



PERGAMON



The Pharmacokinetics and Metabolism of Sucralose in the Rabbit

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Abstract—The excretion and metabolism of ^{14}C -sucralose has been investigated in non-pregnant and pregnant rabbits after administration of single 10 mg/kg oral doses. Means of 22% and 55% of the dose were excreted in urine and faeces, respectively, by non-pregnant animals during 5 days. Excretion was similar in pregnant animals with means of 22% and 65% of the dose in urine and faeces, respectively, during the same time. Following a single oral dose, a mean of approximately 7% of the dose was still being excreted during the 96–120-hr collection period. Only one major radioactive component was detected in urine samples which corresponded to unchanged sucralose. © 2000 Elsevier Science Ltd. All rights reserved

Keywords: sucralose; metabolism; artificial sweetener; pharmacokinetics; rabbit.

Abbreviation: TLC = thin-layer chromatography.

INTRODUCTION

This paper is concerned with the investigations into the metabolism and pharmacokinetics of sucralose in rabbits. Information derived from this study is helpful in the evaluation of results from toxicology studies of sucralose and in extrapolation of the animal data to man. The rabbit has been used in teratology studies with sucralose and this study was designed to investigate the extent of absorption of an oral dose of sucralose in pregnant and non-pregnant rabbits and the structure of the excreted compounds.

MATERIALS AND METHODS

Materials

[U- ^{14}C]sucralose (batch no. CFQ 4360; sp. act. 27 mCi/mmol, radiochemical purity >99% by HPLC) was obtained from Amersham International plc (UK). Non-radioactive sucralose (batch no. KL/5/31) was supplied by Tate & Lyle Group Research & Development (Whiteknights, Reading, Berks, UK). All other chemicals and reagents were of analytical grade and were obtained from commercial sources.

Animals

Three non-pregnant and three pregnant New Zealand White rabbits, aged about 3 months and body weight 3–4 kg, were obtained from Interfauna Ltd (Huntingdon, UK). Pregnant rabbits were esti-

mated to be 16 days pregnant on the day of dosing. All animals received SQC Standard Rabbit Diet (Special Diet Services Ltd, Witham, UK) and water ad lib. throughout the study.

Dosing and sample collection

Oral doses (nominal 10 mg/kg body weight) of ^{14}C -sucralose were administered by syringe as a solution in distilled water (15–20 ml). The doses were washed in with distilled water (5 ml). The specific activity of the dosed material was 1.16 (Ci/mg, and each animal received doses of 32–45 μCi ^{14}C -sucralose. After dosing, animals were housed singly in stainless-steel cages with suspended wire-mesh floors to facilitate the separate collection of urine and faeces. Animals were acclimatized to the metabolism cages for 3 days prior to dosing. After dosing, urine was collected into containers cooled in dry ice at 0–6, 6–24 and then at 24-hr intervals during 5 days. Faeces were collected at 24-hr intervals throughout. Cages were rinsed with water at 24-hr intervals to remove residual urine. All samples were stored at about -20°C until analysed.

Measurement of radioactivity

Radioactivity in all samples was measured by liquid scintillation analysis using a Philips PW 4700 or a LKB Wallac 1219 RackBeta automatic liquid scintillation counter. Details of sample preparation and measurement are given in the previous paper (Wood *et al.*, 2000).

Table 1. Mean rate of excretion of radioactivity by rabbits after oral administration of ^{14}C -sucralose expressed as percentage administered dose

Sample collection (hr)	Non-pregnant animals (n = 3)	Pregnant animals (n = 3)
Urine	% Excretion	% Excretion
0–24	8.3 ± 3.6	8.6 ± 1.7
24–48	5.4 ± 1.2	5.2 ± 1.2
48–72	4.1 ± 0.3	3.4 ± 2.0
72–96	2.6 ± 0.2	2.5 ± 1.4
96–120	2.0 ± 0.4	1.7 ± 1.2
Total urine	22.3 ± 4.0	21.5 ± 4.9
Faeces		
0–24	16.8 ± 5.1	27.8 ± 7.4
24–48	15.0 ± 3.9	15.2 ± 6.8
48–72	9.6 ± 1.3	10.8 ± 1.5
72–96	8.1 ± 1.0	7.1 ± 2.0
96–120	5.3 ± 1.3	4.2 ± 1.6
Total faeces	54.7 ± 7.5	65.2 ± 11.0
Cagewash/debris	3.4*	0.4 ± 0.1
Total recovery	80.5 ± 5.0	87.0 ± 6.0

*Includes 9.0% in cage debris from one animal.

