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Comparative Pharmacokinetics of Clarithromycin (TE-031), A New Macrolide Antibiotic, and Erythromycin in Rats

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Clarithromycin (TE-031) is a newly synthesized macrolide with high stability in acidic conditions. In the present study, the pharmacokinetics of [*N-methyl*-^{14}C]clarithromycin were compared with those of [*N-methyl*-^{14}C]erythromycin in rats by radioassay and bioassay. Both radioactivity and bioactivity of [^{14}C]clarithromycin in plasma and tissues were found to be significantly higher than those of [^{14}C]erythromycin at the same oral dose of 20 mg/kg (body weight). Among the tissues, the peak level of [^{14}C]clarithromycin in the lung was especially high. Levels of radioactivity and bioactivity amounted to 15 and 73 times the corresponding levels of [^{14}C]erythromycin. In the urine, bioactivity recovered after administration of [^{14}C]clarithromycin was sevenfold higher than that for [^{14}C]erythromycin. This accounted for about 60 and 20% of the total radioactivity in the urine for [^{14}C]clarithromycin and [^{14}C]erythromycin, respectively. An examination of metabolites in the urine for [^{14}C]clarithromycin revealed appreciable amounts of bioactive unchanged clarithromycin. These results indicate that clarithromycin has pharmacokinetic properties superior to those of erythromycin. The desirable properties of clarithromycin include high levels in plasma resulting from its high stability in gastric acid; a high tissue affinity, especially to the lung; and favorable urinary excretion.

Clarithromycin (TE-031) is a new macrolide antibiotic with a methoxy substituent for the hydroxy group at position 6 of the erythromycin A lactone ring. It was previously reported that the in vitro antibacterial activity of clarithromycin was almost comparable to that of erythromycin against various bacterial species (S. Morimoto, T. Adachi, Y. Takahashi, T. Asaka, M. Kashimura, Y. Watanabe, S. Omura, and K. Sota, Program Abstr. 26th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 409, 1986). However, in mouse protection tests when the agent was administered orally, clarithromycin was 2 to 10 times more effective than erythromycin against various bacteria (R. Swanson, E. Gade, N. Shipkowitz, R. Bower, K. Jarvis, M. Mitten, N. Ramer, and P. B. Fernandes, 26th ICAAC, abstr. no. 411, 1986).

It is known that erythromycin in acidic media rapidly loses its biological activity because of extensive acid-catalyzed transformation (4, 8). On the contrary, it was found that clarithromycin is highly stable under acidic conditions, probably implying a high stability in gastric acid upon oral administration (10; Morimoto et al., 26th ICAAC). These facts suggest that the superior protective effects of clarithromycin in experimental animal infections may be the result of improved bioavailability.

Many investigators have reported on the metabolic fate of erythromycin (1, 2, 5–7, 11). The aim of the present study was to compare the pharmacokinetic properties of [*N-methyl*-^{14}C]clarithromycin with those of [*N-methyl*-^{14}C]erythromycin in rats by radioassay and bioassay.

MATERIALS AND METHODS

Labeled compounds. [*N-methyl*-^{14}C]clarithromycin was prepared in the Research Center of Taisho Pharmaceutical Co., Ltd. [*N-methyl*-^{14}C]erythromycin was obtained from New England Nuclear Corp. The specific radioactivities of [^{14}C]clarithromycin (two batches) were 8.00 and 5.27 μCi/mg, and that of [^{14}C]erythromycin was 35.21 μCi/mg. These compounds were >97% pure as determined by thin-layer chromatography (TLC) followed by autoradiographic analysis. The chemical structures and labeled positions of both compounds are shown in Fig. 1.

Experimental animals. The animals used were male Wistar rats weighing about 160 g and obtained from Shizuoka Laboratory Animal Center. They were fasted overnight before use, except when given a dose intravenously. The rats were given single oral doses of 5 or 20 mg of [^{14}C]clarithromycin per kg of body weight, 20 mg of [^{14}C]erythromycin per kg as a suspension in 5% gum arabic, or an intravenous dose of 5 mg of both labeled compounds per kg as a solution of saline with equimolar HCl to dissolve each compound.

