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Dosimetry of iodine-123 iodobenzamide in healthy volunteers

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Abstract. The distribution of the dopamine D_2-receptor specific ligand iodine-123 (*S*)-(–)-2-hydroxy-3-iodo-6-methoxy-*N*[(1-ethyl-2-pyrrolidinyl)methyl]-benzamide (^{123}I-IBZM) was investigated in human adults from whole-body scans, blood samples and urine collected up to 48 h after injection. Results from the present study performed in six healthy volunteers were combined with those of five volunteers from a previous study. Using the brain, liver, lungs and spleen as source organs, the MIRD method was applied to calculate the absorbed radiation dose of the radioligand in various organs. The thyroid (despite blockage), gall-bladder wall, large intestinal walls and spleen received the highest absorbed doses. The average effective dose equivalent of ^{123}I-IBZM for adults was estimated to be 0.034 mSv/MBq. The absorbed dose to the thyroid may be a limiting factor for ^{123}I-IBZM studies in children.

Key words: Dosimetry – Iodine-123 – Receptors – Dopamine – Iodobenzamide

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Introduction

The dopamine D_2-receptor specificity of the radioligand iodine-123 (*S*)-(–)-2-hydroxy-3-iodo-6-methoxy-*N*[(1-ethyl-2-pyrrolidinyl)methyl]-benzamide (^{123}I-IBZM), first synthesized by De Paulis et al. [1] and labelled by Kung et al. [2], has been confirmed in laboratory animals in vitro and in vivo [2, 3]. Single-photon emission tomography (SPET) with ^{123}I-IBZM has been performed in human volunteers [4, 5] and in patients with various diseases, such as movement disorders [6, 7] and schizophrenia [6, 8, 9].

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Recently, radiation dosimetry of ^{123}I-IBZM has been described in five healthy volunteers by Kung et al. [4] and reported in six healthy volunteers by Verhoeff et al. [10]. The purpose of this paper is to present the latter study in the six volunteers more extensively and to combine the results with those from the five volunteers of Kung et al. [4] in order to obtain a more accurate assessment of the distribution and dosimetry of ^{123}I-IBZM.

Materials and methods

The synthesis of (*S*)-(–)-2-hydroxy-6-methoxy-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]benzamide [(S)-BZM], the precursor of ^{123}I-IBZM, and the radiolabelling with ^{123}I have been previously discussed [11]. The radiolabelling procedure used was essentially the same as that described by Kung et al. [2]. The production of ^{123}I by the xenon-124 (p,2n) cesium-123 → xenon-123 → ^{123}I reaction provided ^{123}I with high radionuclidic purity (> 99.99%).

In order to visualize and quantify the distribution of ^{123}I-IBZM, whole-body scans were performed in six healthy volunteers (four men; two women; 22–52 years) after intravenous injection of 125–190 MBq ^{123}I-IBZM (specific activity 111–122 MBq/nmol). Potassium iodide in a 10% solution was given to inhibit thyroid uptake of ^{123}I (3 times 10 droplets during the 2 days before the scans, and 20 droplets on the morning of the day of the scans: in total 80 droplets of 10% KI). Written informed consent was obtained, and the study was approved by the hospital medical ethics committee.

Whole-body scans were made at three time intervals after injection: period 1, between 15 and 95 min (five studies); period 2, between 180 and 270 min (five studies) and period 3, between 330 and 360 min (one study). A Technicare Omega 500 scintillation camera with a medium-energy parallel-hole collimator was used. This collimator was selected in preference to the high-resolution low-energy collimator because the latter showed considerable septum penetration of the 3% high-energy photons of ^{123}I, causing considerable image degradation. The 20% energy window was centred over the 159 keV photopeak of ^{123}I.

