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Profound Hypotension during Induction of General Anesthesia with Propofol in Patients with Rifampin Treatment

Hooman Mirzakhani, Ala Nozari, Jesse M. Ehrenfeld, Robert Peterfreund, Michele Szabo, John L. Walsh, Yandong Jiang, Warren Sandberg, Carl Rosow, and Jingping Wang

ABSTRACT

Rifampin is commonly used in the treatment of tuberculosis and staphylococcal infections, as well as for prevention of infection in cardiac valve and bone surgeries. We report a case of profound hypotension after anesthesia induction with propofol in a patient who was treated with two 600 mg doses of rifampin for prophylaxis of infection prior to surgery. In a retrospective case-control study of 75 patients we confirmed this potentially serious drug-drug interaction, showing a significant and prolonged blood pressure reduction after anesthesia induction in patients receiving the two agents.
INTRODUCTION

Rifampin is a synthetic derivative of rifamycin B that inhibits bacterial RNA polymerase by forming a stable drug-enzyme complex. It remains one of the most effective antimicrobials used in the treatment of tuberculosis, but it is also used to treat methicillin-resistant as well as methicillin-sensitive staphylococcal infections, or for prevention of infection in cardiac valve and bone surgeries. Here, we report a case of profound hypotension after anesthesia induction with propofol in a patient who was treated with rifampin. We examined for this potentially important drug interaction with a retrospective case-control study of 75 patients.

Case Report

A 64 year old female (weight 88 kg, height 163 cm and BMI=33) presented to our institution for an elective posterior decompression of a herniated disk at the L5-S1 level. She had a past medical history significant for lumbar stenosis, symptomatic gastro-esophageal reflux disease, hyperlipidemia, osteoporosis, and panic attacks. Her medications were atorvastatin (10 mg/day), esomeprazole (40 mg/day), and naproxen (1000 mg/day). She also took acetaminophen plus hydrocodone (5-325 mg) as needed for pain, and occasional multivitamins. The neurosurgical team prescribed rifampin 600 mg p.o. to be given the night before and 2 hours prior to surgery as prophylaxis for infection. The patient had no known allergies and described herself as physically active. She had a stress test performed three years previously which showed normal exercise tolerance and no evidence of myocardial ischemia. The patient remained NPO for 7 hours after midnight, but she had normal intake of food and fluids before that. She was anxious and the pre-induction heart rate was 102 beats/minute, and BP was 150/90 mmHg. She received 2 mg of midazolam and 150 mcg of fentanyl (1.88 mcg/kg), intravenously. This moderately large premedication caused a decrease in anxiety but minimal respiratory and hemodynamic effects. At 7 minutes after fentanyl administration, rapid sequence induction was conducted using 200 mg of propofol (2.3 mg/kg) and 100 mg of succinylcholine (1.1 mg/kg), and a 7.0 mm endotracheal tube was inserted without difficulty. Three minutes after induction of anesthesia and prior to placing the patient in the prone position, her blood pressure decreased to 60/30 mmHg, and heart rate increased to 112 beats/minute. There was no wheezing or difficulty ventilating and no changes in skin color suggestive of an allergic reaction. Rapid intravenous infusion of normal saline was initiated (800 ml/20 min) in addition to phenylephrine continuous infusion (10 mcg/min) with incremental bolus doses, as needed. Ten mg of ephedrine (two 5 mg doses) and 80 mcg phenylephrine bolus were administered. Despite continued infusion of fluid, phenylephrine and ephedrine, her systolic blood pressure remained 60-70 mmHg (> 40 mmHg reduction from baseline), although all central and peripheral pulses were palpable. Epinephrine was added in 0.04 mg bolus doses in addition to 80 mcg
doses of phenylephrine. After administering two doses of epinephrine (0.08 mg) and three more doses of phenylephrine (240 mcg), the patient's blood pressure finally improved to 92/53 mmHg. (figure 1) Serial EKGs showed no signs of ischemia or dysrhythmia during the hypotensive period or afterwards. She remained stable without additional epinephrine, although phenylephrine infusion was required to maintain systolic blood pressure within 70% of her baseline (90-100 mmHg). After some discussion, it was decided to proceed with the surgery with addition of normal saline infusion (1 L/hr) to her continuous phenylephrine infusion. Approximately 35 minutes after induction, the patient was turned prone without hypotension, and surgery was completed without incident. The patient emerged from anesthesia and was extubated without problems. Her postoperative period was uneventful and she was discharged to her home on postoperative day 3 with a satisfactory outcome.

