Labetalol Reduces Iodine-131 MIBG Uptake by Pheochromocytoma and Normal Tissues

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Iodine-131 metaiodobenzylguanidine [^{131}I]MIBG has proven to be an effective radiopharmaceutical for the scintigraphic localization of pheochromocytomas. Uptake of MIBG is inhibited by blockade of the neuronal uptake pathway for catecholamines ("uptake-1") and by depletion of catecholamine storage vesicle contents, but is not significantly affected by conventional alpha- and beta-adrenoreceptor blocking drugs. Labetalol is an antihypertensive agent with combined alpha- and beta-blocking properties that has been used to manage patients with suspected pheochromocytomas. We report eight patients in whom concurrent or recent therapy with labetalol significantly reduced the uptake of [^{131}I]MIBG into salivary glands, liver, spleen, and general body background. Tumor uptake of MIBG was also reduced in two of the three patients who were proven to have pheochromocytomas. In one case, the effect of labetalol persisted for 36 hr after the drug had been discontinued. The inhibitory effect of labetalol on MIBG uptake in sympathomedullary tissues is likely to be a result of the drug's little-known, additional properties of uptake-1 blockade and depletion of storage vesicle contents, rather than its alpha- or beta-blocking effects. Additionally, labetalol would also appear to hasten clearance of MIBG from other tissues. Labetalol therapy should be discontinued for several days (possibly up to 1 wk) before undertaking [^{131}I]MIBG scintigraphy. A comprehensive list of drugs that should be avoided in patients undergoing MIBG scintigraphy is appended.

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Episodic hypersecretion of the catecholamines, norepinephrine (NE), and/or epinephrine (E) by pheochromocytomas produces the well-known, potentially life-threatening manifestations of these tumors (*1*). Alpha-adrenoreceptor blockade is the mainstay of medical therapy in patients with suspected pheochromocytoma. However, cardiac β_1-adrenoreceptor stimulation by the hypercatecholaminemia frequently produces troublesome palpitations and tachyarrhythmias. These symptoms may be exacerbated by treatment with alpha-adrenoreceptor blockers, since circulating NE levels increase both as a baroreflex response to the hypotensive effect of the alpha-blockers and as a consequence of blockade of presynaptic α_2-adrenoreceptors (which normally inhibit presynaptic NE release). Thus beta-blocker therapy often needs to be added once satisfactory alpha-blockade has been achieved (*1*).

Labetalol (Normodyne, Schering Corp., Galloping Hill Rd., Kenilworth, NJ 07033; Trandate, Glaxo Inc., Five Moore Dr., Research Triangle Park, NC 27709) is a nonselective beta-adrenoreceptor blocking drug which also blocks postsynaptic α_1-adrenoreceptors while sparing presynaptic α_2-receptors (reviewed in *2*). Because of its combined α_1- and beta-blocking effects, labetalol has been used successfully for the perioperative management of patients with pheochromocytoma (*3–7*). Labetalol was first released for general use in the United States in 1984.

The preoperative scintigraphic localization of pheochromocytomas in man using iodine-131 metaiodobenzylguanidine ([^{131}I]MIBG) was first reported in 1981 (*8*). Since then, extensive worldwide experience (reviewed in *9*) has shown that MIBG labeled with iodine-123 (^{123}I) or ^{131}I is a safe, sensitive, and in the appropriate clinical setting, highly specific radiopharmaceutical for locating adrenal, extra-adrenal, and metastatic malignant pheochromocytomas. Animal experiments (*10*,

