The Packaging of Intravenous Persantine®

TO THE EDITOR: Intravenous Persantine® (dipyridamole USP, a registered trademark of Boehringer Ingelheim International GmbH, and manufactured and distributed by DuPont, Billerica, MA, under license from Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT) has been recently approved by the Food and Drug Administration (FDA). This is the first pharmacologic alternative to exercise in thallium myocardial stress imaging for the evaluation of coronary artery disease in patients who cannot perform exercise testing on a treadmill or whose tests are unsatisfactory (*1*). I.V. Persantine® is available in boxes of five 2-ml ampules containing 10 mg of dipyridamole. We would like to address three issues regarding the packaging of I.V. Persantine®.

First, I.V. Persantine® is a parenteral preparation which is stored in a single-dose ampule made entirely of glass. Because glass particles may become dislodged during opening of the ampule, I.V. Persantine® solution must be filtered prior to administration. This can be accomplished by filtering the solution through a sterile/non-pyrogenic filter needle (Monoject® 305, Sherwood Medical, St. Louis, MO). The 18-gauge 1.5 in. needle contains a microporous stainless steel filter that is designed to retain 5 μm or larger particulate matter. Nuclear pharmacists understand that it is standard and necessary practice to filter parenteral preparations packaged in ampules, however, the majority of nuclear medicine technologists are not aware of this procedure. Thus, it would be advisable to include a statement in the package insert and/or on the box label stressing the need to filter I.V. Persantine® solution before clinical use.

Second, labeling on the outside of the package as well as the package insert (*1*) should state specifically that the product should be protected from direct light. However, I.V. Persantine® solution is packaged in clear ampules, while standard practice is to package light-sensitive material in light-resistant (e.g., amber) containers. Ameer et al. (*2*) have studied the effect of light on oral suspension of Persantine® tablets (Boehringer Ingelheim, Ridgefield, CT) and found that light exposure results in a reduction in the stability of the dipyridamole suspension. The issues as to how the intravenous injection of I.V. Persantine® solution reacts to light exposure and for how long a period of time I.V. Persantine® can be exposed to light without causing any noticeable degradation of the drug are not clear. In our laboratory, we have taken reasonable precautions to protect I.V. Persantine® solution from exposure to light. We store the Persantine® ampules in the original box inside an enclosed drawer. During the interim time between drawing up the dose and administering the diluted solution (30–60 min), the filled syringe and tubing are covered to avoid exposure to light.

Finally, as stated earlier, Persantine® is packaged in a 2-ml ampule that contains 10 mg of dipyridamole. The recommended dose is 0.57 mg/kg (although the maximum tolerance dose has not been determined, clinical experience from Camp et al. (*4*) indicate that there is a significant increase in side effects when a total dose of intravenous dipyridamole exceeds 60 mg.), equating to a recommended total dose of 23.3–59.6 mg for a patient whose body weight is within the range of 40.9–104.5 kg (*1,3*). This requires that we use 3–6 ampules per patient dose. It would seem logical that the I.V. Persantine® solution containing either a single patient dose (60 mg, 5 mg/ml) or multiple patient doses should be packaged in glass or plastic opaque vials closed with a rubber stopper and sealed with an aluminum crimp. Vials offer several advantages over ampules:

1. They can be designed to hold multiple patient doses (if prepared with a bacteriostatic agent).
2. They allow for easy access and removal of the product.
3. They eliminate the risk of glass particle contamination during opening.

However, it is unclear whether there is an incompatibility between I.V. Persantine® solution and the rubber stopper, which may cause an undesirable reaction resulting in drug degradation. The other aspect of altering the packaging is that the FDA may require an entirely new series of tests before approval and implementation of the changes, which would be very costly and time-consuming.

REFERENCES

1. Package insert of I.V. Persantine® (dipyridamole USP), February 1991.
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3. Dosage/Dilution guide for I.V. Persantine® (dipyridamole USP), Injection 5 mg/ml, E.I. duPont de Nemours & Co., Billerica, MA.
4. Camp A, Chaitman BR, Goodgold H, et al. Intravenous dipyridamole and body weight considerations and dosage requirements. *Am Heart J* 1989;117:702–704.

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REPLY: Intravenous Persantine® (dipyridamole USP) injection has been commercially available in the United States since January 21, 1991. I.V. Persantine® is the *first* pharmacologic alternative to exercise in thallium myocardial perfusion imaging for the evaluation of coronary artery disease in patients who cannot exercise adequately. Boehringer-Ingelheim (BIPI), the owner of the Persantine® NDA, has granted an exclusive license to Du Pont Merck to market and manufacture I.V. Persantine® for use in thallium imaging in the United States and its territories. Three issues regarding the packaging of I.V. Persantine® have been identified in this issue of *The Journal of Nuclear Medicine* by individuals at the Mayo Clinic in Rochester, MN. Du Pont's response to those issues is as follows.

