Clinical Trial of Nasal Flumazenil Administration

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국문초록

플루마체닐의 경비 투여

홍수진 · 김현정 · 염광원

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플루마체닐은 벤조디아제핀계 약물의 강함계로서, 경주로 동하여 채내에 투여된다. 그러나 경주로 확보되지 않은 상황에서 플루마체닐의 강함작용이 필요한 경우에는 경주로 이외의 채내 투여로가 요구된다. 본 연구에서는 미다졸람으로 심진정을 유도한 후 플루마체닐의 경비투여로 인한 의식 상태의 가역을 임상시험하였다.

성인 남녀 25명을 대상으로 미다졸람을 소량의 0.08mg/kg까지 투여하여 의식소실을 유도하였다. 미다졸람 투여 10분 후 플루마체닐 0.5mg을 1분 동안 주사기를 이용하여 천천히 경비투여하였다. 환자감시에는 심전도, 자동혈압계, 호기량 이상화, 탄소분만, 액박산소포화도 등을 사용하였다. 진정 정도는 진정점수와 뇌파감사를 이용한 bispectral index로 평가하였다. 플루마체닐 투여 직전에 미다졸람과 플루마체닐의 혈중 농도를, 플루마체닐 투여 후 5, 10, 15, 20분 후에 혈청 플루마체닐 농도를 측정하였다.

플루마체닐의 경비투여 후 완전한 강함효과를 나타낸 경우는 전체 25명 중 2명이었다. 혈청 플루마체닐의 농도는 투여 10분 후에 최고치에 도달하였고, 20분간 지속되었다. 진정점수는 미다졸람 투여 후 증가한 뒤 플루마체닐 투여 후 유의하게 감소하였다(p<0.05). 그러나 bispectral index는 미다졸람 투여 후 시간경과에 따라 유의하게 감소하였으나, 플루마체닐 투여 후에는 유의한 변화를 보이지 않았다.

결론적으로 0.1mg/ml 농도의 플루마체닐 0.5mg 경비투여는 미다졸람으로 유도된 심진정시 강함효과가 완전하지 않았으나, 경비투여 후 혈액에서 플루마체닐의 농도측정이 가능하다는 결과는 임상사용 가능성을 제시하며, 경주용으로 사용되는 플루마체닐의 농도가 낮은 점을 보완할 수 있는 새로운 환자의 고단이 필요하다고 생각된다.

주요 : 플루마체닐, 경비투여, 미다졸람, 크로마토그래피

1. Introduction

Benzodiazepine derivatives have been widely used for the purpose of premedication, sedation and induction of anesthesia. Benzodiazepines are known to develop less side effects than any other sedative, and midazolam is one of the most popular benzodiazepines used in dental clinic. It has anxiolytic, hypnotic, anticonvulsant, muscle relaxant and anterograde amnesic effects. In recent years, midazolam has found increasing favor because of rapid onset, relatively short half-life and its pharmacologically inactive metabolites. In addition to these advantages, midazolam sedation is accomplished without loss of airway reflexes or significant cardiovascular changes.

Available routes of midazolam administration are oral, nasal, rectal, intramuscular and intravenous route. The intravenous injection is the most reliable. However, most
dentists are less familiar with intravenous catheterization, and they tend to use other routes.

Benzodiazepines produce dose-dependent respiratory and cardiovascular depression and loss of consciousness. If these side effects develop, the competitive antagonist, flumazenil, is available. Flumazenil, a water-soluble imidazobenzodiazepine, is the first specific competitive benzodiazepine antagonist available for clinical use. Flumazenil, approved for complete and partial reversal of the sedative effects of benzodiazepines, is used during conscious sedation and also in the management of benzodiazepine overdose. It has a high affinity for the GABA-BZ receptor and antagonizes the effects of midazolam on the central nervous system.

The efficacy of intravenous flumazenil administration in reversing the sedation produced by midazolam has been evaluated in several studies. However, midazolam is used for the purpose of conscious sedation via various routes other than intravenous, nasal flumazenil administration may be useful to reverse sedation.

The purpose of this study was to evaluate the safety and efficacy of nasal flumazenil administration for the reversal of midazolam-induced deep sedation in adult volunteers.

II. Materials and Methods

Twenty-five young, healthy, American Society of Anesthesiologists Physical Status (ASA PS) 1 subjects participated in this study. Informed written consent was obtained from all volunteers. They had no systemic diseases and no known allergies to midazolam and flumazenil. All sessions were performed in a post-anesthetic care unit, with airway management and cardiopulmonary resuscitation equipment readily available.

