Can urinary eicosanoids be a potential predictive marker of clinical response to thromboxane A₂ receptor antagonist in asthmatic patients?

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Introduction

Thromboxane (TX) A₂ is an important bronchoconstrictor in the pathogenesis of asthma. Seratrodast, known as AA-2414, is a new oral TXA₂ receptor antagonist which is currently prescribed in asthma therapy in Japan. However its clinical effects have been very different in individual subjects. To assess whether the clinical efficacy of TXA₂ antagonist is predictable on the basis of urinary arachidonic acid metabolites in urine of patients with asthma, an open and multicentre trial was conducted. Fifty adult asthmatic subjects (women/men = 28/22) were enrolled [resting mean forced expiratory volume in 1 sec (FEV₁)% was 82%; range, 50-96%]. Urinary levels of 11-dehydro-TXB₂, leukotriene (LT) E₄, 2,3-dinor-6-keto-prostaglandin F₁₂ and creatinine in 3-h urine collected in the morning at the start of seratrodast (80 mg day⁻¹, once a day at evening for 4 weeks) were measured. Responders were defined by improvements of asthma symptoms score and peak expiratory flow rate (PEFR).

Of the 50 subjects, 45 completed this study. Eighteen patients were responders and the other 27 were non-responders. There were no significant differences between the two groups in patients' characteristics, baseline lung functions, treatments and baseline urinary eicosanoids. The 11-dehydro-TXB₂/LTE₄ ratio of responders was significantly higher (P = 0.0091) than that of non-responders (mean ± se, 7.49 ± 0.71 vs. 5.09 ± 0.67). Eleven patients out of 18 responders agreed to continue this drug for 6 months, the 11-dehydro-TXB₂/LTE₄ ratio decreased during this period, but not significantly.

Our data demonstrated that responders and non-responders to TXA₂ receptor antagonist existed in patients with asthma, and it suggests that the ratio of urinary eicosanoids might be a possible predictor of the effects of TXA₂ receptor antagonist.
phase II study of seratrodast, in patients with mild to moderate asthma, was performed in the United States (15). Oral administration of seratrodast inhibited the bronchoconstriction induced by U-46619 and LTD4 in guinea pig (16). BAY u3405, a selective TXA2 antagonist, was also reported to attenuate bronchoconstriction induced by U-46619 or PGD2 in human (17). Seratrodast (40 mg daily for 4 days) led to a decrease in the dose of methacholine, causing a 20% fall in FEV1 from 0.43 mg ml\(^{-1}\) to 0.93 mg ml\(^{-1}\) in human (18). However its clinical effects have been very different in individual subjects. We hypothesized that the clinical effects of TXA2 receptor antagonist might differ according to the production patterns of several arachidonic acid metabolites. In this study, we measured urinary 11-dehydro-TXB2, 2,3-dinor-6-keto-PGF\(_{1\alpha}\) and LTE4, and assessed whether these urinary metabolites levels might be predictive of the efficacy of seratrodast on asthmatic patients. To our knowledge, no report is on relationship in asthmatic patients between the efficacy of TXA2 receptor antagonist and urinary arachidonic acid metabolites levels.

**Materials and methods**

**SUBJECTS**

All subjects were recruited from Sapporo Medical University Hospital, Kushiro City General Hospital, Sapporo Hospital of Railway Company, Hakodate Municipal Hospital and Tomakomai Prefectural Hospital. Fifty subjects (28 women and 22 men), aged 23–73 years, were chosen at random from a larger group of non-aspirin-sensitive asthmatic patients after giving their informed consent to participate in this study. Patients were excluded from this study if they had a predicted FEV1 under 50% or over 100%, or if they had ischemic heart diseases, hypertension, diabetes mellitus, or nephritis. All patients fulfilled the American Thoracic Society (ATS) criteria for asthma (19) with a rise in the FEV1 of over 15% after \(\beta\)-agonist inhalation, and excluded chronic obstructive pulmonary disease by pulmonary function tests and computed tomographic (CT) scan. All subjects were stable and had not suffered from moderate or severe asthma exacerbation during the month before this study. Their mean resting \%FEV1\(\_1\) was 82% (range, 50–96%). Forty-five subjects were taking inhaled corticosteroid, and two had taken oral corticosteroids. Of the 50 asthmatic individuals, five were classified as severe asthmatics with predicted FEV1 values of less than 60%, and requiring a high dose (>800 \(\mu\)g/day) of inhaled beclomethasone dipropionate (BDP) or oral steroid. Twenty asthmatics had mean predicted FEV1 values between 60 and 80% and were classified as moderate, and the remainder (n = 25) were mild asthmatics who had predicted FEV1 values greater than 80%.