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TABLE 1
Clinical Data

Case	Age, sex	Labetalol (mg/day)	Other drugs	History
1	59, F	600	Meprobamate, Glipizide	Longstanding hypertension; Type II diabetes mellitus; Paroxysmal symptoms
2	52, M	800	Clonidine	Longstanding hypertension; Deteriorating control 2 yr
3	29, F	400	Diazepam	Hypertension with "spells", including loss of consciousness
4	34, F	400	Phenoxybenzamine, Triazolam	Hypertension with paroxysmal symptoms
5	33, F	400	Diazepam, Thyroxine	MEN-2a*; previous MTC† and L. adrenal pheochromocytoma. 3 cm R. adrenal pheochromocytoma
6	46, M	400	Chlorthalidone, Dipyridamole, Aspirin	20 yr "difficult" hypertension complicated by strokes
7	45, M	600	—	Malignant pheochromocytoma; residual retroperitoneal disease
8	15, M	See text	Prazosin, Propranolol	Abrupt onset of symptoms; 26 g R. adrenal tumor

* Multiple endocrine neoplasia, type 2a.
† Medullary thyroid carcinoma.

11) and clinical experience in man (*11*) have shown that treatment with conventional alpha- and beta-blockers does not significantly affect the biodistribution of MIBG, so that treatment need not be discontinued in preparation for MIBG scintigraphy. However, we have observed reduced uptake of [^{131}I]MIBG in several patients who were receiving labetalol for hypertension suspected or known to be a result of pheochromocytomas. In at least one patient with a proven pheochromocytoma, recent labetalol therapy resulted in a false-negative [^{131}I]MIBG scan. In this paper, we review our experience and suggest the likely mechanisms by which labetalol interferes with MIBG uptake.

PATIENTS AND METHODS

Patients receiving labetalol were identified retrospectively from our data base of patients referred for MIBG scintigraphy. We excluded all patients who were known or subsequently found to have been taking other drugs known or suspected to affect MIBG uptake (reserpine [*10,11*], cocaine [*10–12*], tricyclic antidepressants [*10–14*], sympathomimetics including

TABLE 2
Biochemical Data

Case Reference range:	P.E. (ng/ml) <100	P.NE. (ng/ml) <500	U.E. (μg/d) <20	U.NE. (μg/d) <100	U.MN (μg/d) <65	U.NMN (μg/d) <165	U.VMA (mg/d) <7.0
1*	68	198	288	156	33	231	2.7
2*	81	410	8	9	4	13	1.0
3*	199	293	12	18	9	16	1.9
4*	34	88	15	5	85	1,139	2.3
5†	185	656	31	72	1,364	1,681	7.5
6†					33	72	
7†	18	205	1	14	58	636	3.9
8†			47	1,079	277	5,739	

P, plasma; U, urinary; E, epinephrine; NE, norepinephrine; MN, metanephrine; NMN, normetanephrine; VMA, vanillylmandelic acid.
* Plasma catecholamines measured radioenzymatically; urinary catecholamines and metanephrines measured fluorimetrically.
† Plasma and urinary catecholamines and metanephrines measured by HPLC-ED.

