

MIBGen® - Iobenguane [¹²³I] injection (Diagnostic)

Description

MIBGen® is a ready-to-use, single-use, sterile, pyrogen free, colourless radiolabelled injection of iobenguane sulfate [¹²³I] in isotonic phosphate buffer containing 1% Benzyl Alcohol at a pH of 4.0 to 7.0. The solution contains 23 mg/mL of sodium phosphate monobasic dihydrate, 2.8 mg/mL of sodium phosphate dibasic (anhydrous), 10 mg/mL of benzyl alcohol and approximately 0.5mg/ml of ascorbic acid. The chemical concentration of iobenguane sulfate is approximately 0.035 mg/mL. The radioactive concentration of iobenguane sulfate [¹²³I] (Diagnostic dose) is 90.0 to 110.0 MBq/mL at the calibration date and time.

Physical Characteristics of Iodine-123

Iodine 123 has a physical half-life of 13.2 hours, and has 83.6% disintegrations at an energy level of 159 keV.

The specific gamma ray constant for Iodine-123 is 7.478 E-5 mSv/hr per MBq @ 1.0 meter.

The mass attenuation coefficient (μ) in lead is 1.4109 cm²/g, (Ref. 1) and the attenuation factors for lead are as follows:

Thickness of lead (cm)	Factor
0.0433	0.5
0.1439	0.1
0.2876	0.01

To correct for the effect of decay multiply the activity on the calibration time and date by the appropriate factor from the table below.

Hours	Factor	Hours	Factor
1	0.949	9	0.625
2	0.901	10	0.593
3	0.855	11	0.563
4	0.817	12	0.534
5	0.770	13	0.507
6	0.731	14	0.481
7	0.694	15	0.457
8	0.658	16	0.434

Pharmacology

Iobenguane [¹²³I] is a radioiodinated aralkylguanidine. Its structure contains the guanidine-group from guanethidine linked to a benzyl-group into which iodine is introduced. Like guanethidine the aralkylguanidines are adrenergic neuron blocking agents. As a consequence of a functional similarity between adrenergic neurons and the chromaffin cells of the adrenal medulla iobenguane is able to localise preferentially in the medulla of the adrenal glands. In addition localisation in the myocardium, salivary glands, liver, spleen and large bowel occurs.

Pharmacodynamic properties

Of the various aralkylguanidines iobenguane is the preferred substance because of its lowest liver-uptake and its best in vivo stability, resulting in the lowest achievable thyroid uptake of liberated iodine.

Transport of iobenguane across the cell membranes of cells originating from the neural crest is an active process when the

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concentration of the drug is low (as in diagnostic dosages). The uptake mechanism can be inhibited by uptake of inhibitors such as cocaine or desmethylimipramine.

After uptake an active mechanism transfers at least part of the intracellular iobenguane into the storage granules within the cells.

Pharmacokinetic properties

Iobenguane is to a large extent excreted unaltered by the kidneys. 70% to 90% of administered doses are recovered in urine within 4 days. The following metabolic breakdown products are recovered in urine: radioiodide, radioiodinated meta-iodohippuric acid, radioiodinated hydroxy-iodobenzylguanidine and radioiodinated meta-iodobenzoic acid. These substances account for approximately 5 to 15% of the administered dose. The distribution pattern of iobenguane includes rapid initial uptake in liver (33% of administered dose) and much less in lungs (3%), myocardium (0.8%), spleen (0.6%) and salivary glands (0.4%). Uptake in normal adrenals (adrenal medulla) can lead to visualisation with ¹²³I-iobenguane. Hyperplastic adrenals show high uptake. In a study by Blake (Ref 3) it was found that the renal plasma clearance rate of free Iobenguane for a patient with normal GFR of 120 mL/min was 300 mL/min, indicating the importance of tubular secretion. Tobes (Ref 4) reported that the degree of renal insufficiency was directly correlated to whole-body retention. The authors noted that renal insufficiency may affect interpretation of scintigrams and radiation dosimetry.

Clinical Trials

Phaeochromocytomas

The Efficacy of Iodine-123-MIBG as a Screening Test for Pheochromocytoma.