**STUDY DESIGN**

At the start of this trial, patients were trained to measure peak expiratory flow rate (PEFR) using the Mini-Wright Peak Flowmeter (Clement Clark International Ltd., Harlow, Essex, U.K.). They took measurements each morning (between 0600 and 0800 hours) and evening (between 1800 and 2000 hours) 2 weeks prior to this trial. The best of three performances was recorded as the PEFR.

On a Daily Record Card, asthma symptoms such as asthma exacerbation, wheezing, cough, sputum and dyspnoea were recorded four times a day (morning, afternoon, evening and night) from 0 (no symptoms) to 4 (all day), and night-time sleep was also recorded from 0 (no disturbance of sleep) to 4 (little improvement after inhaler use). This symptoms score has been previously reported (20) and we modified it. We summed up these daily six asthmatic symptoms scores (from 0 to 24) for each 2-week period. Adverse events were recorded at each clinic visit. The clinical effects were assessed every 2 weeks by PEFR in the morning and the asthma symptom scores. The 'responder' was defined by both of following: 1. Over 15% decrease of symptom scores in the last 2 weeks (3–4 weeks after the seratrodast treatment) from baseline (2 weeks before the therapy) and 2. Over 5% increase of PEFR in the 3–4 weeks from baseline.

Three-hour urine for 11-dehydro-TXB2, 2,3-dinor-6-keto-PGF\(_{1\alpha}\), LTE4 and creatinine was collected between 09:00 hours and 1200 hours on the first day of this study. Subjects received oral seratrodast of 80 mg once a day at evening for 4 weeks. Regular medication of each patient was not changed during this trial.

Next, in responders who agreed to continue seratrodast treatment for 6 months, we again measured urinary 11-dehydro-TXB2, 2,3-dinor-6-keto-PGF\(_{1\alpha}\) and LTE4 after the treatment.

**METHODS**

**Urinary creatinine**

Urine was diluted with water (1:30) before measuring creatinine. The excretion of urinary eicosanoids was calculated in pg mg\(^{-1}\) creatinine.

**Urinary 11-dehydro TXB2 and 2,3-dinor-6-keto PGF\(_{1\alpha}\)**

Indomethacin was added to the urine sample and stored at \(-20^\circ\)C. A volume of 1 ml octadeccysilisyl silica (ODS) power suspension (80 mg ODS ml\(^{-1}\) 40% ethanol) was added to each 1 ml of urine sample under acidic conditions, to absorb PGs. Then, ethanol-acid solution (15% ethanol with 0.05 N HCl) and petroleum ether were added for washing. Deproteinization and defatting were performed, and PGs were eluted by ethyl acetate. Eluted PGs were applied on a Si mini column BOND ELUT Si (Varian, Harbor City, CA, U.S.A.) and consequently fractionated by eluent 1 (chloroform : acetic acid = 100:0-5), eluent 2 (acetoniitrile : chloroform : acetic acid = 10:90:0-5) and eluent 3 (acetoniitrile : chloroform : acetic acid = 25:75:0-5). The fraction obtained by eluent 3 was evaporated by \(N_2\) gas and...
reconstructed by the buffer of the 6-keto-PGF$_{1a}$ $^{[125]}$ Assay System (Amersham International, Little Chalfont, U.K.). The volume of 2,3-dinor-6-keto-PGF$_{1a}$ was measured with this RIA kit, based on the 31.8% cross-reactivity (21). With the same fraction, 11-dehydro-TXB$_2$ was measured with 11-dehydro-thromboxane B$_2$ $^{[125]}$ RIA kit (New England Nuclear, Boston, MA, U.S.A.). The recovery rates of tritiated 11 I-dehydro-TXB$_2$ and 2,3-dinor-6-keto-PGF$_{1a}$ were 61.5% and 67.4%, respectively.

