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Note

Intramuscular fate of ^{14}C- and ^{131}I-labelled triglycerides

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Viscoleo® and sesame oil which are frequently used as vehicles for parenteral oily depot solutions were dual-labelled with ^{14}C and ^{131}I. After intramuscular administration to rabbits, the fate of the oils was followed using whole body gamma scintigraphy and monitoring of both isotopes in the excised muscle tissue. Results from the determination of radioactivity in excised tissue revealed that the disappearance rates of beta- and gamma-labelled triglycerides were similar. Likewise, disappearance profiles obtained from the excised muscle tissue were comparable to profiles obtained from whole body gamma scintigraphy. Depot neuroleptics for intramuscular injections comprising an oily solution of a lipophilic prodrug of the therapeutic agent have been used for many years. Whereas the pharmacokinetics of various antipsychotic drugs after depot administration have been reported (for review see Davis et al., 1994) only limited information is available concerning the fate of the co-administered oily vehicles. The rate of disappearance of [^{14}C]-methyl oleate from the intramuscular administration site has been estimated by measurements of remaining radioactivity in the muscle excised from rats at different time points after injection (Tanaka et al., 1974). Using a similar experimental set up the intramuscular half-lives of high doses of sesame oil and Viscoleo® were determined in the rat and dog (Svendsen and Aaes-Jørgensen, 1979). The applicability of the non-invasive technique of gamma scintigraphy for the determination of the clearance of [^{131}I]-labelled ethyl oleate and arachis oil from the i.m. site of injection in rabbits has been demonstrated (Howard and Hadgraft, 1983). Comparison of the previous analytical data is difficult due to lack of knowledge about the relative rates of disappearance of ^{14}C-labelled and halogenated triglycerides, added to oily vehicles of different compositions. Thus, the aim of the present study was to compare the data obtained by using these two analyt-

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ical techniques including determination of the fate of a gamma-emitter and a beta-emitter following i.m. injection of dual-labelled commercial oils, Viscoleo® and sesame oil, in rabbits.

Two experiments were performed. In the first 30 female New Zealand White rabbits, with a mean weight ($\pm$ S.D.) of 2.70 ± 0.21 kg were divided into 10 groups of three animals each. Doses of 0.4 ml were administered into the muscle of the upper left hind limb (m. vastus lateralis) using a 0.6×30-mm needle, inserted to a depth of 10–15 mm. Doses comprised 0.35 ml Viscoleo® (fractionated coconut oil, BP 1988) spiked with 0.04 ml (1.85 MBq ml^{-1}) of glycerol tri[1-^{14}C]palmitate (Amersham Life Science, UK) and 0.01 ml of [^{131}I]-triolein. Radioiodinated triolein of approximately 200 MBq ml^{-1} and 500 MBq ml^{-1} was used for rabbits killed up to 24 h postadministration and at 48–240 h, respectively. Triolein (Sigma, UK) was radioiodinated using the iodine-monochloride technique (Lubran and Pearson, 1958). A similar experiment was carried out in a second group of 30 rabbits administered 0.4 ml dual radiolabelled sesame oil intramuscularly. Solutions containing 0.185 MBq [^{14}C]/5 MBq [^{131}I] and 0.185 MBq [^{14}C]/12.5 MBq [^{131}I] per ml were used for the two groups, respectively. The sesame oil was radioiodinated directly and [^{14}C]-palmitate added.

At selected time points after i.m. injection, groups of three animals were killed with an overdose of pentabarbitone (Pentoject, 200 mg ml^{-1}, Animalcare Ltd., UK). The muscle tissues from the injection sites were removed and stored at 4°C prior to homogenisation. The weighed injection sites were homogenised in ultra pure water resulting in final homogenates of 10% w/v. Approximately 0.25-ml aliquots of homogenate were weighed into 20-ml glass liquid scintillation counting vials and 0.5 ml of a tissue solubiliser (Soluene® -350, Canberra-Packard, UK) was added. The radioactivity present was determined by liquid scintillation spectroscopy using a Packard Tricarb liquid scintillation analyser. Calibration curves for ^{14}C and ^{131}I were produced to correct for the variable counting efficiency of each vial. Where appropriate the ^{131}I counts were corrected for decay. Whole body gamma camera images were collected for all animals immediately after injection. In addition, a second image of each animal was collected just prior to sacrifice of the animals. Lateral and ventral images were obtained by using a Maxi Camera II (International General Electric Company, Heyes, NY). The data were stored on the camera computer system. From visual inspection, the lateral views were selected for further analysis as no significant additional information was revealed from the ventral images. The radioactivity remaining in the muscle at each time point was corrected for the background and the radioactive decay of ^{131}I since the time of dosing. The corrected radioactivity was expressed as a percentage of the radioactivity at time zero.

