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*Report*

# Plasma Concentrations of Remoxipride and the Gastrointestinal Transit of $^{111}$In-Marked Extended-Release Coated Spheres

**Christina Graffner,[1] Zoltan Wagner,[2] Maj-Inger Nilsson,[3] and Erik Widerlöv[4]**

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To explore the oral absorption of remoxipride, spheres of remoxipride were labeled with indium-111 colloid before coating with a release-controlling ethylcellulose membrane. Since the labeling remained inside the coating, it was suitable as a marker. Eight healthy volunteers were given a single dose of 100 mg remoxipride in $^{111}$In-marked spheres as a multiple-unit capsule. The radioactivity and the position of the spheres (microcapsules) were followed externally for 30 hr by gamma scintigraphy. Parallel to this, plasma concentrations were drawn for 48 hr to confirm the extended dissolution and absorption of remoxipride. The hard gelatin, multiple-unit capsule released the microcapsules within the stomach. These were then rapidly emptied into the small intestine, within 0.5–1 hr. There was then an immediate distribution in the upper small intestine before collection in the lower portion, within 2–5 hr. After passing into the large intestine, there was again an extended distribution of the microcapsules. A mean $C_{max}$ of 2.7 μM remoxipride was achieved 4 hr after drug administration and a mean AUC of 26.1 $\mu mol \cdot L^{-1} \cdot hr$ was achieved. Judging from the absorption versus time profile, calculated according to the Wagner–Nelson method, and the scintigraphic images, it is concluded that the main absorption occurs from the small intestine. Data from four volunteers, however, indicated a comparatively good absorption also from the large intestine. Due to the good absorption properties, it is reasonable to expect a low variation in the extent of bioavailability of remoxipride after administration in an extended-release, multiple-unit capsule formulation.

KEY WORDS: remoxipride; extended release; gamma scintigraphy; multiple-unit capsule, absorption.

## INTRODUCTION

Absorption of many drug compounds occurs while the dosage form is in the large bowel (1–3). This observation is especially interesting when considering the development of an oral product with an extended release rate which is intended to be taken less frequently than a conventionally releasing dosage form.

The neuroleptic compound, remoxipride (4), has been developed both in a standard capsule preparation and in a multiple-unit capsule preparation with extended release. Based on studies in healthy volunteers, it is shown that the rate of absorption of the compound is controlled by its dissolution rate from a preparation. Further, there is an association between the dissolution rate *in vivo* and the dissolution rate *in vitro* (5,6). Moreover, the extent of bioavailability after administration of ethylcellulose (EC)-coated remoxipride spheres, microcapsules, with a comparatively slow dissolution rate *in vitro*, 60 and 90% dissolved after 10 and 20 hr, respectively, is the same as after an aqueous solution. From these results, it seems reasonable to assume that the absorption is good from an extended portion of the intestine.

The purpose of the present study was to explore further the oral absorption of remoxipride. Remoxipride microcapsules were labeled with $^{111}$In-colloid, which does not dissolve and diffuse through the EC membrane but remains inside the coating. It can therefore be used as a marker. The radioactivity, and thereby the position, can be detected externally by gamma scintigraphy after the oral administration of the preparation to healthy male humans. Parallel to the scintigraphic imaging, the plasma concentrations of remoxipride were followed to confirm that the drug continuously diffuses through the EC membrane and is absorbed.

## MATERIALS AND METHODS

### Subjects

Eight healthy Caucasian males aged 21 to 35 years (median 30) of weight range 71 to 95 kg (median, 78) were in-

[1] To whom correspondence should be addressed at Research and Development Laboratories, Astra Läkemedel AB, S-151 85 Södertälje, Sweden.
[2] Fyzikon AB (Ltd), S-205 12 Malmö, Sweden.
[3] Research and Development Laboratories, Astra Alab AB, S-151 85 Södertälje, Sweden.
[4] Department of Psychiatry and Neurochemistry, University of Lund, S-220 06 Lund, Sweden.