Collection of biological samples. In the distribution study, whole blood was withdrawn from the inferior aorta into heparinized containers at preindicated times after dosing. Plasma was separated by centrifugation at 2,000 × *g*, 4°C, for 10 min. After blood collection, the liver, kidney, lung, heart, and spleen were excised from each animal. All tissues were weighed, and a 20% homogenate of each tissue was prepared with 1/15 M phosphate buffer at pH 7.2. In the excretion study, the rats given a dose were individually housed in metabolic cages which permitted separate collection of urine, feces, and pulmonary CO_2. Bile was collected from rats kept in Bollman restricted cages via a common bile duct cannula. Each sample was collected for 24 h after dosing.

Radioassay. Radioactivity was determined by using a liquid scintillation counter (model 3255; Packard Instrument Co., Inc.) equipped with automatic external standardization and disintegrations per minute computation. Radioactivity in

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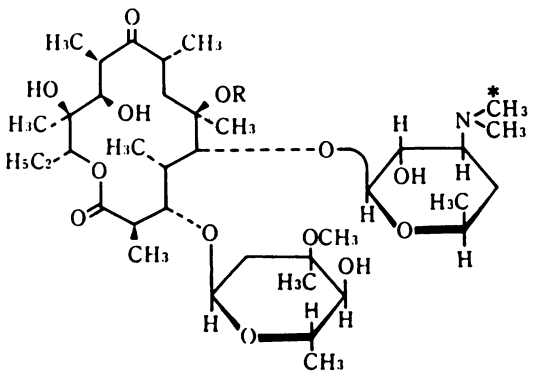

R=CH$_3$: [N-methyl-^{14}C] TE-031

R=H : [N-methyl-^{14}C] Erythromycin

* : Labelled position

FIG. 1. Chemical structures of [^{14}C]clarithromycin and [^{14}C] erythromycin.

urine and bile was determined directly in Aquasol-II (New England Nuclear). Pulmonary CO_2 was trapped in a mixture of monoethanolamine and methanol (3:2, vol/vol). An additional 2 ml of methanol was added to the mixture (0.5 ml) before determination of radioactivity in the scintillator. Plasma and homogenates of both tissues and feces were dissolved with Soluen-350 (Packard) and decolorized by the addition of hydrogen peroxide prior to determination of radioactivity.

Bioassay. Microbiological assays of plasma, tissues, and excreta were performed by the paper disk (8-mm diameter; Toyo Seisakusho) method, with *Micrococcus luteus* ATCC 9341 as the test organism. Plasma, bile, and homogenates of both tissues and feces adjusted to pH 9 with 10% $NaHCO_3$ were extracted with ethyl acetate and concentrated to a small volume before assay. Bioactive concentrations in the samples were calculated from the standard curve by conventional methods. The 95% confidence limit for the assay was better than ±17.2%. Under these extraction and bioassay conditions, the average recoveries of clarithromycin and erythromycin in spiked tissues were 102% ± 15% (standard error of the mean) and 110% ± 13%, respectively. The lower limit of sensitivity of the assay was 0.1 μg/ml for both compounds. Metabolites of each compound did not practically affect the assay.

Autoradiography. The rats given a dose were sacrificed under ether anesthesia by immersion in a mixture of hexane and solid CO_2. The sagittal 40-μm sections of each whole body were cut and dried at −18°C by the tape method. Autoradiograms were made by the opposition of tape-mounted sections to X-ray film (no. 150; Fuji) at 4°C for exposure for 30 days.

TLC. Urine collected for 8 h after dosing was chromatographed directly in tetrahydrofuran-methanol-NH_4OH (16:4:0.02) on silica gel 60F254-precoated plates (Merck & Co., Inc.). Localization of metabolites on the plates was detected by preparation of autoradiograms and bioautograms using *M. luteus* ATCC 9341 as the test organism. Identification of separated metabolites was achieved by cochromatography with reference samples of clarithromycin, erythromycin, and their *N*-demethylated compounds. Biliary metabolites extracted with ethyl acetate were also examined by the methods described above.

RESULTS

Distribution in plasma and tissue. The concentrations in plasma and tissue of [^{14}C]clarithromycin (5 and 20 mg/kg) and [^{14}C]erythromycin (20 mg/kg) orally administered to rats are shown in Table 1.

