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Metabolism of Deltamethrin in Rats

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Objective To study the metabolism of ^{14}C-deltamethrin in rats. **Methods** Rats were dosed orally and i.p. with a single dose of ^{14}C-deltamethrin (0.64 mg/Kg) body weight. The required dose was applied daily for 3 days. At the end of the experiment, selected organs, such as liver, kidney, fat, intestine, and blood were excised for radioassay of ^{14}C-content. **Results** Deltamethrin was almost eliminated from the body within 1-3 days. The main portion of ^{14}C-residues was extracted from urine (38%, 32%) and feces (20%, 24%) with a little amount remained in various organs. **Conclusion** The elimination and distribution of ^{14}C-radioactivity in rats treated orally and intraperitoneally signify that deltamethrin is bioavailable in urine and feces.

Key words: Pyrethroid insecticide ^{14}C-deltamethrin; Oral and intraperitoneally treatment; Bioavailability

INTRODUCTION

Over the last few decades the use of synthetic pyrethroids has increased rapidly because of their greater photostability and enhanced insecticidal activity[1]. These compounds have improved physical and chemical properties and biological activity compared to their natural analogue pyrethrins[2]. Synthetic pyrethroids are the new generation of pesticides that are being developed as good substitutes for unwarranted organochlorine and toxic organophosphorus insecticides[3].

Pyrethroids are a group of highly potent lipophilic insecticides with relatively low mammalian toxicity[4] and one of the least acutely toxic insecticides to mammals because they are quickly deactivated by metabolic processes[5]. They are widely used in agriculture, forestry, horticulture, public health, and households throughout the world[6-7]. They have been heavily used in the pest and remain one of the main insecticides available against insect-pest of field crops[8-12].

One of the important members of this family is the pyrethroid insecticide, deltamethrin [(s)-α-cyano-3-phenoxybenzyl-(1R, 3R)-cis-3-(2,2-dibromovinyl)-2, 2-dimethyl cyclopropane carboxylate 1] which is also known by other names e.g., Decamethrin, Decis, RU-22974, NRDC-161, OMS-198, and K-orthin[3]. Because deltamethrin has a broad spectrum of insecticidal activity and relatively low mammalian toxicity, this compound is widely used for field-treatment of crops and the control of endo- and ecto-parasites on animals[13]. This chemical is relatively susceptible to biotransformation and excretion in mammals compared to organochlorinated and organophosphate compounds[14-15].

The present study was focused on the distribution and metabolic fate of ^{14}C-deltamethrin when administered orally and intraperitoneally to male rats.

MATERIAL AND METHODS

Reagents

Preparation of deltamethrin (I) Deltamethrin was synthesized, according to known method[16]. The specific activity of ^{14}C-deltamethrin is (695.6MBq) 18.8mCi/mmol and a radiometric purity of 98%.

Metabolism

Treatment of rats and collection of samples Adult Wister male rats weighing approximately 140-160 g were housed in metabolism cages (one animal/cage) that permitted

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the separate collection of expired air, urine and feces. All rats were kept under controlled temperature (22±1℃) and humidity (60%±5%). Rats were conditioned for 48 hours to a daily diet of standard chow and drinking water.

Rats were dosed orally using a stomach tube, and intraperitoneally (i.p.) with a single dose of ^{14}C-deltamethrin (0.64 mg/ Kg) body weight. For oral and i.p. treatment, the required dose was dissolved in 1mL pure dimethyl sulphoxide and applied daily for 3 days. Three rats were used in each treatment group. At the end of the experiment, the animals were sacrificed by decapitation. Selected organs, such as liver, kidney, fat, intestine, and blood were excised, weighed and frozen for radioassay of ^{14}C-content. The respiratory carbon dioxide was trapped in 10% potassium hydroxide solution. The expired air, urine and feces were collected daily after the start of treatment, and collection was continued until the end of the experiment.

Analysis of ^{14}C-residues in feces and urine The feces of rats were extracted for 8 hours with methanol until further extraction did not result in any extractable ^{14}C. The methanol extract was evaporated to a small volume, an aliquot was radioassayed for ^{14}C-content, and the remaining portion was analyzed by thin layer chromatography (TLC). The insoluble feces material containing only bound ^{14}C-residues was air-dried and combusted to $^{14}CO_2$ for bound ^{14}C-residues.

An aliquot of urine was radioassayed by scintillation counting. The remaining portion was brought to just dryness under a stream of air and analyzed by TLC on silica gel plates using the following elution systems[17]:

System A: n-hexane-ether (4:1, v/v);
System B: benzene-chloroform (1:1, v/v);
System C: Pet.Ether$_{40\text{-}60}$ – ethyl acetate (5:1, v/v).

Determination of radioactivity Potassium hydroxide, urine and solvent extracts (1 mL) were assayed using liquid scintillation counting (LSC) in a Packard Model 3320 scintillation spectrometer. Solids such as feces and animal tissues were assayed by combustion of a known weight (50-100 mg) in a Harvey biological oxidizer (OX-600), followed by (LSC). The internal standard technique was used for quench correction.

