3. The validation references in the article appear misleading—the authors state that validation of the bioreactance technique is still ongoing and that initial results are conflicting. To support this statement, they cite references where bioreactance is shown to perform positively (references 3–5) and then cite four publications (references 6–9) to support a premise that bioreactance, specifically Cheetah NICOM, is not reliable in estimating cardiac output. Unfortunately, there appear to be several serious issues with the interpretation of these references and the conclusions drawn from these references suggesting poor performance of the NICOM device. Our concerns are as follows:

(i) Reference 6 in the article is not a peer-reviewed study but an observational letter, based on a case series, with only 11 patients.

(ii) Reference 7 in the article—this is a validation study performed utilizing a bioimpedance product (BioZ by Cardiodynamics). This is not a Cheetah NICOM validation study.

(iii) Reference 8 in the article—Weisz and colleagues concluded, ‘Non-invasive cardiac output monitoring is feasible in neonates. Further validation studies in neo-natal animal experimental models and human neonates need to be conducted before routine clinical use’. This is a positive outcome conducted with the Cheetah NICOM monitor as the non-invasive technology. Weisz and colleagues state that further studies are required because although both NICOM and the LVO devices were highly correlated in their values ($R=0.95$, $r<0.001$), there was a consistent 30% bias between them. As neither device is accepted as gold standard, Weisz and colleagues suggested further examination.

(iv) Reference 9 in the article—Marik and colleagues concluded in their study, ‘Monitoring the hemodynamic response to a PLR using the NICOM provides an accurate method of assessing volume responsiveness in critically ill patients’. This is again a positive study involving the Cheetah NICOM monitor.

4. The technology referenced may confuse bioimpedance and bioreactance—in the article, Kupersztych-Hagege and colleagues state that the bioreactance technique is based on phase shifts of electrical current crossing the thorax and they refer the reader to reference 2 in the article. This reference does not correctly describe the bioreactance technology but only a modification to the bioimpedance technology. The reader could be led to understand that the bioreactance and the technology commonly known as bioimpedance are actually the same. We refer the authors to the bioreactance pre-clinical publication by the bioreactance inventor Keren and colleagues for an accurate and comprehensive description of the bioreactance technology.

We therefore believe that this study has several significant deficiencies, which include marked deviation from appropriate use of the Cheetah NICOM, erroneous interpretation of references citing NICOM’s poor performance, and lack of adequate data presented to support the authors’ conclusions.

We at Cheetah Medical welcome a robust and properly conducted evaluation of the technology, but this does not appear to have been done in this instance.

Declaration of interest
W.T.D. is the Chief Medical Officer of Cheetah Medical. C.H. is the CEO & President of Cheetah Medical. B.L. is the Chief Technology Officer of Cheetah Medical.

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8 Marik PE, Levitov A, Young A, Andrews L. The use of bioreactance and Carotid Doppler to determine volume responsiveness and blood flow redistribution following passive leg raising in hemodynamically unstable patients. Chest 2013; 143: 364–70


doi:10.1093/bja/aeu122

Contribution of oxycodone and its metabolites to the analgesic effect

Editor—Kokki and colleagues published an article on central nervous system penetration of oxycodone in humans. These are the first human data available for this drug and also its metabolites. We have recently published a method to calculate...
the contribution of oxycodone and its metabolites to the analgesic effect after oxycodone administration based on published information on blood concentrations of oxycodone and metabolites, protein binding, blood–brain barrier behaviour (animal data), and opioid receptor affinity. Using these data, we found that oxycodone itself is responsible for 83.0% and 94.8% of the analgesic effect after p.o. and i.v. administration, respectively. In contrast, the potent oxycodone metabolite oxymorphone only played a minor role (15.8% after p.o. and 4.5% after i.v. administration). We took the opportunity using the new human data from the study by Kokki and colleagues to re-calculate the contribution of oxycodone and its metabolites to the analgesic effect. Therefore, the cerebrospinal fluid (CSF)/plasma ratio of oxycodone and its metabolites based on AUC or Cmax values available were calculated (Table 1). We applied these ratios to the data available after i.v. administration and compared the results with our previous calculations using animal data for the CSF/plasma ratio. The contribution of oxycodone itself decreased from 94.8% to 77.3% and consequently, oxymorphone contribution increased from 4.5% to 18.9%. However, this was based on the ratios obtained for Cmax, which is probably not the best parameter, but only AUC values of oxycodone itself are reported. It is quite obvious that after epidural oxycodone administration, the analgesic effect must result from the very high oxycodone concentrations in CSF, in relation only negligible concentrations of the metabolites are observed. Using Cmax concentration in CSF, our calculations result in >99% contribution of oxycodone to the overall analgesic effect. The data provided by Kokki and colleagues substantially support the current understanding that active oxycodone metabolites only have a minor contribution to the analgesia after oxycodone administration.

<table>
<thead>
<tr>
<th>Variable</th>
<th>I.V.</th>
<th>Epidural</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxycodone Cmax</td>
<td>0.52</td>
<td>357</td>
</tr>
<tr>
<td>Oxycodone AUC</td>
<td>1.17</td>
<td>111</td>
</tr>
<tr>
<td>Noroxycodone Cmax</td>
<td>0.28</td>
<td>1.32</td>
</tr>
<tr>
<td>Oxymorphone Cmax</td>
<td>0.67</td>
<td>1.67</td>
</tr>
<tr>
<td>Noroxymorphone Cmax</td>
<td>0.067</td>
<td>0.083</td>
</tr>
</tbody>
</table>

**Declaration of interest**
None declared.

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**Spinal catheter observer effect and surgical technique**

Editor—We read with interest Kokki and colleagues’ work on the central nervous system penetration of oxycodone, and reviewed the paper at our regional journal club (http://www.nwrag.com). We congratulate the authors on their novel study of pharmacokinetics and effectiveness of oxycodone given by the epidural route.

Kokki and colleagues have demonstrated much higher cerebrospinal fluid levels of oxycodone after epidural administration compared with i.v., but all their patients had breach of the dura for the placement of a spinal catheter. This may mean that the efficacy of oxycodone administered by the epidural route could be reduced in subsequent studies where spinal catheters are not used.

The authors note that 13 patients had laparoscopic surgery and 11 patients had laparotomy, although they do not state the numbers in each of the study groups. The type of surgery has been demonstrated to be a determinant of analgesic requirements after operation and is therefore an important patient characteristic to be matched in the two study groups. As the study was not powered to detect a difference in efficacy between the two groups, interpretation of the results without accounting for this potential confounder needs to be done with caution.

**Declaration of interest**
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Table 1 CSF/plasma ratio of oxycodone and its metabolites based on AUC or Cmax values. CSF, cerebrospinal fluid; AUC, area under the curve.