

BSPED research award 2015 report - Charlotte J Elder

Pharmacokinetic validation of a non-invasive Short Synacthen Test in children

Background: Increasing use of corticosteroids in a range of paediatric conditions, and growing evidence of adrenal suppression in children on high-dose inhaled corticosteroids, has caused a rise in requests for Short Synacthen Tests (SST)¹. The current SST requires intravenous cannulation and blood sampling and is thus invasive, time-consuming and resource-intensive. Both low-dose (usually 1 mcg) and high-dose (~250 mcg) Synacthen are used in clinical practice, although paediatric endocrinologists tend to favour the low-dose test². Results of meta-analyses do not show significant superiority of one test over another³⁻⁷.

We have been developing a non-invasive alternative to the intravenous SST (both low and high dose), with Synacthen given nasally and saliva used to measure the resultant cortisol and cortisone response. Salivary cortisol is a well-established and validated alternative to serum sampling. To achieve the necessary nasal absorption and maximal adrenal response reformulation was required with an increased dose and concentration and the addition of a nasal drug enhancer, chitosan. Chitosan is derived from the exoskeleton of shellfish, it is thought to both increase nasal drug residence time and aid paracellular transport by transiently opening the tight junctions in the nasal mucosa. We had completed four pharmacokinetic, dose ranging studies in healthy adult males, showing our novel formulation of nasal Synacthen (500 mcg tetracosactide with chitosan – Nasacthin003) to be effective, reproducible and well tolerated. The next stage of our work was to test the formulation in healthy children, and this work was generously part-funded by BSPED research award and Pfizer.

Paediatric study: 24 healthy children (12 female), aged 3-15, were recruited and visited the Children's Clinical Research Facility at Sheffield Children's Hospital on two occasions. At one of the visits they were randomised to receive either high-dose (145mcg/m², N=12) or low-dose (1 mcg, N=12) intravenous Synacthen and at the other Nasacthin003 (N=24). The nasal formulation was administered using a mucosal atomizer device (Teleflex, Wayne, CA, USA). During each 3-hour visit, 14-paired blood and saliva samples were taken and measurements of plasma Synacthen (EIA), plasma cortisol (immunoassay) and salivary cortisol and cortisone (LC-MS/MS) were made. Volunteers were dexamethasone suppressed enabling measurement of Synacthen on an ACTH EIA.

Results: The paediatric results were very similar to those seen in our adult male volunteers, at all doses. The intra-individual reproducibility demonstrated, as it did for the adult males, that the three different doses/formulations of Synacthen gave clinically almost identical responses at 30 minutes. The only difference was the pharmacokinetic analysis, which revealed higher exposure in children compared with adults, due to smaller body size. Exposure was higher for Nasacthin003 compared to 1 mcg IV but lower compared with 250 mcg IV and therefore likely to be a dose that delivers a maximal adrenal stimulus. Salivary cortisol and cortisone had a close and reliable relationship with serum samples. Salivary cortisone was the more sensitive marker of adrenocortical response at lower values. Nasal Synacthen was well tolerated and there were no adverse events during the study.

Benefit to applicant:

The BSPED Research Award was the start of a mini-snowball of success. I was awarded a University of Sheffield Clinical Lecturer pump priming award, directly off the back of it, and I have no doubt it contributed to success in three further grant applications: MRC, Academy of Medical Sciences and The Children's Hospital Charity – totaling £167,000. The success of the study has resulted in further grant funding (MRC), a patent application and industry supported financial and expert advice to support an application for regulatory advice to the MHRA. The project has been shortlisted for a Medipex NHS Innovations award (October 2018). I performed

this work as an NIHR Academic Clinical Lecturer but have recently been appointed as a consultant in paediatric endocrinology at Sheffield Children's Hospital and Senior Clinical Lecturer (fixed term) at The University of Sheffield. The work has led to collaborations both within the University of Sheffield and outside and I am fortunate to have support from senior academics to continue the research and work towards a permanent university appointment. These collaborations have additionally led two recent publications and ongoing/developing projects.

Benefit to department/institution

Both the Endocrinology department at Sheffield Children's Hospital and the Department of Oncology and Metabolism within Sheffield University have long-standing interests in adrenal medicine and adrenal drug development. This work, and the invited presentation at BSPED 2017, has helped to further the Sheffield's reputation for adrenal work and Synacthen tests. I have oral presentations at EPSE and BES in 2018.

Benefit to endocrinology

The success of the nasal administration of a novel formulation of Synacthen in adults and now children was the first step in a work-stream, which aims to develop the non-invasive SST clinically in addition to using it as an important research tool. A validated non-invasive SST has both commercial application and would remove the need to dilute the 250 mcg/ml formulation, which we have shown to be highly variable². The invasive nature of the current diagnostic test makes large cohort research impracticable. I hope that a validated non-invasive alternative to the current SST will enable tests to be carried out in both the outpatient and community settings. It will be more patient-friendly and more cost-effective, negating the need for daycare facilities and specialised personnel to carry out the test. It will allow the generation of robust normative data and ranges for the SST in paediatric populations at differing age, gender and pubertal stages. In addition much needed research on numerous aspects of adrenal suppression in different populations (e.g. neonates, patients on intensive care) will be made easier. The work will ultimately generate data to assist clinicians in establishing which patients on ICS are at greatest risk of AI and will facilitate evidence-based, consensus guidelines as to whom to consider testing with individual patient risk stratification.

I would like to thank BSPED and Pfizer for giving me this prestigious award.

References:

1. Elder CJ, Sachdev P, Wright NP. The short Synacthen test: a questionnaire survey of current usage. *Archives of Disease in Childhood*. 2012;97(10):870-873.
2. Cross AS, Kemp EH, White A, et al. International survey on high- and low-dose synacthen test and assessment of accuracy in preparing low-dose synacthen. *Clinical Endocrinology 2018 DOI 10.1111/cen.13359*.
3. Dorin RI, Qualls CR, Crapo LM. Diagnosis of adrenal insufficiency. *Annals of Internal Medicine*. 2003;139(3):194-204.
4. Kazlauskaitė R, Evans AT, Villabona CV, et al. Corticotropin Tests for Hypothalamic-Pituitary-Adrenal Insufficiency: A Metaanalysis. *Journal of Clinical Endocrinology & Metabolism*. 2008;93(11):4245-4253.
5. Magnotti M, Shimshi M. Diagnosing adrenal insufficiency: which test is best--the 1-microg or the 250-microg cosyntropin stimulation test? *Endocr Pract*. 2008;14(2):233-238.
6. Ng SM, Agwu JC, Dwan K. A systematic review and meta-analysis of Synacthen tests for assessing hypothalamic-pituitary-adrenal insufficiency in children. *Archives of Disease in Childhood*. 2016;101(9):847-853.
7. Ospina NS, Al Nofal A, Bancos I, et al. ACTH Stimulation Tests for the Diagnosis of Adrenal Insufficiency: Systematic Review and Meta-Analysis. *The Journal of Clinical Endocrinology & Metabolism*. 2016;101(2):427-434.