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Awareness of drug laboratory test interactions is important for prevention of unnecessary additional diagnostics: An example

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ABSTRACT

Background: Elevated levels of Chromogranin A (CgA) may be indicative of a neuroendocrine tumour (NET), but increased levels are also observed after intake of proton pump inhibitors (PPIs). The incidence of diagnostic confusion because of this drug-laboratory test interaction (DLTI) was examined.
Methods: Medical records of 238 patients with elevated CgA concentrations were obtained from three hospitals. The following data were extracted: PPI prescription at the time of CgA measurement, medical decision making based on elevated CgA concentrations, final diagnosis, comorbidity and other prescribed drugs.
Results: From 238 patients with elevated CgA concentrations, 132 used PPIs. Of these patients, 57 patients did not have a NET. In 9 of these 57 patients (16%), diagnostic work up revealed no medical cause of an elevated CgA concentration. Somatostatin receptor imaging was ordered in 4 out of 9 cases, with no abnormalities observed. In 6 out of 9 cases, CgA measurement was repeated after PPI discontinuation resulting in normalisation of CgA concentrations.
Conclusion: In this retrospective patient record study we observed that part of the elevated CgA concentrations in patients could be caused by the usage of PPIs causing unnecessary diagnostic work-up for the exclusion of a NET. These observations illustrate the need for better DLTI awareness.

1. Introduction

Diagnostic tests, such as laboratory analysis of body fluids, represent an important part of today's healthcare. The quality of diagnostic testing depends on careful performance of the complete analytical work-up including the so-called 'post-analysis', which includes reporting and interpretation of test results [1]. Deviating laboratory test results are indicative of illness, but may also be a consequence of possible drug-laboratory test interactions (DLTIs). Ignorance of possible interactions between drugs and laboratory tests may lead to incorrect diagnosis and treatment, as well as unnecessary follow-up [2]. An example of such an interaction is an elevated concentration of chromogranin A (CgA) caused by frequently prescribed proton pump inhibitors (PPIs) [3]. PPIs stimulate gastric enterochromaffin-like cells which causes elevated concentrations of CgA. The serum concentration of CgA is used as a marker for neuroendocrine tumours (NETs) [4]. NETs are rare neoplasms which may arise from several anatomical sites, such as the small intestine, pancreas and lungs. NETs are characterized by the ability to

Abbreviations: CgA, Chromogranin A; DLTI, Drug Laboratory Test Interaction; GFR, Glomerular Filtration Rate; NET, Neuro Endocrine Tumour; PPI, Proton Pump Inhibitor.

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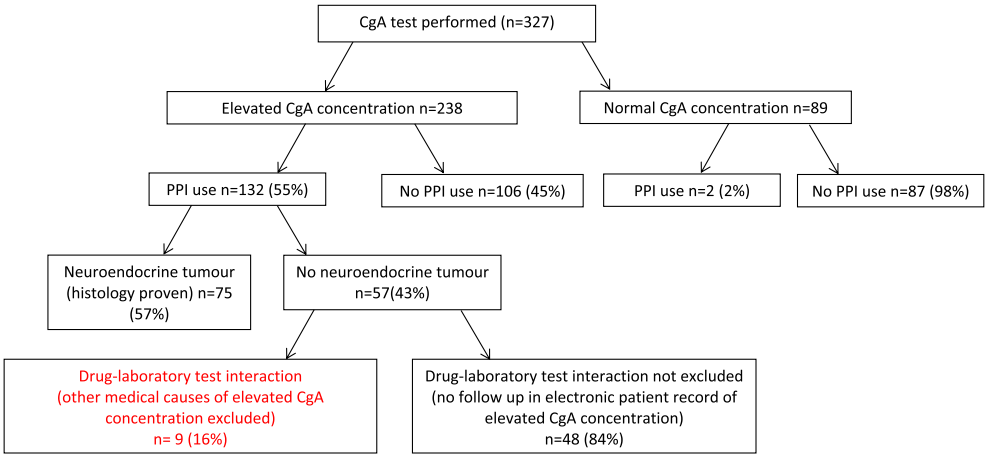

Fig. 1. Flowchart of study design.

synthesize, store and secrete different peptides and neuroamines, such as CgA [5]. Case-reports have described elevated CgA concentrations in patients, who underwent expensive imaging with no abnormalities and a normalized CgA level after discontinuation of the PPI [3]. These cases illustrate that this DLTI is not always immediately recognized in clinical practice with consequent unnecessary discomfort for patients and healthcare expenditure.