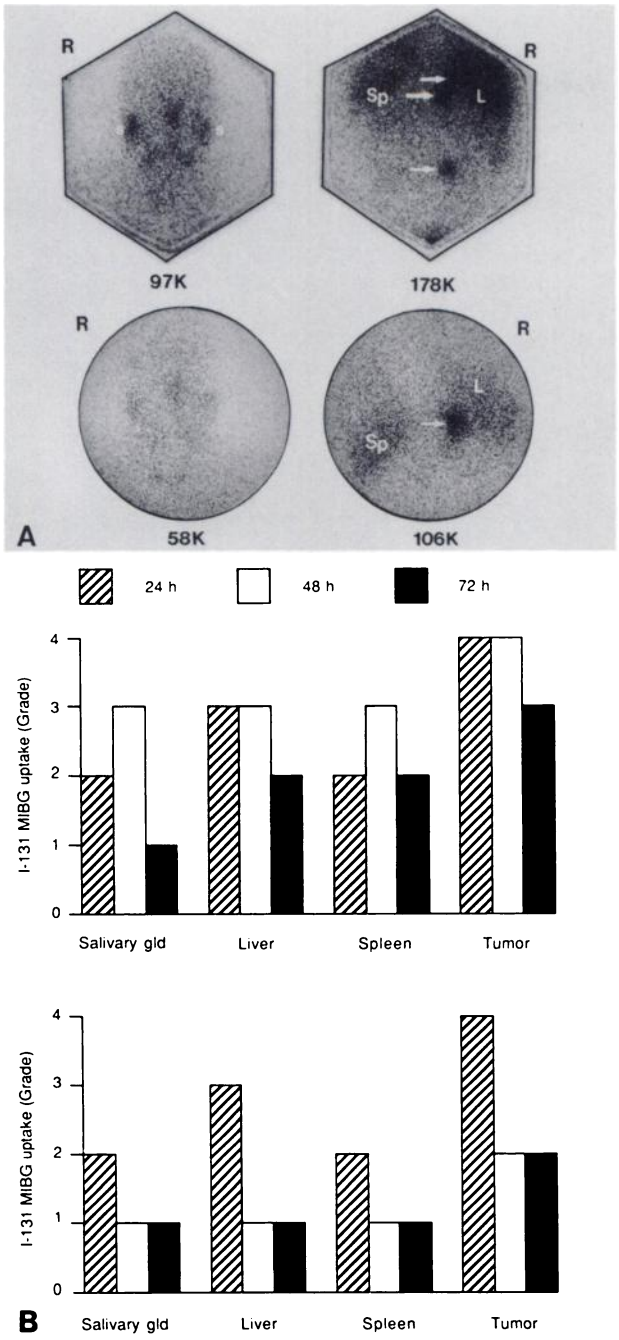

FIGURE 1
Case 7: A: Camera views of anterior head and neck (left column) and posterior abdomen (right column) obtained 48 hr after injection of 1.0 mCi (37 MBq) of [^{131}I]MIBG, while the patient was off (top row) and on (bottom row) labetalol. Each image was acquired over 15 min; total counts per image are indicated. Uptake in salivary glands [s], liver [L],spleen [Sp], and tumor deposits [arrows] is shown. The patient had remained clinically and biochemically stable between the two studies; tumor mass had not changed significantly as judged by x-ray computed tomography. While the patient was taking labetalol, not only was uptake of MIBG by the residual tumor in the right adrenal bed less, but only one focus of uptake could be resolved in this region. (The most caudad, retrocaval deposit seen in the top abdominal image is out of the field of view in the lower image. It was, however, faintly visible on an anterior pelvis/abdomen view which is not comparable to the upper righthand image. Attention should thus be concentrated on the more craniad lesions.) Case 7: B: Histograms of MIBG uptake grades at 24–72 hr for each region with the patient off (top) and on (bottom) labetalol.

nonprescription compounds containing phenylpropanolamine [*13,14*], and calcium channel blocking drugs [*15*]).

Blood samples for catecholamine measurement were obtained in resting, supine, fasted patients through an indwelling venous cannula which had been inserted at least 30 min before sampling commenced. Plasma catecholamine levels were originally measured using a radioenzymatic assay (*16*) and urinary catecholamines and metanephrines (metanephrine [MN] and normetanephrine [NMN]) by a fluorimetric assay (*17*). More recently, plasma and urinary catecholamines and urinary metanephrines have been measured using high performance liquid chromatography with electrochemical detection (HPLC-ED) (*18*). Urinary levels of vanillylmandelic acid (VMA) were measured spectrophotometrically (*19*).

All patients received three drops of a saturated solution of potassium iodide (SSKI, 120 mg iodide) per day for 1 wk, starting from the day before [^{131}I]MIBG injection, to block thyroidal uptake of free (^{131}I) iodide. Iodine-131 MIBG was administered by slow intravenous injection in a dose of 18.5 MBq (0.5 mCi)/(1.7 m^2 of body surface area), to a maximum dose of 37 MBq (1.0 mCi). At 24, 48, and 72 hr after injection (unless otherwise specified), overlapping scintigrams were obtained from the pelvis to the skull using a wide field-of-view gamma camera fitted with a high-energy, parallel hole collimator and interfaced to a computer. Images were acquired for at least 100,000 counts or 20 min per view.

