Food and Drug Administration Grants Approval for ^{131}I MIBG

Drug long in use to image pheochromocytoma and neuroblastoma finally commercially available; researchers look to ^{123}I MIBG

AFTER MORE THAN FIFTEEN YEARS since its invention, ^{131}I metaiodobenzylguanadine (MIBG) received FDA approval under an new drug application (NDA) on March 25. Although the drug has had extensive use under an investigational new drug permit (IND) for many years, it took an extraordinarily long time to receive NDA approval due to the fact that it was first developed at a university, which did not have marketing resources but held onto the patent through years of research until selling the rights to a commercial concern. The company then pushed straightaway to get FDA approval for the drug's commercial distribution.

One of the drug's primary developers, William H. Beierwaltes, MD, former professor of internal medicine, Division of Internal Medicine, University of Michigan Medical Center, describes MIBG's genesis as dating to 1967, upon the first publication of attempts to develop a radiolabeled precursor to epinephrine as an imaging agent for adrenergic tumors. The first two candidates were ^{11}C labeled dopamine and norepinephrine. Later, investigators showed that neuroblastoma and pheochromocytoma took up labeled dopamine at much higher levels than did normal tissue. In the meantime, "we then developed similar radiolabeled compounds," Dr. Beierwaltes said. "The group very carefully planned this out."

Targeting the Tumor

This search for related, artificial compounds that would perhaps perform even better than the earlier compounds resulted, in the late 1970's, in Dr. Donald Wieland's derivation of MIBG (see *Newsline*, May 1994, p. 20N; the inventor received the Aebersold Award for this achievement). This drug's molecular structure was similar to norepinephrine, which is synthesized in normal adrenergic cells and stored in their granules (see Figure 1). These cells also secrete the hormone, which is then taken up by other adrenergic cells and stored in granules, a process that allows MIBG to enter the norepinephrine pathways. Luckily, MIBG has enough chemical difference from norepinephrine that it does not bind to receptors and so elicits little or no pharmacological response and is only slightly metabolized.

With such useful properties, MIBG has been the subject of a rich literature of research into both its imaging and therapeutic values for pheochromocytoma and neuroblastoma, and it has been commercially marketed in Europe and Japan. But MIBG has not been under wraps in the U.S., either. "About ten and a half years ago," said Neil A. Petry, director of the nuclear pharmacy at the University of Michigan Medical Center (UMMC), "when I came on the scene, we were making MIBG more available," expanding the drug's range from UMMC to ten other sites, and eventually to "hundreds of clinics using it on an investigative basis. Technically, its use has been investigative, but here at the University of Michigan, we've been using it regularly in practice. Around 1985, with the Orphan Drug Act, we got MIBG recognized as an orphan radiopharmaceutical."

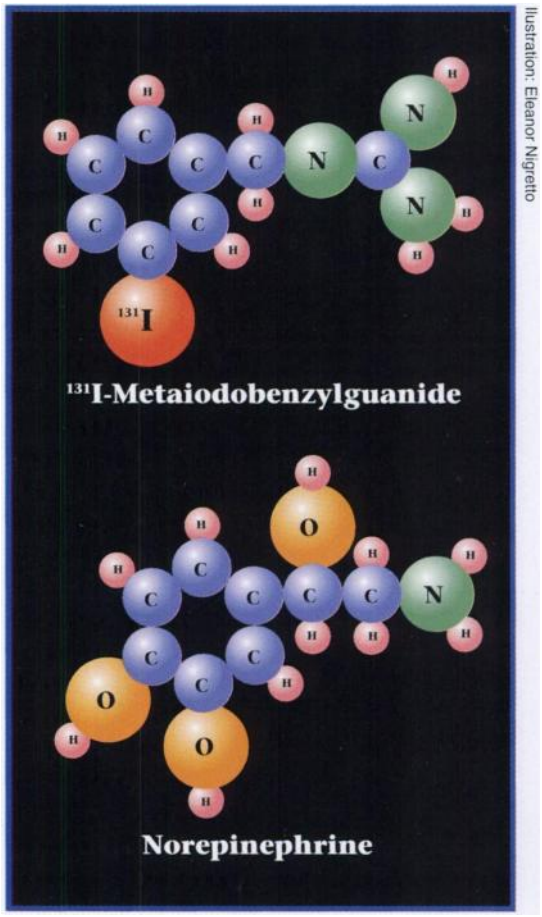

Figure 1. Molecular structures of MIBG and norepinephrine.

