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Abstract:	<p>Sugammadex is a modified γ-cyclodextrin which rapidly reverses rocuronium- and vecuronium-induced neuromuscular blockade. Previous studies suggest that sugammadex is mostly excreted unchanged via the kidneys. This single-center, open-label, non-randomized study used ^{14}C-labeled sugammadex to further investigate the excretion, metabolic and pharmacokinetic (PK) profiles of sugammadex in six healthy male volunteers. ^{14}C-labeled sugammadex 4 mg/kg (0.025 MBq/kg of ^{14}C-radioactivity) was administered as a single intravenous bolus. Blood, urine, feces, and exhaled air samples were collected at pre-defined intervals for assessment of sugammadex by liquid chromatography-mass spectrometry (LC-MS) and for radioactivity measurements. Adverse events were also assessed.</p> <p>Excretion of sugammadex was rapid with $\sim 70\%$ of the dose excreted within 6 h and $\sim 90\%$ within 24 h. Less than 0.02% of radioactivity was excreted in feces or exhaled air. Ninety-five percent of the radioactivity detected in urine could be attributed to sugammadex, as determined by LC-MS, suggesting very limited metabolism of sugammadex. LC-MS analysis of plasma samples found that sugammadex accounted for 100% of total ^{14}C-radioactivity in the plasma. In general, PK parameters determined from radioactivity and sugammadex plasma concentrations were very similar. Any adverse events were of mild-to-moderate intensity, and judged unrelated to sugammadex. These findings demonstrate that sugammadex is cleared rapidly, almost</p>

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Sugammadex is Cleared Rapidly and Primarily Unchanged via Renal Excretion

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Running title: RENAL CLEARANCE OF SUGAMMADEX

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ABSTRACT

Sugammadex is a modified γ -cyclodextrin which rapidly reverses rocuronium- and vecuronium-induced neuromuscular blockade. Previous studies suggest that sugammadex is mostly excreted unchanged via the kidneys. This single-center, open-label, non-randomized study used ^{14}C -labeled sugammadex to further investigate the excretion, metabolic and pharmacokinetic (PK) profiles of sugammadex in six healthy male volunteers. ^{14}C -labeled sugammadex 4 mg/kg (0.025 MBq/kg of ^{14}C -radioactivity) was administered as a single intravenous bolus. Blood, urine, feces, and exhaled air samples were collected at pre-defined intervals for assessment of sugammadex by liquid chromatography-mass spectrometry (LC-MS) and for radioactivity measurements. Adverse events were also assessed.

Excretion of sugammadex was rapid with ~70% of the dose excreted within 6 h and ~90% within 24 h. Less than 0.02% of radioactivity was excreted in feces or exhaled air. Ninety-five percent of the radioactivity detected in urine could be attributed to sugammadex, as determined by LC-MS, suggesting very limited metabolism of sugammadex. LC-MS analysis of plasma samples found that sugammadex accounted for 100% of total ^{14}C -radioactivity in the plasma. In general, PK parameters determined from radioactivity and sugammadex plasma concentrations were very similar. Any adverse events were of mild-to-moderate intensity, and judged unrelated to sugammadex. These findings demonstrate that sugammadex is cleared rapidly, almost exclusively via the kidney, with minimal or no metabolism.

Key words: Sugammadex; Org 25969; pharmacokinetics; gamma-cyclodextrin

Introduction

The modified γ -cyclodextrin, sugammadex, was specifically designed to encapsulate the steroidal neuromuscular blocking agent rocuronium, with structural similarities meaning that it will also encapsulate vecuronium [1,2], and has the ability to rapidly reverse both moderate and deep rocuronium- or vecuronium-induced neuromuscular blockade [3–6]. Sugammadex is approved in various countries for the reversal of rocuronium- or vecuronium-induced neuromuscular blockade in adults at a recommended dose range of 2–16 mg/kg, depending on the level of blockade at the time of administration. It is also approved for the reversal of moderate rocuronium-induced blockade in pediatric patients at a dose of 2 mg/kg [7–9].

Previous studies evaluating the pharmacokinetic (PK) profile of sugammadex have suggested that the majority of an intravenously (i.v.) administered sugammadex dose is excreted unchanged by the kidneys [10–12]. At doses of 2, 4, and 8 mg/kg, the mean recovery of sugammadex in urine within 24 h of administration ranged from 58.8% to 80.4% of the administered dose [10]. Using higher than recommended doses of 32, 64, or 96 mg/kg, urinary recovery within 48 h of administration was ~90% of the administered dose [13]. Despite this relatively high urinary recovery of sugammadex, quantified by tandem liquid chromatography mass spectrometry (LC-MS), a minor role of metabolism in the clearance of sugammadex cannot be excluded. The use of ^{14}C -labeled sugammadex enables determination of the extent of metabolism and the relative contribution of the various routes of excretion to elimination.

The aim of the current trial was to further elucidate the extent of sugammadex metabolism and the relative contribution of various routes of excretion at a therapeutic dose of 4 mg/kg in healthy volunteers. To achieve this, the pharmacokinetic parameters

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3 derived from assessment of sample radioactivity were compared with those derived from
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5 a LC-MS assay.
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Materials and Methods

Study design

This was a single-center, open-label, non-randomized study of six healthy adult male subjects, conducted at PRA International (Zuidlaren, The Netherlands). A total of six subjects were selected because this number is generally considered adequate for studies evaluating the disposition of ^{14}C -labeled compounds. The study protocol was approved by an independent ethics committee (Stichting Beoordeling Ethiek Bio-Medisch Onderzoek, Assen, The Netherlands) and was conducted in compliance with the Declaration of Helsinki, the International Conference on Harmonization Guidelines, Good Clinical Practice, and current regulatory requirements.

Subjects

Subjects were eligible for inclusion in the study if they were aged between ≥ 18 years and ≤ 65 years, had normal 12-lead electrocardiogram (ECG) intervals (PR between ≥ 120 ms and ≤ 210 ms, QRS < 120 ms and QTc ≤ 450 ms), no clinically relevant ECG abnormalities and a heart rate > 50 beats per minute after 5 min rest, had a body mass index between ≥ 18 and ≤ 30 kg/m², and were in otherwise good health for their age. Major exclusion criteria were: evidence of renal or hepatic disease; a history of drug or alcohol abuse, or a positive drug or alcohol screen; smoking > 5 cigarettes/day; hepatitis B, C or HIV infection; febrile illness within 3 days before administration of sugammadex, stool production less than once every 2 days; a history of sensitivity/idiosyncrasy to chemically-related compounds or excipients which may be used in the study or to any other unspecified drug in the past; and drug therapy (excluding paracetamol) within 2 weeks (or 1 month in the case of inducers or inhibitors of drug-metabolizing enzymes) of

1
2 administration of sugammadex. All subjects were required to give written informed
3
4 consent before enrollment in the study.
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9 ***Study drug administration***

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11 Each subject received a single i.v. bolus dose of ^{14}C -labeled sugammadex at a
12
13 therapeutic dose level of 4 mg/kg (with 0.025 MBq/kg bodyweight of ^{14}C -radioactivity,
14
15 about 1.85 MBq per subject); the radiolabel was located on each of the side chains
16
17 (Figure 1). Study drug administration was performed on the morning of day 1, after an
18
19 overnight fast of at least 10 h. The use of any concomitant prescription or non-
20
21 prescription drug (with the exception of intermittent paracetamol) was prohibited during
22
23 the entire treatment period (i.e. from sugammadex administration until follow-up).
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25 Consumption of alcohol and strenuous physical exercise were prohibited from 24 and 48
26
27 h before sugammadex administration, respectively, until collection of the last PK blood
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29 sample. Subjects received a standardized meal on day 1 and were not allowed to smoke
30
31 during the entire study period.
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40 ***Sample collection***

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42 Blood samples for PK evaluation and measurement of radioactivity were collected pre-
43
44 dose (not for radioactivity) and at regular pre-defined intervals at 2, 5, 10, 20, and 35
45
46 min and 1, 1.5, 2.5, 4, 6, 8, 12, 18, 24, and 48 h post-dose. Urine samples were
47
48 collected for PK evaluation and quantification of radioactivity at pre-dose (-12 to 0 h)
49
50 and at 0-6, 6-12, 12-24, and 24-48 h post-dose; sampling for quantification of
51
52 radioactivity continued until at least 48-72 h post-dose. All urine samples were diluted
53
54 1:1 volume for volume with blank human plasma to stabilize drug-related material prior
55
56 to storage. Feces samples were collected for measurement of radioactivity pre-dose
57
58 (from 3 days before sugammadex administration) and at 0-12, 12-24, and 24-48 h
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3 post-dose. Exhaled air samples were collected pre-dose and at pre-defined intervals
4
5 post-dose (1, 2, 6 and 12 h) for radioactivity measurement after administration of ¹⁴C-
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7 labeled sugammadex.
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10 All samples taken for PK evaluation and measurement of radioactivity were stored at –
11
12 20 °C.
13
14

