THE TREATMENT OF BREAST ENGOERING WITH SERRAPEPTASE (DANZEN): A RANDOMISED DOUBLE-BLIND CONTROLLED TRIAL

W H Kee, S L Tan, V Lee, Y M Salmon

SYNOPSIS

We evaluated an anti-inflammatory enzyme drug Danzen (Serrapeptase: Takeda Chemical Industries, Ltd.) on 70 patients complaining of breast engorgement. These patients were randomly divided into 2 groups, a treatment group and a placebo group. A single observer, unaware of the group the patients were in, assessed the severity of each of the symptoms and signs of breast engorgement before treatment was commenced, and daily for 3 days, during which therapy was administered. Danzen was noted to be superior to placebo for improvement of breast pain, breast swelling and induration and while 85.7% of the patients receiving Danzen had "Moderate to Marked" improvement, only 60.0% of the patients receiving placebo had a similar degree of improvement. "Marked" improvement was found in 22.9% of the treatment group and 2.9% of the placebo group. These differences were statistically significant (P < 0.05). No adverse reactions were reported with the use of Danzen. Danzen is a safe and effective method for the treatment of breast engorgement.

Key words: Serrapeptase (Danzen), anti-inflammatory enzyme, repression of fibrinolysis, treatment of breast engorgement.

INTRODUCTION

Breast Feeding is widely encouraged in current obstetric practice. While its advantages to mother and child are well recognised, there are a number of problems associated with it. One common problem that is encountered is breast engorgement, which makes continuation of breast feeding difficult. A number of methods have been suggested for its treatment and these include mechanical compression of the breast, fluid restriction, the use of diuretics, oestrogens and bromocriptine.

Recently, the use of Serrapeptase (Danzen: Takeda Chemical Industries, Ltd.) in the treatment of breast engorgement has been explored and found promising (1). Serrapeptase is an anti-inflammatory proteolytic enzyme drug derived from Serratia E15 isolated from the silk worm intestine and its oral administration to scalded rats has been found to be associated with a marked repression of the activation of fibrinolysis induced by the scalding (2). It is well absorbed orally, and clinically it has been used as an anti-inflammatory agent in the treatment of chronic sinusitis, traumatic injury and post-operative inflammation, to improve the elimination of bronchopulmonary secretions, and to facilitate the therapeutic effect of antibiotics in the treatment of infections (3).

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Since the treatment of breast engorgement remains elusive and as the data on the use of Danzen, in controlled trials, for the treatment of breast are limited, we sought to evaluate its usefulness in a randomised, double blind controlled study in post-partum women with breast engorgement.

MATERIALS AND METHODS

Seventy post-partum patients who were diagnosed to have breast engorgement were included in the trial. Diagnosis of breast engorgement was based on some or all of the following criteria: subjective complaint of pain in the breast and objective evidence of breast swelling, induration and impaired lactation. The severity of each of these symptoms and signs was graded according to a 4 point scale: absent (—), mild (+), moderate (++) and severe (+++). The patients were randomly divided into 2 groups. Those in the treatment group were administered oral Danzen 2 tablets (5mg per tablet) 3 times a day, while those in the control group were given placebo 2 tablets 3 times a day. The placebo tablets were especially manufactured for this study and were identical in appearance to the Danzen tablets. None of the research team was aware of the respective identification during the duration of the study. Both groups were treated for 3 days and during this period, all other drugs were withheld.

An independent observer assessed each symptom and sign daily according to the above 4 point scale commencing on the day before Danzen was first administered, and for each day during which therapy was given (Figure 1). A Global Severity Rating (GSR) of the breast engorgement was also made daily taking into account all the symptoms and signs. At the end of the three days treatment period, the improvement rating (IR) of each individual symptom and sign was determined by comparing its final and initial severity before treatment was started. The improvement rating was scored according to a 5 point scale as follows:

1 — Marked improvement
2 — Moderate improvement
3 — Slight improvement
4 — No change
5 — Worsening of symptom or sign

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This shows the schedule of evaluation of patients in the trial.

### SCHEDULE OF EVALUATION

**Day of delivery**

**Onset of engorgement of the breast**

**Study period**

1 2 3 days

**DANZEN or PLACEBO**

Tablets

(2 tabs. t.i.d. for 3 days)

---

Severity of subjective symptom and objective signs

Global severity rating

Improvement rating of each symptom

Side effects survey

Total improvement rating

---

In addition, the total improvement, taking into consideration the change in severity of every symptom and sign was determined and this was scored on a similar 5 point scale. This was termed the Total Improvement Rating (TIR) (Figure 2). All patients and babies were closely observed for any untoward side effects.