First, the authors have requested that Du Pont Merck include a statement in the package insert and/or on the box label to address the need to filter the I.V. Persantine® solution before clinical administration. Their concern is that even though nuclear pharmacists understand that it is a standard and necessary practice to filter parenteral preparations packaged in ampules, the majority of nuclear medicine technologists are not aware of this

procedure. It is Du Pont's position that this information should be transmitted to nuclear medicine technologists, nuclear pharmacists and any other individuals preparing a dose of I.V. Persantine® through customer education and training. Such instructions do not appear to be a normal part of a drug's package insert (PI). A review of the PDR indicates that no major parenteral product commercially available in ampules includes a statement requiring that these products be filtered prior to administration.

Second, the authors indicate that although the PI clearly states that the product should be protected from direct light, it is not clear why the I.V. Persantine® injection reacts to light exposure and for how long a period of time I.V. Persantine® can be exposed to light without causing any noticeable degradation of the drug. We offer the following information to clarify this concern. Once I.V. Persantine® is diluted, there is an apparent increase in light sensitivity of the dipyridamole molecule. In studies performed by BIPI, the maximum rate of degradation varied from about 3 hr to 30 hr. The 3-hr rate occurs in diluted (reconstituted) I.V. Persantine®, while the 30-hr rate corresponds to relatively more concentrated aqueous I.V. Persantine® solutions. The degradation rate constant is obviously dependent on the light intensity in the laboratory. Thus originates the I.V. Persantine® package insert statements "avoid direct light", "keep the product in the original carton to provide protection from light until dispensed" and "solution should not be used if discolored." Prudent use of I.V. Persantine® would suggest storing the undiluted ampules in a cabinet, free from direct light subject to the expiration date. After dilution, the material should either be stored free from direct light (ideally) or not longer than about 3 hr when exposed to ambient light (prior to patient administration).

Finally, the last question asked by the authors is why is I.V. Persantine® packaged in a 2-ml ampule containing 10-ml of dipyridamole versus a larger single patient dose ampule or multiple patient dose ampule/vial. The 2-ml ampule is the first commercially available form for I.V. Persantine® because data for this "putup" was submitted in the original NDA to the FDA. We are currently working on alternative putups for I.V. Persantine® that must be submitted for FDA review prior to commercialization.

We hope that this adequately answers the questions outlined by the authors from the Mayo Clinic. If anyone has any further questions, please do not hesitate to call the Du Pont Pharma nuclear cardiology hotline at 1-800-343-7851 for further clarification.

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Detection of Myocardial Validity

TO THE EDITOR: The January 1991 issue of the *The Journal of Nuclear Medicine* contains a Clinicopathologic Conference (CPC) on detection of myocardial viability with PET in a patient with probable ischemic cardiomyopathy.

The case is excellently presented by Dr. Weiss. The discussion by Dr. Eisen is topical, informative, and well-written with pertinent references. I am perplexed however by Fig. 1 in the CPC. These images are planar images (the text states that a "tomographic thallium study was performed . . ."). The legend for Figure 1 indicates that the images "show an anterior and upper septal defect with no redistribution." To this reader's eye the "anterior and upper septal defect" could easily represent normal decreased activity in the LV outflow tract/mitral apparatus. I would assume tomography showed fixed defects in the above-mentioned areas, however, other than LV dilation, the images in Figure 1 are unremarkable.

REFERENCE

1. Weiss D, Eisen HJ, Alavi A. Detection of myocardial viability with positron emission tomography in a patient with ischemic cardiomyopathy. *J Nucl Med* 1991;32:130–135.

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REPLY: The question raised by Dr. Campeau regarding the thallium scans in Figure 1 can be explained by the fact that the patient in the CPC underwent two thallium studies. The first was a tomographic thallium study during cardiac pacing and was performed on September 7, 1989. The patient's heart was paced to 87% of predicted maximum and a large fixed defect was noted in the septum, apex and inferior walls with dilatation of the left ventricle. Only slight improvement was noted in the anteroseptal wall. The patient was then transferred to our institution on September 18, 1989. He underwent a stress-rest thallium study on September 22, 1989. This was a planar study and is shown in Figure 1. For this study, the patient achieved 60% of maximal-predicted heart rate. Scintigraphy revealed a dilated left ventricle with fixed defects in the anterior and upper septal walls consistent with scar. No ischemia was noted. Dr. Campeau is correct that these defects could represent decreased activity normally seen in the LV outflow tract and mitral apparatus, although the anterior defect in the LAO 70° view appears to be too extensive to be a normal variant. The findings described for the planar thallium-stress test shown in Figure 1, which was obtained at our institution, are similar to those reported in the pacing tomographic thallium study performed at the referring institution, except that we did not see the inferior wall defect. We were unable to obtain satisfactory images for reproduction purposes from the initial pacing thallium study. The results of both the tomographic thallium scan at the referring hospital and the planar thallium scan obtained at our hospital and shown in Figure 1 are discussed on page 131 of the CPC.

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Determining Gastric Emptying Rate

TO THE EDITOR: Gastric emptying and its rate are determined by multiple complex factors, many of which are inextricably interelated. There is, however, one variable of a test meal that cannot possibly influence gastric motility except indirectly—its caloric content.

In spite of the obviousness of this thesis, the nuclear medicine gastric motility literature offers a litany of ill-conceived hy-