EFFECTS OF 10-METHOXYDESERPIDINE ON THE ECG CHANGES INDUCED BY VASOPRESSIN IN UNANESTHETIZED RABBIT

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Received for publication July 14, 1964

Since the report of hypotensive effect without central depression of 10-methoxydeserpidine (1), several investigators have studied the mode of its action. Mir and Lewis (2) have demonstrated the gradually developing fall of blood pressure following 10-methoxydeserpidine in cats, rabbits and rats. However, unlike reserpine, 10-methoxydeserpidine does not produce significant depletion of brain and heart noradrenaline in mice (3). Recently, Higuchi et al. (4) and Toda et al. (5) in this laboratory have reported that the intravenous or intracarotid injection of 5 to 10 mg/kg of 10-methoxydeserpidine in rabbits produces considerable depletion of catecholamines in the brain, heart and adrenal glands. The latter authors (5) have further shown that the intravenous injection of 10 mg/kg of 10-methoxydeserpidine to rabbits results in a sustained rise of the skin temperature of the ear without modifying the rectal temperature, and that 1 mg/kg of reserpine produces a similar but longer-lasting rise of the ear skin temperature with a significant fall of the rectal one. They suggested that the skin temperature rise might be due to an increased blood flow in the ear. The earlier observation by Guthrie (6) that the inhalation of amyl nitrite, a potent coronary vasodilator, in man produced a flushing of the skin with a temperature rise and a blood flow increase in the neck and face indicates a resemblance of the effects of amyl nitrite to those of 10-methoxydeserpidine and reserpine.

The ECG changes in rabbits and dogs following the posterior pituitary extract were described by Melville (7), Hecht and Nadel (8), and Gruber and Kountz (9). They observed an elevation of ST level, and increase in height of T wave and the ventricular extrasystole with a concomitant blood pressure rise, and ascribed these ECG changes to the anoxia of the heart secondary to the coronary vasoconstriction.

The present report describes the effect of 10-methoxydeserpidine on ECG changes in rabbits following the intravenous administration of vasopressin in an attempt to confirm the coronary vasodilating action of 10-methoxydeserpidine.

METHODS

Unanesthetized albino rabbits, weighing 2.0 to 3.5 kg, were used. The animal was
fixed on the board in a supine position and placed in the electrically shielded room at about 24°C. The sites of leading electrode in the medial part of the right fore and left hind limbs were shaved. The steel electrodes were inserted subcutaneously and fixed by plaster. The ECG (lead II) was registered on the paper by means of the universal recorder (San'ei Sokki, Type 204). External stimuli such as sound, light and touch were made as minimum as possible. Usually about two hours were required before the animal fell into a full calmness to permit stable recording of the ECG.

The drugs used were vasopressin (Pitressin, Parke-Davis), 10-methoxydeserpidine (Decaserpine, Roussel), atropine sulfate and 2,6-bis-(diethylamino)-4,8-dipiperidinopyrimidino (5,4-d)-pyrimidine (Persantin, Boehringer-Sohn). 10-Methoxydeserpidine 500 mg was dissolved in 5 ml of propylene glycol with 0.2 ml of glacial acetic acid and employed as a stock solution. All drugs were injected into the marginal ear vein.

**RESULTS**

1. Effects of vasopressin on ECG

The intravenous injection of 1.0 U/kg of vasopressin produced a variety of ECG changes at various latencies: sinus bradycardia, sinus arrhythmia, prolongation and shortening of PQ interval, ventricular extrasystole, increase in height of T wave, elevation or depression of ST level and flattening or reversal of T wave (Table 1). However, these ECG changes were subjected to individual variations in latency, duration and intensity.

