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## Potential responses to remifentanil supply shortages

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Title: Potential responses to remifentanil supply shortages

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## Summary

Rapid elimination of remifentanyl facilitates the application of intense opioid effect during general anaesthesia whilst maintaining prompt wake-up. Interruptions of remifentanyl supply mean clinicians must re-learn titrating of pharmacokinetically longer acting opioids to achieve appropriate levels of opioid effect whilst achieving acceptable recovery times. Opioid-free anaesthesia is achievable for many minor and intermediate surgical procedures for which remifentanyl might previously have been used.

Introduced in the 1990's, remifentanyl is widely used as the opioid component of balanced anaesthesia and intensive care sedation as well as for obstetric analgesia. Two decades of clinical experience and the availability of remifentanyl at reduced cost from generic manufacturers place it at the centre of contemporary anaesthetic practice, **especially when Total Intravenous Anaesthesia (TIVA) is preferred**. Intermittent interruptions to the supply of remifentanyl have been reported internationally, including the UK<sup>1</sup> and the USA.<sup>2</sup> These interruptions have been variously attributed to manufacturing problems and to increased demand. This editorial considers how and why we use remifentanyl and how we might manage without it.

### **Why do we combine hypnotics with opioids?**

When the relationship between concentration and an effect measure for two agents are explored graphically, a synergistic interaction may be represented as an upwards concave curve – an isobologram **indicating synergy**. The interactions between propofol and opioids or sevoflurane and opioids may usefully be presented this way.

Vuyk<sup>3</sup> and colleagues explored the pharmacodynamic interaction between propofol and alfentanil in women undergoing lower abdominal surgery. Using logistic regression, curves representing 50% probability of no response ( $EC_{50}$ ) for laryngoscopy, intubation and opening of the peritoneum were constructed. Whilst permutations of propofol and alfentanil concentrations yield an infinite number of combinations with equivalent effectiveness (in this case  $EC_{50}$ ) in suppressing response to stimulation, other effects are not consistent. Thus, although single-agent propofol anaesthesia can be achieved with high plasma concentrations, ( $EC_{50}$  15.2 mcg ml<sup>-1</sup>, 95% CI 7.6-22.8),<sup>4</sup> the likelihood of haemodynamic depression and slow recovery render the technique impractical. At the other end of the iso-bologram, **the curve asymptotically approached a non-zero minimum implying that alfentanil is not a 'complete' anaesthetic i.e.** even large doses of opioid cannot guarantee unconsciousness.<sup>5</sup> It therefore makes sense to co-administer an hypnotic with an opioid for induction and maintenance of anaesthesia. Vuyk<sup>3</sup> and colleagues extended their simulations to **generate an effect surface**,

identifying the recovery times associated with particular propofol and alfentanil concentrations. In addition to identifying an optimum concentration for recover of consciousness, the consequences of **intense opioid effect** can be identified – the trade-off being improved hemodynamic stability in return for slower recovery. Clinicians value this stability, and intense opioid effect has for decades been a common component of cardiac and vascular anaesthesia.<sup>5</sup>

### **What does remifentanil offer?**

The pharmacodynamic effect of fentanyl-series opioids are remarkably similar with individual opioids varying only in potency and time-to-peak-effect.<sup>6</sup> Why then should we fret about vagaries in remifentanil supply? Egan and colleagues<sup>7</sup> compared the pharmacokinetics and pharmacodynamics of remifentanil and alfentanil and emphasised that although their times to onset of effect are similar, the off-transients are very different. Remifentanil lends itself to titration against changes in surgical stimulation and unpredictable procedure durations, allowing profound opioid effect whilst retaining recovery times previously only seen in day-surgery. The contrast between remifentanil and fentanyl is even more profound. Arguably, remifentanil has de-skilled opioid titration. Anaesthesia **based on intense opioid effect** is achievable without remifentanil – it just requires careful dosing.

