Institution: University College London

Unit of Assessment: 1 - Clinical Medicine

Title of case study: Buccal midazolam: a novel treatment for generalised convulsive seizures

1. Summary of the impact

As a direct result of work led by Professor Rod Scott and colleagues at the UCL Institute of Child Health (ICH) midazolam, administered by the buccal cavity, has become first-line therapy in the NICE pathway for treating children, young people and adults with prolonged or repeated generalised, convulsive seizures in the community. It also forms part of the APLS guidelines. Buccal midazolam has demonstrated clinical superiority over the previous paediatric standard of care (rectal diazepam) with an equivalent safety profile and greater patient/social acceptability. Its use is now widespread in Europe and the USA and a licensed preparation is now available.

2. Underpinning research

Convulsive status epilepticus (CSE), where epileptic seizures last at least 30 minutes, is the commonest neurological medical emergency in childhood and is associated with significant morbidity and mortality. For many years, a rectal preparation of diazepam was the most commonly recommended treatment for this condition, but this route was unacceptable to many parents and carers and was associated with treatment delay and avoidance, increasing the risk of intensive care admission for treatment of status epilepticus. As most seizures start in the community setting, a safe, effective and socially acceptable agent that can be administered by emergency medical technicians and parents/carers was required. We therefore developed **buccal midazolam** as an alternative to rectal diazepam

Our initial studies (1996–9) evaluated the pharmacokinetics and pharmacodynamics of midazolam (midazolam maleate; a benzodiazepine) administered via the buccal route, using blood sample and electroencephalography (EEG)-based methods, and demonstrated both the drug's easy absorption and rapid effect on the brain **[1]**. Once we had determined the correct dose, we carried out a randomised controlled trial comparing buccal midazolam with rectally administered diazepam. In this study of 79 prolonged seizures in children with very severe epilepsy in a residential school setting, we showed that buccal midazolam was at least as effective as rectal diazepam, and was more socially acceptable **[2]**. Subsequent trials in Europe and Africa have confirmed our findings, and have even demonstrated clinical superiority (seizure termination rate) to rectal diazepam in certain circumstances, along with significantly quicker administration and greater acceptability.

Our research has subsequently moved to exploring the epidemiology of status epilepticus and whether status epilepticus can damage the brain. In 2002 we established the North London Convulsive Status Epilepticus in Childhood Surveillance Study, in which we prospectively collected data on the management of CSE in the community. We demonstrated a low pre-hospital treatment rate (61%) for CSE, with termination of only 22% of episodes. For each minute of delay from CSE onset to arrival at Accident and Emergency, there was a 5% increased risk of seizures lasting >60minutes with attendant risk of adverse outcomes and requirement of higher levels of care (intensive care) **[3]**. This work also confirmed that status epilepticus is common and that the range of causes differs in children when compared to adults **[4]**.

In other research, we have shown that status epilepticus leads to swelling of the hippocampus and that part of the brain subsequently fails to grow as expected during childhood **[5]**. We have also shown that status epilepticus is associated with learning difficulties and difficulties with memory **[6]**. As at least part of these difficulties result directly from the prolonged seizure, this work further demonstrates the need for treatments such as buccal midazolam.

3. References to the research

[1] Scott RC, Besag FM, Boyd SG, Berry D, Neville BG. Buccal absorption of midazolam: pharmacokinetics and EEG pharmacodynamics. Epilepsia. 1998 Mar;39(3):290-4. http://dx.doi.org/10.1111/j.1528-1157.1998.tb01375.x

[2] Scott RC, Besag FM, Neville BG. Buccal midazolam and rectal diazepam for treatment of prolonged seizures in childhood and adolescence: a randomised trial. Lancet. 1999 Feb 20;353(9153):623-6. http://dx.doi.org/10.1016/S0140-6736(98)06425-3

[3] Chin RF, Neville BG, Peckham C, Wade A, Bedford H, Scott RC. Treatment of community-onset, childhood convulsive status epilepticus: a prospective, population-based study. Lancet Neurol. 2008 Aug;7(8):696-703. http://dx.doi.org/10.1016/S1474-4422(08)70141-8

[4] Chin RF, Neville BG, Peckham C, Bedford H, Wade A, Scott RC; NLSTEPSS Collaborative Group. Incidence, cause and short term outcome of convulsive status epilepticus in childhood: prospective population based study. Lancet 2006; 368: 222-9 http://dx.doi.org/10.1016/S0140-6736(06)69043-0

[5] Scott RC, King MD, Gadian DG, Neville BG, Connelly A. Hippocampal abnormality after prolonged febrile convulsion: A longitudinal MRI study. Brain 2003; 126(11):2551-7 http://dx.doi.org/10.1093/brain/awg262

[6] Martinos MM, Yoong M, Patil S, Chin RF, Neville BG, Scott RC, de Haan M. Recognition memory is impaired in children after prolonged febrile seizures. Brain. 2012 Oct;135(Pt 10):3153-64. http://dx.doi.org/10.1093/brain/aws213

4. Details of the impact

As a result of the underpinning research described above, buccal midazolam has become the drug of choice for the treatment of status epilepticus in the community, quoted in guidelines as part of the care pathway for status epilepticus. It was included as first-line therapy in the Advanced Paediatric Life Support (APLS) status epilepticus algorithm for the first time in 2005 **[a]**. In the same year, the Scottish Intercollegiate Guidelines Network recommended the same, citing our study directly **[b]**.

