common, with underestimation of blood loss and hyperkalaemia from transfusion of stored blood being the most common causes. Six of the medication-related arrests were associated with sevoflurane-related cardiovascular depression.

Congenital long QT syndrome is a condition resulting from mutations in cardiac ion channels, which may lead to potentially fatal ventricular tachycardia [5]. Several genotypes have been identified. Susceptible individuals with a normal QT may exhibit an acquired prolongation of the QT interval under adrenergic stimulation or when exposed to provoking drugs. Lists of drugs known to prolong the QT interval are maintained at http://www.qtdrugs.org. Stressors, such as heart block, hypokalaemia, hypomagnesaemia, acute myocardial infarction, subarachnoid haemorrhage and other central nervous system injuries, may increase the risk of developing torsade de pointes in the presence of a culprit drug. Whyte and colleagues concluded that although sevoflurane increases the duration of myocardial repolarization and prolongs the QT interval in children, susceptibility to torsade de pointes arises from increased transmural dispersion of repolarization. This appears to be unaffected by sevoflurane and therefore the incidence of torsade de pointes is likely to be minimal [6]. Nevertheless, it has been described during sevoflurane anaesthesia in a child [7] although in that case the QT prolongation was attributed to the homoeopathic use of caesium chloride supplements.

In conclusion, although QT interval prolonging effects of sevoflurane have been described, the incidence of developing life-threatening ventricular tachycardia is minimal. Therefore, most anaesthesiologists will not anticipate encountering such a life-threatening cardiac incident solely induced by sevoflurane, in a healthy child scheduled for minor surgery. The case we present however does prove that it can happen any time, anywhere.

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Drotrecogin alfa (activated): diffusion from clinical trials to clinical practice

doi:10.1017/S0265021508004468

EDITOR:
Ridley and colleagues present retrospective data on the use of activated protein C (APC) in five UK hospitals in 2002–2005 [1]. To identify patient groups that might benefit from APC the authors considered it more rational to use their cited approach rather than have further formal appraisal of the drug. The authors discuss the European Medicine Agency (EMEA) 2002 approval but, surprisingly, their crucial decision in early 2007 is not mentioned: the EMEA demanded a new randomized, placebo controlled trial of APC in severe sepsis to clarify the risk/benefit balance

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Accepted for publication 11 April 2008 EJA 5082
First published online 14 May 2008

of APC [2] in the currently indicated high-risk population [3].

This EMEA opinion, on the most rational way to proceed, reflects results of the trials requested by the FDA. The PROWESS follow-up trial showed no significant difference in the number of patients discharged home between APC and placebo groups [4]. The authors suggest that ENHANCE confirmed drug efficacy and safety. However, this has been seriously questioned: as a non-randomized, uncontrolled trial it was not designed to assess efficacy; compared with PROWESS the serious bleeding rates were greatly increased in ENHANCE (a NNT of 16 for a serious bleed) [5]. As the authors indicate, ADDRESS did not help APC and the drug's failure to demonstrate efficacy and safety in paediatric sepsis [6] raised further doubts around APC having any beneficial effect, even in adults [7].

It may be a particular concern that the authors' data included a relatively high proportion of surgical patients (50%) vs. PROWESS (455/1690: 27%). Original Phase II and PROWESS trial data showed a higher mortality in the surgical patients randomized to APC [8]. A later retrospective reclassification of PROWESS patients may be difficult to interpret [9]. With treated surgical patients in ADDRESS also having a higher mortality, there is a consistent trend towards poorer outcome, with APC administration, in almost 1500 surgical patients enrolled to all three placebo controlled trials in adults. It may be hazardous to imply that APC has an acceptable benefit/risk profile in this group of patients.

Finally, data from a small number of hospitals in 2002–2005 may not reflect current UK practice. Following recent trial results use may now be very low as in other countries: recent French data (2006) showed that APC was not used in 14 of the 15 ICUs surveyed [10]. Low usage will probably persist unless new trials demonstrate clear benefit in easily identifiable patient groups.

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Reply

doi:10.1017/S0265021508004456

EDITOR:
Thank you for the opportunity to respond to Dr Mackenzie. Dr Mackenzie is wrong to assert that we 'considered it more rational to use *our* cited approach rather than have further formal drug appraisal'. At the time of writing up our collective experience as the five largest UK users of drotrecogin alfa in severe sepsis [1], very little was known about the use of drotrecogin alfa in routine clinical practice. Moreover, it was far from clear that it was ethically justifiable to perform a further trial, given that the drug has been licensed since 2002 and is currently used in high risk cases around the world. The majority of intensive care units in the UK, and many intensivists now have some experience of using the drug. Use of the drug in the UK has remained constant

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Accepted for publication 11 April 2008 EJA 5082a
First published online 20 May 2008