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Occasional survey

Radioiodinated metaiodobenzylguanidine: a review of its biodistribution and pharmacokinetics, drug interactions, cytotoxicity and dosimetry

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Abstract. Since the introduction of radioiodinated metaiodobenzylguanidine in 1980, considerable research has been performed, both in the chemical field and in medical sciences. However, despite the wide use of radioiodinated metaiodobenzylguanidine, knowledge about its pharmacology is still limited. This paper reviews the biodistribution and pharmacokinetics, drug interactions, cytotoxicity and dosimetry of radioiodinated metaiodobenzylguanidine. Iodine-131 metaiodobenzylguanidine therapy is in general well tolerated, but its effectiveness needs improvement. Also whole-body dosimetry as part of treatment planning needs to be improved. Future prospects on these items are included in this review.

Key words: Biodistribution – Cytotoxicity – Dosimetry – Pharmacokinetics – Radioiodinated metaiodobenzylguanidine

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Introduction

Since its introduction in 1980, metaiodobenzylguanidine labelled with iodine-131 or iodine-123 ([^{131}I/^{123}I]MIBG) has occupied a well-established position in diagnostic scintigraphy of several neural crest-derived tumours [1]. Moreover, experience is growing in radionuclide therapy with [^{131}I]MIBG for such tumours [1], and in the scintigraphic assessment of cardiac sympathetic neuronal integrity with [^{123}I]MIBG [2]. The clinical application of radioiodinated MIBG has also yielded human in vivo distribution and pharmacokinetic data, one of the main issues of this review. Furthermore, much knowledge has been gathered through in vitro experiments on the interactions between MIBG and many different adrenergic neuronal and tumoral cells. Also, attention will be paid to drug interactions and radiophysical and radiobiological aspects of radioiodinated MIBG. This information is essential, first for understanding the range of effects of [^{131}I/^{125}I]MIBG therapy seen in clinical practice and second for exploring new regimens of administration and pharmacological intervention with the aim of optimizing clinical performance.

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Biodistribution and pharmacokinetics

Biodistribution

Nakajo et al. [3] studied the [^{131}I]MIBG images, obtained at $t = 24$, 48 and 72 h after tracer injection (18 MBq/1.7 m^2 body surface area), from 84 patients referred for suspected phaeochromocytoma. The patient population included normals without evidence of phaeochromocytoma ($n = 25$), patients suffering from multiple endocrine neoplasia (MEN) type 2 ($n = 11$) and patients with surgically proven phaeochromocytoma ($n = 16$). Distribution of the radioactivity was evaluated by means of a semiquantitative grading system using five grades. The normal 24-h distribution usually showed uptake in the salivary glands, spleen, liver and urinary bladder. The visualization of the salivary glands (due to [^{131}I]MIBG and not due to its degradation product [^{131}I]iodide [4]) and spleen was explained by the extensive sympathetic innervation of these organs, whereas the liver was probably depicted because of its volume, vascularity and extraction capacity [3]. The urinary bladder was visualized because of the predominantly renal excretion of radioactivity after injection of radioiodinated MIBG. Heart, lungs, colon and kidneys were less frequently and less intensely visualized by Nakajo et al. [3], whereas the thyroid (which takes up [^{131}I]iodide) was only visualized when pretreatment with non-radioactive iodide to competitively block the thyroid had been inadequate or omitted [3].

Kline et al. [5] reported imaging of the heart with [^{123}I]MIBG in all of five volunteers during the first 2 h after injection. This high visualization frequency as compared to the results of Nakajo et al. [3] is explained by the time between administration and scintigraphy; the first scans of Nakajo et al. [3] were only at $t = 24$ h. Uptake of radioiodinated MIBG has further been reported to occur in the uterus during the menstrual phase [6] and in the cerebellum, basal nuclei and thalamic regions of the human brain [7]. The normal adrenal glands are seldom visualized (less than 20% and always faintly) by [^{131}I]MIBG [3]: even after therapeutic doses visualization was reported in only one out of five cases [8]. In contrast, adrenal visualization was frequent in phaeochromocytoma patients and in the tumour-bearing glands of MEN type 2 patients in the study of Nakajo et al. [3]. Moreover, visualization of other sites in the MEN type 2 patients represented extra-adrenal and metastatic phaeochromocytoma [3]. Contrasting with [^{131}I]MIBG, visualization of normal adrenal glands with 74–370 MBq [^{123}I]MIBG has been reported in 13 out of 15 patients (87%) [9, 10].

Biodistribution of MIBG can be altered by interactions with other drugs, as will be discussed later, but also by disease. Nakajo et al. compared the clearance of radioactivity from the heart and the liver up to 48 h after a diagnostic dose of [^{131}I]MIBG in patients with adrenergic dysfunction, patients with phaeochromocytoma and controls [11]. Sinclair et al. compared the clearance of radioactivity from the heart, the lungs, the liver and the spleen up to 22 h after administration of [^{123}I]MIBG in controls and phaeochromocytoma/paraganglioma patients before and after treatment [12]. It can be seen from Table 1 that at $t = 4$ h after injection all patients had significantly less radioactivity left in the heart and the liver than controls and that, after treatment of the tumour, values returned to normal. These phenomena were interpreted by the authors as follows [11, 12]: Initial uptake of MIBG in organs is both neuronal and non-neuronal. In the organs of patients with adrenergic dysfunction there are relatively few intact functioning adrenergic neurons to take up and to store MIBG. In the patients with phaeochromocytoma, high levels of circulating catecholamines compete with MIBG in entering adrenergic neurons. Therefore, in both patient groups, the ratio of neuronal to non-neuronal uptake will be lowered compared to controls and, as early clearance (up to 4 h) is predominantly from non-neuronal sites, the retained neuronal radioactivity will represent a smaller fraction of the initial radioactivity in both patient groups compared to controls. The return to normal [^{123}I]MIBG clearance values of the post-treatment phaeochromocytoma/paraganglioma patients parallelled normalization of plasma catecholamine levels [12].

Table 2. Non-visualization rate of the heart after intravenous administration of diagnostic [^{131}I]MIGB [a] [from 13]

Subjects	24 h (n[b])	48 h (n[b])
Non-phaeochromocytoma patients	11% (56)	20% (95)
Phaeochromocytoma patients	86% (28)	93% (29)

[a] Expressed as percentage of subjects in whom the heart did not show retention of radioactivity
[b] n, Number of subjects

The apparent inverse relationship between plasma (and urine) catecholamine levels and cardiac retention of radioiodinated MIBG has been studied by comparing the non-visualization rate of the heart at $t \geq 24$ h in phaeochromocytoma patients and true-negative subjects who were suspected of having phaeochromocytoma [13]. The non-visualization rate was much lower in the non-phaeochromocytoma patients (Table 2). Also for neuroblastoma patients an inverse relationship between myocardial uptake of [^{131}I]MIBG and catecholamine levels has been reported [14].

