



Delving into data

Even before the Domesday book, man was collecting and analysing data in order to describe his condition. The advent of the computer brought the ability to design and operate databases within the grasp of every clinical scientist.

We can all appreciate the importance of large epidemiological studies of diseases and their treatment in guiding and informing research. For example, the hypothesis that the increased mortality in hypopituitarism is due to growth hormone deficiency was generated by studying mortality in a cohort of patients who had undergone surgery for pituitary tumours. The challenge, however, is to define the rules required to gather, process, fund and interpret the massive volume of data that is now being collected in national and international databases.

In this themed issue, we have asked representatives from the management boards of four data-collecting projects to give us some insight into the structure of their studies. KIMS and HypoCCS are both international operations with international boards, yearly meetings and budgets that must exceed millions of pounds, whereas CaHASE and the UK National Acromegaly Database are national operations run on relatively small budgets through the Society for Endocrinology. We are lucky to have received four excellent articles, and hope that they will stimulate a debate within the Society on how to develop and manage the clinical databases of the future.

RICHARD ROSS

HypoCCS: GH replacement in adults

Treatment of adults with growth hormone deficiency (GHD) is very different from treatment in childhood. Experience with adult GHD is limited (the indication was registered in Europe only in 1995), and results cannot be extrapolated from children. For this reason, Eli Lilly and Company committed to a long-term observational study, the Hypopituitary Control and Complication Study (HypoCCS).

The objectives of observational studies include monitoring of safety under routine clinical conditions (including modalities which can influence drug efficacy and safety like indication, dosage, duration and interaction with other treatments); investigation of special risk groups (the elderly, co-morbidity); and assessment of the effect of treatment on outcomes (clinical, quality of life, economic).

These criteria could obviously apply to a study of adult GH replacement. Indeed, adult GHD observational studies have already contributed significantly to optimising treatment, including improved diagnostic and dosing algorithms, and the ongoing assessment of the efficacy and safety profile. However, adult GHD treatment, like almost all endocrine treatments, means lifelong replacement. So, based on our current knowledge of adult GHD and hypopituitary disease, the risks associated with the underlying disease and the cautions regarding therapy, the relevant questions can be specifically reformulated as follows.

1. Does long-term GH replacement have any effect on the incidence of any tumour type?
2. What are the long-term clinical benefits of GH replacement in terms of cardio-/cerebrovascular outcomes, quality of life, fracture incidence, and overall patient care?

Patients' data have been collected into the HypoCCS database since 1996, with patients from registration studies having been on drug exposure since 1991. The HypoCCS International Advisory Board (the experts who govern HypoCCS) soon recognised that the success of the study would be based on its ability to answer the above questions. This implies huge challenges, some of which are discussed here.

In observational studies, assessments are generally performed on person-years available in the database at a given time point. Whatever the study design, this approach may provide statistically significant results. However, the power may be significantly reduced if a prospective sample size calculation is not in place. This would bias the value of any assessment made, for example, on tumour incidence or cardiovascular outcomes under GH treatment. This was recognised in the

HypoCCS protocols that were initially implemented separately in Europe and the USA. Consequently, it was decided to merge the databases into a single protocol, where prospective power calculations are provided for two analytical approaches.

1. Comparison of the GH-treated cohort with a non-randomised group of GH-untreated patients. Non-randomisation creates potential bias, but differences between treatment groups can be balanced using appropriate statistical methodology (propensity score).
2. Comparison of outcomes of GH-treated patients with normal population references. Risk estimates for a given outcome are calculated from incidence rates in a normal reference population.

The HypoCCS study description provides details of sample size calculations for different outcomes using the two analytical approaches. In brief, 8000 patients will be required to detect a 50% increase in non-CNS cancer and a 33% decrease in cardiovascular complications using the first approach. With the second, assuming the database size remains constant, a follow-up until 2005 will be required to confirm a

continued on page 8

HypoCCS: GH replacement in adults

continued from page 7

standard incidence ratio (SIR) of 1.25 for all malignant neoplasms, and of 1.5 for cardiovascular diseases. An SIR of 1.5 will indicate a significant effect of GH treatment, as GH-untreated patients have an SIR twice that of the normal population.

The scenarios created by these calculations are important, because they clearly indicate the patient numbers and the observation time required to provide reliable answers in terms of long-term safety and efficacy of GH replacement in adults.

