Non-steroidal anti-inflammatory drugs and renal response to exercise: a comparison of indomethacin and nabumetone

Niels Vidiendal OLSEN*, Niels Georg JENSEN†, Jesper Melchior HANSEN†, Niels Juel CHRISTENSEN‡, Niels FOGH-ANDERSEN§ and Inge-Lis KANSTRUP†

*Department of Pharmacology, University of Copenhagen, The Panum Institute, DK-2200 Copenhagen, Denmark, and Department of Neuroanaesthesia, section 2091, Copenhagen University Hospital, DK-2100 Copenhagen, Denmark, †Department of Clinical Physiology, Herlev Hospital, DK-2730 Herlev, Denmark, ‡Department of Endocrinology, Herlev Hospital, DK-2730 Herlev, Denmark, and §Department of Clinical Biochemistry, Herlev Hospital, DK-2730 Herlev, Denmark

ABSTRACT

Nabumetone, a newer non-steroidal anti-inflammatory drug (NSAID) which preferentially blocks cyclo-oxygenase-2 activity, may be less nephrotoxic than indomethacin. This study tested whether nabumetone has effects different from those of indomethacin on exercise-induced changes in renal function and the renin–aldosterone system. In a randomized fashion, ten subjects were studied after indomethacin (100 mg), nabumetone (1 g) or no medication (control) administered orally at 22.00 hours on the day before each study day, and again at 8.00 hours upon arrival at the laboratory. Renal function was studied at baseline, during graded 20-min exercise sessions at 25%, 50% and 75% of the maximal oxygen uptake rate, and subsequently during two 1-h recovery periods. Heart rate, arterial blood pressure, cardiac output and plasma catecholamines at rest and during exercise were not altered by indomethacin or nabumetone. Indomethacin decreased urinary rates of excretion of 6-oxo-prostaglandin F1α (6-oxo-PGF1α) and thromboxane B2 in all study periods. Nabumetone decreased 6-oxo-PGF1α excretion during and after exercise. Excretion rates for PGE2 did not change. Neither indomethacin nor nabumetone changed baseline values or exercise-induced decreases in renal plasma flow or glomerular filtration rate. Indomethacin, but not nabumetone, decreased sodium excretion, urine flow rate and free water clearance. The renal response to exercise, however, remained unchanged. In contrast with nabumetone, indomethacin decreased the plasma renin concentration. Thus, during exercise, nabumetone may decrease the excretion of 6-oxo-PGF1α by inhibition of cyclo-oxygenase-1 or by inhibition of specific exercise-induced activation of cyclo-oxygenase-2, or both. None of the drugs changed the renal response to exercise. Inhibition by indomethacin of angiotensin II and thromboxane A2 synthesis may, during exercise, counterbalance renal vasoconstriction caused by blockade of vasodilatory prostaglandins.

Key words: cyclo-oxygenase, exercise, indomethacin, kidney, nabumetone, non-steroidal anti-inflammatory drugs, prostaglandins, renal failure, renal haemodynamics, renin, sodium excretion.

Abbreviations: ANOVA, analysis of variance; CNa, sodium clearance; DTPA, diethylenetriaminepenta-acetate; ERPF, effective renal plasma flow; FENa, fractional clearance of sodium; GFR, glomerular filtration rate; NSAID, non-steroidal anti-inflammatory drug; PAC, plasma concentration of active aldosterone; PGE2 (etc.), prostaglandin E2 (etc.); PRC, plasma concentration of active renin; VO2, rate of oxygen uptake.