A major issue is the distribution of radioiodinated MIBG into and within different tumours. Bomanji et al. [15] compared the uptake of [^{123}I]MIBG by different

Table 1. Radioactivity in different organs 4 h after intravenous administration of diagnostic [^{123}I/^{131}I]MIBG[a]

Subjects	n[b]	Heart	Liver	Reference
Controls[c]	8	80%	79%	[11]
Patients with adrenergic dysfunction	3	57%[d]	43%[d]	[11]
Phaeochromocytoma patients	2	65%[d]	63%[d]	[11]
Normal volunteers	7	74%	74%	[12]
Phaeo-/paraganglioma patients pretreatment	11	48%[e]	47%[e]	[12]
Phaeo-/paraganglioma patients post-treatment	11	70%	71%	[12]

[a] Expressed as percentage of the initial (t=20–30 min) counts
[b] n, Number of subjects
[c] Controls: four normal volunteers+four referred patients without evidence of phaeochromocytoma or adrenergic dysfunction
[d] Remaining radioactivities in heart and liver of the patients (n=5) differed significantly (Student's t-test, $P<0.01$ and $P<0.02$, respectively) from controls
[e] Washout percentages from the organs of pretreatment patients differed significantly (Mann-Whitney U test, $P<0.01$) from both post-treatment values and normal volunteers

neural crest-derived tumours. Predominantly investigating phaeochromocytomas and paragangliomas, they found a positive association between the semiquantitatively (scale of three grades) determined amount of neurosecretory granules and the percentage uptake of radioactivity per gram of tumour tissue at $t = 22$ h after intravenous administration of 130–260 MBq of [^{123}I]MIBG [15]. In contrast, Moyes et al. [16] did not observe such an association for neuroblastomas. These authors did see a positive association, however, between the amount of undifferentiated neuroblastoma cells in the tumour and the percentage uptake of radioactivity per gram of tumour tissue at $t = 24$–48 h [16]. Moreover, an inhomogeneous distribution over different parts of individual tumours was found, which might be related to the degree of differentiation of the different parts of a tumour [16, 17].

Cellular uptake and retention

The lack of a relationship between the amount of neurosecretory granules and radioactivity present in neuroblastomas after administration of [^{125}I]MIBG [16] suggests that, for the retention of radioactivity, in neuroblastomas the neurosecretory granules are not as important as in phaeochromocytoma. A lot of research has been devoted to the elucidation of the uptake and retention mechanisms of different (tumour-)cell types, e.g. by pharmacological intervention studies. The results of these studies may have importance in clinical practice, by elucidating the possible effects of intended drug interactions on the retention of radioiodinated MIBG in different tumours or non-tumoral tissues.

The Ann Arbor group demonstrated that cellular uptake of MIBG and norepinephrine (NE) into cultured bovine adrenomedullary cells (as an in vitro model for phaeochromocytoma) occurs both by a specific uptake system ("uptake-one") and by a non-specific uptake system, presumably passive diffusion [18, 19]. Uptake-one is an active process by the NE transport protein of the cell membrane which catalyses a catecholamine/Na^+ symport and is driven by the Na^+ gradient generated by (Na^+/K^+)-ATPase [20]. The following characteristics of uptake-one were shown for both MIBG and NE: temperature dependence, sodium dependence, high affinity, low capacity, saturability, ouabain [a (Na^+/K^+)-ATPase inhibitor] sensitivity, energy dependence (reduced uptake without glucose in the medium or when metabolic inhibitors like 2-deoxy-D-glucose or sodium azide were added) and desmethylimipramine (DMI) or cocaine sensitivity [18, 19]. DMI and cocaine are selective, competitive inhibitors of the membrane-bound uptake-one transport protein [19, 21]. The non-specific uptake system demonstrated temperature dependence, energy (glucose) independence, ouabain insensitivity and unsaturability at concentrations of at least 5 m*M* MIBG [18].

In cultures from 16 human phaeochromocytomas it was demonstrated that the uptake of 1.0 μ*M* NE or 1.0 μ*M* MIBG is 91%–100% and 56%–78% specific (uptake-one), respectively, and that the uptake becomes increasingly non-specific with increasing MIBG (or NE) concentrations [21]. Buck et al. [22] demonstrated for human SK-N-SH neuroblastoma cells, too, a specific and non-specific uptake mechanism of MIBG, of which the specific uptake has been reported to saturate at a concentration of >1–5 μ*M* [22, 23]. The energy dependence of the specific uptake was demonstrated by a reduced uptake under three circumstances: at 4°C compared to 37°C, after preincubation with 5 m*M* ouabain and after preincubation with 1.5 m*M* of the reducing agent sodium dithionite (which removes all oxygen from the medium at the concentration used) [22]. For human SK-N-SH neuroblastoma cells specific uptake of MIBG is >95% of total uptake at a concentration of 10 n*M* and still 80% at the saturation concentration for specific uptake [23]. Therefore, considering that plasma concentrations of MIBG after therapeutic doses of [^{131}I]MIBG are <0.1 μ*M* ([23] and own observation), it can be concluded that in the clinical setting uptake-one is the predominant uptake system for MIBG.

In agreement with the positive relation between uptake of radioactivity and amount of neurosecretory granules, found for phaeochromocytomas and paragangliomas [15], Gasnier et al. demonstrated that MIBG is taken up by prepared bovine chromaffin granule membranes, which points to the granules being the ultimate sites of MIBG storage within adrenomedullary cells [20]. Uptake was by the common active monoamine transport protein [which also uses NE and serotonin (5HT) as substrates], which catalyses an amine/H^+ antiport and is driven by the electrochemical proton gradient, $\Delta\mu H^+$ (inside positive and acidic) generated by an electrogenic ATP-dependent H^+-pump. Uptake of 1 μ*M* [^{131}I]MIBG was decreased by addition of an H^+-ionophore, tetrabenazine or reserpine (both inhibitors of the granule monoamine transporter) or by the lack of ATP [20].

Many different neuroblastoma cell lines have been evaluated for their capacity for specific uptake and storage of MIBG [22–31]. A lot of neuroblastoma cells, including SK-N-LO, IMR-32 [22], NB-1, LA-N_1 [23, 25], CHP-212, N_1E115, NB4A3, Neuro-2A [23], SK-N-MC [25], GI-LI-N, GI-CA-N [29] and SH-EP1 [31], do not take up MIBG by a specific mechanism. Other neuroblastoma cells, including NB1-G [28], SK-N-AS, SK-N-DZ and BE(2)-M17 [31], do take up MIBG specifically, but lack the ability to retain high levels of MIBG. A third group of neuroblastoma cells, including SK-N-SH [22, 23, 25, 26, 30], NB-G [24], SK-N-BE(2C) [27, 29], LA-N_5 [29], SH-SY5Y, LA-N_{1n}, SMS-KCNR, NGP and SK-N-FI [31], has the capacity for both specific uptake and retention of MIBG. Cellular retention of MIBG in drug-free medium 24 h after preincubation with 10 n*M*–3.5 μ*M* MIBG was reported to be ≥30% of the initial amount for cells of the latter group [22–27, 29–31]

Table 3. Different characteristics of PC-12 and SK-N-SH cells [from 23, 26, 30]

Characteristic	PC-12	SK-N-SH
Storage granules per whole cell section	80–110	8–12
[^{125}I]MIBG in granular fraction[a]	40%	2%–4%
Net depletion (compared to controls) of stored [^{125}I]MIBG[b] by:		
Reserpine (2 μ*M*)	77%[c]	15%[c]
Imipramine (1 μ*M*)	22%[c]	82%[c]
Acetylcholine (ACh, 0.1 m*M*)	12%[d]	3%[d]
K^+ (56 m*M* KCl)	23%[d]	4%[d]
ACh or K^+ + nifedipine (0.01 m*M*)	0[d]	0[d]

[a] After differential centrifugation
[b] Cells were incubated for 2 h with 0.1 μ*M* [^{125}I]MIBG
[c] 4 h after addition of the depleting agent
[d] 5 min (37°C) after addition of the depleting agent

and up to 66% for SK-N-BE(2C) [27]. Under comparable conditions, rat PC-12 phaeochromocytoma cells show an initial decrease in retention of MIBG which is gradually compensated by near-complete re-uptake, yielding a 24-h retention of 94% [30].