<table>
<thead>
<tr>
<th>TABLE 1. The ECG changes following the intravenous injection of vasopressin (1.0 U/kg) in normal rabbits.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rhythm</strong></td>
</tr>
<tr>
<td>The first injection of 1.0 U/kg of vasopressin produced arrhythmia in 21 of 24 rabbits tested. Most of them were of sinus origin, as shown in Fig. 1. In 6 rabbits, other types of arrhythmia such as the bigeminal or trigeminal rhythm, the irregular manifestation of ventricular extrasystole and the ventricular rhythm were also observed. These arrhythmias usually (81% of observations) began to appear 10 to 30 seconds after</td>
</tr>
</tbody>
</table>
injection of vasopressin and lasted for a period of 237.4±83.1 seconds (mean±S.E.). Only in some cases the arrhythmia manifested immediately after receiving vasopressin. However, even in the same individual, the type of arrhythmia varied with the time interval after administration of vasopressin. As shown in Fig. 2, the bigeminal rhythm occurred 20 seconds after injection of vasopressin.

**Fig. 1. Effects of the intravenous injection of 1.0 U/kg of vasopressin on the rabbit ECG.**

A : Before injection.
B : 30 seconds later.
   Marked elevation of ST level associated with increase in height of T wave.
C : 1 minute later.
   Marked sinus bradycardia with arrhythmia and the changes of ST and T similar to those in B.
D : 2 minutes later.
   Slight depression of ST level with marked sinus bradycardia and increase in height of T wave.
E : 20 minutes later.
   Somewhat recovery of the rhythm with increase in height of T wave.

Time scale : 0.5 second.

**Fig. 2. Manifestation of bigeminal and trigeminal rhythm in rabbit ECG following the intravenous injection of 1.0 U/kg of vasopressin.**

A : Before injection.
B : 20 seconds later.
   Bigeminal rhythm with increase in T wave and ST level.
G : 30 seconds later.
   Trigeminal rhythm with increase in T wave and ST level.
D : 40 seconds later.
   Increase in T wave with slight bradycardia.
E : 1 minute later.
   Marked bradycardia with ventricular extrasystole.
F : 1.5 minutes later.
   Marked bradycardia with ventricular extrasystole.
G : Recovery.

Time scale : 0.5 second.
after, the trigeminal 30 seconds after, and the marked bradycardia and sinus arrhythmia 60 seconds after injection of 1.0 U/kg of vasopressin.

The sinus arrhythmia was usually accompanied by different degrees of the sinus bradycardia. In 17 of 24 rabbits tested, the reduction of cardiac rate was more than 50% of initial rate at 2 minutes after injection. In an extreme case, the cardiac rate reduced to 20% of the initial rate. Recovery to approximately 80% of the initial rate was attained 20 minutes later in 9 of 24 rabbits. In the other rabbits, recovery was about 60% of the initial rate.

2. Atrioventricular conduction

The PQ interval was variably affected by administration of 1.0 U/kg: slight prolongation in 6, slight shortening in 4 and no significant changes in 14 of 24 rabbits. Generally, the prolongation of PQ interval was associated with a high degree of sinus bradycardia or a disturbance of atrioventricular conduction, while the shortening was seen with an atrioventricular extrasystole. Extrasystole occurred in 14 of 24 rabbits. Nine of them were ventricular and the remaining 5 were intermingled with the supraventricular one. The ECG in a half of animals which suffered from the extrasystole showed a prolongation or shortening in PQ interval. The frequency, latency and duration of manifestation of the extrasystole varied individually. Numbers of manifestation of the extrasystole during the vasopressin action were less than five in 8 rabbits and more than five in 6 rabbits.

3. Ventricular changes of ECG

The intravenous injection of 1.0 U/kg of vasopressin produced an elevation of ST level, an increase in height of T wave, a depression of ST level and a flattening of T wave. The frequency of occurrence was in order of the above description.

The increase in height of T wave was observed in 21 of 24 rabbits (88%). In 17 of 21 rabbits, this occurred simultaneously with or after some delay to the sinus arrhythmia. Only in 3 rabbits, the increased T wave preceded the arrhythmia in onset. The duration of the changes in T wave also varied individually: 4 within three minutes, 13 from three to eight minutes, and 4 more than eight minutes. Intervals of more than five hours were required to obtain reproducible changes in T wave in the same rabbit.