Mozley P D et al The Journal of Nuclear Medicine 35 (7) 1138-44

Summary: The primary objective of this study was to characterise the effectiveness of ¹²³Iobenguane (MIBG) as a screening test for phaeochromocytoma in routine clinical practice. Methods: Planar images were obtained with a standardised protocol in a diverse group of patients. The intensity of uptake in each adrenal gland was graded on a 0-3 point scale by using the intensity of activity in the liver as a reference. Follow-up data was obtained from both the patients and the referring physicians. A final diagnosis was eventually established in 120 patients who had a total of 238 adrenal glands. Results: There was an intramedullary phaeochromocytoma in 24 of the 238 adrenal glands (10.1%). The uptake was very intense (Grade 3) in 21 of them (87.5%). The uptake was only mildly to moderately increased in the other three intradrenal tumors. There was no visible uptake in 148 of the 214 (69.2%) adrenals without a phaeochromocytoma, but there was mildly to moderately increased activity in 66 (30.7%). Conclusions: Since every intra- and extra-adrenal tumor was visualised, the findings suggest that ¹²³Iobenguane may be the most sensitive screening test available for diagnosing phaeochromocytoma. The test results should be definitive in most patients.

Neuroblastomas

Diagnosis and follow-up of neuroblastoma by means of iodine-123 metaiodobenzylguanidine scintigraphy and bone scan, and the influence of histology.

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Hadji-Djilani N L et al European Journal of Nuclear Medicine 22(4) 322-329.

Summary: The purpose of this work was to compare technetium-99m-diphosphono-propanedicarboxylate (DPD) and iodine-123-metaiodobenzylguanidine (MIBG) scans in the diagnosis and follow-up of neuroblastoma, and to study the role of histological differentiation in the uptake of MIBG. The uptake of MIBG and of DPD were studied retrospectively in 27 patients with neuroblastoma. The findings were related to the histological classification of the tumours as neuroblastoma (N1), differentiating neuroblastoma (N2) or ganglioneuroblastoma (N3). Uptake of MIBG by the primary tumour occurred in 17 of 19 patients, either at diagnosis or during follow-up. There were only two false-negatives with MIBG, both of which were N3. Ten patients were studied preoperatively with both MIBG and DPD. The primary tumour showed MIBG uptake in nine of the ten and DPD uptake in eight of them. Thirty-five sites of cortical bone metastasis were shown in eight patients by both MIBG and DPD, 12 sites in seven patients by MIBG only and seven sites in five patients by DPD only. Overall, MIBG demonstrated more lesions than DPD. Retrospectively several hot spots seen only with the bone scan are to be considered as false-negative. MIBG and bone scans was observed in ganglioneuroblastoma with a predominance of the more mature component (ganglioneuroma).

Skeletal Assessment in Neuroblastoma
- The Pitfalls of Iodine-123-MIBG Scans.

Gordon I et al The Journal of Nuclear Medicine 31 (2) 129-134

This study was carried out to compare iodine-123 metaiodobenzylguanide ([¹²³I]MIBG) and technetium-99m-methylene

diphosphonate bone scans (^{99m}Tc-MDP) in the detection of skeletal involvement by neuroblastoma. Forty-four children with neuroblastoma underwent both [¹²³I]MIBG and ^{99m}Tc-MDP scans within a 4-wk period; bone marrow examination also was performed; all these investigations were done both at diagnosis and at follow-up. At diagnosis, four children with Stage 4 disease had normal [¹²³I]MIBG scans but abnormal ^{99m}Tc-MDP scans, while at follow-up there were four children with negative [¹²³I]MIBG studies who later died from disseminated neuroblastoma. All eight scans were considered false-negatives. In 24 children the [¹²³I]MIBG revealed more extensive disease with 161 positive sites while the ^{99m}Tc-MDP scan showed only 100 positive sites; 34 of these sites were common to both studies. This study shows that underassessment of skeletal involvement by neuroblastoma occurred using [¹²³I]MIBG scans. [¹²³I]MIBG scans do not replace ^{99m}Tc-MDP bone scans in the staging of neuroblastoma.

Indications

- Diagnostic scintigraphic localisation of pheochromocytomas, paragangliomas (chemodectomas), ganglioneuroblastomas and ganglioneuromas.
- Detection, staging and follow-up on therapy of neuroblastomas.

Contraindications

MIBGen® is contraindicated during pregnancy and lactation.

