The effect of melatonin on sedation of children undergoing magnetic resonance imaging

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Background. Melatonin may induce a natural sleepiness and improve predictability of sedation drugs. We have investigated its clinical value in children sedated for magnetic resonance imaging.

Methods. In a stratified randomized double-blind study, 98 children received either melatonin or placebo 10 min before they were sedated with a standard oral regimen. Children >5 and <15 kg received chloral hydrate and those ≥15 and <40 kg had a combination of temazepam with droperidol (T&D). The doses of melatonin were 3 and 6 mg, respectively. One observer recorded the time taken to reach criteria for deep sedation, sedation failure and other sedation-related events.

Results. In the chloral hydrate group (n=50) 50% were deeply sedated by 31 min after melatonin and 40 min after placebo (P=0.57). There were zero and 1 failures, respectively. The geometric mean time taken to reach deep sedation was 39 min in both subgroups. In the T&D group (n=48) 50% were deeply sedated by 70 min in both subgroups (two failures in each); geometric mean times were 68 and 71 min, respectively (P=0.58). Children closed their eyes slightly earlier after melatonin (respective geometric means 42 vs 48, P=0.17), and took slightly longer to achieve discharge criteria (146 vs 135, P=0.47).

Conclusion. In these doses and clinical conditions, melatonin did not contribute to sedation of children.

Keywords: brain, magnetic resonance imaging; hormones, melatonin; paediatrics; sedation, deep sedation

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Children are often not cooperative enough to lie still for magnetic resonance imaging (MRI) unless they are asleep. Anaesthesia or sedation is effective but both have side-effects, carry a small mortality risk and require appreciable manpower resources. Natural sleep is an attractive option provided it is predictable and reliable, but at present, it is practical only in small infants who sleep after a feed.

Melatonin, a hormone involved in the diurnal rhythm of sleep, is a potentially useful oral natural-sleep agent and is available commercially. It is classed as a ‘dietary supplement’ by the United States Food and Drug Administration. Clinically, in children, it has been used to treat sleep disorders and to induce sleep for EEG. Melatonin may also be useful for MRI and has been reported to be successful in 55–76% of children although in that series of cases there was no control group for comparison.

The high demand for MRI requires that ‘sleep’ techniques are predictable. We have developed a nurse-led sedation service that is successful in 95% of selected children, but involves high doses of sedatives which risks both excessive sedation during the scan and prolonged recovery. Melatonin could be useful by inducing a natural sleepiness and, if combined with sedatives, the onset of sedation could be quicker and the doses of sedatives could be reduced. We have studied the clinical value of combining melatonin with sedation for children having MRI. First, in a non-randomized pilot, we tested the safety of the combination, and then we proceeded with a larger, randomized, placebo-controlled, double-blind study to determine efficacy.

Methods

The project was approved by the local research and ethics committee and conducted according to ICH GCP (International Committee on Harmonization, Good Clinical...
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Practice) guidelines. Uncooperative children requiring routine MRI (less than 60 min in duration) were recruited if they were suitable for sedation and if their body weight was between 5 and 40 kg. Parents gave written informed consent.

All children were assessed by a trained nurse (R.N.K.F.) and excluded according to a list of common contraindications published previously. Children were fasted for 4 h for food or milk and 2 h for clear fluids. Ametop local anaesthetic cream was applied to a suitable venepuncture site before sedation began. If a cannula was required for gadolinium (an i.v. contrast agent for MRI), it was inserted at least 30 min after the ametop was applied, and after sedation had been given, when the child was sleepy in order to minimize any distress.