An intravenous catheter was placed in the left antecubital vein, was used for midazolam administration and the other right antecubital intravenous route was used as blood sampling. Heart rate, respiratory rate, automated non-invasive blood pressure, axillary skin temperature, end-tidal carbon dioxide tension (EtCO₂), and arterial oxyhemoglobin saturation (SpO₂) were monitored. Oxygen, at a flow rate of 5 l/min, was supplied to the volunteers via a facial mask during sedation.

Ten minutes after stabilizing periods, we administered 0.08mg/kg of midazolam intravenously over two to three minutes. We measured sedation score (Table 1) and bispectral index (A-2000 BIS™ monitor, Aspect Medical Systems, USA) to evaluate volunteer’s level of consciousness. To evaluate the sedation score with consistency, only one medical personnel engaged in the assessment.

Ten minutes after midazolam injection, 0.5mg flumazenil was administered nasally using a syringe without needle over a period of one minute.

Multiple blood samples were taken prior to and 5, 10 and 20min after flumazenil administration. To measure midazolam concentration, blood samples were also taken prior and 10min after midazolam administration.

The blood samples were immediately centrifuged with 2500 rpm for 15min and were stored at -20°C until assayed. Plasma midazolam and serum flumazenil concentrations were measured using high performance liquid chromatography (HPLC).

Each data have been analyzed statistically by multivariate ANOVA and correlation analysis (P < 0.05).

III. Results

Demographic data of volunteers were shown in Table 2. Sedation score decreased after midazolam administration(p<0.05), which means an increase in sedation depth, and showed a significant increase after flumazenil administration, which means a recovery from the sedation state(Fig. 1). However, BIS decreased during the first 10min after midazolam administration (p<0.05).

Table 1. Sedation Score

<table>
<thead>
<tr>
<th>Score</th>
<th>Response</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Fully awake and oriented</td>
</tr>
<tr>
<td>2</td>
<td>Drowsy</td>
</tr>
<tr>
<td>3</td>
<td>Eyes closed but rousable to command</td>
</tr>
<tr>
<td>4</td>
<td>Eyes closed but rousable to mild stimulation</td>
</tr>
<tr>
<td>5</td>
<td>Eyes closed but unrousable to mild physical stimulation</td>
</tr>
</tbody>
</table>

Table 2. Demographic data of volunteers

<table>
<thead>
<tr>
<th>N</th>
<th>25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (m/f)</td>
<td>15/5</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>23.9±1.6</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>62.6±13.2</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>169.9±7.9</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD.
Fig. 1. Changes of sedation score after midazolam and flumazenil administration (M: midazolam, F: flumazenil).

Fig. 2. Changes of Bispectral Index after midazolam and flumazenil administration (M: midazolam, F: flumazenil).

Fig. 3. Changes in plasma flumazenil concentration after nasal flumazenil administration.

and then no significant changes after flumazenil administration (p>0.05, Fig. 2).

Plasma midazolam concentration 10min after the first administration was 0.61±0.25ng/ml. Serum concentrations of flumazenil show a statistically significant increase over time (p<0.05). Serum flumazenil concentration was 3.61±2.62ng/ml 10min later, representing a wide range of individual variability (Fig. 3). Peak serum concentration of flumazenil was reached at 10min after drug administration. There were only two subjects completely reversed from midazolam deep sedation with nasal flumazenil administration.

N. Discussion

To reverse benzodiazepine induced sedation, the manufacturer recommends an initial intravenous dose of 0.2 mg, which can be repeated at one-minute interval, if necessary, up to a maximum cumulative dose of 1mg\textsuperscript{10}. When flumazenil given intravenously, it reaches peak serum levels within a few minutes and has an initial distribution half-life of 7 to 15min and a volume of distribution of 1.6l/kg, which indicates significant tissue uptake. It is primarily metabolized by the liver, and has a terminal half-life of 41 to 79min. The pharmacokinetics of flumazenil are not significantly affected by age, sex or renal impairmen\textsuperscript{t}. Flumazenil can cause nausea, dizziness, headache, blurred vision, increased sweating, agitation, hot flushes, sweating and may provoke a panic attack in some patients. In various animal studies, flumazenil has been shown to have very low degree of toxicity\textsuperscript{9}. There were no recognizable adverse effects associated with flumazenil in this study, because we used relatively small amount of flumazenil.

