Assessment of side effects of generic injectable ritodrine hydrochloride products

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Aim: To compare the safety and efficacy of Utemerin, an original ritodrine hydrochloride drug formulation, with those of generic Ritodrine.

Methods: We examined patients who developed side effects, targeting 400 cases in which either Ritodrine or Utemerin was administered intravenously between 2006 and 2011.

Results: The number of cases with side effects was significantly greater in the Ritodrine group than in the Utemerin group (96 cases [48%] vs. 55 cases [27.5%], respectively; \( P < 0.001 \)). The most common side effect with both drugs was rash, which was significantly more frequent in the Ritodrine group than in the Utemerin group (40 cases [20%] vs. 25 cases [12.5%], respectively; \( P = 0.04 \)). The number of cases with mid-treatment changes owing to side effects did not significantly differ between groups (Ritodrine: 32 cases [16%] vs. Utemerin: 24 cases [12%]; \( P = 0.31 \)).

Conclusions: Side effects were more frequent with Ritodrine than with Utemerin. It has not been long since the introduction of generic drugs in Japan, and post-use studies conducted shortly after their introduction are insufficient. However, the use of generic drugs that are detrimental to patients are contraindicated, and thus post-use studies are needed to confirm generic drug safety and efficacy.

Introduction

Recently, generic drugs have been extremely useful in combating continuously rising medical costs in Japan. Introduction of the diagnostic procedure combination (DPC)-based fixed payment system of hospitalization costs at advanced treatment hospitals in April 2003 has further driven the switch to generic drugs. At the present hospital, a switch was made in 2008 from the original ritodrine hydrochloride drug formulation Utemerin (“Utemerin”; Kissei Pharmaceutical Co., Ltd., Japan) to the generic version Ritodrine (“Ritodrine”; Pola Pharma Inc., Japan). Ritodrine hydrochloride has been used to suppress uterine contractions in threatened premature labor in Japan, although many adverse effects were reported. Moreover, although the active ingredient is the same in both versions of the drug, it is difficult to conclude that they are completely identical owing to factors such as potential impurities intermixed during the manufacturing process. Here, we compare the side effects of both drugs.

Materials and methods

We selected 400 cases in which either Utemerin or Ritodrine (200 cases each) was administered intravenously to patients hospitalized at our institution for the management of threatened premature labor between 2006 and 2011. During study period, we exclude the case that changed the drugs, concretely “from Utemerin to Ritororine” or “from Ritodorine to Utemerin”, for side effect on the way. Medical records were obtained and...
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Variables including the following were comparatively analyzed between the Utemerin and Ritodrine groups: age, time of administration commencement, dosage, administration duration, presence or absence of side effects (e.g., rash, liver enzyme abnormalities, pulmonary edema, abnormal tachycardia, amylase [AMY] abnormalities, granulocyte reduction, and/or creatine kinase [CK] abnormalities), time of side effect onset, concurrent medications, and timing of delivery.

The methodology to evaluate side effects was determined based on the following criteria. Rash diagnoses were based on an examination by a dermatologist. Determination of improvement following a change in medication (or reduction in dosage), as well as rash grade, were based on the common terminology criteria for adverse events (CTCAE) Ver 4.0. Liver enzyme abnormalities were diagnosed when peak aspartate transaminase (AST) and alanine transaminase (ALT) levels surpassed normal values. Abnormal tachycardia was diagnosed when patient heart rate was at or greater than 120 beats per minute and forced a change in medication.

Statistical analyses were performed using JMP Ver. 10 software (SAS Institute Inc., Cary, NC, USA) and the significance threshold was set at \( P < 0.05 \). Frequency comparisons were made using the Chi-squared test, and assessment values were compared using Student’s \( t \)-test. This study was approved by the Saitama Medical University ethics committee.

### Results

#### Patient background

Patient background is shown in Table 1. While there were no significant differences in age, time of administration commencement, and administration duration, the average dosage in the Utemerin group was significantly lower than in the Ritodrine group (77 ± 3.9 \( \mu \)g/kg/min vs. 108.1 ± 3.9 \( \mu \)g/kg/min, respectively; \( P < 0.001 \)). The most common side effect with both drugs was rash, which was significantly more frequent in the Ritodrine group than in the Utemerin group (40 cases [20%] vs. 25 cases [12.5%], respectively; \( P = 0.04 \)). There were no significant differences in the timing of rash emergence. With both drugs, the majority (roughly half) of rash cases were recorded between the first and second weeks of administration (37/65 cases). Meanwhile, approximately 20% of rash cases were recorded after one month of drug administration (14/65 cases). There were no significant differences in rash grade.