The scans from the patients in the present study were mixed with scans from other patients not taking labetalol. For each image set, uptake of [^{131}I]MIBG by the salivary glands, the right lobe of the liver, the spleen and, where appropriate, pheochromocytoma tissue was graded according to the semiquantitative system previously described (*20,21*), as follows: grade 0, no visible uptake above background; grade 1, uptake just visible; grade 2, uptake clearly visible; grade 3, prominent uptake; grade 4, uptake yielding maximal film density. Grades were assigned by two physicians (FK, BS), one of whom (BS) had also graded the studies in the earlier series (*20,21*). Additionally, the activity in an area of general body background in the left lateral abdomen below the region of the spleen was graded on a semiquantitative scale (distinct from that used for grading organ uptake) in which grade 0 was no visible background, grade 1 was faint but clearly perceptible background, grade 2 was moderate background, and grade 3 was intense background. The scale encompassed by this grading would correspond to intensities of less than grade 1 on the organ scale in patients taking no medications. The grading of background was performed by one physician who had participated in the other gradings (BS). The results of background grading in the labetalol treated patients was compared to those in 12 patients without pheochromocytoma not taking any medications.

The one-sample t-test was used to compare mean uptake of [^{131}I]MIBG for each organ at each interval after injection against the population means previously defined for our clinic (*20*), before labetalol had become available.

