Vaginal absorption of low-dose tranexamic acid from impregnated tampons

J. MOODLEY, M. COHEN, K. DEVRAJ, M. DUTTON

Summary
Tranexamic acid (TA), an antifibrinolytic drug, is usually administered orally to women with menorrhagia. This route of administration is associated with adverse side-effects, therefore tampons impregnated with TA were used to assess the absorption of the drug across the vaginal epithelium. Blood levels of TA in group A (9 patients), who had one tampon inserted, and group B (10 patients), who had a tampon inserted at 2-hourly intervals so that a total of 3 tampons were administered over a 6-hour period, demonstrated absorption of the drug into the blood stream in low concentrations.

Tranexamic acid (trans-4(aminomethyl) cyclohexane carboxylic acid) (TA) has for many years been administered orally to women with menorrhagia, particularly menorrhagia associated with intra-uterine devices.1-3 The drug acts by reducing the enhanced fibrinolytic activity that retards the normal haemostatic mechanisms of the endometrium.

When activated, the fibrinolytic system causes plasminogen to be converted to plasmin, a proteolytic enzyme with a high affinity for the fibrin molecule. Rapid dissolution of the haemostatic fibrin molecule results in excessive or recurrent bleeding. The untimely dissolution of haemostatic fibrin can be prevented by antifibrinolytic drugs that stabilise fibrin structure.

Tranexamic acid is usually administered orally or intravenously in large doses (3 - 6 g). These routes of administration are not only expensive but are associated with side-effects, such as nausea, diarrhoea and dizziness. The application of a fibrinolytic agent directly into the uterus to circumvent these side-effects has been reported and found to reduce the length of the menstrual period by approximately 50% in comparison with a control group.4 Intra-uterine contraceptive devices impregnated with TA have also been reported to result in a subjective reduction in blood loss.5

A study was undertaken to test the feasibility of vaginal administration of TA by establishing the absorption of the drug across the vaginal epithelium. As far as is known, this method has not been previously investigated and could result in the elimination of the gastro-intestinal and systemic side-effects that occur with oral and intravenous administration and a substantial reduction in the costs incurred by large doses.6

A new method for the assay of tranexamic acid, which was specifically developed for this study, is also described.

Patients and methods
Vaginal tampons were prepared as follows: individual tampons were removed from their applicator cartridges and impregnated with TA and re-inserted into the cartridges. The tampons were weighed before and after impregnation with tranexamic acid. The amount of TA impregnated into the tampon ranged from 300 mg to 350 mg per tampon.

Informed consent was obtained from 23 patients attending the outpatient department of King Edward VIII Hospital. All patients were in the reproductive age group (mean age 27.9 years; mean parity 2.7). None of the patients had any history of menstrual abnormality and had attended the outpatient department with complaints unrelated to menstruation. No patient had taken any medication in the preceding 2 weeks.

One patient received a single dose of 1 g of TA intravenously and 2 patients received a single dose of 1 g orally so that TA concentrations in the study group could be compared with levels obtained by these modes of administration. The remaining 20 patients were divided into two groups using random number tables.

In group A patients had 1 medicated tampon inserted at a fixed time (0 h) and removed after 6 hours. In group B, 1 medicated tampon was inserted at 0 h. At 2 h the tampon was removed and a second inserted. At 4 h, the second tampon was removed and a third inserted.

Peripheral venous blood samples were withdrawn from all patients into precooled evacuated plain tubes at 2, 4 and 6 hours after administration of the first dose of TA. The blood was stored on ice and transported to the laboratory where the assay was performed within 24 hours.

All patients were asked whether they had experienced a reduction in the amount of menstrual blood loss during the period of insertion.

Chromatographic method for the assay of TA
The sample of whole clotted blood was centrifuged at 5 000 g for 8 minutes. The serum was decanted and a 500 µl sample was deproteinised by the addition of 100 µl sulphosalicylic and trichloracetic acid mixture (17,5% and 50% w/v, respectively). This was spun at 5 000 g for 8 minutes and the supernatant was removed, 200 µl of which was taken for analysis on a Beckman System 6300 amino acid analyser. The analyser was fitted with a sodium column (Beckman amino acid analytical column — strong cation — with sodium ions as the counter ion), and a 100 µl sample loop, and the analysis performed using the following programme: recoveries were determined by calibration against pure TA at levels of 20,0, 5,0 and 0,5 µg/ml, followed by analysis of a normal human serum sample spiked with the same amount of TA (Table I). Both standards and samples were treated with the sulphosalicylic/ trichloracetic acid precipitant before analysis. Results to date have indicated reproducibilities even at 0,5 µg/ml levels. The limit of detection appeared to be about 0,3 µg/ml.