The results of the excised tissue experiments are summarised in Table 1, where the radioactivity at the injection site for each animal at each sampling time has been calculated relative to the mean activity at time zero. As expected, the study design resulted in significant standard deviations of single determinations at the vast majority of sampling times (range 1.9–57.6%). The data in Table 1 indicate that the radioactivity was cleared more slowly from sesame oil compared to Viscoleo®. In a recent mass balance study (to be published) total excretions of ^{131}I, 10 days after administration, of approximately 70% (Viscoleo®) and 20% (sesame oil) of the administered dose were calculated. To compare the intramuscular clearance of ^{14}C- and ^{131}I-labelled triglycerides the ratio of the beta and gamma counts for each animal has been calculated together with mean ratio at each sampling time (Table 1). For both Viscoleo® and sesame oil mean ratios increased from unity at time zero to approximately 1.2 at 240 h. A slight, but significant (ANOVA) increment took place within the first 2 days with ratios becoming fairly constant in the sampling period 48–240 h suggesting that intramuscular disappearance rates of the beta- and gamma-labelled triglycerides are of the same order of magnitude. The increment in ratios may reflect a minor leakage of the ^{131}I label from the oil.

Representative mean values and standard deviations of single determinations of the remaining radioactivity (^{131}I) at the administration site after

Table 1
Radioactivities of excised muscles at various sampling times (three rabbits) after i.m. injection of 0.4 ml of dual-labelled Viscoleo® and sesame oil, respectively

Sampling time (h)	Viscoleo®				Sesame oil			
	^{14}C	^{131}I	$^{14}C/^{131}I$	Mean ratio (S.D.)	^{14}C	^{131}I	$^{14}C/^{131}I$	Mean ratio (S.D.)
0	100	100			100	100		
1	182	81	1.01	1.04 (4.0%)	52	60	0.87	0.99 (11.2%)
	105	102	1.03		127	126	1.01	
	76	70	1.09		128	117	1.09	
3	77	76	1.01	1.00 (1.7%)	54	58	0.93	0.99 (17.4%)
	93	95	0.98		50	59	0.85	
	78	77	1.01		73	62	1.18	
6	84	86	0.98	1.01 (3.8%)	57	52	1.10	1.04 (6.3%)
	75	76	0.99		77	79	0.97	
	132	126	1.05		138	132	1.05	
10	109	105	1.04	1.01 (4.6%)	111	76	1.46	1.27 (12.7%)
	80	83	0.96		70	60	1.17	
	80	77	1.04		167	140	1.19	
24	57	53	1.08	1.00 (0.7%)	117	136	0.86	1.15 (23.3%)
	90	88	1.02		42	35	1.20	
	67	75	0.89		50	36	1.39	
48	92	81	1.14	1.13 (0.9%)	86	70	1.23	1.20 (2.1%)
	46	41	1.12		112	93	1.20	
	87	77	1.13		80	68	1.18	
72	82	76	1.08	1.11 (2.6%)	66	54	1.22	1.19 (3.5%)
	58	51	1.13		56	49	1.14	
	121	107	1.13		165	138	1.20	
120	100	73	1.37	1.25 (16.8%)	83	69	1.20	1.19 (3.5%)
	92	91	1.01		112	98	1.14	
	54	39	1.38		153	125	1.22	
240	65	57	1.14	1.20 (4.3%)	154	122	1.26	1.25 (3.7%)
	29	24	1.21		89	69	1.29	
	21	17	1.24		110	92	1.20	

The radioactivity for each animal calculated relative to the mean activities determined immediately postadministration.

i.m. injection of dual-labelled Viscoleo® plotted against time are shown in Fig. 1. Although strict statistical analysis has not been performed inspection of the data indicates that the ^{131}I profile measured in tissue samples by scintillation spectroscopy is comparable to that obtained by using the non-invasive gamma camera technique. Likewise similar slopes of the ^{131}I-disappearance profiles, treated according to 1. order kinetics, have been estimated: 3.4×10^{-3} h^{-1} (gamma camera) and 3.9×10^{-3} h^{-1} (scintigraphy).

Viscoleo® triglycerides contain primarily short chain fatty acids (octanoic acid (58%) and decanoic acid (40%)) whereas the dominant constituents of sesame oil are the C-18 acids, oleic acid (45%) and linoleic acid (40%). The reasonable consistency of the data obtained from these different oily vehicles suggests that the determined disappearance rates of both ^{14}C- and ^{131}I-labelled triglycerides might adequately describe the intramuscular fate of the parent oils per se and that the rate of disappearance as measured in excised

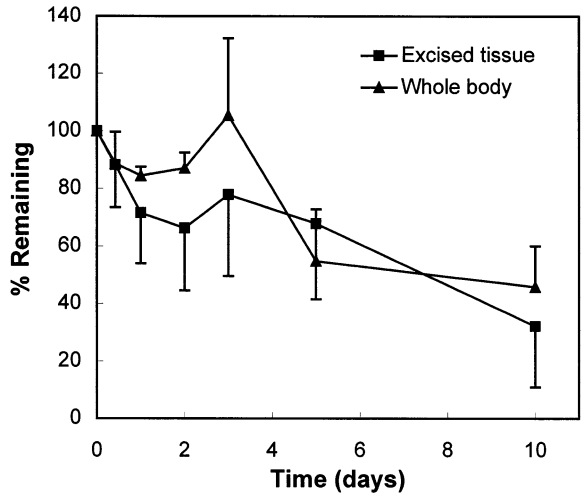

Fig. 1. Mean values ($n = 3$) and standard deviations of radioactivity remaining at the injection site after i.m. injection into rabbits of 0.4 ml of dual-labelled Viscoleo® against time as calculated from ^{131}I measurements of excised muscles and from whole body gamma imaging.

tissue was similar to that measured by the non-invasive technique of gamma scintigraphy.

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