17 **Sample analysis**

19 Sugammadex concentrations in plasma and urine were determined using a validated
20
21 liquid chromatography-mass spectrometry (LC-MS) assay method after solid phase
22
23 extraction (SPE). The sample volumes used for analysis were 250 µl and 100 µl for
24
25 plasma and urine, respectively. Isolute[®] 96-well SPE plates with 25 mg Isolute[®] HAX
26
27 sorbent material per well (Sopachem, Wageningen, The Netherlands) were used for
28
29 SPE of plasma and urine samples.
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35 Chromatographic separations were carried out using an HP1100 series Liquid
36
37 Chromatograph (Agilent Technologies, Palo Alto, CA). Samples were injected by a HTS
38
39 PAL autosampler (CTC Analytics, Switzerland) and pumped at a flow-rate of 1.0 ml/min
40
41 through a Polaris C18-A PEEK (polyaryletheretherketone) high performance liquid
42
43 chromatography analytical column (50 mm length x 4.6 mm internal diameter, 5 µm
44
45 particle size; Varian, Inc., Palo Alto, CA) with a linear mobile phase gradient of 0.1% v/v
46
47 formic acid in water and methanol at ratios of 70:30 to 20:80. The liquid chromatography
48
49 eluate was split 1:10 before entering a Perkin-Elmer Sciex API 3000 triple-quadrupole
50
51 mass spectrometer (Sciex Thornhill, ON, Canada) equipped with a turbo ion-spray
52
53 interface (Applied Biosystems, Foster City, CA). The quadrupoles were operated with
54
55 unit resolution in the negative ion mode. The resulting multiple reaction monitoring
56
57 chromatograms were integrated using Analyst version 1.2 software (Sciex). The Watson
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1
2 Drug Metabolism Laboratory Information Management System (version 6.3.0.03)
3
4 software (Innaphase Corporation, Wayne, PA) was used for all calculations. Calibration
5
6 curves for sugammadex in both human heparin plasma and human urine were
7
8 constructed using linear weighted regression (weighting factor $1/Y^2$) and used to
9
10 calculate sugammadex levels in the calibration, quality control and study samples.
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15 For radioactivity analysis, reference standards of ^{14}C -labeled sugammadex and
16
17 [1-methyl- ^{14}C]-caffeine were used to prepare quality control samples. Human plasma,
18
19 urine, and feces matrices were used for the analysis of blank samples in analytical runs
20
21 and to prepare quality control samples. All scintillation counting were performed using a
22
23 Packard Tri-CarbTM 3100 liquid scintillation analyzer (Downers Grove, IL) equipped with
24
25 low level counting mode (LLCM) and normal counting mode (NCM). All calculations
26
27 were performed in Microsoft Excel (Redmond, WA). Results were recorded in ng
28
29 sugammadex equivalents/ml for plasma, dpm/ml for urine, dpm/g for feces, and in dpm
30
31 for exhaled air and medication (quality control) Samples were assayed as follows:
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39 *Medication (quality control) samples*

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42 Samples were assayed using an aliquot of the i.v. medication solution, transferred into a
43
44 20 ml counting vial and mixed with 10 ml of the scintillation cocktail (Ultima Gold). After
45
46 20 min, the sample was counted for 10 min on NCM of the scintillation counter. The
47
48 administered radioactive dose was calculated by multiplying the mean ($n = 3$) measured
49
50 radioactivity level per g by the exact administered weight of the i.v. solution.
51
52
53

54 *Plasma samples*

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57 Samples were assayed using a 1000 μl aliquot of the plasma sample, transferred into a
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59 20 ml counting vial and mixed with 10 ml of the scintillation cocktail (Ultima Gold). After
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1
2
3 waiting at least 30 min, samples were counted on the LLCM of the scintillation counter
4
5 until a statistical error (2 s) of 0.5% was obtained with a maximum counting time of 10
6
7 min.
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10 11 *Urine samples*

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15 Samples were assayed using a 1000 µl aliquot of the urine sample, transferred into a 7
16
17 ml counting vial and mixed with 5 ml of the scintillation cocktail (Ultima Gold). After
18
19 waiting at least 30 min, samples were counted until a statistical error (2s) of 0.5% was
20
21 obtained with a maximum counting time of 10 min. Samples with a ^{14}C activity level of <
22
23 50000 dpm/ml were counted on the LCCM; samples above 50000 dpm/ml were counted
24
25 on the NCM.
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31 *Feces samples*

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34 Samples were transferred into a fitting bucket per subject and per 24 h time period and
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36 homogenized with a minimum of water (1–2 weight equivalents). After homogenization,
37
38 two 15 g aliquots were taken for determination of total ^{14}C -radioactivity and two 50 g
39
40 aliquots were taken for possible metabolite profiling. An aliquot of ~0.5 g of the feces
41
42 homogenate to be analyzed was then dried at 50 °C for at least 3 h and combusted for a
43
44 max of 1 min using a Packard 307 Sample Oxidizer (Perkin Elmer Life Sciences,
45
46 Groningen, The Netherlands). CarboSorb-E (7 ml) was used to absorb carbon dioxide.
47
48 At the end of the combustion cycle, the absorber was mixed with 13 ml of the scintillant
49
50 Perma Fluor E+, and samples were then placed in the liquid scintillation counter for at
51
52 least 30 min before counting. Samples were counted until a statistical error (2 s) of 0.5%
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54 was obtained with a maximum counting time of 10 min. Samples with a ^{14}C activity level
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2 of <160000 dpm/ml were counted on the LCCM; samples >160000 dpm/ml were
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4 counted on the NCM.
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9 *Exhaled air samples*
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12 Ten ml of the scintillation cocktail (Emulsifier Safe) was mixed with the CO₂-trapped
13
14 exhaled air sample to be analyzed. After at least 90 min, samples were counted on the
15
16 LLCM until a statistical error (2 s) of 0.5% was obtained with a maximum counting time
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18 of 20 min.
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23 On day 3, subjects were discharged from the study center if <1% of the
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25 radioactive dose (sum of the urine and feces) was measured in the days excreta and if
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27 the total cumulative excretion was >90% of the radioactive dose. Subjects remained in
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29 the study center if the above criteria were not met, for a maximum of 7 further days. A
30
31 follow-up assessment was performed on day 10. Furthermore, if radioactivity exceeded
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33 50 dpm/ml in the urine and/or 75 dpm per 100 mg feces at the time of discharge,
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35 subjects were requested to bring 24-h urine samples to the clinic every 2–3 days until
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37 the radioactivity decreased to below these limits.
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42
43 PK analysis was performed by the Clinical Pharmacology and Kinetics
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45 Department of MSD (Oss, The Netherlands). Quantification of radioactivity in all
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47 matrices was performed by the Bioanalytical Laboratory of PRA International (Zuidlaren,
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49 The Netherlands).
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Pharmacokinetic analysis

From the plasma concentration of sugammadex and radioactivity (expressed in mass equivalents of sugammadex) the following non-compartmental PK parameters were calculated: maximum plasma concentration, time to maximum plasma concentration, terminal elimination half life ($t_{1/2}$), effective $t_{1/2}$ ($t_{1/2, \text{effective}} = \log_e 2 \cdot \text{MRT}$ [mean residence time]), area under the concentration versus time curve from time zero to infinity ($\text{AUC}_{0-\infty}$), total plasma clearance, and volume of distribution at steady state.

Urine concentrations of sugammadex and radioactivity were used to calculate the cumulative amount excreted in the urine up to the end of the last collection interval ($\text{Ae}_{\text{cum, tlast}}$) as a percentage of the total dose administered. These parameters were then used to calculate renal clearance ($\text{CL}_R = \text{Ae}_{\text{cum, tlast}} / \text{AUC}_{0-\infty}$) and the fraction of the dose excreted unchanged in the urine ($f_e = \text{Ae}_{\text{cum, tlast}} / \text{dose}$). Cumulative excretion was also calculated for the exhaled air and feces samples based on level of radioactivity.