Anterior and posterior scans were made using a fixed scan speed of 20 cm/min. A reference standard amount of activity was similarly scanned in order to confirm constancy of the technique over the whole time span. Regions of interest were drawn over

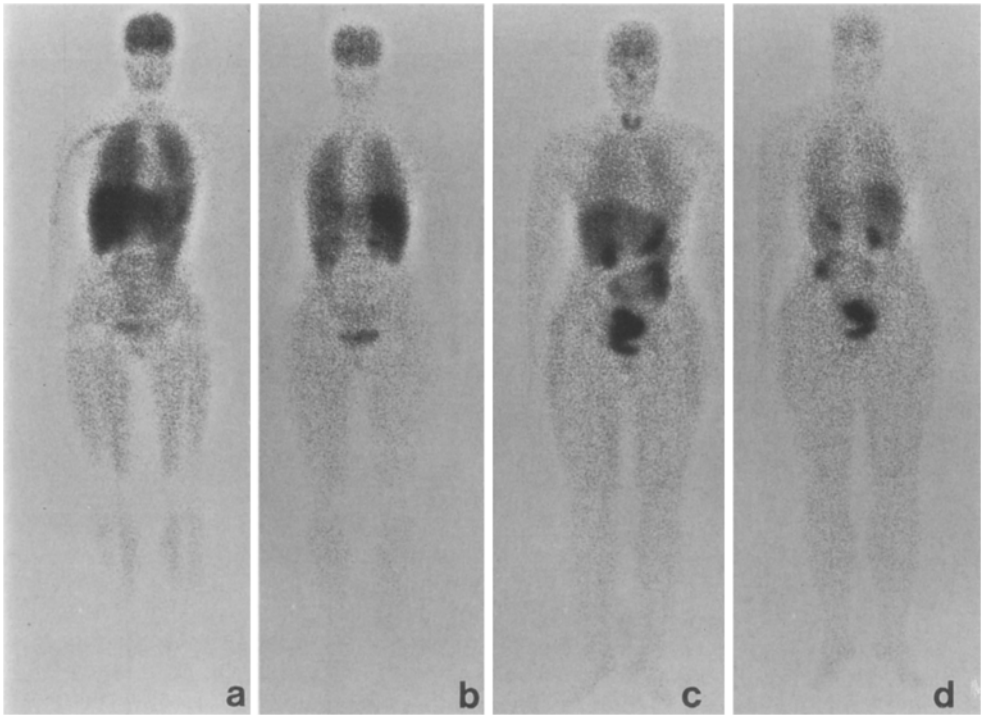

Fig. 1. Whole-body scans from a 22-year-old female volunteer obtained at 15–45 min post injection (**a** anterior, **b** posterior) and at 180–210 min post injection (**c** anterior, **d** posterior)

the total body images, and over various organs. Background subtraction was performed using a region over the shoulders. The geometric mean counts in each region were calculated for each of the time periods. The percentage activity in the organs was taken to be: (geometric mean counts in organ/geometric mean counts in total body) × 100%. The reference standard was not used to quantify the percentage ^{123}I activity in the different organs. For this purpose, the geometric average of the total body counts was taken as the most practical reference which included the dimensions of body dimensions and organ size.

Blood samples were taken just prior to the whole-body scans. The total activity in the blood was calculated using a total blood volume based on total body weight. Urine was collected up to 48 h after injection.

All data were corrected for physical decay to determine the biological half-life of ^{123}I-IBZM in the organs. These results were then pooled with those from Kung et al. [4], and the MIRD methodology, using the MIRDOSE2 software package (Oak Ridge), was applied to calculate residence times of the radioactivity measured in the source organs and to calculate the absorbed dose in various organs [12, 13]. The data were used to calculate absorbed doses in adults as well as in children. The distribution and biological half-lives of ^{123}I-IBZM were estimated in four source organs by fitting retention to one or two exponential clearance compartments, using a non-linear least-squares iterative approach. The following assumptions were made: [1] 30% of the liver activity passes through the gall-bladder, with the remaining 70% passing directly to the small intestine; [2] the gall-bladder voids once every 6 h, with the output going to the small intestine; [3] 20% of the total activity passes through the small intestine and follows gastrointestinal tract kinetics according to the ICRP 30 [14] and the remaining 80% is cleared through the urinary tract. The dynamic bladder model of Cloutier et al. [15] was used to treat activity entering the urinary bladder. The biological half life for the material cleared through the urinary tract was 17.3 h. Urinary bladder voiding interval was assumed to be 4.8 h for adults and 15-year-olds, and 2.0 h for 5- and 10-year-olds.