Since this unrecognized DLTI has serious consequences for an individual patient and healthcare expenditures in general, it is imperative to better estimate its incidence.

Therefore, the aim of this retrospective medical record study was to investigate the incidence and possible impact of diagnostic misinterpretation of an elevated CgA concentration caused by PPIs.

2. Material and methods

All patients with an elevated CgA concentration in two large non-academic hospitals between 2014 and 2018 were included. In addition, in one University Medical Centre, a random selection from a larger cohort of patients was made with elevated CgA concentration. To avoid selection bias, randomization was performed with the function 'sample' in the statistical program 'R'. Patients that were referred from the non-academic hospitals to the University Medical Centre were excluded from the latter study group.

From the patients' medical records, the following data were extracted: sex, age, known NET, CgA concentration, specialism of requesting physician, prescribed PPIs (including type and dosage), indication for CgA measurement, medical decision following the elevated CgA concentration measurement, referral to a tertiary care centre and final diagnosis. Renal, hepatic and gastro-intestinal diseases were also extracted, because it is known that these conditions also cause elevated CgA concentrations [6–8]. Besides PPIs, other prescribed drugs were also registered. All CgA measurements in serum were performed in the university medical center with a generation II assay (BRAHMS Kryptor) [9] as part of the usual care. No extra CgA measurements were performed for this study.

Descriptive statistics were performed (frequency, mean, SD, median, quantiles) and the Mann Whitney *U* test to compare differences, using the R statistical package (version 1.2.5033). P value below 0.05 was considered as statistically significant.

The study was performed under the tenets of the Helsinki declaration, local laws and regulations and was approved by all participating institutions. The Dutch Medical Research involving Human Subjects Act (WMO) did not apply to this study, which was confirmed with a waiver from the Medical Ethical Committee.

Table 1
Demographics of patients with an elevated CgA concentration (n = 238).

	Hospital 1 (n = 101) University medical centre	Non-academic Hospital 2 (n = 86)	Non-academic Hospital 3 (n = 51)
Age			
- Mean (SD)	71(13)	69 (10)	68 (10)
Sex			
- Female: N(%)	51 (51%)	46 (54%)	28(55%)
Medical speciality requesting physician			
	1	0	13
- Gastroenterology	59	30	10
- Internal medicine*	11	36	7
- Surgery	29	15	14
- Oncology	1	5	7
- Other			
CgA concentration median (25–75 quantile) [μg/L]	428 (200–892)	294 (139–605)	283 (159–812)
Diagnosis			
- Neuroendocrine tumour	87 (86%)	22 (26%)	33 (65%)
	9 (9%)	44 (51%)	2(4%)
- Gastro-intestinal, pancreas and bile duct carcinoma	3 (3%)	3 (3%)	0 (0%)
	2 (2%)	15 (17%)	6 (12%)
- Other malignancy	0 (0%)	2 (2%)	10 (20%)
- benign**			
- Unknown			

* Including endocrinology **such as gastritis, pancreatitis, and irritable bowel disease.
From the 142 patients diagnosed with a NET, 75 used a PPI.

3. Results

Fig. 1 shows a flowchart of the study design. In total, 327 patients with a measured CgA concentration were included, of which 141 were diagnosed with a NET.

In the study population, 238 patients had an elevated CgA concentration and 132 of them had a prescribed PPI (55%). Of these patients, 57 received another diagnosis than NET (43%). In this group, CgA test results of 9 patients were probably influenced by PPIs (16%), because no other medical cause of the elevated CgA concentration was identified.Of the 89 patients with a normal CgA concentration, only 2 patients used a PPI (2%)).

Table 1 summarizes the demographics of the study populations with an elevated CgA concentration of the three hospitals. From the university medical centre (hospital 1), 101 patients were included and from the non-academic hospitals (hospital 2 and 3) a total of 137 patients were included. Age and sex were comparable in the populations.

Table 2
Details of cases with an elevated CgA concentration without a medical cause other than PPIs.

