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Pharmacokinetics and Pharmacodynamics of Rapacuronium in Patients with Cirrhosis

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Background: **Delayed elimination kinetics of steroidal neuromuscular blocking agents have been observed in patients with cirrhosis. Like other steroidal muscle relaxants, rapacuronium may, in part, be eliminated by the liver. To determine the influence of liver disease on its neuromuscular blocking effect, we studied the pharmacokinetics and pharmacodynamics of rapacuronium in patients with cirrhosis.**

Methods: **Sixteen patients undergoing elective surgery or endoscopy with general anesthesia, eight with cirrhosis and eight with normal liver function, were studied. Anesthesia was induced with fentanyl 2 μg/kg and thiopental 5–7 mg/kg and maintained with 60% nitrous oxide and 0.6–0.8% isoflurane in oxygen and repeated doses of fentanyl 1 μg/kg. Rapacuronium 1.5 mg/kg was administered intravenously before tracheal intubation. Thumb adduction force evoked by supramaximal ulnar nerve stimulation was recorded in 16 patients. Venous blood was sampled at frequent intervals for 8 h. Rapacuronium and its breakdown product Org 9488 were measured in plasma by high-pressure liquid chromatography. Values are reported as median (range).**

Results: **The central volume of distribution was increased to 131 (104–141) ml/kg in patients with cirrhosis ($P < 0.01$), compared with 75 (47–146) ml/kg in controls. The total apparent volume of distribution was also increased ($P < 0.05$) to 331 (284–488) ml/kg in patients with cirrhosis, compared with 221 (124–285) ml/kg in controls. The elimination half-life was 88 (77–102) min in controls and 90 (76–117) min in patients with cirrhosis. Plasma clearance was increased ($P < 0.05$) to 6.9 (6.1–8.9) ml · min^{-1} · kg^{-1} in patients with cirrhosis, compared with 5.3 (4.2–8.4) ml · min^{-1} · kg^{-1} in controls. Rapacuronium neuromuscular blocking effect was similar between the two groups. Onset time was 65 (40–110) s in controls and of 60 (52–240) s in patients with cirrhosis. Time to return to 90% of thumb adduction force control value was of 49 (28–80) min in controls and 47 (28–71) min in patients with cirrhosis.**

Conclusion: **The neuromuscular blocking effect of a single bolus dose of rapacuronium in patients with cirrhosis is not different from that of patients with normal hepatic function. No decrease in plasma clearance of rapacuronium was observed in patients with cirrhosis. (Key words: Liver disease; neuromuscular relaxants; plasma concentration.)**

RAPACURONIUM (Org 9487) is an aminosteroid nondepolarizing neuromuscular blocking agent with a more rapid onset and duration of action than other currently available nondepolarizing agents.[1,2] The short duration of action of vecuronium and rocuronium is explained, in part, by the hepatic contribution to their elimination in complement to the renal excretion.[3,4] In comparison, longer-acting nondepolarizing neuromuscular blocking agents are principally eliminated by the kidneys.[5–7] Hepatic uptake of steroidal neuromuscular relaxants has been demonstrated experimentally.[8–10] In humans, indirect evidence for liver elimination of these agents is provided from the fact that several studies report a prolonged elimination half-life of steroidal muscle relaxants in patients with decreased hepatocellular function.[11–13] In animals, rapacuronium is predominantly eliminated in the bile (unpublished report, March 1996; Organon, Boxtel, The Netherlands). Although the disposition of rapacuronium is incompletely understood in humans, its renal elimination is of minor importance[14,15]; therefore, it is important to determine its pharmacokinetics and pharmacodynamics in patients with cirrhosis.

Methods

Participants

The study received approval from the ethical committee of Henri Mondor Hospital, and informed consent was obtained from all 16 patients studied. Eight patients were healthy (American Society of Anesthesiologists class 1 or 2) and had no history or biologic evidence of

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hepatic or renal disease, and were undergoing elective peripheral surgery with general anesthesia. Eight patients had liver cirrhosis without encephalopathy and were undergoing sclerotherapy of esophageal varices with general anesthesia. The diagnosis of cirrhosis had been confirmed by liver biopsy in five patients and by liver echography in the remaining three. The degree of hepatocellular insufficiency was estimated in cirrhotic patients from the Child Pugh classification.[16] One patient had ascites controlled by diuretic therapy. Exclusion criteria included neuromuscular disease or treatment with drugs known to prolong the duration of action of neuromuscular blocking agents or to interfere with rapacuronium assay.

