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Abstract

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Effect of *Bryophyllum pinnatum* versus fenoterol on uterine contractility

Birgit Gwehenberger\textsuperscript{a}, Lukas Rist\textsuperscript{b}, Renate Huch\textsuperscript{a}, Ursula von Mandach\textsuperscript{a,\textdagger}

\textsuperscript{a} Department of Gynaecology and Obstetrics, Zurich University Hospital, Frauenklinikstr. 10, CH-8091 Zurich, Switzerland

\textsuperscript{b} Paracelsus-Spital, CH-8805 Richterswil, Switzerland

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Abstract

Objective: To characterise the phytotherapeutic tocolytic *Bryophyllum pinnatum* in vitro versus the conventional betamimetic, fenoterol, in human myometrium. Study design: Contractility (endpoints: area under the curve (AUC), amplitude and frequency of isometric force development) was measured in strips of term myometrium biopsied at caesarean section in 14 women and exposed to increasing concentrations of *B. pinnatum* versus fenoterol/C6 oxytocin 1 U/l.

Results: Inhibition of spontaneous contraction by *B. pinnatum* was concentration-dependent: 16% at maximum concentration (10\textsuperscript{-4} mg/l), or 53% that with fenoterol 5/C2 10\textsuperscript{-8} mol/l. *B. pinnatum* increased contraction frequency by 91% at constant amplitude and inhibited oxytocin-stimulated contractions by 20% (AUC) at constant amplitude with slightly decreased frequency. Fenoterol decreased contraction AUC by 50% with a significant decrease in frequency.

Conclusion: Our in vitro data confirm the tocolytic activity of *B. pinnatum* observed in alternative medicine centres and may justify further clinical studies.

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Keywords: *Bryophyllum pinnatum*; Fenoterol; Uterine contractility; Tocolysis; In vitro

1. Introduction

Although *Bryophyllum pinnatum* (Lam.) (synonym: *Kalanchoe pinnata*, Lam.; common names: life plant, air plant [Mexican], love plant, Canterbury bells, cathedral bells) is widely used in the folk medicine of its indigenous regions (Madagascar, tropical Africa, India, China, Australia, Hawaii and tropical America\textsuperscript{[1,2]}), it remains relatively little researched. The name *Bryophyllum* comes from βρυο ‘sprout’ and καλάκειον ‘leaf’: the plant, classified as a weed, is notorious for its growth potential. Shortly after a leaf falls to the ground, a whole garland of new little plants develops from the notches along the leaf margin. Studies have shown the following in vitro effects in rodent tissue: positive inotropism, sedation, H\textsubscript{1} antagonism (ileum, bronchial muscle, peripheral vasculature), and antimicrobial activity\textsuperscript{[3–5]}. Identified active ingredients include bufadienolides, flavonoids, glycosides, steroids and organic acids\textsuperscript{[6–10]}.

*B. pinnatum* has been used since 1921, mainly as a sedative, by psychiatrists in alternative medicine and was first introduced in 1970 at a German complementary/alternative medicine (CAM) centre, the Herdecke Community Hospital, as a treatment for premature labour\textsuperscript{[11,12]}. A 5% preparation was administered parenterally at a dose of 580 mg/h until contractions ceased, after which it was administered as a 50% slurry at a dose of 200 mg/h, supplemented by fenoterol 120 mg/h if insufficiently effective alone. Clinical outcome and inhibition of labour were similar to those on fenoterol\textsuperscript{[11,12]}. However, in contrast to the well-documented side effects of conventional labour inhibitors, especially of the cardio vascular system, which can be serious for both for mother and baby, no adverse signs or symptoms are known until now. *B. pinnatum* 5% is also used as a 10 ml i.v. bolus during delivery if contractions are too strong, frequent or painful; the effect, which is rapidly visible on the cardiotocogram, is much less a matter of direct inhibition than of inducing more rhythmic contractions\textsuperscript{[11]}. The purpose of the present study was to examine the effect of *B. pinnatum* on the contractility of human myometrium in vitro as a preliminary approach to evaluating its use in clinical practice.
2. Materials and methods

2.1. Design

The study was approved by our institutional ethics committee. Before tissue removal each woman confirmed in writing that she had been fully informed about the purpose of the study and that she consented to the procedure. An 0.5–3 g myometrial biopsy was taken from each volunteer at term during elective or non-elective caesarean section. The inclusion criteria were elective and non-elective caesarean section; the exclusion criteria were prior tocolytic therapy, intra-amniotic or any other infection, and preeclampsia.

