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Metabolism
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Extent and Route of Excretion of Total Carbon-14 in Pregnant Rats
After a Single Oral Dose of Ammonium ¹⁴C-Perfluorooctanoate

June 30, 1983

Conducted At:

Riker Laboratories, Inc.
Subsidiary of 3M
St. Paul, Minnesota 55144

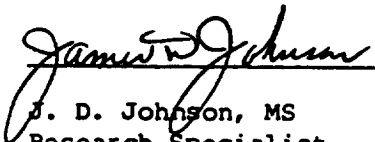
During:

May to June 1981

Conducted by:

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Drug Metabolism

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Summary

Hormonal changes during pregnancy do not appear to cause a change in the rate of elimination of carbon-14 after oral administration of a single dose of ammonium ^{14}C -perfluorooctanoate (mean dose, 15 mg/kg). At 8 or 9 days after conception, four pregnant rats and 2 nonpregnant female rats were dosed and individual urine samples were collected at 12, 24, 36, and 48 hours postdose and analyzed for carbon-14 content. Essentially all of the carbon-14 was eliminated via urine within 24 hours for both groups of rats. These data are consistent with previously reported data for nonpregnant rats. Thus, there is not likely to be any accumulation of ^{14}C -perfluorooctanoate in tissues of pregnant rats during repeated dosing in teratology studies.

Introduction

In a previous study (1) and in published work (2), it has been reported that female rats excrete essentially all of a dose of ^{14}C -perfluorooctanoate within 24 hours after intravenous administration. During the same time period, male rats excrete only 20% of the dose; male rats excrete 83% of the dose via urine by 36 days postdose. A similar gender difference has been reported for rats dosed with 1-aminocyclohexane carboxylic acid (ACHC); ACHC is excreted in urine about ten times faster for female rats than for male rats (3). The gender difference in elimination of ACHC is strongly influenced by hormone treatment; the rates of excretion between the sexes can be reversed by castration and treatment with estrogens (male rats) and by ovariectomy and treatment with testosterone (female rats). The effects of castration, ovariectomy, pregnancy, or treatment with sex hormones on perfluorooctanoate elimination are not known. If there were a shift from fairly rapid elimination to slow elimination during pregnancy as a result of a change in hormone state, the change in metabolism could have a bearing on teratology studies in rats. To provide data relevant to teratologic assessment with ammonium ^{14}C -perfluorooctanoate pregnant rats were dosed with a single oral dose of ammonium ^{14}C -perfluorooctanoate and the rate of elimination of carbon-14 in urine was measured.

Methods

Ammonium ^{14}C -Perfluorooctanoate

The carbon-14 label is at the carbonyl carbon. The specific activity of this lot of ammonium ^{14}C -perfluorooctanoate is 0.51 $\mu\text{Ci/mg}$. Details of specific activity, chemical characterization, and radiochemical purity have been reported separately (4); the material was found to be suitable for metabolism studies.

Animals

Six female Charles River^a rats were bred at 8 or 9 days prior to dosing. The body weights ranged from 217-265 g, (mean, 238 g). The rats were conditioned to individual metabolism cages^b for 24 hours prior to dosing. The rats were allowed free access to Purina^b ground chow and water before and after dosing.

Dosing Solution

The dosing solution was prepared by dissolving ammonium ¹⁴C-perfluorooctanoate in 0.9% aqueous sodium chloride. The dosing solution was analyzed radiometrically and found to contain 1.82 µCi/2.0 ml or 3.58 mg/2.0 ml.

Dosing

The dosing solution was administered intragastrically to each rat with a steel intubation tube fixed to a 3 ml plastic syringe (Monoject^c). Each rat received 2.0 ml of solution; the mean dose was 15 mg/kg.

Sample Collection

Urine samples were collected for each rat from 0-12, 12-24, 24-36, and 36-48 hours postdose. Rats were killed at 8 days and necropsied to determine pregnancy. Liver, lung, kidney, and blood were collected from each rat. Plasma and red blood cells were prepared by centrifugation and the tissue and plasma samples were stored frozen.