Anesthesia

Patients received hydroxyzine 100 mg or flunitrazepam 1 mg orally 1–2 h preoperatively. Anesthesia was induced with fentanyl 2 μg/kg and thiopental 5–7 mg/kg and maintained with isoflurane (0.6–0.8%, end-tidal), nitrous oxide (60% in oxygen), and repeated doses of fentanyl (1 μg/kg). Rapacuronium was supplied as a lyophilized powder of 100 mg in 5-ml vials and stored at 4°C (Organon Teknika, Boxtel, Belgium). The powder was diluted with sterile water immediately before injection. Laryngoscopy was performed 60 s after the administration of a bolus dose of 1.5 mg/kg rapacuronium, and the time of intubation and the intubating conditions were recorded. The intubating conditions were scored as 1 (excellent), 2 (good), 3 (poor), or 4 (impossible). Ventilation was controlled and adapted to maintain end-tidal carbon dioxide to 35 ± 5 mmHg. Central body temperature (esophageal or tympanic) was kept between 35°C and 37°C.

Monitoring

The ulnar nerve was stimulated supramaximally at the wrist with surface electrodes by applying train-of-four stimuli every 12 s, and the evoked twitch tension of the adductor pollicis (TH) was measured with a force transducer and continuously recorded (Myograph 2000; Biometer, Odense, Denmark). Rapacuronium was administered after 3 min of stabilization of twitch tension. The following variables were recorded: maximal depression of the first twitch; the time delay between the injection of rapacuronium and achievement of 90% depression of TH (onset time); the time between the injection of rapacuronium and recovery of the TH to 25%, 75%, and 90% of control (TH25, TH75, and TH90); and the time for the train-of-four ratio to recover to 70% (T4 0.7).

Pharmacokinetic Analysis

In all patients studied, a venous sampling cannula was inserted in the antecubital fossa contralateral to the upper limb where rapacuronium was administered. Blood samples (4 ml) were withdrawn with a syringe before and 2, 4, 7, 10, 20, 30, 45, 60, 75, 90, 120, 150, 180, 240, 300, 360, 420, and 480 min after administration of rapacuronium. The blood was immediately transferred in vacuum tubes prefilled with 1 ml 1 M phosphate buffer (NaH_2PO_4). The vacuum of the tubes was determined so that the volume of the blood sample injected into the tube was 4 ml. The tubes were kept at 4°C and centrifuged within less than 1 h after sampling. The supernatant was withdrawn and kept frozen until subsequent analysis. Blood samples were also obtained for the measurement of hematocrit at 30, 120, and 360 min.

The concentration of rapacuronium and its putative derivatives was determined by high-pressure liquid chromatography coupled with mass spectrometry detection using deuterated Org 9487 as internal standard (Hazelton, Harrogate, United Kingdom). Because a breakdown of rapacuronium into its 3-OH deacetyl derivative (Org 9488) may occur, this metabolite was also assayed in plasma. The concentration of rapacuronium and Org 9488 in plasma was calculated from the concentration measured in the supernatant and the hematocrit value.

A biexponential equation was fitted to the concentration of rapacuronium and of Org 9488 *versus* time data for each patient using the SIPHAR program (Simed, Creteil, France)[16] with a weighing function of $1/y^2$. The best fit for the data was determined using the F ratio test. The following parameters were derived: fast distribution half-life, elimination half-life, total apparent volume of distribution at steady state, volume of distribution of the central compartment, total-body clearance, area under the concentration–time curve, and the terminal half-life of Org 9488.

Statistical Analysis

The chi-square test was used to test for significant difference in the intubating score between the two groups of patients. For statistical analysis, the chi-square test was used to test for significant difference in the intubating score between the two groups of patients. Comparisons between the values (median and extreme values) obtained in normal patients and in cirrhotic patients were performed with the Mann–Whitney U test. A P value < 0.05 indicated a statistically significant difference.

