Oral preanaesthetic medication for children: double-blind randomized study of a combination of midazolam and ketamine vs midazolam or ketamine alone†

W. Funk*, W. Jakob, T. Riedl and K. Taeger

Department of Anaesthesiology, University of Regensburg, 93042 Regensburg, Germany
*Corresponding author

Anxiolysis and sedation with oral midazolam are common practice in paediatric anaesthesia. However, good or excellent results are seen in only 50–80% of cases. For this reason, we investigated if addition of a low dose of oral ketamine (MIKE: ketamine 3 mg kg⁻¹, midazolam 0.5 mg kg⁻¹) resulted in better premedication compared with oral midazolam 0.5 mg kg⁻¹ or ketamine 6 mg kg⁻¹ alone, in a prospective, randomized, double-blind study. We studied 120 children (mean age 5.7 (range 2–10) yr) undergoing surgery of more than 30 min duration. After oral premedication in the ward and transfer, the child’s condition in the induction room was evaluated by assigning 1–4 points to the quality of anxiolysis, sedation, behaviour at separation from parent and during venepuncture (transfer score). On days 1 and 7 after operation, parents were interviewed for changes in behaviour (eating, sleep, dreams, toilet training), recollection and satisfaction, using a standardized questionnaire. The groups were similar in age, sex, weight, intervention and duration of anaesthesia. The transfer score was significantly better in the MIKE group (12.5 (95% confidence interval (CI) 11.9–13.1)) than in the ketamine or midazolam groups (10.6 (9.8–11.4) and 11.5 (10.7–12.3), respectively). Success rates for anxiolysis and behaviour at separation were greater than 90% with the combination, approximately 70% with midazolam and only 51% with ketamine alone. The incidence of salivation, excitation and psychotic symptoms was low in all groups. Vertigo and emesis before induction were significantly more frequent after ketamine premedication. During recovery, there were no differences in sedation or time of possible discharge. After 1 week, parents reported nightmares (ketamine five, midazolam three, MIKE one), restless sleep (five/four/four) or negative memories (three/four/one). There were no major or continuing disturbances in behaviour or development. In summary, significantly better anxiolysis and separation were observed with a combination of ketamine and midazolam, even in awake children (sedation was not successful according to the preset criteria), than with midazolam or ketamine alone. Duration of action and side effects of the combination were similar to those of midazolam. The combination of both drugs in strawberry flavoured glucose syrup (pH 4.5 approximately) is chemically stable for 8 weeks.

Br J Anaesth 2000; 84: 335–40

Keywords: premedication, midazolam; premedication, ketamine; sedation; children

Accepted for publication: October 4, 1999

© The Board of Management and Trustees of the British Journal of Anaesthesia 2000

Anxiolysis and sedation using preoperative medication is still common practice in paediatric anaesthesia.1 Key features of good premedication are easy application, rapid onset, short duration of action and lack of significant side effects. Midazolam meets these criteria with its multiple routes of administration (oral, rectal, nasal), an onset time of 10–20 min, duration of action of approximately 30 min2 and no interference with vital signs in doses less than 0.5 mg kg⁻¹.3 Therefore, it has become the most widely used paediatric premedication in Europe and the USA.4,5 However, good or excellent results are seen in only 60–80% of cases.3,6–7 In our own young patients presenting for dental repair, the success rate was even lower (50%).

Ketamine has similar pharmacodynamics8 after oral administration and has been investigated as an alternative premedication.9–11 In these studies, doses of 3–6 mg kg⁻¹ were used. The authors reported a high overall success rate without significant side effects. However, it is widely acknowledged that ketamine i.v. or i.m. causes hallucina-