Smets et al. [23, 26, 30] have extensively investigated the cellular uptake and storage of MIBG in PC-12 and SK-N-SH cells. For both cell types, variation of incubation time and drug concentration of the medium – with a constant product of these parameters (e.g. 2 h in 0.2 μ*M*, 8 h in 0.05 μ*M* MIBG etc.) – yields maximal cell loading for short incubations at high concentrations [30]. Furthermore, a non-linear relationship was shown between the drug concentration in the medium and the loading capacity of the cells [30]. Therefore, the use of diagnostic [^{131}I]MIBG of very low specific activity was advocated in order to administer the same mass of MIBG for either diagnostic scintigraphy or radionuclide therapy, when dosimetry from a diagnostic dose is used for therapeutic dose prescription [30]. In Table 3 the striking differences in the MIBG retention site between PC-12 and SK-N-SH cells are shown. The small number of neurosecretory granules in SK-N-SH cells contain a small fraction of the radioactivity. Granular storage of MIBG in PC-12 cells is demonstrated by the large effect of the granule depletor reserpine. The potent depletion of MIBG from SK-N-SH cells by the uptake-one inhibitor imipramine points at retention of MIBG in these cells through rapid re-uptake of MIBG diffusing from the cells. Characteristics comparable with SK-N-SH have been found for SK-N-BE(2C) [27]. Moreover, it is shown in Table 3 that depletion of MIBG by acetylcholine- or potassium-induced exocytosis is more important for PC-12 than for SK-N-SH cells and that the use of nifedipine for prolonged retention would only be of value for phaeochromocytoma. For neuroblastoma NB1-G cells – as for SK-N-SH – no effect of nifedipine or reserpine on MIBG retention was found [28].

Searching for an agent that could enhance uptake and retention of MIBG in neuroblastoma cells, Montaldo et al. found a twofold increase in LA-N_5 cell-associated radioactivity after pretreatment with the differentiation-inducing agent interferon-γ [32]. However, they only reported retention up to 6 h after withdrawal of the MIBG-containing medium. Moreover, preliminary positive in vitro results have been reported for pretreatment of SH-SY5Y cells with the differentiation-inducing agent retinoic acid [31]. However, the possible enhanced MIBG uptake and retention by differentiation of neuroblastoma cells is in contrast with the in vivo results obtained by others [16, 17].

In conclusion, not all neuroblastoma cells can take up or retain MIBG with the same efficiency. Another factor affecting the delivery of radioactivity to the tumour might be the state of oxygenation of the tumour cells, since Buck et al. showed in vitro a decreased uptake of MIBG under hypoxic conditions [22].

Regarding the intracellular localization of MIBG in neuroblastoma cells, the minor role of neurosecretory granules has already been mentioned. Conversely, the mitochondria [33] and even the nucleus [34] have been reported to contain radioactivity after incubation with radioiodinated MIBG. However, these results should be interpreted with caution, as the conventional fixation procedures used for analysis could not prevent diffusion of the drug from its original site during preparation [30]. In a recent study using cryotechniques for fixation of MIBG, the earlier finding that no MIBG was present in the nucleus of neuroblastoma cells [33] was confirmed [35]. This may have consequences for the effectiveness of [^{125}I]MIBG due to the short range of its emitted Auger electrons.

After intravenous administration of radioiodinated MIBG, radioactivity is rapidly distributed from the vascular compartment [36]. The small amount remaining within the vascular compartment was found to be concentrated in thrombocytes. At $t = 24$ h the amount of radioactivity per gram protein in thrombocytes was 145 times greater than in erythrocytes, 1.8 times greater than in thrombocytes at $t = 48$ h and 70% of the amount in phaeochromocytoma tissue at $t = 48$ h [37]. In vitro distribution ratios (concentration in erythrocytes or thrombocytes/concentration in plasma) at equilibrium at 37°C are 3: 1 for erythrocytes and 200: 1 for thrombocytes [38]. Uptake and storage of MIBG in thrombocytes are being investigated, since in general thrombocytes are thought to be a model for presynaptic adrenergic neurons (and hence for tumours derived from the adrenergic nerve system), being able to specifically take up NE and 5HT and showing amine storage granules [39]. However, Rutgers et al. recently demonstrated that 5HT was not taken up specifically by PC-12 or SK-N-SH cells, which is an essential discriminator between these cells and thrombocytes [40]. These authors are interested in MIBG uptake and storage mechanisms of thrombocytes since thrombocytopenia is a frequent toxic side-effect of

radionuclide therapy with [^{131}I]MIBG. Specific uptake of 10 n*M* 5HT in human thrombocytes is rapid and levels off within 1 h, in contrast to the slower specific uptake of 10 n*M* MIBG, which gives a plateau after 3 h at a similar level as 5HT [40]. Since 27 μ*M* imipramine has no effect on pre-existing drug levels of both 5HT and MIBG in thrombocytes, it was concluded that retention of either drug is mainly based on granular sequestration [40].

It is still uncertain by which specific uptake system – 5HT transporter or uptake-one – MIBG is taken up by human thrombocytes. Rutgers et al. provided evidence, through experiments with fluvoxamine (a selective inhibitor of 5HT re-uptake), for uptake by the 5HT transporter [40]. However, Glowniak et al., who studied cells transfected with the human NE transporter, the rat 5HT transporter or the bovine dopamine transporter, reported that specific uptake of 20 n*M* MIBG is exclusively by the human NE transporter [41]. Anyhow, it is of pharmacological and toxicological interest that clinically relevant levels of fluvoxamine (0.1 μ*M*) can selectively reduce MIBG uptake in thrombocytes with minimal effects on its uptake into neuro-adrenergic cells [40]. The possibility that the earlier mentioned thrombocytopenia is caused by direct radiation-induced damage of radioiodinated MIBG specifically taken up in thrombocytes seems unlikely since thrombocytes lack a nucleus, being the main target for radiation-induced cell death [42], and because of the delayed manifestation of thrombocytopenia in patients [40]. Therefore, megakaryocytes – the nucleus-containing progenitors of thrombocytes – might be the targets of radioiodinated MIBG in relation to thrombocytopenia, a hypothesis which has still to be proven [40].

Bioanalysis, pharmacokinetics, metabolism and excretion

Human pharmacokinetic data procured after administration of diagnostic doses of [^{123}I/^{131}I]MIBG to controls [5, 43] and patients [36, 44–47] and of therapeutic doses of [^{131}I]MIBG [47] have been published (Tables 4, 5). These data concern measurements of total radioactivity without taking into account the presence of [^{123}I/^{131}I]iodide and possible metabolites of [^{123}I/^{131}I]MIBG. Moreover, the numbers of subjects are small and the sampling times are very limited; data about the mass dose of MIBG (in mg) are mostly incomplete. Nevertheless, it can be concluded that, following intravenous administration of radioiodinated MIBG, radioactivity is distributed from the vascular compartment within 1 h, rapidly followed by a slow redistribution from the peripheral compartment into the central compartment.