Table 1. Demographic and Biological Values and Degree of Hepatocellular Dysfunction of Patients Studied

	Normal Hepatic Function (n = 8)	Cirrhosis (n = 8)
Age (yr)	49 (35–68)	54 (44–74)
Weight (kg)	77 (59–83)	76 (58–93)
Height (m)	174 (160–181)	169 (160–182)
Gender (M/F)	5/3	8/0
Creatinine (μM)	82 (63–108)	72 (53–132)
ALAT* (U/l)	19 (7–63)	32 (5–249)
ASAT* (U/l)	16 (8–34)	38 (15–295)†
Albumin (g/l)	40 (34–45)	35 (21–42)†
Bilirubin (μM)	9 (4–14)	22 (5–56)‡
Prothrombin (%)	97 (83–100)	62 (33–100)‡
Child Pugh score (points)	ND	7 (5–10)

Values are median (extreme values).

ALAT = alanine aminotransferase; ASAT = aspartate aminotransferase; ND = not done.

* Normal values < 30 U/L.

† $P < 0.05$ *versus* normal.

‡ $P < 0.01$ *versus* normal.

Results

Patient characteristics and results of liver function tests are summarized in table 1. The plasma concentration decay curves of rapacuronium for the two groups of patients are shown in figure 1. At 2, 5, 7, and 10 min, mean plasma concentration of rapacuronium was significantly lower in patients with cirrhosis than in normal patients. The Org 9488 compound could be detected in every plasma sample. The highest concentration was found at 2 min and then declined progressively (fig. 2). The level of rapacuronium in the batches used for the study varied between 89% and 103%, and the level of Org 9488 varied between 1% and 7% (unpublished data, December 1997; Organon, Boxtel, The Netherlands). Therefore, the pharmacokinetic parameters were computed according to the actual dose of rapacuronium injected to each patient. The distribution half-life [values given as median (range)] was 7.9 (4.6–11.6) min in patients with normal hepatic function and 8.0 (5.7–13.1) min in those with cirrhosis (table 2). A significant ($P < 0.01$) increase in volume of distribution of the central compartment was observed in cirrhotic patients: 131 (104–141) ml/kg compared with 75 (47–146) ml/kg in controls. The volume of distribution at steady state was increased ($P < 0.01$) to 331 (284–488) ml/kg in patients with cirrhosis, compared with 221 (124–285) ml/kg in controls. Area under the concentration–time curve was significantly ($P < 0.01$) diminished in patients with cirrhosis: 202 (157–230) $\text{min} \cdot \mu\text{g}^{-1} \cdot \text{ml}^{-1}$ compared with 274 (166–348) $\text{min} \cdot \mu\text{g}^{-1} \cdot \text{ml}^{-1}$ in controls. The elimination half-life was not different between the two groups: 88 (77–146) min in controls and 91 (76–117) min in patients with cirrhosis. Plasma clearance was significantly ($P < 0.05$) increased to 6.9 (6.1–8.9) $\text{ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ in patients with cirrhosis, compared with 5.3 (4.2–8.4) $\text{ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ in controls. Terminal half-life of Org 9488 was 151 (130–190) min in normal patients and was prolonged ($P < 0.05$) to 235 (132–430) min in patients with cirrhosis. The intubation time and the intubation score differed between the two groups (table 3). The onset time was similar between the two groups: 65 (40–110) s in controls, and 60 (52–240) s in patients with cirrhosis. Maximal depression of the first twitch was not different between the two groups. TH25, TH75, TH90, and T4 0.7 were not significantly different between the two groups.

Discussion

The current study demonstrates that, in patients with cirrhosis, a single dose of 1.5 mg/kg rapacuronium exerts the same neuromuscular blocking effect as in patients with normal hepatic function. The main pharmacokinetic change induced by cirrhosis consists in an increase in both the volume of the central compartment and the total apparent volume of distribution of rapacuronium.