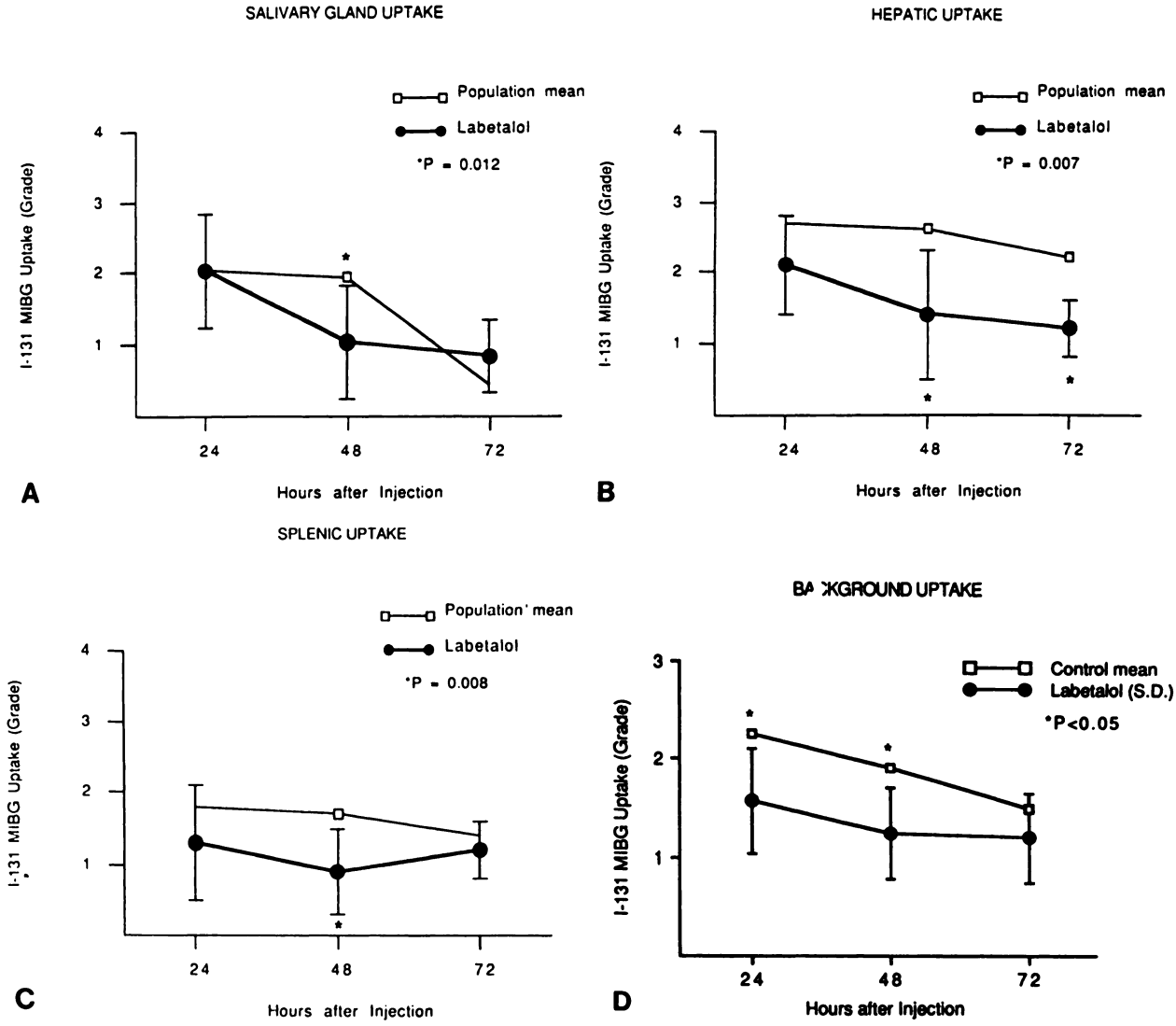

FIGURE 2
Time course of uptake of [^{131}I]MIBG (mean ± s.d.) by salivary glands (A), right hepatic lobe (B), and spleen (C) in patients receiving labetalol. "Population means" from data in Nakajo et al. (*20*). D: Time course of uptake of [^{131}I]MIBG (mean ± s.d.) in general body background, labetalol treated patients compared to medication-free controls. Note uptake grading scale is different to that used in (A), (B), (C).

RESULTS

Eight patients who met our criteria for inclusion in the study were identified. Their clinical details are summarized in Table 1, and their biochemical data in Table 2. Cases 1–7 were receiving labetalol at the time of [^{131}I]MIBG injection. Case 8 had been treated elsewhere with labetalol and phenoxybenzamine; upon transfer to our hospital, his therapy was changed to propranolol and prazosin—he received his last dose of labetalol 36 hr before [^{131}I]MIBG injection.

Only three of these patients were proven to have pheochromocytomas. Case 5 had a 3-cm right adrenal tumor; tumor uptake of [^{131}I]MIBG was grade 4 at 24 and 48 hr postinjection. Case 7 had stable, metastatic, malignant pheochromocytoma with known residual disease in the right adrenal bed and the distal retrocaval region; tumor [^{131}I]MIBG uptake was grade 4 at 24 hr, but only grade 2 at 48 and 72 hr postinjection. The results of [^{131}I]MIBG scans performed in this patient off and on labetalol are illustrated in Figure 1. Case 8 had a 4 × 3 cm, 26 g, right adrenal tumor; tumor uptake of [^{131}I]MIBG was only grade 1 at 48 and 72 hr (a scan was not obtained at 24 hr postinjection).

The time course of uptake of [^{131}I]MIBG in the salivary glands, liver and spleen is shown in Figure 2, and compared with our previously published data (Table 3) (*20*). Uptake was generally lower than expected; this trend was statistically significant ($p < 0.05$) for all three regions at 48 hr postinjection.

