

Interpretation of dynamic test results in secondary hypocortisolism post pituitary surgery and hydrocortisone replacement doses.

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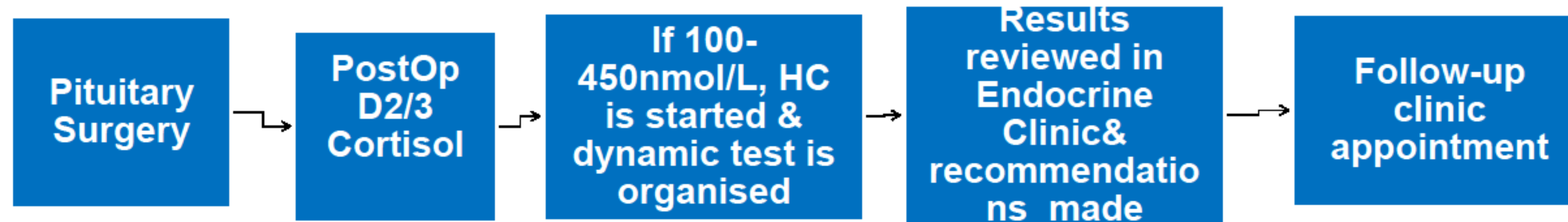
Topic: Pituitary Clinical

Background

In secondary hypocortisolism, glucocorticoid replacement is usually given with Hydrocortisone (HC) in 2-3 daily doses, with a half to two-thirds in the morning: starting HC regimen of 10mg on waking, 5mg at 12:00 and 5mg at 16:00. Among other factors, intestinal absorption, bioavailability and cortisol binding globulin modulate cortisol concentrations. High glucocorticoid replacement doses are associated with adverse effects, and the optimal replacement dose is unknown.

In order to identify patients with ACTH deficiency following pituitary surgery in our centre, a day 2 or 3 (D2/3) 8-9am cortisol is measured: if D2/3 cortisol is <100nmol/L, HC replacement is commenced, and if D2/3 cortisol is >450nmol/L patients are classified as ACTH sufficient. In patients with a D2/3 cortisol 100-450nmol/L, dynamic testing with insulin tolerance (ITT) or glucagon stimulation testing (GST) is used in order to identify patients with ACTH deficiency who require glucocorticoid replacement. In patients with epilepsy, ischaemic heart disease, or above the age of 65, the GST is used instead of the ITT. We use a peak cortisol of ≥550nmol/L for both tests to indicate ACTH sufficiency.

Figure 1. Protocol for testing for hypocortisolism following Pituitary Surgery



Aim

To assess the interpretation of dynamic testing post pituitary surgery in clinical practice and its relation with the hydrocortisone replacement doses used.

Methods

Retrospective review of all dynamic testing results post pituitary surgery between 2004-2014 in a tertiary centre, and of the medical notes. Data captured included comorbidities, medications, doses of HC recommended at 1st appointment post testing and in follow-up appointments, and length of follow-up.

Patients with Cushing's disease, incomplete data, or those who did not reach adequate hypoglycaemia on ITT were excluded. Data were analysed with Excel and XLSTAT. In graphs the red horizontal line depicts the mean and the cross the median. Asterisk (*) indicates p values as follows: *p<0.05 **p<0.005 ***p<0.001.

Results

- 101 patients were included, out of which 61 were tested with an ITT and 40 with a GST. Demographic characteristics of the patients and their underlying diagnoses, that led to surgery, are presented in Table 1.

Table 1.

	All	ITT	GST	p
N Patients	101	61 (60.4%)	40 (39.6%)	
N Males	55 (54.5%)	33 (54.1%)	22 (55.0%)	NS
Mean age (years, range)	55.6 (19-84)	47.4 (19-68)	69.0 (46-84)	<0.001
Length of follow up (years ±SD)	4.4 ±3.0	4.5 ±2.9	4.2 ±3.2	NS
Diagnosis				
NF Adenoma	67 (66.3%)	37 (60.7%)	30 (75.0%)	
Acromegaly	8 (7.9%)	6 (9.8%)	2 (5.0%)	
Rathke's Cleft Cyst	6 (5.9%)	5 (8.2%)	1 (2.5%)	
Prolactinoma	6 (5.9%)	3 (4.9%)	3 (7.5%)	
Craniopharyngioma	3 (3.0%)	2 (3.3%)	1 (2.5%)	
Other	11 (11.0%)	8 (13.1%)	3 (7.5%)	

- 27 patients failed ITT testing and 26 patients failed the GST, and all were started on HC. In table 2, HC and other hormone replacement is shown for each group.
- There were 30 (56.6%) patients on <20mg HC/day, 20 (37.7%) patients on ≤10mg HC/day and 7 (13.2%) patients on Emergency (Em) HC only. The total daily doses of HC for patients who failed ITT are shown in Figure 2, and for those who failed GST are presented in Figure 3.
- Most patients (86.8%) continued the steroid dose recommended in the first review post dynamic testing and did not require dose changes in stable conditions with a follow-up of 4.4 ±3years.
- However, 3 patients on emergency HC only, needed to restart HC (peak cortisol in testing 359nmol/L, 434nmol/L, 521nmol/L), in one patient on HC 10mg/day, the final HC dose was 20mg/day (peak cortisol 470nmol/L), and in 3 patients, HC recommended, but patients stopped (peak cortisol 222, 452 and 533nmol/L).