Statistical Analysis

Descriptive statistics were calculated for the plasma concentrations of sugammadex and radioactivity by time point for the cumulative excretion of radioactivity and sugammadex, and for PK parameters.

The PK analyses were performed using SAS version 8.2 (SAS Institute Inc., Cary, NC).

Safety

The tolerability and safety of sugammadex were evaluated based on adverse event (AE) reporting, vital signs (including systolic and diastolic blood pressure and heart rate), ECG monitoring (12-lead ECG at screening, baseline, and 2, 35, and 60 min post dose,

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2 and follow-up), physical examination, and clinical laboratory values (hematology, blood
3 chemistry, and urinalysis). Information on AEs and serious AEs (SAEs) was obtained
4 from regular questioning of the subjects or on clinical examination. AEs were
5 categorized according to their severity and relation to the study drug and were coded
6 using MedDRA (version 8.1; MedDRA Maintenance and Support Services Organization,
7 Chantilly). Safety data were evaluated for the all-subjects-treated (AST) group.
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Results

Enrollment and subject baseline characteristics

All six subjects who entered the study received the study medication and were evaluable for PK assessment. All six subjects were healthy Caucasian males with a mean (standard deviation [SD]) age of 52.8 (16.3) years, a mean (SD) weight of 75.8 (9.9) kg and a mean (SD) BMI of 23.8 (1.9) kg/m².

Safety and tolerability

Each of the subjects experienced one or more AEs, all of which were of mild or moderate intensity and resolved without sequelae. There were no SAEs or discontinuations because of AEs and none of the AEs were considered by the investigator to be related to sugammadex. The most frequent AEs were abnormally frequent urination ($n = 3$) and headache ($n = 2$). No clinically significant abnormalities in ECG findings, vital signs, or clinical laboratory results were reported.

Pharmacokinetic profile

Excretion of sugammadex was rapid, with ~70% (mean [range] of 73 [27–92]%) of the radioactive dose excreted within 6 h, 92 (81–102)% within 24 h, and 95 (83–105)% within 48 h. The mean total cumulative excretion of sugammadex, as analyzed both by total ¹⁴C-radioactivity and LC-MS, is presented in Figure 2. At 48 h the mean (range) total cumulative amount of sugammadex (quantified by LC-MS) recovered in the urine during 48 h was 91 (85–94)% of the dose (Table 1). So, on average, 95% of the radioactivity detected in the urine could be attributed to sugammadex, as analyzed by LC-MS, suggesting there was very limited, if any, metabolism of sugammadex.

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2 Moreover, the cumulative amount of radioactivity excreted in either feces or exhaled air
3 was <0.02% in all patients.
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8 In plasma, sugammadex measured by LC-MS, accounted for 100% of the total
9 ^{14}C -radioactivity, illustrated by the overlapping concentration curves (Figure 3). This
10 suggests that there were either no radiolabeled metabolites of sugammadex in the
11 plasma or that they were present at extremely low concentrations. Generally, the PK
12 parameters determined from radioactivity and sugammadex plasma concentrations were
13 very similar (Table 1). The small difference in $t_{1/2}$ between these two methods of
14 detection can be explained by the lower limit of quantification of the radioactivity
15 measurements versus the LC-MS method of detection, resulting in a later time interval
16 for determination of the $t_{1/2}$. In accordance with the similar plasma concentrations
17 observed (Figure 3), comparison of the $\text{AUC}_{0-\infty}$ of ^{14}C and sugammadex revealed that
18 on average 100% of the radioactivity in the plasma could be attributed to sugammadex.
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Discussion

This study aimed to determine the pharmacokinetics and excretion profile of ^{14}C -sugammadex and compare them with sugammadex concentrations as determined by LC-MS analysis. Radiolabeled sugammadex was excreted rapidly and almost exclusively via the kidneys. Total ^{14}C detection mirrored the concentrations determined by LC-MS both in the plasma and also in urine (Figures 2 and 3). Furthermore, in the urine collected over 48 h following dosing, the mean cumulative amount of sugammadex quantified by LC-MS in the urine was 91% of the dose. Moreover, 95% of the radioactivity detected in the urine was attributed to sugammadex. This suggests that there was minimal to no metabolism of sugammadex, which is consistent with the findings of previous studies evaluating sugammadex in surgical patients and healthy volunteers [10–13]. Less than 0.02% of the dose was excreted in exhaled air and feces, suggesting that in man these routes of excretion play no role in the clearance of sugammadex. Interestingly, in rat and dog, a minor role for excretion in feces is observed with 4.22–6.82% and 0.33–0.80%, respectively, of the dose collected in the feces. For ^{14}C α -cyclodextrin and ^{14}C γ -cyclodextrin given i.v. to rat [14,15] excretion into the feces has also been demonstrated to be a minor route of excretion (3–8% of the dose); however, as shown in the current study, this route is not applicable for sugammadex in man.

In this trial, the mean total cumulative amount of radioactivity recovered in the urine during 48 h was 95 (range 83–105) %, suggesting that at the most only a small fraction of the radioactivity was unaccounted for. There may be many causes of incomplete recovery of the radiolabel in mass balance trials (such as technical limitations and tissue retention), and it is actually rare for the mass balance in radiolabeled excretion studies to truly achieve 100% recovery [16].

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3 The minimal role of metabolism in the clearance of sugammadex is fully in line
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5 with the excretion profile of other cyclodextrins, which has been noted to be almost
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7 entirely renal [14,15,17,18], particularly in man. Subsequent profiling for metabolites in
8
9 urine and plasma samples demonstrated that the major part of total radioactivity could
10
11 be attributed to the parent compound, sugammadex (data on file).
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15 Studies in volunteers and surgical patients receiving sugammadex to reverse
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17 rocuronium- or vecuronium-induced blockade have also demonstrated that the
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19 predominant route of elimination for the complex is via the renal route, and in the
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21 presence of sugammadex, the major route of elimination of rocuronium changes from
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23 the hepatic to the renal route [10–12]. Based on data from surgical patients and healthy
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25 volunteers, the cumulative excretion of rocuronium in the urine over 24 h is in the region
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27 of 12–26% and increases to up to 74% after administration of sugammadex 4–8 mg/kg
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29 [10–12,19–21]. Given the importance of renal elimination, the efficacy and safety of
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31 sugammadex has been assessed in patients with impaired renal clearance, most of
32
33 whom were receiving dialysis. The available data suggest that sugammadex is well
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35 tolerated and effective in patients with severe renal impairment, albeit with reduced
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37 plasma clearance of sugammadex and a significantly prolonged terminal elimination half
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39 life and MRT [22,23]. However, despite longer retention of the sugammadex-rocuronium
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41 complex, no signs of recurarization were reported among renal patients in the 48 h after
42
43 administration of rocuronium followed by sugammadex [22]. Currently, for patients with
44
45 mild-to-moderate renal impairment (creatinine clearance ≥ 30 and < 80 ml/min), the dose
46
47 recommendations for sugammadex are the same as for other adult patients i.e. a single
48
49 i.v. bolus dose of 2–16 mg/kg [8]. For patients with severe renal impairment (creatinine
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51 clearance < 30 ml/min), including patients requiring dialysis, sugammadex is not
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2 recommended at present. However, further safety and PK studies are ongoing in this
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4 patient population.
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8 Sugammadex 4 mg/kg (containing 0.025 MBq/kg of ^{14}C -radioactivity) was well
9
10 tolerated in all six healthy male subjects in this study. There were no drug-related AEs
11
12 and no clinically significant abnormalities, changes, or trends were found with respect to
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14 safety laboratory data, vital signs, or ECGs, further adding to the safety profile of
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16 sugammadex that has been generated to date.
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Conclusion

In conclusion, this study in healthy volunteers shows an i.v. dose of sugammadex to be cleared rapidly and almost exclusively via the kidneys, with minimal fecal excretion and minimal to no metabolism, as determined by LC-MS analysis. The mean total recovery of radiolabel from all routes in 48 h at the dose of 4 mg/kg was 95%. Pharmacokinetic parameters were similar whether calculated from total ^{14}C radioactivity assessments or by LC-MS estimation of sugammadex concentrations.

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Conflict of interest

Pierre Peeters, Alex Zwiers, Marcel de Zwart, Saskia van de Wetering-Krebbbers, Marlou van Iersel, and Diels van den Dobbelssteen are employees of MSD (Oss, The Netherlands). Paul Passier and Jean Smeets were previously employees of MSD (Oss, The Netherlands).