The elevation of ST level was seen in 22 of 24 rabbits. The latency before onset was 10 to 30 seconds in 17 of 22 rabbits, and the ST elevation manifested at most within 30 seconds after the increase in height of T wave. Only in 2 rabbits, ST level elevated without the T increase. The duration of the ST elevation varied from 5 to 130 seconds, 16 of 22 being within a range of 50 to 90 seconds. The recovery to the initial ST level was usually gradual, and sometimes recurrence of the ST elevation intervened in a partial recovery. When ST depression occurred, it followed the ST elevation and usually began to appear with latencies of 1 to 3 minutes and lasted for about 3 to 5 minutes.
4. Optimal dose of vasopressin as coronary vasoconstrictor

Although the intravenous injection of 1.0 U/kg of vasopressin produced marked ECG changes characteristic of myocardial hypoxia without behavioral changes other than somewhat respiratory stimulation and defecation of loose stool, more than five hours were required to obtain similar pattern of the ECG changes following repeated injections of the dose. To determine a dose of vasopressin which produces definite but easily reproducible changes in ECG, the single injection of 0.5 and 0.25 U/kg was tested in 12 rabbits. The results are shown in Table 2. The decrease in the dose resulted in reduced onset and degree of ECG changes.

**Table 2.** The ECG changes following the intravenous injections of vasopressin in graded units in normal rabbits.

<table>
<thead>
<tr>
<th>Dose of vasopressin (U/kg)</th>
<th>1.0</th>
<th>0.5</th>
<th>0.25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of animals</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of animals</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>responded</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinus bradycardia</td>
<td>17</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>sinus arrhythmia</td>
<td>21</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Extrasystole</td>
<td>14</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Increase in height of T wave</td>
<td>21</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Elevation of ST level</td>
<td>22</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Depression of ST level</td>
<td>14</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Flattening of T wave</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

The dose of 0.5 U/kg produced the sinus arrhythmia in 10 of 12 rabbits (83%) following the latent period of 10 to 30 seconds. The duration of arrhythmia was less than 3 minutes in 6 rabbits, and the longest was approximately 7 minutes. The sinus bradycardia occurred simultaneously with or somewhat delayed to the onset of arrhythmia in 11 of 12 rabbits. In 5 of them, the decrease in rate at 2 minutes following injection was nearly 50% of the initial rate. Recovery to 80% of initial rate was attained 20 minutes later in 8 rabbits. The extrasystole was observed in only one rabbit. In another rabbit, PQ interval was slightly prolonged 40 seconds to 3 minutes after vasopressin. The extent of T increase and ST elevation following 0.5 and 0.25 U/kg was less than that following 1.0 U/kg. With decrease in the dose of vasopressin, in general, the onset and extent of the vasopressin-induced ECG changes were reduced. In addition, nearly equal interval to that following 1.0 U/kg was required to allow sufficient time for reproducing the same type of ECG changes following successive injections. Therefore, the dose of 1.0 U/kg was adopted in order to evaluate coronary vasodilating effect of 10-methoxydeserpidine.

5. Reproducibility of ECG changes following repeated injections of vasopressin

Stable recording of ECG and, consequently, consistent ECG changes following vaso-
pressin were obtained in fully calmed animals. The reproducibility of the ECG response to the repeated injections of vasopressin at various time-intervals was tested in the same animals. Three to five hours after a first injection of 1.0 U/kg of vasopressin, the heart rate of 2 rabbits returned to nearly original, and 6 rabbits maintained a 10% decrease and remaining 4 rabbits showed a 10% increase. But in all these animals, the T and ST changes were completely recovered. A second injection of the same dose level of vasopressin, then, produced the sinus arrhythmia in 10 of 12 rabbits (83%). The latency and duration of the arrhythmia, and onset of the ventricular extrasystole did not significantly differ from those following the first injection. Further, there was no significant difference between patterns of T wave and ST level following the first and second injections of vasopressin. Thus, a repetition of the injection of 1.0 U/kg of vasopressin at intervals of more than 5 hours within a day was able to reproduce practically same response in ECG.