RESULTS

Metabolism of Deltamethrin in Rats

The elimination and distribution of ^{14}C-radioactivity in rats treated orally and intraperitoneally with a dose of 0.63 mg/kg body weight ^{14}C-deltamethrin in expired air, urine, and feces are shown in Table 1. The obtained urinary and biliary excretion of the radioactivity from animals treated with radio-labelled compound signified that the compound was bioavailable.

TABLE 1

Elimination and Distribution of ^{14}C-deltamethrin Residues in Rats after Oral and i.p. Treatment for 3 Days

Sample Analyzed		Time (Day)	A*		B*	
			μg	%	μg	%
CO_2		0-1	10.8	1.8	9	1.5
		1-2	7.2	1.2	6	1.0
		2-3	1.8	0.3	1.2	0.2
Urine		0-1	116.4	19.4	96	16
		1-2	61.2	10.2	49.8	8.3
		2-3	48.0	8.0	45.0	7.5
Feces	Methanol Extracted	0-1	44.4	7.4	3.9	6.5
		1-2	33.6	5.6	17.4	2.9
		2-3	23.4	3.9	19.8	3.3
	Unextractable	0-1	21.6	3.6	12.6	3.0
		1-2	13.8	2.3	9.6	1.6
		2-3	19.8	3.3	18	2.1

Note. A= Oral treatment. B= Intraperitoneal treatment. *Administered dose = (100 μg equivalent/rat/day).

After three days of treatment, a large amount of ^{14}C-residues was excreted from urine and feces. On the other hand, a very small amount of radioactivity was detected in expired air as carbon dioxide. The major part of the residues was excreted from the urine (37.5 %, 32%) after three days of treatment. While about 50% of the total radioactivity was excreted during the first day of the experiment (19 %, 16 %) in case of oral and i.p. treatment, respectively.

Extraction of the feces with methanol showed that a large amount of ^{14}C-residues was found in methanol extract (13 % and 9.4%), however a small

amount of ^{14}C-residues (5.9 % and 4.6 %) remained tightly bound in the feces. These extractable and unextractable ^{14}C-residues were obtained after the first and second days of rat treatment orally and intraperitoneally, respectively. On the third day of the experiment, about 16.9 %, 12.7 % and 9.2 %, 6.7 % of the total applied dose, were obtained as extracted and unextracted residues in the feces of rats in both treatments.

A small amount of radioactivity, not exceeding 3 %, was eliminated as carbon dioxide through expired air of rats treated either orally or intraperitonealy throughout all the time of the experiments (Table 1).

The nature of ^{14}C-residues excreted from urine and methanol extract of feces of rats after oral and intraperitoneal administration of deltamethrin was determined by thin layer chromatography (Table 2).

The major product detected in urine and feces was the unchanged deltamethrin, besides a small amount of 3-(2,2-dibromoethenyl)-2,2-dimethylcyclopropane carboxylic acid (Dibromoacid acid) and 3-phenoxybenzoic acid.

Table 3 illustrates the residual radioactivity in various organs after treatment of rats either orally or intraperitoneally with deltamethrin. Different amounts of radiocarbon were detected in all analyzed organs. Fat and liver contained the highest ^{14}C-residues (6.1 %, 4.8 %) in case of i.p. administration and (4.8 %, 3.6 %) in case of oral administration. A considerable amount of radioactivity ranged 2.3-2.9 % was also observed in the kidney, blood and brain of rats at the end of the experiments.

Figure 1 shows the cumulative excretion and distribution of radioactivity of ^{14}C-deltamethrin in expired air, urine, feces and various organs of rats treated orally and intraperitoneally after three days. Total excretion of ^{14}C-residues from the urine was 38% and 32% of the total dose administered. Similarly, the cumulative fecal excretion of radioactivity accounted for 26% and 19%. A considerable amount of ^{14}C-residues was also detected in different organs, about 22% after oral treatment and 26% after intraperitoneally treatment at the end of the experiment.

A good recovery of radioactivity, which is generally over 80% of the actual applied dose, could be achieved by the analytical procedures used.

TABLE 2

R_f and R_t Values for Deltamethrin and Its Metabolites

Compounds	R_f Values			Retention Time (R_t) (min)
	A	B	C	
Deltamethrin	0.65	0.88	0.68	9.22
Dibromoacid	0.28	0.11	0.38	5.04
3-Phenoxybenzoic Acid	0.04	0.06	0.38	2.23

Note. TLC: System A: n-hexane-ether (4:1, v/v); System B: benzene-chloroform (1:1, v/v); System C: Pet.Ether$_{40\text{-}60}$ – ethyl acetate (5:1, v/v). HPLC: System D: Aceteonitrile: Water (8:2, v/v) mobile phase; UV Detection: at 190 nm; column 10μC$_{18}$.