Correspondence: Dr N. V. Olsen, Department of Pharmacology, University of Copenhagen, 3 Blegdamsvej, DK-2200 Copenhagen, Denmark (e-mail fino@farmakol.ku.dk).
INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) may possess serious nephrotoxic potential when used under conditions where renal prostaglandin synthesis is activated in response to increased renal sympathetic nervous activity and elevated circulating levels of renal vasoconstricting hormones [1,2]. This includes patients and individuals with decreased effective blood volume, in whom NSAIDs may cause marked decreases in renal blood flow, glomerular filtration rate (GFR) and the renal excretion of sodium and water [3,4]. The renal synthesis of the vasodilators prostaglandin I$_2$ (PGI$_2$) and PGE$_2$, which are involved in counteracting the effects of vasoconstricting and sodium- and water-retaining agents, is mediated by the constitutively expressed cyclooxygenase-1 enzyme, which is also responsible for the production of prostaglandins involved in gastric cytoprotection and vascular homoeostasis [5,6]. On the other hand, the co-existing inducible cyclo-oxygenase-2 enzyme system appears to be expressed more selectively, to produce prostaglandins in inflamed tissue [4,5]. The prodrug nabumetone, which is transformed in the liver into the active metabolite 6-methoxy-2-naphthylacetic acid, preferentially inhibits cyclo-oxygenase-2, whereas indomethacin is a strong inhibitor of cyclo-oxygenase-1 [5,6]. Previous studies have indicated that nabumetone does not decrease renal prostaglandin synthesis [7–9], and suggested that nabumetone may be less nephrotoxic than conventional NSAIDs in the treatment of elderly patients and patients with renal impairment [9,10].

Exercise induces increases in circulating levels of catecholamines, renin, angiotensin II and vasopressin, and may also cause volume depletion [11,12]. The renal response to exercise includes intensity-dependent decreases in renal blood flow, GFR and the excretion rates of sodium and water [11–13]. Some cases have been reported of acute renal failure following strenuous exercise and the use of NSAIDs [14–16]. Recently, Walker et al. [17] showed that indomethacin aggravated exercise-induced decreases in renal blood flow in athletes. The present study tested whether nabumetone has effects different from those of indomethacin on exercise-induced changes in renal function and the renin–aldosterone system.

METHODS

Subjects and experimental protocol

Ten healthy males, aged 21–33 years (mean 24 years), entered the study after having given their informed consent. Mean height and weight were 184 cm (range 170–193 cm) and 82.7 kg (range 72.7–92.4 kg) respectively. The study was approved by the regional scientific ethical committee of Copenhagen County. On a separate occasion before the study, the maximal oxygen uptake rate ($V_O_2_{max}$) was measured using a bicycle ergometer, by increasing the workload by 25 W every 1 min until exhaustion. $V_O_2$ was measured continuously by the use of a cardiopulmonary gas exchange monitoring device (CPX; Medical Graphics Corp., St. Paul, MN, U.S.A.).

After at least 7 days, each subject was then investigated on three different occasions, separated by intervals of at least 7 days. The subjects were instructed to maintain the same diet with a sodium intake of 140–150 mmol/day, and to avoid sexual and strenuous physical activity for 3 days prior to each study day. In a randomized sequence, the subjects orally took indomethacin (Conforttid®; 100 mg), nabumetone (Relifex®; 1 g) or no medication (control) at 22.00 hours on the evening before each study day, and again at 08.00 hours upon arrival at the laboratory on the study day. The experimental protocol was identical on each of the three study days (Figure 1), and was performed at the same time of day. After an overnight fast, water diuresis was induced by oral administration of an initial load of tap water (750–1000 ml), and was then maintained by drinking 250 ml of water every 20 min during the study. A venous catheter was inserted into an antecubital vein in each arm for infusion and blood sampling respectively. The subjects were confined to a sitting position and were instructed to void every 20 min. Steady state was considered to be achieved when urine flow rates approximately equalled water intake. Thereafter, three 20-min periods of rest (periods 1–3; baseline) were followed by exercise performed by sitting and bicycling on a mechanically braked ergometer with a pedalling rate of 60 rev./min. The subjects exercised for 20 min at submaximal workloads adjusted to levels of exercise equal to 25% (period 4; E25%; Figure 1), 50% (period 6; E50%) and 75% (period 8; E75%) of the individual $V_O_2_{max}$, with 20 min resting intervals between the exercise sessions (periods 5 and 7) (Figure 1). During exercise, proper adjustments of workload levels were ensured by continuous measurement of heart rate and $V_O_2$. Following the final exercise session, the subjects were studied during two 3 × 20 min recovery periods (periods 9–11, RC1; periods 12–14, RC2; Figure 1). The subjects voided every 20 min, at the end of each exercise and rest session.