A third injection of the same dose

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**TABLE 3. The ECG changes following the intravenous injection of vasopressin (1.0 U/kg) in atropinized rabbits.**

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th></th>
<th>Atropinized</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of animals</td>
<td>Number of animals responded</td>
<td>%</td>
<td>Number of animals</td>
</tr>
<tr>
<td>Sinus bradycardia</td>
<td>95</td>
<td>71</td>
<td>75</td>
<td>6</td>
</tr>
<tr>
<td>Sinus arrhythmia</td>
<td>95</td>
<td>86</td>
<td>91</td>
<td>6</td>
</tr>
<tr>
<td>Extrasystole</td>
<td>95</td>
<td>34</td>
<td>36</td>
<td>6</td>
</tr>
<tr>
<td>Increase in height of T wave</td>
<td>95</td>
<td>84</td>
<td>88</td>
<td>6</td>
</tr>
<tr>
<td>Elevation of ST level</td>
<td>95</td>
<td>89</td>
<td>94</td>
<td>6</td>
</tr>
<tr>
<td>Depression of ST level</td>
<td>95</td>
<td>42</td>
<td>44</td>
<td>6</td>
</tr>
<tr>
<td>Flattening of T wave</td>
<td>95</td>
<td>9</td>
<td>9</td>
<td>6</td>
</tr>
</tbody>
</table>

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**Fig. 3. Effects of atropinization on the ECG changes caused by the intravenous injection of 1.0 U/kg of vasopressin.**

A: 1 hour after atropine (2.0 mg/kg, i.v.).
B: 30 seconds after injection of vasopressin.
Sinus bradycardia and arrhythmia with increase of T wave and ST level.
C: 1 minute later.
Sinus bradycardia and arrhythmia with the changes of T wave and ST level.
Extrasystole is not seen.
D: 2 minutes later.
Marked sinus bradycardia with the changes of T wave and ST level.
E: 20 minutes later.
Almost complete recovery.
Time scale: 0.5 second.
of vasopressin in the same interval produced the sinus arrhythmia in a similar manner to the first and second injections. However, in 3 of 4 rabbits the bradycardia was of high degree, and a recovery was never obtained within 20 minutes. On the other hand, the changes in T wave and ST level following the third injection were less in extent and shorter in duration than those following the first or second injection.

When the animal was given a daily dose of 1.0 U/kg of vasopressin in successive days, the ECG changes became, though qualitatively similar, less prominent at and after the third day. It was probably due to diarrhea with subsequent emaciation. Therefore, each animal was employed for experiments only once, or twice a day at intervals of more than 5 hours, and at least 3 days were allowed before subsequent use. According to this schedule, all animals were tested on the ECG response to vasopressin prior to the evaluation of the effect of drugs described below. Thus, total number of controls amounted to ninety-five.

II. Effects of atropinization on the ECG changes following vasopressin

Atropinization of the animal with a dose of 2.0 mg/kg produced tachycardia only in a slight degree from 2 minutes after injection. However, it modified the vasopressin effect on ECG (Table 3).

The occurrence and duration of the sinus arrhythmia markedly reduced. The arrhythmia was encountered only in 50% of animals tested. The sinus bradycardia was also significantly reduced in onset, degree and duration. In addition, the occurrence of ventricular extrasystole was almost completely prevented by atropinization. On the other hand, the changes of T and ST were obtained as usual following vasopressin in atropinized rabbits (Fig. 3).