Terminal elimination half-lives of radioactivity from blood have been reported to be 47–90 h (medullary thyroid carcinoma, $n = 3$ [45]) and 9–130 h (neuroblastoma, $n = 8$ [46]). The difference in these values is probably related not to the underlying disease but to the pharma-

Table 4. Total radioactivity[a] in whole blood or plasma[b] after intravenous administration of diagnostic and therapeutic[b] amounts of [^{123}I/^{131}I]MIBG

Subjects	*n*[c]	Dose	5 min	30 min	1 h	2 h	6 h	24 h	48 h	Reference
Neuroblastoma, children	1?	[^{131}I]MIBG 26 MBq=0.5 mg	Blood: 1% Plasma: 0.7%	0.4% 0.3%	0.3% 0.2%	–	–	–	–	Munkner [36]
Phaeochromocytoma, male adults	3	0.19–0.20 GBq [^{123}I]MIBG (0.42–0.49 GBq/mg[d])	–	–	–	536 Bq/ml	–	226 Bq/ml	–	Shulkin et al. [44]
Medullary thyroid carcinoma, adults	3	37 MBq [^{131}I]MIBG	<10%	–	–	–	–	–	<1%	Clarke et al. [45]
Neuroblastoma, children 9–32 kg	8	20 MBq [^{131}I]MIBG=0.27 mg or 3.7 MBq/kg [^{123}I]MIBG= 10 μg/kg	–	–	1.5%–10% 4.4%[e]	–	–	–	–	Lashford et al. [46]
Neuroblastoma, children 1.5–10 years	9	Diagnostic [^{131}I]MIBG 75 MBq=2.6 mg	–	–	–	–	0.6%–1.7% 1.2%[e]	0.4%–1.0% 0.6%[e]	–	Fielding et al. [47]
Neuroblastoma, children 1.5–10 years	3	Therapeutic [^{131}I]MIBG (1.6–8.0 mg)	–	–	–	–	1.0%[e]	0.5%[e]	–	Fielding et al. [47]

–, Not reported
[a] Expressed as percentage of the administered dose present at the indicated time after injection or expressed as concentration in whole blood
[b] Solely where indicated
[c] *n*, Number of subjects studied
[d] Specific activity
[e] Mean

cokinetic model used [45, 46]. In future pharmacokinetic studies concerning the vascular compartment more attention needs to be paid to separate detection of free radioiodide and radioiodinated MIBG, since Blake et al. reported 1 h after intravenous injection of [^{123}I]MIBG containing 0.5%–1.0% of free [^{123}I]iodide, 10%–15% levels of free [^{123}I]iodide in serum [48], which may be the result of different distribution patterns for the two compounds. Unfortunately, no details or validation figures were given for the separation method [48]. The other differentiation that can be made is between whole blood and plasma, since as early as 2 min after injection of [^{123}I]MIBG, 53% of intravascular radioactivity was reported to reside in the blood cells, increasing to 72% and 78% at 2 h and 24 h, respectively [44].

Table 5 demonstrates that, following intravenous administration of [^{123}I/^{131}I]MIBG, radioactivity is rapidly and almost entirely excreted in urine and that the rate of excretion is similar for a diagnostic or a therapeutic dose, although more data after therapeutic [^{131}I]MIBG are needed. The importance of renal excretion is confirmed by faecal recoveries of radioactivity ≤2% (0–24 h or 0–4 days) [5, 44, 49]. Blake et al. [48] observed that the glomerular filtration rate (GFR) had a major influence on MIBG pharmacokinetics. Statistically significant correlations were found between GFR and the renal plasma clearance rate (RPCR) of total radioactivity (r = 0.87) and between GFR and RPCR of [^{123}I]MIBG (r = 0.92) with GFR ranging from 60 to 120 ml/min [48]. Moreover, both the RPCR of total radioactivity and that of [^{123}I]MIBG were higher compared to GFR, by factors 1.93 and 2.48, respectively [48]. This may indicate that MIBG is also excreted by a tubular secretion mechanism. The importance of renal function for MIBG pharmacokinetics was also reported by Tobes et al., who, in an anephric patient, observed a relatively slow clearance of radioactivity from the blood and only marginal removal of radioactivity by haemodialysis [50]. The increased intravascular amounts of radioactivity in the anephric patient and, to a lesser extent, in patients with moderate or mild renal insufficiency, were reflected by higher plasma/blood cell distribution ratios [50].

Mangner et al. [49, 51] developed a procedure, including sample pretreatment, high-performance liquid chromatographic separation and on-line UV and radioisotope detection, to make possible study of the metabolic pattern in urine of patients who underwent [^{131}I]MIBG therapy. The authors investigated spot urine samples, and not total urinary output, up to 6 days after intravenous administration of 4.1–7.9 GBq (specific activity: 0.9–1.5 GBq/mg) [^{131}I]MIBG in nine malignant phaeochromocytoma patients. In eight of the nine patients [^{131}I]MIBG represented 60%–92% of total radioactivity per sample [49]. In the urine of the remaining patient, [^{131}I]MIBG and its metabolite [^{131}I]metaiodohippuric acid ([^{131}I]MIHA) each represented >40% of total radioactivity [49]. In all urine samples [^{131}I]MIHA (usually 2%–16%) is, in addition to [^{131}I]iodide (2%–6%), the pri-

Table 5. Cumulative radioactivity excreted in urine[a] after intravenous administration of diagnostic and therapeutic[b] amounts of [^{123}I/^{131}I]MIBG

Subjects	n[c]	Dose	0–3 h	0–4 h	0–12 h	0–1 days	0–2 days	0–3 days	0–4 days	0–6 days	Reference
Controls, male adults	5	74 MBq [^{123}I]MIBG=0.4 mg	–	–	–	53%–70% 64%[d]	–	–	–	–	Kline et al. [5]
Controls, male adults	6	18.5 MBq [^{131}I]MIBG	7.9%–26% 19%[d]	–	–	35%–52% 46%[d]	–	62%–76% 68%[d]	–	–	Chambon et al. [43]
Phaeochromocytoma, male adults	2	0.19–0.20 GBq [^{123}I]MIBG (0.42–0.49 GBq/mg[e])	–	–	50%[d]	65%[d]	–	–	–	–	Shulkin et al. [44]
Medullary thyroid carcinoma, adults	3	37 MBq [^{131}I]MIBG	–	–	–	30%–60%	40%–80%	–	–	–	Clarke et al. [45]
Neuroblastoma, children 9–32 kg	7	20 MBq [^{131}I]MIBG=0.27 mg or 3.7 MBq/kg [^{123}I]MIBG= 10 μg/kg	11%–26% 13%[d]	–	–	–	–	–	–	–	Lashford et al. [46]
Phaeochromocytoma	8	16–20 MBq [^{131}I]MIBG (0.057–0.23 GBq/mg[e])	–	–	–	40%–55%	–	–	70%–90%	–	Mangner et al. [49, 51]
Neuroblastoma (2) paraganglioma (1)	3	Therapeutic [^{131}I]MIBG 5.6–7.4 GBq (1.5–2.0 GBq/mg[e])	–	10%–30%	–	–	–	–	85%–95%[f]	91%[g]	Wafelman et al. [52]

–, Not reported; [a] Expressed as percentage of the administered dose excreted during the indicated period; values are corrected for radioactive decay; [b] Solely where indicated; [c] n, Number of subjects; [d] Mean; [e] Specific activity; [f] Neuroblastoma patients (n=2); [g] Paraganglioma patient

mary metabolite [51]. The metabolites [^{131}I]parahydroxymetaiodobenzylguanidine and [^{131}I]metaiodobenzoic acid ([^{131}I]MIBA) were found to be present in only very small quantities (0.5%), or not at all [49]. Identification was accomplished by addition of authentic unlabelled or labelled compounds to selected samples and comparison of retention times, using a pH shift in the chromatographic system as an extra identifier for the metabolites [^{131}I]MIHA and [^{131}I]MIBA [49]. Preliminary experiences with a modified version of the method have been published by our group [52, 53]. The merits of our study include measurement of the total urinary output after therapeutic doses (Table 5) and the greater diversity of the patient population, which includes neuroblastoma patients. As in patients with malignant phaeochromocytoma [49, 51], apart from [^{131}I]MIBG (77%–96% of the radioactivity per urine sample) and [^{131}I]iodide, [^{131}I]MIHA and occasionally [^{131}I]MIBA were found in the urine of neuroblastoma patients [52, 53]. These results conflict with those of Ehninger et al. [54], who also studied the pharmacokinetics of [^{131}I]MIBG in neuroblastoma patients and reported the absence of metabolites. However, Ehninger et al. [54] limited themselves, by the solid phase extraction technique they used for the patient samples instead of high-performance liquid chromatography (HPLC), to only two discernible fractions that in fact might be mixtures of compounds. An important finding of Mangner et al. is that the radioactivity in two extracted tumour species consisted to ≥97% of [^{131}I]MIBG, the remainder being [^{131}I]iodide [49]. It can be concluded that in general MIBG is metabolized to a minor degree and that it is excreted predominantly unchanged in urine.