Haemodynamic measurements

Heart rate was monitored continuously by ECG and recorded in 2-min periods with the subject in the sitting position before voiding at the end of each 20-min clearance period. Arterial blood pressure (measured by sphygmomanometry) was determined at the end of each 20-min period. Cardiac output was measured by a CO$_2$-rebreathing method using the cardiopulmonary gas exchange monitoring device (CPX) according to the
principles described previously [18,19]. Cardiac output was determined at rest (period 2), during each exercise session, and during recovery (periods 11 and 14), as the mean of two measurements.

**Urinary excretion of prostaglandins**
Renal excretion rates of PGE$_2$, 6-oxo-PGF$_{1_{\alpha}}$ and thromboxane B$_2$ were measured at baseline (period 3), during each exercise session, and during recovery [period 11 (RC1) and period 14 (RC2)]. Excretion rates of 6-oxo-PGF$_{1_{\alpha}}$ and thromboxane B$_2$ were taken as representative of the renal rate of formation of PGI$_2$ and thromboxane A$_2$ respectively [20].

**Renal measurements**
Effective renal plasma flow (ERPF) and GFR were measured by a constant infusion technique and urine collection, using $^{131}$I-Hippuran (priming dose, 0.33 MBq; infusion rate, 0.011 MBq/min) and $^{99m}$Tc-diethylenetriaminepenta-acetate (DTPA) (priming dose, 2.41 MBq; infusion rate, 0.037 MBq/min) respectively. After an equilibration period of at least 1 h, renal clearances of $^{131}$I-Hippuran, $^{99m}$Tc-DTPA and sodium ($C_{Na}$), and osmolal clearance and free water clearance were determined at baseline and during periods E25%, E50%, E75%, RC1 and RC2. Each value was calculated from the 20-min urinary excretion rates and the corresponding plasma values from blood samples drawn at the middle of each 20-min period. Thus the renal clearance values in the baseline period and the two recovery periods were each expressed as the mean of three 20-min clearance periods, whereas values during each exercise session were based on only one 20-min period.

**Hormones**
Plasma concentrations of active renin (PRC), aldosterone (PAC), noradrenaline and adrenaline were measured at baseline (period 3) and in periods E25%, E50%, E75% and RC2 (period 14).

**Analytical methods**
Activities of $^{131}$I-Hippuran and $^{99m}$Tc-DTPA in plasma and urine were determined in a well-counter. Plasma sodium was measured with a Technicon RA 1000 instrument, and urinary sodium with a Technicon RA-XT instrument (Technicon, Tarrytown, NY, U.S.A.). Urinary concentrations of 6-oxo-PGF$_{1_{\alpha}}$, thromboxane B$_2$ and PGE$_2$ were measured by competitive radioimmunoassays with $^{131}$I-6-oxo-PGF$_{1_{\alpha}}$, $^{131}$I-thromboxane B$_2$, and $^{131}$I-PGE$_2$ as tracers, and with antisera specific for each prostaglandin (Biotrak; Amersham International). The intra-assay coefficients of variation were 3%, 5% and 6% respectively.

PRC was measured by a two-site, two-monoclonal-antibody immunoradiometric assay with plastic beads for the solid phase (Nichols Institute, San Juan Capistrano, CA, U.S.A.). A value of 1 m-i.u./litre obtained by the assay is equivalent to 0.6 l g$^{-1}$ litre active renin [21]. The limit of detection was 2 m-i.u./litre. Intra- and inter-assay coefficients of variation were 4% and 5% respectively. PAC was measured by radioimmunoassay in unextracted serum (Diagnostic Products Corp., Los Angeles, CA, U.S.A.). The detection limit was 41 pmol/litre. Intra- and inter-assay coefficients of variation were 10% and 15% respectively. Plasma noradrenaline and adrenaline were measured with a radioenzymic assay. Samples of 1 ml of blood were drawn into ice-chilled tubes containing 1.7 mg ml$^{-1}$ EDTA and 1.1 mg ml$^{-1}$ GSH. Intra-assay coefficients of variation in samples ($n = 10$) containing normal basal levels of adrenaline and noradrenaline were 6% and 8% respectively, and interassay coefficients of variation were 7% and 11% respectively [22].

