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Fospropofol Assay Issues and Impact on Pharmacokinetic and Pharmacodynamic Evaluation

To the Editor:

Fospropofol disodium (GPI 15715 or AQUAVAN® Injection, MGI PHARMA, Bloomington, MN) is a water-soluble, phosphono-O-methyl prodrug of propofol for IV injection. It has been evaluated for sedation during diagnostic and routine therapeutic procedures.¹⁻⁶ Following IV administration, fospropofol is rapidly metabolized by alkaline phosphatase enzymes, releasing propofol. Several studies have shown that the propofol pharmacokinetic and pharmacodynamic profiles were different compared with propofol in a lipid solution.¹⁻⁵ We have recently discovered an assay problem that may have affected the measurement of propofol plasma concentrations reported in previously published studies.

In the earlier studies,^{1-4,6} blood samples were collected in tubes containing sodium orthovanadate (SOV) 60 mg added as a solid powder to maintain 10 mg/mL concentration) to prevent further *in vitro* conversion of fospropofol to propofol by alkaline phosphatase enzymes. This was found to result in incomplete dissolution of the SOV powder and variable concentrations of SOV that altered plasma pH and caused hemolysis of many samples, leading to changes in propofol extraction recovery and storage stability. As a result, the propofol concentrations obtained in previous studies^{1-4,6} could possibly be inconsistent and unreliable as the impact of the above mentioned factors was neither known nor controlled, and therefore, the originally reported propofol pharmacokinetic and pharmacodynamic results and the derived conclusions could be inaccurate. It was shown that the assay and stability problem was limited to quantitation of propofol and that it did not affect the fospropofol concentrations. The new drug application (NDA) for fospropofol disodium was submitted to the Food and Drug Administration in September 2007. The propofol assay problem was reported in detail in the NDA as well as details of the revised assay methodology. Subsequent to the discovery of the problem, the sample handling procedure was standardized to reduce variation in SOV concentration (e.g., SOV was added as a solution), and improved sample handling and processing techniques that resolved the problems were developed and validated. Additional studies were then conducted using an appropriate assay to assess the pharmacokinetics and pharmacodynamics of fospropofol in healthy volunteers and patients. We plan to publish these results shortly, along with an estimate of the degree of error from the previously published studies that reported results using the old assay.

We very much regret the magnitude of the originally published incorrect information and the confusion that it has and will cause in the pharmacokinetics of propofol from the use of fospropofol.

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In Response:

This letter led to discussions among the Editors-In-Chief of *Anesthesiology*, *Anesthesia & Analgesia*, and the *European Journal of Anesthesiology* regarding how to