All bioanalytical procedures mentioned thus far measure the radioisotope ^{131}I, either as [^{131}I]MIBG, [^{131}I]-labelled metabolite or free [^{131}I]iodide. However, in the literature two bioanalytical methods have been described which use HPLC separation and UV detection for the selective determination of MIBG [55, 56]. These methods are valuable when determination of the samples has to be postponed until the radioisotope has decayed or when patients receiving only unlabelled MIBG need to be investigated.

Drug interactions

In tumour imaging and therapy using radiopharmaceuticals the aim is to obtain the highest possible uptake in the targets at the lowest possible radiation burden to the rest of the patient's body. In this respect, drug interactions may play a role, either planned or unintentional. Recently, an overview has been published on medication interfering with MIBG [57]. The drugs were classified according to their mechanism of interaction, i.e. (1) inhibition of uptake-one, (2) inhibition of granular uptake, (3) competition for granular uptake, (4) depletion of content from storage granule, (5) calcium mediated or (6) other possible unknown mechanisms [57]. According to this system the drugs mentioned earlier in the *Cellular uptake and retention* section can be classified as follows: (1) (desmethyl-) imipramine, cocaine and – although indirectly through inhibition of (Na^+/K^+)-ATPase – ouabain, (2) reserpine and tetrabenazine, (3) NE, (4) reserpine and tetrabenazine and (5) nifedipine. Considering the described differences between SK-N-SH and PC-12 cells (Table 3), it can be expected that for granule-poor neuroblastomas only interaction (1) will be of clinical importance, whereas for granule-rich phaeochromocytomas all mechanisms of interaction will apply. Indeed, in the literature there is only one report on interactions with neuroblastoma cells, presumably through mechanism (1); this report concerned the in vitro 50% inhibition of uptake of 0.1 μ*M* [^{125}I]MIBG in SK-N-BE(2C) cells by 70 n*M* chlorpromazine, 0.3 μ*M* prochlorperazine (both imipramine-related phenothiazines) or 0.2 μ*M* haloperidol. Interestingly, metoclopramide and two other dopamine/serotonin receptor antagonists did not inhibit [^{125}I]MIBG uptake at concentrations up to 10 μ*M* [58]. Therefore, when anti-emetics are needed during [^{131}I]MIBG therapy, metoclopramide can be used.

The interaction most reported in vivo is the inhibition of MIBG uptake in both phaeochromocytomas [59–61] and the myocardium [62] by labetalol, which is widely used for the perioperative management of phaeochromocytoma patients due to its combined α_1- and β-blocking effects. Labetalol is reported to interfere with MIBG uptake by mechanisms (1) and (4) [59]. Of a group of patients with myocardial infarction, none of those ($n = 3$) on labetalol treatment showed any myocardial uptake of [^{123}I]MIBG, whereas patients on other medication did [61]. However, in general, myocardial uptake in patients with a myocardial infarction was slightly reduced by calcium antagonists or amiodarone [61]. Similarly, in patients with left ventricular hypertrophy secondary to valvular aortic stenosis the myocardial uptake of [^{123}I]MIBG was significantly reduced by amiodarone or digoxin [63]. This is in conflict with the view of Khafagi et al. [59], who mentioned digitalis glycosides in a list of drugs with no significant effect on MIBG uptake. However, the in vitro inibitory effect on MIBG uptake of the digoxin analogue ouabain [21, 22] also justifies some reservation in using MIBG and cardiac glycosides concomitantly. The overview by Solanki et al. [57] includes a list of intranasal anti-asthmatic sympathomimetics that are expected to reduce the uptake of MIBG in targets. Indeed, in normal man ($n = 3$) a single oral dose of 75 mg of the sympathomimetic phenylpropanolamine resulted in a significant increase in the cardiac washout and the excretion in urine of [^{123}I]MIBG [64]. In the same study imipramine (25 mg t.i.d. for 7 days) also resulted in a significant increase in the cardiac washout of [^{123}I]MIBG, combined with a significant (50%) inhibition of uptake [64].

So far, only unintentional drug interactions have been reviewed. However, Blake et al. reported an attempt at planned interaction using oral nifedipine (20 mg slow-

release tablets, t.i.d., starting 48 h before injection of [^{123}I/^{131}I]MIBG) in phaeochromocytoma patients, expecting prolonged retention of [^{123}I/^{131}I]MIBG in the tumour by blocking of Ca^{2+}-dependent exocytosis (see also Table 3) [65]. In three out of eight patients an increase in tumour uptake by a factor of 1.3–1.5 was reported at t = 24 h after tracer administration, and in two patients there was a prolonged biological half-life of radioactivity in the tumour, from 1.4 to 2.2 days and from 3.5 to 4.4 days, respectively, compared with a tracer dose without nifedipine in the same patients [65]. However, to be effective, nifedipine plasma concentrations had to be greater than the therapeutic level of 15–35μg/l.

Cytotoxicity, dosimetry and side-effects

Cytotoxicity

In in vitro studies Smets et al. [66] observed anti-proliferative activity of non-radioactive MIBG using different cell lines including neuroblastoma (LA-N_1, N_1E115 and CHP212) and melanoma cells. Cell numbers after 72 h of incubation with 60 μ*M* of MIBG were 7%–44% of control values without greater reduction of the neuroblastoma or melanoma cells compared with the other cells, presumably since none of the cells showed a significant, specific uptake of MIBG [66]. Others reported blocking of proliferation of the human premonocytic cell line U937 after overnight incubation with 100 μ*M* MIBG [67]. In vivo toxicology studies in mice with daily i.p. push injections of 50 mg/kg MIBG for 5 days yielded 100% mortality (n = 16) after one to four doses, whereas 40 mg/kg for 5 days showed no toxic effects [66]. Regimens of four daily injections of 20 mg/kg MIBG to leukemia-bearing mice and nine daily injections of 40 mg/kg to N_1E115 neuroblastoma-bearing mice yielded 177% and 186% prolongation of survival, respectively [66]. Metaiodobenzylamine tested at 50 mg/kg in the same schedules showed no effect, indicating the importance of the guanidine group of MIBG for its cytotoxic and antitumour activities [66]. Since plasma concentrations of MIBG after therapeutic doses of 7.4 GBq [^{131}I]MIBG (specific activity >1.1 GBq/mg) are <0.1 μ*M* ([23] and own observation), it can be concluded that MIBG does not contribute to the antitumour activity of [^{131}I]MIBG therapy. Moreover, only two out of ten carcinoid patients treated with escalating doses of MIBG up to 80 mg experienced some short-term (1–3 weeks) palliation without any objective response [68].