Although there were no significant differences in the frequency of liver enzyme abnormalities, an examination of the timing of peak AST levels indicated that peak AST was reached significantly earlier in the Utemerin group than in the Ritodrine group (13.4 ± 1.6 days vs. 21 ± 1.6 days, respectively; \( P = 0.006 \)).

There were no significant differences between groups in incidence of pulmonary edema, abnormal tachycardia, AMY abnormalities, granulocyte reduction, and CK abnormalities.

Furthermore, the number of cases wherein suppressant drugs were switched or dosages were reduced did not differ significantly between groups (24 cases [12%] vs. 32 cases [16%] for Utemerin and Ritodrine groups, respectively; \( P = 0.31 \)).

#### Concurrent medications

Medications that were frequently, concurrently, and intravenously administered in both groups are shown in Table 3. Frequently administered concurrent medications included magnesium sulfate hydrate, as well as antibiotics such as sultamicillin tosylate, clindamycin, and cefozopran hydrochloride. Magnesium sulfate hydrate was administered in significantly more cases in the Ritodrine group than in the Utemerin group (57 cases vs. 21 cases; \( P < 0.001 \)). Meanwhile, sultamicillin tosylate, which is used to treat intravaginal infection and chorioamnionitis due to bacteria, was administered in significantly more cases in the Utemerin group than in the Ritodrine group (168 cases vs. 97 cases; \( P < 0.001 \)). There were no significant differences in the administration of clindamycin, cefozopran hydrochloride, and saccharated ferric oxide.

### Table 1. Patient background

<table>
<thead>
<tr>
<th></th>
<th>Utemerin</th>
<th>Ritodrine</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases</td>
<td>200</td>
<td>200</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>32.3 ± 0.3</td>
<td>32.5 ± 0.3</td>
<td>0.6756</td>
</tr>
<tr>
<td>Time of administration commencement (pregnancy day)</td>
<td>193.2 ± 2.4</td>
<td>192.9 ± 2.4</td>
<td>0.9321</td>
</tr>
<tr>
<td>Average dosage (( \mu )g/kg/min)</td>
<td>77.0 ± 3.9</td>
<td>108.1 ± 3.9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Number of days administered (days)</td>
<td>24.9 ± 1.7</td>
<td>27.8 ± 1.7</td>
<td>0.2272</td>
</tr>
</tbody>
</table>
Delivery timing and methods

Of the 400 cases in the present study, the delivery day and method are shown in Table 4 for 174 and 185 cases in the Utemerin and Ritodrine groups, respectively, for which tracking was possible. Delivery timing was significantly later in the Utemerin group than in the Ritodrine group (pregnancy day 252.5 ± 2.0 vs. pregnancy day 245.7 ± 1.9, respectively; \( P = 0.014 \)). There were no significant differences in premature birth rates between the Utemerin and Ritodrine groups. Although there were no significant differences in the frequency of optional and emergency caesarean sections, forceps deliveries were significantly more frequent in the Ritodrine group than in the Utemerin group (9 cases vs. 1 case, respectively; \( P = 0.02 \)).
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| Table 5. Multiple logistic regression analysis of factors influencing side effect occurrence |
|---------------------------------------------|-----------------|-----------------|
|                                            | Odds ratio (95% CI) | P               |
| Average dosage                             | 1.002 (0.997–1.006) | 0.4501          |
| Ritodrine (vs. Utemerin)                   | 2.303 (1.428–3.743) | 0.0006          |
| Magnesium sulfate hydrate                  | 2.163 (1.187–3.961) | 0.0119          |
| Sultamicillin tosylate                     | 1.393 (0.857–2.286) | 0.1821          |

The odds ratio for average dosage shows instances in which dosage increased by 1 μg/min.

| Table 6. Multiple logistic regression analysis of factors influencing rash occurrence |
|---------------------------------------------|-----------------|-----------------|
|                                            | Odds ratio (95% CI) | P               |
| Average dosage                             | 0.997 (0.991–1.003) | 0.2984          |
| Ritodrine (vs. Utemerin)                   | 2.475 (1.338–4.650) | 0.0038          |
| Magnesium sulfate hydrate                  | 1.147 (0.507–2.484) | 0.7343          |
| Sultamicillin tosylate                     | 2.261 (1.192–4.464) | 0.0120          |

The odds ratio for average dosage shows instances in which dosage increased by 1 μg/min.