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Precautions

General

- Radiopharmaceuticals should be administered by medical practitioners who are qualified and licensed to handle radioisotopes.
- In clinical trials used to assess I-123 Iobenguane's diagnostic efficacy, thyroid blockade (e.g. with Lugol's iodine) was typically started ~1-2 days before I-123 Iobenguane was given, and continued for ~3 days after the dose of I-123 Iobenguane.
- Use to detect hepatic tumour involvement has been associated with significantly reduced sensitivity in clinical trials.
- Use to detect tumours (other than those listed under "Indications") that embryologically stem from the neural crest has been associated with limited sensitivity. In addition, few studies of I-123 Iobenguane's role in localising ganglioneuroblastomas, ganglioneuromas or paragangliomas have been published. The utility of I-123 Iobenguane in localisation of these tumours is less well established than for phaeochromocytomas and neuroblastomas.
- Autonomic denervation (e.g. Horner's syndrome, diabetic autonomic neuropathy) has been reported to reduce Iobenguane uptake in denervated organs.
- Distribution of I-123 Iobenguane as shown by gamma scintigraphy will differ compared to distribution of I-131 Iobenguane as shown by gamma scintigraphy.
- In renal insufficiency, altered disposition may affect interpretation of scintigrams and radiation dosimetry.
- In clinical trials used to assess I-123 Iobenguane's efficacy, there was one reference to poor dialysability of Iobenguane in a dialysis patient.

Check the following before administration

- Verification of the dose to be administered and patient identification. The patient dose should be measured by a suitable radioactivity calibrator system immediately prior to administration.
- Visually inspect for the absence of particulate matter or colour.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term animal studies have been performed to evaluate carcinogenic or mutagenic potential or whether MIBGen® (¹²³I-iobenguane sulfate) affects fertility in males or females.

Dose Handling

Radiation exposure to staff must be minimised. For each patient, exposure to ionising radiation must be justified on the basis of likely benefit.

Patient Care

Care should be taken to minimise unwanted radiation exposure to patients, consistent with proper patient management.

Use during Pregnancy

MIBGen® is contraindicated during pregnancy. Animal reproductive toxicity studies have not been performed with MIBGen®, and there have been no studies in pregnant women. Any woman who has missed a period should be assumed to be pregnant unless proven otherwise. Alternative techniques that do not involve ionising radiation should be considered.

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Use during Lactation

Radiolabelled compounds have been found in breast milk during lactation; therefore, it is likely that MIBGen® could be excreted in breast milk. Therefore, MIBGen® should not be used in lactating mothers. Before administering a radioactive medicinal product to a mother who is breast feeding, consideration should be given as to whether the investigation could be reasonably delayed until the mother has ceased breast feeding and as to whether the most appropriate choice of radiopharmaceutical has been made, bearing in mind the potential secretion of activity in breast milk. If the administration is considered necessary, breast feeding should be interrupted for three days and the expressed feeds discarded.

Interaction with Other Drugs

The following drugs are known, or may be expected to, prolong or reduce the uptake of iobenguane in neural crest tumours and should be stopped before treatment. (usually for three biological half-lives)

- Nifedepine (a Ca-channel blocker) is reported to prolong retention of iobenguane.
- Decreased uptake was observed under therapeutic regimens involving the administration of reserpine, labetalol, calcium-channel blockers (diltiazem, nifedepine, verapamil), tricyclic antidepressives (amitrypyline, imipramine and derivatives), sympathomimetic agents (present in nasal decongestants, such as phenylephrine, ephedrine or phenylpropanolamine), cocaine, and phenothiazine.

Long-term Effects

None known.

Adverse Reactions

It should be noted that there are few data about adverse events following administration of Iobenguane and that clinical studies have not extensively examined I-123 Iobenguane's safety and tolerability.

In rare cases the following undesirable effects have occurred: blushes, urticaria, nausea, cold chills, and other symptoms of anaphylactic reaction. When the drug is administered too fast palpitations, dyspnoea, heat sensations, transient hypertension and abdominal cramps may occur during or immediately after administration. These symptoms disappear within one hour.

Dosage and administration

Iobenguane-[¹²³I] is administered according to the following dosage scheme:

- Children under 6 months: 4 MBq per kg body weight (max. 40 MBq).
- Children between 6 months and 2 years: 4 MBq per kg body weight (min. 40 MBq).
- Children over 2 years: a fraction of the adult dose should be chosen, dependent on body weight.

The recommended doses are as follows:

Weight	Dose	Weight	Dose	Weight	Dose
3 kg	20 MBq	15 kg	76 MBq	35 kg	140 MBq
4 kg	28 MBq	20 kg	92 MBq	40 kg	152 MBq
6 kg	38 MBq	25 kg	110 MBq	45 kg	162 MBq
8 kg	46 MBq	30 kg	124 MBq	50 kg	176 MBq
10 kg	54 MBq				

The above table refers only to children over 2 years of age.

Adults: 200 MBq - No special dosage-scheme is required for the elderly patient.

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Each vial should be used in one patient on one occasion only, and any residue discarded.

Administration

Iobenguane-[¹²³I] is administered by slow intravenous injection or infusion. If desired the administration volume can be increased by dilution.

