Commentary

A different kind of case report: I

Editors have long argued over the merits and otherwise of publishing case reports, and the power of the anecdote, despite their lowly ranking in the hierarchy of evidence. Indeed, case reports remain ever popular; as journals have shied away from a regular case report section, so has grown an increasing number of online case report resources (see for example http://www.anaesthesiacases.org/).

The following account [1] by McGuire and Dalton is a case report in which the 'case' is not a clinical curiosity or challenge, but a project that started innocently enough but illustrates how easy it is for clinicians, keen to explore ways of improving the quality of care they provide, to run into trouble without realising it. McGuire and Dalton's tale should serve as a lesson to all those embarking on a clinical project, however it might be labelled, and emphasises how important it is to have: i) an understanding of the basic ethical principles involved in even the simplest study; ii) proper governance oversight of projects within organisations; and iii) awareness of the local regulatory processes and mechanisms.

I commend McGuire and Dalton for their openness and willingness to share their experience and the lessons learnt, after what was evidently a rather unpleasant experience – after all, that's the whole point of case reports, isn't it?

Competing interests

No external funding and no competing interests declared. I was the Editor-in-Chief to whom McGuire and Dalton refer in their editorial.

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Editorial

Sugammadex, airway obstruction, and drifting across the ethical divide: a personal account

We and two colleagues (one senior trainee, three consultants, with a combined anaesthetic experience of 74 years) recently embarked on what we considered to be a service evaluation relating to a tracheal extubation technique used in our head and neck surgery theatres. As clinicians with a special interest in anaesthesia for head and neck surgery, we aim to provide the best conditions for our surgical colleagues and we commonly evaluate drugs, equipment and techniques involved within this sub-specialty. The Difficult Airway Society (DAS) extubation guidelines [1] refer to advanced techniques in the management of the

perceived 'at-risk' extubation. As a group, we felt that these techniques are not always as straightforward as the literature might suggest. Hence, we viewed that exploring one of the techniques described, namely supraglottic airway device (SAD) exchange (Bailey's manoeuvre [2]), was justified. We decided to perform an evaluation of this specific technique in clinical practice as we felt there were very limited published data to support this as a good technique. The aim was to examine the efficacy and safety of the exchange. An essential component of performing a SAD exchange is to ensure an adequate depth of anaesthesia and/or neuromuscular blockade. Hence, we proposed to perform the exchange under deep general anaesthesia and full neuromuscular blockade using routinely used drugs, including desflurane, remifentanil and rocuronium, before reversal of paralysis with neostigmine or sugammadex. The aim was the demonstration of safe, smooth emergence from anaesthesia following head and neck surgery, without airway excitation.

We wrote to the Local Research Ethics Committee (LREC), seeking approval for the project without needing formal NHS ethical review. This was duly granted. We also sought and obtained approval by the Caldicott Guardian to use routinely recorded and patient/procedure-specific (non-identifiable) data to support the evaluation. We did not register the project with the Clinical Governance Department as it was our understanding that this was not a formal requirement, although we have subsequently learnt that the Research and Development Department does recommend such registration and that it was documented in the LREC literature (we, and colleagues we have since asked, were unaware of this at the time). In an attempt to obtain the most reliable data from the evaluation, we were advised to record a recommended technique including general anaesthetic drugs (Table 1) and SAD

Table 1 Criteria for inclusion/exclusion and anaesthetic technique.

Inclusion criteria	Ninewells West Block Theatre Suite (ENT/OMFS/plastics/ophthalmology) adult cases requiring general anaesthesia and tracheal tube
Exclusion criteria	Age < 16 years, BMI > 30 kg.m^{-2}, ASA physical status > 3, aspiration risk requiring rapid sequence induction
Anaesthetic technique	Propofol induction; remifentanil TCI (3 ng.ml^{-1} minimal effect site concentration at end of case); desflurane maintenance of anaesthesia (0.7 MAC minimal end-tidal concentration); rocuronium/vecuronium for neuromuscular blockade
Exchange according to DAS extubation guidelines	Suction airway under direct vision; place LMA Unique® and inflate cuff; deflate tracheal tube cuff and withdraw tube; attach breathing system to LMA Unique and ventilate using anaesthetic circuit, then Mapleson-C system Give sugammadex 200 mg or neostigmine 2.5 mg Observe accelerometer return to TOF ratio 90% and concurrently switch off remifentanil/desflurane Hand/machine ventilate lungs to confirm correct LMA Unique position Transfer to recovery area with LMA Unique and Mapleson-C system using spontaneous/assisted ventilation Remove LMA on awakening

ENT, ear nose and throat; OMFS, oral and maxillofacial surgery; LMA Unique, LMA is a registered trademark of The Laryngeal Mask Company Ltd, an affiliate of Teleflex Incorporated, San Diego, CA, USA; TCI, target-controlled infusion; MAC, minimum alveolar concentration.

