Pharmacological interference with $^{123}$I-metaiodobenzylguanidine: a limitation to developing cardiac innervation imaging in clinical practice?

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Abstract. – BACKGROUND: $^{123}$I-metaiodobenzylguanidine (MIBG) scintigraphy is considered a valid imaging test to evaluate the cardiac sympathetic nervous system. However, scientific literature showed that some drugs are able to or are expected to interfere with MIBG uptake. Thirty years after introduction of the method and over 15 years since the appearance of the first document on pharmacological interference with MIBG, an update on this issue has become necessary.

AIM: The aims of this review paper are: (1) to identify the pharmacological basis of interference of a variety of substances with MIBG uptake; and (2) to update the list of drugs that definitely interfere with MIBG on the grounds of evidence in the literature.

MATERIALS AND METHODS: A MEDLINE search was conducted. Scientific studies, case report and review articles were collected. Papers published demonstrating drugs interfering with MIBG uptake were evaluated.

RESULTS: Drugs may interact with MIBG uptake by 5 mechanism: (1) type-1 uptake inhibition; (2) inhibition of active transport to vesicles; (3) competition in transport to vesicles; (4) depletion of neurosecretory vesicle content; (5) calcium-mediated mechanism. We find that drugs like cocaine, antidepressants, some antipsychotic, tramadol, labetalol, sympatho-mimetics, reserpine and some calcium antagonists (as diltiazem, verapamil and nifedipine) do interfere with MIBG uptake. On the other hand, we find that controversial data are available on scientific literature regarding digoxin and amiodarone.

CONCLUSIONS: A compiled statement of MIBG interfering medicines is now recommended to help nuclear medicine physicians in clinical practice to avoid potential pitfalls and improve the efficacy of $^{123}$I-MIBG scintigraphy as a diagnostic tool.

Key Words: Metaiodobenzylguanidine, MIBG imaging, Pharmacological interference.

Introduction

$^{123}$I-metaiodobenzylguanidine (MIBG) scintigraphy is considered a valid imaging test to evaluate the cardiac sympathetic nervous system. MIBG is a guanethidine analogue and accumulates in the adrenergic nervous system at post-gangliar pre-synaptic nerve synapses. Following depolarization, MIBG is released into the synaptic space as occurs for norepinephrine, but is not metabolised. $^{123}$I-labelled MIBG enables the adrenergic nervous system to be studied in vivo. In fact MIBG scintigraphy allows the clinician not only to check the presence of cardiac adrenergic innervation, but also to evaluate its function for diagnostic/prognostic purposes, both in the heart and nervous system and potentially in the lungs.

Thirty years after introduction of the method and over 15 years since the appearance of the first document on pharmacological interference with MIBG, an update on this issue has become necessary, in the light of copious evidence published in the literature (Figure 1) and as the prospect of wider clinical application remains threatened by inadequate knowledge on the subject.

The aims of this review are: (1) to identify the pharmacological basis of interference of a variety of substances with MIBG uptake; and (2) to update the list of drugs that definitely interfere with MIBG on the grounds of evidence in the literature.

MIBG Uptake Mechanism

It is well known that the cellular mechanism of MIBG uptake and storage in pre-synaptic vesicles is identical to that of norepinephrine. As demonstrated in 1984 at Ann Arbor, MI, USA, MIBG and norepinephrine share two up-
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Take systems: one specific (type-1 or “uptake-1”), and one non-specific, with passive diffusion (type-2).\textsuperscript{10,11}

Type-1 uptake is an active process catalysed by a temperature- and Na-dependent membrane carrier protein with high affinity, low capacity, and which is oxygen-dependent and desipramine- and cocaine-sensitive.\textsuperscript{11,12} Type-2 uptake is temperature-dependent, but Na- and oxygen-independent, and is non-saturable up to concentrations as high as 5 mM of MIBG.\textsuperscript{10} At low concentrations MIBG is taken up mainly via the type-1 mechanism; at high concentrations, as in the case of \textsuperscript{131}I-MIBG treatment, the type-2 mechanism prevails. After passing through the cell membrane, the tracer is conveyed into the neurosecretory vesicles by an active transport mechanism.\textsuperscript{13} Providing confirmation that MIBG and norepinephrine share the same intracellular transport systems, DeGrado et al\textsuperscript{14} carried out an in vitro study on laboratory rat hearts, demonstrating MIBG cardiac uptake inhibition both by type-1 blocking mechanism (obtained with desipramine) and by type-2 (obtained with SFK 550).