TABLE 3

^{14}C-Residues in Selective Tissues of Rats after Oral and i.p. Administration of ^{14}C-Deltamethrin for 72 h

Sample Analyzed (Organs)	A*		B*	
	μg	%	μg	%
Liver	21.6	3.6	28.8	4.8
Kidney	13.8	2.3	14.4	2.4
Tests	4.2	0.7	3.0	1.0
Lungs	10.8	1.8	10.2	1.7
Fat	28.8	4.8	36.6	6.1
Intestine	11.4	1.9	15.0	2.5
Spleen	3.0	0.5	10.2	1.7
Blood	17.4	2.9	13.8	2.3
Heart	6.0	1.0	3.0	1.0
Brain	13.8	2.3	16.8	2.8

**Note*. A= Oral treatment*Note*. B= Intraperitoneal treatment. *Administered dose = (100 μg equivalent/rat/day).

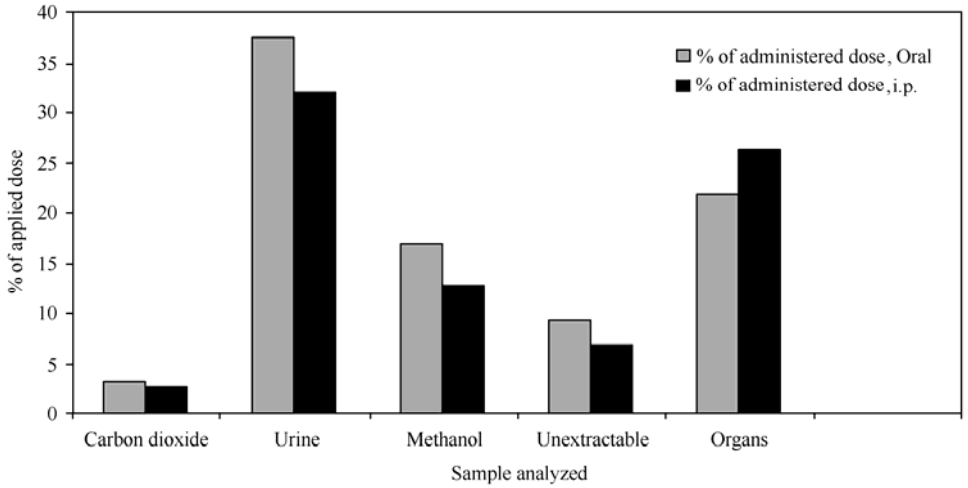

FIG. 1. Cumulative secretion of ^{14}C-residues from rats treated with ^{14}C-deltamethrin at a dose of 0.63 mg/Kg b.w. after 3 days of oral and i.p. administration in expired air, urine, feces, and various organs.

DISCUSSION

When rat treated orally and intraperitoneally with ^{14}C-deltamethrin, the radiocarbon from the insecticide is rapidly and almost completely eliminated from the body and appears in the urine, carbon dioxide, and feces with little amount in many tissue organs within three days as shown in Tables 1 and 3.

These data are in line with many other studies which reported that elimination of the pyrethroid insecticide deltamethrin in rats occurs within 2-4 days of administration and it is supported by analogy with permethrin metabolism in rats[21]. Khan *et al.*[22] suggested that when rats were fed with bound ^{14}C-residues of deltamethrin in stored wheat, most of the ^{14}C-residues excreted from urine and feces (about 90 %) in a nearly equal proportion.

It is worth to mention that pyrethroids are rapidly metabolized by a hydrolytic cleavage of the ester bond, followed by oxidation yielding the non-toxic acid metabolites[23]. These metabolites are partly conjugated and mostly eliminated renally [24-25]. As markers of absorption the pyrethroid metabolites are useful [26-27]. Deltamethrin pesticide is considered environmentally safe because it works rapidly on insect, has low solubility in water and is quickly degraded.

The two metabolites 3-(2, 2-dibromovinyl) 2, 2-cyclopropane carboxylic acid (dibromoacid) and 3-phenoxybenzaldhyde can be obtained through hydrolysis of deltamethrin by liver microsomal enzymes[28].

Although this chemical is relatively susceptible to biotransformation and execration in mammals compared to organochlorinatrd and organophosphate compounds, the presence of considerable amount of ^{14}C-residues in fat almost may be due to high lipophilicity of the insecticide.

Many studies showed that deltamethrin has a half-life of 1 to 2 days in the rat brain, but it is more persistent in body fat, with a half-life of 5 days[21, 28]. Trace amounts of radioactivity are present in kidney, liver and lung of rats fed with bound ^{14}C-residues of deltamethrin in stored wheat, liver containing the highest ^{14}C-residues[22].

It has been suggested that the highest percentage of fecal and urinary execration of ^{14}C in case of oral treatment, compared to i.p. treatment, may be due to absorption of radiocarbon from the gastrointestinal tract as shown in fig 1. On the other hand, the percentage amount of ^{14}C detected in various organs after i.p. treatment, were more than in case of oral treatment particularly in liver and fat as shown in Fig. 1 and Table 3.

Ruzo *et al.*[21] found that ^{14}C-deltamethrin which treated orally to rats was rapidly and almost completely eliminated from the body and appears in the urine and feces. Very little amount of ^{14}C-deltamethrin is detectable in various organs.

Bioavailability test in laboratory animals cold be extrapolated to predicated potential effects on man and livestock at a much lower dose. Deltamethrin is reported to cause various adverse effects in epidemiological and experimental studies[29].

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