Finding a Marketer

It was this peculiar status of the drug, along with the non-commercial position of the university, that kept the drug in an unusual limbo for years, without NDA approval. "For the NDA—

what happened was—producing this [drug] was not what the university of Michigan or the patent-holders wanted to do—getting into the business of manufacturing," said James Sisson, MD, assistant chief and professor of nuclear medicine at UMMC. For Mr. Petry, the delay in getting approval "comes down to one thing—money: who is going to do it and provide the money." But a staff member of the FDA elaborated on the scenario. "This was an orphan drug: no manufacturer wanted to take it up since there was no profit.," said A. Eric Jones, medical officer at the FDA. "We could not get a company to come in and market it; this was a problem."

Yet, as MIBG was already being marketed in Europe, he pointed out, it took a European firm, about four years ago, to come into the scene and put in an NDA application. The company, CIS-US (Bedford, MA), an American subsidiary of the French company, CIS, then worked assiduously at compiling all the necessary data, much of which was already in the literature. Dr. Jones said this included "the safety data [derived] by proper drug trials, efficacy from the literature, and most clinical data from the IND's at Michigan." Once the company set its sights on approval, the process went at the normal speed. (According to David Woodbury, another medical officer at the FDA, radiopharmaceutical approval takes two to ten years, with a mean of 39 months.)

Despite the delay, Dr. Jones commended UMMC's handling of the situation. "I think Michigan deserves some recognition in this because they could have thrown up their hands and said they didn't want to take the risk and get sued." This perseverance "sets an example for nuclear medicine: if more universities could do what the University of Michigan did, we might get some more products developed."

Looking Toward the Commercial Availability of ^{123}I MIBG

Yet the effect that the approval of ^{131}I MIBG will have on the medical community has gotten mixed reactions. "I suspect change will not be that great at all: MIBG has been available, except now you get it through CIS and not us," said Dr. Sisson. But in light of this new, wider availability, he cautioned that since it is an orphan drug and used only rarely on rare diseases, physicians may be tempted to use it without having developed sufficient experience. Mr. Petry related that ^{131}I MIBG's approval was only a first step for MIBG: "I think it will be helpful—having it commercial is important—but I don't think it's the best drug. ^{123}I [for MIBG], I think, is a better radionuclide—better resolution, better image quality." One problem with ^{123}I, though, is cost: it has a half-life of 13.1 hours, compared to eight days for ^{131}I, making the latter much more readily available. UMMC makes ^{123}I available only two Tuesdays per month, "so the patients have to be run through the mill all at once," Mr. Petry said. "It would be good to encourage CIS to make 123 available."

Glenn Alto, product manager at CIS-US, said that the company is still trying to figure out how to handle ^{123}I MIBG. Because of the isotope's short half-life, distribution *for his company* is a major hurdle to overcome, he said, because the isotope disintegrates rapidly. "Though it's considered... to be a superior isotope, it's difficult to provide on a commercial basis," he said. Thus, "At the moment, it remains undecided [at CIS-US] on whether to get FDA approval."

However, a growing number of nuclear medicine practitioners agree with Mr. Petry about ^{123}I MIBG's importance—especially for cardiovascular nuclear medicine. "There's no doubt of the much better quality image from 123," said Michael W. Dae, MD, associate professor of radiology and medicine in the Department of Radiology and Nuclear Medicine, University of California at San Francisco. "There are other potential applications for 123 involving the heart, for patients with congestive heart failure. Also there's a potential for helping to determine patients with sudden death. Studies have been done to confirm that this is where the diagnostic capability of 123 will be far superior to 131. Quantitation is easier with it."

E. Gordon De Puey, MD, pointed out that ^{123}I MIBG, with its potential to select therapeutic agents for heart failure patients and determine which patients need heart transplantation, has already become widely used in Japan and Europe (see *Newsline*, April 1994, p. 17N). In fact, the 1994 SNM annual meeting will have at least six papers and posters on ^{123}I MIBG, five of these from Europe or Japan, and four of these five on cardiovascular nuclear medicine. If this is any indication, MIBG has a whole new life after ^{131}I approval, reaching beyond neuroendocrine imaging and into cardiac imaging with ^{123}I. As Dr. Dae summed up, "If any encouragement can be made to the distributor to make 123 available, it would be an advantage to the community."

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