Investigation of metabolites

Analysis of samples was performed by thin-layer chromatography (TLC) using silica gel plates of layer thickness 0.25 mm (E. Merck A.G., Darmstadt, Germany). The developing solvents were ethyl acetate–methanol–water–ammonia (sp. gr. 0.88) 60:20:10:2 (by vol.) and ethyl acetate–methanol–water 6:2:1 (by vol.). Aliquots of urine samples (25 μl) were applied directly to the TLC plates. A reference standard of ^{14}C -sucralose added to control urine was chromatographed simultaneously on each TLC plate. Radioactivity on chromatograms was detected and quantified by a Berthold LB 2832 or LB 2842 Automatic TLC-Linear Analyser.

RESULTS AND DISCUSSION

After administration of single oral doses of ^{14}C -sucralose to rabbits, excretion of radioactivity was prolonged in both urine and faeces (Table 1). For non-pregnant animals, means of 22.3% and 54.7% were excreted in urine and faeces, respectively, during 5 days, and about 8% and 17%, respect-

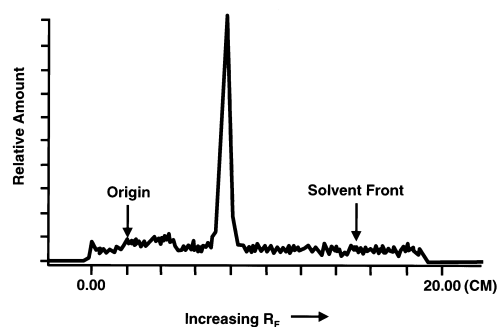


Fig. 1. Thin-layer radiochromatogram of 24–48-hr urine from a female rabbit after oral administration of ^{14}C -sucralose developed in solvent system ethyl acetate–methanol–water–ammonia (60:20:10:2, by vol).

ively, during the first 24 hr. The excretion pattern was very similar in pregnant animals, with 21.5% and 65.2% of the dose being excreted in urine and faeces, respectively, during 5 days, and about 9% and 28%, respectively, during the first 24 hr. During 96–120 hr, means of about 2% and 4–5% of the dose were excreted in urine and faeces, respectively, indicating that excretion of the dose was incomplete at this time. This was confirmed by the total recoveries of radioactivity which were 81% and 87% in non-pregnant and pregnant animals, respectively. It is not known with certainty why the rabbit demonstrates prolonged excretion and lower total recovery of radioactivity, per unit time, compared with the other species tested (John *et al.*, 2000; Roberts *et al.*, 2000; Sims *et al.*, 2000; Wood *et al.*, 2000). However, the results could be influenced by the coprophagic behaviour of the rabbit. Coprophagy is extensive in the rabbit, even when housed in wire mesh cages, with 30–80% of the total daily faecal excreta being ingested (Hunt and Harrington, 1974). This would amount to oral recycling of faecally excreted material with partial absorption and urinary excretion of each portion of reingested material. Based on the urine excretion, at least 20% of the oral dose was absorbed. Radioactivity in faeces may be derived from non-absorbed material, but there may be a contribution from material excreted in the bile and/or secreted

Table 2. Amounts of sucralose in urine of rabbits after oral administration expressed as percentage administered dose

Time interval (hr)	Non-pregnant animals			Pregnant animals		
	1	2	3	4	5	6
0–24	7.5	5.8	1.7	6.4	4.1	5.4
24–48	5.1	3.4	3.8	3.5	5.4	3.6
48–72	3.5	2.9	3.0	2.5	4.8	1.4
72–96	2.3	2.2	1.7	1.6	3.5	IR
96–120	1.9	1.1	1.6	1.1	2.6	IR
Total 0–120	20.3	15.4	11.8	15.1	20.4	10.4

IR = insufficient radioactivity in sample for accurate determination.

into the gastrointestinal tract. Biliary excretion and enterohepatic circulation could also account for the prolonged excretion of material in urine and faeces.

TLC of urine samples showed the presence of only one major radioactive component which corresponded to unchanged sucralose (Fig. 1, Table 2). The remainder of the radioactivity appeared to be associated with material more polar than sucralose which was undifferentiated by the TLC linear analyzer.

With the notable difference of a relatively prolonged excretion phase compared with the other species tested, the excretory pattern of an oral dose of ^{14}C -sucralose in the rabbit was comparable with other species. In the rabbit an oral dose of ^{14}C -sucralose was mainly excreted in the faeces, with approximately 20% excreted in the urine. The metabolic fate of sucralose in the rabbit also appears to be similar to other species tested. The major portion of an oral dose was excreted as unchanged sucralose, with the remainder generally associated with radioactivity of a more polar nature. In the rabbit this more polar material could not be differentiated

by the TLC linear analyzer into discrete components, such as M1, M2 or M3, as noted in other species.

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