**Figure 1.** Blood pressure, heart rate and oxygen saturation curves in the reported patient; including administered vasopressors and fluids in treatment of profound induced hypotension after induction. SBP-NI= systolic blood pressure-noninvasive, DBP-NI=diastolic blood pressure-noninvasive

**Retrospective data**
Rifampin is not frequently administered for infection prophylaxis, but it had been used this way for several years by members of our neurosurgical division (MGH) doing spinal surgery. There had been anecdotal descriptions of similar hypotensive episodes by the neuroanesthesiologists in our department, and a connection with rifampin had been raised as a possibility. After the present dramatic episode occurred, we felt it was important to investigate our anesthesia and medical record database with the aim of identifying a potential new drug-drug interaction.
After institutional review board approval, we reviewed 194 anesthesia records and medical charts of patients who had undergone spine surgery under general anesthesia between 2008 and 2010 in our institution. We randomly selected 25 patients for each of three groups that were matched for type of surgery and surgeon:

1. Patients receiving propofol for induction of anesthesia and preoperative rifampin prophylaxis, (experimental group).

2. Patients receiving propofol for induction but no rifampin pre-treatment (propofol control).

3. Patients receiving thiopental for induction and preoperative rifampin (thiopental control).

Our prospective power analysis indicated that group sizes of 25 would have 90% power to detect a 10 mmHg difference in MAP reduction at a significance level of 0.05 (two-sided comparison), assuming a standard deviation of 10 mmHg. The prophylactic dose of rifampin was uniformly 600 mg p.o., the night before and on the morning of surgery (usually about 2 hours before) in both the propofol and thiopental groups. Patient characteristics (sex, age, height, weight, ASA physical status classification, Charlson Comorbidity Index (CCI), first and total dose of intravenous anesthetics, total doses of vasopressors, fentanyl dose and volume of administered fluids were recorded. Baseline (time of induction) and post-induction values of systolic, diastolic and mean blood pressure were obtained from the electronic anesthesia record system.

Differences between the groups in sex, age, weight, ASA, and CCI were examined by ANOVA for continuous variables and Kruskal–Wallis ANOVA for quantal variables. Mean blood pressure responses were compared by two-way ANOVA for repeated measures. Our dependent variable, change in MAP, was normally distributed for the three groups as assessed by the Shapiro-Wilk test. There was homogeneity of variance between groups as assessed by Levene’s test for equality of error variances. The change in MAP with time was analyzed for each of the study groups using a general linear univariate model to account for the impact of age, type and dose of anesthetic agent, fentanyl dose prior to induction, ASA status, CCI, presence of diabetes and hypertension, weight, location of surgery (cervical vs. lumbar), vasopressor doses and amount of fluid administered.

The significant covariates (duration of hypotension, fluid amount, anesthetic agent, presence or absence of rifampin) were examined in a general linear multivariate model. In the multivariate analysis, anesthetic agent was an independent predictor of hypotension (p<0.001).
The induction dose of propofol did not differ between the groups. Patients’ baseline characteristics (Table 1) did not significantly influence nadir MAP. We did not find any association between preexisting hypertension and hypotensive events using chi square and binary logistic regression (p=0.564). Patients receiving rifampin and propofol had a significantly greater reduction in their MAP and duration of hypotension than propofol alone or thiopental with rifampin (Table 2) despite the fact that they received lower doses of fentanyl for induction (250 ± 65 mcg) (Table 1). A post hoc test (Tukey’s Honestly Significant Difference [HSD]) also showed a significant difference in nadir MAP (p=0.004) and reduction of MAP (p<0.001) in patients with rifampin and propofol vs. propofol alone or thiopental-rifampin. The dose of phenylephrine was not normally distributed, and the Kruskal-Wallis ANOVA showed a significantly greater dose of phenylephrine in the propofol-rifampin group vs. our control groups (p=0.039, Table 2).

<table>
<thead>
<tr>
<th>Table 1. Demographics and baseline clinical characteristics of the study groups</th>
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<tbody>
<tr>
<td><strong>Propofol-rifampin</strong></td>
</tr>
<tr>
<td>N=25</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
</tr>
<tr>
<td><strong>Sex (F:M)</strong></td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
</tr>
<tr>
<td><strong>Range</strong></td>
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<tr>
<td><strong>ASA</strong></td>
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<td><strong>Range</strong></td>
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<tr>
<td><strong>Comorbidity Index</strong></td>
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<td><strong>Range</strong></td>
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<tr>
<td><strong>Diabetes Mellitus (no.)</strong></td>
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<tr>
<td><strong>Hypertension (no.)</strong></td>
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<tr>
<td><strong>Baseline MAP (mmHg)</strong></td>
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<tr>
<td><strong>Range</strong></td>
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<tr>
<td><strong>Induction dose (mg)</strong></td>
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<td><strong>Range</strong></td>
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<tr>
<td><strong>Fentanyl induction dose (mcg)</strong></td>
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<td><strong>Range</strong></td>
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*Standard deviation (SD), unless otherwise indicated
Table 2: Hemodynamic responses and vasopressor treatments during induction