### **Is alfentanil an alternative?**

**The times to peak effect of remifentanil and alfentanil are similar. When (after adjusting for potency) single doses are combined with propofol to provide anaesthesia for tracheal intubation or brief procedures the results are acceptable with either opioid. For longer procedures supported by opioid infusions, the differences in context sensitive half time become material, with faster recovery from remifentanil.**

### **Heterogeneity of recovery**

The evanescent effect of remifentanil doesn't just bring ease of titration – it also offers certainty. All drug effects show inter-patient variability in both pharmacokinetics (PK) and pharmacodynamics

(PD). In plain language, following equivalent doses, achieved blood and brain concentrations will be higher in some patients than in others (PK variability). Likewise, for a particular achieved concentration, some patients show a greater response than others (PD variability). Inadequate anaesthesia is intolerable so dosing, especially in paralysed patients must embrace this variability by using doses sufficiently generous to ensure that all patients stay anaesthetised. **Remifentanyl collapses the variability of drug-offset thereby making relative overdosing almost consequence free (at least in terms of recovery of consciousness).** Whilst electronic brain monitoring may support some down-titration of anaesthesia in 'sensitive' patients this may be restricted by clinician **concerns about inadequate anaesthesia. Further, the effect of opioids on processed EEG parameters is subject to complex interactions with surgical stimulation and the sedative-opioid ratio.**<sup>8, 9</sup>

When volunteers received 3hr equi-effective infusions of alfentanil or remifentanil<sup>10</sup>, the context-sensitive half-time for alfentanil was 47.3 +/- 12 min and for remifentanil 3.2 +/-0.9 min. These differences are reflected in clinical trials. When alfentanil (n=118) or remifentanil (n=116) were combined with nitrous oxide and isoflurane to provide anaesthesia for major abdominal surgery the median times for times for extubation were 12 minutes in both groups.<sup>11</sup> However, there was a striking difference in outliers with seven patients who had received alfentanil with extubation times over 40 min compared with one in the remifentanil group. Likewise when remifentanil and alfentanil were compared in patients undergoing percutaneous nephrolithotripsy, recovery times were shorter and also more consistent amongst those who received remifentanil.<sup>12</sup>

### **What next?**

How then should we address the intermittent shortage of remifentanil? Like analgesia, a multi-modal approach is required. Health systems and their funders must engage with manufacturers to ensure continuity of supply. Low-price generics may decrease the per-patient cost of treatment but uncertainties about returns disincentivise manufacturers from investing in facilities and supply chains.

Clinicians could use less remifentanyl, substitute alternative opioids, or (where feasible) do without opioids altogether. Using less remifentanyl makes sense. Higher rates of remifentanyl infusion may be associated with acute opioid tolerance and hyperalgesia although the evidence underpinning these phenomena and their clinical significance remains controversial.<sup>13</sup> A threshold of 0.2-0.25 mcg kg<sup>-1</sup> min<sup>-1</sup> has been suggested. Clinicians can re-learn the art of opioid titration using other fentanyl-series opioids which are pharmacokinetically longer acting than remifentanyl. Finally, we can press-on with developing and extending opioid-free anaesthesia and post-operative analgesia for minor and intermediate surgeries.

### **Do we need opioids at all?**

Although pure-propofol anaesthesia is not useful, opioid-free anaesthesia is a reality, at least for certain forms of surgery. The use of loco-regional anaesthesia and adjunct analgesia with paracetamol and Non-Steroidal Anti-Inflammatory Drugs supports opioid-free anaesthesia for minor and many intermediate procedures with reduction in morbidity (nausea, vomiting, constipation and pruritus) and perhaps a reduction in the risk of subsequent opioid dependency. Such techniques have been advocated for years, however the majority of surgical patients continue to receive at least some opioid. A meta-analysis of 26 Randomised Controlled Trials of opioid-free anaesthesia concluded that: "Opioid-free anaesthesia can improve postoperative outcomes in several surgical settings without evidence of adverse effects on patient safety and pain management." The benefits of avoiding opioids continue after discharge from hospital and a systematic-review and meta-analysis of trials comparing opioid versus opioid-free postoperative analgesia for surgical patients concluded that opioids increased adverse events without reducing pain-intensity.<sup>14</sup> Nevertheless, opioid-free anaesthesia remains controversial.<sup>15</sup> Certainly, opioid-free anaesthesia based upon dexmedetomidine is less safe than a conventional technique<sup>16, 17</sup> and the absence of opioid decreases the scope for therapeutic titration.<sup>18</sup>

Intermittent unavailability of remifentanyl is annoying, but it isn't a showstopper. We can revisit the well described pharmacokinetics and pharmacodynamics of other fentanyl-series opioids to achieve the same results – albeit with some inconvenience.

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**Social media – tweets @robsneyd**

- Anaesthetists can manage without remifentanyl – but it's annoying!



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