Table 2 Difficult Airway Society extubation guideline: sequence for laryngeal mask exchange in 'at-risk' extubation [1].

1	Administer 100% oxygen
2	Avoid airway stimulation: either deep anaesthesia or neuromuscular blockade is essential
3	Perform laryngoscopy and suction under direct vision
4	Insert deflated laryngeal mask behind the tracheal tube
5	Ensure laryngeal mask placement with the tip in its correct position
6	Inflate cuff of laryngeal mask
7	Deflate tracheal tube cuff and remove tube whilst maintaining positive pressure
8	Continue oxygen delivery via laryngeal mask
9	Insert bite block
10	Sit patient upright
11	Allow undisturbed emergence from anaesthesia

exchange according to the DAS extubation guidelines (Table 2). This was not deemed to be a 'protocol': the drugs were all routinely used for such cases, and it was not felt that there was rigidity regarding their administration. The SAD exchange technique is used on occasion in our institution, but is not our 'routine practice' for the majority of cases.

Clinical events

The first two patients in the evaluation were given sugammadex following successful SAD exchange. Both developed apparent upper airway obstruction around 120 s after sugammadex 200 mg, having previously demonstrated an entirely patent airway with a square wave capnography trace and cuff seal pressures > 15 cmH_2O. Both resolved spontaneously over 2-3 min with positive end-expiratory pressure (and without arterial desaturation).

At this stage, we discussed the pathogenesis of this and reflected on the techniques and drugs used. We agreed to continue the evaluation and decided that, in subsequent patients, examination of the larynx with a flexible fibreoptic endoscope was indicated after sugammadex to help ascertain the likely cause of the apparent obstruction.

We were uncertain of the reasons for the airway obstruction – was it simply related to inadequate depth of anaesthesia? In deciding to examine the glottis endoscopically in subsequent patients (something we do occasionally as part of our anaesthetic technique in head and neck surgery), we were unconsciously straying from the proposed project and technique. We did not discuss with subsequent patients any potential risk of the technique following the adverse event in the first two cases. At the time, this did not feel like an irresponsible decision, nor was it an attempt to disregard our ethical responsibilities. We proposed to continue the evaluation, with what we considered to be meticulous airway management, involving two senior head and neck anaesthetists planning the technique and present at all times, delivering smooth, safe anaesthesia with optimally maintained oxygenation throughout and quantitative neuromuscular monitoring to ensure complete reversal of paralysis.

We proceeded with the evaluation, curious to explain our unexpected finding. Patient 3 had the same anaesthetic as the previous two, with the same pattern of airway obstruction after sugammadex administration. A fibrescope was inserted and we noted that the vocal cords were completely closed. This again self-resolved without arterial desaturation. We then made subtle variations to the anaesthetic drugs administered. Patient 4 had fentanyl rather than remifentanil; patient 5 received sevoflurane maintenance rather than desflurane; patient 6's neuromuscular blockade was reversed with neostigmine rather than sugammadex; patient 7 underwent SAD exchange 'unparalysed' (train-of-four (TOF) ratio > 90%); patient 8 had a volatile-free anaesthetic with propofol by target-controlled infusion (TCI), and patient 9 had propofol, rocuronium, fentanyl, sevoflurane and sugammadex. All patients who received sugammadex experienced very similar transient upper airway obstruction following administration, regardless of any changes in other anaesthetic drugs. One patient experienced arterial desaturation to 90% which resolved rapidly; no other patients experienced any desaturation. The patient receiving TCI propofol rather than volatile agent appeared to have less airway obstruction, while those receiving neostigmine or no reversal had no obstruction. Three patients underwent fibreoptic examination of the glottis after sugammadex and all demonstrated powerful adduction of the vocal cords, commencing ~2 min after sugammadex and coinciding with a return of TOF ratio > 90%, i.e. confirmed full muscle power. This resolved spontaneously and entirely after a further 3 min. We concluded that the administration of sugammadex was resulting in a rapid increase in upper airway tone.

At this point, we decided to cease the evaluation, now convinced that we had indeed unearthed an adverse effect of sugammadex in patients with unintubated tracheas. We proceeded to write up our findings and submitted what we termed a 'case series audit' to *Anaesthesia*.