**Multiple logistic regression analysis for causal factors of side effects**

Because there were significant differences in the occurrence of side effects, particularly rash, between the Utemerin and Ritodrine groups (Table 2), multiple logistic regression analysis was performed to identify factors influencing this occurrence.

Although there were significant differences between groups in dosage and concurrent medication (Tables 1 and 3), Ritodrine and magnesium sulfate hydrate were found to be significantly correlated with the overall occurrence of side effects (Table 5). Furthermore, Ritodrine and sultamicillin tosylate were found to be significantly correlated with the occurrence of rash (Table 6). Ritodrine played the largest role in overall side effect occurrence and the occurrence of rash.

**Discussion**

Preterm birth is said to occur at a rate of 9.6% and is implicated in 70% of newborn deaths. Therefore, the treatment of threatened premature labor and prevention of premature birth are extremely important issues in obstetrics and neonatology. By stimulating β2 adrenergic receptors and antagonizing prostaglandin production in a dose-dependent manner, ritodrine hydrochloride exerts a relaxing effect on uterine muscles, and has been an indispensable drug in daily obstetrics treatment since its approval and sale in 1986. Especially in Japan, ritodrine has been used to prolong pregnancy as much as possible, while in most western countries, it is restrictively and temporarily used to maintain pregnancy for a period less than 48 hours, which is long enough to allow women to be transferred to tertiary care or to complete a course of antenatal corticosteroids for the maturation of fetal lungs.

In many countries including Japan, a DPC-based fixed payment system for hospitalization costs has been introduced to the health insurance system, which prioritizes economic efficiency. As such, changes from original to generic drugs are frequently demanded. Because ritodrine hydrochloride is a frequently used drug, a shift to the use of its generic version is most likely to occur. Nevertheless, it is extremely important to investigate whether or not the generic version can be used safely. The results of the present study suggest that the occurrence of side effects, the most common being rash, is more frequent with Ritodrine than with Utemerin. Potential causes of this are discussed below.

Data regarding manufacturing standards, testing methodology, stability, and molecular biological similarities of generic drugs with their originals are required for the authorization of pills and capsules medications. However, very few investigations have been conducted on the amount of impurities contained with respect to intravenous drugs. Although the osmotic pressure ratios and pH of Utemerin and Ritodrine are similar, the buffer and stabilizing agents used are not necessarily so, and indeed, there are known to be large differences in impurities. Such differences may underlie the differences in side effect emergence, even though the active ingredient of the drugs is identical. It is also thought that the amount of impurities present due to intermixing during the manufacturing process, even in the generic product, is variable, and that differences in the added stabilizing and buffering agents contained in each product give rise to differences in stability of the finished product.

However, in the present study, there was a difference in the average dosages of Utemerin and Ritodrine, with that of Ritodrine being approximately 1.4 times greater (Table 1). This could also be attributed to the higher frequency of side effects, but multiple logistic regression analyses showed that the greater dosage did not significantly influence side effect occurrence (Tables 5 and 6). Because our institution is the exclusive multidisciplinary perinatal medical center in our prefecture, it receives a large number of patients with severe symptoms early on in pregnancy who require long-term care and large volumes of uterine contraction suppressant drugs. Thus, determining the safety of the generic versions of these drugs is extremely important.

In Japan, it has not been long since the introduction of generic drugs. Post-use studies conducted shortly after the introduction of generic drugs have been insufficient,
and there has been a tendency to prioritize immediate cost reduction. However, the use of generic drugs that are detrimental to patients is contraindicated, and thus, post-use studies are needed to confirm their safety and efficacy.

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**Conflict of interest**

There are no conflicts of interest.

**References**