Sample Analysis

Duplicate 1.0 ml aliquots of urine were counted in Aquasol[®] in a liquid scintillation spectrometer. Counting efficiency was determined for each sample by adding a known amount of internal standard and recounting. Only urine samples were measured.

Results and Discussion

Of the six rats dosed with ammonium ¹⁴C-perfluorooctanoate, two were found not to be pregnant. The results of the urine analysis from the four pregnant rats and the two nonpregnant rats are shown in Table 1. The urine data are expressed as percent of the total carbon-14 in urine. In terms of dose, these totals are 104-113% (mean, 109%). At 24 hours there does not appear to be any difference in the cumulative amount of carbon-14 eliminated via urine by pregnant rats as compared to the amount eliminated by nonpregnant female rats. Thus, the gender difference in rate and extent of elimination of ¹⁴C-perfluorooctanoate in rats (1,2) is not affected by pregnancy at 8 or 9 days after conception. In addition, since no radioactivity was detected in tissues of nonpregnant rats at 17 days after a single 17 mg/kg dose (1), there is not likely to be any accumulation of perfluorooctanoate in plasma and tissues of pregnant rats during repeated dosing in teratology studies.

^aCharles River Breeding Laboratories, Wilmington, Massachusetts.

^bPurina Lab Chow, Ralston Purina Company, St. Louis, Missouri.

^cSherwood Medical Industries, Inc., Deland, Florida

References

- (1) Johnson JD: Extent and Route of Excretion and Tissue Distribution of Total Carbon-14 in Male and Female Rats after a Single IV Dose of FC-143-¹⁴C (Report) January 30, 1980.
- (2) Hanhijarvi H, Ophaug RH, and Singer L: The Sex-Related Difference in Perfluorooctanoate Excretion in the Rat. Proc. Soc. Exp. Biol. Me 171:50-55, 1982.
- (3) Janssen FW, Young EM, and Ruelius HW: Effect of Sex Hormones on the Disposition in Rats of 1-aminocyclohexane Carboxylic Acid, a Metabolite of a Semisynthetic Penicillin. Drug Metab. Disp., 4:540-546, 1976.
- (4) Behr FE, ¹⁴C and Johnson JD: Synthesis and Characterization of FC-143-¹⁴C (Report) December 28, 1979.

Table 1

Carbon-14 Content of Urine of Pregnant and Nonpregnant Female Rats
after a Single Oral Dose of Ammonium ¹⁴C-Perfluorooctanoate
(Mean Dose, 15 mg/kg)

Time Interval (hours)	Rat Identification Number							
	Pregnant Rats					Nonpregnant Rats		
	2	4	5	7	$\bar{X}$	1	6	$\bar{X}$
0-12	92.9 ^a	88.6	92.0	93.5	91.8	87.0	69.2	78.1
12-24	6.8	10.5	6.7	5.2	7.3	12.2	29.6	20.9
24-36	0.2	0.7	0.9	0.8	0.7	0.4	1.0	0.7
36-48	0.1	0.3	0.5	0.5	0.4	0.4	0.3	0.4

^aData are expressed as percent of total carbon-14 eliminated within 48 hours. (The mean percent of dose eliminated via urine was 109.7% $\pm$ 3.2).

Distribution List

M. T. Case	218-3S-03
S. F. Chang	270-3S-05
G. J. Conard	270-3S-05
H. E. Freier	201-1S-07
F. D. Griffith	220-2E-02
D. F. Hagen	201-1W-29
L. I. Harrison	270-3S-05
J. D. Johnson	270-3S-05
E. G. Lamprecht	270-3S-06
J. D. Lazerte	236-1B-21
W. C. McCormick	220-2E-02
R. L. McQuinn	270-3S-05
R. A. Nelson/T.C. Coyne	270-3A-01
R. E. Ober	270-3S-05
W. H. Pearlson	223-6S-04
R. A. Prokop	236-2B-01
F. Ubel/D. Roach	220-2E-02
C. E. Weeks	270-3S-05
DM Central Files	270-3S-05
Technical Communications	201-2CN-12