The results of the grading of [^{131}I]MIBG in the general body background are presented in Figure 2D and Table

TABLE 3
Tissue Uptake of [^{131}I]MIBG in Patients Receiving Labetalol

		Interval following [^{131}I]MIBG injection		
		24 hr	48 hr	72 hr
Salivary gland uptake	Expected*	2.0 ± 0.7 (n = 119)	1.9 ± 0.6 (n = 172)	0.4 ± 0.7 (n = 10)
	Labetalol†	2.0 ± 0.8 (n = 7)	1.0 ± 0.8 (n = 8)	0.8 ± 0.5 (n = 4)
	P =	1.000	0.012	0.256
Hepatic uptake (R. lobe)	Expected	2.7 ± 0.5 (n = 229)	2.6 ± 0.8 (n = 314)	2.2 ± 0.9 (n = 94)
	Labetalol	2.1 ± 0.7 (n = 7)	1.4 ± 0.9 (n = 8)	1.2 ± 0.4 (n = 5)
	P =	0.077	0.007	0.007
Splenic uptake	Expected	1.8 ± 0.6 (n = 226)	1.7 ± 0.6 (n = 311)	1.4 ± 0.8 (n = 94)
	Labetalol	1.3 ± 0.8 (n = 7)	0.9 ± 0.6 (n = 8)	1.2 ± 0.4 (n = 5)
	P =	0.122	0.008	0.374
Background uptake‡	Controls	1.57 ± 0.54 (n = 12)	1.25 ± 0.29 (n = 12)	1.20 ± 0.52 (n = 12)
	Labetalol	2.25 ± 0.62 (n = 7)	1.92 ± 0.46 (n = 8)	1.50 ± 0.45 (n = 5)
	P =	0.028	0.001	0.280

* Mean uptake grade ± s.d., recalculated from previously published data (*20*).
† Mean uptake grade ± s.d.
‡ Note scale for background intensity is different from that for organs mean uptake grade ± s.d.

3. Here, too, the results were lower in the labetalol treated patients and this was significant at 24 and 48 hr.

DISCUSSION

MIBG is an iodinated aralkylguanidine that is structurally similar to guanethidine and NE. There is now considerable evidence that MIBG is taken up into the adrenal medulla and tissues with a rich sympathetic innervation (e.g., salivary gland, heart, spleen) by the specific neuronal catecholamine uptake mechanism, "uptake-1", and actively transported into catecholamine storage vesicles. In the canine adrenal medulla, [^{131}I]MIBG localizes in the same subcellular fraction as the storage vesicles (*10*). Reserpine, which selectively blocks the active transport of catecholamines into storage vesicles and depletes NE stores, reduces both uptake and storage of MIBG in the canine adrenal medulla (*10,11*). The uptake-1 inhibitors, cocaine and desmethylimipramine (DMI), reduce uptake of both iodine-125 (^{125}I) MIBG and tritiated NE (^{3}H NE) in canine adrenal medulla (*10,11*), cultured bovine adrenomedullary cells (*12*) and rat heart (*13*). Similarly, chemical sympathectomy with 6-hydroxydopamine reduces MIBG and NE uptake in the canine spleen (*11*) and rat heart (*13*), while increasing their uptake into the canine adrenal medulla (*11*). Finally, the discharge of [^{125}I]MIBG from the rat heart in response to feeding or phenylpropanolamine administration parallels that of ^{3}H NE (*13*).

In man, salivary gland uptake of [^{131}I]MIBG is reduced ipsilaterally in patients with Horner's syndrome, and bilaterally in patients who have severe autonomic neuropathy or are receiving tricyclic antidepressants (*11,22*). Myocardial uptake of [^{131}I]MIBG (*11*) and [^{123}I]MIBG (*14*) is likewise reduced in autonomic neuropathy or following imipramine or phenylpropanolamine administration, and imipramine significantly increases the rate of loss of [^{123}I]MIBG from the liver (*14*).