Case	CgA [μg/L]	Sex (M/F)	Age [years]	Medical specialty requesting physician	PPI (total daily dose)	Use of other drugs known to cause CgA elevation	Presence of comorbidity known to cause CgA elevation	Further diagnostics as a consequence of elevated CgA result	Repeated CgA [μg/L][a]	Diagnosis
1	129	M	51	Internal Medicine	Omeprazole 40 mg	–	–	^{68}Ga-DOTATATE PET/CT scan	–	Cyclic vomiting syndrome
2	137	F	65	Internal Medicine	Pantoprazole 40 mg	–	–	No further diagnostics because of spontaneous improvement of symptoms	–	Chronic diarrhoea without known cause
3	154	F	56	Gastroenterology	Omeprazole 40 mg	–	Chronic pancreatitis, IBD or IBS	^{68}Ga-DOTATATE PET/CT scan	–	Chronic pancreatitis
4	314	F	56	Gastroenterology	Omeprazole 80 mg	–	IBD and asthmatic bronchitis	^{68}Ga-DOTATATE scan and repeated CgA measurement after discontinuation PPI	271	Chronic diarrhoea without known cause
5	440	F	47	Oncology	Pantoprazole 40 mg	–	–	Repeated CgA measurement after discontinuation PPI	29	Cured from radically removed NET
6	830	F	72	Oncology	Omeprazole 80 mg	–	Pancreatic adenocarcinoma	Repeated CgA measurement after discontinuation PPI	311	Pancreatic adenocarcinoma
7	1270	F	61	Internal Medicine	Omeprazole 20 mg	H2 receptor antagonist	Hypertension	Repeated CgA measurement after discontinuation PPI	56	Diarrhoea and flushes without known cause
8	3912	F	66	Internal Medicine	Omeprazole 40 mg	Selective serotonin reuptake inhibitor	Hypertension and heart failure	^{111}In-DTPA-Octreotide PET/CT scan and repeated CgA measurement after discontinuation PPI	132	Chronic diarrhoea without known cause
9	4993	F	75	Gastroenterology	Pantoprazole 80 mg	–	Hypertension and COPD	Repeated CgA measurement after discontinuation PPI	247	Reflux without known cause

CgA: Chromogranin A, IBD: Irritable bowel disease, IBS: Irritable bowel syndrome, COPD: Chronic obstructive pulmonary disease PPI: Proton Pump Inhibitor.
[a]upper reference limit 100 μg/L.

CgA measurement was most frequently requested by the department of internal medicine in hospital 1, whereas surgery and oncology were the main requesting departments in hospital 2 and 3 respectively. In hospital 1, the median CgA concentration was the highest, as well as the number of diagnosed NETs.

Table 2 shows details of nine patients with an elevated CgA concentration, probably as a consequence of an interaction with PPIs. The CgA concentration ranged from 129 up to 4993 μg/L (reference value < 100 ug/L). All patients were from non-academic hospitals. From the 9 patients, 8 were female with an age between 47 and 75 years. In 6 out of 9 patients, CgA measurement was repeated between 3 weeks and 2 months after discontinuation of the PPI. The CgA concentration decreased in the repeated measurement, but not always below the upper reference limit. In 4 out of 9 patients somatostatin receptor PET imaging was performed without discovering any abnormalities. In 6 out of 9 patients no diagnosis was made, other than a description of the symptoms.

Fig. 2 shows boxplots of the CgA concentration in patients with and without prescribed PPIs. These groups were divided in patients with and without NET. In the patients without a NET, CgA concentrations were significantly higher compared to those without prescribed PPIs (median 324 versus 162 μg/L, $p < 0.05$). This difference was not seen in patients with a NET.

Supplemental Table 1 shows the association between diseases that are known to possibly increase the CgA concentration [5]. We found no statistically significant difference in CgA concentration between patients with and without renal failure, hypertension, pancreas carcinoma, obstructive lung disease and/or gastrointestinal or liver disease, but subgroups were small. In the study population, 62 patients had renal failure, defined as an estimated glomerular filtration rate below 60 ml/min. All these patients had elevated CgA concentrations with an average of 2875 μg/L (range 103–87430 μg/L). Of these patients, 46 were diagnosed with a NET and their main CgA concentration was 3495 μg/L (range 103–87340 μg/L). In the other 16 patients without a NET, the main CgA concentration was 1096 μg/L (range 112 – 2329 μg/L).