Consequently, the radionuclide is responsible for the anti-tumour activity of radioiodinated MIBG. The antitumour activity depends on the radiophysical characteristics of the radionuclide and, in relation to that, on its subcellular localization. Specific activity of the radiopharmaceutical and size of the tumour may also play a role, as will be discussed.

Radiation-induced cell death is generally assumed to result primarily from damage to the nucleus, with the chromosomes being the main target [42]. Using radionuclides for therapy, cellular death is caused primarily by emitted particles – rather than photons as in external beam radiotherapy – that have a finite range [69]. Table 6 lists earlier reported [69, 70] radiophysical and radiobiological (calculated using a mathematical model) characteristics of the radionuclides in use or under investigation as therapeutic agents bound in radiohalogenated MXBG, i.e. ^{131}I, ^{125}I and astatine-211. Assuming a cell diameter of 10–20 μm [71, 72], it follows from Table 6 that [^{125}I]MIBG would have no cytotoxic effect, since it has an ultra-short particle range and has not been found within the nucleus [33, 35]. Kassis et al. [71] reported interesting results regarding the relation between in vitro (sub)cellular localization and cytotoxicity of ^{125}I using mammalian cells. Intranuclear 5-[^{125}I]iododeoxyuridine ([^{125}I]IUdR) appears to be 80-fold more cytotoxic than cytoplasmic [^{125}I]iododihydrorhodamine, whereas extracellular $Na^{125}I$ has no effect on cell survival. Moreover, Chan et al. showed by in vitro studies using the same cell type and [^{125}I/^{131}I]IUdR that, when delivered intranuclearly, ^{125}I has a tenfold higher cytotoxic potency compared to ^{131}I [42]. For [^{125}I]MIBG, in vitro cytotoxicity

Table 6. Radiophysical and radiobiological characteristics of different radionuclides used for tumour sterilization [from 69, 70]

Radionuclide	Emission	D_{eq}[a]	f_{abs}[b] (100 μm)	f_{abs}[b] (500 μm)	Mean range	Tumour diameter corresponding to optimal curability	Cell number corresponding to optimal curability
^{211}At	α	405[c]	≈0.5	≈0.9	60 μm	<0.6 mm	≤10^4
^{131}I	β	89[c]	0.17	0.54	800 μm	≈3 mm	≈10^6
	gamma	268[c]	<0.01	<0.01	–	–	–
^{125}I	Auger electrons	–	1	1	≈ 1 μm	1 cell	1 cell

–, Not reported

[a] D_{eq}, Absorbed dose under equilibrium conditions, i.e. when the fraction absorbed=1

[b] f_{abs}, Fraction of the equilibrium absorbed dose which is absorbed in tumour spheres of 100 μm and 500 μm radii

[c] Expressed as 10^{-10} J/Bq

towards SK-N-SH cells has been reported [25, 73], but the effects were comparable with [^{131}I]MIBG using the same dose and specific activity [73]. This may represent confirmation that radioiodinated MIBG is present in the cellular cytoplasm but does not enter the nucleus. In a preliminary report about human neuroblastoma xenografted mice, 50 MBq [^{131}I]MIBG (>1.1 GBq/mg) showed a fourfold higher cytotoxicity than 56 MBq [^{125}I]MIBG (111 MBq/mg) [74]. However, in vivo studies under uniform conditions (e.g. specific activity) and with tumour size as a controlled parameter are still needed to compare the potency of both radiopharmaceuticals.

In an attempt to understand better and to predict the clinical outcome of [^{131}I]MIBG therapy, O'Donoghue et al. [75] developed a mathematical model for tumour sterilization. The tumour dose received is dependent on the effective half-life of [^{131}I]MIBG in the tumour and, according to the model, is dependent on the tumour diameter up to 2 cm in such a way that a decreasing diameter is correlated with a decreased absorbed dose per gram of tumour. Tumours of ≤0.2 mm in diameter appear particularly hard to cure, which is related to the radiophysical characteristics of ^{131}I (Table 6) [75]. The same group calculated that in theory for targetted ^{131}I, tumour recurrence probability curves show a nadir around the cell number of 10^6 [72]. The increased recurrence probability with decreased cell numbers per tumour has already been mentioned [75]. The increased recurrence probability with larger tumour sizes, seen both with external beam radiotherapy and with targeted ^{131}I – only at cell numbers $>10^6$ –, was explained by the increased number of clonogenic cells [72]. The authors suggest that failure of conventional treatment modalities (e.g. chemotherapy, external beam radiotherapy, surgery) is most likely due to failure of sterilization of tumours just below the threshold of clinical detectability (i.e. range 1 mm to 1 cm diameter). Larger tumours can be subjected to surgery and smaller tumours would be more susceptible to chemotherapy and external beam radiotherapy [72].

In accordance with the predicted tumour diameter corresponding to optimal curability of 3 mm for ^{131}I and single cell (e.g. 10–20 μm) for ^{125}I (Table 6), [^{131}I]MIBG was reported to have a greater in vitro cytotoxic effect on 400-μm than on 250-μm SK-N-BE(2C) spheroids [76] and on 250-μm than on 90-μm SK-N-SH spheroids [77], whereas the effect of [^{125}I]MIBG is not tumour size related within the range 90–250 μm [77]. The cross-fire phenomenon (radiation-induced cell damage caused by radionuclides localized in neighbouring cells) [69, 70] is a characteristic of ^{131}I, but not of the ultra-short-ranged ^{125}I, and is the reason for the larger calculated tumour diameter for optimal curability with ^{131}I (Table 6). The advantage of cross-fire is that, theoretically, for tumour sterilization homogeneous distribution of the radiopharmaceutical in all tumour cells is not required; at the same time it implies radiation damage to non-targets as well [69]. However, it is encouraging that after [^{131}I]MIBG therapy of neuroblastoma at diagnosis, only 6 out of 22 patients developed thrombocytopenia and only two patients had a moderate bone marrow depression, despite the fact that nine patients had bone marrow involvement by tumour [78]. Interestingly, in agreement with Table 6, the α-emitting [^{211}At]*meta*-astatobenzylguanidine ([^{211}At]MABG) was recently found to induce in vitro cytotoxicity towards SK-N-SH cells much more efficiently than β^--emitting [^{131}I]MIBG [79]. Moreover, the particle range of ^{211}At, being several cell diameters, predicts some cross-fire effects (Table 6). However, the short physical half-life ($t_{1/2}$ = 7.2 h) and logistic problems (a cyclotron is needed for production) will limit future use of [^{211}At]MABG for radionuclide therapy.

The finding that in vitro [^{131}I]MIBG of high specific activity (0.74–1.1 GBq/mg) showed a 20-fold higher incorporation of radioactivity in SK-N-SH cells (and therefore a higher cytotoxicity) compared to [^{131}I]MIBG of low specific activity (7.4–11 MBq/mg) [73] may not hold in vivo. Rutgers et al. [80] recently reported the influence of specific activity (1.5 MBq/mg, 15 MBq/mg, 0.15 GBq/mg and 1.5 GBq/mg) of [^{131}I]MIBG on tumour uptake and tumour/normal tissue ratios of SK-N-SH and PC-12 xenografted mice. Whereas in PC-12 xenografts, as expected, tumour uptake of radioactivity decreased with decreasing specific activity, in SK-N-SH xenografts tumour (and adrenal) uptake was not decreased at 15 MBq/mg compared to 1.5 GBq/mg, while tumour/(liver, heart, salivary glands) ratios were higher at 15 MBq/mg. Predosing with MIBG instead of lowering specific activity gave comparable results [80].