Table 2. HC and other hormone replacement in each group.

	ITT		GST	
	Yes (n=27)	No (n=34)	Yes (n=26)	No (n=14)
Hydrocortisone	Yes (n=27)	No (n=34)	Yes (n=26)	No (n=14)
Thyroxine	20 (74.0%)	17 (50%)	20 (76.9%)	8 (57.1%)
Oestrogen	4 (14.8%)	1 (2.9%)	1 (3.9%)	0 (0%)
Testosterone	10 (37.0%)	8 (23.5%)	8 (30.8%)	3 (21.4%)
DDAVP	5 (18.5%)	3 (8.8%)	1 (3.9%)	0 (0%)
Growth Hormone	8 (29.6%)	5 (14.7%)	1 (3.9%)	0 (0%)

Figure 2.

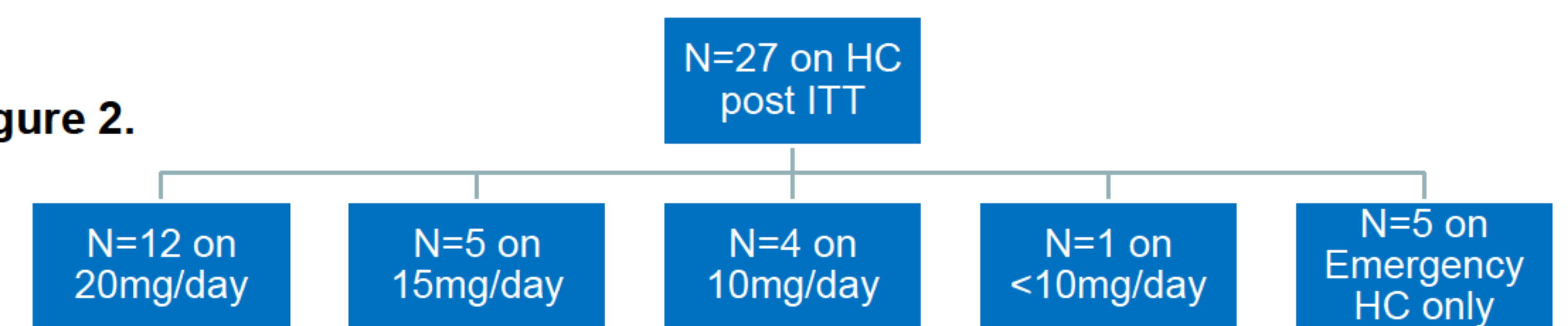
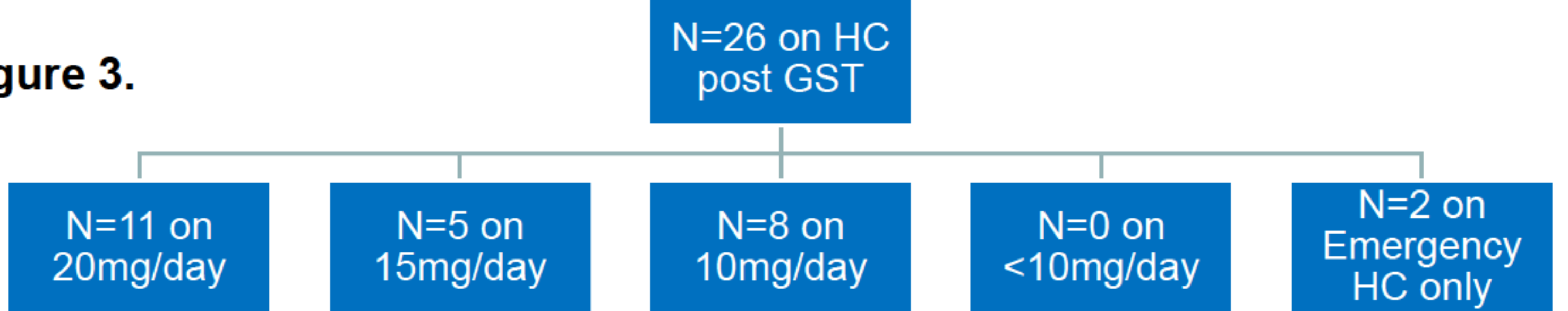