III. Effects of 10-methoxydeserpidine on the ECG changes following vasopressin

The intravenous injection of 10 mg/kg of 10-methoxydeserpidine provoked a squeak-

<table>
<thead>
<tr>
<th>Intervals after 10-methoxydeserpidine</th>
<th>1 hr</th>
<th>2 hr</th>
<th>5 hr</th>
<th>6 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of animals</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Number of animals responded</td>
<td>%</td>
<td>Number of animals responded</td>
<td>%</td>
</tr>
<tr>
<td>Sinus bradycardia</td>
<td>7</td>
<td>88</td>
<td>6</td>
<td>75</td>
</tr>
<tr>
<td>Sinus arrhythmia</td>
<td>6</td>
<td>75</td>
<td>8</td>
<td>100</td>
</tr>
<tr>
<td>Extrasystole</td>
<td>3</td>
<td>38</td>
<td>3</td>
<td>38</td>
</tr>
<tr>
<td>Increase in height of T wave</td>
<td>6</td>
<td>75</td>
<td>7</td>
<td>88</td>
</tr>
<tr>
<td>Elevation of ST level</td>
<td>5</td>
<td>63</td>
<td>7</td>
<td>88</td>
</tr>
<tr>
<td>Depression of ST level</td>
<td>2</td>
<td>25</td>
<td>2</td>
<td>25</td>
</tr>
<tr>
<td>Flattening of T wave</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
ing response and increased a tendency to diarrhea. The ECG changes observed was bradycardia.

The effect of 1.0 U/kg of vasopressin was tested in the rabbit treated with 10 mg/kg of 10-methoxydeserpidine 1, 2, 5, and 6 hours previously. The results are shown in Table 4.

The pretreatment with 10-methoxydeserpidine increased the rate of manifestation of the sinus arrhythmia and bradycardia following vasopressin. However, the latent period and duration of them varied individually. The occurrence of the ventricular extrasystole was significantly reduced at 6-hour interval. Even if the animals responded with the extrasystole to vasopressin, the frequency of occurrence in the individual reduced markedly. The increase in height of T wave following vasopressin was prevented in 4 of 8 rabbits treated with 10-methoxydeserpidine 5 hours previously. In remaining 4 rabbits, the duration and degree of the T increase were significantly reduced, as illustrated in Fig. 4. Moreover, the latent period of manifestation of the T change was prolonged by the pretreatment with 10-methoxydeserpidine. The ST elevation following vasopressin was also markedly depressed and sometimes completely abolished. The ST depression or the flattening of T wave, sometimes followed the T increase or ST elevation, was almost completely abolished.

These protective effects of 10-methoxydeserpidine against the vasopressin-induced ECG changes were more marked at 5 or 6-hour interval than at 1 or 2-hour interval.

**IV. Effects of Persantin on the ECG changes following vasopressin**

The intravenous injection of Persantin in doses of 0.2 to 5.0 mg/kg did not produce significant changes in behavior and ECG rhythm and patterns. Two to five minutes after the doses of Persantin, the intravenous injection of 1.0 U/kg of vasopressin produced the ECG changes similar to those observed without Persantin. Only ventricular extrasystole was significantly reduced in frequency. The results are shown in Table 5. The
duration and latency of the T and ST changes were also unaffected by Persantin. Persantin failed to modify the ECG changes following a decreased dose (0.5 U/kg) of vasopressin, too. There was only reduction in number and duration of the sinus arrhythmia with a slight increase in frequency of the ventricular extrasystole. Rather, Persantin tended to increase manifestation of the ST depression following vasopressin.

Unexpected failure of Persantin to prevent the action of vasopressin on ECG might have been due to the hypotensive effects of Persantin. Consequently, Persantin was administered by continuous infusion of a rate of 0.02 mg/kg/min for 10 minutes without markedly affecting systemic blood pressure. Vasopressin was injected 5 minutes after start of the infusion. Although the T increase was produced by vasopressin, the duration was significantly shortened. In addition, the ST elevation and depression were reduced in onset and extent, and the T flattening was prevented in onset.

DISCUSSION

Relative importance of several determinants of coronary blood flow remains unsettled. Toda et al. (5) have reported a similarity of the temperature rise of the ear skin following administration of 10-methoxydeserpidine and amyl nitrite in unanesthetized but restrained rabbits. The skin temperature rise was markedly depressed by anesthesia or surgical procedure. It is possible that the increase in regional blood flow results in a rise of the ear temperature, and that such changes occur only in unanesthetized animals under a minor affection by external stimuli. Therefore, the effects of 10-methoxydeserpidine on the action of vasopressin on ECG were tested in unanesthetized but restrained rabbits.