During the duration of the study, breast feeding was encouraged and concomitant breast massage and milk expression allowed.

### RESULTS

Out of a total of seventy patients included in the study, thirty-five patients each were given Danzen or placebo. There was no deviation from the protocol with regards to the administration of the tablets. The demographic data of the two groups of patients were analysed and it was found that there was no statistical difference between the two groups with regards to the age of the patients, parity, duration of gestation, mode of delivery and timing of the onset of breast engorgement after delivery. Four patients in the treatment group and eight in the placebo breast-fed their babies during the study period. Three patients in the Danzen group undertook breast massage and pumping during the duration of the trial while there were five patients given placebo who did the same. Analysis of these data using the Chi Square test showed no statistically significant differences.

Figure 2

This illustrates the form in which patients data were recorded daily.
**CASE RECORD**

<table>
<thead>
<tr>
<th>Name of Patient:</th>
<th>Age:_____ yrs</th>
<th>Race:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis: Breast Engorgement, ☐ nilateral</td>
<td>☐ Unilateral (☐ right, ☐ left)</td>
<td>Date of onset of the disease:</td>
</tr>
<tr>
<td>Past history of engorgement of breast ☐ None (______ times)</td>
<td>Gestation Period: ______ months (______ weeks)</td>
<td></td>
</tr>
<tr>
<td>Date of Delivery:</td>
<td>Birth Weight: ______ g</td>
<td></td>
</tr>
<tr>
<td>Condition of delivery: ☐ Normal</td>
<td>☐ Abnormal</td>
<td>☐ Cesarean section</td>
</tr>
<tr>
<td>☐ Premature</td>
<td>☐ Still birth</td>
<td>☐ Others (</td>
</tr>
<tr>
<td>Date of onset of the disease:</td>
<td>Past history of engorgement of breast ☐ None (______ times)</td>
<td></td>
</tr>
<tr>
<td>Date of Delivery:</td>
<td>Birth Weight: ______ g</td>
<td></td>
</tr>
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<td>Condition of delivery: ☐ Normal</td>
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<tr>
<td>☐ Premature</td>
<td>☐ Still birth</td>
<td>☐ Others (</td>
</tr>
<tr>
<td>Date of onset of the disease:</td>
<td>Past history of engorgement of breast ☐ None (______ times)</td>
<td></td>
</tr>
</tbody>
</table>

**Complication:** ☐ None, ☐ Yes ( |

**Concurrent drugs (if given, Pls. state name of drug(s) & daily dose):**

<table>
<thead>
<tr>
<th>Concurrent therapy</th>
<th>Before Treatment</th>
<th>After 1 Day</th>
<th>After 2 days</th>
<th>After 3 days</th>
<th>After ____ days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concurrent therapy</td>
<td>Breast massage</td>
<td>☐ None</td>
<td>☐ None</td>
<td>☐ None</td>
<td>☐ None</td>
</tr>
<tr>
<td>Concurrent therapy</td>
<td>Breast pumping</td>
<td>☐ None</td>
<td>☐ None</td>
<td>☐ None</td>
<td>☐ None</td>
</tr>
</tbody>
</table>

**Subjective Symptom**

<table>
<thead>
<tr>
<th>Spontaneous pain</th>
<th>Absent</th>
<th>Slight</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>+</td>
<td>++</td>
<td>+++</td>
<td></td>
</tr>
</tbody>
</table>

**Objective Signs & Symptoms**

<table>
<thead>
<tr>
<th>Swelling at breast</th>
<th>Absent</th>
<th>Slight</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>+</td>
<td>++</td>
<td>+++</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Induration</th>
<th>Absent</th>
<th>Slight</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>+</td>
<td>++</td>
<td>+++</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lactation</th>
<th>Good</th>
<th>Fair</th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>+</td>
<td>++</td>
<td>+++</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other Symptoms or Sign (Plat state)</th>
<th>Absent</th>
<th>Slight</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>+</td>
<td>++</td>
<td>+++</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Global Severity Rating of Symptoms and Signs</th>
<th>Absent</th>
<th>Slight</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>+</td>
<td>++</td>
<td>+++</td>
<td></td>
</tr>
</tbody>
</table>

**Side-effects:** ☐ None, ☐ Yes (If yes, Pls state the details)

Pls. state severity, measure taken & its course (Continued, Reduced in dosage, Withdrawn)

