Therapeutic Interchange of Clevidipine For Sodium Nitroprusside in Cardiac Surgery

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ABSTRACT

Background: Generic price inflation has resulted in rising acquisition costs for sodium nitroprusside (SNP), an agent historically described as the drug of choice for the treatment of perioperative hypertension in cardiac surgery.

Purpose: To describe the implementation and cost avoidance achieved by utilizing clevidipine as an alternative to SNP in cardiac surgery patients. Consistent with current guidelines for therapeutic interchange, the goal was to encourage a less expensive alternative that was demonstrated to be at least therapeutically equivalent to SNP based on data derived from clinical trials published in peer-reviewed literature. A comprehensive literature review identified clevidipine as an alternative to SNP for perioperative hypertension in cardiac surgery. Clevidipine was considered as well, but was not chosen as a substitute due to lack of strong evidence and comparative data with SNP.

Results: Clevidipine was implemented successfully in our cardiac surgery patients and will result in a net cost avoidance of approximately $300,000 in 2016. This is thought to be driven largely by the difference in acquisition cost between clevidipine and SNP. The operating room in our institution no longer keeps SNP stocked in anesthesia trays as a result of the success of our interchange. No requests have been made to return to the SNP standard.

Conclusion: Through effective communication and multidisciplinary collaboration, our institution was able to develop an evidence-based and effective therapeutic interchange program for SNP.

Keywords: clevidipine, sodium nitroprusside, therapeutic interchange, perioperative hypertension, cardiac surgery, generic price inflation

BACKGROUND

Sodium nitroprusside (SNP) has been used clinically for decades for the treatment of hypertension associated with cardiac surgery, and it is often described as the drug of choice for this indication.1 SNP’s short half-life, quick onset and offset, and its ability to be rapidly titrated make it suitable for both intraoperative and postoperative use in the cardiac surgery patient.2 However, SNP does not have a predictable dose-response curve and has boxed warnings pertaining to precipitous blood pressure (BP) reduction and risk of cyanide toxicity.1,3 Because SNP dilates both venous and arterial vessels, it has the ability to produce “unlimited” BP reduction, and careful monitoring is required.2,3 SNP received Food and Drug Administration (FDA) approval in 19744 and has been generically available for many years. Despite its generic status, the price of one 50-mg vial of SNP has increased by more than 1,500% over the past three years (Figure 1) and can cost more than $800.5,6 Although these price increases have purportedly been based on a comprehensive value analysis,6 we are unaware of any published data to support this price point. The high cost of SNP has garnered scrutiny from legislators and the lay media, especially after several other recent high-profile drug price increases were thrust into the public eye.6,7

BUDGETARY IMPACT OF CLEVIDIPINE

Englewood Hospital and Medical Center (EHMC), located in Englewood, New Jersey, is a 520-bed acute-care teaching hospital with an active cardiac surgery program. In 2015, more than 300 patients underwent cardiothoracic surgeries at EHMC. Historically, SNP has been the mainstay for the treatment of hypertension in cardiac surgery patients at our institution.

At the end of the first quarter of 2015, SNP appeared on EHMC’s quarterly Pareto report. Pareto reports, also known as 80/20 reports, are used by directors of pharmacy to monitor the budgetary impact of a relatively small number of pharmaceutical agents that generate approximately 80% of total drug budget costs.8 Monthly expenditures on SNP were reaching as much as $30,000. It was quickly ascertained that the majority of SNP use was during the perioperative care of the cardiac surgery patient. Pharmacy staff collaborated with cardiac anesthesiologists, cardiac surgeons, and intensivists to identify potential therapeutic alternatives. Consistent with current guidelines

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for therapeutic interchange, the goal was to encourage a less expensive alternative that was demonstrated to be at least therapeutically equivalent to SNP based on data derived from clinical trials published in peer-reviewed literature. With this charge in mind, after a comprehensive review of the literature, a multidisciplinary team decided to implement clevidipine injectable emulsion (Cleviprex, Chiesi USA) in place of SNP for perioperative BP control in patients undergoing cardiac surgery.

