FLUNITRAZEPAM AS AN INDUCTION AGENT IN CHILDREN

A clinical and pharmacokinetic study

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SUMMARY

Flunitrazepam was studied as an induction agent in paediatric patients. The onset of action was slow and its efficacy uncertain following single doses of 0.03 mg kg\(^{-1}\) (n = 4), or 0.04 mg kg\(^{-1}\) (n = 6) i.v. Long-lasting sedative effects were observed following operation. A strong anterograde but not retrograde amnestic effect was obtained, and a possible analgesic sparing property. Flunitrazepam has a faster and more extensive tissue distribution and a more rapid elimination (half-life about 12 h) in children than in adults.

Flunitrazepam has proved to be a satisfactory premedicant in children older than 5 yr when administered by oral or parenteral routes (Lindgren, Saarnivaara and Himberg, 1979, 1980; Richardson and Manford, 1979; Kanto, 1981). However, its usefulness as an induction agent has not been studied widely in children. Generally, flunitrazepam, like other benzodiazepines, has been regarded as a slower acting sedative rather than as a short-acting induction agent (Dundee, 1979a, b; Kanto and Klotz, 1982). This is mainly because flunitrazepam fails to produce an acceptable depth of anaesthesia in one arm–brain circulation time, leading to great individual variation in drug response. However, because flunitrazepam has been considered a satisfactory induction agent in adult patients (Stovner, Endresen and Østerud, 1973; Freuchen, Østergaard and Mikkelsen, 1976), we have studied its properties in children. In addition, pharmacokinetic parameters were calculated to determine the possible relationship between kinetic and clinical indices (Klotz, Kangas and Kanto, 1980).

PATIENTS AND METHODS

Anaesthesia was induced with flunitrazepam in 10 children (ASA 1 or 2) about to undergo major surgical procedures. Their ages, weights and heights ranged from 3 to 10 yr (mean 4.8 yr), 12.6 to 28.0 kg (mean 21.4 kg), and 89 to 135 cm (mean 113.2 cm), respectively. Atropine 0.01 mg kg\(^{-1}\) and pethidine 1 mg kg\(^{-1}\) were administered i.m. as premedication about 60 min before the beginning of anaesthesia. Flunitrazepam 0.03 mg kg\(^{-1}\) (n = 4), or 0.04 mg kg\(^{-1}\) (n = 6) was injected in 20–30 s, and venous blood samples were drawn from a contralateral antecubital vein at the time of administration and subsequently at the intervals given in figure 1. The largest dose (0.03 mg kg\(^{-1}\)) recommended for adult patients by the manufacturer was used initially, but because of an inadequate response the dose was increased later to 0.04 mg kg\(^{-1}\). The other components of the anaesthetic were 70% nitrous oxide in oxygen and pethidine 0.8–2.8 mg kg\(^{-1}\). Suxamethonium 0.8–1.8 mg kg\(^{-1}\), and pancuronium 0.10–0.80 mg kg\(^{-1}\) were administered to provide appropriate neuromuscular blockade. Atropine 0.02 mg kg\(^{-1}\) and neostigmine 0.04–0.05 mg kg\(^{-1}\) were used to reverse the neuromuscular blockade.

Anaesthesia lasted for 0.75–3.0 h (mean 1.62 h). Systolic and diastolic arterial pressures and heart rate were recorded frequently before and during anaesthesia (at 3–5-min intervals) and in the recovery room (at 5–10-min intervals). The degree of postoperative sedation was determined by an anaesthetist (E.I.) 5, 30, 60 and 90 min after the end of anaesthesia (asleep, very sedated, moderately sedated, alert). On the day following the operation the patients were questioned by the anaesthetist as to their memory for being taken to the operating theatre, the induction of anaesthesia, recovery from anaesthesia, time spent in the recovery room, return to the ward, or the evening of the day of operation at the ward. The use of analgesics after operation was recorded. In addition, the possible retrograde amnesic effect of flunitrazepam was assessed. Just before the induction of anaesthesia the patients were shown two pictures (a horse and a car). On the first
day after operation these two pictures were mixed with eight others (presenting four different flowers, and four different butterflies) and the patients were asked to recognize the two pictures shown to them before anaesthesia. Serum concentrations of flunitrazepam were determined according to Kangas (1977) and the pharmacokinetic parameters for the agent calculated as described previously (Kanto et al., 1981).

