Letters to the Editor

Quantifying the Effects of Renal Impairment on Plasma Concentrations of the Neuroendocrine Neoplasia Biomarkers Chromogranin A, Chromogranin B, and Cocaine-and Amphetamine-Regulated Transcript

To the Editor:

Neuroendocrine neoplasia (NEN) accounts for 2% of all malignancies (1). Patients with NEN often present with nonspecific symptoms and thus represent a major diagnostic challenge. There are several circulating NEN biomarkers, and chromogranin A (CgA) is regarded as the gold standard (2). Chromogranin B (CgB) has been found to be a useful diagnostic addition to CgA measurements (3). The peptide product of cocaine- and amphetamine-regulated transcript (CART) is also increased in patients with NENs, particularly in those with pancreatic NENs (4).

Renal impairment or failure can increase circulating concentrations of CgA (2) and CART (4); however, CgB may be unaffected by mild renal impairment and is increased only in severe renal failure (3). The population most likely to be affected by NEN is also susceptible to renal impairment: Chronic kidney disease (CKD) occurs in approximately 10% of the population between 50 and 60 years of age, and the mean age of patients with a NEN diagnosis is 61 years (1, 5). We therefore examined the effect of varying degrees of renal impairment/failure on plasma concentrations of CgA, CgB, and CART in patients without NEN.

Ethics approval for this study was obtained from the Hammer Smith and Queen Charlotte’s and Chelsea Hospitals Research Ethics Committee (04/Q0406/80). After informed written consent was obtained, 5 mL of blood was collected from 40 healthy volunteers. In addition, samples from 107 patients with different stages of renal impairment were obtained and reversibly anonymized as per Royal College of Pathology, UK, guidelines (D035, September 2007). All blood samples were collected into EDTA-containing tubes and centrifuged at 10,000g for 10 min within 15 min of venipuncture. Plasma samples were then stored at −20 °C until analysis. CgA, CgB, and CART concentrations were measured by immunoactivity (IR) (CgA-IR, CgB-IR, and CART-IR) with an in-house RIA (4) at the National Gut Hormone Specialist Assay and Advisory Laboratory, Imperial College Healthcare NHS Trust, UK.

To test for significant differences between healthy volunteers and individuals at different CKD stages, we analyzed the data by Kruskal–Wallis one-way ANOVA and adjusted for multiple comparisons with the Dunn test (Fig. 1).

Median concentrations for the healthy control group were as follows: CgA-IR, 29 pmol/L (range, 22–47 pmol/L); CgB-IR, 70 pmol/L (range, 55–111 pmol/L); CART-IR, 56 pmol/L (range, 22–84 pmol/L). Patients were divided into groups by CKD stage according to their values for the estimated glomerular filtration rate (eGFR).

Concentrations of the biomarkers CgA, CgB, and CART were statistically significant (P < 0.05); *P = 0.036; **P = 0.026; ***P < 0.001. Dashed line indicates upper reference limit for each biomarker.

Fig. 1. Plasma CgA concentrations as measured by IR (CgA-IR), CgB-IR concentrations, and CART-IR concentrations increase with decreasing eGFR.

One-way ANOVA with Dunn a posteriori test compares groups of patients in different CKD stages against healthy volunteers for each biomarker. NS, not statistically significant (P > 0.05); *P = 0.036; **P = 0.026; ***P < 0.001.
concentrations increased with decreasing eGFR for all 3 biomarkers; the highest median concentrations were detected in patients with eGFR values $< 15 \text{mL} \cdot \text{min}^{-1} \cdot (1.73 \text{m}^2)^{-1}$ (Fig. 1).

Forty percent of the patients with eGFR values $\geq 60 \text{mL} \cdot \text{min}^{-1} \cdot (1.73 \text{m}^2)^{-1}$ had an increased CgA-IR value; this percentage rose to 100% in patients with an eGFR $< 29 \text{mL} \cdot \text{min}^{-1} \cdot (1.73 \text{m}^2)^{-1}$. The highest measured plasma concentration for CgA-IR was 489 pmol/L (reference interval, $< 60 \text{pmol/L}$).

The CgB-IR concentration was less affected by renal function than the CgA-IR concentration. Only 16% of the patients with eGFR values between 16 and 29 mL·min^{-1}·(1.73 m^2)^{-1} had increased concentrations. This percentage increased to 84% for patients with eGFR values $< 15 \text{mL} \cdot \text{min}^{-1} \cdot (1.73 \text{m}^2)^{-1}$. The highest measured CgB-IR concentration was 232 pmol/L (reference interval, $< 150 \text{pmol/L}$). Plasma CART-IR concentrations were normal in patients with eGFR values $\geq 60 \text{mL} \cdot \text{min}^{-1} \cdot (1.73 \text{m}^2)^{-1}$ but were increased in 80% of patients with eGFR values $< 15 \text{mL} \cdot \text{min}^{-1} \cdot (1.73 \text{m}^2)^{-1}$. The highest measured CART-IR concentration was 494 pmol/L (reference interval, $< 125 \text{pmol/L}$).

The accuracy of GFR estimation decreases at near-normal levels of kidney function. Hence, consistent with common practice, normal eGFR values are reported as $\geq 60 \text{mL} \cdot \text{min}^{-1} \cdot (1.73 \text{m}^2)^{-1}$ in our laboratory. Therefore, eGFR cannot be used to distinguish between individuals with a normal renal function and those with stage I or II CKD. Therefore, the group of individuals with eGFR values $\geq 60 \text{mL} \cdot \text{min}^{-1} \cdot (1.73 \text{m}^2)^{-1}$ in our study included patients with mild renal impairment (CKD stages I and II). Although there were no significant differences with respect to CgB-IR ($P = 0.070$) and CART-IR ($P = 0.0858$), CgA-IR was increased significantly ($P = 0.036$) in patients with eGFR values $\geq 60 \text{mL} \cdot \text{min}^{-1} \cdot (1.73 \text{m}^2)^{-1}$, compared with the healthy volunteers. These results are interesting because they suggest that although all 3 peptides are affected to varying degrees by renal failure, CgA-IR may increase even with mild renal impairment [eGFR $\geq 60 \text{mL} \cdot \text{min}^{-1} \cdot (1.73 \text{m}^2)^{-1}$]. Thus, CgB-IR may be a more reliable marker than CgA-IR in patients with mild renal impairment [eGFR $> 45 \text{mL} \cdot \text{min}^{-1} \cdot (1.73 \text{m}^2)^{-1}$]. CgB is larger than CgA and CART and therefore may not be as dependent on glomerular filtration, which may explain the fewer cases of increased concentrations of CgB-IR among patients with renal disease.

Interestingly, no patients with renal failure had CgA-IR or CART-IR concentrations $> 500 \text{pmol/L}$ or CgB-IR concentrations $> 250 \text{pmol/L}$. Therefore, although the diagnostic sensitivity of these NEN markers is low at these higher cutoffs (CgA-IR, 20% at 500 pmol/L; CART-IR, 17% at 500 pmol/L; CgB-IR, 12% at 250 pmol/L), the diagnostic specificity for NEN diagnosis is very high (100% for all 3 biomarkers). Patients with concentrations above these cutoffs must be investigated for NENs, even in the presence of renal failure. Our results indicate the need for additional studies to determine the diagnostic cutoffs with optimal sensitivity and specificity for the neuroendocrine biomarkers to enable NEN diagnosis in renally impaired patients.

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References

Letters to the Editor

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