†Part of this work originates from the dissertation of T. Riedl (unpublished).
tions in many patients. Even subanaesthetic concentrations of ketamine produce psychedelic effects when given i.v.\textsuperscript{12} There are no such data in paediatric patients for oral administration, following which there is a high first pass metabolism.\textsuperscript{8} The metabolite norketamine causes sedation and analgesia also, but little is known of its side effects. A comparative study of oral ketamine or midazolam in children was aborted after undesirable side effects from ketamine 6 mg kg\textsuperscript{-1}, including increased secretions, hallucinations and dysphoria.\textsuperscript{13} Beebe and colleagues\textsuperscript{14} were the first to compare a combination of rectal midazolam 0.5 mg kg\textsuperscript{-1} and rectal ketamine 3 mg kg\textsuperscript{-1} with both drugs given alone. They found that both midazolam alone and the combination were equally useful techniques when i.v. induction of anaesthesia was desired. Psychotomimetic side effects were not addressed. Another study by Warner, Cabaret and Velling\textsuperscript{6} compared midazolam 0.5 mg kg\textsuperscript{-1} orally with either ketamine 6 mg kg\textsuperscript{-1} orally or a combination (0.4 and 4 mg kg\textsuperscript{-1}), and found the mixture to be the most effective premedicant as judged by ease of separation and mask acceptance. They stated that ‘no psychological disturbances were noted in the immediate postoperative period’, but gave no details on the method of assessment.

Considering the small data base and lack of studies on possible psychotomimetic side effects, we have investigated if the combination of a low dose of oral ketamine with midazolam provides better premedication than either oral midazolam or ketamine alone, in a prospective, randomized, double-blind study. With the intention of maintaining the anxiolysis provided by midazolam and adding the sedative and analgesic qualities of ketamine without psychodelic side effects, we chose to combine midazolam 0.5 mg kg\textsuperscript{-1} with ketamine 3 mg kg\textsuperscript{-1}.

### Patients and methods

After obtaining approval from the Ethics Committee of the Medical Faculty, we studied 120 healthy children (ASA I/II), aged 2–10 yr, undergoing surgery of more than 30 min expected duration. Exclusion criteria were ASA III or higher, severe dysfunction of the CNS or increased intracranial pressure, malformations of the cardiovascular system, hypertonus, hyperthyroidism and long-term therapy with theophylline or hepatic enzyme-inducing drugs. Informed parental consent was obtained at least 24 h before the start of operation. Children were allocated to one of three study groups using computer-generated random numbers (MS-EXCEL): group 1 received midazolam 0.5 ml kg\textsuperscript{-1}, group 2 was given ketamine 6 mg kg\textsuperscript{-1} and group 3 received midazolam 0.5 mg kg\textsuperscript{-1} with ketamine 3 mg kg\textsuperscript{-1} (MIKE). Medications were prepared by the pharmacist according to the randomized sequence using strawberry flavoured glucose syrup as a carrier and filled into bottles containing 12.5 ml (maximum dose) tagged with the study number only. The combination of both drugs in glucose syrup (pH 4.5 approximately) is chemically stable for 8 weeks (own data, remaining activity >90% for both, HPLC). Concentrations of midazolam and ketamine were chosen to result in doses of 0.5 ml kg\textsuperscript{-1} body weight.

One to two hours before surgery, a mixture of local anaesthetics (EMLA, Astra Chemicals, Germany) was applied to possible sites of venepuncture. Thirty minutes before induction, premedication was given in the presence of one of the investigators (T. R.). Patients who refused to take the whole dose were excluded from further analysis. Before medication and every 5 min thereafter, sedation and emotional status were assessed using the descriptions given in Table 1.

Twenty minutes after oral premedication in the ward, children were transferred with a parent to the operating room entrance. The child’s condition was evaluated after 30 min by the anaesthetist on duty with a scale assigning 1–4 points to the quality of sedation and anxiolysis, behaviour at separation from parent and during venepuncture using the terms given in Table 2. Scoring of sedation, anxiolysis and behaviour was performed immediately after the parents were out of sight, with no further transfer. Venepuncture was done approximately 5 min later in the induction room.

The scores were adopted from published studies investigating paediatric premedication.\textsuperscript{9} 14–17 Similar scores are used commonly to reduce subjectivity but are not validated in a strict sense for this or any other paediatric age group. For statistical evaluation, the scores were condensed to a dichotomous variable consisting of success (scores 3 and 4) or no success (scores 1 and 2). Furthermore, the items of the evaluation at entrance to the operating room were combined by simple addition to a single variable called transfer score (4–16 points).