**Improvement Rating by Symptom or Sign**

1: Marked Improvement
2: Moderate Improvement
3: Slight Improvement
4: No Change
5: Worsening of Symptom or sign

**Side-effects:** ☐ None, ☐ Yes (If yes, Pls state the details)

Pls. state severity, measure taken & its course (Continued, Reduced in dosage, Withdrawn)

**Doctor's Signature**

(Date)

Figure 2
With regards to the Total Improvement Rating (Table 1), the results showed that there was marked improvement in the degree of breast engorgement in 22.9% of the patients in the Danzen group and only 2.9% of the patients in the placebo group. 85.7% of the patients receiving Danzen had either marked or moderate improvement as compared with 60% of the patients receiving placebo. These differences in favour of Danzen were statistically significant (P < 0.05).

The improvement rating for each individual symptom and sign was also analysed. The results showed that Danzen was superior to placebo for relief of breast pain, breast swelling and induration, but these differences did not reach a statistically significant level (Table 2, 3, 4). The change in the global severity rating (GSR) on a day by day basis was also analysed (Table 5).

Of those patients who had severe breast engorgement before commencement of therapy, 6% of those who were given Danzen had only mild engorgement by the end of the first day while none of those given placebo had such a significant improvement. 69% of the patients in the Danzen group had changed from having marked to moderate, or from moderate to slight, breast engorgement (that is, they had a one step improvement in the severity of breast engorgement) and this change was evident by the end of the first day. In comparison, only 40% of those in control group had a similar one step improvement by the end of the first day. These differences were found to be statistically significant (P < 0.05). There were no adverse reactions to the drug reported by any of the patients given either Danzen or placebo.

Table 1
TOTAL IMPROVEMENT RATING

<table>
<thead>
<tr>
<th>Rating Group</th>
<th>Marked improvement</th>
<th>Moderate improvement</th>
<th>Slight improvement</th>
<th>No change</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Danzen</td>
<td>8</td>
<td>22</td>
<td>5</td>
<td>0</td>
<td>35</td>
</tr>
<tr>
<td>Placebo</td>
<td>1</td>
<td>20</td>
<td>12</td>
<td>2</td>
<td>35</td>
</tr>
</tbody>
</table>

X² test  
P < 0.05

Table 2
This illustrates the improvement rating of induration in the treatment group as compared to the placebo group. Note the greater percentage of improvement in the Danzen group as compared to the placebo group.

Table 2
IMPROVEMENT RATING OF INDIVIDUAL SYMPTOM

Induration

<table>
<thead>
<tr>
<th>Rating Group</th>
<th>Marked improvement</th>
<th>Moderate improvement</th>
<th>Slight improvement</th>
<th>No change</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Danzen</td>
<td>1</td>
<td>12</td>
<td>12</td>
<td>0</td>
<td>35</td>
</tr>
<tr>
<td>Placebo</td>
<td>1</td>
<td>5</td>
<td>28</td>
<td>1</td>
<td>35</td>
</tr>
</tbody>
</table>
This illustrates the improvement rating of breast swelling in the treatment group as compared to the placebo group. Note the greater percentage of improvement in the Danzen group as compared to the placebo group.

**Table 3**

**IMPROVEMENT RATING OF INDIVIDUAL SYMPTOM**

<table>
<thead>
<tr>
<th>Rating Group</th>
<th>Marked improvement</th>
<th>Moderate improvement</th>
<th>Slight improvement</th>
<th>No change</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Danzen</td>
<td>6 17.1%</td>
<td>20 74.3%</td>
<td>9 100.0%</td>
<td>0 100.0%</td>
<td>35</td>
</tr>
<tr>
<td>Placebo</td>
<td>3 8.6%</td>
<td>20 65.7%</td>
<td>9 97.4%</td>
<td>3 100.0%</td>
<td>35</td>
</tr>
</tbody>
</table>

This illustrates the improvement rating of spontaneous pain in the treatment group as compared to the placebo group. Note the greater percentage of improvement in the Danzen group as compared to the placebo group.