Statistics. The results obtained were analysed using profile analysis6 and a P-value of < 0,05 was regarded as significant.

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TABLE I. RECOVERY RATES OF TA

<table>
<thead>
<tr>
<th>Concentration of TA (µg/ml)</th>
<th>Recovery rates (%)</th>
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<tbody>
<tr>
<td>20.0</td>
<td>90.5</td>
</tr>
<tr>
<td>5.0</td>
<td>86.7</td>
</tr>
<tr>
<td>0.5</td>
<td>85.0</td>
</tr>
</tbody>
</table>

Results

The results obtained from the assay technique described for measurement of TA levels in blood of patients receiving the usual 1 g oral dose and 1 g intravenous dose were found to be uniformly higher compared with the levels achieved in both study groups (Tables II - IV).

TABLE II. TA CONCENTRATIONS (µg/ml) IN BLOOD OF PATIENTS RECEIVING A SINGLE 1 g DOSE OF TA IN RELATION TO TIME

<table>
<thead>
<tr>
<th></th>
<th>2 h</th>
<th>4 h</th>
<th>6 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single oral dose (2 patients)</td>
<td>4.30</td>
<td>6.42</td>
<td>6.41</td>
</tr>
<tr>
<td>Single intravenous dose (1)</td>
<td>9.82</td>
<td>8.68</td>
<td>12.33</td>
</tr>
<tr>
<td>Mean levels in group A</td>
<td>2.16</td>
<td>0.91</td>
<td>0.90</td>
</tr>
<tr>
<td>Mean levels in group B</td>
<td>0.81</td>
<td>1.02</td>
<td>1.28</td>
</tr>
</tbody>
</table>

Fig. 1. Mean blood tranexamic acid concentration in both groups measured against time.

The overall response for group A was 1.29 µg/ml and for group B 1.07 µg/ml at 2 h; 0.91 µg/ml at 4 h and 1.16 µg/ml at 6 h, which did not differ significantly from each other.

All patients in group A and group B reported a subjective reduction in the amount of menstrual flow over the period of tampon application. The tampons were well tolerated in all patients, with no patients reporting side-effects.

Discussion

One of the primary objectives of this study was to evaluate the transvaginal absorption of TA. This has been clearly shown to occur despite the lower serum levels of TA achieved in the study group compared with those achieved by the standard doses administered orally or intravenously. There is also a subjective reduction in normal menstrual blood loss. This, however, would need to be confirmed under well-controlled conditions with a much larger study population.

We have also demonstrated that the response to a single application (group A) did not differ significantly from more frequent vaginal applications (group B). This result is surprising, especially in the graph (Fig. 1) at 2 h and is probably due to the large variation in the data of group A at 2 h (Table II).

It would seem that the medicated tampon may have a practical application for situations where a reduction in the amount of menstrual flow is required. Vaginal application of TA has several advantages: gastro-intestinal side-effects were avoided; the drug was easily administered on a vehicle that in any case absorbs the menstrual loss; the method was well tolerated; and infrequent applications were as effective as more frequent applications resulting in reduction of the cost by applications of low doses.

More detailed studies, however, would have to be done to document the actual reduction in menstrual blood loss, TA tampons, clinical effectiveness in reducing pathological uterine bleeding, and the most cost-effective dose of the drug per application.
Salivary calcium, magnesium, phosphate, chloride, sodium and potassium in pregnancy and labour

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Summary

Pregnancy and labour produce significant changes in salivary calcium, magnesium, phosphate and chloride when pregnant patients in labour are compared with non-pregnant patients. There is a decrease in concentration of these constituents in the 3rd trimester of pregnancy followed by a marked increase when labour occurs. Magnesium and chloride are the constituents most significantly affected and show the largest increase during labour. Changes in saliva flow rate were accounted for and are not responsible for these changes noted. Sodium and potassium follow a similar pattern. When their levels are corrected for saliva flow rate changes, both show a significant increase with the onset of labour.

A number of publications exist in which the authors have shown varying effects of normal pregnancy on the homeostasis of calcium, magnesium, phosphate and electrolytes in blood during pregnancy and labour.1-6

At the time we undertook this study we were unable to find any reports determining the effects of normal pregnancy and labour on the abovementioned constituents and electrolytes in saliva. Given the findings that the salivary progesterone profile in pregnancy mimicked the progesterone in magnesium follow a similar pattern. When their levels are corrected for saliva flow rate changes, both show a significant increase with the onset of labour.

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Results

The mean and SE of salivary calcium, magnesium, phosphate, chloride, sodium and potassium and osmolality are shown in Table I.

Table 1. The mean and SE of salivary calcium, magnesium, phosphate, chloride, sodium and potassium and osmolality are shown in Table I.

References