Both available pharmaceutical formulations of buccal midazolam have arisen as a result of work conducted at UCL. The first, Epistatus (midazolam maleate), was developed by Scott and Neville at ICH, and was brought to market under a commercial licence agreement between UCL Business and Special Products Ltd **[c]**. It has been employed clinically for over 10 years, being manufactured under a 'specials' licence issued by the MHRA. The second, Buccolam (midazolam hydrochloride), arose from work conducted at UCL School of Pharmacy and resulted in the foundation of Therakind Limited, a spin-out company designed to develop the product further**.** In 2010, a controlling interest in Therakind was sold to ViroPharma Inc. **[d]**, and in 2011, Therakind was granted a centralised Paediatric Use Marketing Authorisation (PUMA) by the European Medicines Agency (EMA) for Buccolam as a treatment of prolonged acute seizures in individuals 3 months to 18 years of age, the first of its kind **[e]**. The pharmacokinetic and pharmacodynamic properties of Buccolam described within the EMA application cite and rely upon the initial data generated on buccal midazolam at the ICH [1, above] **[f]**.

This authorisation has allowed distribution and access to Buccolam to the one million children and adolescents with epilepsy in Europe. Importantly, as Buccolam is a licensed product (unlike almost all other paediatric prescriptions), it is easier to obtain as a repeat prescription in the community rather than having to return to secondary or tertiary care – a significant advantage for patients/caregivers.

In 2012, buccal midazolam was recommended in NICE Clinical Guideline 137 on Epilepsy as first line therapy for treating children, young people and adults with prolonged or repeated generalised, convulsive seizures in the community **[g]**.

In addition to the inclusion in National Guidelines, buccal midazolam is included in many local guidelines for treatment of status epilepticus in the UK, for example North Bristol NHS Trust **[h]** and Great Ormond Street Hospital **[i]** and in other parts of the world **[j]**. The charity Young Epilepsy report that: "*Professor Scott's work on buccal midazolam has fundamentally changed practice in the management of status epilepticus. The research has led to the development of a new product that has not only proven to be an effective drug therapy for status epilepticus but also a more socially acceptable method of administration*" **[k]**. Buccal midazolam has now clearly superseded rectal diazepam as the drug of choice for treating status epilepticus in the pre-hospital setting **[l]**.

Scott and colleague have worked with the charity Young Epilepsy to develop training programmes for professionals and schools on all aspects of epilepsy in children, including training packages for the administration of emergency medication.

Benefits are not isolated to clinical metrics such as seizure termination rate, requirement for hospital or intensive care admission. Patients and their care-givers are afforded a higher quality of life through freedom of activity, retention of dignity and security in the knowledge that they may safely give/receive an effective treatment. The Scottish Medicines Consortium approved buccal midazolam in Scotland in 2012 and estimated that for the approximately 1,000 patients who will receive it annually there would be a cost saving on the drugs budget of £100,000 per annum **[m]**.

5. Sources to corroborate the impact

[a] Advanced Paediatric Life Support (APLS), status epilepticus guidelines. https://www.apls.org.au/sites/default/files/uploadedfiles/Algorithms%20-%20Status%20Epilepticus.pdf

[b] SIGN National Clinical Guideline 81: Diagnosis and management of epilepsies in children and young people. http://www.sign.ac.uk/pdf/sign81.pdf See p. 21 and ref. 212

[c] Commercial agreement between UCLB and Special Products Ltd. http://www.sciencebusiness.net/news/75300/UCLB-and-NCYPE-announce-a-commercialisation-agreement-with-special-products-limited-for-Epistatus

[d] http://www.therakind.com/news/sale-interest-product

[e] Award of PUMA for Buccolam®. http://www.therakind.com/news/granted-european-marketing-authorisation-treatment-acute-seizures

[f] European Medicines Agency marketing authorisation. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002267/WC500112312.pdf

[g] Guidelines on the diagnosis and management of the epilepsies in primary and secondary care National Institute of Health and Clinical Excellence, 2004, update 2012 http://guidance.nice.org.uk/CG137/Guidance/pdf/English. See Appendix N, ref. 126

[h] http://www.nbt.nhs.uk/sites/default/files/filedepot/incoming/Buccal%20midazolam%20NBT002519.pdf

[i] http://www.gosh.nhs.uk/medical-conditions/medicines-information/buccal-midazolam/

[j] For example, in Australia: http://www.rch.org.au/kidsinfo/fact_sheets/Buccal_midazolam/.

[k] http://youngepilepsy.org.uk/ Supporting statement from Director of Operations, Young Epilepsy. Copy available on request.

[l] Sutcliffe A and Bhome R. Buccolam® (buccal midazolam) for acute, prolonged seizures in

children: a new treatment option. British Journal of Clinical Pharmacy. 2012;Sept:e1-4 http://www.clinicalpharmacy.org.uk/images/stories/Article_1_Indesign__copyright.pdf

[m] http://www.scottishmedicines.org.uk/files/advice/midazolam_Buccolam_FINAL_Jan_2012_Amended_310112_for_website.pdf