Impact of Drug Label Changes on Propofol Use in Pediatrics for Moderate Conscious Sedation

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ABSTRACT

Background: Drug product labeling is a critical component of communication regarding the appropriate use of medications. The information contained in a drug label is often complex, including contraindications and warnings that may be difficult to understand. In an attempt to further examine this issue, this article looks at one such difficult-to-understand label concerning anesthetic propofol and its use in the pediatric population.

Objective: The objective of this study was to describe the use of propofol for moderate conscious sedation (MCS) in pediatric patients (0–17 years) after drug warnings were disseminated.

Methods: This study was a retrospective, observational study from January 2001 to December 2007 that used data from the Premier Perspective Comparative Hospital database. This database includes approximately 425 hospitals with a broad range of hospital types and contains a weighting scheme that allows for the generation of national estimates in the United States. The main outcome measure was use of propofol during hospitalization.

Results: The study included 307,779 discharges in which MCS was used. Both the number of discharges for MCS and the percent of discharges using propofol increased from 2001 to 2007. After multivariable adjustment, there was more than a 3-fold increase in the odds of receiving propofol between 2001 and 2007 (odds ratio [OR] = 3.32; 95% CI, 2.96–3.72) for MCS.

Conclusions: The results of this study suggest that the label changes and a "Dear Doctor" letter did not affect propofol utilization. A more cohesive approach to the assessment of safety and the dissemination of label change information to practitioners is needed. (*Clin Ther*. 2011;33:886–895)

Key words: drug approval, propofol, safety.

INTRODUCTION

Drug product labeling is a critical component of communication regarding the appropriate use of medications. The drug product label contains results of safety and efficacy studies, dosing recommendations, contraindications, and absolute warnings for use, known as black box warnings (BBWs). Previous research has shown that new information contained in label changes has variable impact on prescribing. For example, use of antidepressants in children and adolescents decreased after a BBW,[1,2] whereas use of cisapride, a gastrointestinal tract promotility agent, did not change after this medication received a BBW regarding increased risk of fatal arrhythmias.[3] The use of medications with BBWs is common; in a large health plan, approximately 40% of all enrollees received a drug that had a potentially applicable BBW.[4] It is uncertain what factors affect the influence of the BBW.

The information contained in a drug label is often complex, including contraindications and warnings that may be difficult to understand. In an attempt to further explore this issue, this manuscript sought to look at one such difficult-to-understand label concern-

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ing anesthetic propofol* and its use in the pediatric population.[5] Propofol is a sedative hypnotic agent that has a rapid onset and a short duration of action. The drug product label for propofol has a series of important warnings for both pediatric and adult care (eg, avoid long-term sedation or high-dose short-term infusions).

In February 2001, the drug product label was modified in the United States to describe an increase in mortality in a randomized controlled trial of pediatric intensive care unit (ICU) patients. Although the study is described twice in the label, to our knowledge the study results have not been published in a peer-reviewed journal. In the second description of the study, the product label states the following:

> In one multicenter clinical trial of ICU sedation in critically ill pediatric patients that excluded patients with upper respiratory tract infections, the incidence of mortality observed in patients who received DIPRIVAN Injectable Emulsion (n = 222) was 9%, while that for patients who received standard sedative agents (n = 105) was 4%. While causality has not been established, DIPRIVAN Injectable Emulsion is not indicated for sedation in pediatric patients until further studies have been performed to document its safety in that population (see CLINCAL PHARMACOLOGY – Pediatric Patients: and Dosage and Administration).[5]

In March 2001, a "Dear Health Care Provider" letter was sent by AstraZeneca Pharmaceuticals in the United States that stated, "*We would like to reemphasize that propofol is currently not approved for sedation in pediatric ICU patients in the US and should not be used for this purpose*" [italics reproduces boldface emphasis in original].[6] Although this letter did not comment on the safety of propofol use outside of the ICU setting, the labeling does not differentiate the safety of pediatric sedation by clinical setting.

The AstraZeneca Pharmaceuticals International Web site does not mention the same label warning about pediatric propofol sedation. Instead, it simply states that "Conscious sedation for surgical and diagnostic procedures" is an approved indication, and that "Diprivan (propofol) is indicated for use in the elderly and for children over 1 month old."[7] However, the Web site also has "Global Prescribing Information and International Prescribing Notes" for propofol that do not mention the aforementioned study that led to the drug product label change but do state, "DIPRIVAN *is not recommended for conscious sedation in children as safety and efficacy have not been demonstrated*"[8] [emphasis added]. Instructions are provided regarding pediatric sedation during intensive care, stating that propofol is contraindicated in children receiving intensive care who have croup or epiglottitis or who are younger than 3 years old and have a serious viral respiratory infection. The instructions also warn against the risk of fat overload syndrome after prolonged infusion in intensive care.

Using a large inpatient database, we describe the use of propofol for moderate conscious sedation (MCS) in pediatric patients from 2001 to 2007 and compare characteristics between patients receiving propofol for MCS and patients receiving other anesthetics. Our goal was not to evaluate whether the safety concern is valid but to understand the impact of the 2001 label change on subsequent propofol use in pediatrics.

METHODS

Data Source

We used the Premier Perspective Comparative Hospital database (Premier, Inc, Charlotte, North Carolina), which contains data from a broad range of hospital types, including community hospitals and 26 stand-alone pediatric hospitals. The database included all payer data from approximately 425 hospitals, more than 5 million discharges, and 240 million claims. Premier used a standardized charge master catalogue to capture more than 47,000 items from the patient's detailed inpatient bill, providing a high level of granularity, especially for pharmacy data. The database also contained discharge-level weights, which were created by Premier. These weights were applied to the data to generate estimates that reflect national hospital care.

Study Design and Study Period

This study was a retrospective trend analysis limited to inpatient pediatric (aged 0–17) discharges from January 2001 to December 2007.

Identification of Moderate Conscious Sedation

We limited our analysis to patients receiving MCS, excluding patients receiving unconscious sedation or monitored anesthesia care, because the AstraZeneca Web site specifies that Diprivan is not recommended

*Trademark: Diprivan® (AstraZeneca Pharmaceuticals LP, Wilmington, Delaware).