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 \( C_{\text{max}} \) values available were calculated.

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 \( C_{\text{max}} \), 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 \( C_{\text{max}} \) 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 1 CSF/plasma ratio of oxycodone and its metabolites based on AUC or \( C_{\text{max}} \) values. CSF, cerebrospinal fluid; AUC, area under the curve

<table>
<thead>
<tr>
<th>Variable</th>
<th>I.V.</th>
<th>Epidural</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxycodone ( C_{\text{max}} )</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 ( C_{\text{max}} )</td>
<td>0.28</td>
<td>1.32</td>
</tr>
<tr>
<td>Oxymorphone ( C_{\text{max}} )</td>
<td>0.67</td>
<td>1.67</td>
</tr>
<tr>
<td>Noroxymorphone ( C_{\text{max}} )</td>
<td>0.067</td>
<td>0.083</td>
</tr>
</tbody>
</table>

### 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

None declared.

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Miosis with dexmedetomidine: every little helps, every picture tells a story

Editor—Guedel used ocular signs as part of his classic description of the four stages of ether anaesthesia in 1937. These were deemed to be relevant clinical tools when ether, cyclopropane, and chloroform were in use, but with newer drugs and advanced monitoring, the eye signs gradually faded into obscurity.

We report a case of off-label use of dexmedetomidine with bupivacaine for epidural anaesthesia that led to deep sedation and bilateral miosis.

A 62-yr-old female patient, ASA I, was to undergo vaginal hysterectomy. Under strict asepsis, an 18 G epidural catheter was placed in the L3–4 space. A test dose of 3 ml of 2% lidocaine with epinephrine 5 μg ml⁻¹ was given after which 12 ml of 0.5% bupivacaine with dexmedetomidine 1 μg kg⁻¹ was administered through the epidural catheter. After an initial increase to 190/110 mm Hg, arterial pressure decreased to 90/40 mm Hg and heart rate to 46 beats min⁻¹ over the next 5 min. The patient was breathing normally with 99% oxygen saturation but was deeply sedated and was not responding even to painful stimulus (Ramsay score 6). Rapid infusion of i.v. fluids was started and i.v. atropine 0.6 mg was given. Oxygen was delivered by a facemask and a quick re-check was done to exclude any medication error. The pupils were pinpoint in ambient light and a possibility of pontine haemorrhage was also considered. However, the patient started to stabilize gradually and the sedation score improved to 3 after 30 min. The sensory block was adequate and the surgery could be performed as planned. The rest of the perioperative period was uneventful without any neurological sequelae.

While a plethora of information exists about the clinical effects of dexmedetomidine in the anaesthesia journals, little has been said about its effects on the pupils. We examined the current medical literature for its mechanism of action and the effect on reflex pupillary reaction in humans.²⁻⁴

The regulation of sedation, autonomic function, and pupillary reaction are all inter-related and controlled centrally at the locus coeruleus (LC) due to stimulation of presynaptic α₂- adrenergic receptors by dexmedetomidine. The LC is the largest group of noradrenergic neurones in the central nervous system and gives rise to fibres innervating most structures of the neuraxis. Any pharmacological alteration to this neuronal circuitry would affect the activity at the LC and clinically result in changes in the level of sedation, heart rate, arterial pressure, and pupil size.

There is a biphasic response with dexmedetomidine, with an initial transient sympathomimetic action (peripheral post-synaptic action leading to hypertension) followed by a persistent sympatholytic effect (hypotension and bradycardia). The central sympatholytic action also causes a reduction in pupil diameter due to attenuation of the activity of the coeruleo-spinal pathway and reduction in noradrenergically mediated inhibition of the Edinger–Westphal nucleus. This action is known to predominate in comparison with the peripheral post-synaptic α₂-adrenoceptors activation in humans.¹

This insight into the mechanism of action unravels the fact that constriction of pupils, sedation, and a decrease in heart rate and arterial pressure are possibly correlated. Given the hypothesis then, that pupillary size and autonomic effects may possibly be a measure of the depth of sedation with dexmedetomidine, perhaps it would be clinically useful in the assessment of the level of sedation in the intensive care unit and a study designed to prove it would be worthwhile. Are we on the threshold of reviving an elementary clinical sign that would make the science of sedation an art?

Declaration of interest

None declared.

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Ventilation with the Ventrain through a small lumen catheter in the failed paediatric airway: two case reports

Editor—We would like to report two cases of ventilation through small lumen intubating and tube exchange catheters to manage critical paediatric airways using the Ventrain, a manually operated, flow-controlled ejector ventilator for emergency use.¹

A 2.1 kg premature baby was undergoing cryocoagulation therapy of the eyes. Following repeated intubation attempts...