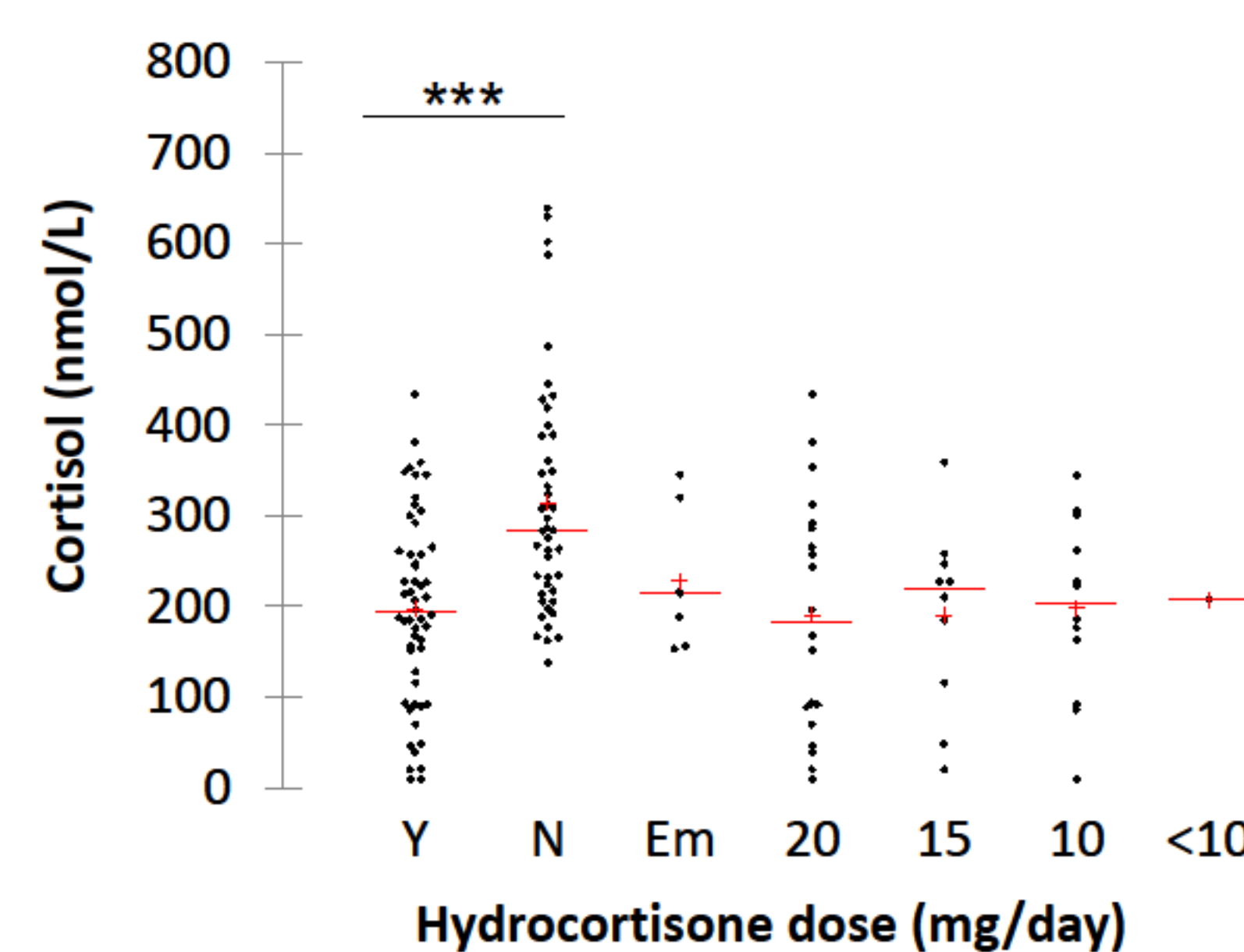
Figure 3.



We then wanted to examine if the baseline or the peak cortisol during testing was related to the HC dose recommended.