\textbf{MIBG Uptake and Pharmacological Interference}

According to an earlier review on the subject by Solanki et al\textsuperscript{6}, the drugs that interfere with MIBG uptake can be categorised according to their interactive mechanism (Table I):

- Type-1 uptake inhibition
  - Inhibition of active transport to vesicles
  - Competition in transport to vesicles
  - Depletion of neurosecretory vesicle content
  - Calcium-mediated mechanism

\textbf{Discussion}

\textbf{Type-1 Uptake Inhibition}

It is well established that cocaine interacts with neuronal uptake 1 system and, thus, interferes with MIBG uptake as several studies have demonstrated in animal model.\textsuperscript{10,13} Labetalol, an \(\alpha\)- and \(\beta\)-adrenergic blocker, significantly interacts with MIBG uptake (Table I). Various experiments carried out on animals and humans have suggested that labetalol action is mediated by blocking the type-1 uptake system. Khafagi et al\textsuperscript{15} demonstrated that labetalol reduces MIBG uptake in normal tissues, such as salivary glands, liver and spleen, and in phaeochromocytoma. However, there was no mention in this report of heart uptake. In addition, also Apeldoorn et al\textsuperscript{16} found labetalol interference with MIBG uptake in a patient suffering from phaeochromocytoma. In a subsequent study other Authors\textsuperscript{17} confirmed that labetalol significantly reduces MIBG uptake in the heart both in healthy individuals and in patients suffering from post-ischaemic cardiopathy. Mayer et al\textsuperscript{18} demonstrated in an in vitro study on
<table>
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<td>Pseudoephedrine, phenylpropanolamine, chlorphenamine</td>
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animal myocardial tissue that – in addition to labetalol – metoprolol also depresses $^{123}$I-MIBG uptake in the heart by more than 40%. Moreover, the same study did not show sotalol (another β-blocker) to have any effect. In another work, conducted in vivo on human platelets, various cardiovascular drugs were tested including β-blockers, calcium antagonists, digoxin and amiodarone. In this case, too, it was confirmed that labetalol inhibits radioiodinated MIBG uptake. It was also demonstrated that propanolol can interfere, but in this in vitro study concentrations exceeded therapeutic human doses so, this findings may not be applicable to patients.

Tricyclic antidepressants can also interfere via type-1 uptake$^{20,21}$ (Table I). Confirming this, one study demonstrated increased $^{1}$C-hydroxyephedrine (epinephrine analogue) wash-out from the heart following desipramine loading$^{22}$. Pre-treatment of dogs with desmethylimipramine one hour prior to MIBG administration reduced the radiopharmaceutical uptake in adrenomedullary tissue approximately tenfold$^{10}$. In studies on laboratory rats it was demonstrated that chronic administration of antidepressants produces a smaller reduction in MIBG uptake in adrenomedullary tissue compared with acute treatment. Estorch et al$^{24}$ reported a case-study of six patients suffering from movement disorders with normal MIBG cardiac scans, showing in three of the patients reduced MIBG uptake after loading with 25 mg of amitriptyline. In a study by Nakajo et al$^{25}$, four patients who were administered with imipramine showed reduced uptake of radioiodinated MIBG in salivary glands, similar to that found in patients with severe autonomic neuropathy.

Finally, in vitro reports confirm that neuroleptics such as haloperidol and levomepromazine reduce $^{123}$I-MIBG uptake by around 40%, as does clomipramine$^{18}$ (Table I).

Tramadol is a centrally acting opioid analgesic whose action mechanism depends on an increased serotonergic transmission. Moreover, tramadol is able to inhibit noradrenaline re-uptake as Franceschini et al$^{26}$ demonstrated in a rat cortical model: tramadol decreased the uptake of the cathecolamine transmitter, so it is expected to interfere with MIBG uptake.