2.2. Procedure

After delivering the child and placenta and securing haemostasis, an approximate 2 cm × 0.5 cm × 0.5 cm strip of myometrium was taken from the superior edge of the hysterotomy incision, placed immediately in iced Ringer or modified Krebs solution (NaCl 118; KCl 4.7; CaCl₂ 2.48; KH₂PO₄ 1.24; MgSO₄ 1.21; NaHCO₃ 24.9; glucose 10.0; EDTA 0.034 mmol/l), and transported immediately to the laboratory for processing. Approximate 2 × 10 mm longitudinal strips of muscle fibre were prepared as delicately as possible, then immediately clamped vertically in the experimental apparatus and immersed in the organ bath filled with Krebs solution maintained at 37 °C and gassed (95% O₂, 5% CO₂, pH 7.4). Immediately after immersion, a 2 g load was applied to the strips, causing initial relaxation or twitching. Experimental data were not recorded until at least five regular contractions were obtained. Strips which did not contract regularly were not included in the study. We recorded the number of spontaneously contracting strips per patient.

2.3. Apparatus

The apparatus consisted of a jacketed organ bath with water and gas feed lines. Each myometrial strip was clamped at one end, while the other end was fixed to a clamp connected to the force transducer via a thin plastic thread. The force transducer (max green and red, output black and white 350 Ω, 60 g, 12 mm, input 7.5 V, Scaine France-74105 Annemasse) recorded the contractions of the muscle strips isometrically. An amplifier (MT8P, Lectromed, Letchworth SG6 1HT, UK) dispatched the starting signals to an electronic recorder (408 W + W electronic).

2.4. Analytical procedure

2.4.1. Test compounds

- **Oxytocin**: Syntocinon® ampoules (5 IU/ml), Novartis Pharma, Basel, Switzerland.

2.4.2. Dose-finding study

- **B. pinnatum**: Various amounts of Bryophyllum stock solution (100%) were added to the organ bath to establish an approximate range of myometrial tolerability.
- **Fenoterol**: Based on the range of plasma levels with physiological activity (225–6000 ng/l, equivalent to 6.5 × 10⁻¹⁰ to 1.6 × 10⁻⁸ mol/l) [13], fenoterol was used at concentrations between 10⁻¹⁰ and 5 × 10⁻⁸ mol/l.

2.4.3. Experiment 1: Effect of B. pinnatum or fenoterol on spontaneous contractions

After obtaining good spontaneous activity in Krebs solution (baseline), **B. pinnatum** or fenoterol was added at increasing concentrations (test). The timing of each addition was standardised to take place during the post-contraction relaxation phase. Before each addition the volume to be added was removed from the organ bath. An otherwise identically treated muscle strip with no added test substance (i.e. Krebs solution only) was run in parallel over each entire experiment as a control.

2.4.4. Experiment 2: Effect of B. pinnatum or fenoterol on oxytocin-stimulated contractions

Oxytocin (Syntocinon® 1 IU/l) triggered a contraction whose area under the curve (AUC) over 10 min served as the baseline value [14]. Over the following 1 h the Krebs solution was replaced every 10 min to wash out the oxytocin. **B. pinnatum** or fenoterol followed by oxytocin 1 U/l were then added (test). An otherwise identically treated muscle strip with only 1 IU/l oxytocin in Krebs solution (the oxytocin was added for both the baseline and test values) was run as the control.

