HALF-LIFE OF OXYTOCIN IN BLOOD OF PREGNANT AND NON-PREGNANT WOMEN

By

Gunnar Rydén* and Ingvar Sjöholm

ABSTRACT

Using tritium-labelled oxytocin with a high specific activity, the half-life in the blood and the urinary excretion of intravenously injected oxytocin were followed in the female. The following groups of patients were studied: normally menstruating women during different phases of the menstrual cycle, women using a combination of gestagenic and oestrogenic hormones for oral contraception, and pregnant women in the first and second trimester. The pregnant women were admitted to the hospital for legal abortion in the 10th–20th week of gestation.

In the proliferative phase, $t_{1/2}$ was 272 seconds ($n = 14$), in the secretory phase 221 seconds ($n = 5$), and in women using oral contraceptives 199 seconds ($n = 10$). In pregnant women during the first trimester, $t_{1/2}$ was 178 seconds ($n = 6$). The corresponding value in women examined during the 14th–17th weeks and during the 18th–20th weeks of gestation was 295 seconds ($n = 6$) and 282 seconds ($n = 6$), respectively. $T_{2/3}$ was also determined within 24 h of abortion in patients in the second trimester, where the abortion was induced by intra-amniotic instillation of 50% glucose. In all cases a decrease in $t_{1/2}$ was found. The decrease was most marked in women during the 18th–20th weeks of gestation. Altogether 25–50% of the radioactivity injected was recovered in the urine from pregnant women within 3 h of the injection. Thin-layer chromatography of the urine did not reveal the presence of any intact oxytocin.

The results demonstrate that the disappearance of oxytocin from the blood seems to be influenced by the sex hormones. Thus, an oestrogen-dominated stage shows a lower disappearance rate, whereas gestagens produce the reverse effect. The pronounced decrease in $t_{1/2}$ in pregnant women during the 18th–20th weeks of gestation indicates that the sex hormones, especially oestrogen, are involved in controlling the half-life of oxytocin.

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women immediately after abortion might be due to a change to a more progesterone-dominated stage induced by the death of the foetus, or by an alteration in the affinity of oxytocin to the myometrium.

In previous papers, the half-life of oxytocin in the blood and the uptake in different tissues were described in the rat, using tritiated oxytocin with a high specific activity (Sjöholm & Rydén 1967, 1969). Oxytocin was found to be rapidly distributed, $t_{1/2}$ being calculated to be 73–97 s. The lowest value was found in oophorectomized rats. Oestrogen treatment significantly increased $t_{1/2}$. Moreover, the studies on the uptake of oxytocin showed that the liver and the kidneys effectively removed the hormone from the blood and rapidly degraded it. In fact, 150 s after injection, no intact oxytocin could be detected chromatographically in these tissues.

Studies on $t_{1/2}$ of oxytocin in the blood of human subjects under different hormonal conditions have not been performed previously, owing to difficulties in the biological determination of oxytocin in the blood with reasonable accuracy. However, with radioactively labelled oxytocin, $t_{1/2}$ can be determined with precision. The present paper describes the clearance of oxytocin from the blood in different groups of non-pregnant and pregnant women, as well as the urinary excretion of the radioactivity after intravenous injection of oxytocin.

**MATERIALS**

Altogether 29 non-pregnant and 18 pregnant women were studied. The non-pregnant women were healthy, and were either menstruating normally or using a combination of a gestagen and an oestrogen for contraception. The pregnant women examined were in the first or second trimester, and were admitted to hospital for legal abortion on psychiatric or socio-medical indications. The pregnant women in the first trimester were examined just before the operation. The women in the second trimester, in whom abortion was induced by intra-amniotic instillation of 50% glucose, were examined twice; the first time just before the instillation, and the second time within 24 h of the abortion, 3–8 days after the first examination.

Tritiated oxytocin was prepared according to Carlsson & Sjöholm (1966) and Sjöholm & Carlsson (1967). L-3-$^3$H-tyrosine was used as starting material for the synthesis. The specific activity was 4.2 μCi/IU. When necessary, the oxytocin was purified by partition chromatography on Sephadex G-25 according to Yamashiro (1964) and gel filtration on Sephadex G-15 (Sjöholm & Carlsson 1967).