<table>
<thead>
<tr>
<th>Group</th>
<th>MAP Nadir Mean (SD) mmHg</th>
<th>MAP Nadir Mean (SD) mmHg</th>
<th>Time to Nadir Hypotension Duration Mean (SD)(^b) min</th>
<th>Phenylephrine Median [Range] mg</th>
<th>Ephedrine Median [Range] mg</th>
<th>Fluid (SD) RL/NS(^c) Mean (SD) mL</th>
<th>Odds ratio(^d) (95 % CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propofol-rifampin</td>
<td>58 (13)*</td>
<td>-38 (3)**</td>
<td>13 (11)**</td>
<td>33 (13)***</td>
<td>17 [0-77]****</td>
<td>1950 (753)**</td>
<td>11 (3-39)***</td>
</tr>
<tr>
<td>Propofol</td>
<td>71 (15)</td>
<td>-22 (2)</td>
<td>6 (5)</td>
<td>13 (8)</td>
<td>7 [0-16]</td>
<td>1320 (593)</td>
<td>4 (1-13)</td>
</tr>
<tr>
<td>Thiopental-rifampin</td>
<td>76 (11)</td>
<td>-16 (3)</td>
<td>5 (4)</td>
<td>9 (5)</td>
<td>2 [0-10]</td>
<td>1290 (394)</td>
<td>0.36 (0-10)</td>
</tr>
</tbody>
</table>

\(^*\)p<0.004 vs. propofol alone or thiopental-rifampin
\(^**\)p<0.001 vs. propofol alone or thiopental-rifampin
\(^***\)p<0.005 vs. propofol alone or thiopental-rifampin
\(^****\)p=0.039 vs. propofol alone or thiopental-rifampin

\(^b\) Duration of hypotension was defined as time of reduction of mean blood pressure (MAP) after induction to nadir and its return to 90 % of pre-induction (baseline) value. \(^c\) RL (Ringer’s lactate), NS (normal saline). \(^d\) Hypotension was defined as occurrence of SBP<90 mmHg or more than 40 % change from baseline SBP. Odds of occurrence of hypotension were calculated in each group and adjusted for the covariates. Change from baseline values of mean arterial pressure (delta MAP).
DISCUSSION

This case report and the retrospective data analysis demonstrated that the risk of a prolonged hypotensive episode increased almost three-fold when propofol rather than thiopental was used for induction in patients who received rifampin. In 10 of 25 cases, this exaggerated hemodynamic response required vigorous treatment with vasopressors and fluids, i.e., hypotension persisted despite more than 2 L Ringer’s lactate (or normal saline) as well as repeated doses of vasopressors. The peak hypotension might actually have been underestimated, since these patients did not have continuous measurements with an arterial line.

In our retrospective data analysis the duration of fluid abstinence did not differ between the groups, nor did the dose or type of pre-induction anxiolytic agent (midazolam). The induction dose of propofol was similar with or without rifampin, and the fentanyl dose was lower in the propofol-rifampin group. However, the hemodynamic response was significantly greater in the propofol-rifampin group, suggesting a drug-drug interaction as the cause. Hemodynamic instability was not seen when rifampin was given with thiopental, indicating that the interaction is unique to propofol.

The mechanism for this interaction was not investigated. Intravenous administration of rifampin alone can induce hypotension by a direct, dose-dependent reduction of vascular tone and SVR, and propofol-induced hypotension is largely due to venodilation. However, it is not clear if oral administration of rifampin will do the same and whether any such effect would be relevant for propofol administration so many hours after the first and second doses.

Anaphylactic or anaphylactoid reactions caused by the induction agent or rifampin are unlikely, given the lack of hypotension in the control groups. In no case, did the clinicians record urticaria or flushing, bronchospasm, or mucosal edema. One mechanism that is suggested to promote hypotension after propofol administration is related to its direct effect on venous smooth muscle tone, presumably through increased endothelial production and release of nitric oxide (NO). Rifampin might augment this effect as a result of increased NO production by upregulating iNOS mRNA transcription. This increase in NO levels has only been demonstrated in vitro, but it does occur within 20 hours after exposure to clinically relevant concentrations of rifampin (10 to 100 μg/ml). The serum concentration of rifampin after 2 hours following a single 600-mg oral dose was reported to be 8.8-12 mcg/ml and in another study 15.9 mcg/ml, so the NO mechanism is a plausible explanation with the antibiotic concentrations likely present in our case. The serum concentrations of rifampin in the latter study dropped from 15.9 ± 6.5 mcg/ml at 2 hr, to 7.1 ± 4.3 at 8 hr, with 1.6 ± 1.6
mcg/ml still detectable at 24 h. (4) This suggests that sufficient rifampin may be present to cause drug-drug interactions for a significant period of time after typical oral dosing.

Rifampin is commonly used for treatment of tuberculosis and less often for prophylaxis of staphylococcal infections and nisseria meningitidis infections. It is rarely used for routine preoperative antimicrobial prophylaxis, which could explain why this interaction with propofol may not have been appreciated previously. Clinicians should be aware of this potentially dangerous interaction and if rifampin is necessary, consider using alternative agents for induction of anesthesia. A prospective study is desirable to investigate the mechanism of this drug-drug interaction.
REFERENCES