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Table 1. Pharmacokinetic parameters based on ^{14}C -radioactivity detection and sugammadex concentrations determined by LC-MS ($n = 6$ subjects)

	^{14}C (expressed as sugammadex mass equivalents)		Sugammadex (LC-MS)	
	Geometric mean	Geometric CV (%)	Geometric mean	Geometric CV (%)
Urine				
CL_R (ml/min)	92.7	29	88.3	25
fraction excreted unchanged (% dose; last collection interval) ^a	96.1	85–106	91.1	85–94
Plasma				
C_{\max} ($\mu\text{g/ml}$)	33.0	22	32.2	19
t_{\max} (min) ^b	4	2–5	5	2–10
$t_{1/2}$ (min)	190	20	152	31
$t_{1/2 \text{ effective}}$ (min)	110	16	100	19
$\text{AUC}_{0-\infty}$ ($\mu\text{g}\cdot\text{min/ml}$)	2632	25	2629	23
CL (ml/min)	96.8	25	96.9	24
V_{SS} (ml)	15360	19	14027	19

^aData presented as arithmetic mean and range; samples were taken until 48 h after dosing for measurement of sugammadex (LC-MS) in urine, and until 332 h after dosing for measurement of ^{14}C in urine

^bData presented as median and range

$\text{AUC}_{0-\infty}$, area-under-the-plasma concentration-time curve to time infinity; C_{\max} , maximum plasma concentration; CL, plasma clearance; CL_R , renal clearance; CV, coefficient of variation; LC-MS, liquid chromatography-mass spectrometry; $t_{1/2}$, terminal half-life; $t_{1/2 \text{ effective}}$, effective half-life; t_{\max} , time to C_{\max} ; V_{SS} , volume of distribution at steady state.

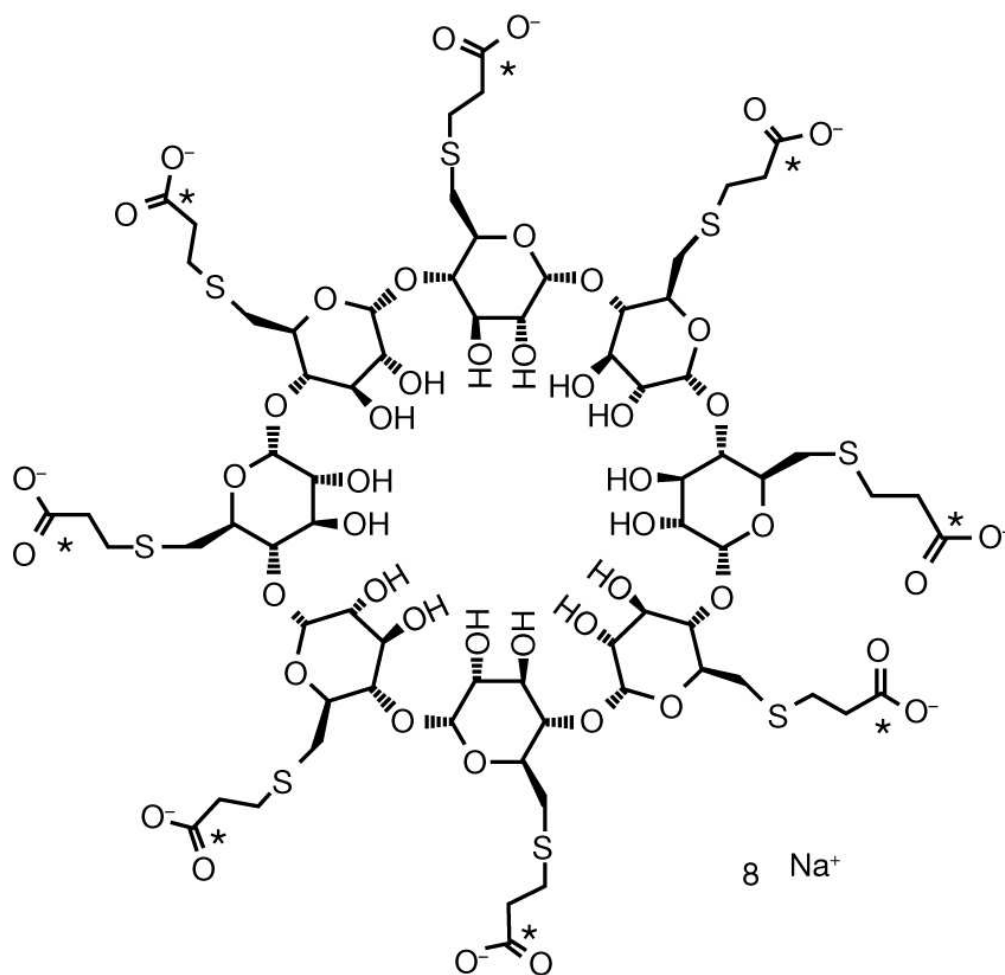


Figure 1. Structure of ¹⁴C-labeled sugammadex
*denotes position of radiolabel

71x70mm (300 x 300 DPI)

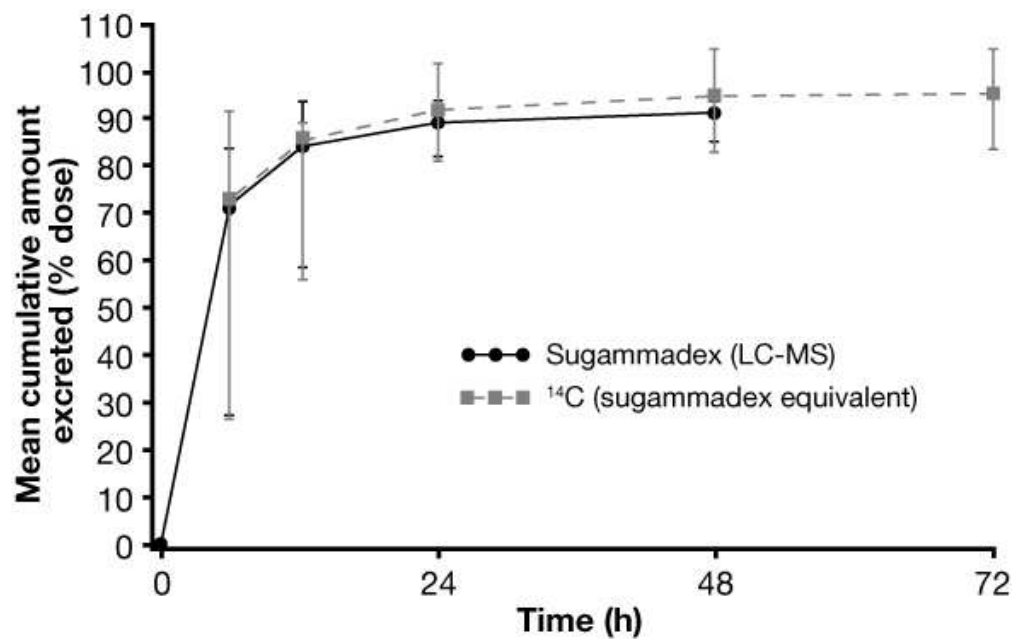


Figure 2. Mean (range) cumulative percentage of total ¹⁴C-radioactivity and sugammadex dose (determined by LC-MS) excreted in urine during 48 h (n = 6 subjects).
LC-MS, liquid chromatography with mass spectrometry detection

74x46mm (200 x 200 DPI)