The effect of labetalol on [^{131}I]MIBG uptake in our patients is similar to that observed in patients taking tricyclic antidepressants (*11,14,22*) and is in contrast to

the lack of any noticeable effect of more conventional alpha-blocking and beta-blocking drugs (*11*). Case 8 shows that this effect may persist for 36 hr or more after labetalol has been discontinued; uptake of [^{131}I] MIBG in this patient was markedly reduced in all areas, including his large tumor mass. We have recently studied an 80-yr-old woman in whom we discontinued labetalol for 1 wk before injecting [^{131}I]MIBG: the uptake of MIBG in her salivary glands, liver, and spleen was normal up to 72 hr postinjection. Based on this limited experience, it seems advisable to discontinue labetalol for at least several days before administering MIBG.

Pharmacologic experiments in laboratory animals (*23,24*) and in the isolated, perfused cat spleen (*25,26*), and rat vas deferens (*27*) have shown that labetalol inhibits the uptake and metabolism of NE in the same way as, but less potently than, cocaine and DMI. In addition, labetalol has been shown to release NE from storage vesicles in the isolated rat ventricle (*28*) and anococcygeus muscle (*29*) and in isolated canine saphenous vein (*30*); this effect is similar to that of the indirect sympathomimetics (*28*) and guanethidine (*29*). The i.v. administration of labetalol to hypertensive patients produces a fourfold greater rise in plasma NE levels (measured radioenzymatically) for any given reduction in blood pressure than a sodium nitroprusside infusion (*31*), i.e., labetalol produces an increase in circulating NE above that attributable solely to baroreflex activation. In patients receiving chronic, oral labetalol therapy, the pressor effects of exogenous NE are enhanced despite labetalol's α_1-blocking properties,

TABLE 4
Drugs Known or Expected to Reduce MIBG Uptake

	Drug	Mechanism
A. Known:		
	Antihypertensive/cardiovascular	
	• Labetalol	• Uptake-1 inhibition • Depletion of storage vesicle contents
	• Reserpine	• Depletion of storage vesicle contents • Inhibition of vesicle active transport
	• Calcium-channel blockers • Diltiazem • Nifedipine • Verapamil	• Uncertain (Also enhance retention of previously stored NE and MIBG by blocking Ca^{++}-mediated release from vesicles.)
	Tricyclic antidepressants • Amitriptyline and derivatives • Imipramine and derivatives • Doxepin • Amoxapine • Loxapine (antipsychotic agent)	• Uptake-1 inhibition
	Sympathomimetics • Phenylephrine • Phenylpropanolamine • Pseudoephedrine, ephedrine	• Depletion of storage vesicle contents These drugs occur in numerous nonprescription decongestants and "diet aids"—their use should be ruled out
	Cocaine	• Uptake-1 inhibition
B. Expected:		
	Antihypertensive/cardiovascular	
	• Adrenergic neurone blockers • Bethanidine, debrisoquine • Bretylium • Guanethidine	• Depletion of storage vesicle contents • Competition for transport into vesicles
	"Atypical" antidepressants • Maprotiline • Trazolone	• Uptake-1 inhibition

Table 4—continued

Drug	Mechanism
Antipsychotics ("Major tranquilizers")	• Uptake-1 inhibition
• Phenothiazines	
• Chlorpromazine,* triflupromazine,* promethazine*	
• Fluphenazine, acetophenazine, perphenazine*	
• Prochlorperazine,* thiethylperazine,* trifluoperazine	
• Thioridazine, mesoridazine	
• Thioxanthines	
• Chlorprothixene	
• Thiothixene	
• Butyrophenones	
• Droperidol	
• Haloperidol	
• Pimozide	
Sympathomimetics	• Depletion of storage vesicle contents
• Amphetamine and related compounds	
• Amphetamine and derivatives	
• Diethylpropion	
• Fenfluramine	
• Mazindol	
• Methylphenidate	
• Phenmetrazine and derivatives	
• Phentermine and derivatives	
• Beta-sympathomimetics†	
• Albuterol (salbutamol)	
• Isoetharine	
• Isoproterenol	
• Metaproterenol	
• Terbutaline	
• Dobutamine	
• Dopamine	
• Metaraminol	

* Frequently used as antiemetic/antipruritic agents.
† Systemic use. Effect unlikely with aerosol administration in conventional doses.

without any change in the vasopressor threshold dose of NE (*32*). Like DMI (*33*), labetalol reduces the systemic clearance of NE from plasma in man (*32*).