Baseline cortisol on day of dynamic testing and HC replacement doses

On the day of dynamic testing:

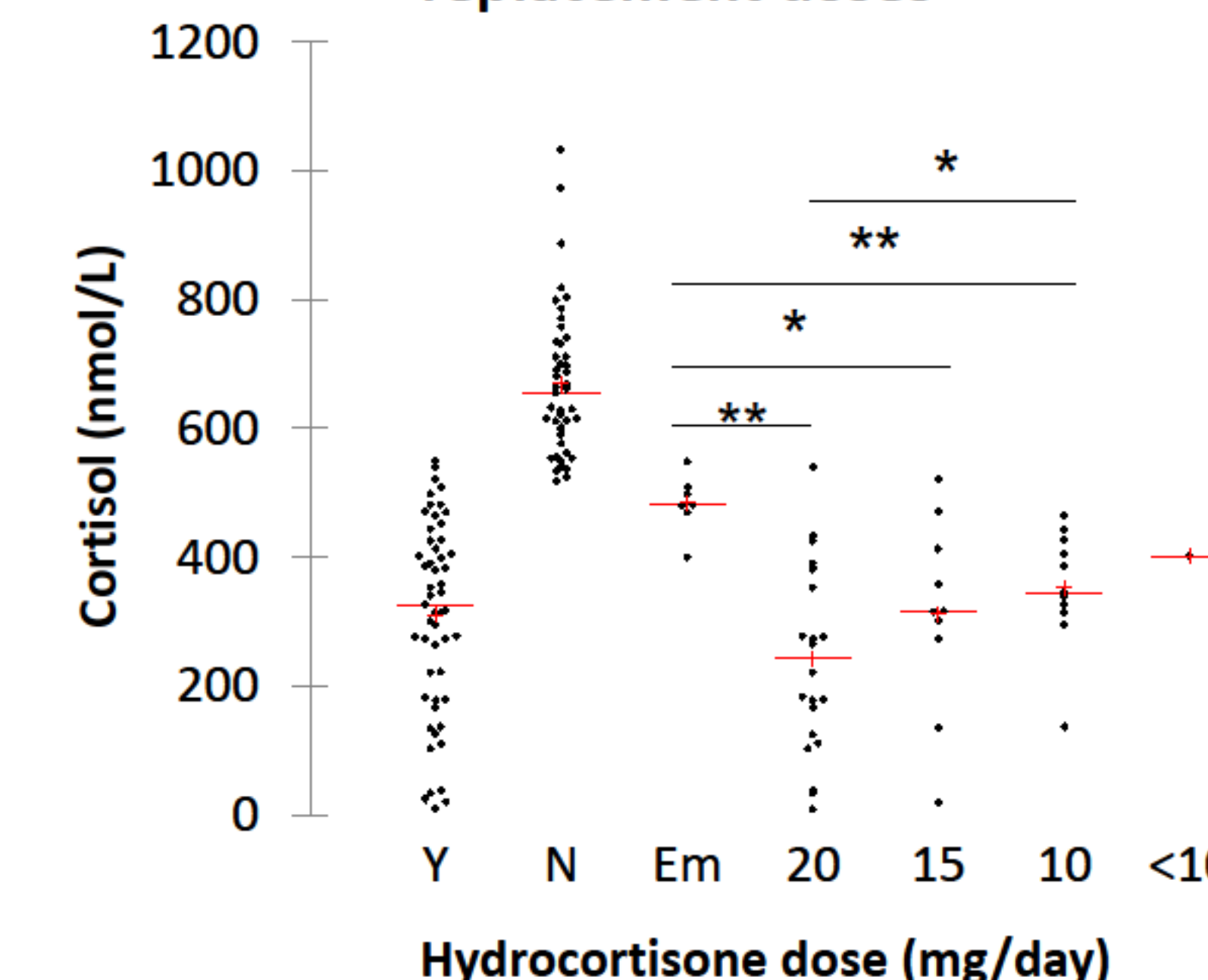


- patients that failed ITT or GST had baseline cortisol of 196 ±105nmol/L (mean ±SD).

- patients that passed compared to patients that failed ITT or GST had significantly higher baseline cortisol (284 ±128nmol/L).

- there was no relation between the final HC replacement dose and the baseline cortisol measurements.

Peak cortisol on ITT/GST and HC replacement doses



- patients on HC 20mg/day had lower peak cortisol compared to those on 10mg/day (252 ±142nmol/L vs 356 ±95nmol/L, p<0.05) or emergency HC only (484 ±45nmol/L, p<0.005).

- patients on HC 10mg/day or 15mg/day had significantly lower dynamic testing peak cortisol compared to those on emergency HC only (p<0.005 and <0.05 respectively).

Conclusions

- Patients diagnosed with hypocortisolism on dynamic testing post-pituitary surgery have partial ACTH deficiency, and do well on variable dose HC replacement. The benefits of this approach are the reduction of total daily steroid doses and of complications from steroid over-replacement, and less tablets/day for patients.
- The peak cortisol level on dynamic testing may be useful when deciding the glucocorticoid replacement scheme.

References

Bleicken B et al, Clin Endo, 2010; Arlt W et al, Lancet, 2003; Inder W et al, JCEM, 2002; Inder W et al, JCEM, 2002; Bleicken B et al, Clin Endo, 2010; Debono et al, EJE, 2009; Wichers M et al, Clin Endo 1998