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doi:10.1093/bja/aeu009

EDITORIAL V

‘For now we see through a glass, darkly’: the anaesthesia syndrome

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In this issue of the British Journal of Anaesthesia, Zand and colleagues1 revisit the isolated forearm technique (IFT) pioneered in obstetric anaesthesia by Tunstall.2 Their data are consistent with Tunstall’s early studies during anaesthesia for Caesarean section showing that 33–42% of patients may respond intra-operatively.2,3 Zand and colleagues1 made similar observations after rapid sequence induction with thiopental: 41, 46, and 23% of the subjects responded at laryngoscopy, intubation, and skin incision, respectively. Prima facie, these are potentially alarming statistics, raising questions over the ‘adequacy of anaesthesia’ provided during and after rapid sequence induction, and hence a thorough critique of their methodology is warranted.

Strengths of this paper include the standardized and clinically relevant approach (including drug dosing), relatively large

1 CONSciousness, Connectedness, IntraOperative Unresponsiveness Study (ConsCIOUS) Group: Anthony Absalom, Rom Adapa, Vincent Bonhomme, Mark Coburn, Robert D. Sanders, Gerhard Schneider, Jamie Sleigh, Rob Stephens.
sample size (n=61), and clear commands for the isolated forearm test. However, the authors used a seemingly more complex command structure than previously described. Patients were asked to ‘open and close their hand’, and the subsequent response was then graded. The above-mentioned frequencies of positive responses were for hand movements graded as either 1 (‘non-specific movement’) or 2 (‘firm flexing/clenching of the fist’). Whereas a Grade 2 response would typically have been referred to as a positive IFT response in previous studies, a Grade 1 response would often have been classified as a negative result. Hence, if only the Grade 2 responses are considered, the response rates are slightly lower: 29.5, 36, and 13% of the subjects responded during laryngoscopy, intubation, and skin incision, respectively. Nonetheless, even this more stringent definition of positive responses shows many patients responding under anaesthesia.

Of course these frequencies of responses may not be generalizable to other induction techniques, patient cohorts, or both. The goal of rapid sequence induction is to achieve a balance between cardiovascular safety and optimal ‘anaesthesia’ on the one hand, and rapid anaesthesia and airway protection on the other. This necessitates administration of an a priori determined anaesthetic dose, rather than careful titration of the dose to effect. Careful titration may, however, not be superior. The seminal study by Schneider and colleagues, showed that the response rates are slightly lower: 29.5, 36, and 13% of the subjects responded during laryngoscopy, intubation, and skin incision, respectively. Nonetheless, even this more stringent definition of positive responses shows many patients responding under anaesthesia.

Despite the study by Zand and colleagues including a relatively large cohort of patients, it remains possible that genetic or environmental factors did influence the results, limiting their generalizability to other institutions. Countering this, the consistency of the data with that found in other obstetric studies, and with our systematic review of all studies, is remarkable. Indeed the findings that the BIS is a poor predictor of IFT responsiveness and that relatively low BIS values are required to prevent IFT responsiveness appear similarly consistent. Zand and colleagues show that only very low BIS values (< 30) were associated with the absence of responsiveness to the isolated forearm test. Deep anaesthesia thus appears necessary to prevent IFT responsiveness after significant clinical stimuli such as laryngoscopy.

‘For now we see through a glass, darkly.’
1 Corinthians 13:12

The IFT offers a window into the complex neurobiology of anaesthesia. The variability in the patient’s response to standardized drug doses and stimuli suggest that the multi-dimensional phenomenon, which we term ‘anaesthesia’, actually is a syndrome of different effects. In order to explore the ‘anaesthesia syndrome’ in a more systematic manner, we have proposed some additional terminology. While IFT responsiveness was originally termed wakefulness, we would suggest that a more accurate description of this intra-operative awareness is ‘connected consciousness’. The reasons for our proposed nomenclature are that the IFT-positive subject usually does not actually appear overtly wakeful (‘eyes open’). Nevertheless, they remain ‘connected’ to their environment (they can follow commands) and they are conscious (they can communicate a response to the observer about their current experience). Another important difference between IFT responsiveness and wakefulness is poverty of spontaneous movement. During the IFT, the hand rarely moves spontaneously even after noxious stimulation, whereas in wakefulness, spontaneous movement would be the norm (Table 1). We have proposed a biological model (centred on the interaction of the basal ganglia and limbic systems with the corticothalamic network) to explain why patients do not move spontaneously, but retain goal-directed movement (the ability to follow commands), during the isolated forearm test.