The increased volume of distribution of muscle relaxants induced by cirrhosis has now been clearly demonstrated by several studies [12,17–19] and has been proposed as an explanation for the so-called resistance of patients with cirrhosis to muscle relaxants. In the present study, the intubating time and conditions were similar between the two groups. This increase in the volume of distribution of rapacuronium is most probably a result of the enlarged extracellular fluids space, which is a common finding in patients with cirrhosis; however, only one of the patients studied had clinical evidence of ascites. In a previous study of rocuronium, we observed that the volume of the central compartment was increased and associated with a longer onset time in patients with cirrhosis.[18] In the present study, we could not demonstrate such a correlation between onset time and the central volume of distribution. Because the onset time of rapacuronium is particularly short, it may be more complex to show difference between the two groups. Pharmacokinetic analysis demonstrates that cirrhosis does not cause a delayed elimination of rapacuronium. On the contrary, we observed an increase in the plasma clearance of rapacuronium in patients with cirrhosis. Several

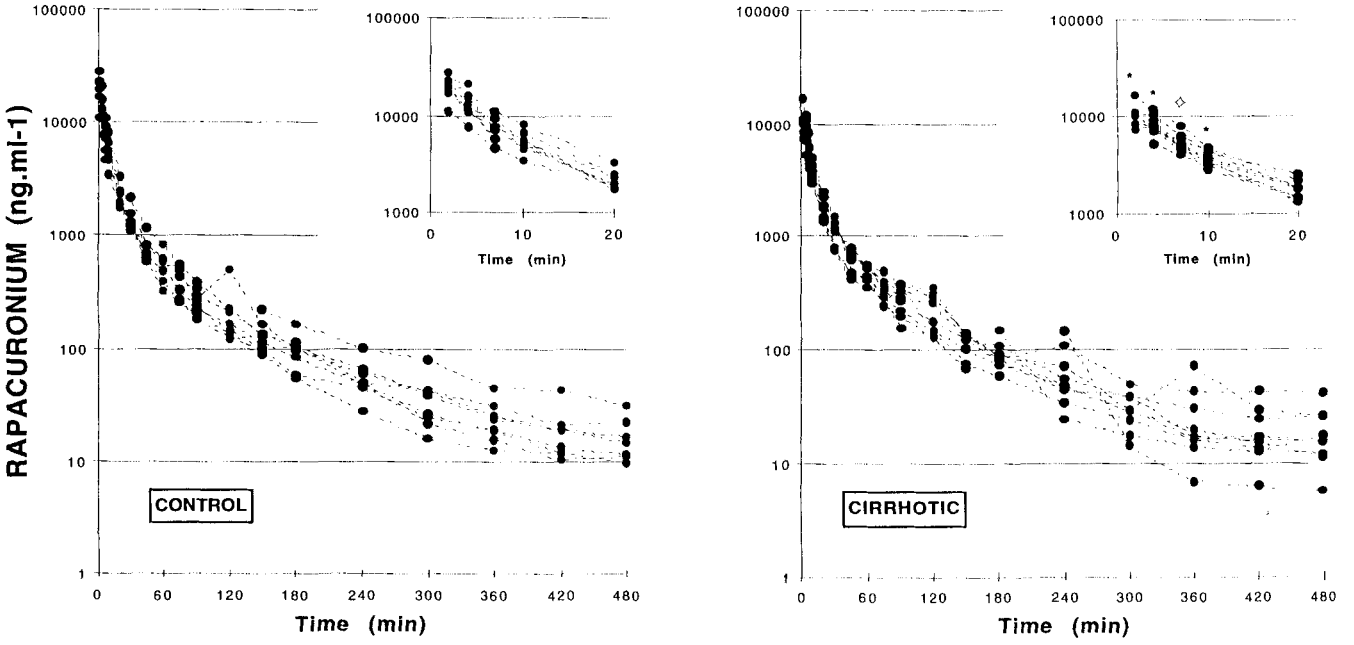

Fig. 1. Rapacuronium plasma concentration *vs.* time in patients with normal liver function (*left*) and in those with cirrhosis (*right*). (*Top*) Data between 0 and 20 min are presented on an expanded scale. ◇$P < 0.05$ and *$P < 0.01$ *vs.* concentration in patients with normal hepatic function.