Intravenous injection of vasopressin produced a variety of ECG changes: sinus bradycardia, sinus arrhythmia, prolongation of PQ interval, supraventricular or ventricular extrasystole, increase in height of T wave, elevation or depression of ST level
and flattening of T wave. These ECG changes consistently appeared when given more than 0.5 U/kg of vasopressin. The repetition of the injection of 1.0 U/kg of vasopressin twice a day at intervals of more than 3 days reproduced almost same pattern of the ECG changes each time. Atropinization of the animal markedly reduced the manifestation and duration of sinus arrhythmia and sinus bradycardia following 1.0 U/kg of vasopressin. In addition, atropine almost completely blocked the manifestation of ventricular or supraventricular extrasystole. The depression of the ventricular extrasystole following atropinization is incompatible with the report of Hecht and Nadel (8) that atropine exerts negligible effect on the vasopressin-induced extrasystole. On the other hand, the changes in T wave and ST level were hardly affected by atropinization. Therefore, it is likely that the ventricular extrasystole, sinus arrhythmia and sinus bradycardia are, at least in part, related to cholinergic reflex mechanism. The changes in T wave and ST level, on the other hand, might be due to the hypoxia of the heart resulted from the coronary vasoconstriction following vasopressin. Tardos and Leszkovszky (10) assayed the coronary vasodilating activity of reserpine in rats, using the changes in T and ST following vasopressin as criteria for coronary vasoconstriction. They demonstrated that reserpinization increased the ED50 value of vasopressin to evoke the changes in T and ST.

In the present experiment the pretreatment with 10 mg/kg of 10-methoxydeserpidine reduced the manifestation of ventricular extrasystole, despite the increased evoking of sinus arrhythmia and sinus bradycardia. In addition, the pretreatment with the drug reduced the extent of the T increase and the occurrence of the ST elevation following vasopressin. The ST depression and the T flattening, sometimes followed the T increase and ST elevation, were also annulled. These effects of 10-methoxydeserpidine on the ECG changes following vasopressin were more marked at 5- or 6-hour interval than at 1- or 2-hour interval. Although whether catecholamine depletion in the coronary vessel is related to the preventive effect of 10-methoxydeserpidine against vasopressin was not determined in the present experiment, the time course of the preventive action of 10-methoxydeserpidine coincided well with the course of the skin temperature rise of the rabbit ear shown by Toda et al. (5).

The coronary vasodilating action of Persantin was confirmed by several investigators (11-14) using the direct measuring method of coronary flow. However, in the present method the intravenous injection of 0.2 to 5.0 mg/kg Persantin was ineffective on the ECG changes due to vasopressin. Mosher et al. (15) demonstrated that coronary blood flow is dependent not only on coronary vascular resistance and cardiac rate but also on perfusion pressure. Since the blood pressure fall reaches its lowest level 3 to 5 minutes after Persantin and the rise to the original level is very slow (11), the decreased perfusion pressure might have masked the coronary vasodilating action of Persantin injected 2 to 5 minutes prior to vasopressin. The assumption was confirmed by the finding that the intravenous infusion of a rate of 0.02 mg/kg/min of Persantin for 10 minutes, if slightly, depressed the onset and extent of the T and ST changes following
The effects of 10-methoxydeserpidine on the ECG changes produced by vasopressin (1.0 U/kg, i.v.) were studied in unanesthetized but restrained rabbits. 10-Methoxydeserpidine reduced the occurrence of ventricular extrasystole but promoted the manifestation of sinus arrhythmia and sinus bradycardia. The increase in height of T wave and the elevation of ST level following vasopressin were markedly reduced in occurrence and extent. The ST depression and the flattening of T wave, sometimes followed the ST elevation and the T increase, were abolished.

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