**METHODS**

**Blood sampling.** 5 IU of tritiated oxytocin ($4.5 \times 10^6$ dpm) were injected into a cubital vein. The injection time was 15–20 s. Before the administration of oxytocin, a polyethylene catheter was introduced into a cubital vein in the opposite arm, from which blood samples of about 2 ml were taken during 5 min at regular intervals.
usually every 20 s. The blood samples were immediately transferred to specially graduated test tubes, and centrifuged.

Urine samples. A Foley catheter was introduced into the bladder, and the urine was collected in Uri-bags during 180 min after the oxytocin injection.

Determination of the tritium content and thin-layer chromatography were performed as described previously (Sjöholm & Rydén 1967; Sjöholm & Ryrfeldt 1967).

RESULTS

After the intravenous injection of oxytocin, the decrease in radioactivity in the blood followed an exponential curve during at least the first 210 s, giving a straight line in semi-logarithmic diagrams (Fig. 1), from which the half-life could be calculated. The results obtained in the non-pregnant women are summarized in Table 1. As demonstrated, $t_{1/2}$ is dependent on the hormonal stage of the women. Thus, the highest $t_{1/2} = 272$ s – was found in the proliferative phase, a value which was almost significantly higher ($P < 0.05$) according to Student's $t$ test than $t_{1/2}$ in the secretory phase. The difference between the group

![Disappearance of radioactivity in the blood of a woman in the 17th week of gestation after intravenous injection of 5 IU of tritiated oxytocin. 1. Before instillation of hypertonic glucose for legal abortion. 2. 3 days later, 12 h after abortion.](image)

**Fig. 1.**

Disappearance of radioactivity in the blood of a woman in the 17th week of gestation after intravenous injection of 5 IU of tritiated oxytocin. 1. Before instillation of hypertonic glucose for legal abortion. 2. 3 days later, 12 h after abortion.

**Table 1.**

<table>
<thead>
<tr>
<th>Proliferative phase</th>
<th>Secretory phase 18th–22nd day</th>
<th>Oral contraception</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of experiments</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>$t_{1/2}$ seconds ± S. E.</td>
<td>$272 \pm 14.2$</td>
<td>$221 \pm 14.9$</td>
</tr>
</tbody>
</table>
using oral contraceptives and the group in the proliferative oestrogen-dominated phase was highly significant \( (P < 0.001) \). The results in the pregnant women are given in Table 2. In the first trimester, \( t_{1/2} \) was of the same magnitude as in the gestagen-dominated non-pregnant group. In the second trimester, however, \( t_{1/2} \) increased markedly. Statistically, the difference compared with early pregnancy is significant \( (P < 0.002) \) in the last group (18–20 weeks of gestation) and almost significant \( (P < 0.05) \) in the middle group (14–17 weeks).

In all 12 patients examined in the second trimester, \( t_{1/2} \) was lowered after the abortion, and generally the change was very evident.

The urinary excretion of radioactivity was followed during 3 h after the injection of the labelled oxytocin in 9 patients in the second trimester. During this period, a total of 25–50% of the injected dose was recovered in the urine. An example is given in Fig. 2. Thin-layer chromatography disclosed no traces

<table>
<thead>
<tr>
<th>Length of pregnancy</th>
<th>( \leq 12 ) weeks; before abortion</th>
<th>14–17 weeks</th>
<th>18–20 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of experiments</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>( T_{1/2} ) ± S. E. seconds</td>
<td>178 ± 13.9</td>
<td>295 ± 47.2</td>
<td>229 ± 21.5</td>
</tr>
</tbody>
</table>

\[ \text{Fig. 2.} \]

Urinary excretion of radioactivity after intravenous injection of 5 IU of tritiated oxytocin \( (45 \times 10^6 \text{ dpm}) \) in a woman in the 17th week of pregnancy. The dotted line denotes the cumulative amount excreted.

428
of intact oxytocin (Fig. 3a, b, c). In the two earlier samples, most of the radioactivity migrated as tyrosine, whereas the last sample chiefly contained slowly migrating metabolites.