Table 1. Percentage of radioactivity distribution in various organs measured in three time periods after i.v. administration of ^{123}I-IBZM. Data are mean ± SD

Time p.i. No. of studies	Period 1 15–95 min 5	Period 2 180–270 min 5	Period 3 330–360 min 1
Total body	100[a]	86.7 ± 6.2[a]	75.9[a]
Brain	4.0 ± 0.7	2.0 ± 0.5	0.6
Kidneys	3.6 ± 0.7	2.9 ± 1.0	3.2
Bladder	1.6 ± 0.8	2.9 ± 1.8	10.0
Liver	14.6 ± 3.3	7.7 ± 0.8	5.8
Lungs	13.0 ± 4.2	5.9 ± 0.9	4.1
Spleen	2.7 ± 0.8	1.6 ± 1.0	1.1
Bowel	8.6 ± 3.4	14.0 ± 3.3	10.0
Gall-bladder	1.9 ± 1.0	3.9 ± 2.5	2.5
Heart	4.9 ± 1.5	2.4 ± 0.5	2.1
Thyroid	0.6 ± 0.6	0.5 ± 0.2	0.5
Parotid	0.2 ± 0.0	0.2 ± 0.1	0.1
Submandibular	0.4 ± 0.2	0.2 ± 0.1	0.2
Testes	0.2 ± 0.2	0.6 ± 0.1	0.3
Blood	5.5 ± 1.2	5.9 ± 0.6	5.1
Urine	0	13.3 ± 6.2	24.1

[a] The total body radioactivity was assumed to be equal to the total injected dose minus the total dose measured in the urine collected just before the scan. This assumption was in agreement with the change in total body counts measured in the second and third time periods compared with the first time period

Results

The radioactivity distribution at 15–45 min and 180–210 min after administration of ^{123}I-IBZM in one of the volunteers is shown in Fig. 1. Table 1 shows the aver-

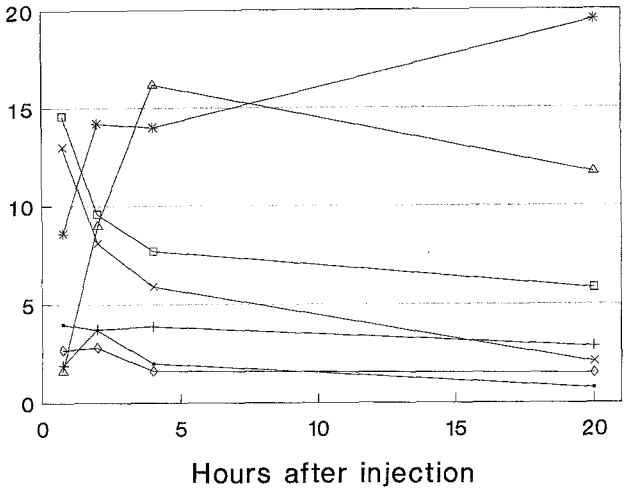

Fig. 2. Percentages of injected activity in various organs (—•— Brain; —+— Gall bladder; —✳— Small intestine; —⊟— Liver; —×— Lung; —◇— Spleen; —△— Bladder contents + urine) of healthy volunteers after i.v. injection of ^{123}I-IBZM. Data at 0.75 and 4 h p.i. derived from six subjects studies by Verhoeff et al. [10]. Data at 2 and 20 h p.i. derived from five subjects studied by Kung et al. [4]

age activity measured in the various organs of the six healthy volunteers. These data were obtained at other time periods after injection of ^{123}I-IBZM than those data from the five volunteers reported by Kung et al. [4]. The data from the present study were, however, combined with the data from Kung et al., taking into account the appropriate measurement times. The results are shown in Fig. 2. The remarkably good fit of the two sets of data was considered to provide a more accurate estimation of biological distribution and changes with time than each of the single data sets taken separately.

The estimated distribution and biological half-lives in the four source organs, based on the combined data, and in the gall-bladder, small intestine and urinary bladder, are shown in Table 2. Total urine excretion of ^{123}I-IBZM was >40% of the dose injected at 24 h after injection and >60% at 48 h after injection.

Radiation dose estimates for the standard adult and 5-, 10- and 15-year-olds are given in Table 3. The calculations were based on 100% pure ^{123}I. The highest doses were received by the thyroid (despite blockage), the gall-bladder wall, the large intestinal walls and the spleen. The mean effective dose equivalent for adults was 0.034 mSv/MBq.

