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Original Contribution

Taxane modulation of anesthetic sensitivity in surgery for nonmetastatic breast cancer☆

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Abstract

Study objective and design: The mechanism of action of commonly used general anesthetics is largely unknown. One hypothesized mechanism is through modulation of microtubule stability. Taxanes, a subset of chemotherapeutic drugs known to alter microtubule stability and commonly used to treat breast cancer, offer a natural experiment to test our hypothesis that patients exposed to taxanes prior to surgery, as compared to after surgery, would have a partial resistance to general anesthetics.

Setting, patients, and measurements: The anesthetic record of adult women with nonmetastatic breast cancer was used to obtain changes in heart rate and blood pressure surrounding incision, and the amount of inhaled anesthetic agent, induction, and rescue drugs administered.

Main results: Change in blood pressure in response to incision was significantly higher in the neoadjuvant group (P = .03), whereas change in heart rate was not (P = .53). A greater amount of morphine was administered in the neoadjuvant group (26.3 vs 15.5 mg, P = .02), although not a higher concentration of inhaled anesthetics (P = .15).

Conclusion: These results suggest that the alteration of microtubule stability is one of a number of mechanisms of inhaled anesthetics.

1. Introduction

The mechanism of action of the commonly used general anesthetics remains unclear [1,2]. A better understanding of their mechanisms could improve the safety profile of current drugs through a reduction in off-pathway effects. One mechanistic hypothesis is that general anesthetics produce their desired effects by modulating microtubule stability [3,4]. There is evidence of specific tubulin binding for most of the general anesthetics, as well as evidence of modulation of tubulin polymerization by these drugs in vitro [3,4]. Tubulin is a plausible direct target in that it polymerizes into

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microtubules that are responsible for cellular and organellar motility; receptor trafficking; and, indirectly, signaling [5].

Per this hypothesis, sensitivity to anesthetic drugs should be modulated by other tubulin-active compounds. Taxanes, specifically paclitaxel and docetaxel, are β-tubulin binding compounds that have proven to be efficacious in the treatment of breast cancer [6], presumably because they hyperstabilize microtubules [7,8]. Because it has been shown that at least some general anesthetics destabilize microtubules [3], the taxanes should antagonize this effect and cause at least partial resistance to general anesthetics.

Nonmetastatic breast cancer patients receiving taxane chemotherapy either before (neoadjuvant) or after (adjuvant) surgery is a natural experiment in which one can examine the association of taxane exposure with resistance to general anesthetics. In this study, we hypothesized that the neoadjuvant group of patients, being somewhat resistant, would be less adequately anesthetized after standard induction of anesthesia and have a greater change in heart rate and blood pressure as compared with patients who received taxane chemotherapy adjuvantly.

2. Methods

2.1. Participants

Eligibility criteria for this retrospective cohort study have been published previously [9]. Eligible participants were adult female, nonmetastatic breast cancer patients with an adjuvant or neoadjuvant treatment plan including docetaxel or paclitaxel between June 1, 2009, and December 31, 2011, at the Rena Rowan Breast Center of the Abramson Cancer Center, part of the University of Pennsylvania Health System. Patients were excluded if they had metastatic disease, previous neurotoxic chemotherapy, or preexisting clinically documented neuropathy. Women were also excluded if they were pregnant or within 3 months postpartum, or if they had a prosthetic limb or amputation, as these conditions would result in altered weight and impact body mass index (BMI) and body surface area (BSA) dosing calculations.

2.2. Measures

Data from the electronic medical record were abstracted for the primary and secondary outcomes and covariates of interest. The medical oncologist consultation visit prior to initiation of chemotherapy served as baseline for patient demographics, breast cancer diagnosis information, and comorbidities. The anesthesia record from the surgical procedure visit was used to obtain all primary and secondary outcome data. The primary outcome of interest was general anesthetic sensitivity. Although difficult to ascertain in the routine clinical setting, the surrogate for anesthetic sensitivity used universally in the clinical setting is the hemodynamic response (eg, change in heart rate and blood pressure) to incision. Secondary outcomes were anesthetic and analgesic drugs used in response to initial hemodynamic changes.

2.3. Statistical analysis

Quality assurance procedures for data collection activities included double data abstraction and entry by an independent researcher on a 10% random sample of the first 200 participants. The result was 99.9% agreement of data fields. Actual weight-based dosing was verified by calculating the BSA based on the abstracted baseline height and weight and comparing that with the BSA documented in each patient's chemotherapy order. We found that no dosing adjustments had been made; all patients were administered doses based on the BSA calculated from their actual weight.

Categorical variables were summarized by frequencies and proportions; and continuous variables were summarized by the mean, standard deviation, and range. The paired Student t test was used to test the difference in means of continuous variables, and the χ^2 test was used to test the difference in proportions of categorical variables. To account for the significant difference in the proportion of patients undergoing a lumpectomy versus mastectomy procedure between the 2 groups, analyses were completed for the whole sample (N = 339), a 1:1 matched sample (n = 156), and a 2:1 matched sample (n = 234); the matching factor was surgical procedure (lumpectomy or mastectomy). The matched analyses served as sensitivity analyses, with the 2:1 analysis having increased statistical power over the 1:1 matched analysis [10]. All statistical analyses were completed with Stata 11.2 Software (StataCorp LP, College Station, TX). All reported P values are 2-sided with .05 considered statistically significant. This study was approved by the Institutional Review Board of the University of Pennsylvania.

3. Results

We identified 339 patients who met the inclusion criteria of adjuvant or neoadjuvant taxane chemotherapy who underwent mastectomy or lumpectomy. Table 1 details patient demographics, type of chemotherapy, and surgical procedure. A significantly larger percentage of paclitaxel was used in the neoadjuvant group ($P < .001$), and this group contained a larger percentage of patients undergoing mastectomy ($P = .01$).

Table 2 details the hemodynamic changes in response to incision at 5 and 10 minutes before and after incision. Change in systolic blood pressure at 5 minutes was significantly greater in the neoadjuvant group in the original data but not in matched analyses ($P = .02, .20, .10$). Change in diastolic blood pressure at 5 minutes was significantly greater in the neoadjuvant group in the original data and the