**Calculations**
Mean arterial blood pressure was determined as one-third of the pulse pressure plus the diastolic pressure. ERPF, GFR, $C_{Na}$, osmolal clearance and free water clearance were calculated using a standard formula (renal clearance = excretion rate/plasma concentration). Frac-
tional excretion of sodium \( (\text{FE}_{\text{Na}}) \) was determined as \( \frac{\text{C}_{\text{Na}}}{\text{GFR}} \).

**Statistical analysis**

Differences within and between study days were analysed by two-way analysis of variance (ANOVA) for repeated measures. If variances showed statistically significant differences \( (P < 0.05) \), paired Student's \( t \) tests corrected for multiple comparisons were used to analyse differences between the study day without medication (control) and the study days with indomethacin or nabumetone. All results are presented as means with 95% confidence intervals.

**RESULTS**

**\( \text{VO}_2 \) and workloads**

The \( \text{VO}_{\text{max}} \) determined before the study averaged \( 4141 \pm 369 \text{ ml/min} \). The maximal workload and the maximal heart rate were \( 264 \pm 17 \text{ W} \) and \( 183 \pm 5 \) beats \( \text{min}^{-1} \) respectively. Workloads and \( \text{VO}_2 \) corresponding to 25%, 50% and 75% of those at maximal exercise are shown in Table 1.

<table>
<thead>
<tr>
<th>Workload (W)</th>
<th>E25%</th>
<th>E50%</th>
<th>E75%</th>
</tr>
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<tbody>
<tr>
<td>Control</td>
<td>63 ± 2</td>
<td>119 ± 10</td>
<td>175 ± 14</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>67 ± 5</td>
<td>121 ± 11</td>
<td>174 ± 11</td>
</tr>
<tr>
<td>Nabumetone</td>
<td>65 ± 6</td>
<td>121 ± 12</td>
<td>177 ± 14</td>
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</tbody>
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<table>
<thead>
<tr>
<th>( \text{VO}_2 ) (ml/min)</th>
<th>Control</th>
<th>E25%</th>
<th>E50%</th>
<th>E75%</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>1388 ± 79</td>
<td>2208 ± 168</td>
<td>3104 ± 233</td>
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<td>1365 ± 65</td>
<td>2245 ± 157</td>
<td>3195 ± 229</td>
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<tr>
<td>Nabumetone</td>
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**Table 1** Workloads and \( \text{VO}_2 \) during graded exercise at 25% (E25%), 50% (E50%) and 75% (E75%) of \( \text{VO}_{\text{max}} \)

Values are means with 95% confidence intervals \( (n = 10) \).

**Plasma catecholamines (Table 2)**

Baseline values for the plasma concentrations of noradrenaline and adrenaline did not differ between study days. Exercise-induced increases \( (\text{ANOVA}: P < 0.001) \)
Non-steroidal anti-inflammatory drugs and renal response to exercise

The rates of excretion of 6-oxo-PGF$_{1a}$, thromboxane B$_2$ (TXB$_2$) and PGE$_2$ were measured at baseline (BL), during graded exercise at 25% (E25%), 50% (E50%) and 75% (E75%) of VO$_{2\text{max}}$, and in two 1-h recovery periods (RC1 and RC2). Values are means with 95% confidence intervals (n = 10). Within all groups, values decreased during exercise (ANOVA: P < 0.001). Significance of differences: *P < 0.05 compared with control; +P < 0.05 compared with control and nabumetone. Excretion rates of PGE$_2$ did not differ between study days.