explanations can be proposed for our findings. First, the liver may not be a pathway of elimination of rapacuronium in humans. Second, the degree of liver insufficiency of the patients studied may be not severe enough to diminish the hepatic excretion of rapacuronium. However, the patients with cirrhosis who we studied are representative of the category of patients with hepatic insufficiency undergoing elective procedures with general anesthesia. The elimination half-life of rapacuronium was unchanged between the two groups. The sampling time was 480 min and provided a good interval of time to characterize the elimination half-life of rapacuronium, which was approximately 90 min in patients with normal hepatic function. Such value must be compared with the values of 72 and 88 min reported previously.[2-15] These data suggest that the short clinical duration of action of a single bolus dose of rapacuronium is controlled by distribution phenomena and that after repeated administration, rapacuronium may be a less promising short-acting agent. The clinical duration of action of rapacuronium, estimated as the time from injection to 25% recovery of TH, was similar to values of 14.5 to 16.5 min reported previously, [20-22] although a shorter value of 10.3 min has been reported.[1,23] However, the results of our study suggest that the spontaneous recovery of the neuromuscular blocking effect of rapacuronium is not as short as initially expected. In two previous studies, T4 0.7 was 24 min[1] and 30 min[23] after a 1.5-mg/kg dose of rapacuronium, compared with 67 min in our study. This difference may be explained, in part, by the fact that T4 0.7 was measured while patients were anesthetized with isoflurane, which is known to potentiate the effect of neuromuscular blocking agents.[24]

The simultaneous measurement of the plasma concentration of Org 9488 showed that this compound was present at the highest concentration in the earliest samplings. This suggests that Org 9488 was present in the injectate. In addition, the analysis of the batch used for the study showed that Org 9488 was present in the amount of 2-7%; therefore, this was taken into account to calculate the actual dose delivered to the patients. The spontaneous breakdown of rapacuronium does not exclude an additional *in vivo* biotransformation. The apparent half-life of Org 9488 was longer than that of the parent compound and longer in patients with cirrhosis than in control subjects, which may suggest that Org 9488 is eliminated by the liver. This half-life may reflect

