concentration of metoprolol spectrophotometrically at λ=274 nm. The volume of medium sampled was dripped back into the vessels. Every minute during the first 10 min followed by every 5 min up to 210 min (fasted conditions) or 300 min (non-fasted conditions) for metoprolol IR tablets, the release of metoprolol was calculated. For metoprolol CR tablets every 60 min up to 1440 min, the release of metoprolol was calculated.

When simulating conditions after RYGB, for metoprolol IR tablets, at pre-set time points, samples were manually taken from the dissolution vessels up to 120 min (fasted conditions) or 220 min (non-fasted conditions), using an adjustable Gilson pipette. Sample volumes, ranging from 200 to 700 µL, depended on the required dilution factor. After proper dilution and mixing, samples were centrifuged. Concentrations of metoprolol were determined spectrophotometrically. Because of the dilution, after each withdrawal the volume of medium sampled was not replaced into the vessels but accounted for in the calculations. For metoprolol CR tablets, samples of 3.0 mL were manually taken from the dissolution vessels up to 120 min (fasted conditions) or 220 min (non-fasted conditions), using an adjustable Gilson pipette. After measurement, samples were replaced into the dissolution vessels. Thereafter, up to 1440 min continuous UV measurement of the solution was performed with every 60 min calculation of the release of metoprolol.

Table 4 Composition of the switch solutions gastrointestinal simulation system (GISS) after Roux-en-Y gastric bypass

	From	To	Composition
At start			0.125 g sodium chloride, 5.0 µl hydrogen chloride 37%, demineralised water q.s. 50.0 mL
Switch solution I	Phase I	Phase II	2.53 g potassium dihydrogen phosphate, 5.7 mL sodium hydroxide 2.0 M, demineralised water q.s. 80.0 mL
Switch solution II	Phase II	Phase III	2.04 g potassium dihydrogen phosphate, 9.0 mL sodium hydroxide 2.0 M, demineralised water q.s. 310.0 mL
Switch solution III	Phase III	Phase IV	8.0 mL hydrogen chloride 3.0 M, demineralised water q.s. 60.0 mL

Analytical quantification

The ultraviolet spectrum of metoprolol tartrate in simulated gastric fluid at pH 1.2 showed an absorption maximum at λ=274 nm, with a specific absorbance of 40 in the simulated gastric fluid (phase I, tables 1 and 2). In the range between pH 1.2 and pH 10, no changes in absorption maximum and specific absorbance were observed. Therefore, a calibration curve for metoprolol tartrate was constructed in triplicate by preparing metoprolol tartrate 25, 50, 100, 200, 250 and 350 mg/L dissolved in pH 1.2 simulated gastric fluid and analysing at λ=274 nm. The observed correlation coefficient for the calibration curve ($y=0.0078x+0.021$) was $r^2=0.9996$.

The calibration curve was used to obtain concentrations of metoprolol in the samples from the absorbance value.

Data analysis

Concentrations of metoprolol for all samples of each product tested, as determined spectrophotometrically, were converted into release using Microsoft Excel (2008). For comparing dissolution profiles in simulated conditions after RYGB versus before RYGB, the similarity factor f2 was used.[15] The similarity factor f2 measures the closeness between the two profiles. The factor f2 is inversely proportional to the average squared difference between the two profiles, with emphasis on the larger difference among all the time points. At least 12 units should be used for each profile determination. Only one measurement should be considered after 85% dissolution of the product. When the two profiles are identical, f2=100. An average difference of 10% at all measured time points results in an f2 value of 50.[15] The Food and Drug Administration has set a public standard for the f2 value of between 50 and 100 to indicate similarity between the two dissolution profiles. Two dissolution profiles were considered similar when the f2 value was ≥50.[13]

RESULTS

The dissolution profiles of metoprolol tartrate 100 mg IR tablets in simulated conditions before and after RYGB in the fasted and non-fasted state are shown in figure 1. In simulated conditions before RYGB in the fasted state a release of >85% in 25 min was reached, but in simulated conditions after RYGB in 15 min. With an f2 value of 26, dissolution profiles were not considered similar. In the non-fasted state in simulated conditions both before and after RYGB, a release of >85% in 25 min was observed. Dissolution profiles were not similar either (f2=33).

The dissolution profiles of metoprolol succinate 95 mg CR tablets in simulated conditions before and after RYGB, in the fasted and non-fasted state, are presented in figure 2. In simulated conditions both before and after RYGB, in the fasted and non-fasted state, a release of >90% in 22 hours was found. Dissolution profiles in the fasted and non-fasted state were similar with f2 values of 81 and 84, respectively.