Inhibition of Active Transport to Vesicles

Reserpine is an alkaloid extracted from rauwolfia serpentina roots and used as an antihypertensive drug. Its mechanism of action consists of irreversibly blocking the active transport of noradrenaline, serotonin and dopamine to the neurosecretory vesicles with consequently decreased peripheral resistance. For this reason reserpine also affects MIBG uptake in the cardiac sympathetic nervous system, as shown in researches on guinea-pigs (Table I). Wieland et al$^{27}$ demonstrated that pre-treatment of dogs with reserpine decreases myocardial concentration of radioiodinated MIBG of about 30%, while in a study by the same Authors$^{28}$ reserpine was found to reduce MIBG uptake in adrenomedullary tissue by around 90%. These results were later confirmed by a study of our group in 2003 on laboratory rats$^{29}$, which showed MIBG uptake to fall by 56% four hours after injection of reserpine (Table I).

Competition in Transport to Vesicles

MIBG is carried through the neurosecretory vesicle membrane by a saturable monoamine transport system that is shared by norepinephrine and serotonin. Transport from the cytoplasm to the neurosecretory vesicles is triggered by a greater substrate concentration in the cytoplasm. Adrenergic blockers – for example guanethidine – can compete with this transport mechanism$^{30}$ (Table I).

Depletion of Neurosecretory Vesicle Content

Many drugs cause neurosecretory vesicle depletion; these include trazodone (an antidepressant), reserpine, labetalol and adrenergic blockers such as guanethidine. Sympathomimetic substances including phenylpropanolamine and amphetamines also have the same effect as the above-mentioned drugs (Table I). Guilloteau et al$^{31}$ demonstrated that treatment with sympathomimetic substances causes notably decreased MIBG concentration in the adrenergic tissue of the left atrium, the left ventricle, the spleen and the parotid glands of laboratory rats. Sherman et al$^{32}$ reported reduced MIBG uptake of around 80% in adrenergic tissue when pseudoephedrine, phenylpropanolamine and phenylephedrine were injected intraperitoneally into laboratory rats. Moreover, small quantities of these substances – administered to healthy volunteers via nasal sprays – reduced MIBG uptake, suggesting that high doses of β-sympathomimetics such as salbutamol and terbutaline might also interfere with cardiac uptake of $^{123}$I-MIBG (Table I).

Calcium-Mediated Mechanism

There are three types of calcium-dependent channels involved in cell membrane depolariza-
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...sequent research carried out on laboratory rats presenting hypertensive patients. However, a sub-
study demonstrated that cilnidipine can suppress the sympathetic nervous system hyperactivation whereas the L channels (sensitive to calcium channel blockers) are found in the neuron cell body and are inactive during stimulation.

Jacques et al. demonstrated in bovine adrenomedullary tissue culture that radioiodinated MIBG release is partially inhibited when the tissue is simultaneously exposed to acetylcholine (used as a stimulator) and calcium antagonists at low doses. Calcium antagonists thus encourage MIBG retention in the cell, representing an advantage for MIBG therapy. The study also referred that pre-treatment of cells with calcium antagonists (100 µM) prior to acetylcholine stimulation inhibits MIBG uptake by 15% with diltiazem, 47% with nifedipine and 86% with verapamil. In a study by Blake et al. of eight patients with malignant phaeochromocytoma administered with 20 mg nifedipine 48 hours prior to MIBG injection, three patients presented increased uptake and extended retention of MIBG in the tumor, with simultaneously increased dose of radiation absorbed, of approximately 1.5-2 times. These works, therefore, suggest that non-dihydropyridine calcium antagonists and nifedipine increase cell retention of MIBG, in contrast with the drugs described above (Table I).

