SUMMARY

ZENECA PHARMACEUTICALS

FINISHED PRODUCT: Diprivan™[1]

ACTIVE INGREDIENT: propofol (ZD0859#1)

Trial title (number): A Multicenter, Comparative, Randomized Trial to Determine the Overall Safety and Efficacy of 1% Diprivan™ vs 2% Diprivan vs Standard Agents Without Disodium Edetate for Sedation of Trauma, Postsurgical, or Critically Ill Pediatric Subjects (0859IL/0068-Pediatric Trial 1)

Clinical phase: IIIb

First patient recruited: 12 December 1996
Last patient completed: 26 July 1998
Zeneca approval date: 17 May 1999

Publications: None

OBJECTIVES

Primary: to compare the safety and efficacy of Diprivan 2% versus Diprivan 1% versus standard sedative agents without disodium edetate (SSA) in trauma, postsurgical, and critically ill pediatric patients

[1] Diprivan contains 0.005% disodium edetate.

Secondary: to evaluate the change in urinary zinc, cobalt, copper, iron, and calcium excretion to estimate the amount of trace metal and calcium supplementation required during continuous sedation with Diprivan compared with SSA in a subset of patients with urinary catheters; to examine significant differences in the overall safety profiles of intensive care unit sedation with Diprivan 2% versus Diprivan 1% versus SSA; to evaluate the safety and efficacy of Diprivan 2% and Diprivan 1% monotherapy versus Diprivan 2% and Diprivan 1% with continuous analgesia (at Center 1 only)

METHODS

Design: multicenter, comparative, randomized, Phase IIIb trial; patients stratified by age (aged newborn through 1 year, 2 through 11 years, and 12 through 16 years) without limiting the number of patients required for each age group; within each completely stratified group, patients were allocated to be given either Diprivan 2%, Diprivan 1%, or a standard sedative agent without disodium edetate; at Center 1 the investigator was blinded as to which analgesic agent was used for patients randomized to be given either fentanyl or normal saline for analgesia

Population: approximately 360 trauma, postsurgical, or critically ill patients aged newborn through 16 years who were on mechanical ventilation, expected to require sedation for at least 24 hours, and had comfort scale scores of 26 points or greater

Key inclusion criteria: intubated boys or girls aged newborn through 16 years who had comfort scale scores of 26 points or greater and who were expected to require sedation for at least 24 hours

Key exclusion criteria: history of hypersensitivity to Diprivan or fentanyl or their constituents or patients with croup or respiratory epiglottitis

Dosage: Diprivan 2%, Diprivan 1%, or SSA were administered continuously using volumetric infusion pumps or administered as a bolus dose when appropriate. A continuous infusion of fentanyl was to be administered to all patients (except for Center 1) for analgesia. At Center 1, patients were randomized to the following groups: Diprivan 2% and fentanyl, Diprivan 2% and normal saline, Diprivan 1% and fentanyl, Diprivan 1% and normal saline, or standard sedative agent without disodium edetate and fentanyl.

Key assessments:

Efficacy assessments:

Primary measures: total daily dosage requirements of trial medication and assessments of the depth of sedation using comfort scale scores assessed at baseline, before changing the dose given during the first 4 hours of sedation, and daily to maintain comfort scale scores between 17 and 26 points

Secondary measure: At Center 1 only, the efficacy of Diprivan monotherapy compared with Diprivan given with continuous analgesia was evaluated by dosage requirements needed to maintain adequate sedation as assessed by the comfort scale scores of the patients.

Pharmacokinetic assessments: propofol and disodium edetate levels (Center 1 only) were determined at baseline, Days 2 through 7, every 7 days thereafter, and at the end of sedation

Safety assessments:
Primary measures: blood gases including base excess at baseline, daily at approximately the same time each day through Day 7, every 7 days thereafter, at the end of sedation, and 24 hours post-sedation if the arterial line of the patient was still in place
Secondary measures: serum and 24-hour urinary concentrations of trace metals; hematology, serum chemistry, and urinalysis assessments; vital signs measurements; adverse event monitoring including evaluation for sepsis; assessment of baseline severity of illness using Pediatric Risk of Mortality (PRISM) scores; and reason for trial discontinuation
Statistical considerations: At the request of the FDA, all data in this report are summarized into 4 age groups as well as the combined age group: all ages, birth to less than 2 months, 2 months to less than 2 years, 2 to less than 12 years, and 12 to less than 17 years. All results will be discussed according to these groupings. Maintenance dosage requirements were summarized for both Diprivan 2% and Diprivan 1%. Trace metal excretion levels for 24-hour urine samples and acid-base balance for arterial blood gases were compared among treatment groups at each protocol time point using analysis of covariance (ANCOVA) with center, age, and total PRISM scores as covariates.