Discussion

The data presented here for the distribution of ^{123}I-IBZM in six volunteers agreed well with the data from the five volunteers reported earlier by Kung et al. [4]. Even though different quantification techniques were used at the two centres and measurements were made at different times after injection, when combined the time-distribution curves did not show any incongruity (Fig. 2). This indicates that the pooling of data from different centres seems to be possible and collaboration should be encouraged in order to obtain larger series of data for dosimetric calculations. An identical protocol should preferably then be used.

Table 2. Distribution and retention of ^{123}I-IBZM in human adults. A. Based on the most optimal curve fit (mono- or bi-exponential) for four source organs derived from the combined data of six volunteers studied by Verhoeff et al. [10] and five volunteers studied by Kung et al. [4]. Phase 1 starts immediately after i.v. injection of ^{123}I-IBZM. The fractional standard deviations (SD) of the fitted curves are estimated from the total sum of squares. B. For the gall-bladder and small intestine, derived from gastrointestinal kinetics described in the ICRP 30 [14], and for the urinary bladder, derived from the dynamic bladder model of Cloutier et al. [15].

A.

Organ	Phase	% Distribution	$T_{1/2}$ biological (h)	Fractional SD (%)
Brain	1	4.5	2.28	16.1
	2	0.64	Infinite[a]	
Liver	1	13.2	1.12	1.3
	2	5.8	Infinite[a]	
Lungs	1	14.5	1.26	0.05
	2	3.5	26.6	
Spleen	1	2.9	21.7	3.1
Total body	1	4.4	2.4	1.3
	2	95.6	26.6	

B.

Gall-bladder:	Receives 30% of the activity leaving the liver, voids once every 6 h
Small intestine:	Receives 70% of the activity leaving the liver, plus activity leaving the gall-bladder. Thereafter activity follows gastrointestinal tract kinetics as in ICRP 30
Urinary bladder:	Receives 80% of total body clearance. $T_{1/2}$ biological = 17.3 h (fractional SD = 2.2%). Bladder voiding interval: 4.8 h for adults and 15-year-olds, 2.0 h for 10- and 5-year-olds

[a] Infinite means that ^{123}I distribution remains constant with time. The effective $T_{1/2}$ then equals the physical $T_{1/2}$ for ^{123}I

Table 3. Radiation dose estimates for ^{123}I-IBZM (mSv/MBq) based on the MIRD method, applied to the combined data of six volunteers studied by Verhoeff et al. [10] and five volunteers studied by Kung et al. [4]

	5-year-olds	10-year-olds	15-year-olds	Adults
Thyroid	0.86	0.39	0.26	0.16
Urinary bladder wall	0.10	0.067	0.090	0.070
Lower large intestine	0.22	0.14	0.082	0.064
Spleen	0.19	0.13	0.083	0.059
Upper large intestine	0.18	0.12	0.073	0.057
Gall-bladder wall	0.14	0.082	0.061	0.052
Liver	0.089	0.062	0.041	0.032
Small intestine	0.084	0.058	0.036	0.029
Lungs	0.072	0.048	0.034	0.023
Ovaries	0.062	0.041	0.028	0.022
Uterus	0.053	0.034	0.025	0.020
Bone surfaces	0.050	0.033	0.021	0.017
Pancreas	0.051	0.032	0.020	0.016
Kidneys	0.038	0.026	0.018	0.014
Adrenals	0.041	0.027	0.018	0.014
Stomach	0.043	0.028	0.017	0.013
Red marrow	0.031	0.020	0.013	0.011
Muscle	0.031	0.020	0.013	0.010
Thymus	0.031	0.019	0.012	0.0095
Testes	0.029	0.018	0.012	0.0094
Brain	0.014	0.011	0.0094	0.0090
Breasts	0.023	0.014	0.0093	0.0073
Skin	0.020	0.012	0.0077	0.0064
Effective dose equivalent	0.11	0.065	0.046	0.034

Several intrinsic errors exist in the determination of the dose estimates. First, the quantification of organ uptake by the data from the whole-body scans. Neither a reference standard nor scatter and attenuation correction was used in this study; the geometric mean whole-body uptake was used instead. Second, the biological variability of ^{123}I-IBZM uptake in populations with a different sex or age distribution than the studied group is unknown. Third, we do not know well the uncertainty in dose conversion factors (*S* values). Although a nominal value (20%–30%) can be assigned to this uncertainty, this value is population dependent as well. Fourth, the curve fitting was applied to the averaged, pooled data. Therefore, caution should be exercised when applying data from this study for dosimetric limitation of administered radioactivity in ^{123}I-IBZM studies in general.