In the conscious sedation, mean midazolam plasma concentration of 160±64ng/ml, the mean half-life of the equilibration rate constant of flumazenil reversal is 5.0±2.5min, and the mean effect site concentration causing 50% of Emax is 13.7±5.8ng/ml. However, in the deep sedation level, with a mean midazolam plasma concentration of 551±196ng/ml, the mean half-life of the equilibration rate constant of flumazenil reversal is 3.9±1.5min, and the mean effect site concentration causing 50% of Emax is 20.6±6.8ng/ml\textsuperscript{11}. Previous studies indicated that a midazolam serum concentration plateau of 600ng/ml is necessary to produce a deep hypnotic effect\textsuperscript{12}. Because the level of consciousness was titrated to produce sleep in this study, mean plasma midazolam concentration was 610ng/ml, which was compatible with deep sedation at ten minutes after midazolam injection.

A sedation scale was developed to measure the level of
alertness in sedated patients. This scale was tested for reliability and validity, and was found to be sensitive to the amount of midazolam administered. In addition to sedation score, BIS was adopted to monitor the depth of sedation, or hypnotic state. BIS is a single-processing technique that determines the harmonic and phase relations among the various frequencies in the electroencephalogram. BIS above 70 represents light sleep, or light to moderate sedation, state BIS 60–70 represents moderate sleep or deep sedation state, and a BIS below 60 represents a deep level of hypnosis. According to BIS in this study, above 70, volunteers were maintained under condition of light to moderate sedation state during the study. After nasal flumazenil administration, sedation scores are improved, but BIS were not changed. More clinical studies are needed to find the causes of this discrepancy between sedation score and BIS.

There have been many studies about nasal administration of midazolam. However, this is the first report about nasal administration of flumazenil concerning our knowledge. Though it is not so effective as intravenous drug administration, nasal route is more effective than any other route, such as oral, rectal and intramuscular methods. Therefore, it would be desirable to consider nasal flumazenil administration, in general, the drug administered by nasal route is more potent than a drug administered rectally.

The manufacturer’s recommended method of flumazenil administration is limited to intravenous sedation. However, it was reported that rectal administration of flumazenil to children aged between 1 month and 9 years to reverse midazolam sedation, turned out to be an effective method. Considering the advantages of intranasal route, intranasal administration of flumazenil to children may be more effective than rectal administration.

The nasal method does not have a first-pass effect, is less embarrassing than the rectal route and is a less invasive method than intra-muscular and intravenous administration, especially for those patients who show anxiety and are phobic to needles. On condition that an intravenous catheterization is clinically impossible, the nasal method appeared to be an effective alternative.

Nasal drug administration via syringe was performed in this study. Equal volume of the drug was administered to right and left nasal cavities. This method showed a wide range of individual variability, due to the possibility of inadvertent drug swallowing and difficulty in administering an accurate dose of the drug. To compensate for the disadvantages of nasal administration, technical improvement of nasal administration is needed.

In this study, complete reversal of midazolam by nasal flumazenil administration was observed in only two cases. We used low concentrated flumazenil, which is suitable for the intravenous injection. If more concentrated flumazenil is used clinically or flumazenil is used in child patient, more reversal cases would be observed. However, the fact that peak plasma flumazenil concentration was reached in 10 min after administration, represents an availability of nasal flumazenil administration against midazolam sedation, without using an intravenous route.

V. Conclusions

Although the onset time of nasal administration of flumazenil is slower than intravenous administration, it is possible that nasal route could be the initial route to administer flumazenil in patients without intravenous catheter to reverse the benzodiazepine sedation.

References

8. McCoy RF: Reversal of conscious sedation by


Abstract

CLINICAL TRIAL OF NASAL FLUMAZENIL ADMINISTRATION

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Flumazenil is a competitive antagonist of benzodiazepines. It is usually administered intravenously. However, if the intravenous route is not available then other routes of drug administration should be considered. This study was designed to evaluate the reversal effects of flumazenil after nasal administration.

Twenty-five young, healthy adult volunteers participated in this clinical trial. The dosage of 0.08mg/kg midazolam was administered intravenously to induce deep sedation. Ten minutes after midazolam administration, 0.5mg of flumazenil was dropped nasally, over a period of one minute. Blood samples were taken to measure the concentration of midazolam and flumazenil at 0, 5, 10, and 20min after nasal administration of flumazenil, using High Performance Liquid Chromatography. The degree of sedation was evaluated with sedation score and bispectral index (BIS). Statistical analysis was performed by multivariate ANOVA and correlation analysis (P < 0.05).

Peak serum flumazenil concentration was reached in 10min. Sedation score decreased after midazolam administration and showed a significant increase after flumazenil administration. However, BIS decreased during the first 10min after midazolam administration, and then no significant changes after flumazenil administration. There were two instances representing rapid and complete reversal of midazolam after intranasal administration of flumazenil.

In conclusion, intranasal flumazenil administration may be effective in some patients when intravenous route is not available in condition of benzodiazepine overdose.

Key words: flumazenil, intranasal administration, benzodiazepines, chromatography.