Dosimetry

In radiopharmaceutical therapy dosimetry is required to assess absorbed radiation doses to tumours and normal tissues. Sufficient approximation of absorbed doses may aid clinical decision making and treatment strategy planning. In order to perform tumour dosimetry one must have knowledge of the following parameters: the mass of the tumour to be treated, the amount of radiopharmaceutical taken up by the tumour, the effective half-life of the radiopharmaceutical in the tumour and the effective energy of the radionuclide. It has been suggested that a tumour dose exceeding 150 Gy is necessary to produce beneficial effects [8]. However, complete responses have been reported at much lower calculated tumour doses, e.g. 65 Gy [81] or even <10 Gy [14]. It is generally accepted that with the techniques currently used in vivo the correlation between the calculated absorbed radiation dose and tumour response remains poor [14, 81–83]. The procedures include computer tomography, ultrasonography or magnetic resonance imaging for the assessment of tumour volume; repeated conjugate view imaging of the patient after a diagnostic dose and extrapolation to a therapeutic dose to establish tumour uptake and effective half-life; and the Medical Internal Radiation

Table 7. Absorbed radiation doses[a] to the whole body and selected organs

Organ	Fielding et al. [47][b] Children (n=26) (Gy)	Fielding et al. [47][b] Children (n=26) (mGy/MBq)	Kimmig et al. [87][c] (n=13)[d] (mGy/MBq)	Ertl et al. [92][c] Adults (n=3) (mGy/MBq)	Jacobsson et al. [93][c] (n=14)[d] (mGy/MBq)
Whole body	0.7–2.6	0.14–0.65	0.22	0.112	0.055–0.12
Red marrow	0.9–2.6	0.17–0.63	0.22	0.12[c e]	0.046–0.087
Blood	0.2–1.9	0.04–0.17	–	–	–
Bladder	18–38 (n=5)	2.2–5.3	–	–	0.6
Liver	1.6–11.3	0.3–1.9	0.62	0.152[e]	0.50–1.2

–, Not reported

[a] Expressed as range of values or mean value

[b] Data from therapeutic doses of [^{131}I]MIBG (see text)

[c] Data from diagnostic doses of [^{131}I]MIBG (see text)

[d] Although not indicated in the text, the patients are presumably adults, since both studies investigated patients who were referred for suspected phaeochromocytoma

[e] Organ doses in this study were calculated by extrapolation of data from mice to man

Dose (MIRD) scheme for assessment of the cumulated absorbed dose. A new technique for the determination of tumour uptake – using single-photon emission tomography – has been reported [84]. Also, initial results of positron emission tomography (PET) using [^{124}I]MIBG have been published [85]. The greater spatial resolution of PET may improve dosimetric calculations [85]. However, inaccuracies still remain in estimating not only tumour volume but also, more importantly, the actual mass of viable tumour tissue to be treated. Moreover, the MIRD scheme assumes homogeneous uptake of the radiopharmaceutical in a tumour, which may not be the case for a variety of reasons (e.g. hypoxic or necrotic parts of the tumour, or tumour consisting of different cell lines, not all of which take up and retain MIBG specifically).

In order to establish the maximum allowable dose in relation to toxicity, the critical organ should be known. As treatments with [^{131}I]MIBG are associated with reduced numbers of circulating thrombocytes and – to a lesser extent – leucocytes, bone marrow is considered to be the critical organ [86], with a maximum acceptable radiation absorbed dose of 2.5 Gy [87]. In order to limit the bone marrow dose, in adults the maximum allowable blood dose is 2 Gy [88] and in children the effects of a whole-body dose up to 2.5 Gy after [^{131}I]MIBG therapy have recently been investigated in a multicentre setting [89]. In 1983, from scintigraphic studies using 18.5 MBq (specific activity 0.13 GBq/mg) [^{131}I]MIBG in 13 patients, Kimmig et al. estimated that 7.4 GBq [^{131}I]MIBG, yielding a whole-body dose of 1.6 Gy, is the maximum acceptable single dose for therapy [87]. Consequently, in the Netherlands Cancer Institute a dose of 3.7, 5.6 or 7.4 GBq [^{131}I]MIBG is routinely given, generally starting with 7.4 GBq, except in infants (aged <1 year) [90].

Another method of establishing a therapeutic dose regimen is based on individual calculation of the expected dose to the limiting organ. As part of the earlier mentioned multicentre study [89] Fielding et al. [91] compared the predictive value of three different methods for the calculation of the whole-body dose in childhood patients with resistant neuroblastoma. These authors found that the method based on the whole-body dose data of the pretherapy tracer study of an individual patient was most predictive. Using this method, similar kinetics of a tracer or a therapeutic MiBG dose were assumed. The other procedures used the patient's body weight or the average whole-body retention curve, referring to collective [^{131}I]MIBG therapy data [91]. However, even with the most predictive method only eight (31%) out of 26 patients received the expected whole-body dose to within 5%, whereas in 65% of the patients too little activity was administered [91]. Similar observations were reported by Sisson et al. [86], who found that whole-body dosimetry after therapy yielded 72%–93% (n = 6) of the expected absorbed whole-body dose calculated from a tracer dose. Apparently, there was accelerated clearance of [^{131}I]MIBG for therapy (1.7–8.0 mg MIBG administered) compared to tracer [^{131}I]MIBG (0.8–2.7 mg MIBG administered) [91]. This may be explained by the difference between a tracer and therapeutic MIBG mass dose [30] and by different pharmacokinetic behaviour due to cell damage caused by therapy. If the same 26 patients had received a fixed dose of 7.4 GBq [^{131}I]MIBG, calculated whole-body doses would have ranged from 0.9 to 4.8 Gy [91]. Regarding clinical outcome, although toxicity was the main interest of the study, no relationship could be established between prescribed activity, mass of MIBG administered or absorbed whole-body radiation dose and tumour response [89].

Absorbed radiation doses to the whole body and some important organs after therapeutic amounts of [^{131}I]MIBG [47] are shown in Table 7. For comparative reasons data from other studies [87, 92, 93] are also shown, although most of these results concern adult patients and are based on tracer doses (18.5–40 MBq

Table 8. Whole-body elimination kinetics of radioactivity after intravenous injection of [^{131}I]MIBG in different species [from 92]

	First phase			Second phase		Third phase	
Subjects	n^a	Q_1^b	T_1^c	Q_2^b	T_2^c	Q_3^b	T_3^c
Human adults	3	23%–37%	0.27–0.61	62%–75%	1.3–1.6	1.0%–2.4%	5.1–6.6
		28%[d]	0.45[d]	70%[d]	1.4[d]	1.7%[d]	5.9[d]
Human child	1	57%	0.35	42%	1.3	0.6%	5.9
Mice	20	87%[d]	0.24[d]	12%[d]	1.4[d]	0.7%[d]	5.3[d]

[a] n, Number of subjects studied
[b] $Q_{1,2,3}$, Percentage of radioactivity excreted in the first, second or third component, respectively
[c] $T_{1,2,3}$, Effective half-life of elimination (in days) of the first, second or third component, respectively
[d] Mean

[^{131}I]MIBG); information on specific activities and administered mass doses of MIBG is sometimes lacking [92, 93]. The data from Fielding et al. (Table 7) indicate a high absorbed dose for the bladder wall – despite a fluid intake of ≥3 l/m^2 during the first 24 h and frequent voidings – and therefore in addition to bone marrow the bladder is considered as a dose-limiting organ [47]. However, no acute toxicity related to the bladder has yet been reported [47]. Interestingly, calculated absorbed doses to the liver are within the tolerance dose, which is 20 Gy [87]. Accordingly, no acute hepatic toxicities have been reported [47]. Ertl et al. compared the whole-body retention of radioactivity after intravenous injection of [^{131}I]MIBG (specific activity not reported) in adults (20 MBq, $n = 3$), one child (20 MBq) and mice (administered activity not reported, $n = 20$) [92]. In all three species the authors found a triphasic elimination; the main difference was the percentage of radioactivity excreted in the first (rapid) phase of elimination, increasing in the following order: adults < child < mice (Table 8) [92].