(i) Radioactivity. When [^{14}C]clarithromycin was administered at doses of 5 and 20 mg/kg, the peak levels in plasma of radioactivity achieved at 2 h were 2.6 and 5.3 μg eq/ml, respectively. The levels declined gradually with time. In the tissues, concentrations of radioactivity for both doses were generally higher than those in the plasma. The highest concentration was found in the liver for the dose of 5 mg/kg. Concentrations were moderate in the lung, kidney, and spleen. On the other hand, at a dose of 20 mg/kg, tissue/plasma concentration ratios were relatively higher than those at the 5-mg/kg dose. The highest concentration was found in the lung; it was 13 times that of plasma 2 h after administration, followed in descending order by concentrations in the liver, spleen, kidney, and heart.

When [^{14}C]erythromycin was administered at a dose of 20 mg/kg, the levels of radioactivity in plasma were significantly lower than those of [^{14}C]clarithromycin, with a peak level of 2.8 μg eq/ml. Among the tissues, the highest concentration was found in the liver; however, the concentrations in all other tissues were considerably lower than those of [^{14}C]clarithromycin; the lung peak level was just 1/15 of that found for [^{14}C]clarithromycin.

(ii) Bioactivity. Concentrations of bioactivity in plasma and tissue after [^{14}C]clarithromycin dosing were generally lower than those of radioactivity. Among the tissues, the bioactivity/radioactivity ratio was relatively high in the lung, heart, and spleen for doses of both 5 and 20 mg/kg, whereas it was very low in the plasma and liver. Concentrations in all tissues increased over the dose range; levels in plasma 2 h after administration of 5 and 20 mg/kg were <0.1 and 1.2 μg eq/ml, respectively. At the dose of 20 mg/kg, the highest concentration was observed in the lung at 2 h; it was 36 times that of plasma, followed in descending order by concentrations in the spleen, kidney, liver, and heart. As for [^{14}C]erythromycin, concentrations of bioactivity in all tissues were significantly lower than those of radioactivity. Consequently, levels of [^{14}C]clarithromycin in plasma were 7 to 13 times higher than those of [^{14}C]erythromycin over the experimental period. In the lung, the peak level of [^{14}C]clarithromycin was 73 times higher than that of [^{14}C]erythromycin, and 1/4 of the peak level still remained 8 h after [^{14}C]clarithromycin administration.

Autoradiography. Whole-body autoradiograms of rats after intravenous administration of [^{14}C]clarithromycin or [^{14}C]erythromycin at a dose of 5 mg/kg are shown in Fig. 2. Five minutes after the administration of [^{14}C]clarithromycin, radioactivity was distributed widely in the body, with the exception of the central nervous system. Remarkably high radioactivity was observed in the lung, followed in descending order by the kidney, intestine, urinary bladder, spleen, hypophysis, thyroid, and salivary gland. When the same dose of [^{14}C]erythromycin was administered, the distribution pattern was similar; however, radioactivity in the lung was relatively low compared with that found for [^{14}C] clarithromycin.

Excretion. Excretion patterns in rats after oral administration of [^{14}C]clarithromycin (5 or 20 mg/kg) or [^{14}C]erythromycin (20 mg/kg) are shown in Fig. 3. After administration of [^{14}C]clarithromycin at a dose of 5 mg/kg, 25 and 29% of the radioactive dose were excreted into the urine and feces,

TABLE 1. Concentrations in plasma and tissue after oral administration of [^{14}C]clarithromycin and [^{14}C]erythromycin to rats