More recent clinical trials studied the effect of third-generation dihydropyridine calcium antagonists (including amlodipine) on sympathetic activity. It was demonstrated that, compared with nifedipine, third-generation calcium antagonists act on sympathetic nervous system activation to a lesser degree. Nevertheless, the findings regarding their effects on MIBG uptake are controversial. Sakata et al. demonstrated that 24 patients suffering from essential hypertension showed no change in cardiac MIBG uptake after 3 months treatment with nitrendipine. In contrast, a study by the same group showed that after 3 months treatment with cilnidipine, higher MIBG uptake was observed in the heart, while amlodipine had less effect on sympathetic activity. This study demonstrated that cilnidipine can suppress the sympathetic nervous system hyperactivation present in hypertensive patients. However, a subsequent research carried out on laboratory rats showed that cilnidipine administration had no effect on cardiac uptake of MIBG, while nifedipine interfered in cardiac imaging through increased sympathetic activity. Another calcium antagonist, efonidipine, seems to increase MIBG uptake, both in healthy individuals and in patients suffering from essential hypertension.

Controversial Topics

Beyond the well-established MIBG interfering drugs, it seems there are others drugs affecting the radiopharmaceutical uptake.

A study carried out on neuroendocrine cell lines revealed that menadione, a vitamin K analogue, can inhibit MIBG uptake in a dose-dependent manner. Moreover, comparing menadione inhibition of MIBG uptake and retention with that of imipramine and reserpine, the Authors suggested that menadione may act both via the type-1 uptake mechanism and by vesicle uptake.

Many clinical trials have demonstrated that drugs currently used in clinical practice (some β-blockers, ACE inhibitors, angiotensin receptor blockers, spironolactone, amiodarone) can improve MIBG uptake in the heart. However, it is important to emphasise that this improvement does not depend on the direct interference of these drugs with MIBG uptake, but rather on improvement in heart performance and therefore sympathetic tone. Moreover, β-blockers commonly used in cardiovascular settings, as metoprolol, atenolol (selective β receptors antagonists) and carvedilol (non-selective β-and α-receptor blocker) may not play interference with MIBG uptake since they do not interact via type-1 uptake mechanism as well as labetalol (an α- and β-adrenergic blocker) does.

The mechanism of action of amiodarone on MIBG and norepinephrine metabolism has yet to be defined and data on its interaction on MIBG uptake are not conclusive. Huguet et al. found no interference in an in vitro platelet report. Conversely, Fagret et al. showed that amiodarone inhibited myocardial MIBG uptake in patients with left ventricular hypertrophy secondary to valvular aortic stenosis. Moreover, in two studies conducted on heart failure patients, amiodarone seemed to improve sympathetic tone and, thus, cardiac MIBG uptake as the Authors demonstrated an increased H/M ratio and a decreased WR.

Digoxin is a cardioactive drug which may exert some interference with MIBG uptake. However, data available from literature are conflicting as an in vitro platelet study by Huguet et al. showed no interaction with MIBG uptake, whereas Fagret et
al found a partial inhibition of myocardial MIBG uptake, due to the action of digoxin on the MIBG cell transport mechanisms.

Finally, some considerations about study settings have to be discussed. Most of the works mentioned above are conducted on animal models. Findings on animal studies represent a lower level of evidence compared with studies performed in humans as the contribution of uptake 1 vs uptake 2 is completely different.

Moreover, in vitro studies are not reproductive of in vivo human mechanism so, MIBG uptake interference observed in cell cultures may not simulate real clinical setting.

Conclusions

Once the usefulness of subjecting a patient to MIBG scintigraphy has been confirmed, a check should then be made of which drugs the patient is regularly administered: those that interfere with MIBG uptake – taking account of the drug half-life – should be withdrawn. This issue is mostly important for cardiac MIBG imaging studies, where a semiquantitative approach (based on heart to mediastinum uptake ratio or wash-out rate calculation) and reproducible data are crucial for assessing adrenergic function.

Table I outlines treatment withdrawal times based on the literature available.

In the light of the findings reviewed here, knowledge now available regarding drugs that interfere with MIBG should be disseminated to support clinicians in their practice, i.e. the cardiologist or neurologist who might overestimate the number of drugs that interfere with MIBG uptake and, therefore, limiting their requests for MIBG scintigraphy. Indeed, the need for a wider knowledge of these findings is even more urgent, since it is timely for the method to be taken up widely in view of the literature data now available and of the North American FDA approval.

Conflict of Interest

None.

References


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