Urinary LTE$_4$

Approximately 30 ml of urine was collected in polypropylene containers from each patient. An internal standard of $^3$H-LTE$_4$ (20 000 dpm, 33pg LTE$_4$, DuPont New England Nuclear Research, Boston, MA, U.S.A.) was added to the remaining sample. Immediately after collection, 4 ml of solution 1 (ethyl acetate:methanol = 2:1) was added to each 1 ml of urine specimen to eliminate proteins; the specimens were then frozen at $-70^\circ$C until the assays for urinary creatine and LTE$_4$ could be performed. All samples were analysed within 1 month of collection. The method that was used to analyse urinary LTE$_4$ levels was modified from Tagari et al. (22). Briefly, 5 ml of each urine sample was centrifuged at 2000 g for 15 min to remove any particulates. The supernatant was washed with 3 ml of petroleum ether and centrifuged at 2000 g for 15 min. A volume of 5 ml of 0.05 M acetic acid buffer (pH4.0) was added to the lower layer to eliminate lipid and loaded into a C8 mini column (Bond Elut C8, Varian, Harbur City, CA, U.S.A.) and washed consecutively with 4 ml of hexane, 8 ml of solution 2 (hexane:ethyl acetate = 95:5), 4 ml of solution 3 (hexane:ethyl acetate = 30:70) and 4 ml of solution 4 (acetone:methanol = 50:50). The fraction obtained by solution 4 was evaporated by N$_2$ gas and reconstructed by 200 l of solution 5 (methanol:water:acetic acid = 65:35:1, pH 5-6 with triethylamine). A reverse phase-high pressure liquid chromatography (RP-HPLC) gradient system equipped with a Nova Pak C18 column (Waters Assoc., Milford, MA, U.S.A.) was used to separate the individual peptidoleukotrienes from each other and from other potential non-leukotriene cross reacting substances. The sample (150 $\mu$l) was injected into the column at a flow rate of 1 ml/min and LTE$_4$ was eluted at 11-13.5 min with this system. Each fraction was evaporated, and the residue was redissolved in 125 $\mu$l of the buffer of a commercial radioimmunoassay (RIA) kit, peptidyl leukotriene $^3$H RIA kit (DuPont New England Nuclear Research, Boston, MA, U.S.A.). LTE$_4$ was also measured using the same kit assay buffer. The RIA was carried out according to the method by Hayes et al. (23) with some modifications. The measurements were corrected by the creatinine content of urine; levels were expressed as pg mg$^{-1}$ creatinine. The recovery rate of tritiated LTE$_4$ was 50-65%. The intra-assay and interassay coefficients of variation were 11% and 10%, respectively.

DATA ANALYSIS

The data of patients' backgrounds (in Table 1) and urinary eicosanoids are described as mean ± se, and the differences between the groups were tested with the Mann–Whitney $U$-test. The chi-square test was used to test the association of categorical variables. Comparisons of PEFR and Asthma Symptoms Score at baseline and every 2-week interval were made by analysis of variance (ANOVA) and Scheffe’s test, and described as mean ± se. The Wilcoxon test was used in the comparisons of urinary level eicosanoids and their ratios between before and after 6 months seratrodast treatment. Pearson’s least squares linear regression analysis was used to determine correlations. Differences with a $P$ value of less than 0.05 were considered statistically significant.

Results

Of the 50 patients entering this study, four were excluded because of an incomplete examination and one was eliminated because of nausea caused by the adverse effect of seratrodast, which disappeared one day after the cessation of administration. In the remaining 45 patients, 18 were defined as responders and 27 as non-responders. The Asthma Symptoms Score at week 3–4 were significantly ($P<0.001$) reduced in responders (–25.1%, from baseline), but not in non-responders (–2.6%, from baseline). Mean PEFR of all 45 patients at week 3–4 increased in both the morning (5.8% ± 1.8) and evening (4.8% ± 1.3). PEFRs of responders in weeks 3–4 were significantly increased ($P<0.01$) compared with those of the baseline period; morning (10.7% ± 1.6) and evening (9.2% ± 1.9) (Fig. 1). The mean increased PEFR values in morning and evening were 40.1 min$^{-1}$ and 34.1 min$^{-1}$, respectively.