Agent (mg/kg) and tissue	Assay[a]	Concn (μg eq/g or ml) at[b]:			
		1 h	2 h	4 h	8 h
Clarithromycin (5)					
Plasma	R	1.7 ± 0.1	2.6 ± 0.1	2.2 ± 0.1	1.7 ± 0.1
	B	<0.1	<0.1	<0.1	ND[c]
Lung	R	7.3 ± 0.4	7.6 ± 0.7	6.2 ± 0.3	2.5 ± 0.1
	B	2.5 ± 0.1	4.1 ± 0.5	1.6 ± 0.3	0.4 ± 0.1
Liver	R	9.9 ± 0.3	16.4 ± 0.8	10.7 ± 0.7	8.4 ± 0.6
	B	0.7 ± 0.1	0.8 ± 0.1	<0.1	ND
Kidney	R	3.0 ± 0.1	6.3 ± 0.5	4.4 ± 0.1	3.0 ± 0.1
	B	0.3 ± 0.0	0.6 ± 0.1	0.2 ± 0.0	<0.1
Heart	R	1.0 ± 0.3	1.6 ± 0.2	1.3 ± 0.0	1.0 ± 0.1
	B	0.4 ± 0.1	0.7 ± 0.1	0.3 ± 0.0	<0.1
Spleen	R	3.2 ± 0.5	4.9 ± 0.4	3.8 ± 0.1	2.2 ± 0.1
	B	1.5 ± 0.1	2.5 ± 0.3	1.0 ± 0.2	0.2 ± 0.1
Clarithromycin (20)					
Plasma	R	3.9 ± 0.1	5.3 ± 0.1	5.0 ± 0.3	4.9 ± 0.7
	B	0.7 ± 0.1	1.2 ± 0.1	0.4 ± 0.1	0.1 ± 0.0
Lung	R	54.7 ± 4.9	69.2 ± 3.5	42.6 ± 2.9	16.8 ± 2.4
	B	26.3 ± 1.6	43.5 ± 4.7	19.0 ± 3.2	10.5 ± 0.2
Liver	R	61.1 ± 3.0	56.9 ± 3.9	33.4 ± 1.3	19.7 ± 3.7
	B	10.5 ± 1.1	8.6 ± 1.0	3.2 ± 0.4	2.5 ± 0.4
Kidney	R	24.9 ± 2.6	31.5 ± 0.7	17.4 ± 1.0	10.2 ± 1.6
	B	10.9 ± 1.2	12.6 ± 0.5	7.4 ± 1.1	3.0 ± 0.5
Heart	R	8.1 ± 0.5	7.2 ± 0.6	5.1 ± 0.3	2.8 ± 0.2
	B	7.4 ± 1.1	7.2 ± 0.1	4.8 ± 0.4	1.4 ± 0.4
Spleen	R	30.0 ± 2.0	34.0 ± 0.8	19.4 ± 1.0	11.0 ± 1.0
	B	18.4 ± 1.0	36.8 ± 4.6	12.8 ± 0.7	4.7 ± 0.5
Erythromycin (20)					
Plasma	R	1.1 ± 0.1	2.0 ± 0.4	2.8 ± 0.3	2.5 ± 0.3
	B	0.1 ± 0.0	0.1 ± 0.0	ND	ND
Lung	R	1.6 ± 0.2	4.5 ± 0.6	4.1 ± 0.3	2.6 ± 0.1
	B	0.4 ± 0.2	0.6 ± 0.1	ND	ND
Liver	R	8.5 ± 0.9	23.2 ± 2.7	12.2 ± 1.3	8.6 ± 0.8
	B	0.4 ± 0.1	2.0 ± 0.5	ND	ND
Kidney	R	2.4 ± 0.3	6.3 ± 0.5	4.5 ± 0.4	3.4 ± 0.2
	B	<0.1	ND	ND	ND
Heart	R	1.0 ± 0.2	2.7 ± 0.2	1.5 ± 0.1	1.1 ± 0.1
	B	0.3 ± 0.1	0.7 ± 0.1	<0.1	ND
Spleen	R	2.1 ± 0.3	6.1 ± 1.0	4.3 ± 0.4	2.4 ± 0.1
	B	0.5 ± 0.2	2.4 ± 0.4	0.5 ± 0.1	ND

[a] R, Radioassay; B, bioassay.
[b] Each value represents the mean ± standard error of the mean for four animals.
[c] ND, Not detected.

respectively, within 24 h. Further, 36% of the dose was recovered in the pulmonary CO_2. When the agent was given at a dose of 20 mg/kg, urinary excretion increased to 35%, while excretion into the feces and pulmonary CO_2 decreased to 20 and 27% of the dose, respectively. In the case of [^{14}C]erythromycin, about half of the radioactivity administered was recovered in the feces at the dose of 20 mg/kg.

Biliary excretion of radioactivity after oral administration of [^{14}C]clarithromycin (5 mg/kg) accounted for 19% of the dose within 24 h and decreased to 15% at the dose of 20 mg/kg. With the administration of [^{14}C]erythromycin, the amount of biliary excretion was double that of [^{14}C]clarithromycin.

