PTH infusion ameliorates seizures in autosomal dominant hypocalcemia type 1

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This work was supported by: a Wellcome Trust Investigator Award (grant number 106995/Z/15/Z) (RVT); National Institute for Health Research (NIHR) Oxford Biomedical Research Centre Programme (to R.V.T.); NIHR Senior Investigator Award (to R.V.T.) (grant number NF-SI-0514–10091); Horizon 2020 Programme of the European Union (Project ID: 675228) (to F.M.H., and R.V.T.); and Erasmus Plus Mobility Programme (2018-1-IT02-KA103-047045) (to K.V.). We thank H. Boon and T. Cranston from the Oxford Molecular Genetics Laboratory, Churchill Hospital, Oxford, UK, for providing the DNA diagnostic service that identified the CaSR mutations; and Dr N. Crabtree from the Department of Endocrinology and Diabetes, Birmingham Women's and Children's NHS Foundation Trust, for providing a graph of pediatric BMAD normal ranges; and Professor Bockenhauer, Department of Nephrology, Great Ormond Street Hospital for Children NHS Foundation Trust, for his help with assessments of nephrocalcinosis.

TO THE EDITOR: Autosomal dominant hypocalcemia type 1 (ADH1) is caused by gain-of-function calcium-sensing receptor (CaSR) mutations[1,2] that result in hypocalcemia and seizures, hypomagnesemia, hyperphosphatemia, reduced parathyroid hormone (PTH), and hypercalciuria. Calcium and vitamin D analogs for treating ADH1 predispose to nephrocalcinosis and renal impairment[1,3]. CaSR antagonists, known as calcilytics, represent a possible treatment[2], but are clinically unavailable. However, recombinant PTH(1-34) may increase serum calcium without causing hypercalciuria in patients with forms of hypoparathyroidism[4,5]. We assessed the effectiveness of continuous subcutaneous PTH(1-34) infusion (CSPI) in a retrospective cohort of six ADH1 patients (aged 5 weeks-22 years), who were selected as they experienced hypocalcemic seizures despite using calcium and vitamin D analogs, and/or bolus PTH injections (Fig. 1A and Methods section in the Supplementary Appendix). Calcium and vitamin D analogs also failed to cease anticonvulsant therapy in two of three patients on phenobarbitone, and were associated with nephrocalcinosis and renal impairment in two patients, respectively. All patients had gain-of-function CaSR mutations, with three being constitutively active mutations that had arisen *de novo* and showed diminished signalling responses to the calcilytic, NPS-2143 (Fig. 1A, Fig. S1, Fig. S2 and Methods section in the Supplementary Appendix). CSPI treatment over 0.8-5.5 years increased mean serum adjusted-calcium by 0.30mmol/L (95% confidence interval (CI), 0.12 to 0.48) and reduced mean serum phosphate by 0.92mmol/L (95%CI, 0.69 to 1.14) in all six patients, when compared to calcium and vitamin D analog treatment (Fig. 1B). This was associated with decreased mean calcium-phosphate product by 1.15mmol^2/L^2 (95%CI, 0.63 to 1.66) in 5 patients, and increased mean serum magnesium by 0.09mmol/L (95%CI, 0.03 to 0.14) in 4 patients (Fig. 1B). CSPI reduced seizures in all patients from 2.0 (95%CI, -1.6 to 5.6) to 0.01 (95%CI, -0.01 to 0.02) seizures per month, with no patients requiring further anticonvulsants, and resulted in fewer emergency admissions (Fig. 1C). Serious adverse effects were not

observed during CSPI. Tachyphylaxis was suspected in one patient with a slipped upper femoral epiphysis, but bone mineral apparent density in three children remained within the reference interval, and CSPI did not worsen nephrocalcinosis or increase calcium excretion, which was reduced in three patients (Table S1, Fig. S3 and Fig. S4 in the Supplementary Appendix). All CSPI-treated infants attained developmental milestones. Thus, CSPI represents a long-term therapy for increasing serum calcium, ameliorating seizures and reducing hospital admissions in young ADH1 patients. A prospective study is required to confirm these findings.

Word count = 400

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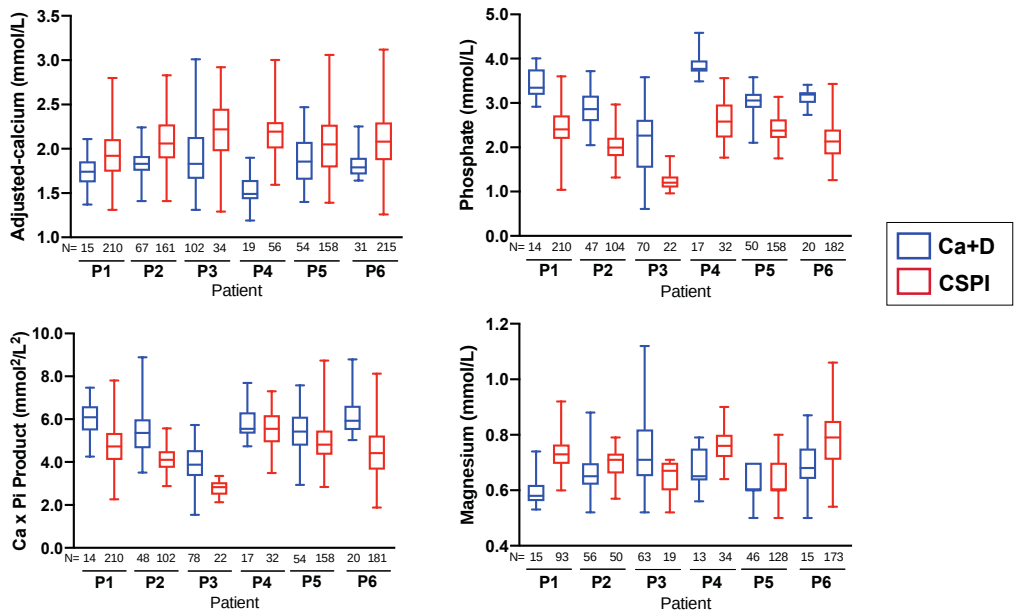
Figure 1. Clinical findings and responses to PTH infusion in ADH1 patients.

