Prescriber Beware: It Is Ill Advised to Administer Compounded Sincalide

Because of the current unavailability of Kinevac, the form of sincalide for injection, approved by the U.S. Food and Drug Administration (FDA), nuclear medicine clinics may consider alternatives, including purchasing a compounded product, and some pharmacists may be considering compounding this drug (*1*). However, several concerns relative to compounded sincalide make such practices ill advised.

The FDA recognizes that pharmacists traditionally have extemporaneously compounded and manipulated reasonable quantities of human drugs on receipt of a valid prescription for an individually identified patient from a licensed practitioner (*2*). For more than 40 years, nuclear pharmacies have demonstrated an outstanding record of providing safe and reliable compounded drugs. However, evidence suggests that an increasing number of establishments with retail pharmacy licenses are engaged in manufacturing and distributing unapproved new drugs for human use in a manner that is clearly outside the bounds of traditional pharmacy practice. In several instances, pharmacies have cloaked large-scale manufacturing activities under the guise of compounding. The U.S. Centers for Disease Controls (CDC) continue to investigate a multistate outbreak of fungal meningitis in patients receiving compounded preservative-free methylprednisolone acetate prepared by the New England Compounding Center (NECC). This single product is believed to have caused 750 cases of fungal meningitis in 20 states, resulting in 64 deaths. The FDA and CDC have also found bacterial and fungal contamination in numerous drugs prepared by NECC that have been linked to reports of other persistent illnesses. Such large-scale compounding establishments and their activities are now the focus of increased regulatory and legislative efforts that seek to ensure the safety of patients receiving compounded drugs.

State boards of pharmacy provide oversight of pharmacy practices, including drug compounding. When the FDA learns of compounding practices that raise public health concerns, the agency may refer the matter to state boards of pharmacy for investigation. Using a risk-based approach, the FDA may also take enforcement action against pharmacies for circumstances described in FDA guidance that are not consistent with traditional compounding, including but not limited to (*2*): (1) Compounding drugs prior to receipt of a valid prescription; (2) compounding drugs removed from the market for safety reasons; and (3) compounding drugs that are essentially copies of commercially available products.

The FDA recognizes that in cases of supplier outages of commercially available pharmaceuticals or radiopharmaceuticals, short-term compounding of such preparations is appropriate. When compounding any drug, adherence to "good pharmacy practice" is necessary to ensure a safe and effective product. These practices include sourcing components from qualified suppliers, seeking FDA-approved components whenever available, and employing qualified compendial testing methods. If FDA-approved components are not available, verification of the strength, identity, quality, and purity of all components of the final compounded preparation is required, using qualified compendial (e.g., USP) testing methods. Special consideration must also be used when compounding biological products.

In the case of sincalide, these verifications are not possible because of the unique nature of the product and the lack of a compendial method to determine strength (potency). Therefore, it is ill advised to administer compounded sincalide. Concerns regarding the use of compounded sincalide include:

Sterility. Compounded sincalide involves starting with a nonsterile component. Thus, it is considered a High-Risk Level Compounded Sterile Product (CSP) according to USP <797>. The maximum beyond-use time (BUD) for such products is 24 hours at controlled room temperature (20°–25°C), 3 days at 2°–8°C, and 45 days in a solid frozen state at –25° to –10°C. These time periods are unreasonable for batch production followed by end-product testing using compendial methods, as well as for most large-scale distribution networks. BUDs could be extended but require validated sterility testing and stability evaluations. Lack of sterility could result in infections in patients.

Strength or potency. For bioactive compounds, the same mass does not necessarily produce the same biologic effect. The USP monograph for sincalide requires that gallbladder contractile studies in guinea pigs be performed to determine the potency of the sincalide batch. This is somewhat analogous to insulin, which requires blood sugar assays in rabbits to determine potency. Superpotent sincalide could result in increased frequency and severity of side effects, whereas subpotent sincalide could result in falsely low gallbladder emptying that might be misinterpreted as chronic cholecystitis.

For many years the USP contained a monograph for sincalide for injection, but this was dropped in USP 36. At the time, the *Pharmacopeial Forum* stated: "It is proposed to omit this monograph from USP for the following reasons: (1) USP's attempts to develop the USP Sincalide RS

have been unsuccessful, because sincalide is a very expensive synthetic peptide with a very limited market; (2) The monograph became official in May 1999, but it remained unenforceable because the procedures requiring the use of USP Sincalide RS were postponed pending its availability. (3) In addition, the Assay procedure in the monograph employs a complex functional bioassay which is not suitable for use as a public standard. USP's attempts to replace the functional bioassay with a quantitative chemical assay have not been successful. (SM4: R. Ravichandran)" (*3*).

Stability. Some bioactive compounds exhibit adherence to container components and/or degrade over time. Compounded sincalide stored/transported in a plastic syringe may or may not adhere to components (syringe wall, plunger) and/or degrade. Stability studies are necessary to evaluate this possibility. Adherence and/or degradation may result in less than the expected amount of sincalide available for injection, which could result in falsely low gallbladder emptying that might be misinterpreted as chronic cholecystitis.

Impurities and contaminants. Some drug substances are difficult to purify and thus may contain impurities and contaminants. Rigorous quality control testing using compendial (e.g., USP) methods is necessary to characterize the presence of impurities and contaminants. Administration of impurities and contaminants may result in adverse reactions.

Compliance with medication management standards. The Joint Commission (TJC) and other accrediting bodies require policies and procedures for ensuring the quality of all drugs used within an institution. Compliance requires that all drug products must be evaluated by the Pharmacy and Therapeutics (P&T) Committee and approved for use. The P&T Committee should have policies and procedures regarding procurement of outsourced compounded drugs and qualification of outsourced suppliers. Some institutions do not allow any compounded drugs to be outsourced. The nuclear medicine staff, therefore, does not have the unilateral authority to procure compounded sincalide. Instead, the nuclear medicine staff must consult with their pharmacy department and/or P&T Committee to determine what options are available.

Reimbursement. Some third-party insurance carriers routinely deny payment for compounded products. If the nuclear medicine department routinely bills for sincalide (i.e., the commercial product Kinevac), billing for compounded sincalide without clarifying that it is compounded sincalide instead of Kinevac could be construed as fraud.

Liability. Prescribers are cautioned that the use of compounded drugs may lead to exposure for personal liability (*4*). The prescribing of drugs involves the triad of patient, physician prescriber, and pharmacist. When prescribing an FDA-approved drug according to labeled indications, the physician is protected by the FDA approval process in the event of an adverse outcome and, therefore, is unlikely to face personal liability. Compounded drugs, however, lack an FDA finding of safety, efficacy, and qualification of manufacturing facilities. As a consequence, prescribers of compounded products may be personally exposed should an adverse event result from administration of a product that neither the prescriber nor the compounder has shown to be free of contaminants, sterile, at the correct dose, etc. The FDA has encouraged physicians to avoid such risks by its policy against the use of compounded products when an FDA-approved drug exists. When considering the use of a compounded drug, physicians should seek documentation of strength, identity, and purity from pharmacies. Prescribers should also be aware that their liability, as a *learned intermediary*, can be significant. Possible negative consequences can include invalidation of malpractice insurance, personal liability, and possible criminal prosecution.[3]

In summary, given these and other concerns associated with the use of compounded biological preparations such as sincalide, caution is needed. Physicians should seek results of appropriate testing of compounded biological products and carefully weigh potential risks and benefits before prescribing them to patients.

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