In 111 children, anaesthesia was induced with propofol 2–3 mg kg\textsuperscript{-1} i.v.; two patients had inhalation induction with sevoflurane. Anaesthesia was maintained according to the anaesthetist’s usual practice with propofol or sevoflurane, mivacurium and alfentanil, as needed. Postanaesthetic recovery was evaluated using a modified Aldrete score\textsuperscript{18} every 10 min. A score of 9 points was considered sufficient for discharge to the ward. On days 1 and 7 after operation, parents were interviewed either in person (day 1) or by telephone (day 7) for changes in behaviour (eating, sleep, dreams, toilet training), quality of recollection and satisfaction using the questionnaire shown in Table 3. The content of recollections was assessed by age-appropriate questions about puncture, induction or surroundings. Parents were

<table>
<thead>
<tr>
<th>Score</th>
<th>Sedation</th>
<th>Emotional status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Alert</td>
<td>Combative</td>
</tr>
<tr>
<td>2</td>
<td>Awake</td>
<td>Tearful</td>
</tr>
<tr>
<td>3</td>
<td>Drowsy</td>
<td>Calm</td>
</tr>
<tr>
<td>4</td>
<td>Asleep</td>
<td>Amiable</td>
</tr>
</tbody>
</table>

Table 1 Scoring of sedation and emotional status in the ward.
Table 2 Scoring of sedation, emotional status and behaviour during separation from parent and on venepuncture. Patients with a score of 1 and 2 were combined for evaluation as ‘no success’, and those with scores of 3 and 4 as ‘success’

<table>
<thead>
<tr>
<th>Score</th>
<th>Sedation</th>
<th>Anxiolysis</th>
<th>Separation</th>
<th>Puncture</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Alert</td>
<td>Panicky</td>
<td>Comitative, clinging</td>
<td>Fight w/o success</td>
</tr>
<tr>
<td>2</td>
<td>Awake</td>
<td>Moaning</td>
<td>Anxious, consolable</td>
<td>Fight with success</td>
</tr>
<tr>
<td>3</td>
<td>Drowsy</td>
<td>Composed</td>
<td>Calm</td>
<td>Minor resistance</td>
</tr>
<tr>
<td>4</td>
<td>Asleep</td>
<td>Friendly</td>
<td>Sleeping</td>
<td>No reaction</td>
</tr>
</tbody>
</table>

Table 3 Assessment of postanaesthetic course on days 1 and 7 after operation

<table>
<thead>
<tr>
<th>Sleep</th>
<th>Wakes up often</th>
<th>Restless</th>
<th>Like before</th>
<th>Better</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dreams</td>
<td>Nightmores</td>
<td>Negative</td>
<td>None</td>
<td>Positive</td>
</tr>
<tr>
<td>Contience</td>
<td>New enepressis</td>
<td>New enuresis</td>
<td>No change</td>
<td>Better</td>
</tr>
<tr>
<td>Eating</td>
<td>Refusal</td>
<td>New habits</td>
<td>No change</td>
<td>Better</td>
</tr>
<tr>
<td>Recollection</td>
<td>Negative</td>
<td>Indifferent</td>
<td>None</td>
<td>Positive</td>
</tr>
<tr>
<td>Development</td>
<td>Regression</td>
<td>New achievements</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td>Same procedure if needed?</td>
<td>Never again</td>
<td>Other</td>
<td>Indifferent</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Table 4 Patient characteristics (mean (SD or range) or number)

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>Sex (M/F)</th>
<th>OR time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketamine (n=36)</td>
<td>5.8 (2.2–9.8)</td>
<td>20.8 (4.8)</td>
<td>14/22</td>
</tr>
<tr>
<td>Midazolam (n=38)</td>
<td>5.7 (2.5–10.1)</td>
<td>19.6 (4.7)</td>
<td>19/19</td>
</tr>
<tr>
<td>MIKE (n=39)</td>
<td>5.7 (2.0–9.3)</td>
<td>19.6 (4.6)</td>
<td>17/22</td>
</tr>
</tbody>
</table>