The characteristics and baseline urinary eicosanoid levels of the 45 patients are shown in Table 1. There were no significant differences between the two groups in patients' characteristics, asthma severity, baseline lung functions, treatments and each urinary eicosanoid. However, the ratio of 11-dehydro-TXB$_2$ to LTE$_4$ of responders was significantly higher (7.49 ± 0.71 vs. 5.09 ± 0.67; $P = 0.0091$) than that of non-responders (Fig. 2). Urinary LTE$_4$ levels and the LTE$_4$/2,3-dinor-6-keto-PGF$_{1a}$ ratio were lower in responders, but not significantly.

In all 45 patients there was a trend of correlation between urinary 11-dehydro-TXB$_2$/LTE$_4$ ratio and the decrease of Asthma Symptoms Score at weeks 3–4 ($r=0.40, P=0.07$), however there was no significant relationship between the other urinary eicosanoids ratios and Asthma Symptoms Score.

In the 11 patients with 6 months treatment of seratrodast, Asthma Symptoms Scores at week 23–24 were significantly ($P<0.05$) reduced in the responders (–20.3%, from baseline), and PEFRs in weeks 23–24 were significantly ($P<0.05$) increased from the baseline, both in the morning (9.9% ± 2.0) and evening (8.2% ± 1.9). Only the 11-dehydro-TXB$_2$/LTE$_4$ ratio had a tendency to decrease during the 6 months treatment as shown in Table 2.
Table 1. Characteristics of patients and response to seratrodast

<table>
<thead>
<tr>
<th></th>
<th>Responder ( n = 18 )</th>
<th>Non-responder ( n = 27 )</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex; women/men</td>
<td>8/10</td>
<td>16/11</td>
<td>0.33</td>
</tr>
<tr>
<td>Age; yr (range)</td>
<td>58 ± 2 (23–69)</td>
<td>58 ± 2 (36–69)</td>
<td>0.80</td>
</tr>
<tr>
<td>Atopy; yes/no</td>
<td>12/6</td>
<td>10/17</td>
<td>0.051</td>
</tr>
<tr>
<td>Duration of asthma; yr (range)</td>
<td>11 ± 3 (3–40)</td>
<td>12 ± 2 (2–36)</td>
<td>0.57</td>
</tr>
<tr>
<td>Smoking; yes/no</td>
<td>4/14</td>
<td>5/22</td>
<td>0.76</td>
</tr>
<tr>
<td>Baseline FEV(_1), L</td>
<td>2.30 ± 0.18</td>
<td>1.96 ± 0.16</td>
<td>0.13</td>
</tr>
<tr>
<td>Predicted FEV(_1), %</td>
<td>87.8 ± 6.2</td>
<td>79.5 ± 5.6</td>
<td>0.23</td>
</tr>
<tr>
<td>Asthma symptoms score</td>
<td>19.5 ± 0.9</td>
<td>21.3 ± 0.8</td>
<td>0.12</td>
</tr>
<tr>
<td>Oral steroid, Yes/no</td>
<td>1/17</td>
<td>1/26</td>
<td>0.77</td>
</tr>
<tr>
<td>Inhaled BDP, yes/no</td>
<td>17/1</td>
<td>25/2</td>
<td>0.81</td>
</tr>
<tr>
<td>Dose of BDP, mg day(^{-1}) (range)</td>
<td>694 ± 75 (400–1200)</td>
<td>600 ± 60 (400–1200)</td>
<td>0.29</td>
</tr>
<tr>
<td>Theophyllin, yes/no</td>
<td>12/6</td>
<td>19/8</td>
<td>0.79</td>
</tr>
<tr>
<td>Severity of asthma, severe &amp; moderate/mild</td>
<td>8/10</td>
<td>15/12</td>
<td>0.46</td>
</tr>
<tr>
<td>Baseline urinary aracidonate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11-dehydro-TXB(_2), pg mg(^{-1}) creatinine</td>
<td>905 ± 73</td>
<td>826 ± 73</td>
<td>0.40</td>
</tr>
<tr>
<td>LTE(_4), pg mg(^{-1}) creatinine</td>
<td>136 ± 15</td>
<td>223 ± 31</td>
<td>0.068</td>
</tr>
<tr>
<td>2,3-dinor-6-keto-PGF(_{1\alpha}), pg mg(^{-1}) creatinine</td>
<td>364 ± 36</td>
<td>312 ± 38</td>
<td>0.14</td>
</tr>
<tr>
<td>11-dehydro-TXB(_2)/LTE(_4) ratio</td>
<td>7.49 ± 0.71</td>
<td>5.09 ± 0.67</td>
<td>0.0091</td>
</tr>
<tr>
<td>11-dehydro-TXB(<em>2)/2,3-dinor-6-keto-PGF(</em>{1\alpha}) ratio</td>
<td>4.3 ± 1.5</td>
<td>3.6 ± 0.37</td>
<td>0.22</td>
</tr>
<tr>
<td>LTE(<em>4)/2,3-dinor-6-keto-PGF(</em>{1\alpha}) ratio</td>
<td>0.54 ± 0.17</td>
<td>1.39 ± 0.45</td>
<td>0.057</td>
</tr>
</tbody>
</table>