Overdose

The effect of an overdose of Iobenguane is due to the release of adrenaline. This effect is of short duration and requires supportive measures aimed at lowering the blood pressure. Prompt injection of a rapid acting alpha-adrenergic blocking agent (phentolamine) followed by a beta-blocker (propranolol). To reduce the influence of radiation it is essential to maintain the highest possible urine flow.

The nature of the radioisotope and the amount of Iobenguane [¹²³I] present make overdosing improbable.

Radiation Dosimetry

Absorbed dose

Per unit activity administered (mGy/MBq.) (Ref. 2)

Organ	Adult	15yr	10yr	5yr	1yr
Adrenals	0.017	0.022	0.032	0.045	0.071
Bladder	0.048	0.061	0.0780	0.084	0.15
Bone surfaces	0.011	0.014	0.022	0.034	0.068
Breast	0.0053	0.0068	0.011	0.017	0.032
GI tract -					
Stomach	0.0084	0.011	0.019	0.030	0.056
Small intest.	0.0084	0.011	0.018	0.028	0.051
Colon	0.0086	0.011	0.018	0.029	0.052
ULI	0.0091	0.012	0.020	0.033	0.058
LLI	0.0079	0.010	0.016	0.023	0.043
Heart	0.018	0.024	0.036	0.055	0.097
Kidneys	0.014	0.017	0.025	0.036	0.061
Liver	0.067	0.087	0.13	0.18	0.33

Organ	Adult	15yr	10yr	5yr	1yr
Lungs	0.016	0.023	0.033	0.049	0.092
Muscles	0.0066	0.0084	0.013	0.020	0.037
Oesophagus	0.0068	0.0088	0.013	0.021	0.037
Ovaries	0.0082	0.011	0.016	0.025	0.046
Pancreas	0.013	0.017	0.026	0.042	0.074
Red marrow	0.0064	0.0079	0.012	0.018	0.032
Skin	0.0042	0.0051	0.0082	0.013	0.025
Spleen	0.020	0.028	0.043	0.066	0.12
Testes	0.0057	0.0075	0.012	0.018	0.033
Thymus	0.0068	0.0088	0.013	0.021	0.037
Thyroid	0.0056	0.0073	0.012	0.019	0.036
Uterus	0.010	0.013	0.020	0.029	0.053
Remaining organs	0.0067	0.0085	0.013	0.020	0.037
Effective dose (mSv / MBq)	0.013	0.017	0.026	0.037	0.068

Note: The above data are valid in normal pharmacokinetic behaviour. When renal function is impaired the effective dose equivalent and the radiation dose delivered to organs may be increased. Thyroid dosimetry assumes a blocked thyroid.

Presentation

MIBGen is supplied as a single-use liquid in a sealed glass vial in a lead pot of appropriate thickness to provide adequate shielding. Each vial contains either 2ml or 4ml of solution with a radioactive concentration of 90.0 to 110.0-MBq/mL at the calibration time and date.

Expiry

16 hours after calibration.

Storage

Store below 25°C, protect from light, inside its original shielded container.

Storage and disposal of all radioactive wastes should be carried out in accordance with the NH & MRC "Code of practice for the disposal of radioactive wastes by the user" (1985).

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References

- Ref. 1 The Health Physics and Radiological Health Handbook ISBN 0-917251-00-8, MicroShields v5.01, Sigma plot v4
- Ref. 2 The ICRP publication 80 (Vol 28, No 3 p79 1998).
- Ref. 3 Glomerular filtration rate and the kinetics of I-123 MIBG
Blake GM et al
Eur J Nucl Med 1989; 15:618-623
- Ref. 4 Alterations of I-131 MIBG distribution in an anephic patient: comparison to normal and impaired renal function
Tobes MC et al
J Nucl Med 1989; 30: 1476-1482

General Reference

- “The Committee for Proprietary Medicinal Products” Commission of the European Communities - 111 / 3246 / 93 - EN, March 1993.

Manufacture

This product is manufactured by ANSTO Radiopharmaceuticals and Industrials (ARI) at the Australian Nuclear Science and Technology Organisation, Lucas Heights, NSW.

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The Australian Register of Therapeutic Goods
Number AUST R. 101670

Contact Details

ANSTO Radiopharmaceuticals and Industrials (ARI)
Private Mail Bag 1
Menai NSW 2234

Telephone: 1800 251 572
Facsimile: 02 9543 6511

ANSTO Radiopharmaceuticals and Industrials (ARI) is a commercial Enterprise of the Australian Nuclear Science Organisation (ANSTO), which is located at Lucas Heights, Sydney. ARI manufactures and markets radioisotopes produced in ANSTO's research reactor, OPAL, and its National Medical Cyclotron.

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