EVIDENCE TO SUPPORT CLEVIDIPINE

Clevidipine injectable emulsion is a dihydropyridine calcium-channel blocker indicated for the reduction of BP when oral therapy is not feasible or not desirable. Clevidipine exerts its antihypertensive effects through direct arterial vasodilation, and its pharmacokinetic and pharmacodynamic profile makes it a suitable choice for intra- and postoperative BP control in cardiac surgery patients (Table 1). Importantly, in addition to having a favorable pharmacological profile, clevidipine has been extensively studied for BP control in cardiac surgery in both placebo and active-comparison studies. Of particular relevance to the therapeutic interchange program at EHMC was the Evaluation of Clevidipine in the Perioperative Treatment of Hypertension Assessing Safety Events (ECLIPSE) trial, which included a direct comparison to SNP.

The main objective of ECLIPSE (N = 1,512) was to compare the safety of clevidipine with three other perioperative antihypertensive drugs (SNP, nitroglycerin, and nicardipine) in a cardiac surgical population primarily undergoing coronary artery bypass grafting. Efficacy of BP control, a secondary endpoint, was determined by measuring the magnitude and duration of BP excursions above or below the predefined BP target range. These excursion data were reported as the area under the curve, expressed in units of mm Hg times min/hour. The safety analysis demonstrated no differences in the rates of myocardial infarction, stroke, or renal dysfunction for clevidipine-treated patients compared with the other groups. Mortality was similar across the study arms, with the exception that SNP-treated patients had higher mortality rates compared with clevidipine-treated patients ($P = 0.04$). However, SNP use was not independently associated with mortality on multivariate analysis, suggesting either a type I error likely due to multiple comparisons or unmeasured confounders in baseline characteristics.

Compared with SNP, clevidipine was found to be more effective in keeping BP within the target range ($P = 0.003$). Both excursions above and below (overshoot) the prespecified target BP range were significantly higher in the SNP cohort compared with clevidipine. These data, along with a small (N = 30) pilot study that demonstrated similar outcomes between clevidipine and SNP in cardiac surgery, confirm that clevidipine is at least therapeutically equivalent to SNP for perioperative BP control in cardiac surgery. Clevidipine was also found to be significantly more effective at keeping BP within the target range when compared with nitroglycerin ($P = 0.0006$).

Of note, in ECLIPSE, the comparison between nicardipine and clevidipine was restricted to the postoperative setting only. The longer half-life of nicardipine compared with SNP and clevidipine (Table 1) and its FDA-approved titration schedule (initiate at 5 mg/hour, increase dose by 2.5 mg/hour every five to 15 minutes) preclude it from being used routinely for intraoperative hypertension associated with cardiac surgery. Indeed, to our knowledge, very limited data exist using nicardipine for intraoperative BP control in cardiac surgery. In one study, nicardipine was initiated at 3 mcg/kg/min, and
the average dose required to maintain goal BP, defined as a systolic BP of 80% to 120% of baseline or a mean arterial pressure of less than 100 mm Hg, was 2.9 mcg/kg/min. In order to maintain adequate BP control, some patients required doses that exceeded 14 mcg/kg/min, and at least one patient required a dose of 25 mcg/kg/min. While these high doses were given for only a few minutes, these data highlight some of the difficulty in using nicardipine for intraoperative BP control during cardiac surgery. In a second study, Chen et al. utilized nicardipine for intraoperative BP control in 20 patients undergoing surgery, of which only five were cardiac surgeries. Nicardipine was initiated at a mean dose of 2.2 mcg/kg/min (9.2 mcg/hour in a 70-kg patient). This front-loading strategy resulted in a time to therapeutic response of approximately 10 minutes. The authors suggested that an initial bolus of nicardipine might enhance the use of this agent. However,
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bolus dosing of nicardipine has not been adequately studied and is associated with rates of hypotension between zero and 60%, depending on the dose.\(^{20}\) Given these findings, it was felt that there were insufficient data to establish nicardipine as a therapeutic alternative to SNP, particularly for intraoperative use during cardiac surgery. Nicardipine remains a reasonable option for postoperative BP control in cardiac surgery.\(^{14,21–23}\)

IMPLEMENTATION AND COST SAVINGS

The Director of Pharmacy met with the Director of Cardiothoracic Anesthesia (who also serves as Chair of the P&T committee) to discuss the current issues related to SNP and the possibility of using alternative agents. As described above, clevidipine was considered the best option due to its similar onset and offset to SNP and its comparable efficacy to SNP throughout the perioperative spectrum in cardiac surgery. Of note, clevidipine had previously been approved for use at EHMC in 2010, but utilization had been limited. After additional discussions with key stakeholders (anesthesiologists, cardiac surgeons, and intensivists), education on the use of clevidipine was initiated.