Biological activity recovered in 24-h urine after oral ad-

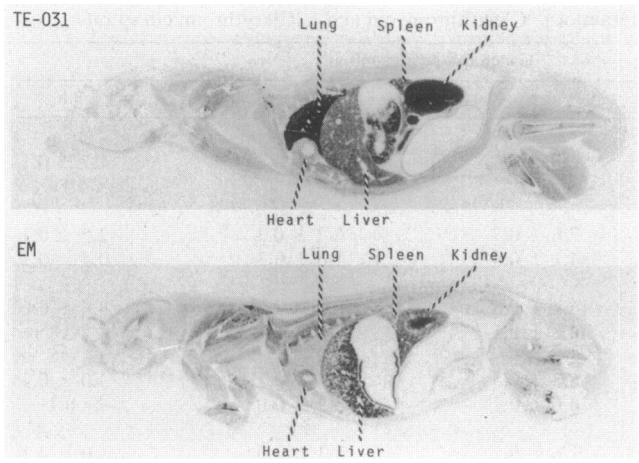

FIG. 2. Whole-body autoradiograms showing the distribution of radioactivity 5 min after intravenous administration of [^{14}C]clarithromycin and [^{14}C]erythromycin (EM) (5 mg/kg) to rats.

ministration of [^{14}C]clarithromycin (20 mg/kg) accounted for 21% of the dose, which was about sevenfold higher than that for [^{14}C]erythromycin. In the feces and bile, only small amounts of biological activity were recovered with both [^{14}C]clarithromycin and [^{14}C]erythromycin.

Metabolites in excreta. Figure 4 shows the TLC autoradiograms and bioautograms of metabolites in the urine after oral administration of [^{14}C]clarithromycin or [^{14}C]erythromycin to rats. The radioactive spot corresponding to the authentic compound was detected mainly in the urine for [^{14}C]clarithromycin. Other metabolites, including *N*-demethyl-clarithromycin, were also found. As for [^{14}C]erythromycin, urinary radioactivity consisted of unknown metabolites and negligible amounts of erythromycin and *N*-demethyl-erythromycin. Bioautograms of urinary metabolites of [^{14}C]clarithromycin and [^{14}C]erythromycin each showed one spot, which corresponded to the authentic clarithromycin and erythromycin, respectively. With both [^{14}C]clarithromycin and [^{14}C]erythromycin, the bile contained *N*-demethyl and other minor metabolites, including a trace of unchanged clarithromycin or erythromycin, respectively.

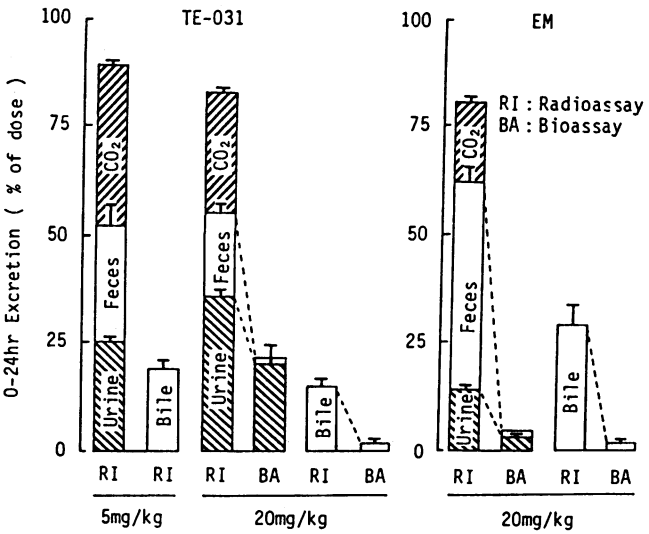

FIG. 3. Excretion of [^{14}C]clarithromycin and [^{14}C]erythromycin (EM) after oral administration to rats. Each point represents the mean ± standard error of the mean for four animals.