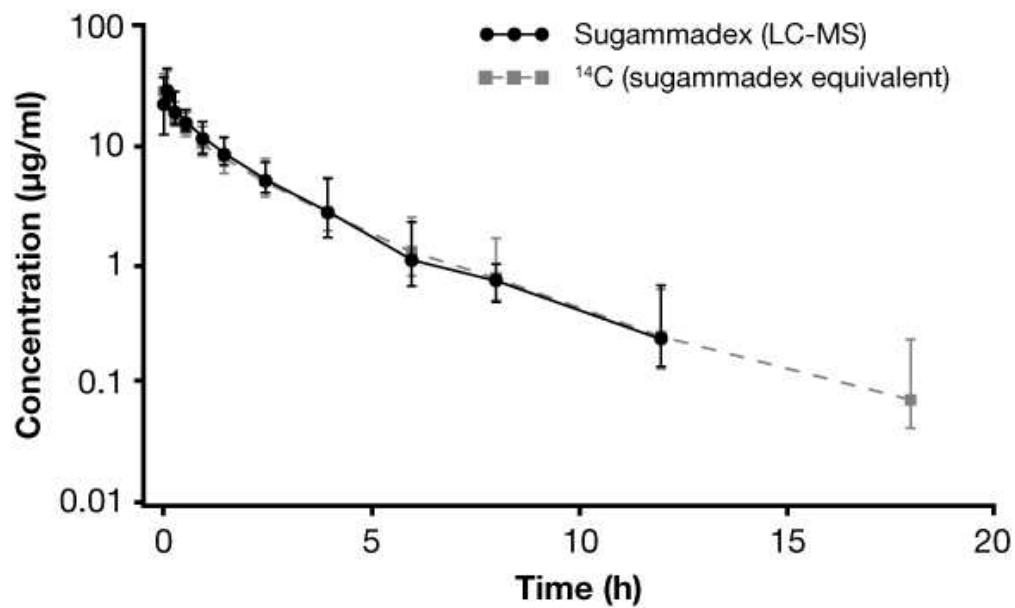


Figure 3. Geometric mean (range) sugammadex plasma concentration on a logarithmic scale, determined by LC-MS and ¹⁴C-radioactivity (n = 6 subjects). LC-MS, liquid chromatography with mass spectrometry detection

73x44mm (200 x 200 DPI)

Sugammadex is Cleared Rapidly and Primarily Unchanged via Renal Excretion

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Running title: RENAL CLEARANCE OF SUGAMMADEX

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ABSTRACT

Sugammadex is a modified γ -cyclodextrin which rapidly reverses rocuronium- and vecuronium-induced neuromuscular blockade. Previous studies suggest that sugammadex is mostly excreted unchanged via the kidneys. This single-center, open-label, non-randomized study used ^{14}C -labeled sugammadex to further investigate the excretion, metabolic and pharmacokinetic (PK) profiles of sugammadex in six healthy male volunteers. ^{14}C -labeled sugammadex 4 mg/kg (0.025 MBq/kg of ^{14}C -radioactivity) was administered as a single intravenous bolus. Blood, urine, feces, and exhaled air samples were collected at pre-defined intervals for **assessment of sugammadex by liquid chromatography-mass spectrometry (LC-MS) PK, and for radioactivity measurements, and metabolite profiling**. Adverse events were also assessed.

Excretion of sugammadex was rapid with ~70% of the dose excreted within 6 h and ~90% within 24 h. Less than 0.02% of radioactivity was excreted in feces or exhaled air. Ninety-five percent of the radioactivity detected in urine could be attributed to sugammadex, as determined by ~~liquid chromatography-mass spectrometry (LC-MS)~~, suggesting very limited metabolism of sugammadex. LC-MS analysis of plasma samples found that sugammadex accounted for 100% of total ^{14}C -radioactivity in the plasma. ~~However, as a result of post-sampling oxidation or a minor impurity in the dose formulation, high performance liquid radiochromatography analysis of urine and plasma samples revealed up to nine radioactive peaks.~~ In general, PK parameters determined from radioactivity and sugammadex plasma concentrations were very similar. Any adverse events were of mild-to-moderate intensity, and judged unrelated to sugammadex. These findings demonstrate that sugammadex is cleared rapidly, almost exclusively via the kidney, with minimal or no metabolism.

Key words: Sugammadex; Org 25969; pharmacokinetics [metabolism](#); gamma-cyclodextrin

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Introduction

The modified γ -cyclodextrin, sugammadex, was specifically designed to encapsulate the steroidal neuromuscular blocking agent rocuronium, with structural similarities meaning that it will also encapsulate vecuronium [1,2], and has the ability to rapidly reverse both moderate and deep rocuronium- or vecuronium-induced neuromuscular blockade [3–6]. Sugammadex is approved in various countries for the reversal of rocuronium- or vecuronium-induced neuromuscular blockade in adults at a recommended dose range of 2–16 mg/kg, depending on the level of blockade at the time of administration. It is also approved for the reversal of moderate rocuronium-induced blockade in pediatric patients at a dose of 2 mg/kg [7–9].

Previous studies evaluating the pharmacokinetic (PK) profile of sugammadex have suggested that the majority of an intravenously (i.v.) administered sugammadex dose is excreted unchanged by the kidneys [10–12]. At doses of 2, 4, and 8 mg/kg, the mean recovery of sugammadex in urine within 24 h of administration ranged from 58.8% to 80.4% of the administered dose [10]. Using higher than recommended doses of 32, 64, or 96 mg/kg, urinary recovery within 48 h of administration was ~90% of the administered dose [13]. Despite this relatively high urinary recovery of sugammadex, quantified by tandem liquid chromatography mass spectrometry (LC-MS), a minor role of metabolism in the clearance of sugammadex cannot be excluded. The use of ^{14}C -labeled sugammadex enables determination of the extent of metabolism and the relative contribution of the various routes of excretion to elimination.

The aim of the current trial was to further elucidate the extent of sugammadex metabolism and the relative contribution of various routes of excretion at a therapeutic dose of 4 mg/kg in healthy volunteers. **To achieve this,** the pharmacokinetic parameters

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3 derived from assessment of sample radioactivity were compared with those derived from
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5 a LC-MS assay.
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Materials and Methods

Study design

This was a single-center, open-label, non-randomized study of six healthy adult male subjects, conducted at PRA International (Zuidlaren, The Netherlands). A total of six subjects were selected because this number is generally considered adequate for studies evaluating the disposition of ^{14}C -labeled compounds. The study protocol was approved by an independent ethics committee (Stichting Beoordeling Ethiek Bio-Medisch Onderzoek, Assen, The Netherlands) and was conducted in compliance with the Declaration of Helsinki, the International Conference on Harmonization Guidelines, Good Clinical Practice, and current regulatory requirements.

Subjects

Subjects were eligible for inclusion in the study if they were aged between ≥ 18 years and ≤ 65 years, had normal 12-lead electrocardiogram (ECG) intervals (PR between ≥ 120 ms and ≤ 210 ms, QRS < 120 ms and QTc ≤ 450 ms), no clinically relevant ECG abnormalities and a heart rate > 50 beats per minute after 5 min rest, had a body mass index between ≥ 18 and ≤ 30 kg/m², and were in otherwise good health for their age. Major exclusion criteria were: evidence of renal or hepatic disease; a history of drug or alcohol abuse, or a positive drug or alcohol screen; smoking > 5 cigarettes/day; hepatitis B, C or HIV infection; febrile illness within 3 days before administration of sugammadex, stool production less than once every 2 days; a history of sensitivity/idiosyncrasy to chemically-related compounds or excipients which may be used in the study or to any other unspecified drug in the past; and drug therapy (excluding paracetamol) within 2 weeks (or 1 month in the case of inducers or inhibitors of drug-metabolizing enzymes) of

1
2 administration of sugammadex. All subjects were required to give written informed
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4 consent before enrollment in the study.
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9 ***Study drug administration***

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11 Each subject received a single i.v. bolus dose of ^{14}C -labeled sugammadex at a
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13 therapeutic dose level of 4 mg/kg (with 0.025 MBq/kg bodyweight of ^{14}C -radioactivity,
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15 about 1.85 MBq per subject); the radiolabel was located on each of the side chains
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17 (Figure 1). Study drug administration was performed on the morning of day 1, after an
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19 overnight fast of at least 10 h. The use of any concomitant prescription or non-
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21 prescription drug (with the exception of intermittent paracetamol) was prohibited during
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23 the entire treatment period (i.e. from sugammadex administration until follow-up).
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25 Consumption of alcohol and strenuous physical exercise were prohibited from 24 and 48
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27 h before sugammadex administration, respectively, until collection of the last PK blood
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29 sample. Subjects received a standardized meal on day 1 and were not allowed to smoke
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31 during the entire study period.
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40 ***Sample collection***