Cardiovascular effects (Figure 2)

Graded exercise on the three study days increased heart rate, mean arterial blood pressure and cardiac output in an intensity-dependent manner (ANOVA: P < 0.001). Compared with the control day, pretreatment with indomethacin or nabumetone had no effect on baseline values, and none of the drugs changed the response to exercise.

Urinary excretion rates of prostaglandins (Figure 3)

Compared with baseline levels, exercise on all study days decreased urinary excretion rates of 6-oxo-PGF$_{1a}$, thromboxane B$_2$ and PGE$_2$ (ANOVA: P < 0.001). On the control day, the excretion rate of 6-oxo-PGF$_{1a}$ was increased in the first recovery period compared with baseline (P = 0.011). Compared with the other study days, indomethacin decreased the excretion rates of 6-oxo-PGF$_{1a}$ and thromboxane B$_2$ at baseline, during exercise and in the recovery periods. Nabumetone had no effect on baseline prostaglandin excretion rates, but decreased the excretion of 6-oxo-PGF$_{1a}$ during exercise and in both recovery periods. Nabumetone did not change the excretion rates of thromboxane B$_2$. Excretion rates of PGE$_2$ did not differ between study days.

Renal haemodynamics (Figure 4)

Exercise decreased ERPF and GFR on all study days (ANOVA: P < 0.001). Compared with baseline, ERPF was decreased significantly during all workloads, and also in the first recovery period (RC1), but had returned to values not different from baseline in RC2. On the three study days, GFR was decreased by all workloads, but did not differ from baseline values in either recovery period. Neither indomethacin nor nabumetone altered the baseline values of ERPF and GFR, and neither of the drugs changed the response to exercise.
Sodium and water excretion

Nabumetone had no effect on baseline values of \( C_{Na} \), \( FE_{Na} \) and urine flow rate (Figure 5). Compared with nabumetone, indomethacin decreased the baseline values of \( FE_{Na} \) and urine flow rate. Whereas similar exercise-induced decreases in \( C_{Na} \) and \( FE_{Na} \) were observed on the study days under control conditions and with nabumetone treatment (ANOVA: \( P < 0.001 \)), values in the exercise sessions after indomethacin did not decrease significantly. In the recovery periods, \( C_{Na} \) and \( FE_{Na} \) after indomethacin were lower compared with the values after nabumetone. Exercise decreased urine flow rate in an intensity-dependent manner (ANOVA: \( P < 0.001 \)), with no differences between study days. Compared with baseline, urine flow rate remained depressed in the first recovery period on all study days, but was lower after indomethacin compared with the other treatments. In the final 1-h recovery period, none of the values differed from baseline, but in this period both indomethacin and nabumetone decreased urine flow rate compared with that on the control day.

The baseline value of free water clearance was decreased by indomethacin (Figure 6). Exercise on all study days induced similar decreases in osmolal clearance and free water clearance (ANOVA: \( P < 0.001 \)). During recovery, osmolal clearance and free water clearance were decreased by indomethacin compared with that on the other study days.

Renin and aldosterone (Figure 7)

Graded exercise progressively increased PRC and PAC on all study days (ANOVA: \( P < 0.001 \)). Compared with the other study days, indomethacin decreased PRC at baseline, during exercise and in the final recovery period. Values of PRC during recovery on any day did not differ from baseline. Compared with the control day, nabumetone had no effect on PRC. None of the drugs changed baseline values of PAC, and exercise-induced increases in PAC did not differ significantly between study days. Values of PAC during recovery did not differ from baseline, and showed no differences between study days.
The well-known cardiovascular, hormonal and renal response to dynamic exercise [11–13] was successfully reproduced in the present experimental model. Because of increased activity of renal sympathetic nerves and the renin–aldosterone system, with high circulating levels of catecholamines and angiotensin II, maintenance of renal haemodynamic and excretory function during exercise may very much depend on increased renal synthesis of vasodilatory prostaglandins. The observed decrease in renal prostaglandin excretion rates during exercise is most probably due to the decrease in GFR and urinary output. However, it is likely that the finding of increased rates of excretion of 6-oxo-PGF$_{1\alpha}$ during recovery on the control day reflected an exercise-induced increase in the rate of formation of PGI$_{2\alpha}$.