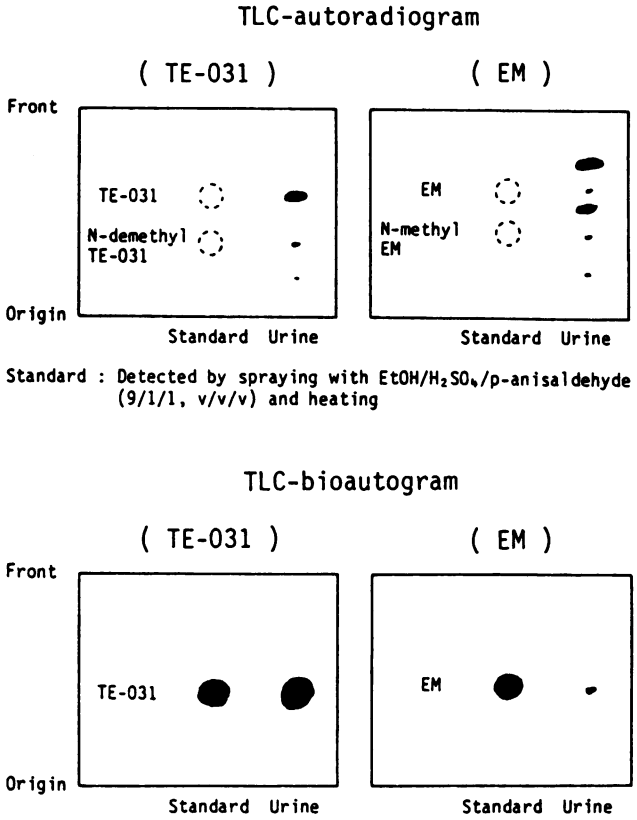

FIG. 4. TLC autoradiograms and TLC bioautograms of metabolites in urine after oral administration of [^{14}C]clarithromycin and [^{14}C]erythromycin (EM) (20 mg/kg) to rats.

DISCUSSION

In the present study, the distribution, excretion, and metabolic properties of [^{14}C]clarithromycin were compared with those of [^{14}C]erythromycin in rats by both radioassay and bioassay. The general metabolic fate of [^{14}C]erythromycin observed in this study was in agreement with results reported previously (2, 7, 11).

Levels of radioactivity in plasma peaked around 2 h with oral dosing with both [^{14}C]clarithromycin and [^{14}C]erythromycin, indicating favorable absorption of both compounds. However, at the same dose of 20 mg/kg, the levels of [^{14}C]clarithromycin in plasma were found to be about twice as high as those of [^{14}C]erythromycin. Moreover, concentrations of radioactivity in all tissues were significantly higher for [^{14}C]clarithromycin than for [^{14}C]erythromycin. Murphy et al. (11) measured the absorption of [^{14}C]erythromycin in rats by measuring the rate of disappearance of radioactivity from the stomach and intestine and reported the substantially complete absorption of this compound. Thus, the difference in radioactivity between these two compounds may not be the result of differing rates of absorption but may be the result instead of the possibility that the absorbed [^{14}C]erythromycin is subject to first-pass effect in the liver more easily than [^{14}C]clarithromycin, i.e., rapid metabolism and inactivation of [^{14}C]erythromycin in the liver and subsequent biliary excretion at higher rates. Actually, in the present study, the biliary excretion of [^{14}C]

erythromycin was observed to be double that of [^{14}C] clarithromycin.

On the other hand, as measured by bioassay, differences in the levels in plasma and tissue between [^{14}C]clarithromycin and [^{14}C]erythromycin were more pronounced. Levels of [^{14}C]clarithromycin in plasma were 7 to 12 times higher than those of [^{14}C]erythromycin during the examined period. Among the tissues, the level of [^{14}C]clarithromycin in the lung was especially high. There it amounted to 73 times the level of [^{14}C]erythromycin, and this level was rather long lasting. Erythromycin in acidic media rapidly loses its biological activity because of extensive acid-catalyzed transformation (4, 8). On the contrary, clarithromycin is far more acid resistant. After a 30-min exposure of clarithromycin and erythromycin to a dilute HCl solution (pH 2), their retained biological activities against *Staphylococcus aureus* were 95 and 0.5%, respectively (10). Thus, it seems that clarithromycin is better absorbed from the gastrointestinal tract than erythromycin, mostly as an intact and bioactive form owing to its vastly greater stability in gastric acid after oral dosing. This sequence may largely account for the markedly higher bioactivity of [^{14}C]clarithromycin in plasma. In addition, it may be indicative that absorbed bioactive clarithromycin is transferred remarkably well into tissues, especially the lung. To elucidate the distribution characteristics of both labeled compounds, comparative autoradiography was performed 5 min after intravenous dosing. Autoradiograms clearly demonstrated that clarithromycin itself has a significant affinity to lung tissue.