2.5. Data processing

Contractility endpoints were AUC, amplitude and frequency. The curves were scanned from thermal paper and processed in Adobe Photoshop 5.0. AUC values were calculated using the Windows version of the NIH Image program (Scion Image Beta 4.02 Win; US National Institute of Health: http://www.rsb.info.nih.gov/nih-image/). The amplitude of each contraction was measured from baseline to peak (by hand to the nearest 0.25 mm). Frequency was calculated from the time (in seconds) required for the respective number of contractions (usually 2–3). Since this yielded very low values, it was multiplied by 1000 to give the number of contractions/1000 s.

Spontaneous contractions: the mean of the five contractions in Krebs solution before any administration of test substance was defined as 0 (baseline) and the corresponding AUC was defined as 100% spontaneous contractile activity; the mean of the subsequent two contractions was used as the test value for the respective concentration of **B. pinnatum** or fenoterol. Oxytocin-stimulated contractions: the first
post-oxytocin contraction in Krebs solution over the 10 min period was defined as the (Krebs + oxytocin) baseline; the test value for the respective concentration of *B. pinnatum* or fenoterol was defined as the mean contractions occurring in the 10 min post-substance administration period (*B. pinnatum* or fenoterol followed by 1 IU/l oxytocin).

### 2.6. Statistical methods

The statistical analysis was performed in Stat View 4+. Mean AUC, amplitude and frequency (absolute contractility endpoints) were calculated from the data obtained at each concentration with the standard error and median. The relative contractility endpoint was the fraction (%) of the mean AUC value in Krebs solution before test substance addition (baseline = 100%).

### 3. Results

#### 3.1. Population

Muscle samples were taken from a total of 18 donors. Those from subjects 1, 5, 10 and 13 were excluded due to absence of spontaneous contraction, leaving a total of 14 donors, the majority of whom (*n* = 12) underwent elective section. In eight patients it was the first section, in five their second section, and in one her third section; the six repeat sections formed 43% of the total (Table 1). Patients undergoing elective section received local (peridural) anaesthesia; those undergoing non-elective section received general anaesthesia.

#### 3.2. Spontaneous contractility without test substance administration

Each donor muscle biopsy yielded an average of six strips. Of the original total 85 strips from the 14 donors, 54 (64%) were included in the final analysis. Of the 50 strips from first-section donors (*n* = 8), 33 (66%) displayed on average good spontaneous contractions; without the one non-elective section with very poor contractility (2 strips = 29%, due to arrested labour and prior oxytocin induction), the success rate would have been 72%. The corresponding value for samples from repeat (*x* ≥ 2) sections was 60%.

#### 3.3. Dose/effect study: *B. pinnatum*

*Spontaneous contraction:* After the addition of Bryophyllum stock solution (final organ bath concentration: 20% = 2 × 10⁵ mg/l), a contraction of rather smaller amplitude occurred followed by incomplete relaxation. After 60 min, no further contractions could be triggered even after washout and with oxytocin (Fig. 1). *B. pinnatum* 10⁵ mg/l gave a similar result. Concentrations <10⁵ mg/l were therefore used in subsequent studies.

Oxytocin-stimulated contractions: The lowest relaxant concentration of *B. pinnatum* was 5 × 10⁻¹ mg/l.

#### 3.4. Effect on spontaneous contractions

**3.4.1. *B. pinnatum***

Experiment 1 yielded the following results (Table 2):

- A relaxant effect, as shown by a concentration-dependent reduction in AUC (to 16% of baseline at 10⁴ mg/l, *P* < 0.01) (Fig. 2a); the control muscle strips in Krebs solution displayed no major changes throughout the experiment (contractions 5–25) (Fig. 3a).
- Amplitudes virtually unchanged from the pre-administration baseline.
- A concentration-dependent increase in frequency (up to 90% more at a concentration of 10⁴ mg/l).