DISCUSSION

GISS

In this study a GISS was developed simulating conditions before and after RYGB for investigating dissolution characteristics of oral medications. For conditions used in a GISS, Schellekens *et al* identified the most relevant parameters for drug release from modified release forms.[14] For mimicking conditions before

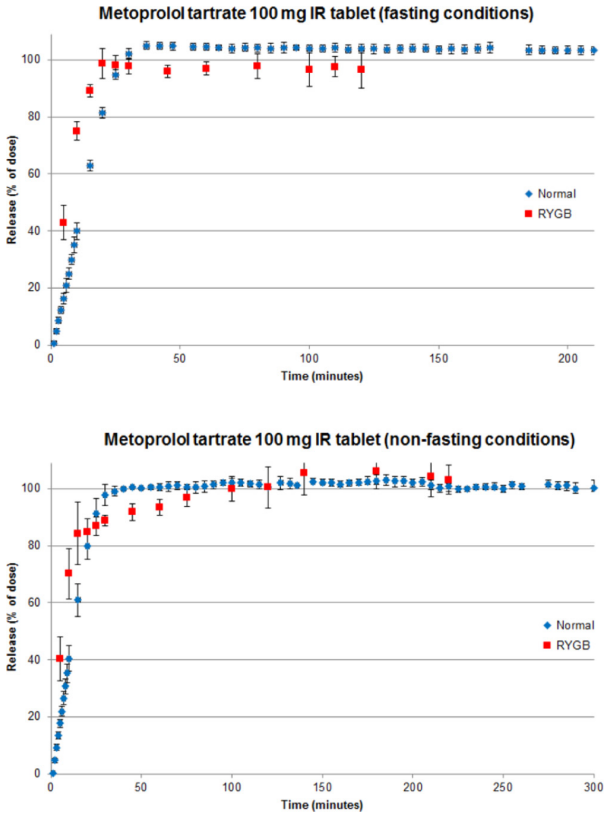

Figure 1 Dissolution profiles of metoprolol tartrate 100 mg immediate-release (IR) tablets in simulated conditions before and after Roux-en-Y gastric bypass (RYGB), in the fasted and non-fasted state.

and after RYGB in the GISS, we postulated that pH, volume, residence time in the gastrointestinal tract, osmolality and agitation are important parameters. In RYGB a small stomach pouch (30–50 mL) is created and the entire duodenum and proximal jejunum are bypassed. To simulate conditions before RYGB, we added an extra phase ('duodenum') to the four phases of the original GISS ('stomach', 'jejunum', 'distal ileum' and 'proximal colon') as developed by Schellekens *et al*.[14] With a volume of 50 mL, a residence time of 15 min, a pH of 5.5 and osmolality of 250 mosmol/kg, conditions for the duodenum were simulated.[16 17] In patients who have undergone RYGB, the pH in the newly created stomach increases to approximately 5.[6] This considerable increase in gastric pH, as well as the small volume of the stomach pouch may potentially alter drug dissolution and solubility.[5 6] Therefore in the GISS simulating conditions after RYGB, the pH of the stomach pouch, with a volume of 50 mL, was adjusted to 5.

The residence time of a drug in the gastrointestinal tract affects the time available for a drug to dissolve and to be absorbed. The transit time of a dosage form through different segments of the gastrointestinal tract depends on factors such as gastric emptying rate and flow rate, and can vary considerably, intraindividually and interindividually.[18] Obese patients have a normal gastric emptying.[19] Values for residence time in the stomach in humans in both the fasted and non-fasted state, as reported in the literature, vary. For complete emptying of the stomach in a fasted state, a mean residence time of 25 min has been reported.[18] In a fed state residence time is considerably longer, with time of half-emptying the stomach ranging from 32 to 105 min.[18] In simulating conditions before RYGB we therefore applied residences time of 30 (fasted) and 120 min (non-fasted), respectively, for the stomach section of the GISS. After RYGB, various effects on gastric emptying have been reported. RYGB results in an accelerated gastric emptying time for liquids,[20] but creation of a small stomach pouch, and the small anastomosis promotes slowed gastric emptying for food and drugs to pass through to the intestine.[6] Because of the smaller volume of the stomach pouch after RYGB in the GISS, we applied a residence time of 15 min in the stomach for the fasted state. For the non-fasted state we maintained the same residence time as in conditions before RYGB (120 min). In RYGB a part of the jejunum is bypassed. Therefore, we applied a shorter residence time in the jejunum in simulating conditions after RYGB (70 min compared with 120 min before RYGB).

Release of dosage forms containing metoprolol

Although dissolution profiles of metoprolol from IR tablets in simulated conditions before and after RYGB in the fasted and non-fasted state were not similar (f2 value <50), after 25 min >85% of metoprolol was released, for all conditions applied. Dissolution profiles of CR tablets were considered similar for all conditions tested (f2 values ≥50). From CR tablets after 22 hours, >90% of metoprolol was released.

