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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[1]. 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[2-5].

Thirty years after introduction of the method and over 15 years since the appearance of the first document on pharmacological interference with MIBG[6], 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[7-9].

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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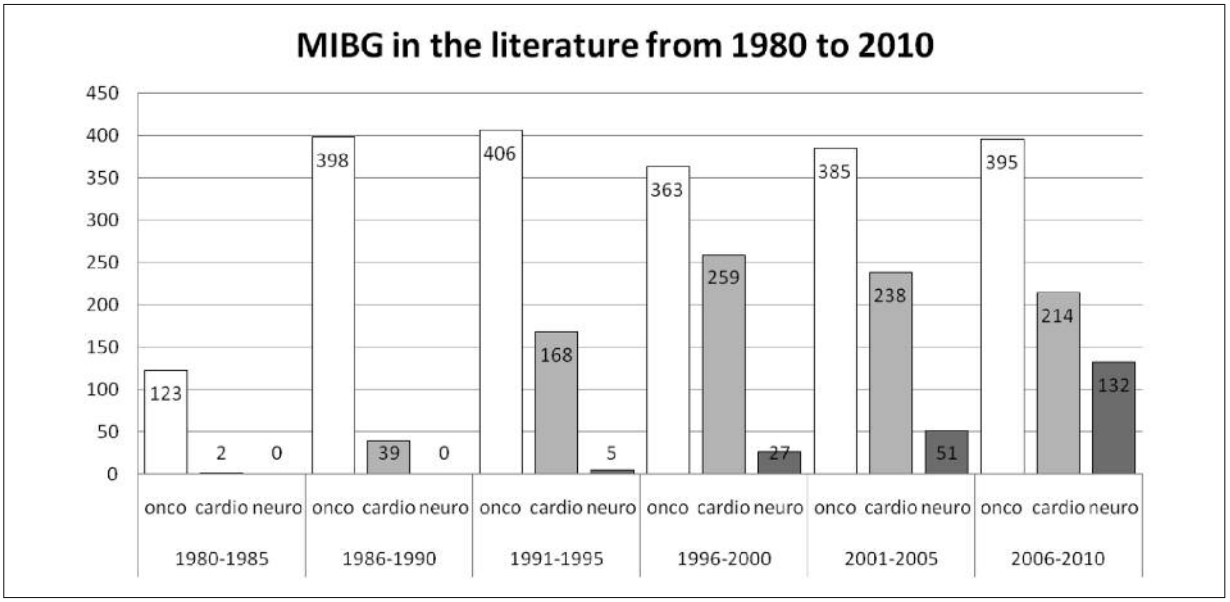

Figure 1. Research literature on MIBG scintigraphy in oncology, cardiology and neurology from 1980 to 2010 (source: Pubmed/MEDLINE.

take systems: one specific (type-1 or "uptake-1"), and one non-specific, with passive diffusion (type-2)[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[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[10]. At low concentrations MIBG is taken up mainly via the type-1 mechanism; at high concentrations, as in the case of ^{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[13]. Providing confirmation that MIBG and norepinephrine share the same intracellular transport systems, DeGrado et al[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).

MIBG Uptake and Pharmacological Interference

According to an earlier review on the subject by Solanki et al[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

Discussion

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[10,13]. *Labetalol*, an *α- and β-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[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[16] found labetalol interference with MIBG uptake in a patient suffering from phaeochromocytoma. In a subsequent study other Authors[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[18] demonstrated in an *in vitro* study on

Table I. Drugs known to interfere with MIBG.

Interference mechanism	Drug category	Active ingredient	Half-life	Suspension
Calcium-mediated	Dihydropyridine calcium antagonists	Nifedipine, amlodipine	110 hrs	14 days
	Non-dihydropyridine calcium antagonists	Diltiazem, verapamil	14 days	14 days
Type-1 uptake	Alkaloid	Cocaine	1 hr	7-14 days
	Non-selective monoamine reuptake inhibitors (antidepressants)	Desipramine, imipramine, clomipramine, imipramine, clomipramine, dosulepine, maprotiline	21-28 days	7-21 days
	Selective monoamine reuptake inhibitors	Fluoxetine	4-6 days	7-21days
		Citalopram	33-37 hrs	
		Paroxetine	21 hrs	
		Sertraline	26 hrs	
		Fluvoxamine	15 hrs	
		Escitalopram	22-32 hrs	
	Antipsychotics	Butyrophenones (haloperidol, droperidol)	12-36 hrs	21-28 days
		Phenothiazine (levomepromazine, chlorpromazine, promethazine, fluphenazine)	6-7 hrs	21-28 days
	Opiod analgesics	Tramadol	5-7 hrs	7-14 days
Depletion of neurosecretory vesicle content	Antidepressants	Trazodone	150 hrs	21-28 days
	Sympathomimetics for systemic use such as nasal decongestants	Pseudoephedrine, phenylpropanolamine, chlorphenamine	5-6 hrs	7-14 days
	Sympathomimetics for systemic use such as cardiac stimulants	Ethylephrine	5-6 hrs	7-14 days
Mixed (type-1 uptake; depletion of neurosecretory vesicle content)	α-β blockers	Labetalol	7-14 days	21 days
Mixed (inhibition of active transport to vesicles; depletion of neurosecretory vesicle content)	Rauwolfia alkaloids	Reserpine	5-100 hrs	14 days

Modified by "Proposal for standardization of ^{123}I-metaiodobenzylguanidine (MIBG) cardiac sympathetic imaging by the EANM Cardiovascular Committee and the European Council of Nuclear Cardiology" Eur J Nucl Med Mol Imaging 2010; 37: 1802-1812.

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 vitro* on human platelets, various cardiological 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[19], 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 ^{11}C-hydroxyephedrine (epinephrine analogue) wash-out from the heart following *desipramine* loading[22]. Pretreatment 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[23] 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 opiod 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 norepinephrine, 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[23] 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[31] 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-

tion: L channels (long-lasting), T channels (short-acting, present in many cells) and N channels (present only in nerve tissue). Neurotransmitter release from synaptic end bulbs is a calcium-dependent process that is generally resistant to calcium channel blockers[32]. Calcium ions enter the axon ends via N channels (insensitive to calcium channel blockers), whereas the L channels (sensitive to calcium channel blockers) are found in the neuron cell body and are inactive during stimulation.

Jaques et al[33] 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[34] 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[35-37]. It was demonstrated that, compared with nifedipine, third-generation calcium antagonists act on sympathetic nervous system activation to a lesser degree[38]. Nevertheless, the findings regarding their effects on MIBG uptake are controversial. Sakata et al[39] 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[40] 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[41] 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[42].

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[43] 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 receptors 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[44-47]. Moreover, β-blockers commonly used in cardiovascular settings, as metoprolol, atenolol (selective 1 receptor antagonists) and carvedilol (non selective β-and α1-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[19] found no interference in an *in vitro* platelet report. Conversely, Fagret et al[48] 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[49,50].

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[19] showed no interaction with MIBG uptake, whereas Fagret et

al[17] found a partial inhibition of myorcardial 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 model. 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 coltures 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.

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