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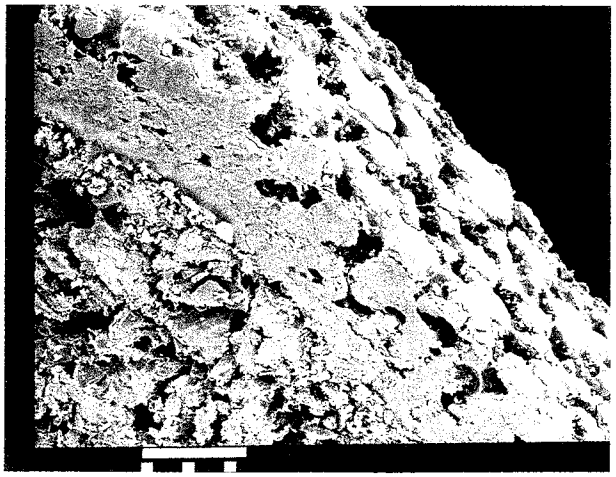

Fig. 1. Cross section of a $^{111}$In-microcapsule of remoxipride, showing the distinction between core and coating layer. Bar represents 100 μm.

cluded in the study. All were healthy according to medical history, physical examination, blood and urine analyses, and ECG. The volunteers were informed both orally and in writing about the aim of the study and about possible risks according to the Helsinki declaration. After this information, all subjects gave their signed consent to participate in the study.

### Study Dosage Form

#### *Radioactive Material*

The utilization of short-lived radionuclides in conjunction with gamma scintigraphy in the study of the *in vivo* behavior of dosage forms was introduced in 1976 (1). We selected $^{111}$In because of its comparatively long half-life (2.8 days) and its emitting of two gamma-ray energies (173 keV, 89%, and 247 keV, 94%). The source was the Indium $^{113m}$In Liver Scanning Kit (Code N 82 from Amersham, UK), where $^{113}$In-chloride was exchanged for $^{111}$In-chloride.

The tagging procedure was done according to the manufacturer. The characterization of the formed radioactive particles was performed within 10 hr after the tagging procedure. This included a measurement of the particle size distribution by light-scattering spectroscopy and of the radioactivity distribution over the differently sized particle fractions by a microfilter technique. The activity of the filter and of the filtrate was measured in a NaI(TI) well detector. From the measurements, one was able to conclude that more than 98% of the radioactivity was tagged to the colloid.

#### *Formulation*

Remoxipride spheres (size range, 1.0–1.4 mm) were produced by extrusion and spheronization. An amount corresponding to 3 g was collected and wetted with $^{111}$In-colloid (150 MBq). The wetted spheres were dried using a hair drier. Following dilution with sugar spheres (nonpareils; size, 0.71 mm), the total mass was coated with EC dissolved in organic solutions in fluidized bed equipment. Following the coating and drying procedures, the remoxipride microcapsules were separated by sieving and manually filled into hard capsules. A cross section of a coated sphere is visualized in Fig. 1. The *in vitro* dissolution of remoxipride was determined in water with the paddle technique, 50 rpm, as previously reported (6). The mean values of six determinations were found to be 32, 82, and 101% after 2, 5, and 10 hr, respectively. The initial radioactivity of each capsule was measured by a dose calibrator (Capintec, CRC-4), and the radioactivity of the dissolution liquid as well as of the emptied microcapsules was checked in a NaI(TI) well detector after completion of the dissolution test. The results indicated that only about 5% (range, 4.0–5.5%) of the radioactivity had leaked through the coating membrane within 20 hr.

A linear correlation was found between the remoxipride assay and the radioactivity results from five individual hard capsules. This permitted us to estimate the dose of each separate capsule used in the absorption study.

### *In Vivo* Study Design

The study was designed as an open study, with one experiment in each subject. The experimental part of the study was performed at Fyzikon AB in Malmö, Sweden. The study was approved by the Human Ethics Committee and the Local Committee on Radioisotopes in Research at the University of Lund, Sweden.