Metoprolol tartrate and metoprolol succinate are both highly water soluble. The CR tablet as used in these experiments, rapidly disintegrates into micropellets. Each pellet delivers the drug at a more or less constant rate, essentially relatively independent of physiological variations within the gastrointestinal tract.[21 22] The results obtained from the dissolution of metoprolol from CR tablets in simulated conditions before and after RYGB, meet the acceptance criteria for dissolution of metoprolol succinate extended-release tablets as stated in the USP monograph, test

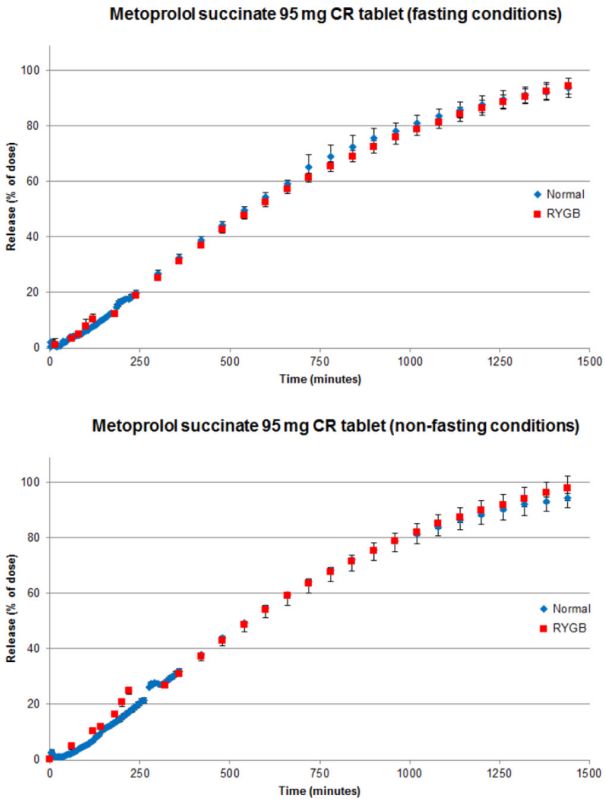

Figure 2 Dissolution profiles of metoprolol succinate 95 mg controlled-release (CR) tablets in simulated conditions before and after Roux-en-Y gastric bypass (RYGB), in fasted and non-fasted state.

1 (ie, amount dissolved after 1 hour not more than 25%, after 20 hours not less than 80%).[23]

In the GISS under all conditions applied, metoprolol IR and CR tablets showed adequate dissolution of metoprolol, implying that in patients after RYGB no problems in pharmaceutical availability of metoprolol are to be expected. However, in vivo pharmacokinetic studies are necessary to establish whether RYGB affects absorption and bioavailability of metoprolol from various tablet formulations. Results from an explorative, two-phase, single oral dose pharmacokinetic study of metoprolol in female patients 1 month before and 6 months after RYGB (EudraCT numbers 2013-002260-10 and 2013-002274-41) will be available shortly.

CONCLUSION

For investigating dissolution characteristics of oral medications a GISS was developed, able to expose the dosage form in a biorelevant sequence to different fluid compositions, simulating physiological conditions before and after RYGB. This GISS model may be a valuable tool to predict the pharmaceutical availability of medicines frequently used by patients before and after RYGB. With the GISS, under various conditions applied, the dissolution of metoprolol IR and CR tablets was tested. Under all conditions applied the metoprolol IR and CR tablets showed adequate dissolution, fully complying with pharmacopoeial requirements. In patients who have undergone RYGB, no problems in pharmaceutical availability of metoprolol IR and CR tablets are to be expected. Any changes in response to metoprolol in patients after RYGB should therefore be ascribed to changes in bioavailability.

What this paper adds?

What is already known on this subject?

- Roux-en-Y gastric bypass (RYGB) induces major changes in the gastrointestinal tract that may alter the absorption and bioavailability of orally administered medicines, especially modified-release products.
- Predicting the specific pharmacokinetic changes associated with bariatric surgery and their clinical importance is challenging.

What this study adds?

- For investigating dissolution characteristics a gastrointestinal simulation system is able to expose an oral solid dosage form in a biorelevant sequence to different fluid compositions, simulating conditions before and after RYGB.
- Under all conditions applied, metoprolol immediate-release (IR) and controlled-release (CR) tablets showed adequate dissolution, fully complying with pharmacopoeial requirements.
- In patients who have undergone RYGB, no problems in pharmaceutical availability of metoprolol IR and CR tablets are to be expected. Any changes in response to metoprolol in patients after RYGB should therefore be ascribed to changes in bioavailability.

Contributors Study concept and design: JPY, ENvR, BW, RJP, ME, HWF, HJW. Acquisition of data: JPY, RJP, HJW. Analysis and interpretation of data: JPY, ENvR, BW, HWF, RJP, HJW. Drafting of the manuscript: JPY. Critical revision of the manuscript for important intellectual content: JPY, ME, RJP, HJW, HWF, BW, ENvR. Study supervision: JPY, HJW, ENvR.

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