Supplemental Table 2 shows the association between prescribed drugs and the CgA concentration. Except for PPIs, we did not find a statistically significant difference in CgA concentration in patients with a specific drug.

H2 receptor antagonists and serotonin reuptake inhibitors have been described to cause elevated CgA concentrations [7]. In our population these drugs were prescribed in twelve patients. Of these patients, all measured CgA concentrations were elevated, ranging from 181 to 4629 μg/L. Among them, eight were diagnosed with a NET. In the non-NET group, 2 patients had CgA concentration > 1000 μg/L.

4. Discussion

This multicentre retrospective medical record study demonstrates the importance of awareness of DLTIs, specifically when CgA is measured in patient with prescribed PPIs. We studied the incidence of the interaction between CgA and PPIs and the possible impact of this DLTI. We found that in patients without a NET, an elevated CgA concentrations as a consequence of PPIs may lead to extra diagnostic testing (16%) for the exclusion of a NET, i.e. repeated CgA measurements and even somatostatin receptor PET imaging and referral to a tertiary care centre. In the other 84% of patients with an elevated CgA concentration and prescribed PPIs, no follow-up was described in the electronic patient record. In these cases, clinicians might have attributed the elevated CgA concentration to prescribed PPIs.

In patients without a NET we also showed a significantly higher CgA concentration in patients with versus those without a prescribed PPI