Sample size determination and statistical analysis

Sample size determination and statistical analysis

The study was designed to detect an increase in success rate from 65% to 90% with a power of 80% and an alpha error of less than 5%. Success was defined as a score of 3 or 4 for the items ‘sedation’, ‘anxiolysis’ and ‘separation’. The 65% success rate was taken from a pilot study using our routine premedication with midazolam 0.5 mg kg⁻¹ (n=20). A success rate of 90% was seen as a clinically meaningful improvement justifying addition of ketamine. Using an empirical calculation given by Lerman,¹⁹ ²⁰ sample size was estimated as 40 patients in each group for comparison of midazolam and the combination. Another 40 patients were included as a control group receiving ketamine only. For evaluation of the proportion of successful premedications, non-parametric one-way analysis of variance (Kruskal–Wallis) was used followed by chi-square tests for ‘success’, side effects, sex and operative procedure. To identify differences in age, weight and transfer score, Wilcoxon’s rank sum test was applied. The time course of sedation in the ward was analysed using Duncan’s multiple range test.²¹

Results

Groups were comparable in age, sex, weight, intervention and duration of anaesthesia (Table 4). Age variance was the same in all three groups. Operative procedures were evenly distributed and included strabismus correction (56%), dental repair (17%), tonsillectomy (17%) and laser coagulation of port wine stains (10%). Seven patients were excluded: six children did not drink the total volume and one child did not have surgery on the same day.

Time course of effects

After just 10 min, an increase in the proportion of successfully premedicated children was observed. After 20 min, transfer was initiated. At this time, approximately 60% of children were sedated successfully (Fig. 1). Success was independent of the substance used. Based on our method of judgement, the time course of the effects was similar in the three groups. No differences were found in emotional status. Most children were calm or even amiable before ingestion of the syrup.

Transfer score and success of premedication

On transfer, patients were scored by the anaesthetist on duty who was unaware of the substances used and time of
application. The transfer score at this time was significantly better in the MIKE group (median 13 (range 4–16)) than in the ketamine or midazolam groups (11 (4–15) and 12 (4–15)). Success rates for anxiolysis and behaviour at separation were greater than 90% with the combination, approximately 70% with midazolam and only 51% with ketamine alone (ns) (Fig. 2). The success rate of sedation was low in all groups. However, the sedation score used in this study classifies an awake state as no success. Venepuncture was painless for most patients probably because of the use of EMLA cream, with no difference between midazolam and the combination.

Side effects
Clinically significant side effects were observed only with ketamine (Table 5). One child vomited during induction but had an uneventful recovery. The increased incidence of emesis and vertigo ($P<0.05$ vs midazolam and MIKE) caused severe discomfort and was probably responsible for the low success rate in the ketamine group. Psychodelic symptoms (‘high’) such as visual or auditory hallucinations, altered sensations of self or surrounding during recovery, or parent reports of unusual behaviour (anxiety, happiness) were assessed as free observations by a single investigator (T. R.). No differences were found between groups. Salivation was similar with all premedicants and was not of concern during induction of anaesthesia. Oxygen saturation before induction was $\geq 97\%$ in all children. Excessive sedation did not occur.

Postanaesthetic recovery
During recovery from anaesthesia, no differences were observed in times to extubation and possible discharge, as assessed by an Aldrete score of 9 or 10 points ($P>0.05$) (Table 6). More children vomited during early recovery with ketamine. Statistical evaluation of the incidence of PONV during the first 24 h revealed no difference.