Editorial review

After a slightly protracted wait for a reply (the reason for which soon became clear), we received a disappointing, but detailed letter from the Editor-in-Chief of *Anaesthesia*; 'disappointing' because, on reading the first paragraph, we realised that we had a (big) problem. The editorial team had raised some 'serious ethical issues'; a number of not unreasonable concerns were listed and several key questions were asked. These

included: whether we had halted the study and sought advice from the LREC after the initial three patients; whether we had discussed with them the change in 'protocol'; whether we had reported the adverse findings locally; whether the risks of Bailey's manoeuvre were discussed with patients; and whether patients had given consent for fibreoptic examination of the glottis. There was also concern whether this technique was genuinely 'routine' practice for such surgery. What exactly constitutes *routine practice* is a moot point. Anaesthetists in our institution do use Bailey's manoeuvre for some 'at-risk' extubations, but we accepted that it was not routine enough in our unit to justify this project as a 'service evaluation' for this group of patients.

All of these concerns and queries were reasonable and we all felt contrite and somewhat naïve in equal measure. Our patients had given written consent for fibreoptic examination, but otherwise we had a negative response to the remainder of the aforementioned queries. However, we also felt that we had given extremely safe anaesthesia throughout, with optimal patient care, and that our finding may be of significant clinical relevance to the general anaesthetic community.

Documentation was requested – all the correspondence leading to the LREC's waiver of the need for a formal ethical application and all other communications with the Research and Development Department, Clinical Governance Department and Caldicott Guardian. We had a very helpful telephone conversation with the Editor-in-Chief, who, by that stage, had already spoken with the LREC chairperson in our Trust.

The issue of patients' consent was again raised. One could argue that the LREC's opinion was that formal ethical review was not required. However, the reviewers felt that consent was still indicated in this case, particularly if their care was not considered 'routine'. This issue became more acute once complications had arisen and in retrospect, it was apparent that at this stage it had been unwise of us to continue without seeking ethical advice.

We attempted to answer all the questions asked, but our failings remained evident and concerning, perhaps now more for our Trust rather than the Journal. Our LREC chairperson voiced similar concerns to those of the editors, centred on what was deemed routine practice in our patient group and failings in communication with them and the LREC.

In our defence, we cited our absolute commitment to safe anaesthesia, but also our comfort dealing with all of the complexities of anaesthesia for head and neck surgery, including challenging airway management scenarios such as these. However, we acknowledged that we had become distracted by the unexpected clinical finding. We also felt that there was a lack of clarity regarding the exact processes and regulations that come under the academic umbrella of research/audit/service evaluation. Arguably, this uncertainty extends into issues of consent, risk evaluation and explanation, particularly for academic work not deemed to be research. Was this project service evaluation, case series audit or scientific research? Despite attempts to provide clear guidance, there are many grey areas and it can be difficult to define what some have described as indefinable [3]. Were we unwise to formulate a 'protocol' for general anaesthesia and SAD exchange, i.e. did this essentially make our project *research*? We didn't consider at any stage that we were in fact performing research.

Local events

It was agreed that a Local Adverse Event Review (LAER) would take place involving the clinicians concerned, our Anaesthesia Clinical Director, representatives from the LREC, Risk Management and Clinical Governance Departments and two local, non-anaesthetic consultant colleagues. The resultant report criticised our failure to seek consent or provide written information of the procedure and any potential risks, our failure to stop the evaluation once a problem had been observed, and our decision to alter the proposed technique without discussion with the LREC. However, the panel acknowledged that we felt we were working under the umbrella of service evaluation. We received support from our non-anaesthetic colleagues, who stressed that our desire to improve clinical practice by developing skills and techniques was evident and has been a part of our practice for many years. There was also acknowledgement that, unlike research projects within the remit of the LREC, where stringent supervision takes place, there was no such facilitation of our project and that perhaps this could be more explicit

in future work of this ilk. The LAER concluded with the recommendation to proceed to a Significant Clinical Event Analysis (SCEA).

The SCEA was chaired by the Trust's Medical Director. The stated aims were to: establish the background and sequence of events surrounding the case; identify the underlying contributory factors in Trust management and organisational systems; identify lessons learned; and develop a list of recommendations to prevent similar, future incidents. Finally, the SCEA required communication of any findings and recommendations amongst relevant individuals and the organisation as a whole.

