Editorial

The remarkable memory effects of propofol

Not so long ago, the tried and true amnesic drug was diazepam, which was quickly replaced by midazolam when it became available. These drugs are often referred to as ‘prototypical benzodiazepines’, and the prototypical effect of greatest interest is well described by Sebel. He recounts the ability to eat dinner and have a conversation after a somnolent dose of ‘a benzodiazepine’, with no recollection of any bit of that transatlantic dinner the next day. This remarkable ability to wipe out episodic memory has been put to sinister use in the case of Rohypnol (flunitrazepam), which now has the unfortunate label of a ‘prototypical date-rape’ drug. It is an amazing state of affairs when a person can behave in essentially a normal fashion, yet have no recollection of any action, even traumatic ones, during this time period. Now it can be said that propofol is on the list of prototypical amnesic drugs.

In this issue of the BJA, Russell has clearly described a situation of preserved conscious awareness and ability to follow complex commands with little or no recollection of these events after the fact. He has also shown that this most interesting situation cannot be identified using a Narcotrend brain monitor (more precisely, whether the brain is awake or asleep cannot be identified). Quite conceivably, this could also be true for other depth of anaesthesia (brain function) monitors in current use. As Russell states: ‘To date, no anesthesia brain monitor has been adequately validated in the presence of muscle relaxants for the duration of surgery with reference to individual patients’.

Nordstrom and Sandin have reported a similar effect on memory during propofol administration in the clinical setting. In fact, anaesthesia practice crucially depends on the production of a state of awareness and ability to follow commands without recollection of potentially traumatic situations later. This strange state of affairs is induced for procedures such as awake intubation and intra-operative ‘wake-up’ tests. Many practitioners remember an experience of a patient opening their eyes and looking at them when they should have been fully asleep! A typical response in such a situation is to give a sizeable dose of a readily available sedative/hypnotic drug. The nervous practitioner was then reassured when no memory of this event was present at the post-operative visit. Such experiences may lead to the false impression that a large dose of an amnesic drug will wipe out memory before the drug is given—the much sought after retrograde memory effect. Such an effect has never been demonstrated in humans. In reality, ongoing anterograde amnesia was present as the declining amount of anaesthetic drug had reached a sedative concentration. In fact, if anything, sleep after an experience will improve memory of it.

Anecdotal and measured observations of amnesia with propofol lead to the question of what is it that we want to do? Though Russell focuses on the specific question whether consciousness is present, his descriptions of memory, or more correctly, the lack thereof for intraoperative events are very relevant. The important fact is that conscious awareness during surgery with muscle relaxation does not equate with horrible accounts of intra-operative awareness (the continuing low incidence of which is the focus of so much of the specialty’s and the public’s attention). The use of propofol as an amnesic drug has become possible because it can be given as a controlled i.v. infusion. Amnesia is present, as long as the pump functions correctly. Otherwise, it redistributes so quickly that periods of low drug concentration can easily occur, and then memory of events is possible. Falling drug concentrations at the end of the procedure likely account for the instances of memory reported by Russell. Yet, these recollections do not seem at all unpleasant—a dog walking on your stomach is quite different than being buried alive. It is interesting that the recollections reported by Russell are those that may be considered salient—‘this is Dr Russell…’, or a good dream about a daughter, as opposed to ‘green pear’. The brain does indeed respond more to personally relevant information, as measured by fMRI imaging during sleep.

Thus, as we understand pharmacology and physiology better, and have better tools such as target controlled infusion pumps and monitors that measure the brain’s...
response to these drugs, do we need to aim for a continuous state of unconsciousness? It will be a brave new world when we can tell a patient undergoing a breast biopsy ‘don’t worry—you won’t remember this’ with confidence, rather than dialling up the propofol until they are snoring away. Russell makes the excellent point that we need to predict response in a given individual. Probabilities do not mean much when it is you at the end of the i.v. tubing. How your neighbour fared in a similar situation matters little at such a time. The way to individual predictability is understanding how amnesic drugs work in the brain and then developing a monitor to measure this effect.

What is known about how propofol produces its amnesic effect? The translation of observations of Russell, and Nordstrom and Sandin into measurable responses that can inform us of mechanisms of drug action on memory is a difficult one. Using memory paradigms such as a continuous recognition task, or deep vs shallow processing, we have shown that information is encoded into long-term memory in the presence of propofol. However, this information is then forgotten over time.9 Looking at task related changes in regional cerebral blood flow, there is preliminary evidence that the brain’s response to encoding of new information is normal in the presence of propofol, even when this information is then later forgotten.10 These findings make sense of observations such as Sebel’s transatlantic dinner. But, as with Churchill’s Russia, why the brain forgets what it has learned when an amnesic drug is present is still a riddle wrapped in a mystery inside an enigma.

Russell has described what could be a ‘gold-standard’ for critical testing of depth of anaesthesia (brain function) monitors. The realization that, in itself, being aware but having no memory of the episode is not a traumatic event allows ethical research to be done in the setting of the surgical procedure itself. As most brain function monitors have been developed using surrogate measures, such as responsiveness during induction of anaesthesia or in volunteer studies, or by explicit recall after surgery, it is unclear how other monitors would fare in Russell’s operating theatre.

Also unclear is the influence of the combination of epidural or spinal anaesthesia with a general anesthetic on the ability to remember stimuli. It has been well demonstrated that negative stimuli are remembered better than pleasant ones, secondary to hormonal responses affecting the amygdala, which in turns affects the ability to remember events.11 This differentiation is exaggerated at sedative concentrations with certain drugs.12 Such modulatory influences on memory formation during anaesthesia is a question of current interest.13 14 On the other hand, spinal or epidural anaesthesia, and possibly drugs such as dexmedetomidine, may be expected to blunt hormonal responses and diminish influences of the amygdala on memory formation, as is the case with beta blockers.15 Thus, memory for events in Russell’s paradigm may be greater without epidural blockade, as responsiveness of the brain is influenced by the spinal cord.16

A welcome portion of Russell’s study is data on the ease of use of the Narcotrend monitor in a clinical situation. The information about time required and the number of electrodes needed to get the system working or the time the screen was blank during the case is very helpful and is reminiscent of my own experiences with various brain function monitors. It is a hopeful transition to see studies not only examine important scientific questions but ones important to the practising clinician as well.

Based on Russell’s keen observations, one can state that the Narcotrend monitor cannot reliably detect the transition from consciousness to unconsciousness in individual cases. However, this statement needs to be tempered with the fact that no depth of anaesthesia monitor may be able to do this in Russell’s setting. I have no doubt that monitors can be refined to work well in Russell’s paradigm, but then the question is whether we want a monitor to detect unconsciousness or one that detects amnesia?

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References
1 Sebel PS. Memory during anesthesia: gone but not forgotten? [editorial; comment] Anesth Analg 1995; 81: 668–70
6 Mathews DM, Rahman SS, Cirullo PM, Malik RJ. Increases in bispectral index lead to interventions that prevent possible intraoperative awareness. Br J Anaesth 2006; in press
7 Glass PS. Prevention of awareness during total intravenous anaesthesia [letter; comment]. Anesthesiology 1993; 78: 399–400
12 Pryor KO, Veselis RA, Reinsel RA, Feshchenko VA. Enhanced visual memory effect for negative versus positive emotional content is potentiated at sub-anaesthetic concentrations of thiopental. Br J Anaesth 2004; 93: 348–55