One day after anaesthesia, some children had restless sleep, nocturia or bad dreams, but there were no significant differences between the three groups. Almost 50% of patients had complete amnesia for the time between leaving the ward and reunion with the parent in the recovery room (Table 7). To investigate the quality of recollections, children were asked for specific features of rooms, wall paints, colour of blankets and clothes, anaesthesia machines, specific sounds, circumstances of venepuncture and induction, pain and anxiety. Only very few children remembered pain or other negative feelings, and there was no difference between groups. One week later, most children had resumed their previous routines. There were no signs of regression, despite two instances of new, transient nocturia. Parents reported restless sleep but no bad dreams in approximately $10\%$ of patients. Nine children had one or more episodes of nightmares during the first week. Differences in the incidence of this event between groups were not statistically significant. Only two children had nightmares for more than 4 days (one after midazolam, one after MIKE) which both continued for 2 weeks. Thereafter, sleep returned to normal. After 1 week, only eight of 113 children had a negative recollection of the anaesthetic procedure.

Discussion
Our study provides evidence that a combination of midazolam and ketamine results in better premedication than the individual drugs given alone. The study was performed at a large university hospital treating predominantly adult patients. Our facility does not include specifically equipped child care areas. Only a few members of the anaesthesia team have long-term experience in paediatric anaesthesia. For these reasons, and in accordance with the ethics committee, we decided not to include a placebo control. The majority of specialized hospitals in Germany (>95%) use midazolam as premedication. Most parents expect premedication for their children because of previous experience or information available to the public. In contrast, a 1990 review of placebo-controlled studies on pre-induction behaviour in children reported satisfactory behaviour of 52–92% (median 71%) of patients allocated randomly to oral placebo premedication. There was no proof for the superiority of midazolam over placebo. Since 1990, several studies have been published demonstrating a slight advantage of midazolam over placebo. Others found no difference. A smooth transition from parental care to nurse and physician care and back is dependent on individual institution and patient factors, rendering comparison of different studies difficult. In addition, differences in the scores used impede direct comparison. With midazolam 0.5 mg kg$^{-1}$, investigators from the Hospital for Sick Children in Toronto found a comparably low success rate for sedation using the same score. However, anxiolysis (score comparable with our ‘separation’) in their study was very successful. In our environment, separations after midazolam premedication were unsatisfactory and prompted us to investigate another regimen.
Oral ketamine was used in the 1970s by dentists to facilitate the treatment of mentally handicapped children. In 1982, Cetina\textsuperscript{24} found that rectal or oral preanaesthetic medication with ketamine 15 mg kg\textsuperscript{-1} combined with droperidol was superior to i.m. or i.v. premedication. At first glance, 15 mg kg\textsuperscript{-1} seems to be a very high dose, but only 16\% of oral ketamine is bioavailable because of high hepatic first pass metabolism.\textsuperscript{9} Part of the clinical effects of oral ketamine are attributable to its metabolite norketamine which has approximately one-third the potency, but reaches higher blood concentrations. An early controlled and blinded study was published by Steward and colleagues\textsuperscript{25} in 1990. They found that a combination of ketamine 10 mg kg\textsuperscript{-1} and trimipramine was superior to morphine and trimipramine in paediatric cardiac surgery. Gutstein and colleagues\textsuperscript{9} compared oral premedication with ketamine 3 or 6 mg kg\textsuperscript{-1}, in a blinded, randomized, placebo-controlled study. With 3 mg kg\textsuperscript{-1}, 73\% of their children were sleepy or asleep after 30 min (100\% with 6 mg kg\textsuperscript{-1}). Significant side effects were not observed. Sekerci and colleagues\textsuperscript{11} presented a similar study in 1996. They observed 80\% successful separations with ketamine 3 mg kg\textsuperscript{-1}. Ketamine 6 mg kg\textsuperscript{-1} did not improve success but increased side effects such as nystagmus and vomiting. We were unable to reproduce the success of these studies in our ketamine group (6 mg kg\textsuperscript{-1}) and have no obvious explanation. Alderson and Lerman\textsuperscript{17} compared ketamine 5 mg kg\textsuperscript{-1} with midazolam 0.5 mg kg\textsuperscript{-1} and reported similar clinical characteristics. However, as in our study, more children were tearful with ketamine 15 mg kg\textsuperscript{-1} combined with droperidol was superior to i.m. or i.v. premedication. At first glance, at separation and induction in the ketamine group. No significant side effects were observed.\textsuperscript{15} 15 mg kg\textsuperscript{-1} seems to be a very high dose, but only 16\% of oral ketamine is bioavailable because of high hepatic first pass metabolism.\textsuperscript{8} Part of the clinical effects of oral ketamine are attributed to its metabolite norketamine which has similar side effects have been published for oral administration.\textsuperscript{13 26} Even subanaesthetic plasma concentrations produced psychedelic effects in volunteers.\textsuperscript{12} A combination with a minor tranquilizer seems to be a logical answer to this problem and could at the same time broaden the pharmacodynamic profile.