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42 Blood samples for PK evaluation and measurement of radioactivity and metabolic
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44 profiling were collected pre-dose (not for radioactivity) and at regular pre-defined
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46 intervals at 2, 5, 10, 20, and 35 min and 1, 1.5, 2.5, 4, 6, 8, 12, 18, 24, and 48 h post-
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48 dose. ~~The exceptions to this were that blood samples for radioactivity measurements~~
49
50 ~~were not collected pre-dose and samples for metabolite profiling were not collected at 2~~
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52 ~~and 5 min post-dose.~~ Urine samples were collected for PK evaluation and quantification
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54 of radioactivity and metabolite profiling at pre-dose (-12 to 0 h) and at 0-6, 6-12, 12-24,
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56 and 24-48 h post-dose; sampling for quantification of radioactivity continued until at
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58 least 48-72 h post-dose. All urine samples were diluted 1:1 volume for volume with
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3 blank human plasma to stabilize drug-related material prior to storage. Feces samples
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5 were collected for measurement of radioactivity ~~and metabolite profiling~~ pre-dose (from 3
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7 days before sugammadex administration) and at 0–12, 12–24, and 24–48 h post-dose.
8
9 Exhaled air samples were collected pre-dose and at pre-defined intervals post-dose (1,
10
11 2, 6 and 12 h) for radioactivity measurement after administration of ¹⁴C-labeled
12
13 sugammadex.
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18 All samples taken for PK evaluation ~~and~~ measurement of radioactivity ~~and metabolite~~
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20 ~~profiling~~ were stored at –20 °C.
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23 24 **Sample analysis** 25

26
27 Sugammadex concentrations in plasma and urine were determined using a validated
28
29 liquid chromatography-mass spectrometry (LC-MS) assay method after solid phase
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31 extraction (SPE). The sample volumes used for analysis were 250 µl and 100 µl for
32
33 plasma and urine, respectively. Isolute[®] 96-well SPE plates with 25 mg Isolute[®] HAX
34
35 sorbent material per well (Sopachem, Wageningen, The Netherlands) were used for
36
37 SPE of plasma and urine samples.
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43 Chromatographic separations were carried out using an HP1100 series Liquid
44
45 Chromatograph (Agilent Technologies, Palo Alto, CA). Samples were injected by a HTS
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47 PAL autosampler (CTC Analytics, Switzerland) and pumped at a flow-rate of 1.0 ml/min
48
49 through a Polaris C18-A PEEK (polyaryletheretherketone) high performance liquid
50
51 chromatography analytical column (50 mm length x 4.6 mm internal diameter, 5 µm
52
53 particle size; Varian, Inc., Palo Alto, CA) with a linear mobile phase gradient of 0.1% v/v
54
55 formic acid in water and methanol at ratios of 70:30 to 20:80. The liquid chromatography
56
57 eluate was split 1:10 before entering a Perkin-Elmer Sciex API 3000 triple-quadrupole
58
59 mass spectrometer (Sciex Thornhill, ON, Canada) equipped with a turbo ion-spray
60

1
2 interface (Applied Biosystems, Foster City, CA). The quadrupoles were operated with
3
4 unit resolution in the negative ion mode. The resulting multiple reaction monitoring
5
6 chromatograms were integrated using Analyst version 1.2 software (Sciex). The Watson
7
8 Drug Metabolism Laboratory Information Management System (version 6.3.0.03)
9
10 software (Innaphase Corporation, Wayne, PA) was used for all calculations. Calibration
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12 curves for sugammadex in both human heparin plasma and human urine were
13
14 constructed using linear weighted regression (weighting factor $1/Y^2$) and used to
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16 calculate sugammadex levels in the calibration, quality control and study samples.
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22 For radioactivity analysis, reference standards of ^{14}C -labeled sugammadex and
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24 [1-methyl- ^{14}C]-caffeine were used to prepare quality control samples. Human plasma,
25
26 urine, and feces matrices were used for the analysis of blank samples in analytical runs
27
28 and to prepare quality control samples. All scintillation counting were performed using a
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30 Packard Tri-CarbTM 3100 liquid scintillation analyzer (Downers Grove, IL) equipped with
31
32 low level counting mode (LLCM) and normal counting mode (NCM). All calculations
33
34 were performed in Microsoft Excel (Redmond, WA). Results were recorded in ng
35
36 sugammadex equivalents/ml for plasma, dpm/ml for urine, dpm/g for feces, and in dpm
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38 for exhaled air and medication (quality control) Samples were assayed as follows:
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46 *Medication (quality control) samples*

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49 Samples were assayed using an aliquot of the i.v. medication solution, transferred into a
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51 20 ml counting vial and mixed with 10 ml of the scintillation cocktail (Ultima Gold). After
52
53 20 min, the sample was counted for 10 min on NCM of the scintillation counter. The
54
55 administered radioactive dose was calculated by multiplying the mean ($n = 3$) measured
56
57 radioactivity level per g by the exact administered weight of the i.v. solution.
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2
3 *Plasma samples*
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6 Samples were assayed using a 1000 µl aliquot of the plasma sample, transferred into a
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8 20 ml counting vial and mixed with 10 ml of the scintillation cocktail (Ultima Gold). After
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10 waiting at least 30 min, samples were counted on the LLCM of the scintillation counter
11
12 until a statistical error (2 s) of 0.5% was obtained with a maximum counting time of 10
13
14 min.
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20 *Urine samples*
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23 Samples were assayed using a 1000 µl aliquot of the urine sample, transferred into a 7
24
25 ml counting vial and mixed with 5 ml of the scintillation cocktail (Ultima Gold). After
26
27 waiting at least 30 min, samples were counted until a statistical error (2s) of 0.5% was
28
29 obtained with a maximum counting time of 10 min. Samples with a ¹⁴C activity level of <
30
31 50000 dpm/ml were counted on the LCCM; samples above 50000 dpm/ml were counted
32
33 on the NCM.
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39 *Feces samples*
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42 Samples were transferred into a fitting bucket per subject and per 24 h time period and
43
44 homogenized with a minimum of water (1–2 weight equivalents). After homogenization,
45
46 two 15 g aliquots were taken for determination of total ¹⁴C-radioactivity and two 50 g
47
48 aliquots were taken for possible metabolite profiling. An aliquot of ~0.5 g of the feces
49
50 homogenate to be analyzed was then dried at 50 °C for at least 3 h and combusted for a
51
52 max of 1 min using a Packard 307 Sample Oxidizer (Perkin Elmer Life Sciences,
53
54 Groningen, The Netherlands). CarboSorb-E (7 ml) was used to absorb carbon dioxide.
55
56 At the end of the combustion cycle, the absorber was mixed with 13 ml of the scintillant
57
58 Perma Fluor E+, and samples were then placed in the liquid scintillation counter for at
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2 least 30 min before counting. Samples were counted until a statistical error (2 s) of 0.5%
3
4 was obtained with a maximum counting time of 10 min. Samples with a ^{14}C activity level
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6 of <160000 dpm/ml were counted on the LCCM; samples >160000 dpm/ml were
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8 counted on the NCM.
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11 12 13 *Exhaled air samples*

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17 Ten ml of the scintillation cocktail (Emulsifier Safe) was mixed with the CO_2 -trapped
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19 exhaled air sample to be analyzed. After at least 90 min, samples were counted on the
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21 LLCM until a statistical error (2 s) of 0.5% was obtained with a maximum counting time
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23 of 20 min.
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28 On day 3, subjects were discharged from the study center if <1% of the
29
30 radioactive dose (sum of the urine and feces) was measured in the days excreta and if
31
32 the total cumulative excretion was >90% of the radioactive dose. Subjects remained in
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34 the study center if the above criteria were not met, for a maximum of 7 further days. A
35
36 follow-up assessment was performed on day 10. Furthermore, if radioactivity exceeded
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38 50 dpm/ml in the urine and/or 75 dpm per 100 mg feces at the time of discharge,
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40 subjects were requested to bring 24-h urine samples to the clinic every 2–3 days until
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42 the radioactivity decreased to below these limits.
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48
49 PK analysis was performed by the Clinical Pharmacology and Kinetics
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51 Department of MSD (Oss, The Netherlands). Quantification of radioactivity in all
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53 matrices was performed by the Bioanalytical Laboratory of PRA International (Zuidlaren,
54
55 The Netherlands). ~~Radioactive high performance liquid chromatography (HPLC) for~~
56
57 ~~metabolite profiling and identification by mass spectrometry was performed by~~
58
59 ~~Huntingdon Life Sciences Ltd (Huntingdon, UK).~~
60

Metabolite profiling

A total of 36 plasma samples (consisting of the samples taken 20 min, 1, 1.5, 2.5, 4, and 6 h after sugammadex administration from each subject), 14 urine samples (consisting of the 0–6 and 6–12 h post-sugammadex samples from all subjects, and the 12–24 and 24–48 h post-sugammadex samples from one subject with protracted urinary excretion of sugammadex) and one sample of the original dose formulation were used for metabolite profiling.