Panel A shows clinical characteristics and treatments for all six unrelated ADH1 patients (P1-P6). [a]M, male; F, female. [b]S, seizures; NC, nephrocalcinosis; RI, renal impairment; BC, bilateral cataracts; BS, Bartter syndrome; H, hyperinsulinism. [c]Received phenobarbitone anticonvulsant therapy. [d]f, familial; dn, *de novo*; c, constitutively active. [e]Normal ranges: adjusted-calcium, 2.20-260 mmol/L; phosphate, 1.30-2.60 mmol/L (<1 month), 1.30-2.40 mmol/L (1 month-1 year), 0.90-1.80 mmol/L (1-16 years), 0.80-1.50 mmol/L (>16 years); magnesium, 0.70-1.0 mmol/L; creatinine, 27-77 μmol/L (<1 month), 14-34 μmol/L (<1 year), 15-31 μmol/L (1-3 years), 23-37 μmol/L (3-5 years), 25-42 μmol/L (5-7 years), 30-47 μmol/L (7-9 years), 29-56 μmol/L (9-11 years), 39-60 μmol/L (13-15 years), 40-68 μmol/L (>15 years); parathyroid hormone (PTH) 1.6-6.9 pmol/L; urine calcium: creatinine (Ca:Cr) ratio, <1.50 mmol/mmol (0-1 years), <1.25 mmol/mmol (1-2 years), <1.0 mmol/mmol (2-5 years), <0.70 mmol/mmol (5-10 years), <0.60 mmol/mmol (10-18 years). [f]CSPI, continuous subcutaneous PTH(1-34) infusion; NA, not available; [g]Mg, magnesium; K, potassium; T, thiazide, Di, diazoxide; Do, doxazosin; Fe, ferrous fumarate; Epo, erythropoietin. All children were taking cholecalciferol or ergocalciferol. Panel B shows effects of CSPI compared to prior therapy with oral calcium supplements and vitamin D analogs (Ca+D) on serum concentrations of adjusted-calcium; phosphate; calcium-phosphate product (Ca x Pi); and magnesium. Number of serum biochemical values per treatment group in each patient (P1-P6) are shown below respective box and whisker plot. Panel C shows effects of CSPI compared to prior therapy with Ca+D (Pre-CSPI) on numbers of seizures per month and hospital admissions (days per month) in six ADH1 patients (P1-P6).

A

Variable	P1	P2	P3	P4	P5	P6
Sex[a]	F	M	F	M	F	F
Family history	Yes	No	Yes	No	No	No
Age at presentation	12 days	28 days	1 day	7 days	9 days	6 days
Clinical features[b]	S[c]	S, NC	S, NC, RI	S[c], BC	S[c], BS, H	S, BS, RI
CASR mutation[d]	F821L (f)	T828N (dn)	T828N (f)	Y829C (dn, c)	A843E (dn, c)	A843E (dn, c)
Biochemistry[e]						
Calcium (mmol/L)	1.74	1.38	0.70	1.26	1.45	1.48
Phosphate (mmol/L)	3.60	2.77	2.49	4.28	2.69	NA
Magnesium (mmol/L)	0.58	0.54	0.52	0.62	0.50	0.65
Creatinine (μmol/L)	20	21	NA	20	46	NA
PTH (pmol/L)	0.6	0.6	NA	<0.13	NA	<0.5
Urine Ca:Cr (mmol/mmol)	3.3	0.82	NA	2.1	3.2	3.8
Treatment prior to CSPI[f]						
Alfacalcidol (ng/kg)	80-150	90	25	130	130	Nil
Calcium (mmol/kg)	4-10	4	Nil	4	10	Nil
Magnesium (mmol/kg)	2.0	0.2	0.2-1.0	1.5	1.5	1.0
Bolus PTH (μg/kg/d)	Nil	Nil	1.0	Nil	Nil	2.0
Age at start of CSPI	5 weeks	10 months	22 years	7 weeks	11 weeks	6 years
Initial CSPI dose (μg/kg/d)	0.58	0.59	0.60	0.47	0.57	3.60
Current CSPI dose (μg/kg/d)	0.51	0.29	0.98	0.31	0.90	2.40
Duration of CSPI (years)	3.2	2.9	3.2	3.6	0.8	5.5
Additional regular treatment[g]	Mg, T	Mg	Nil	Mg	Mg, T, K, Di, Fe	Mg, Do, Fe, Epo

B



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