From the total combined series of 11 (6+5) healthy volunteers, the mean effective dose equivalent for adults was estimated to be 0.034 mSv/MBq. Although in both studies an agent was administered for blocking thyroid uptake of ^{123}I, there was noticeable retention of ^{123}I in the thyroid, possibly indicating circulating free iodide. The thyroid dose estimated for the mean uptake of 0.6% and the maximum uptake in the series of 1.7% would be 0.084 mSv/MBq and 0.24 mSv/MBq, respectively, based on the model for sodium iodide in MIRD Dose Estimate Report No. 5 [13]. This would add 0.0025 or 0.0072 mSv/MBq to the effective dose equivalent. Similar levels of absorbed radiation dose to the thyroid have also been reported by Seibyl et al. [16]. Knowledge of this additional radiation dose should be borne in mind, especially when investigating children with ^{123}I-IBZM. More aggressive thyroid blocking schemes might then be considered.

Based on an effective dose equivalent of 0.034 mSv/MBq, patients and volunteers could be studied with up to 150 MBq (4.0 mCi) of ^{123}I-IBZM, which gives an average effective dose equivalent of 5 mSv. This effective dose equivalent value is comparable to the average effective dose equivalent per patient from nuclear medicine studies as reported from surveys in the United States and Europe [17, 18].

In the case of volunteers, a 5 mSv average effective dose equivalent is the upper limit of category II of the World Health Organisation [19] and is considered an acceptable level of risk that corresponds to the former dose limits for members of the public. However, the study should not be repeated in the same year. A quantity of 150 MBq of ^{123}I-IBZM could be administered for a single study or divided over two or three studies if a dedicated brain SPET system that offers high counting efficiency is used or if a longer imaging time is selected, as long as reliable count images are acquired. As recommended by the World Health Organisation [19], subjects under 18 years old should not be studied except when problems specific to their age are under investigation.

In the United States the current radiation dose limits for volunteers are based on the absorbed dose to indi-

Table 4. Activity limits for studies with ^{123}I-IBZM in healthy volunteers based on Technical Report Series 611 of the World Health Organisation (1977) and on Regulation 21CFR361 of the US General Services Administration (1992), based on dose limit to thyroid

	5-year-olds	10-year-olds	15-year-olds	Adults
WHO category II:	45 MBq	77 MBq	110 MBq	150 MBq
Yearly activity	1.2 mCi	2.1 mCi	3.0 mCi	4.0 mCi
Regulation 21CFR361:	6 MBq	13 MBq	19 MBq	310 MBq
Single study activity	0.16 mCi	0.35 mCi	0.52 mCi	8.4 mCi
Yearly activity	17 MBq	38 MBq	58 MBq	940 MBq
	0.47 mCi	1.0 mCi	1.6 mCi	25 mCi

vidual organs [20]. For "adult research subjects" the radiation dose limits are: whole-body, active blood-forming organs, lens of the eye and gonads, 30 mSv in a single dose, 50 mSv annually; other organs, 50 mSv in a single dose, 150 mSv annually. Based on these dose limits, the maximum administered radioactivity allowed for a single study would be 310 MBq (8.4 mCi), and the maximum allowed annual activity would be 940 Bq (25 mCi). Therefore, for adults, it seems that none of the organs would present a particular problem for a single study. Using activities of 185 MBq (5 mCi) ^{123}I-IBZM, four studies could be performed per annum in adults. For "research subjects under 18 years of age", the radiation doses mentioned above are to be reduced by a factor of 10. For research subjects under 18 years of age the annual number of studies must therefore be limited to one (Table 4).

We conclude that thyroid blocking is necessary for absorbed dose reduction in ^{123}I-IBZM studies, especially in young persons. Furthermore, the maximum activity allowed for a single study in adult subjects would be 310 MBq in the United States and 150 MBq in the majority of the rest of the world. For persons below 18 years old, the allowed activities are considerably more restricted, mainly due to the absorbed dose in the thyroid.

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