The plasma samples taken 20 min after sugammadex administration and urine samples collected at 0–6 and 6–12 h after sugammadex administration were analyzed as individual samples. A representative plasma sample of 1–6 h post-sugammadex administration was prepared for each subject by pooling equal volume aliquots from each of the 1, 1.5, 2.5, 4, and 6 h samples. Furthermore, a representative urine sample of 6–48 h after sugammadex administration was prepared for one subject with protracted renal excretion by pooling equal percentages by volume of the 6–12, 12–24, and 24–48 h samples.

Samples were then used for metabolite profiling after partial purification by solid phase extraction by a validated HPLC method. In samples in which radioactivity was sufficiently high, radioactive components were quantified using the on-line radioactivity detector software (Laura V1.4a, Lablogic, Bioscan, Washington, DC). Where sample radioactivity levels were too low for quantification by this method, fractions of HPLC eluate/scintillator were collected at 0.5 min intervals for the full duration of the analysis using an automatic fraction collector and the radioactive concentration determined. The total radioactivity associated with each radioactive component detected was expressed as a proportion of the total radioactivity eluted. Qualitative LC-MS analysis of a 0–6 h urine sample, as well as reference standards of ^{14}C -labeled sugammadex, unlabeled

1
2 ~~sugammadex, a related cyclodextrin, and two monosulphoxides of sugammadex, was~~
3
4 ~~performed to aid metabolite identification.~~
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9 **Pharmacokinetic analysis**

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11 From the plasma concentration of sugammadex and radioactivity (expressed in mass
12
13 equivalents of sugammadex) the following non-compartmental PK parameters were
14
15 calculated: maximum plasma concentration, time to maximum plasma concentration,
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17 terminal elimination half life ($t_{1/2}$), effective $t_{1/2}$ ($t_{1/2, \text{effective}} = \log_e 2 \cdot \text{MRT}$ [mean residence
18
19 time]), area under the concentration versus time curve from time zero to infinity (AUC_{0-}
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21 ∞), total plasma clearance, and volume of distribution at steady state.
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26
27 Urine concentrations of sugammadex and radioactivity were used to calculate the
28
29 cumulative amount excreted in the urine up to the end of the last collection interval
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31 ($\text{Ae}_{\text{cum, tlast}}$) as a percentage of the total dose administered. These parameters were then
32
33 used to calculate renal clearance ($\text{CL}_R = \text{Ae}_{\text{cum, tlast}} / \text{AUC}_{0-\infty}$) and the fraction of the dose
34
35 excreted unchanged in the urine ($f_e = \text{Ae}_{\text{cum, tlast}} / \text{dose}$). Cumulative excretion was also
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37 calculated for the exhaled air and feces samples based on level of radioactivity.
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43 **Statistical Analysis**

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45 Descriptive statistics were calculated for the plasma concentrations of sugammadex and
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47 radioactivity by time point for the cumulative excretion of radioactivity and sugammadex,
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49 and for PK parameters.
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54 The PK analyses were performed using SAS version 8.2 (SAS Institute Inc., Cary,
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56 NC).
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Safety

The tolerability and safety of sugammadex were evaluated based on adverse event (AE) reporting, vital signs (including systolic and diastolic blood pressure and heart rate), ECG monitoring (12-lead ECG at screening, baseline, and 2, 35, and 60 min post dose, and follow-up), physical examination, and clinical laboratory values (hematology, blood chemistry, and urinalysis). Information on AEs and serious AEs (SAEs) was obtained from regular questioning of the subjects or on clinical examination. AEs were categorized according to their severity and relation to the study drug and were coded using MedDRA (version 8.1; MedDRA Maintenance and Support Services Organization, Chantilly). Safety data were evaluated for the all-subjects-treated (AST) group.

Results

Enrollment and subject baseline characteristics

All six subjects who entered the study received the study medication and were evaluable for PK assessment. All six subjects were healthy Caucasian males with a mean (standard deviation [SD]) age of 52.8 (16.3) years, a mean (SD) weight of 75.8 (9.9) kg and a mean (SD) BMI of 23.8 (1.9) kg/m².

Safety and tolerability

Each of the subjects experienced one or more AEs, all of which were of mild or moderate intensity and resolved without sequelae. There were no SAEs or discontinuations because of AEs and none of the AEs were considered by the investigator to be related to sugammadex. The most frequent AEs were abnormally frequent urination ($n = 3$) and headache ($n = 2$). No clinically significant abnormalities in ECG findings, vital signs, or clinical laboratory results were reported.

Pharmacokinetic profile

Excretion of sugammadex was rapid, with ~70% (mean [range] of 73 [27–92]%) of the radioactive dose excreted within 6 h, 92 (81–102)% within 24 h, and 95 (83–105)% within 48 h. The median mean total cumulative excretion of sugammadex, as analyzed both by total ¹⁴C-radioactivity and LC-MS, is presented in Figure 2. At 48 h the mean (range) total cumulative amount of sugammadex (quantified by LC-MS) recovered in the urine during 48 h was 91 (85–94)% of the dose (Table 1). So, on average, 95% of the radioactivity detected in the urine could be attributed to sugammadex, as analyzed by LC-MS, suggesting there was very limited, if any, metabolism of sugammadex.

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3 Moreover, the cumulative amount of radioactivity excreted in either feces or exhaled air
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5 was <0.02% in all patients.
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9 In plasma, sugammadex measured by LC-MS, accounted for 100% of the total
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11 ^{14}C -radioactivity, illustrated by the overlapping concentration curves (Figure 3). This
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13 suggests that there were either no radiolabeled metabolites of sugammadex in the
14
15 plasma or that they were present at extremely low concentrations. Generally, the PK
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17 parameters determined from radioactivity and sugammadex plasma concentrations were
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19 very similar (Table 1). The small difference in $t_{1/2}$ between these two methods of
20
21 detection can be explained by the lower limit of quantification of the radioactivity
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23 measurements versus the LC-MS method of detection, resulting in a later time interval
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25 for determination of the $t_{1/2}$. In accordance with the similar plasma concentrations
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27 observed (Figure 3), comparison of the $\text{AUC}_{0-\infty}$ of ^{14}C and sugammadex revealed that
28
29 on average 100% of the radioactivity in the plasma could be attributed to sugammadex.
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36 ***Metabolite profiling***

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38 ~~Metabolite profiling of plasma and urine samples revealed the presence of up to nine~~
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40 ~~radioactive peaks (designated M1–M9) (Figure 4A–D). The amount of radioactivity in the~~
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42 ~~feces samples was too low (<0.02% cumulative radioactivity) to allow metabolite~~
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44 ~~profiling. Most radioactivity in all plasma and urine samples was associated with M8 (co-~~
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46 ~~eluting with sugammadex and identified by mass spectrometry) and most of the~~
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48 ~~remaining radioactivity was associated with M6 and M7 (collectively associated with 14~~
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50 ~~to 28% of radioactivity in plasma samples, 8 to 12% of radioactivity in 0–6 h urine~~
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52 ~~samples and 23 to 30% in ≥ 6 h urine samples [Tables 2A and B]). Peaks M6 and M7~~
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54 ~~were consistent with two of the reference standards, both monosulphoxides of~~
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56 ~~sugammadex, as determined by LC-MS. Peaks M3, M4, and M5 each accounted for~~
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3 <4% of radioactivity and M9 accounted for <3% of radioactivity. M1 and M2 were mostly
4 associated with <1% and occasionally 4% of radioactivity, and were present in only
5 some of the samples. In the sugammadex dose formulation, four peaks were observed
6 (Figure 4E): a major peak representing 94% of the radioactivity and consistent with ¹⁴C-
7 sugammadex, and three minor peaks, two of which were consistent with reference
8 standards (and peaks M6 and M7 in the plasma and urine samples), and accounting for
9 1.1 and 1.6% of total radioactivity, respectively. The fourth peak accounted for 2% of
10 radioactivity, did not co-elute with any reference standards, but was consistent with peak
11 M9 observed in the patient samples and was also present in a similar proportion to that
12 observed in patient samples. Therefore M9 can be excluded as a metabolite, and most
13 likely this peak relates to a minor impurity in the ¹⁴C-sugammadex dose formulation. Org
14 48302 (substituted with one hydroxyl group on one of the eight glucosyl units instead of
15 the thiopropionate group) did not co-elute with any of the radioactive peaks (data not
16 shown), indicating that this related γ -cyclodextrin is not a metabolite of sugammadex.
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Discussion