Two oral sedation-drug regimens were used according to body weight. In the pilot study, children weighing >5 and <12 kg were given chloral hydrate (50–100 mg kg\(^{-1}\)), and those weighing 12–40 kg had temazepam (1 mg kg\(^{-1}\), maximum dose 25 mg) with droperidol (0.25 mg kg\(^{-1}\), maximum dose 5 mg). The dose of chloral was chosen by R.N.K.F. to suit the length of the scan. Before the randomized controlled trial the body weight that separated the two groups was changed from 12 to 15 kg because of a change in clinical practice. Sedation level was assessed by R.N.K.F. using a validated paediatric sedation observational scale\(^{11}\) with minor modification (Table 1). Children were considered ready for scanning when they were both ‘deeply sedated’ which corresponded to level 3 (deeply asleep and rousable only with significant physical stimulation—Table 1), and when they met ‘safe sleep criteria’ for scanning (Table 2).

If necessary, further ‘top-up’ sedation was administered 15 min after chloral or 40 min after temazepam and droperidol had been given, or if the child awakened later during the scan. Those having chloral were given a further dose (up to a total maximum dose of 100 mg kg\(^{-1}\) or 1 g) and then, if this was ineffective, i.v. diazepam (diazemuls\(^{\circ}\), 0.1–0.2 mg kg\(^{-1}\)) was used. Children who received temazepam were topped-up with i.v. diazepam (bolus doses 0.1 mg kg\(^{-1}\), maximum dose 10 mg). If maximum sedation was ineffective, a general anaesthetic was administered later.

Each sedated child was managed by an experienced nurse, and monitored with pulse oximetry throughout the sedation period. If necessary, head position was adjusted to ensure a clear airway and oxygen was administered to maintain \(\text{SpO}_2\) higher than 93%. Children were considered recovered and ready for discharge only after they could respond easily to command and if they could eat or drink normally: this corresponded to sedation level 1 or 2. All children were observed for at least 2 h after scanning.

**Pilot study**

Twenty children having chloral hydrate received one capsule (3 mg) of melatonin and 20 having temazepam and droperidol had two (6 mg). These doses where chosen because they are used in our hospital to induce sleep for EEG. Melatonin capsules (Life Extension\(^{\text{TM}}\) Foundation, Hollywood, FL, USA) were opened and the contents (melatonin 3 mg mixed with rice flour and gelatin) were dissolved in 10–20 ml of water and administered 10 min before sedation. The level of sedation was observed and recorded every 10 min (except during scanning) until recovery criteria had been met. In addition, observation was continuous and R.N.K.F. recorded the time taken (after melatonin) to reach deep sedation (level 3). Any undesirable effects were noted.

**Randomized controlled trial**

Children were randomized to receive either melatonin or a placebo capsule 10 min before routine sedation. The pharmacy directed R.N.K.F. to administer capsules coded A or B. Placebo and melatonin were indistinguishable and the code was not broken until the end of the study. Block randomization ensured that equal numbers of children received A or B. Children less than 15 kg received melatonin 3 mg and those who were heavier received 6 mg.

Sedation level was recorded every 5 min for the first 30 min after the administration of melatonin, and every 10 min thereafter. The primary outcome variable was the time taken after melatonin to reach sedation level 3, according to the judgement of R.N.K.F. We anticipated that even though some children would reach sedation level 3, they could rouse later and require further sedation drugs: these events were recorded but not used as the primary outcome. Secondary outcome measures included the time to fall asleep (quiet, not moving and eyes closed), the requirement for further top-up sedation, the scan success rate and, after scanning, the time taken to achieve criteria for discharge. Other recorded details and events included any airway effects, the scan length and the indications for scanning.

<table>
<thead>
<tr>
<th>Table 1 University of Michigan sedation scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 Awake and alert</td>
</tr>
<tr>
<td>1 Minimally sedated: tired/sleepy, appropriate response to verbal conversation and/o sound</td>
</tr>
<tr>
<td>2 Moderately sedated: asleep but easily roused with light tactile stimulation or a simple verbal command (tactile stimulation—raise arms to detect resistance)</td>
</tr>
<tr>
<td>3 Deeply sedated: deeply asleep and rousable only with significant physical stimulation (repositioning into supine position or i.v. cannulation) but settles soon afterwards</td>
</tr>
<tr>
<td>4 Unrousable</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2 Safe sleep criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep: eyes closed, minimal movement, stays asleep during transport to scanner (either by carrying or on lifting from trolley)</td>
</tr>
<tr>
<td>Safety: clear airway, ventilatory frequency appropriate for age (minimum 12 min(^{-1})), (\text{SpO}_2) &gt;93% with oxygen (max 5 litres min(^{-1}) via a face mask or 2 litres min(^{-1}) via nasal cannulae) and heart rate appropriate for age (minimum 80 min(^{-1}))</td>
</tr>
</tbody>
</table>
(patients were categorized according to the specialty that requested the scan).