Finally, different radiobiological effects from different radionuclides need to be considered. Sisson et al. stated that absorbed whole-body radiation doses of 1 Gy from [^{125}I]MIBG and 2 Gy from [^{131}I]MIBG produce thrombocytopenia in the same order of magnitude [94]. More recently, however, the same authors reported that, unlike with [^{131}I]MIBG, whole-body dosimetry does not reliably predict thrombocytopenia from [^{125}I]MIBG therapy [95]. On the other hand, a dose administered per square meter of body surface area (GBq/m^2) gave an acceptable prediction of thrombocytopenia from both [^{131}I]MIBG and [^{125}I]MIBG [95].

Side-effects

In general, [^{131}I]MIBG treatment is well tolerated. In a group of 14 adults treated for neural crest-derived tumours, only one carcinoid patient experienced haematological side-effects. The bone marrow of this patient was invaded by tumour [96]. In 29 children treated for neuroblastoma with [^{131}I]MIBG after conventional treatment, haematological side-effects, mainly thrombocytopenia, occurred in 25. The influence of the bone marrow status on the haematological toxicity was striking when the patients were treated with [^{131}I]MIBG after conventional chemotherapy: 12 out of 13 patients with invaded bone marrow at the time of [^{131}I]MIBG therapy developed severe bone marrow depression [96]. Also, the reduction in the number of circulating leucocytes and thrombocytes is more pronounced in patients who have undergone bone marrow transplantation than in patients with a normal bone marrow status [86].

In the multicentre study on the toxicity of [^{131}I]MIBG therapy in chemoresistant neuroblastoma patients, Lashford et al. [89] found a significant association between the anticipated whole-body absorbed radiation dose (1.0 Gy, 2.0 Gy or 2.5 Gy) and the development of thrombocytopenia or neutropenia. Whereas an absorbed dose of 1.0 Gy did not yield any major toxicity, at 2.0 Gy and 2.5 Gy, 31% and 80% of patients, respectively, developed grade 3 or 4 thrombocytopenia. Moreover, grade 3 or 4 neutropenia was observed in 40% of the patients with an intended whole-body absorbed radiation dose of 2.5 Gy [89]. In contrast, it is encouraging that when [^{131}I]MIBG was used for therapy at diagnosis (without previous chemotherapy), only 6 of 22 patients developed thrombocytopenia and only two had moderate bone marrow depression, although nine showed bone marrow involvement of the tumour [78].

Renal toxicity (decreased GFR) has occasionally been reported when [^{131}I]MIBG has been used after conventional therapy [89, 97]. Lashford et al. noticed a trend towards greater renal toxicity with increases in the intended whole-body dose [89]. However, since the patients were often intensely pretreated with platinum derivatives, it is uncertain whether [^{131}I]MIBG was the (only) cause of the nephrotoxicity [96, 97]. There is one report of toxicity to the adrenal gland, which resulted in hypoadrenalism, requiring substitution therapy [96]. Further reported minor toxicities include transient hepatic enzyme increase, nausea, vomiting, fever [86, 96, 98, 99] and chest pain [100]. No long-term adverse reactions of radioiodinated MIBG have as yet been described.

There is a lot of experience with [^{131}I]iodide, which is used for radionuclide therapy of thyroid carcinoma. Hoefnagel [90] reviewed the reported side-effects of [^{131}I]iodide therapy, and found no increased incidence of fertility disorders or birth abnormalities during long-term follow-up after treatment and emphasized the rarity of induction of leukaemia. Recent papers confirm the lack of a significant increase in birth anomalies or a significant decrease in fertility after [^{131}I]iodide therapy [101–103]; nevertheless, avoidance of pregnancy is advocated for at least 1 year after [^{131}I]iodide therapy [101].

Conclusions and future prospects

The biodistribution of (radioiodinated) MIBG, initially introduced for the visualization of the adrenal medulla and related neoplasms, allows its clinical use for diagnosis and therapy of various neural crest-derived tumours [1]. The early myocardial uptake of radioiodinated MIBG and significant changes in it due to various cardiomyopathies are being investigated [2]. Especially [^{123}I]MIBG – given its gamma photons that are ideally suited for gamma cameras and the early myocardial uptake – may have a role as a cardiac function tracer.

Table 4 shows that pharmacokinetic data for radioiodinated MIBG are incomplete. Moreover, since these data concern total radioactivity, validated separation techniques are needed in order to assess blood pharmacokinetics of radioiodinated MIBG and radioiodide individually.

Regarding metabolism and excretion, investigations after diagnostic doses in patients revealed that radioactivity is excreted rapidly and predominantly in urine (Table 5), whereas a study after therapeutic doses demonstrated that [^{131}I]MIBG is metabolized only to a minor degree. Excretion data and more metabolism data after therapeutic doses of [^{131}I]MIBG are needed from a more diverse patient population in order to assess possible age- or tumour type-related differences.

In vitro research revealed that, for the amounts of MIBG used in clinical practice, specific uptake-one is the main MIBG uptake mechanism for phaeochromocytoma and neuroblastoma. Retention in phaeochromocytoma cells is based on specific granular uptake, contrasting with the cytoplasmic residence and a dynamic equilibrium (leaking out and rapid re-uptake) in neuroblastoma. This may have consequences for the effect of intended drug interactions. Medication interfering with granular storage or exocytosis will have less effect on neuroblastoma than on phaeochromocytoma.

In general, therapy of neural crest-derived tumours with [^{131}I]MIBG is well tolerated, but its effectiveness needs improvement. From in vitro studies it appears that, for phaeochromocytomas and neuroblastomas, short infusions (i.e. 2 h) might provide an optimal tumour loading dose. Selective blocking of uptake of MIBG by thrombocytes (and possibly megakaryocytes) with fluvoxamine may be an interesting future method of decreasing the haematological toxicity while increasing the tumour absorbed dose. Alternatively, decreasing the specific activity of [^{131}I]MIBG may lead to an unchanged [^{131}I]MIBG uptake in neuroblastoma combined with a decreased uptake in normal tissues; this may also allow the administration of higher amounts of radioactivity without increasing the toxicity. Other neural crest tumour cell lines (e.g. carcinoid) and human carcinoid xenografts are needed, because of the different uptake and retention behaviour of radioiodinated MIBG in different tumours.

Regarding the theoretical models on the radiobiological effects of different radioisotopes and external beam radiotherapy, before considering the combination of these therapies, more xenografted animal studies are needed in order to prove the hypothesis that [^{125}I]MIBG, external beam radiotherapy and chemotherapy are more effective in the sterilization of micrometastases compared to [^{131}I]MIBG.

Estimates of tumour absorbed radiation dose from [^{131}I]MIBG are currently unreliable; improvement of in vivo dosimetric techniques is needed to implement adequate dosimetry in clinical decision making and strategy planning. An alternative may be to use whole-body absorbed radiation dose estimates from individual pretherapeutic [^{131}I]MIBG tracer studies in order to prescribe therapeutic doses based on estimated toxicity. For correct dosimetry it may be desirable to use diagnostic [^{131}I]MIBG of such a low specific activity that the same mass dose of MIBG is administered as with therapeutic [^{131}I]MIBG.

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