The subjects arrived after an overnight fasting period of 10 hr. At 8 AM, one hard gelatine capsule with an aimed dose of 100 mg of remoxipride hydrochloride monohydrate was swallowed together with 100 ml of tap water in front of a gamma camera. Each capsule contained 6.1 MBq (mean; SD, 0.5 MBq) of $^{111}$In-colloid. The effective dose equivalent of the radioisotope was calculated to be 1.5 mSv. A standardized lunch and supper was given 4 and 10 hr, respectively, after drug intake. Caffeine-containing beverages (coffee, tea, Coca-Cola) and smoking were not allowed during Day 1 of the experimental session. No other drugs or alcohol were allowed during the 48 hr prior to or during the experimental sessions. The subjects stayed at the study unit during all of Day 1.

### Blood Sampling and Analysis

Blood specimens (5 ml) were collected into heparinized Venoject tubes before and 0.5, 1, 1.5, 2, 3, 4, 7, 10, 12, 24, 30, 36, and 48 hr after drug administration. The samples were

Table I. Remoxipride Plasma Concentrations (μ*M*) After Administration of a Multiple-Unit Capsule to Eight Healthy Volunteers

| | Hours | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | 0.5 | 1 | 1.5 | 2 | 3 | 4 | 7 | 10 | 12 | 24 | 30 | 36 | 48 |
| Mean | <0.05 | 0.15 | 0.64 | 1.36 | 2.16 | 2.95 | 3.18 | 2.38 | 1.54 | 1.09 | 0.17 | 0.08 | 0.04 | <0.05 |
| SD | | 0.11 | 0.35 | 0.38 | 0.41 | 0.38 | 0.41 | 0.51 | 0.49 | 0.35 | 0.09 | 0.06 | 0.03 | |

Table II. The Pharmacokinetic Parameters of Remoxipride Following Oral Administration in Healthy Male Volunteers[a]

| Subject No. | $C_{max}$ ($\mu M$) | $t_{max}$ (hr) | AUC ($\mu mol \cdot L^{-1} \cdot hr$) | MRT (hr) | $K_E$ ($hr^{-1}$) | (MRT-$t_{1/2}$) (hr) | Actual dose of remoxipride (mg) |
|---|---|---|---|---|---|---|---|
| 1 | 2.92 | 4 | 26.3 | 8.1 | 0.14 | 3.2 | 112 |
| 2 | 2.75 | 4 | 26.6 | 8.1 | 0.14 | 3.2 | 124 |
| 3 | 3.09 | 4 | 27.1 | 7.9 | 0.15 | 3.3 | 116 |
| 4 | 2.71 | 4 | 28.2 | 9.1 | 0.16 | 4.7 | 124 |
| 5 | 2.87 | 4 | 26.5 | 8.5 | 0.11 | 2.4 | 114 |
| 6 | 2.13 | 4 | 18.0 | 8.0 | 0.17 | 4.0 | 112 |
| 7 | 2.23 | 4 | 20.5 | 8.1 | 0.15 | 3.4 | 124 |
| 8 | 2.74 | 4 | 35.9 | 10.9 | 0.11 | 4.7 | 125 |
| Mean | 2.68 | 4 | 26.1 | 8.7 | 0.14 | 3.6 | 119 |
| SD | 0.33 | — | 5.3 | 1.0 | 0.02 | 0.80 | 5.9 |

[a] The actual doses administered are included, but the parameters are dose-corrected to a remoxipride dose of 100 mg.

centrifuged and the plasma was separated and stored frozen (−20°C) in polypropylene tubes until analysis. The plasma concentrations of remoxipride were analyzed by HPLC (5). The limit of detection under the chosen conditions was 0.02 μmol/liter.

### Radioactivity Measurements and Calculations

Anatomical markers ($^{57}Co$) were placed on the chest of the volunteers for repositioning in front of the camera. The gamma camera (Nuclear Chicago PHO/Gamma HP) was mounted with a high-energy parallel-hole collimator. The energy window was ±12.5% of the 173-ke V peak. The gammagraphs were stored on a computer (Digital PDP 11/34, Gamma-11 V3.1) in a matrix format of 64 × 64 pixels. The collection time per measurement was 1 min. Measurements from anterior and posterior were performed from 0 to 30 hr after administration to establish the location of the microcapsules and an analysis of the spreading of microcapsules was accomplished. The location was determined by reviewing the gammagraphs on the computer monitor. Photoprints of gamma scintigraphs together with the anatomical markers confirmed the locality.