Based on previous experience, we estimated that the mean time to become sedated was approximately 40 min (SD 10 min). We calculated that we would need 44 children (22 in each treatment group) in order to have a 90% chance (at P-value 0.05%) of determining a reduction in the sedation onset time by 10 min; we therefore aimed to study 50 in each sedation group, a total of 100 children. A small number of children were expected not to reach deep sedation and therefore the groups were compared with Kaplan–Meier survival analysis and logrank test: children who did not achieve deep sedation were censored at 120 min. For simplicity, time data were compared with t-tests and children who did not achieve deep sedation were treated as missing values. None of the time data was normally distributed except for time to deep sedation in children who received temazepam and droperidol. For consistency, all time data were transformed to log base 10 to improve the normality of data distribution. Time results are presented as geometric means (=anti-log of mean of log10 times) with anti-logs of the 2.5% lower and 97.5% upper limits of log-transformed sample data (in square brackets) to the nearest minute. Student t-tests were performed on log-transformed data and the P-values are presented alone. The SD of the raw time to reach deep sedation is also quoted. Cox regression analysis was used to estimate the effect of single and multiple factors upon the time taken to reach deep sedation.

Following a review of the results, the uniformity of both weight and content of melatonin capsules were determined on a sample of 20 capsules remaining from the clinical trial, using precision balances and a validated high-pressure liquid chromatography method.

**Results**

**Pilot study**

All children tolerated melatonin well, all were scanned successfully and none became excessively sedated or had unexpected effects. The mean time taken to reach deep sedation was 29 min (SD 13, range 8–69) for children given chloral hydrate, and 53 min (SD 20, range 18–90) for those who had temazepam and droperidol.

**Randomized controlled trial**

In total, 99 children were studied. Randomization was lost in one patient and he was excluded from analysis. The distributions of age, body weight, gestation, length of scan, top-up and failure rates were similar between the melatonin and placebo groups (Table 3). All children became sufficiently sleepy to close their eyes but five failed to reach deep sedation (discharge times were not analysed in these patients). Another child was deeply sedated and had airway obstruction during the scan: the airway was easily cleared and the saturations did not decrease below 90%. When the airway was cleared the child then awoke and sedation was abandoned. There were no other appreciable airway or breathing effects. The numbers of patients referred by specialty were similar in the melatonin and placebo groups (Table 4).

**Chloral group**

There was no statistical difference in the initial dose of chloral between the two groups (mean difference 33 mg, 95% CI=-173 to 108). The time at which 50% of children were deeply sedated was 31 min after melatonin and 40 min after placebo (logrank statistic 0.32, P=0.57, Fig. 1A). The geometric mean time taken to reach deep sedation was 39 min [20–74] after melatonin compared with 39 [21–71] after placebo (P=0.92). The SD of the raw time to reach deep sedation was 14 min in both groups.

Children closed their eyes slightly earlier after melatonin than placebo (respective geometric means 19 [9–42] vs 21 [12–37], P=0.27), and took slightly longer to achieve discharge criteria (113 [59–214] vs 106 [53–218],

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### Table 3 Patient characteristic data details. Scan length is the geometric mean in minutes with anti-log of the 2.5% lower and 97.5% upper limits of log-transformed sample data, in square brackets

