**Science vs supposition: the case of target-controlled propofol infusion**

Editor—I continue to be confounded by the use of target-controlled propofol infusion (TCI) dosing paradigm as an accepted basis for presenting the scientific study in anaesthesia journals without specific documentation of instantaneous and total dose infusion rates, in conjunction with body weight and duration of infusion at the study point. Although TCI may be utilitarian in the clinical administration of drug for clinical anaesthesia, the recent study by Yufune and colleagues\(^1\) clearly documented a real and important departure from scientific measured blood levels using the ‘black box’ technology of TCI. This non-clinical study was also undertaken in patients removed from surgical stimulation: surgery imparts significantly sympathetic responses which change haemodynamics and, expectantly, drug kinetics. Although bispectral index (BIS) ranged between 25 and 50 with the average BIS near 35–40, in spite of TCI set for induction at 6 s then at 90 s reduced for the study period to 4 \(\mu\)g ml\(^{-1}\), this BIS indicates significant overdose, as the ‘Target/desired’ BIS level for minimizing drug administration in clinical anaesthesia is the Target of 50–60.

TCI infusion rates were apparently chosen to reflect surgical needs, but were based on a paradigm for children per reference and resulted in measured median blood levels of 2.5 \(\mu\)g ml\(^{-1}\), instead of the set 4 \(\mu\)g ml\(^{-1}\) by study documented measurements.\(^2\) To state that the BIS was significantly decreased in the remifentanil 0 \(\mu\)g kg\(^{-1}\) min\(^{-1}\)-group is further an odd statement, as no drug was administered and this logically, simply reflects only the natural course over time of the non-stimulated anaesthetic state on BIS, as the haemodynamic effects of preparatory (i.e. ‘surgical’) stimuli of intubation, etc. spontaneously decline, something quite commonly noted clinically. BIS is known to vary directly to the surgical stimulation, exhibit extinction/regression phenomenon over time after termination of surgical stimulation, and is not specific to the depth of anaesthesia in all instances. The utility of narcotic administration during clinical anaesthesia is to reduce hypnotic doses, inhibit spinal reflexes, and to offset haemodynamic effects of surgical stimulation. The effects on anaesthetic depth in the absence of surgery would be expected to be quite different than in this non-surgical setting. The authors also presumed to study if: ‘remifentanil may decrease the blood flow at propofol clearance sites and increase the \(C_p\) during constant propofol infusion’, but TCI by definition is not a constant infusion rate and specifically varies to maintain a projected (and apparently erroneous, as documented here) plasma concentration.

I would like to simply plea that internationally, TCI presentation in scientific journals no longer be acceptable without presenting drug administration rates, total doses, and duration times, including BMI, body weight, or both, to allow documentation of scientific vs supposition data, especially as multiple TCI paradigms exist worldwide and are not always readily accessible to or can be translated into drug administration rates by the readership. Thankfully, the remifentanil dosing was scientifically dosed in \(\mu\)g kg\(^{-1}\) min\(^{-1}\), and not in TCI ‘supposition units’. Why should propofol be exempt from the standard scientific System International units?

**Conflict of interest**

None declared.

P. M. Kempen*
Cleveland, USA

*E-mail: kmpnpm@yahoo.com


doi:10.1093/bja/aer043

**Reply from the authors**

Editor—We thank Dr Kempen for his comments regarding our article.\(^1\) Propofol target-controlled infusion (TCI) is used during general anaesthesia. Although propofol TCI is set by \(\mu\)g ml\(^{-1}\), which is also the unit used to represent plasma propofol concentration, the target plasma concentration is not the same as the actual plasma propofol concentration. Furthermore, many factors (co-administered drugs, surgical stimulation, haemodynamic instability, etc.) may affect the discrepancy between the target and actual plasma propofol concentration. When a TCI system is used, the operator should know how these factors affect the actual propofol concentration during propofol TCI. In this study, we investigated the effect of remifentanil, which is commonly used with propofol anaesthesia, on the plasma propofol concentration in the absence of other factors (before surgical stimulation) during propofol TCI.

The propofol infusion rate is not constant even when the predicted plasma/effect site propofol concentration is constant. We agree that the sentence ‘remifentanil may decrease the blood flow at propofol clearance sites and increase the \(C_p\) during constant propofol infusion’ in the Introduction section is confusing: ‘during constant propofol infusion’ should be changed to ‘during propofol TCI’.

To investigate the effect of remifentanil on plasma propofol concentration, the target plasma concentration of propofol was constant during the data-sampling period in our study. When TCI was set at 2.5 \(\mu\)g ml\(^{-1}\) in a preliminary study, the bispectral index (BIS) was over 60 before the data-sampling period (during the 15 min maintenance period) in some patients; therefore, we set TCI to 3 \(\mu\)g ml\(^{-1}\) in this study. Please note that, after tracheal intubation,
propofol TCI was reduced to 3 μg ml⁻¹. However, this information was not included in the Methods section of our article. In contrast, however, BIS was relatively low at 3 μg ml⁻¹ of TCI.