Thus, there is direct experimental evidence in animals and indirect evidence in man that labetalol is an inhibitor of neuronal catecholamine uptake and storage. This is the probable explanation for the reduction in [^{131}I]MIBG uptake observed in our patients. MIBG scintigraphy should not be attempted until at least several days (possibly up to 1 wk) after the withdrawal of labetalol, or the likelihood of a false-negative study will be increased. Conventional alpha- and beta-blocking drugs may be substituted.

The lower body background activities observed in the labetalol treated subjects cannot be ascribed to the inhibition of the type 1 uptake mechanism but may result from inhibition of body-wide endothelial MIBG uptake which is by a different mechanism. This would then result in more rapid clearance as MIBG is rapidly excreted in the urine with little metabolism. Thus far the exact mechanisms for the interference of labetalol with MIBG uptake in sympathomedullary and other tissues are speculative but the phenomenon itself is significant and has been independently observed by others (*34*).

A further drawback to the use of labetalol in patients

TABLE 5
Drugs with No Significant Effect on MIBG Uptake

ANTIHYPERTENSIVE/CARDIOVASCULAR
Alpha-blockers
(clonidine, phenoxybenzamine, phentolamine, prazosin)
Alpha-methyldopa*
Angiotensin Converting Enzyme Inhibitors
(captopril, enalapril)
Beta-blockers
Digitalis glycosides
Diuretics
ANALGESICS
Major (morphine and other opioids)
Minor (aspirin, acetaminophen)†
HYPNOTICS, MINOR TRANQUILIZERS
ALPHA-METHYLPARATYROSINE*

* Will falsely elevate catecholamine and metabolite levels in fluorimetric assays.

† Often combined with sympathomimetic agents in nonprescription "cold remedies", use of which should be specifically ruled out.

who are being evaluated for pheochromocytoma is the ability of the drug to interfere with many of the current assays for catecholamines and their metabolites. Falsely elevated results have been reported with the fluorimetric assay for urinary catecholamines (*35*), the spectrophotometric assay for urinary metanephrines (*35,36*) and VMA (*36*), and more recently with the HPLC-ED assay for plasma epinephrine (*37*). There is no apparent correlation between the magnitude of the effect and the dose of labetalol (*35*). The apparently elevated urinary levels of catecholamines or metabolites in our Cases 1 and 4 may have been at least partly a result of their labetalol therapy. The interference has been ascribed to as yet poorly characterized metabolites of labetalol rather than the parent drug, and has been documented to persist for up to 4 days after discontinuing the drug. The last finding further supports our recommendation to defer MIBG scintigraphy for several days after the withdrawal of labetalol. There have been no reports of interference by labetalol in the radioenzymatic assay.

In conclusion, although labetalol may be a useful agent for the management of patients with pheochromocytomas, hypertensive patients should not be investigated for possible pheochromocytoma while they are taking this drug. Labetalol may lead to a false-positive biochemical diagnosis of this rare disease. More importantly, labetalol should be added to the list of drugs which may give rise to false-negative MIBG scans in patients with pheochromocytomas. In order to maintain the high sensitivity and specificity of MIBG scintigraphy for the localization of pheochromocytomas, we have appended what we believe to be a current and comprehensive list of drugs known (from clinical or experimental evidence) or expected [on the basis of their known pharmacologic actions (*38*)] to interfere with MIBG scintigraphy (Table 4). We have also included a list of drugs which may be required in patients with suspected pheochromocytoma but which do not appear to affect MIBG uptake significantly (Table 5).

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