### Calculations

The maximum plasma concentration of remoxipride, $C_{max}$, and the time to reach it, $t_{max}$, were estimated in each subject. The areas under the plasma concentration versus time curves (AUC) between 0 and 36 hr were calculated using the trapezoidal rule. The log mean was used in order to increase the accuracy of the estimate of the AUC. The remaining areas were calculated from the ratios between the last determinable plasma concentration and the calculated elimination rate constant, $K_E$. This was determined for each subject by linear regression analysis from the log-linear part of the plasma concentration versus time curve. The overall elimination half-life, $t_{1/2}$, is calculated from $0.693/K_E$.

Mean residence time *in vivo*, MRT (7), was calculated by means of moment analysis using the log mean trapezoidal rule in the falloff portion of the zeroth and first moment of the plasma concentration curves.

Based on the assumption of a pharmacokinetic one-compartment model and a complete absorption, an absorption versus time profile was calculated for each volunteer according to the Wagner–Nelson method (8).

Table III. Individual Resistance Times ($t$) of $^{111}In$-Labeled Microcapsules in the Gastrointestinal Tract

| Subject No. | Stomach (hr) | Small intestine (hr) | Large intestine (hr) |
|---|---|---|---|
| 1 | $0.5 \leq t < 1.0$ | 3.5 | $t < 48$ |
| 2 | $0.5 \leq t < 1.0$ | 2 | $t < 48$ |
| 3 | $0.5 \leq t < 1.0$ | 3.5 | $t < 48$ |
| 4 | $0.5 \leq t < 1.0$ | 2.5 | $t < 48$ |
| 5 | $0.5 \leq t < 1.0$ | 5.0 | $t < 48$ |
| 6 | $0.5 \leq t < 1.0$ | 3.5 | $t < 48$ |
| 7 | $0.5 \leq t < 1.0$ | 3.5 | $t < 48$ |
| 8 | $0.5 \leq t < 1.0$ | 4.5 | $t < 48$ |

## RESULTS AND DISCUSSION

### Pharmacokinetics

The mean plasma remoxipride concentrations versus time are shown in Table I. No distribution phase could be distinguished in any of the volunteers, but a continuous increase in the levels up to a mean $C_{max}$ of 2.7 $\mu M$ at 4 hr is seen. A pharmacokinetic one-compartment model was, thus, judged to be applicable for the calculations of the absorption rate. The individual and mean pharmacokinetic parameters derived are presented in Table II. The values are consistent with our previous results (6) indicating an overall elimination rate corresponding to a mean half-life of 5 hr and an extent of bioavailability comparable to that of an oral solution. The difference between the MRT values and the $t_{1/2}$ indicates that three of the volunteers (Nos. 4, 6, 8) had a slower absorption rate than the others.

### Gastrointestinal Transit of Microcapsules

The residence times of remoxipride microcapsules in

Table IV. Mean Individual Absorption *Versus* Time Profile of Remoxipride ($n$ = 8) Calculated by the Wagner–Nelson Method (8)

| | Percentage absorbed after (hr) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 0.5 | 1 | 1.5 | 2 | 3 | 4 | 7 | 10 | 24 |
| Mean | 3.1 | 14.7 | 31.7 | 51.3 | 74.5 | 90.1 | 97.5 | 98.9 | 100.0 |
| SD | 2.6 | 7.2 | 9.7 | 10.0 | 9.8 | 8.2 | 3.3 | 2.0 | |

the gastrointestinal tract are shown in Table III. The hard gelatine capsule was observed to release the microcapsules within the stomach. The microcapsules are rapidly emptied into the small intestine, within 0.5–1 hr. There is an immediate extended distribution of the microcapsules in the upper small intestine. However, they are to some extent collected before entering the large intestine. The interindividual variation in the small intestinal transit time is 2–5 hr, which is consistent with what is found by other research groups (2,3,9–14). After passage into the large intestine, there is again an extended distribution of the microcapsules.