**3.4.2. Fenoterol**

- A relaxant effect, shown by a concentration-dependent reduction in AUC; reduction was maximal 30% at a concentration of 5 × 10⁻⁸ mol/l (*P* < 0.05 versus baseline) (Fig. 2b).
- A slight, concentration-dependent decrease in amplitude (17% decrease at a concentration of 5 × 10⁻⁸ mol/l, *P* < 0.05 versus baseline).
- The frequencies showed two minima, falling by 9% at a concentration of 5 × 10⁻¹⁰ mol/l, then increasing again to 99%, with a second minimum of 79% (21% decrease) at a concentration of 5 × 10⁻⁸ mol/l (NS).

#### 3.5. Effect on oxytocin-stimulated contractions

**3.5.1. *B. pinnatum***

Experiment 2 gave the following results after the administration of *B. pinnatum* with oxytocin 1 U/l in a concentration range of 5 × 10⁻¹ to 10⁰ mg/l:

<table>
<thead>
<tr>
<th>Patient</th>
<th>Indication</th>
<th>Section (E/NE*, no.)</th>
<th>Gestational age (completed weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Patient request</td>
<td>E, 1</td>
<td>37</td>
</tr>
<tr>
<td>3</td>
<td>Cephalopelvic disproportion</td>
<td>E, 2</td>
<td>38</td>
</tr>
<tr>
<td>4</td>
<td>Mucoviscidosis</td>
<td>E, 1</td>
<td>34</td>
</tr>
<tr>
<td>6</td>
<td>Cephalopelvic disproportion</td>
<td>E, 2</td>
<td>40</td>
</tr>
<tr>
<td>7</td>
<td>Breech presentation</td>
<td>NE, 1</td>
<td>38</td>
</tr>
<tr>
<td>8</td>
<td>Third caesarean section</td>
<td>E, 3</td>
<td>38</td>
</tr>
<tr>
<td>9</td>
<td>Cephalopelvic disproportion</td>
<td>E, 2</td>
<td>38</td>
</tr>
<tr>
<td>11</td>
<td>Diabetes mellitus</td>
<td>E, 1</td>
<td>38</td>
</tr>
<tr>
<td>12</td>
<td>Breech presentation</td>
<td>E, 1</td>
<td>38</td>
</tr>
<tr>
<td>14</td>
<td>Arrested labour</td>
<td>NE, 2</td>
<td>40</td>
</tr>
<tr>
<td>15</td>
<td>Fetal malformation</td>
<td>E, 1</td>
<td>37</td>
</tr>
<tr>
<td>16</td>
<td>Previous vacuum extraction</td>
<td>E, 1</td>
<td>38</td>
</tr>
<tr>
<td>17</td>
<td>Cephalopelvic disproportion</td>
<td>E, 2</td>
<td>38</td>
</tr>
<tr>
<td>18</td>
<td>Patient request</td>
<td>E, 1</td>
<td>40</td>
</tr>
</tbody>
</table>

* Patients 1, 5, 10 and 13 were excluded.
* Elective/non-elective.
A concentration-dependent reduction in AUC of just under 10% with *B. pinnatum* $5 \times 10^{-1}$ mg/l and of just under 20% with *B. pinnatum* $10^4$ mg/l (Fig. 3a). The mean reduction over the entire test concentration range was 15% ($P < 0.05$ versus the oxytocin/Krebs baseline). The control oxytocin/Krebs strips displayed no significant change.

Unchanged amplitudes at $5 \times 10^{-1}$ mg/l and an 8% decrease in mean amplitude at $10^4$ mg/l.

A 33% decrease in frequency with *B. pinnatum* $5 \times 10^3$ mg/l (Fig. 4a).

### 3.5.2. Fenoterol

At a concentration of $5 \times 10^{-9}$ mol/l, fenoterol decreased AUC by a mean 23%, and by 50% at the higher concentration of $10^{-7}$ mol/l (Fig. 3b). The mean relaxant effect of the test concentration range was a 39% reduction in AUC ($P < 0.05$ versus the oxytocin/Krebs baseline).