The process began with positive aspects. These included our completing a *British National Formulary* 'yellow alert' card and informing the producers of sugammadex of our findings before submitting the original manuscript. Despite our failed local communication of the adverse finding, our initial contact with the Caldicott Guardian and LREC was commended, as were our regular discussions within the project team and liaison with clinical colleagues. As clinicians, we were all up-to-date with our personal appraisals and Good Clinical Practice training, and it was noted that patient safety had been paramount in our clinical conduct throughout the evaluation. The criticisms had largely been covered during the LAER and were summarised before agreement of the key learning points and actions required. The main learning point related to our transition from evaluation/improvement project to what was essentially clinical research: all that we failed to do should have been done! We agreed to design an online module for education within the Trust to help others avoid our mistakes; this would clarify the distinction between service evaluation, audit and research, and stress what is required for each in terms of ethics, governance, consent and communication. The SCEA also asked our Clinical Governance Department to review its processes of project surveillance, support and guidance in order to prevent similar mistakes by overzealous clinicians. Finally, we were requested to write to the patients we had evaluated, explaining what had happened and offering each the opportunity for further discussion. All consented to the publication of this article.

Conclusion

As two of the clinicians involved in this whole process, we have to stress that we all felt extremely supported throughout, both locally and by the Editor-in-Chief on behalf of *Anaesthesia*.

The submitted manuscript to *Anaesthesia*, titled 'Unexpected airway obstruction following sugammadex', described our nine cases in sequence and our perception of the accumulating evidence that we had witnessed laryngospasm secondary to sugammadex administration. We included 'before and after' photographs as the glottis changed from full patency to opposed vocal cords. Video footage, via the fibrescope through the SAD, was the most compelling of all the evidence. The apparent clarity of our finding and our interpretation of its potential significance further blinkered us. At the outset, it had never been our intention to publish our data. It had been planned as a small service evaluation project that might have provided data that could be presented locally or perhaps nationally. Our decision to publish subsequently, as a case series, related to our desire to share an unexpected and potentially significant finding with the anaesthetic community. A case report by Curtis et al. [4] describes use of sugammadex in a 'can't intubate, can't ventilate' scenario. They stated that "*rocuronium induced neuromuscular block was successfully reversed by sugammadex as evidenced by the restoration of diaphragmatic movement, the ability of the patient to move her limbs, and the presence of a train-of-four nerve stimulation with no fade; however, ventilation was still not possible*". An emergency cricothyroid puncture was required for rescue oxygenation. Another case report by Paton et al. [5], in which sugammadex was used following a failure to ventilate, states: "*Approximately 1 minute after receiving sugammadex (3-4 minutes post induction), the patient began to show signs of spontaneous respiratory effort. Eye opening occurred shortly thereafter. Throughout this period, oxygen saturation remained 100%. There then followed a difficult few minutes with improving spontaneous effort against a degree of upper airway obstruction.*" We consider that both these cases fitted into the timescale we observed for laryngospasm secondary to sugammadex, with the latter a contributing factor to the problems encountered.

Finally, the purpose of this article is two-fold: to lay bare the perils

of performing small scale academic work; and, once again, to raise the possibility that a drug used relatively commonly in anaesthetic practice may have a serious unwanted effect.

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Competing interests

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Commentary

A different kind of case report: II

The issues and lessons raised by McGuire and Dalton in their brave account [1] are multiple: the difficulty distinguishing between 'research' and 'non-research'; how those close to something are not in the best position to see the bigger picture; the potential harm arising from new drugs and techniques; and the danger of including what may seem sensible advice into guidelines without a good evidence base.

I have long argued against the current position in this country whereby projects are classified, and the need or otherwise of formal ethical review is determined, according to what they are called, instead of what they actually involve [2, 3]. Thus a 'service evaluation' or 'staff survey' is exempt from formal review whilst 'research' (whatever that means) is. In the USA, for example, the situation is clearer: any project involving human subjects, whatever its nature or title, requires independent review [4]. Advice on whether a study should be called this or that, or whether research ethical approval should be sought (or should have been), is probably the most common request I used to receive as Editor-in-Chief, illustrating how confusing and frustrating it can be for investigators and authors – and editors – within the current system. Looking back at my time with the Journal, my only surprise really is that there haven't been more cases like that described by McGuire and Dalton.

I recall a manuscript many years ago, describing experimental administration of a therapeutic drug intravenously to two people, both of whom were the paper's authors, and the discussion amongst the editorial team that ensued. The ethical issues raised by self-experimentation are complex [5], but at their core is the (admittedly paternalistic) concern that investigators often need protecting from themselves and from their own enthusiasm. When those who may be harmed by experiments are patients, then the need to protect study participants becomes greater, hence the long-established requirement for local regulatory mechanisms to oversee and manage such projects. As illustrated by McGuire