BDP: beclomethasone dipropionate. Mean ± SE.

Discussion

This is the first clinical trial demonstrating the relationship between the efficacy of TXA\(_2\) receptor antagonist and baseline urinary eicosanoids levels in asthmatic patients. We found that seratrodast was more effective in patients with a high ratio of urinary 11-dehydro-TXB\(_2\)/LTE\(_4\), and that this ratio had a weak correlation with changes in the Asthma Symptom Score. These results suggested that responders to seratrodast might have an imbalance of TX and LT production in terms of relative ratio, but not in absolute levels. However, Urinary LTE\(_4\) level was lower,
but not significantly so, in responders and the fact that the
LTE4/2,3-dinor-6-keto-PGF1α ratio was also lower may be a
result of the low LTE4 level. We could not explain the
interindividual difference of each eicosanoid production.
One possible reason could be the difference in the number
and sensitivity of each eicosanoid receptor. The 11-
dehydro-TXB2/LTE4 ratio had a tendency to decrease after
6 months treatment with seratrodast. As seratrodast had no
inhibitory effect on TXA2 synthesis, this decrease might
occur following an improvement of asthma by seratrodast.
Theophylline infusion had hardly any effect on platelets (28),
but is now known to be released from other
inhibitory effect on TXAz synthesis, this decrease might
take place following an improvement of asthma by seratrodast.
There were no significant differences in asthma severity
between responders and non-responders in this study.
TXA2 was originally described as being released from
platelets (28), but is now known to be released from other
cells, including macrophages and neutrophils in the airway
(29). Wenzel et al. (11) reported that the ongoing release of
TXA2, PGI2 or LTs production measured as urinary metabolites
(24), and systemic steroids had little effect on arachidonic acid metabolites (25). However therapeutic
regimens of glucocorticoids suppressed the release of TXB2
and LTs (26,27). Since no significant differences existed
between responders and non-responders in the doses of
inhaled corticosteroid and theophylline, baseline treatments
in this study would not affect the results of urinary
arachidonic acid metabolites.

Table 2. Changes in urinary arachidonic acid metabolites before and after 6 months treatment with seratrodast in asthmatic patients (n=11)

<table>
<thead>
<tr>
<th>Eicosanoid Metabolite</th>
<th>Before treatment</th>
<th>After 6 months</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>11-dehydro-TXB2 (pg mg⁻¹ creatinine)</td>
<td>862 ± 106</td>
<td>751 ± 93</td>
<td>0.33</td>
</tr>
<tr>
<td>LTE4 (pg mg⁻¹ creatinine)</td>
<td>156 ± 30</td>
<td>169 ± 32</td>
<td>0.53</td>
</tr>
<tr>
<td>2,3-dinor-6-keto-PGF1α (pg mg⁻¹ creatinine)</td>
<td>283 ± 50</td>
<td>247 ± 39</td>
<td>0.86</td>
</tr>
<tr>
<td>11-dehydro-TXB2/LTE4 ratio</td>
<td>6.7 ± 1.3</td>
<td>4.5 ± 0.7</td>
<td>0.083</td>
</tr>
<tr>
<td>11-dehydro-TXB2/2,3-dinor-6-keto-PGF1α ratio</td>
<td>4.4 ± 1.0</td>
<td>3.5 ± 0.5</td>
<td>0.48</td>
</tr>
<tr>
<td>LTE4/2,3-dinor-6-keto-PGF1α ratio</td>
<td>1.2 ± 0.5</td>
<td>1.8 ± 0.7</td>
<td>0.53</td>
</tr>
</tbody>
</table>

Mean ± SE.