So, at least 8000 patients need to be followed for several years in order to be able to assess long-term outcomes in HypoCCS. Over 5000 patients have enrolled in the study, and data from over 21 000 patient visits have been collected. This amounts to over 10 000 patient-years' experience, but, as outlined above, it is clear that the follow-up time now needs to be increased to properly evaluate safety outcomes. The mean duration of follow-up is currently just over 2 years, but sufficient numbers exist to provide analysis of some variables up to at least 4 years. Such a large sample size generates major logistical challenges.

Given the observational nature of the study, the most critical (and resource-consuming) aspect is to ensure the quality of the collected data. Adverse events in particular are scrutinised for completeness and consistency and, where necessary, sites queried as they would be in a clinical trial, but without source data verification. Internally, we also conduct cross-validation checks with our pharmacovigilance database. With the advent of electronic data entry systems, we expect this laborious process to become streamlined, and for it to be possible to maintain high data quality even in an observational setting over many years. The provision of central laboratory services and quality of life instruments developed for hypopituitary patients improves the consistency of data used in outcomes analysis. For a multi-centre study like HypoCCS, it is necessary to use a robust data management process of the type available in pharmaceutical companies or in contract research organisations. This provides an audit trail and an infrastructure that allows access to the data in the appropriate format for analysis.

An advisory board reviews the data and makes recommendations for further analyses or changes to the data collection or analysis process. This group is charged with publication of periodic reports. Increasingly, bodies concerned with outcomes, like NICE in the UK, expect to be able to review such data, and thus

HypoCCS data were made available to NICE during its recent appraisal of adult GH replacement. The results of annual reviews provide feedback for contributing physicians and regulatory bodies, as well as a means of checking whether results fit current scientific opinion.

Resourcing requirements change as the study develops, but support is needed for: study set up and developments; site management (training, advice etc.); laboratory services; data collection, management (entry, queries, quality assurance etc.) and analysis; scientific steering committee for periodic result analysis; publications and reports; advisory board and consultants.

Studies like HypoCCS can provide valuable data sampled from the full spectrum of patients and outcomes. These complement data obtained in clinical trials, where the patient population is carefully selected. By comparing outcomes of treated patients with those of untreated groups, or with population norms, it is possible to increase the knowledge base that underpins our clinical practices significantly.

A F ATTANASIO, D J EDWARDS
ELI LILLY AND COMPANY

CaHASE: CAH beyond childhood

Congenital adrenal hyperplasia (CAH) can be a very distressing disease. Parents whose children are diagnosed at birth may have to come to terms with both their need for lifelong steroid treatment and, in females, the issues associated with ambiguous genitalia. CAH is characterised by a defect in one of the enzymes required for adrenal cortisol biosynthesis (usually 21-hydroxylase). There are varying severities of the disease, depending on the actual genetic defect inherited.

Most of the current literature on CAH concentrates on the disease in childhood. To try to redress this imbalance, the Society for Endocrinology recently conducted an audit of adults with CAH in the UK. This audit revealed a lack of consensus on methods of treatment and monitoring for adults with CAH (see *Journal of Endocrinology* 2000 **164** Suppl S38). There is a need for further research to improve treatment of these patients and thus their physical and psychological well-being.

Seven of the UK's leading endocrinologists have therefore come together to form CaHASE (or the Congenital Adrenal Hyperplasia Adult Study Executive). Its remit is to specifically address CAH in adult patients. The current members are John Connell (Glasgow), Gerry Conway (London), Ashley Grossman (London), Richard Ross (Sheffield), Paul Stewart (Birmingham), Helen Turner (Oxford) and Brian Walker (Edinburgh). In the future, CaHASE hopes to recruit new centres to make the project a truly UK-wide initiative.

CaHASE has now set up a multi-centre prospective study, to enable collection of informative data by investigating a suitably large cohort of UK adults with CAH.

The aim is to gather information on a range of clinical indices (treatment, body composition, biochemical analysis including lipid profiles and fasting insulin, and fertility), as well as the psychological/quality of life issues that affect adults with all forms of CAH (classical and non-classical, salt-wasting and non-salt-wasting, and all genotypes). The ultimate objective is to generate original research that will help to inform the day-to-day management of adults with CAH.

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CaHASE PROJECT MANAGER

CaHASE are very grateful to the Clinical Endocrinology Trust, who have supplied a grant for this project. Melissa Hines' article on page 11 addresses further issues associated with CAH.