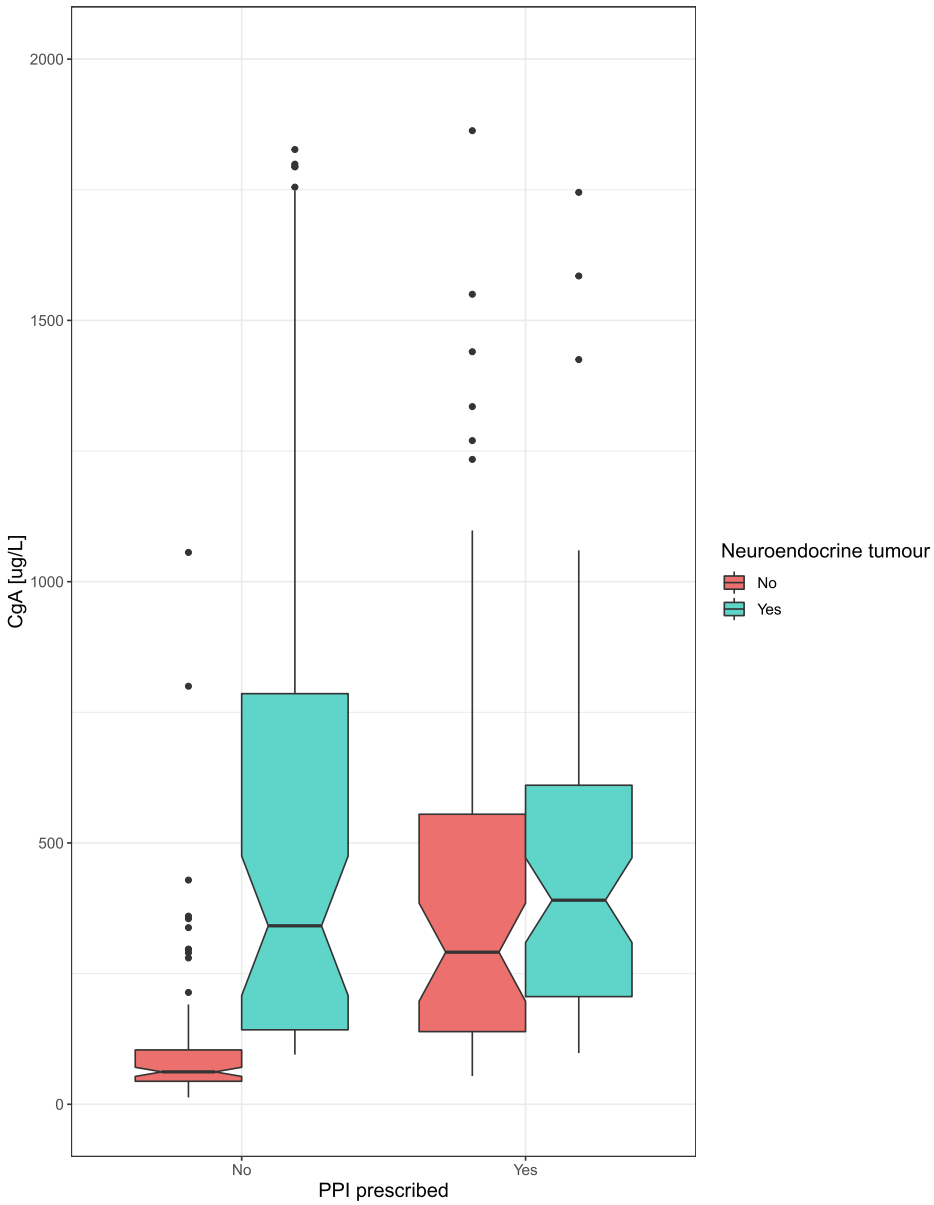

Fig. 2. Boxplot of CgA concentration in patients with and without prescribed PPI and with and without a neuroendocrine tumourPatients with a performed CgA test (n = 327): neuroendocrine tumour (n = 142), no neuroendocrine tumour (n = 168), Patients without known diagnosis were excluded (n = 17) Limit of Y-axis = 2000 Boxplot represent interquartile range (25-75th percentile), bold line in the middle represents median.

(Fig. 2). However, in patients with a NET, PPIs do not significantly change CgA concentrations (Fig. 2). Therefore, these data suggest that PPIs do not have to be discontinued in case of a CgA measurement in patients with a histologically proven NET.

CgA concentrations in patients with prescribed PPIs and no other causes for CgA elevations were both mildly and severely elevated, suggesting that the degree of elevation does not reflect possible PPI interaction.

In patients with an estimated eGFR < 60 ml/min, all CgA concentrations were elevated, even in the absence of a NET. Therefore, our data confirm that the CgA concentration as a marker for a NET is inadequate in patients with renal failure.

When determining the diagnosis and treatment of a NET, histopathology of the tumour mass is leading [10]. CgA is mainly recommended as a marker for follow-up according to the European Neuroendocrine Tumour Society guideline [2]. The specificity of CgA assays as a diagnostic marker is limited in a population with other diseases, such as inflammatory bowel disease and renal failure [11,12]. In our population, CgA concentrations > 1000 μg/L were found in patients without a histopathology proven NET. These data confirm the low specificity of CgA as a diagnostic marker, even when CgA concentrations are high (>3 times the upper reference limit). However, it is clear that CgA is still used in clinical practice to exclude or judge the probability of a NET.

The NET prevalence in patients with prescribed PPIs and an elevated CgA concentration is high (57%). These data underline the fact that it is not possible to exclude a NET in a patient with an elevated CgA concentration and prescribed PPIs. To prevent extra diagnostics for the exclusion of a NET, we would suggest to alert at the time of CgA test ordering. In case a CgA test is already performed under prescribed PPIs, we would recommend to first retest CgA after one week discontinuation of a PPI since this is less invasive and expensive than immediate radioactive labeled imaging.

Diagnostic uncertainty caused by DLTIs is undesirable. This study shows that the interaction between CgA and PPIs causes extra diagnostic work-up in a substantial number of patients with extra healthcare

expenditure and may harm patients. An electronic clinical decision support system that alerts for possible DLTIs is a promising solution and clinicians are positive about the concept [13]. It may increase the awareness of DLTI and thereby prevent diagnostic confusion and improve patient safety.

CRediT authorship contribution statement

Jasmijn A van Balveren: Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Visualization. **Lale Erdem-Eraslan:** Data curation, Investigation, Project administration, Data curation, Formal analysis, Investigation, Project administration. **Wilhelmine P.H.G. Verboeket-van de Venne:** Data curation, Formal analysis, Funding acquisition, Investigation, Project administration, Writing – review & editing. **Carine J.M. Doggen:** Conceptualization, Supervision, Writing – review & editing. **Johannes Hofland:** Conceptualization, Methodology, Validation. **Wytze P. Oosterhuis:** Conceptualization, Methodology, Validation, Writing – review & editing. **Yolanda B. de Rijke:** Conceptualization, Writing – review & editing. **Rein M.J. Hoedemakers:** Conceptualization, Funding acquisition, Supervision, Writing – review & editing. **Ron Kusters:** Conceptualization, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Declaration of interest statement

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cca.2022.03.013.

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