The mean decrease in amplitude after fenoterol $5 \times 10^{-9}$ mol/l was just under 30%; after fenoterol $10^{-7}$ mol/l, it was 7%.

The mean decrease in frequency was 30% after fenoterol with oxytocin at both concentration ranges ($P < 0.05$ versus oxytocin/Krebs baseline) (Fig. 4b).

### 4. Comment

This is the first study showing the relaxant effect in vitro of *B. pinnatum* on the contractility of human myometrium and reinforcing therefore its tocolytic activity observed in alternative medicine centres.

### Table 2

<table>
<thead>
<tr>
<th>Concentration</th>
<th>AUC (cm$^2$)</th>
<th>Baseline (%)</th>
<th>Amplitude (mm)</th>
<th>Frequency (s$^{-1}$) ($\times 10^{-3}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± S.E. (median)</td>
<td></td>
<td>Mean ± S.E. (median)</td>
<td></td>
</tr>
<tr>
<td><em>Bryophyllum pinnatum</em> ($n=12$) (mg/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$0^b$</td>
<td>0.95 ± 0.19 (0.87)</td>
<td>100</td>
<td>26.15 ± 3.99 (27.30)</td>
<td>2.09 ± 0.37 (1.82)</td>
</tr>
<tr>
<td>$10^{-2}$</td>
<td>0.94 ± 0.19 (0.88)</td>
<td>99</td>
<td>27.23 ± 4.41 (28.13)</td>
<td>2.28 ± 0.49 (1.78)</td>
</tr>
<tr>
<td>$5 \times 10^{-2}$</td>
<td>0.88 ± 0.18 (0.80)</td>
<td>93</td>
<td>27.04 ± 4.46 (27.75)</td>
<td>2.19 ± 0.37 (1.84)</td>
</tr>
<tr>
<td>$10^{-3}$</td>
<td>0.89 ± 0.17 (0.81)</td>
<td>94</td>
<td>27.39 ± 4.30 (28.19)$^*$</td>
<td>2.18 ± 0.34 (1.85)</td>
</tr>
<tr>
<td>$5 \times 10^{-3}$</td>
<td>0.81 ± 0.16 (0.74)**</td>
<td>85</td>
<td>26.99 ± 4.42 (28.69)</td>
<td>2.93 ± 0.51 (2.53)***</td>
</tr>
<tr>
<td>$10^{-4}$</td>
<td>0.80 ± 0.16 (0.67)$^{**}$</td>
<td>84</td>
<td>26.92 ± 4.26 (29.70)</td>
<td>3.99 ± 0.94 (3.12)***</td>
</tr>
<tr>
<td><em>Fenoterol</em> ($n=7$) (mol/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$0^b$</td>
<td>0.79 ± 0.24 (0.77)</td>
<td>100</td>
<td>23.43 ± 5.74 (23.10)</td>
<td>2.80 ± 0.71 (2.02)</td>
</tr>
<tr>
<td>$10^{-10}$</td>
<td>0.77 ± 0.25 (0.74)</td>
<td>97</td>
<td>23.73 ± 5.82 (24.88)</td>
<td>2.87 ± 0.71 (2.41)</td>
</tr>
<tr>
<td>$5 \times 10^{-10}$</td>
<td>0.75 ± 0.24 (0.66)</td>
<td>95</td>
<td>23.96 ± 5.81 (25.50)</td>
<td>2.56 ± 0.61 (2.03)</td>
</tr>
<tr>
<td>$10^{-9}$</td>
<td>0.75 ± 0.25 (0.66)</td>
<td>95</td>
<td>23.62 ± 6.00 (26.00)</td>
<td>2.76 ± 0.64 (2.25)</td>
</tr>
<tr>
<td>$5 \times 10^{-9}$</td>
<td>0.70 ± 0.23 (0.63)$^c$</td>
<td>89</td>
<td>23.11 ± 6.13 (25.50)</td>
<td>2.64 ± 0.56 (2.46)</td>
</tr>
<tr>
<td>$10^{-8}$</td>
<td>0.66 ± 0.21 (0.62)$^c$</td>
<td>84</td>
<td>22.31 ± 6.15 (24.88)</td>
<td>2.53 ± 0.57 (2.17)</td>
</tr>
<tr>
<td>$5 \times 10^{-8}$</td>
<td>0.63 ± 0.21 (0.55)$^c$</td>
<td>70</td>
<td>22.18 ± 5.68 (24.00)$^c$</td>
<td>2.30 ± 0.69 (1.86)</td>
</tr>
</tbody>
</table>

$^a$ Krebs solution only.