<table>
<thead>
<tr>
<th>Specialty</th>
<th>Chloral</th>
<th>Melatonin (n=25)</th>
<th>Placebo (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr) [mean (range)]</td>
<td>1.5 (0.3–4.1)</td>
<td>2.0 (0.3–4.2)</td>
<td></td>
</tr>
<tr>
<td>Weight (kg) [mean (SD)]</td>
<td>10.7 (2.5)</td>
<td>11.5 (2.1)</td>
<td></td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>11/14</td>
<td>10/15</td>
<td></td>
</tr>
<tr>
<td>L.V. cannula inserted</td>
<td>10</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Scan length (min)</td>
<td>32 [18–56]</td>
<td>35 [16–73]</td>
<td></td>
</tr>
<tr>
<td>Needed sedation top-up</td>
<td>7</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Failed to reach deep sedation</td>
<td>–</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

### Table 4 Specialty requesting MRI. *One patient did not become deeply sedated

<table>
<thead>
<tr>
<th>Specialty (n)</th>
<th>Chloral</th>
<th>Melatonin and droperidol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncology (13)</td>
<td>4</td>
<td>5*</td>
</tr>
<tr>
<td>Neurology (35) (taking anticonvulsants)</td>
<td>10 (2)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Audiology (11)</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Vascular (12)</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Orthopaedic (5)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Ophthalmology (7)</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Dermatology (6)</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Other (12)</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

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Univariate Cox regression analysis showed that heavier children took longer to reach deep sedation (hazard ratio 0.89, *P*=0.06) and those who had not had an i.v. cannula slept earlier (hazard ratio 0.33, *P*=0.004). There were no appreciable interactions between body weight, i.v. access and melatonin use.

**Temazepam and droperidol group**
The time at which 50% of children were deeply sedated was 70 min after both melatonin and placebo (logrank statistic=0.14, *P*-value=0.71, Fig. 1A). The geometric mean time taken to reach deep sedation was 68 min [39–119] after melatonin and 71 [41–124] after placebo (*P*=0.58). The SD of the raw time to reach deep sedation was 18 and 22 min, respectively.

Children closed their eyes slightly earlier after melatonin than placebo (respective geometric means 42 [22–81] vs 48 [29–77], *P*=0.17), and took slightly longer to achieve discharge criteria (146 [72–295] vs 135 [68–269], *P*=0.47). Cox regression analysis did not demonstrate any statistically significant effects of any factor upon the time to reach deep sedation.

**Analysis of melatonin capsules**
Of 20 capsules analysed 3 contained less than 90% of 3 mg (2.3, 1.3 and 0.8 mg) and 1 contained more than 110% (4.1 mg). Only one capsule out of 20 contained just over 10% of powder fill (112%) and the rest were within an acceptable range (±10%).

**Discussion**
Life Extension™ melatonin capsules did not contribute to sedation of children for MRI under clinical conditions and in the doses used. Children tended to fall asleep more quickly after melatonin and were slower to recover, but these differences were neither appreciable nor statistically significant. The data demonstrate that there was wide variation in the onset of sedation and that this problem was greatest for children over 15 kg who received temazepam and droperidol. Chloral sedation, for smaller children, was less variable but we do not use it in older children because the higher doses cause gastric irritation and vomiting and, even when it is tolerated, its success rate may not be as high.12 Children who need MRI are a disparate group and some have characteristics that resist sedation which may explain some of the variation in sedation times.

Two studies have suggested that melatonin alone is useful for children having MRI:10,13 Wassmer and colleagues13 used melatonin 0.25–0.5 mg kg$^{-1}$ in 27 children in whom 16 could be scanned successfully, and Johnson and colleagues10 reported that 55% of children who received 10 mg became sufficiently asleep (the success rate increased to 76% if children had been sleep deprived). Whereas these results suggest that melatonin, at a higher dose, may have an effect, neither study was randomized and patients who were ‘easy to sedate’ may have been unintentionally selected. Other studies have demonstrated that melatonin can induce sleep for the EEG investigation of epilepsy9,13 but this experience may not be relevant because MRI is noisy and requires the child to be immobile. In our experience of EEG testing, there is wide variation in the sleep effect of melatonin.