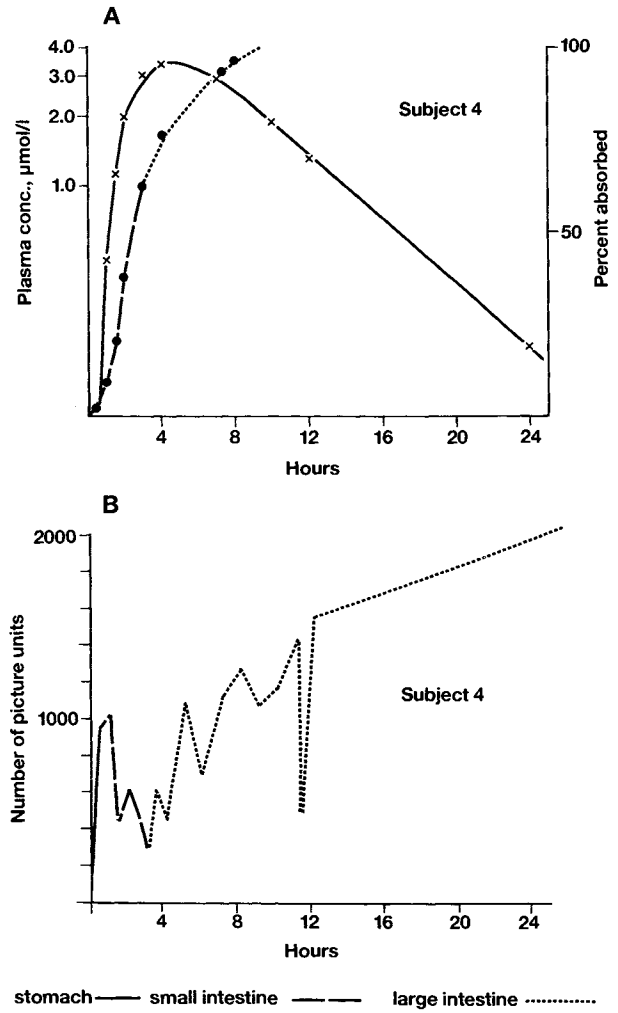


Fig. 2. (A) An example of a plasma concentration versus time curve of remoxipride and the calculated percentage absorbed versus time curve. (B) An example showing the localization of $^{111}$In-microcapsules following the analysis of the scintigraphic images.

### Absorption and the Position of Microcapsules

The mean individual absorption versus time profile calculated by the Wagner–Nelson method is given in Table IV. The initial absorption into plasma is slow even if it is obvious that it starts as soon as the microcapsules are released from the hard gelatin capsule. Such a release is reported to occur within 10–30 min (15). After that, an average of 15–35% remoxipride is absorbed hourly up to 4 hr, when the process is finalized in four of the volunteers, i.e., when the microcapsules still are in the small intestine. Four volunteers had an ongoing absorption for more than 4 hr (Subjects 2, 4, 6, 8), i.e., when the microcapsules were in the large bowel. In three of these a similar slow absorption was seen based on the difference between the MRT values and the $t_{1/2}$. The results from the four slow-absorbing volunteers indirectly indicates that a nonnegligible amount of remoxipride is absorbed when the microcapsules have passed over into the large intestine, about 25–35%. The plasma concentration versus time curve, the percentage absorbed versus time curve, and an analysis of the scintigraphic images from one slow-absorbing subject (No. 4) are given in Fig. 2.

## CONCLUSION

In the present study it is confirmed that the transit of $^{111}$In-marked microcapsules of remoxipride, followed by gamma scintigraphy, gives complementary and valuable information to traditionally studied plasma concentrations versus time data. It is, thus, possible to draw conclusions, based on the position of the microcapsules, that the absorption is occurring from an extended portion of the gastrointestinal canal. The data give support to the assumption that some absorption of remoxipride is occurring even from the large intestine.

Based on these results it seems reasonable to use an extended-release formulation of remoxipride, thereby making it possible to reduce the daily frequency of drug administrations.

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