RESULTS
Flunitrazepam was found to be an unsatisfactory induction agent for general anaesthesia in children. After the 0.03 mg kg\(^{-1}\) i.v. dose, the eyes closed spontaneously in 40, 50 and 70 s in three of four patients, and the palpebral reflex disappeared in 55, 90 and 180 s. However, all three reopened their eyes, and were given thiopentone 25–50 mg to deepen anaesthesia. The fourth patient, who received flunitrazepam 0.03 mg kg\(^{-1}\) i.v., did not close his eyes at all until 5 min after administration, and he then received thiopentone 50 mg. In two of the six patients receiving flunitrazepam 0.04 mg kg\(^{-1}\) i.v. the eyes closed spontaneously in 30 and 35 s, and the palpebral reflex disappeared in 55 and 85 s. No additional thiopentone was needed. The other four patients receiving flunitrazepam 0.04 mg kg\(^{-1}\) i.v. did not fall asleep until 5 min after administration, and they were given additional thiopentone 25–50 mg. Three of these four patients began to cry before the injection of thiopentone.

Good cardiovascular stability was observed during and after anaesthesia. Immediately afterwards, two patients vomited, one complained of nausea and hypoventilation lasting 30 min was noted in one patient (flunitrazepam 0.04 mg kg\(^{-1}\) i.v.).

In general, the patients were over sedated in the recovery room for up to 90 min. The four patients who had received flunitrazepam 0.03 mg kg\(^{-1}\) i.v. were either asleep (n = 2), or very sedated (n = 2) for up to 60 min after the end of anaesthesia. At 90 min the anaesthetist's assessment was: asleep (n = 1), moderately sedated (n = 2), alert (n = 1). Three of the six patients receiving flunitrazepam 0.04 mg kg\(^{-1}\) i.v. were asleep in the recovery room for up to 30 min, very sedated at 60 min, and moderately sedated at 90 min. The remainder were either moderately sedated (n = 2), or alert (n = 1) although they had experienced the longest anaesthetics (2.1, 2.5 and 3 h). The nursing staff in the recovery room

<table>
<thead>
<tr>
<th>Table I. Pharmacokinetic parameters (mean ± SD) derived from the serum concentrations of flunitrazepam after a single 0.03-mg kg(^{-1}) (n= 4) or 0.04-mg kg(^{-1}) (n= 6) injection i.v.</th>
<th>T1(^{a}) (h)</th>
<th>V(^a) (litre kg(^{-1}))</th>
<th>T1(^{b}) (h)</th>
<th>V(^b) (litre kg(^{-1}))</th>
<th>T1(^{c}) (h)</th>
<th>V(^c) (litre kg(^{-1}))</th>
<th>T1(^{d}) (h)</th>
<th>V(^d) (litre kg(^{-1}))</th>
<th>CI (ml min(^{-1}) kg(^{-1}))</th>
<th>AUC (µg litre(^{-1}) h(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flunitrazepam 0.03 mg kg(^{-1})</td>
<td>Mean</td>
<td>0.05</td>
<td>1.24</td>
<td>0.57</td>
<td>4.13</td>
<td>11.77</td>
<td>8.64</td>
<td>7.98</td>
<td>67.13</td>
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<tr>
<td></td>
<td>SD</td>
<td>0.02</td>
<td>0.90</td>
<td>0.32</td>
<td>1.46</td>
<td>3.65</td>
<td>4.42</td>
<td>2.08</td>
<td>22.35</td>
<td></td>
</tr>
<tr>
<td>Flunitrazepam 0.04 mg kg(^{-1})</td>
<td>Mean</td>
<td>0.06</td>
<td>0.93</td>
<td>0.72</td>
<td>9.52</td>
<td>11.99</td>
<td>12.57</td>
<td>11.93</td>
<td>83.96</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>0.06</td>
<td>0.88</td>
<td>0.41</td>
<td>3.66</td>
<td>4.40</td>
<td>11.02</td>
<td>8.15</td>
<td>58.98</td>
<td></td>
</tr>
</tbody>
</table>
and in the ward considered the patients over sedated and this required more nursing supervision.

Surprisingly, five of 10 patients did not need any analgesia after operation, and the other five patients only required analgesia at 60 min, 90 min, 5.5 h, 6 h and 7 h after anaesthesia.

No retrograde amnesia was observed: all the patients remembered the two pictures the following day, and they all remembered being taken to the operating theatre. However, strong anterograde amnesia was reported. No patient had any recollection of the induction of anaesthesia or of the subsequent awakening, and only one patient remembered the period in the recovery room. Three had no recollection of returning to the ward, but all remembered being in the ward on the evening of the day of operation. The youngest patient (3 yr), however, was not able to report this drug effect very reliably.