Larger doses of melatonin may have had a greater effect but we decided that it was unreasonable to ask parents to consent to test high doses without testing our standard ‘EEG’ doses first. A dose-dependent effect of sublingual melatonin has been demonstrated in women by Naguib and Samarkandi14 and they found that 0.1 mg kg$^{-1}$ caused...
but for some families, this is impractical and can make
12 after 0.2 mg kg$^{-1}$ for those heavier. A study of the anxiolytic effect of melatonin in children has showed that 0.25 and 0.5 mg kg$^{-1}$ were equally effective.$^{15}$

The timing of melatonin may also be important and we chose to administer it 10 min before sedation for practical reasons. The sleep onset effect of oral melatonin has been reported to be in the range 30–35 min$^{10,13}$ and if melatonin has an appreciable effect by 40 min then our study design should have shown it. Melatonin is not a direct sleep agent but acts indirectly as a ‘circadian switch’ and is therefore likely to be most effective at provoking sleep at the usual time of an individual’s sleep onset.$^{23}$ Sleep deprivation alone could encourage sleep for a painless procedure$^{16,17}$ but for some families, this is impractical and can make children irritable instead of sleepy.$^{18}$ The coordination of the timing of sleep deprivation and of melatonin administration may be useful in some circumstances but, unless this combination is reliable, it would not justify the resource implications.

Our study was not designed to demonstrate whether or not melatonin caused sleep, but rather to determine whether it was useful under clinical conditions for MRI. The accuracy of determining the onset of deep sedation, even when using a validated sedation scale, is dependent on observer reliability and, in this study, variation was minimized by using one trained unbiased observer. Before undertaking the study we estimated that the SD of the time taken to reach deep sedation would be 10 min and our power calculation was based on detecting a difference between the groups of 1 SD. We found that the raw time data was not normally distributed, and therefore we used log transformation to achieve normality and to enable the use of parametric statistical analysis. The anti-log of the SD of log-transformed data is not meaningful but the distribution of sample times is described by the less familiar anti-logs of the 2.5% lower and 97.5% upper limits of log-transformed sample data.

Melatonin, manufactured in the USA, is classified as a dietary supplement and not a drug, and therefore is not submitted to stringent manufacturing quality control. Even though the Life extension$^{TM}$ melatonin had a certificate of analysis stating the drug content was at least 95% (equivalent to melatonin 2.85 mg), 15% of capsules contained less than expected. As the powder filling of the capsules was uniform, the problem is likely to be with the mixing of melatonin and the excipients. Nevertheless, this finding does not appreciably weaken the power of our study to determine an effect of melatonin because, even if a pessimistic assumption is made that 20% of capsules contain no melatonin at all, the number who received melatonin was 20 in each sedation group and we calculate that the power of the study is reduced to not less than 85%. Further analysis of melatonin capsules from other manufacturers is warranted.

Despite the variation in the content of the capsules, our study does not support the use of a combination of melatonin and sedation in children for MRI, although higher doses of melatonin given earlier may be more successful. We have also shown that although sedation is usually successful, it is the timing of the onset of sedation, especially in those over 15 kg, that is so unpredictable. This justifies continued attempts to develop new combinations of sedatives that could prove to be reliable, effective and safe enough for non-anaesthetists to use. Now droperidol is no longer available in the UK and we are trying other combinations of oral sedatives. The use of α2 adrenoreceptor agonists such as clonidine or dexmedetomidine may be promising. A recent study has shown that 80% of children can be sedated for MRI with i.v. dexmedetomidine alone and that the remainder can be topped-up successfully with midazolam.$^{19}$ Nevertheless, a sedation technique cannot be recommended for use by non-anaesthetists unless it has a wide margin of safety$^{20,21}$ and the experience of any technique must be large enough to justify confidence in it.

Developing safe and successful techniques in ‘high demand’ services such as MRI will need the study of large numbers of children and this could be more easily achieved with cooperation between institutions. In the UK, few centres are developing sedation for MR because anaesthesia services are thought to be more efficient but, if a reliable sedation technique was available, this could change.

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