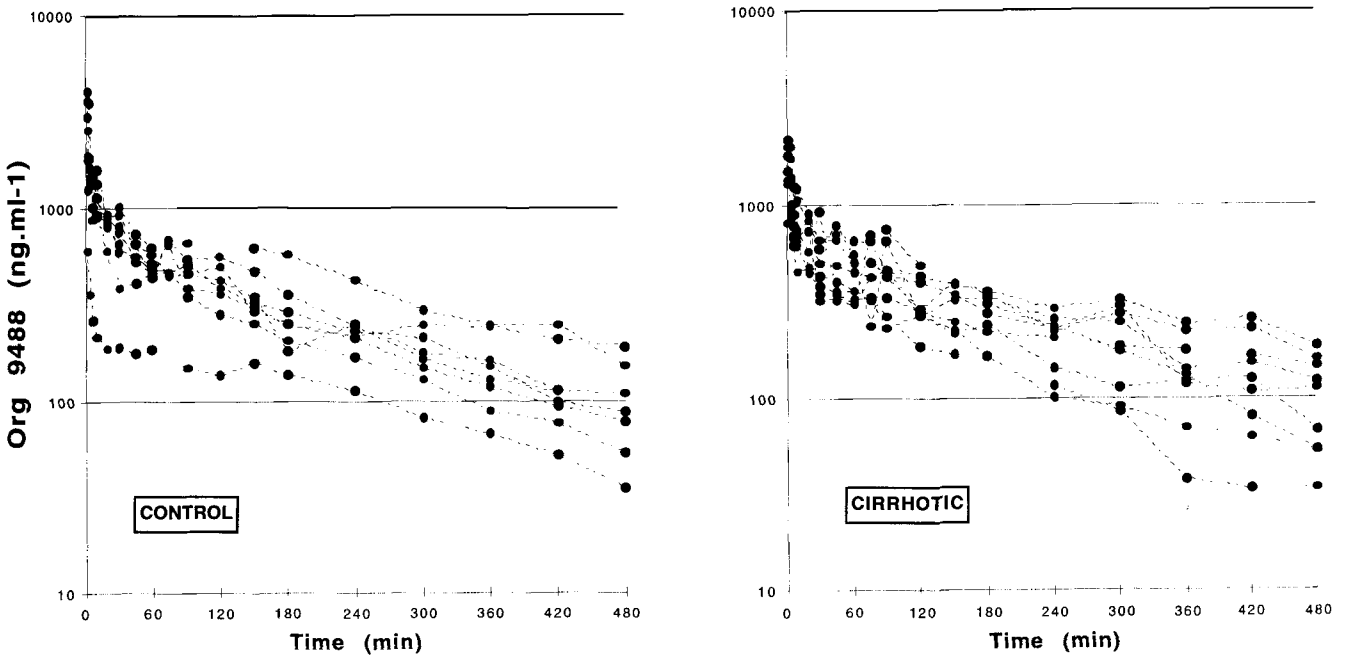

Fig. 2. Org 9488 plasma concentration *vs.* time in patients with normal liver function (*left*) and in those with cirrhosis (*right*) after the administration of a bolus dose of 1.5 mg/kg rapacuronium.

both the elimination and the production of Org 9488. It has been shown recently that Org 9488 is an active metabolite, with a neuromuscular blocking effect at least two times greater than that of rapacuronium.[25] The concentration of Org 9488 at the effect site that corresponds to a 50% depression of the twitch height has been estimated to be 1.8 μg/ml in humans.[25] Because the plasma concentration of Org 9488 in each individual decreased rapidly (within < 10 min) below this effective concentration, we suggest that Org 9488 did not contribute significantly to the neuromuscular blocking effect observed after a single bolus dose of rapacuronium.

One limitation of our study is the use of venous blood

Table 2. Pharmacokinetics of Rapacuronium and Org 9488 in Patients with Normal Hepatic Function and with Cirrhosis

	Normal Hepatic Function (n = 8)	Cirrhosis (n = 8)
$T_{1/2}$ α (min)	7.9 (4.6–11.6)	8.0 (5.7–13.1)
$T_{1/2}$ β (min)	88 (77–102)	90 (76–117)
V_1 (ml/kg)	75 (47–146)	131 (104–141)*
Vd_{ss} (ml/kg)	221 (124–285)	331 (284–488)*
Cl (ml · min^{-1} · kg^{-1})	5.3 (4.2–8.4)	6.9 (6.1–8.9)†
$T_{1/2}$ Org 9488 (min)	151 (130–190)	235 (132–430)†

Values are median (extreme values).

$T_{1/2}$ = half-life; V_1 = volume of distribution; Vd_{ss} = volume of distribution at steady state; Cl = plasma clearance.

* $P < 0.01$ *versus* normal.

† $P < 0.05$ *versus* normal.

Table 3. Onset and Recovery of Neuromuscular Blocking Effect of Rapacuronium (1.5 mg/kg) and Intubating Conditions in Patients with Normal Hepatic Function and with Cirrhosis

	Normal Hepatic Function (n = 8)	Cirrhosis (n = 8)
OT 90 (s)	65 (40–110)	60 (52–240)*
Emax (%)	100 (95–100)	100 (85–100)*
T25 (min)	19 (14–32)	15 (7–29)
T75 (min)	38 (22–60)	31 (19–62)
T90 (min)	49 (28–80)	47 (28–71)
T4 0.7 (min)	67 (50–110)	51 (28–64)
Time of intubation (s)	75 (65–105)	80 (65–160)
Intubating score (number of patients)		
1	2	4
2	5	4
3	1	0
4	0	0

Values are median (extreme values).

OT = onset time; Emax = maximal depression of the first twitch.

* One patient did not develop more than 85% of depression of twitch response; onset time was considered at the time of achievement of maximum effect in this patient.

samples, which are less appropriate for pharmacokinetic analysis than arterial samples but less invasive, especially in patients undergoing peripheral surgery or endoscopy. Therefore, we did not proceed to the simultaneous pharmacokinetic-pharmacodynamic analysis of our data. However, it was shown recently that arterial and venous blood concentrations of rapacuronium were nearly identical during the first 20 min after administration.[26]

In conclusion, onset and recovery rate of neuromuscular blocking effect of a single bolus dose of rapacuronium are similar in patients with cirrhosis compared with those with normal hepatic function. Plasma concentration of rapacuronium are initially lower in patients with cirrhosis because of an increase in the volume of distribution. The elimination half-life of rapacuronium is similar in patients with cirrhosis and in those with normal hepatic function. The plasma clearance of rapacuronium is higher in patients with cirrhosis than in patients with normal hepatic function, suggesting that the liver is not the main pathway of elimination in humans.

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