Seratrodast has an antagonism to TXA2/PGH2 receptor
(TP receptor) on bronchial smooth muscle cells and
platelets (30). PGD2, as well as TXA2, contributes to
bronchoconstriction through the TP receptor on smooth
muscle cells (31) and therefore the clinical effects of
seratrodast might also be dependent on this mediator. This
could be one of the reasons why the ratio of urinary 11-
dehydro-TXB2/LTE4 did not significantly correlate with
changes in asthma symptoms in this study. The relationship
between the efficacy of seratrodast and urinary PGD2
metabolites, such as 9α, 11β-PGF2α, should also be further
examined.

We measured 3 h urine collected between 0900–1200
hours. Urinary levels of LTE4 and 11-dehydro-TXB2
increase after asthma exacerbation (5,6), so to exclude this
influence we selected patients without asthma exacerbation
within the 1 month period before this trial. Urinary 11-
dehydro-TXB2 level had a circadian rhythm with acrophase
in early morning, but the circadian rhythmicity of urinary
LTE4 was inconsistent (32–34). We recently measured every
3 h urine in different asthmatic patients over a 24 h period
and both urinary 11-dehydro-TXB2 and LTE4 had circadian
rhythmicity (35), and the mean of every 3 h value was
close to that collected between 0900–1200 hours. It seems
important to consider circadian rhythmicity in an evalua-
tion of urinary eicosanoids.

In our study, tachyphylaxis did not occur during
seratrodast treatment, and urinary levels of 11-dehydro-
TXB2 did not increase for 6 months. This result suggested
that there was no feedback mechanism in systemic TXA2
generation by long-term treatment with oral TXA2 receptor
antagonist. Other eicosanoids also did not change, there-
fore TXA2 antagonist might not affect individual baseline
arachidonic acid metabolites production patterns. Urinary
11-dehydro-TXB2 excretion has been shown to increase
during severe asthmatic exacerbations (36). It is well known
that urinary eicosanoids levels may vary due to physiologi-
ical events. However, the measurements of arachidonates

11-dehydro-TXB2 (pg mg⁻¹ creatinine) | 862 ± 106 | 751 ± 93 | 0.33 |
| LTE4 (pg mg⁻¹ creatinine) | 156 ± 30 | 169 ± 32 | 0.53 |
| 2,3-dinor-6-keto-PGF1α (pg mg⁻¹ creatinine) | 283 ± 50 | 247 ± 39 | 0.86 |
| 11-dehydro-TXB2/LTE4 ratio | 6.7 ± 1.3 | 4.5 ± 0.7 | 0.083 |
| 11-dehydro-TXB2/2,3-dinor-6-keto-PGF1α ratio | 4.4 ± 1.0 | 3.5 ± 0.5 | 0.48 |
| LTE4/2,3-dinor-6-keto-PGF1α ratio | 1.2 ± 0.5 | 1.8 ± 0.7 | 0.53 |
using spot urine samples seemed to be a reliable method if acute exacerbation had not occurred within one month prior to this.

In conclusion, we assessed the clinical efficacy of 4 weeks treatment with seratrodast and 18 out of 45 asthmatic patients were responders. The ratio of 11-dehydro-TXB2/LTE4 of responders was significantly higher than that of non-responders. In all 45 subjects there was a weak, but not significant, correlation between urinary 11-dehydro-TXB2/LTE4 ratio and changes in the Asthma Symptom Score. There was no tachyphylaxis during the 6 months treatment, and this urinary ratio had a tendency to decrease during this period. These results suggested that the clinical response to seratrodast in asthmatic patients might be predictable from the ratio of urinary eicosanoids.

Acknowledgement

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References