RESULTS
Demography: 348 patients from 24 centers entered the trial; 21 patients were withdrawn before treatment; 327 patients (205 boys and 122 girls) aged birth to less than 2 months (36 patients), 2 months to less than 2 years (146 patients), 2 to less than 12 years (109 patients), and 12 to less than 17 years (36 patients) were included in safety analysis; 268 patients were at least partially included in the efficacy analysis; demographic characteristics were similar among treatment groups.
Efficacy: For all age groups, the mean daily propofol dose (mg/kg) was higher for patients given Diprivan 2% than for patients given Diprivan 1% on Days 1 and 2 (except patients aged birth-<2 months and 12-<17 years [Day 2 only]) and at the end of sedation. Patients at Center 1 given Diprivan 1% combination therapy had higher values for mean daily propofol dose on Days 1 and 2, but lower values at the end of sedation, than patients given Diprivan 1% monotherapy. Patients at Center 1 given Diprivan 2% combination therapy had lower values for mean propofol dose than patients given Diprivan 2% monotherapy on Days 1 and 2, and at the end of sedation.
Comfort scale scores between patients given Diprivan as monotherapy or in combination with analgesia were similar.
Pharmacokinetics: At Center 1, mean plasma propofol concentrations were highest on Day 2 for patients given Diprivan 2% combination therapy. At the end of sedation, mean plasma propofol concentrations were higher for patients given Diprivan 1% monotherapy than for any other group.
Safety: In the evaluation of Diprivan 2% versus Diprivan 1% versus SSA for safety, no clinically meaningful differences were noted among treatment groups for arterial blood gases, renal function, or hemodynamic measurements.
Zinc excretion was higher in patients treated with either Diprivan 2% or Diprivan 1% compared with patients treated with SSA, and copper excretion was higher in patients treated with

Diprivan 2% compared with patients treated with Diprivan 1% or SSA. No clinically meaningful differences were noted for cobalt, iron, or calcium excretion among treatment groups.

Mean serum copper concentrations generally were slightly higher for patients treated with either Diprivan 2% or Diprivan 1% compared with patients treated with SSA. No other important differences for serum trace metal concentrations were noted among treatment groups. The only statistical significance noted for serum zinc concentrations was between Diprivan 1% and SSA for the mean change from baseline to Day 3.

Renal function of patients treated with either Diprivan 2% or Diprivan 1% did not deteriorate compared with patients treated with SSA.

Although in this trial of over 300 patients, no adverse events directly attributable to zinc deficiency were seen, attention should be paid to maintaining adequate nutritional support for children sedated with Diprivan in the ICU. Supplemental zinc administration should be considered to compensate for zinc losses, especially in those patients who are predisposed to zinc deficiency such as those with burns, diarrhea, and major sepsis.

More deaths occurred for patients given Diprivan 2%; however, none of the deaths that occurred during sedation, or within 72 hours after sedation, were considered by the investigators related to trial treatment. Relationship to trial treatment was not determined for deaths that occurred more than 72 hours after sedation. The patient population used in this trial consisted of seriously ill children; therefore deaths that occurred were not unexpected.

The number of patients with adverse events was higher for patients given either Diprivan 2% or Diprivan 1% when compared with patients given SSA. The total number of patients with adverse events and the number of patients withdrawn because of adverse events was highest for patients given Diprivan 1%. The most frequent adverse events were hypotension and drug withdrawal. Drug withdrawal was characterized by the occurrence of jitteriness, warm flushing of the hands and feet, tachycardia, and an increased temperature following rapid discontinuation of Diprivan. The events associated with drug withdrawal all subsided with reinstitution of drug and a more tapered weaning. The aforementioned withdrawal syndrome was attributed to be causally related to the abrupt discontinuation of Diprivan.

Trigylcerides and free fatty acids were increased for patients given Diprivan 1%. These increases correlated with an increased incidence of the adverse event reports of hyperlipemia that was noted for patients given Diprivan 1%.

The safety of Diprivan was similar between age groups; the safety of Diprivan 2% and Diprivan 1% monotherapy was similar to the safety of Diprivan 2% and Diprivan 1% combined with continuous analgesia.