Cardiac surgery team members and cardiac surgery intensive care unit (ICU) staff were first educated on clevidipine via a series of in-service sessions led by the pharmacists at EHMC, with additional assistance from the manufacturer of clevidipine. Main components of the education were clevidipine dosing and titration; pharmacokinetics and pharmacodynamics; and potential adverse effects. Awareness was also created for the potential of look-alike medication errors between clevidipine and propofol because both are supplied as lipid emulsions. Although clevidipine is stable for two months at room temperature, it is stored mainly in the operating room (OR) refrigerator consistent with the manufacturer’s storage recommendations. This physical separation of propofol and clevidipine may aid in minimizing medication error risk and is a recommended practice when dealing with drugs with similar appearances.\(^{24}\)

An open line of communication was kept between the cardiac surgical staff and the pharmacy staff in order to ensure a successful rollout of clevidipine. Currently, our cardiac anesthesiologists initiate clevidipine therapy during cardiac surgery, as needed, with titration based on clinical response. After clevidipine is started in the OR, it is typically continued in the cardiac surgery ICU for a short time, usually 24 hours or less. If intravenous BP control is still required after 24 hours, EHMC intensivists often transition patients to alternative agents.

Overall, implementation of clevidipine was accomplished successfully. The learning curve for the safe and effective administration of clevidipine was accomplished in a short period. The cardiac anesthesiologists, cardiac surgeons, and intensivists have been satisfied with the conversion to clevidipine from SNP and, to date, there have been no requests to return to the SNP standard.

Although our institution selectively utilizes clevidipine in place of SNP for cardiac surgery, no formal therapeutic substitution program has been mandated. SNP remains on EHMC’s formulary to the present day, but usage has dropped considerably. During the month of May 2015, 37 vials of SNP were used during cardiac surgeries. In comparison, during the period of June 2015 to February 2016 only three vials of SNP had been used. Given the low utilization, SNP is no longer routinely stocked in the cardiac surgery OR trays. A small supply of SNP is maintained in the OR automated dispensing cabinets in case an emergent need for the drug arises, but there has been little utilization of the drug since the switch, as described above. The usage patterns for clevidipine have tracked in an opposite and equivalent manner compared with SNP during these time periods. Fourteen vials of clevidipine were used in May 2015, and between June 2015 and February 2016, 117 vials were utilized.

The coordinated practice change between the departments of pharmacy, anesthesia, critical care, and cardiac surgery at EHMC has been facilitated solely due to effective communications and a collective institutional desire to provide high-quality care through judicious utilization of health care resources. In total, a net cost avoidance of approximately $185,000 was captured during the remainder of calendar year 2015, and an estimated $300,000 will be avoided in 2016. This is largely driven by the acquisition cost of clevidipine being less than 10% of that of SNP on a vial-per-vial basis (Table 1).

CONCLUSION

As the number of drastic price hikes increases among generic injectable drugs due to market trends and single-source manufacturing, pharmacy departments must remain vigilant and seek creative, safe, and effective substitutions. These interchange programs are especially important when there is a solid evidence base to support them. Even without formal restrictions in place, our department was able to defray a potentially major budgetary increase in drug expenditures using an evidence-based alternative to SNP by merely...
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coordinating a preference for clevidipine for this specific indication with buy-in from our institution’s anesthesiologists, surgeons, and intensivists. The pharmacy department and other key stakeholders are currently evaluating whether to remove SNP from the formulary entirely, but there has been no rush to formally restrict its use at this time due to the success of the current implemented system.

REFERENCES