![Graphs showing distribution of radioactivity and references](attachment:image.png)

**Fig. 3a.**

**Fig. 3b.**

**Fig. 3c.**

Thin-layer chromatography in n-butanol-dioxane-2 N ammonia (4:1:5) on cellulose-silica gel G of urine samples from a woman in the 17th week of gestation. The samples were taken a. 6–10 min, b. 20–30 min and c. 60–120 min after the intravenous injection of 5 IU of tritiated oxytocin (45 × 10⁶ dpm). The upper part of the figures shows the distribution of the radioactivity and the lower that of the references, oxytocin (Oxyt), the opened oxytocin nonapeptide (Nona) and tyrosine (Tyr).
DISCUSSION

Clearance studies of oxytocin in the blood of human subjects are scarce, owing to the difficulties of estimating small amounts of oxytocin by means of biological methods. González-Panizza et al. (1961) estimated $t_{1/2}$ in a total of 4 patients, either with a dead foetus near the calculated term, or post partum after macroinfusions of 8–16 IU of oxytocin per min. All values obtained ($t_{1/2} = 1.2–4$ min) showed that oxytocin is rapidly distributed from the blood. Similarly Fitzpatrick (1961) found a very rapid distribution from the blood in a male subject. In the present work, tritium-labelled oxytocin with a high specific activity was used in women under different hormonal conditions.

The results indicate that the disappearance rate of oxytocin from the blood and hence its metabolism is influenced by the sex hormones. This is most evident in the non-pregnant women examined. Thus in stages when the oestrogenic influence predominates, i.e., in the proliferative phase of a normal menstrual cycle, $t_{1/2}$ reached its highest values. This is in agreement with previous results in the rat (Sjöholm & Rydén 1967). On the contrary in women using oral contraceptives – when the gestagenic hormones predominate – $t_{1/2}$ was low.

In early pregnancy, i.e., in the first trimester, $t_{1/2}$ was about the same as in women under gestagenic influence. According to Bengtsson & Forsgren (1966) in the first trimester neither oestriol nor pregnanediol excretion differs significantly from that during the secretory phase. In the second trimester, on the other hand, the conditions influencing $t_{1/2}$ seemed to be more complicated. Thus a remarkable increase in $t_{1/2}$ was found after 14 weeks of gestation, reaching the values observed in the proliferative phase in non-pregnant women. This might be explained by a changed relation between the oestrogen and progesterone production which is observed in the second trimester (Klopper et al. 1961).

An interesting observation is the decrease in $t_{1/2}$ after abortion in all 12 women studied, which might indicate a change to a more progesterone-dominated stage. Cassmer (1959) demonstrated that foetal death brings about an immediate cessation of oestrogen production, whereas the placenta continues to produce progesterone. In the present study, the legal abortions were performed by intra-amniotic injections of hypertonic glucose, which causes immediate foetal death. Klopper et al. (1966) have found that following intra-amniotic injection of hypertonic saline the urinary output of pregnanediol remains at almost normal values until placental separation occurs. Likewise Christie et al. (1966) using histological techniques, demonstrated that at least 80 per cent of the placenta is undamaged and apparently continues its endocrine function after intra-amniotic injection of hypertonic saline. These results indicate a change to a more progesterone dominated condition in association with abortion.

Table 2 also shows that the decrease in $t_{1/2}$ after the abortion was more marked in the women examined during the 18th–20th week of pregnancy than
in the 14th–17th weeks. This might reflect the increasing myometrial weight in later pregnancy being responsible for a greater uptake of oxytocin in the target organ. In distribution studies on rats Sjöholm & Rydén (1969) in some experiments found a high initial uptake of oxytocin in the uterus which may indicate a preferential distribution of oxytocin for the uterus. In the rat, the liver and kidneys are the most important organs involved in the metabolism of oxytocin. Although these matters are difficult to study in human subjects, the urinary analyses nevertheless disclosed a high uptake and excretion of oxytocin and its metabolites. In fact, the degradation of oxytocin in the kidneys seems to be very effective, as no oxytocin could be detected in the urine chromatographically. Thus, it can be concluded that the kidneys also play an important role in the metabolism of oxytocin in human subjects.

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