This study aimed to determine the pharmacokinetics and excretion profile of ^{14}C -sugammadex and compare them with sugammadex concentrations as determined by LC-MS analysis. Radiolabeled sugammadex was excreted rapidly and almost exclusively via the kidneys. Total ^{14}C detection mirrored the concentrations determined by LC-MS both in the plasma and also in urine (Figures 2 and 3). Furthermore, in the urine collected over 48 h following dosing, the mean cumulative amount of sugammadex quantified by LC-MS in the urine was 91% of the dose. Moreover, 95% of the radioactivity detected in the urine was attributed to sugammadex. This suggests that there was minimal to no metabolism of sugammadex, which is consistent with the findings of previous studies evaluating sugammadex in surgical patients and healthy volunteers [10–13]. Less than 0.02% of the dose was excreted by in exhaled air and feces, suggesting that in man these routes of excretion play no role in the clearance of sugammadex. Interestingly, in rat and dog, a minor role for excretion in feces is observed with 4.22–6.82% and 0.33–0.80%, respectively, of the dose collected in the feces. For ^{14}C α -cyclodextrin and ^{14}C γ -cyclodextrin given i.v. to rat [14,15] excretion into the feces has also been demonstrated to be a minor route of excretion (3–8% of the dose); however, as shown in the current study, this route is not applicable for sugammadex in man.

In this trial, the mean total cumulative amount of radioactivity recovered in the urine during 48 h was 95 (range 83–105) %, suggesting that at the most only a small fraction of the radioactivity was unaccounted for. There may be many causes of incomplete recovery of the radiolabel in mass balance trials (such as technical limitations and tissue retention), and it is actually rare for the mass balance in radiolabeled excretion studies to truly achieve 100% recovery [16].

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3 Subsequent metabolite profiling, performed on plasma and urine samples (stored
4 at -20°C) approximately 8 months after the LC-MS analysis, visualized up to nine
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6 radioactive peaks in high performance liquid radiochromatograms of urine and plasma
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8 samples from the subjects involved in this trial. Three of these peaks also eluted when a
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10 sample of dose formulation underwent high performance liquid radiochromatography,
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12 but the radioactivity associated with two of these peaks, consistent with
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14 monosulphoxides of sugammadex, was found at considerably lower concentrations than
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16 in the patient samples. Although formation of these monosulphoxides by metabolism *in*
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18 *vivo* up to a few percent cannot be formally excluded, the presence of additional peaks
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20 in these samples is most likely the result of selective oxidation of the radiolabeled
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22 sugammadex in the plasma and urine samples during storage or sample work-up.
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24 Further evidence for this comes from the lower amount of ^{14}C radioactivity eluted in the
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26 M8 sugammadex peak corresponding with unchanged sugammadex during the high
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28 performance liquid radiochromatography compared with LC-MS analysis. The selective
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30 oxidation of ^{14}C sugammadex has also been noted when rat plasma was spiked with the
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32 radiolabel; the radiochemical purity of [^{14}C] sugammadex appeared to decrease from
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34 $\geq 99\%$ to $\geq 84\%$ during a 3 h incubation at 37°C , although unlabeled sugammadex is
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36 fully stable under these conditions. It is well known that in particular sulphur in ^{14}C -
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38 labeled compounds is very sensitive to radio-oxidation. The minimal role of metabolism
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40 in the clearance of sugammadex is fully in line with the excretion profile of other
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42 cyclodextrins, which has been noted to be almost entirely renal [14,15,17,18],
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44 particularly in man. Subsequent profiling for metabolites in urine and plasma samples
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46 demonstrated that the major part of total radioactivity could be attributed to the parent
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48 compound, sugammadex (data on file).
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3 Studies in volunteers and surgical patients receiving sugammadex to reverse
4 rocuronium- or vecuronium-induced blockade have also demonstrated that the
5 predominant route of elimination for the complex is via the renal route, and in the
6 presence of sugammadex, the major route of elimination of rocuronium changes from
7 the hepatic to the renal route [10–12]. Based on data from surgical patients and healthy
8 volunteers, the cumulative excretion of rocuronium in the urine over 24 h is in the region
9 of 12–26% and increases to up to 74% after administration of sugammadex 4–8 mg/kg
10 [10–12,19–21]. Given the importance of renal elimination, the efficacy and safety of
11 sugammadex has been assessed in patients with impaired renal clearance, most of
12 whom were receiving dialysis. The available data suggest that sugammadex is well
13 tolerated and effective in patients with severe renal impairment, albeit with reduced
14 plasma clearance of sugammadex and a significantly prolonged terminal elimination half
15 life and MRT [22,23]. However, despite longer retention of the sugammadex-rocuronium
16 complex, no signs of recurarization were reported among renal patients in the 48 h after
17 administration of rocuronium followed by sugammadex [22]. Currently, for patients with
18 mild-to-moderate renal impairment (creatinine clearance ≥ 30 and < 80 ml/min), the dose
19 recommendations for sugammadex are the same as for other adult patients i.e. a single
20 i.v. bolus dose of 2–16 mg/kg [8]. For patients with severe renal impairment (creatinine
21 clearance < 30 ml/min), including patients requiring dialysis, sugammadex is not
22 recommended at present. However, further safety and PK studies are ongoing in this
23 patient population.
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53 Sugammadex 4 mg/kg (containing 0.025 MBq/kg of ^{14}C -radioactivity) was well
54 tolerated in all six healthy male subjects in this study. There were no drug-related AEs
55 and no clinically significant abnormalities, changes, or trends were found with respect to
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2 safety laboratory data, vital signs, or ECGs, further adding to the safety profile of
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5 sugammadex that has been generated to date.
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For Peer Review

Conclusion

In conclusion, this study in healthy volunteers shows an i.v. dose of sugammadex to be cleared rapidly and almost exclusively via the kidneys, with minimal fecal excretion and minimal to no metabolism, as determined by LC-MS analysis. The mean total recovery of radiolabel from all routes in 48 h at the dose of 4 mg/kg was 95%. Pharmacokinetic parameters were similar whether calculated from total ^{14}C radioactivity assessments or by LC-MS estimation of sugammadex concentrations. ~~The formation of the monosulphoxide related γ -cyclodextrins is due to selective post-sampling oxidation of the ^{14}C -sugammadex radiolabel and metabolism plays no significant role in the clearance of sugammadex.~~

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Conflict of interest

Pierre Peeters, Alex Zwiers, Marcel de Zwart, Saskia van de Wetering-Krebbbers, Marlou van Iersel, and Diels van den Dobbelssteen are employees of MSD (Oss, The Netherlands). Paul Passier and Jean Smeets were previously employees of MSD (Oss, The Netherlands).

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Table 1. Pharmacokinetic parameters based on ^{14}C -radioactivity detection and sugammadex concentrations determined by LC-MS ($n = 6$ subjects)

	^{14}C (expressed as sugammadex mass equivalents)		Sugammadex (LC-MS)	
	Geometric mean	Geometric CV (%)	Geometric mean	Geometric CV (%)
Urine				
CL_R (ml/min)	92.7	29	88.3	25
fraction excreted unchanged (% dose; last collection interval) ^a	96.1	85–106	91.1	85–94
Plasma				
C_{max} ($\mu\text{g/ml}$)	33.0	22	32.2	19
t_{max} (min) ^b	4	2–5	5	2–10
$t_{1/2}$ (min)	190	20	152	31
$t_{1/2 \text{ effective}}$ (min)	110	16	100	19
$\text{AUC}_{0-\infty}$ ($\mu\text{g}\cdot\text{min/ml}$)	2632	25	2629	23
CL (ml/min)	96.8	25	96.9	24
V_{SS} (ml)	15360	19	14027	19

^aData presented as arithmetic mean and range; samples were taken until 48 h after dosing for measurement of sugammadex (LC-MS) in urine, and until 332 h after dosing for measurement of ^{14}C in urine

^bData presented as median and range

$\text{AUC}_{0-\infty}$, area-under-the-plasma concentration-time curve to time infinity; C_{max} , maximum plasma concentration; CL, plasma clearance; CL_R , renal clearance; CV, coefficient of variation; LC-MS, liquid chromatography-mass spectrometry; $t_{1/2}$, terminal half-life; $t_{1/2 \text{ effective}}$, effective half-life; t_{max} , time to C_{max} ; V_{SS} , volume of distribution at steady state.