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.
2. Ameer B, Callahan RJ, Dragotakes SC. Preparation and stability of an oral suspension of dipyridamole. *J Pharm Tech* 1989;5:202–205.
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