The term connected consciousness is also useful, as it naturally differentiates the states of wakefulness, unconsciousness, and dreaming. In dreaming (disconnected consciousness), we are caught up in an internally generated experience. External sensory stimulation does not faithfully trigger an experience during a dream—we are unaware of our environment. As dreaming appears common during anaesthesia, and is typically a benign experience, it is important to be able to differentiate disconnected and connected consciousness. A monitor that is able to detect consciousness, but unable to differentiate between disconnected and connected consciousness, would detect dreaming, potentially prompting the anaesthetist to deepen the anaesthetic. This may be an unnecessary manoeuvre. What is required of a monitor is to detect whether the

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<th>Table 1 Multiple states of consciousness and responsiveness</th>
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<td><strong>Motor Response</strong></td>
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patient is experiencing surgery. Zand and colleagues’ data reinforce the fact that the BIS may not be able to do this.

**Understanding the ‘anaesthesia syndrome’**

The complexity of the neurobiology of the ‘anaesthesia syndrome’ is exemplified by the varying phenotypic effects of anaesthetic drugs on consciousness, connectedness, spontaneous movement, or goal-directed movement (Table 1). While, at present, we have no way of knowing whether the patients are unconscious under anaesthesia, in states such as burst suppression, it is likely that there is little conscious activity. However it is clear that even in unconscious states, reflex movement may occur. Conscious activity may be associated with disconnection (unawareness of the environment) such as during dreaming, or it may be connected to the environment, as is typical during wakefulness.

However, the association of these different states with movement is complex. Dreaming is not typically associated with spontaneous movement (with the exception of parasomnias) or goal-directed movement (e.g. following commands). Connected consciousness (such as wakefulness) may be associated with both; however, this is not always the case, for example, if there is a pharmacological ‘block’ in the system preventing movement. An obvious example is spinal anaesthesia blocking a motor response from the legs. However, we have proposed that, under a general anaesthetic, a ‘block’ in responsiveness may occur at the limbic level (where value is ascribed to an action, e.g. ‘is it worth responding?’), the basal ganglia (where action selection occurs), or the spinal level (where motor activity is controlled). We suspect that the poverty of spontaneous movement that accompanies connected consciousness under anaesthesia results from a combination of these effects. It appears that goal-directed movement may be preserved, at least in some subjects, under anaesthesia. The differences with catatonia are striking. In catatonia, spontaneous movement to pain but not verbal command may occur. Conscious activity may be associated with disconnection (unawareness of the environment) such as during dreaming, or it may be connected to the environment, as is typical during wakefulness.

Beyond insights into the anaesthesia syndrome, another challenging question that has been incompletely explored is the long-term significance of responsiveness detected by the positive IFT, but without subsequent recall. As observed by Zand and colleagues and confirmed in our systematic review, awareness with explicit recall is rare in IFT responders. However to our knowledge, long-term cognitive and psychological assessments in IFT responders without recall have not been completed, and so it is unclear whether this state has long-term consequences. Amnesia in the intensive care unit may be associated with an increased incidence of cognitive sequelae; therefore, it may be imprudent to assume that amnesia is protective in patients undergoing general anaesthesia. Finally, few would consider it morally acceptable to paralyse a patient with an amnesic dose of midazolam and a β-blocker (to control the haemodynamic response) as a surrogate of general anaesthesia; our aim should be to ablate the experience of surgery.

One proposed way of reducing IFT responsiveness is to modulate connectedness (the consciousness of external stimuli such as surgery) during anaesthesia, rather than merely induce complete unconsciousness with large doses of general anaesthetic drugs. The underlying hypothesis suggests that unperturbed noradrenergic signalling maintains connectedness during anaesthesia and is based on (i) the poor suppression of noradrenergic signalling during general anaesthesia (even though other neuromodulators such as histamine are suppressed), (ii) the high incidence of awareness of intra-operative events as assessed by the IFT, and (iii) the known biological effect of norepinephrine signalling in drawing attention to external stimuli. Indeed, norepinephrine acting through the ‘ventral attention network’ in the brain acts as a circuit breaker to redirect attention to external stimuli. As such, suppression of noradrenergic pathways, resulting in a reduced ability to focus on external events, appears to be a sensible end point of anaesthesia. It may represent one route to reducing isolated forearm test responsiveness.

The fact that the study by Zand and colleagues raises more questions than answers enhances rather than detracts from its value. Perhaps most critically, the work highlights deficits in our knowledge that require further action: (i) studies are required to define the longer-term consequences of IFT responsiveness and (ii) in the meantime, we should seek to reduce the incidence of IFT responsiveness for the sake of patient comfort. How these aims may be interpreted within the bounds of standard anaesthetic techniques such as rapid sequence induction requires both further data and more dialogue among the anaesthetic community.

**Declaration of interest**

R.D.S. has received speaker fees from Hospira, Chicago, USA and Orion Pharma, Turku, Finland and has received a small grant from Orion Pharma. Neither company had any role in the contents of this editorial.

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