The effect of cinacalcet on intraoperative findings in tertiary hyperparathyroidism patients undergoing parathyroidectomy

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Introduction. *Tertiary hyperparathyroidism (3HPTH) patients who undergo parathyroidectomy (PTX) are often managed with calcium lowering medications such as cinacalcet (Sensipar) before surgery. Here, we assess how cinacalcet treatment influences intraoperative parathyroid hormone (IOPTH) kinetics and surgical findings in 3HPTH patients undergoing PTX.*

Methods. *We reviewed retrospectively 113 patients 3HPTH who underwent PTX, 14 of whom were taking cinacalcet and 112 who were not taking the drug. IOPTH levels fitted to linear curves versus time were used to evaluate the role of cinacalcet.*

Results. *Cinacalcet did not correlate with rates of cure (*$P = .41$*) or recurrence (*$P = .54$*). Patients taking cinacalcet experienced a steeper decrease in IOPTH compared with those not taking the medication (*$P = .005$*). Cinacalcet treatment was associated with an increase in rate of hungry bones (*$P = .04$*). Weights of the heaviest glands resected (*$P = .02$*) and preoperative PTH levels (*$P = .0004$*) were greater among patients taking cinacalcet.*

Conclusion. *Perioperative cinacalcet treatment in patients with 3HPTH alters IOPTH kinetics by causing a steeper decrease in IOPTH, but does not require modification of the standard IOPTH protocol. Although cinacalcet use does not adversely affect cure rates, it is associated with greater preoperative PTH and an increased incidence of hungry bones, hence serving as an indicator of more severe disease. Cinacalcet does not need to be held before operation. (Surgery 2014;156:1308-14.)*

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Tertiary hyperparathyroidism (3HPTH) is an endocrine disorder characterized by the persistent hypersecretion of parathyroid hormone (PTH) in patients with longstanding secondary HPTH (2HPTH) who have undergone successful kidney transplantation to correct their chronic kidney disease.[1,2] Although most transplant recipients experience a return to normal PTH secretion after restoration of renal function, ≤8% of patients retain abnormally functioning parathyroid tissue that fails to resolve.[3,4] Consequently, serum levels of PTH remain increased, thereby increasing serum calcium levels leading to a constellation of debilitating symptoms, including atherosclerosis, nephrolithiasis, osteopenia, osteoporosis, and neuropsychiatric changes.[3-7]

The mainstay curative approach for patients with 3HPTH is subtotal or total parathyroidectomy (PTX) with forearm implantation of the remnant parathyroid.[3-5,8-10] Notably, medical management before operative intervention often employs the use of calcimimetic agents to decrease serum calcium.[11] These agents exert their effect by allosterically, activating the calcium-sensing receptors of the parathyroid glands, thus directly suppressing PTH secretion.[12] Prior interventions, such as the use of sterols and vitamin D supplementation, proved to be effective in controlling PTH levels, but resulted frequently in hypercalcemia and hyperphosphatemia.[13] The advent of the calcimemetic agent cinacalcet (Sensipar, Amgen Inc, Thousand Oaks, CA) introduced a viable therapeutic option for effectively decreasing plasma levels of PTH in patients with 2HPTH on dialysis, while

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simultaneously decreasing calcium and phosphorous levels and avoiding associated symptoms.[12-14] In addition to its registered indication for 2HPTH in patients with end-stage renal disease on maintenance dialysis, cinacalcet is also approved to decrease hypercalcemia in patients with parathyroid carcinoma and primary HPTH patients in whom PTX is contraindicated.[15,16] Given its mechanism of action and favorable pharmacokinetics, however, cinacalcet has been prescribed increasingly for patients with 3HPTH as described in a number of reports.[17-22] Since its introduction, many 3HPTH patients now opt for medical management with cinacalcet in place of PTX.[18,23] Accordingly, PTX is often performed in conjunction with calcimimetics such as cinacalcet when managing symptomatic 3HPT patients.[23] The purpose of this study was to investigate the influence of cinacalcet treatment on preoperative and postoperative findings, intraoperative PTH (IOPTH) kinetics, and the etiology of disease in patients with 3HPTH.

METHODS

We reviewed retrospectively 116 patients with 3HPTH undergoing PTX at our institution between March 2001 to March 2013. We defined 3HPTH patients as those who previously had 2HPTH and underwent successful renal transplantation. Patients who were undergoing reoperative PTX from persistent or recurrent HPTH were excluded. These patients were divided into 2 groups composed of those taking cinacalcet and those not taking cinacalcet at the time of PTX. Patients taking cinacalcet before PTX but for whom it was discontinued were categorized in the nontreated group. Patients previously taking cinacalcet who were considered to be in the nontreated group had an average duration of discontinuation before PTX of 428 days. Approval from the University of Wisconsin Institutional Review Board was granted for data collection and analysis. Patients underwent bilateral neck exploration with identification of all parathyroid glands. The number of glands excised depended on the disease etiology. Patients with hyperplasia underwent subtotal PTX. IOPTH monitoring was performed according to our previous report.[24] PTH laboratory values were drawn after anesthesia, and at 5, 10, and 15 minutes after excision of all hyperfunctioning glands. A decrease in IOPTH of 50% was used as the criteria to end the operation. Trends in IOPTH monitoring within each group were assessed by calculating the average linear slope of IOPTH change based on the initial and final levels drawn during the operation. Slopes between the 2 groups were then compared. Furthermore, we assessed the correlation between cinacalcet treatment and the number of glands discovered. We defined operative cure as serum calcium <10.2 mg/dL at 6 months after PTX. Persistence was defined as a return to calcium levels >10.2 mg/dL within 6 months after PTX, and disease recurrence was defined as a resurgence of serum calcium levels >10.2 mg/dL after a period of normal calcium for ≥6 months after PTX. Hypocalcemia as a complication of PTX was specified in the setting of hypoparathyroidism with normal renal functioning retained. Such cases were defined as having a calcium level of <8.5 mg/dL, a PTH of <8 pg/mL, and a normal glomerular filtration rate and creatinine level within 1 week after PTX. If these levels did not resolve within 6 months, these patients were classified as having permanent hypoparathyroidism. We diagnosed hungry bone syndrome in patients who had calcium levels <10.2 mg/dL after PTX beyond postoperative day 4, and these determinations were made initially based on clinical manifestations of prolonged hypocalcemia. Statistical analysis was performed using SPSS software (version 10.0, SPSS Inc, Chicago, IL) using Pearson's Chi-square test, Fisher's exact test, and a 2-sided Student *t* test for continuous variables. Continuous variable are expressed as mean values ± standard error of the mean.

RESULTS

Patients and demographics. Among the 116 patients with 3HPTH undergoing PTX, 14 (12%) were taking cinacalcet at the time of operation, and 102 (88%) were on no calcimemetics. The median treatment time of cinacalcet was 26 months (range, 1.9–56). The percentage of male patients was 64% among cinacalcet-treated patients and 49% among patients not taking the drug, which was statistically similar (Table I). Vitamin D levels among both groups were also similar, but were on the lower end of normal (Table I). Furthermore, creatinine levels were significantly greater among those taking cinacalcet compared with those not taking the drug (Table I). Although preoperative calcium levels did not differ statistically between the 2 groups, those taking cinacalcet had greater preoperative PTH levels (681 pg/mL) versus those not taking the drug (271 pg/mL; $P = .0004$; Table I). Interestingly, although etiology was not affected by cinacalcet treatment,