$^b$ Baseline: Krebs solution before adding test substance.

$^c$ Only six myometrial strips (baseline AUC: 0.90 ± 0.26 (0.98); amplitude: 26.78 ± 5.51 (26.03); frequency: 2.91 ± 0.83 (2.01)).

$^* P < 0.05$ vs. baseline.

$^{**} P < 0.01$ vs. baseline.

$^{***} P < 0.005$ vs. baseline.
4.1. Tissue

The success rate—64% of well-contracting muscle strips—was acceptable considering the high proportion of repeat sections (43%) and the decreased contractility resulting from the higher proportion of connective tissue neighbouring old hysterotomy scars. David et al. [14] reckoned on a 75% success rate with 10% repeat sections.

4.2. Concentration range of B. pinnatum and toxicity

In the absence of pharmacokinetic data on B. pinnatum, we were forced to rely on the doses in clinical use to determine the concentration range. The test preparation of B. pinnatum was based on an aqueous fresh leaf extract obtained as directed by the German Homeopathic Pharmacopoeia (HAB). This can be termed the 100% solution in that all the preparations were diluted from it. Treatment is usually administered parenterally at a dosage of 580 mg/h (5 \times 10^4 mg/(l h)) using 5% ampoules (Weleda, CH-4144 Arlesheim). As soon as contractions cease, treatment is switched to a dosage of 200 mg/h using a 50% oral solution. On this basis, we established the range of concentrations that were minimally to maximally active in vitro (compatible with a reversible myometrial response) in the preliminary dose-finding experiments and only used concentrations <10^4 mg/l in the further experiments.

The most feared components of Bryophyllum preparations are the bufadienolides, which have cardiac glycoside activity and are notorious in veterinary medicine for causing fatal cardiotoxicity in calves. Veterinary toxicity occurred after the ingestion of large amounts of the very fresh plant [16,17]. To date no side effects have been reported at the dosages in clinical use [11,12,15]. In fact, analysis of the test preparation (100% aqueous leaf extract) by the manufacturer, Weleda, detected no bufadienolides. This result is confirmed by other sources indicating that bufadienolides are present in aqueous solution at much lower levels than in fresh roots or a non-aqueous extract [4,18].

We should also bear in mind that the activity of phytopharmaceuticals in vivo reflects the interactions between their multiple constituents [19]. However, this aspect is not necessarily reflected in vitro.

4.3. Spontaneous contractions

B. pinnatum displayed concentration-dependent inhibition of spontaneous contractility. The maximum reduction in AUC was 16%. Bárany and Bárány [20] also observed an increase in frequency associated with the decrease in AUC after adding isoproterenol and 3-isobutyl-1-methylxanthine to carbachol-stimulated myometrial contractions in estrogen-stimulated rats. Despite the increase in frequency they found an overall inhibition of contractility. It thus follows that the individual parameters of amplitude and frequency cannot be evaluated in isolation, since in calculating the AUC the increase or decrease in the basal tone of the contraction curve is a major factor. B. pinnatum is at least half as active as fenoterol, which exerts maximum inhibition (30%) at a concentration of 5 \times 10^{-8} mol/l.
A further possible explanation for the effect of *B. pinnatum* on spontaneous contractions is its antihistamine activity. Animal studies by Nassis et al. [21] revealed an H1-receptor antagonist in the pressed juice of *B. pinnatum*. In vitro studies by Bergant et al. [22] with human myometrium showed that the biogenic amine, histamine, augments uterine activity. Martinez-Mir et al. [23] also showed inhibition of histamine-induced contraction in vitro by the H1-receptor antagonist clemizole, contrasting with augmentation by the H2-receptor antagonist, ranitidine, leading them to the conclusion that myometrium contained both H1 and H2 receptors, with contraction-inhibiting and promoting properties, respectively.