The combination of ketamine and midazolam was described initially in 1992 by Beebe and co-workers\textsuperscript{14} for rectal, and in 1993 by Lin, Moynihan and Hackel\textsuperscript{27} for oral administration. Both groups used a combination of midazolam 0.5 mg kg\textsuperscript{-1} with ketamine 3 mg kg\textsuperscript{-1}. In Beebe’s study,\textsuperscript{14} separation was satisfactory with midazolam alone. Complications were low and similar between groups. Psychedelic side effects were not reported by the investigators. Lin, Moynihan and Hackel\textsuperscript{27} reported no differ-
ence in behaviour at separation or induction after administration of midazolam 0.75 mg kg$^{-1}$, ketamine 6 mg kg$^{-1}$ or the same combination, as in our study. Their success rate using the combination was about 80% at separation and 70% at induction. However, they found a faster onset time (vs both other groups), less oral secretions and nystagmus (vs ketamine) and faster recovery (vs midazolam). No postoperative complications, such as dreaming or nightmares, were observed. Warner, Cabaret and Velling found that a mixture of midazolam 0.4 mg kg$^{-1}$ and ketamine 4 mg kg$^{-1}$ was significantly more effective than midazolam 0.5 mg kg$^{-1}$ or ketamine 6 mg kg$^{-1}$ alone in their partially blinded study. They noted no psychological disturbances in the immediate postoperative period but gave no details about the evaluation of this crucial issue.

It has been suggested that oral rather than i.m. ketamine should produce less side effects because of the different pharmacodynamics of its metabolite norketamine. However, a study of 100 children undergoing oral surgical procedures reported hallucinations in 20% of patients with ketamine 5 mg kg$^{-1}$–midazolam 0.35 mg kg$^{-1}$. This high incidence may be a result of an unfortunate combination of doses. However, it is surprising that studies using only ketamine found no such problem. We tried to address the issue of psychedelic side effects with two structured interviews. The ketamine group had a slightly higher incidence of restless sleep and nightmares, but midazolam and the combination were equally well tolerated, as judged by our simple questions. In contrast, the incidence of vertigo and vomiting in children premedicated with ketamine alone precludes the further use of this regimen in our institution.

In summary, the results of our randomized, double-blind study confirm the basic findings of previous work which indicate that adding a low dose of ketamine to oral midazolam increases the success of premedication to greater than 90% without increasing side effects or prolonging recovery. The lower degree of sedation in our study is no disadvantage as long as successful separation and venepuncture coincide with good anxiolysis. Side effects were low and similar to midazolam alone.

References

6 Warner DL, Cabaret J, Velling D. Ketamine plus midazolam, a most effective paediatric premedicant. Paediatr Anaesth 1995; 5: 293–5
8 Grant IS, Nimmo WS, Clements JA. Pharmacokinetics and analgesic effect of i.m. and oral ketamine. Br J Anaesth 1981; 53: 805–9
13 Gingrich BK. Difficulties encountered in a comparative study of orally administered midazolam and ketamine. Anesthesiology 1994; 80: 1414
20 Lerman J. Sample size estimation for nominal data. Can J Anaesth 1997; 44: 901
26 Donahue PJ, Dineen PS. Emergence delirium following oral ketamine. Anesthesiology 1992; 77: 604–5
27 Lin YC, Moynihan RJ, Hackel A. A comparison of oral midazolam, oral ketamine and oral midazolam combined with ketamine as preanesthetic medication for pediatric outpatients. Anesthesiology 1993; 70: A1177