It has been reported that levels of various macrolide antibiotics in tissue are much higher than levels in plasma of both radio- and bioactivities (3, 12, 14, 17). A similar pattern was confirmed in the present study with [^{14}C]clarithromycin and [^{14}C]erythromycin. It must be noted, however, that bioactivity/radioactivity ratios in plasma and tissues for most macrolides are in general rather low, as was previously found to be the case for [^{14}C]erythromycin (3, 13, 17). These characteristics may mean a relatively high tissue affinity and easy metabolism for macrolides, including erythromycin. However, this is not the case for clarithromycin. The levels of [^{14}C]clarithromycin derived from radio- and bioassay were found to be roughly comparable in the lung, heart, and spleen; and they were rather long lasting. Therefore, it is suggested that, in addition to having high stability for gastric acid, clarithromycin may be less easily metabolized in the body.

Lee et al. (7) studied the general pattern of erythromycin excretion in rats after administration of [*N-methyl*-^{14}C]erythromycin. They reported that erythromycin was rapidly metabolized in the liver, mainly through the demethylation process, and excreted in the bile as biologically inactive *N*-demethyl-erythromycin. The isotopic methyl group was eliminated in the expired air as $^{14}CO_2$. In the present excretion study, appreciable percentages of both [^{14}C]clarithromycin and [^{14}C]erythromycin doses were recovered in the pulmonary $^{14}CO_2$. This indicates that clarithromycin underwent an *N*-demethylating process in the liver in a manner similar to that of erythromycin. However, urinary and fecal excretion patterns for the two components were different. After an oral dose of 20 mg/kg, 35 and 20% of the [^{14}C]clarithromycin dose were recovered in the urine and feces, respectively, whereas about half of the [^{14}C]erythromycin dose was recovered in the feces. Moreover, corresponding to fecal excretion, biliary excretion of [^{14}C]erythromycin was found to be double that of [^{14}C]clarithromycin. These data suggest that most radioactivity found in the feces probably originated in the bile for both compounds, and biliary transport was indicated to be a more important excretion route for erythromycin than for clarithromycin.

Regarding the different excretion patterns of [^{14}C]clarithromycin at doses of 5 and 20 mg/kg, it is noteworthy that urinary excretion of radioactivity increased as the dose increased, while fecal and biliary excretions decreased. When macrolide antibiotic SF-837 was administered intravenously to rats, it was reported that the biliary-to-urinary-excretion ratio decreased with increasing dosage, suggesting a metabolic saturation in the liver (15, 16). These results coincide with the above-described results with [^{14}C]clarithromycin. Similarly, there may be metabolic saturation at higher doses. In addition, Mashimo et al. (9) examined the metabolic features of the macrolide josamycin in dogs and revealed some important points. Orally administered josamycin is predominantly excreted into the bile, and only after the biliary excretion is saturated does it flow into the hepatic veins. All josamycin flowing from the liver is carried through the right heart and pulmonary artery to the lung. From this point of view, the observations of the present distribution study, i.e., the increasing tissue/plasma ratios of radioactivity at higher doses of [^{14}C]clarithromycin and increasing tissue concentrations of bioactivity over the dose range, might be the result of the saturation of the first-pass metabolism of clarithromycin in the liver and also of its high tissue affinity, especially to the lung.

Biological activity recovered in the urine for [^{14}C]clarithromycin was sevenfold that for [^{14}C]erythromycin at the same dose. This could account for about 60 and 20% of the total radioactivity recovered in the urine for [^{14}C]clarithromycin and [^{14}C]erythromycin, respectively. Besides, examination of metabolites in the urine revealed that the appreciable amount of bioactive substance corresponding to authentic clarithromycin was the main component, whereas with [^{14}C]erythromycin the urine had unknown metabolites and a trace of bioactive erythromycin. These data may well explain the remarkable difference of bioactivities in the urine for [^{14}C]clarithromycin and [^{14}C]erythromycin.

In conclusion, taking into consideration all the results described above, clarithromycin has pharmacokinetic properties superior to those of erythromycin owing to its higher tissue affinity, especially to the lung, and favorable urinary excretion. This may provide clinical usefulness not only for respiratory tract infections but for urinary tract infections, for which most previously known macrolides have failed to have significant impact.

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