**Table 4**

**IMPROVEMENT RATING OF INDIVIDUAL SYMPTOM**

<table>
<thead>
<tr>
<th>Rating Group</th>
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<th>Moderate improvement</th>
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<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Danzen</td>
<td>5 14.3%</td>
<td>25 85.7%</td>
<td>5 100.0%</td>
<td>0 100.0%</td>
<td>35</td>
</tr>
<tr>
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<td>5 14.3%</td>
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**DISCUSSION**

Breast engorgement is a common complication of the early puerperium and usually occurs between 2-5 days after delivery (4). It arises either as a result of venous and lymphatic stasis prior to the onset of milk secretion, or by obstruction of the lactiferous ducts following the onset of lactation. As it is painful, impairs breast feeding and may predispose to mastitis, appropriate treatment at an early stage is of paramount importance.

Many methods have been suggested for the treatment of breast engorgement and these include the use of mechanical breast binding, fluid restriction and diuretics. For many years, the favoured method was to use oestrogens, either alone or in combination with androgens. Oestrogens, however, are often ineffective when used to treat a fully established lactation (5), and may produce side effects such as nausea, prolonged lochial discharge and withdrawal bleeding. There is also rebound engorgement in up to 40% of cases when treatment is discontinued (6), and an increased risk of puerperal thromboembolism (7). It would thus appear prudent nowadays to discontinue the practice of oestrogen administration for the treatment of breast engorgement.

Administration of the dopamine receptor agonist, bromocriptine has been found to be effective in relieving breast engorgement (8). Side effects, predominant nausea and dizziness (5) are common and rebound lactation may occur in 20% of cases (9). A quicker return of ovulation is frequently observed and this may lead to an inadvertent pregnancy. In general, 2 weeks of bromocriptine is considered necessary if the patient does not desire breast feed and a further week of therapy has been advocated to prevent rebound lactation (6). The practice of using oestrogens is thus not advisable.

In the absence of any single ideal therapy, we decided to evaluate the efficacy of Danzen for the treatment of breast engorgement. As divergence of opinions relating to the effectiveness of different treatment regimes probably reflect the varying degree of maternal stoicism in the absence of objective assessment (6), we sought to ensure a greater objectivity in this study by having one single observer perform every assessment of breast engorgement for all the patients in this trial. Both the tablets Danzen and placebo, were identical in appearance and both the patients as well as the observer did not know which group the patients belonged until the code was broken.

**Table 3**

**IMPROVEMENT RATING OF INDIVIDUAL SYMPTOM**

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opened at the completion of the study. The results of this study indicate that Danzen is significantly superior to placebo for relief of breast engorgement and the moderate to marked improvement in 85.7% of patients makes it comparable to other drugs commonly in use for this purpose (5, 8). It relieved engorgement rapidly and within 24 hours of commencing therapy, 69% of patients had experienced some relief of breast engorgement. A significant fact is that these results in the Danzen group were achieved without any other form of therapy in thirty-two out of thirty-five patients and only three of the thirty-five patients had concomitant breast massage or milk expression. This is important because in the only comparable study of the use of Danzen (1), 75% of the patients in that study performed concomitant breast massage or pumping.

The mechanism of action of Danzen in relieving breast engorgement is probably by relieving the inflammatory response outside the lactiferous ducts and dissolving viscous milk obstructing the lumen of these ducts. Local lymphatic and venous stasis is thereby reduced and if breast feeding is still desired this will be facilitated. On the other hand, if the patient does not wish to breast feed, the absence of suckling allows serum prolactin levels to be reduced and milk production to cease. As the action of Danzen is not mediated through hormonal pathways, rebound lactation is, therefore, not a significant problem (8, 9).

In the present study, no side effects associated with the use of Danzen were observed. Danzen is an inexpensive, effective and safe non-hormonal agent for the treatment of breast engorgement.

Figure 5
This shows the changes in global severity rating on a day to day basis in the 2 groups of patients. Note that 6% of the patients in the Danzen group had a 2 grade improvement while 69% had a 1 grade improvement at the end of the 1 day therapy. None of the patients in the placebo group had a 2 grade improvement and only 40% had a 1 grade improvement. (p < 0.05).

ACKNOWLEDGEMENT
We thank Takeda Chemical Industries, Ltd. for the supplies of Danzen tablets (Serrapeptase).
REFERENCES


4TH ASEAN OTORHINOLARYNGOLOGICAL HEAD & NECK CONGRESS
4TH – 9TH APRIL 1989 SINGAPORE

Scientific Highlights include:
- Cochlear Implant
- Laryngo Tracheal Strictures
- Audiology
- Skull Base Surgery
- Cancer of Larynx
- Cholesteatoma
- Parotid Tumours
- Tinnitus
- Allergy in ENT
- Middle Ear Surgery
- Management of Cervical Nodal Metastasis
- Facial Nerve Dysfunction
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