The serum concentrations of flunitrazepam are presented in figure 1 and the pharmacokinetic parameters derived from these are shown in table I. There was no correlation between any of these parameters and the observations obtained during the induction and maintenance of anaesthesia, or in the period after operation. The sole finding was that the three patients with the lowest degree of postoperative sedation woke up from anaesthesia during the flunitrazepam elimination phase when there were no longer any great alterations in the serum concentrations.

Discussion

Our results suggest that flunitrazepam is not an ideal agent with which to induce anaesthesia in children. It produces marked anterograde but no retrograde amnesia, and may have some analgesic sparing effect following operation. The pharmacokinetics of this nitrobenzodiazepine derivative in children differ substantially from those obtained in adults.

Although the age range of our patients was wide (3–10 yr) and the type of operation varied, there was no clear age dependency in the pharmacodynamic drug action of flunitrazepam as an induction agent, nor in its pharmacokinetics.

The main disadvantages of flunitrazepam as an induction agent were its slow and varying onset of action, and the long lasting postoperative sedation. The latter property clearly increased the nursing time both in the recovery room and in the ward in comparison with that required by patients given thiopentone. Thus, flunitrazepam, like other benzodiazepine derivatives, is a basic hypnotic com-
The two distribution phase half-lives of flunitrazepam were shorter in children than in adults (0.05–0.06 h v. 0.08–1.02 h, and 0.57–0.72 h v. 1.37–1.90 h) and the respective distribution volumes greater (0.93–1.24 litre kg⁻¹ v. 0.58–0.97 litre kg⁻¹, and 4.13–9.52 litre kg⁻¹ v. 1.43–2.40 litre kg⁻¹) (Kanto et al., 1981, Hovi-Viander et al., 1982; Kangas, Kanto and Pakkanen, 1982). Thus the tissue distribution of this agent was faster and more extensive in the paediatric patients.

REFERENCES


LE FLUNITRAZEPAM COMME AGENT D'INDUCTION CHEZ L'ENFANT

Etudes clinique et pharmacocinétique

RESUME

Le flunitrazepam a été étudié comme agent d’induction chez l’enfant. Le début d’action était lent et son efficacité incertaine après des injections intraveineuses uniques de 0,03 mg kg⁻¹ (n = 4) ou 0,004 mg kg⁻¹ (n = 6). Des effets sédatifs prolongés ont été observés après la fin de l’intervention. Une amnésie antérograde puisante a été obtenue ainsi qu’une économie possible d’analgésique, mais sans amnésie rétrograde. Le flunitrazepam a, chez l’enfant, une distribution tissulaire plus rapide et plus importante que chez l’adulte, ainsi qu’une élimination plus précoce ( demi-vie d’environ 12 h).

FLUNITRAZEPAM ALS EINLEITUNGSMEDIKAMENT BEI KINDERN

Eine klinische und pharmakokinetische Studie

ZUSAMMENFASSUNG

Flunitrazepam wurde als Einleitungsmedikament bei pädiatrischen Patienten untersucht. Der Wirkungseintritt erfolgte langsam, und nach Einzeldosen von 0,03 mg kg⁻¹ (n = 4) oder 0,04 mg kg⁻¹ (n = 6) war die Wirksamkeit unsicher. Nach der Operation wurden lange anhaltende sedative Effekte beobachtet. Es wurde ein starker anterograd, jedoch kein retrograd anamnestischer Effekt und eine mögliche Analgetika-sparende Eigenschaft gefunden. Flunitrazepam hat bei Kindern eine schnellere und ausgedehntere Gewebeverteilung und eine schnellere Elimination (Halbwertzeit nur 12 Stunden) als bei Erwachsenen.

EL FLUNITRAZEPAN COMO AGENTE DE INDUCCION EN NIÑOS

Un estudio clínico y farmacocinético

SUMARIO

Se estudió el flunitrazepán como agente de inducción en pacientes pediátricos. El principio de la acción era lenta y su eficacia incierta después de dosis únicas de 0,03 mg kg⁻¹ (n = 4) o 0,04 mg kg⁻¹ (n = 6) por vía i.v. Se observaron efectos sedativos de larga duración después de la operación. Se obtuvo un efecto amnésico fuerte anterogrado pero no retrogrado y una propiedad probable de economía analgésica. El flunitrazepán posee una distribución en los tejidos más rápida y más extensa y una eliminación más rápida (medida vida de 12 h aproximadamente) en los niños que en los adultos.