Although the TCI system does not predict plasma propofol concentration completely, a BIS monitor can be used during general anaesthesia. Remifentanil, however, affects the EEG characteristics during propofol anaesthesia.² Therefore, we also wanted to know how remifentanil affects BIS per se during propofol anaesthesia. Unexpectedly, our findings indicate the possibility that BIS does not reflect the actual plasma propofol concentration when co-administered with remifentanil. Thus, anaesthetic depth management using propofol TCI with remifentanil co-administration may be complicated, even when surgical stimulation is absent. Because remifentanil is used under surgical stimuli in a clinical setting, we think that further studies are necessary to clarify the effect of remifentanil on plasma propofol concentration or BIS during surgical stimulation. We cannot say whether presenting TCI is acceptable in scientific journals, but we believe that our findings are important for readers, especially those who use propofol TCI clinically.

Conflict of interest
None declared.

I. Takamatsu*
Saitama, Japan
*E-mail: tisao@ndmc.ac.jp

doi:10.1093/bja/aer048

Vertebral canal haematoma and coagulopathy
Editor—Vertebral canal haematoma (VCH) is a rare but potentially devastating complication of epidural analgesia requiring rapid confirmation and urgent neurosurgical decompression.¹ ² We witnessed such a case after a Whipple’s procedure in a 73-yr-old man with pancreatic carcinoma. Our case was associated with an unanticipated perioperative coagulopathy, which delayed definitive neurosurgery and contributed to a poor neurological recovery.

The patient’s liver function was abnormal before operation [bilirubin 50 mmol litre⁻¹, alkaline phosphatase 645 IU litre⁻¹, aspartate transaminase 207 IU litre⁻¹, gamma GT 1030, international normalized ratio (INR) 1.36] but all other results were normal. Epidural insertion required attempts at more than one level due to contact with bone but was otherwise atraumatic and there were few other risk factors for VCH (Table 1).³ Surgery was uneventful and recognized intraoperative causes for coagulopathy such as acidosis, hypothermia, and hypocalcaemia were absent.⁴ However, after 2 litre of Hartmann’s, 2.5 litre of Gelofusine, and 2 units of packed cells, haemodilution cannot be excluded.

Two hours into recovery, the patient complained of weakness and decreased sensation in his legs. Repeat clotting tests showed: INR 2.5, activated partial thromboplastin time (APTT) ratio 1.6, and platelets 288 × 10⁹ litre⁻¹. Over 12 h and several rounds of concentrated clotting factors (in total 3 × 500 IU Beriplex, 15 ml kg⁻¹ fresh frozen plasma, 2 pools of cryoprecipitate, and 10 mg vitamin K) were required to reduce the INR below 1.5 and permit decompressive laminectomy. In spite of ‘correcting’ standard laboratory coagulation values, the neurosurgeons reported heavy blood loss consistent with an ongoing coagulopathy.

Haemostasis maintains blood flow and, in the event of vessel injury, rapidly arrests blood loss and promotes repair of the damaged vessel. Cholestatic liver disease impairs absorption of fat-soluble vitamins including vitamin K, leading to the reduced synthesis of vitamin K-dependent factors (II, V, VII, IX, and X) and may prolong the INR. However, INR, APTT, and fibrinogen results only provide information on coagulation and delineate neither formation of the primary platelet plug nor fibrinolysis. INR and APTT were developed to assess the therapeutic effects of warfarin and unfractionated heparin, respectively, and were not designed to answer the question ‘will the patient bleed’?⁵ They do not provide a surrogate to guarantee normal haemostatic function and yet these values are still used as endpoints to guide haemostatic therapy, perhaps driven by the perception of medico-legal safety.⁵ So how might intraoperative bleeding risk be best predicted?

The use of a screening questionnaire and, if indicated, further platelet function analysis has been shown to be more efficacious and cost-effective at detecting patients at increased risk of intraoperative bleeding.⁶ Family history of bleeding and previous bleeding after minor trauma should be recorded in addition to a full drug history.

Vertebral canal haematoma and coagulopathy

<table>
<thead>
<tr>
<th>Spinal pathology</th>
<th>Procedural</th>
<th>Coagulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoporosis (post-menopausal females)</td>
<td>Multiple needle passes</td>
<td>Anticoagulant therapy</td>
</tr>
<tr>
<td>Degenerative disease</td>
<td>Needle trauma above L1</td>
<td>Intrinsic coagulopathy</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>Bloody tap</td>
<td>Liver dysfunction</td>
</tr>
<tr>
<td>Orthopaedic patients</td>
<td>Catheter withdrawal (on anticoagulant therapy)</td>
<td>Chronic kidney disease</td>
</tr>
</tbody>
</table>

Table 1 Risk factors for vertebral canal haematoma as a complication of epidural analgesia¹ ³