Since *B. pinnatum* has also been postulated to have anti-inflammatory activity [11], it may also inhibit prostaglandin synthesis. Prostaglandin E2, in particular, by potentiating the effect of oxytocin, plays an important role in the initiation of contractions [24].

### 4.4. Oxytocin-stimulated contraction

*B. pinnatum* had a relaxant effect on oxytocin-stimulated contraction at a minimum concentration almost 100-fold lower than in the case of spontaneous contraction (10% reduction in AUC even at $5 \times 10^{-1}$ mg/l, and 20% at $10^{1}$ mg/l followed by oxytocin 1 U/l. $P < 0.05$ overall *B. pinnatum* vs. Krebs solution without *B. pinnatum*. No significant changes in Krebs + oxytocin 1 U/l ((▼) control). (b) Mean area under the curve (AUC) of muscle strip contractility ($n = 7$) in response to fenoterol ($\bullet$ $5 \times 10^{-9}$ mol/l and $\square$ $10^{-7}$ mol/l followed by oxytocin 1 U/l. $P < 0.05$ overall fenoterol vs. Krebs solution without fenoterol. No significant changes in Krebs + oxytocin 1 U/l ((▼) control).

Fig. 3. (a) Mean area under the curve (AUC) of muscle strip contractility ($n = 13$) in response to *B. pinnatum* ($\bigcirc$ $5 \times 10^{-1}$ mg/l, $\bigcirc$ $5 \times 10^{1}$ mg/l, and $\bullet$ $10^{1}$ mg/l followed by oxytocin 1 U/l. $P < 0.05$ overall *B. pinnatum* vs. Krebs solution without *B. pinnatum*. No significant changes in Krebs + oxytocin 1 U/l ((▼) control). (b) Mean area under the curve (AUC) of muscle strip contractility ($n = 7$) in response to fenoterol ($\bullet$ $5 \times 10^{-9}$ mol/l and $\square$ $10^{-7}$ mol/l followed by oxytocin 1 U/l. $P < 0.05$ overall fenoterol vs. Krebs solution without fenoterol. No significant changes in Krebs + oxytocin 1 U/l ((▼) control).
Fig. 4. (a) Mean frequency of muscle strip contractility (n = 13) in response to B. pinnatum (○) 5 × 10⁻⁵ mg/l, (●) 5 × 10⁻⁴ mg/l, and (●) 10⁻³ mg/l, followed by oxytocin 1 U/l. (b) Mean frequency of muscle strip contractility (n = 7) in response to fenoterol (▲) 5 × 10⁻⁵ mol/l and (●) 10⁻³ mol/l, followed by oxytocin 1 U/l. P < 0.05 overall fenoterol vs. Krebs solution without fenoterol.

Nor do in vitro studies always provide a reliable guide to clinical activity. Thus, the betamimetic fenoterol, a standard clinical tocolytic, does not totally inhibit spontaneous contraction in vitro, but simply modifies the contraction pattern. The promising clinical efficacy of B. pinnatum is what prompted us to investigate its effect on uterine contractility in vitro. Our results show inhibition of contraction, combined with a change in contraction pattern. Spontaneous contraction decreases in amplitude while increasing in frequency, corresponding to the increased rhythmicity of labour often observed clinically in response to B. pinnatum; in the case of oxytocin-stimulated contraction, frequency decreases too. On this basis, we believe that clinical use of B. pinnatum is entirely legitimate, whether as monotherapy or in combination with synthetic tocolytics, depending on the intensity of labour. However, dose and effect still require more detailed characterisation in prospective clinical studies.

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