In spite of the widespread use of NSAIDs in sports medicine, only a little attention has been devoted to the question of whether the concomitant use of NSAIDs may potentiate exercise-induced depression of renal function. The study of Walker et al. [17] showed that indomethacin (50 mg every 8 h for 36 h) enhanced the decreases in renal blood flow, renal vascular conductance and free water clearance in the first hours after treadmill running for 30 min at 80% of VO$_{2\text{max}}$. The decrease in GFR was the same with and without indomethacin [17].

In our present study, however, indomethacin did not aggravate the renal response to exercise. The discrepancy between the studies can perhaps be explained by the differences in both the intensity of the exercise and the duration of indomethacin administration. More prolonged pretreatment with indomethacin and more strenuous exercise than used in our study may be necessary to significantly change the renal response to exercise. The hydration used in the present study to facilitate urine collections was comparable with that used by Walker et al. [17], and in both studies this ensured that the subjects exercised in volume-replete conditions. It may be speculated, however, that the use of NSAIDs during exercise in individuals with more pronounced volume depletion than in experimental renal clearance studies would result in deleterious effects on renal function.

Prostaglandins, especially PGE$_2$ and PGI$_{2\alpha}$, stimulate renin release in various renal structures by mechanisms that are independent of renal sympathetic activity and stretch receptors [20]. The exercise-induced increase in PRC is mediated mainly by stimulation of $\beta$$_2$-adrenergic receptors [28]. In line with previous studies [26–28], the present decrease in PRC caused by indomethacin did not prevent exercise-induced increases in PRC and PAC, indicating that this response does not depend on changes in renal prostaglandin synthesis. Nonetheless, indomethacin lowered the overall levels of PRC and, presumably, angiotensin II.

Furthermore, the results indicate that indomethacin, in addition to inhibiting vasodilatory prostaglandins, also inhibited the vasoconstricting
thromboxane A₂. Thus the unchanged renal haemodynamic response to exercise on the study day with indomethacin may reflect the fact that blockade of vasodilatory prostaglandins was counterbalanced by proportionate decreases in angiotensin II generation and thromboxane A₂ synthesis.

Nabumetone had no effects on the renal and renin–aldosterone responses to exercise, but the decrease in the rates of excretion of 6-oxo-PGF₁α during and after exercise indicates that nabumetone may inhibit renal PGI₂ synthesis under these conditions. The relationship of the renal properties of nabumetone to selective inhibition of inducible cyclo-oxygenase-2 systems remains unsettled. First, nabumetone has been reported also to inhibit human platelet cyclo-oxygenase-1 in a dose-dependent manner (500 and 1000 mg daily for 7 days) [29]. Secondly, growing evidence from studies in rats indicates that cyclo-oxygenase-2 systems in the kidney are not exclusively activated by inflammatory mediators, but are also activated by dietary sodium intake [30], renal ablation [31] and tubulo-glomerular-feedback-mediated changes in afferent arteriolar tone [32]. Furthermore, renal cyclo-oxygenase-2 is involved in the regulation of macula densa-stimulated renin secretion [33,34], and is up-regulated in animal models of congestive heart failure [35] and renovascular hypertension [36]. It is noteworthy that recent studies have demonstrated that exercise stimulates the release of cytokines [37–39]. It is not known, however, whether cyclo-oxygenase-2 is activated by exercise. Thus it remains possible that the decrease in renal PGI₂ synthesis reflected the fact that nabumetone at the doses used also inhibited cyclo-oxygenase-1, but an effect of nabumetone on specific exercise-induced activation of cyclo-oxygenase-2 cannot be excluded. Further studies using more specific inhibitors of cyclo-oxygenase-2 activity are needed in order to delineate the role of renal prostaglandins during exercise.

In summary, acute administration of indomethacin in doses normally used in the treatment of musculoskeletal injury blunted renal prostaglandin synthesis, decreased renin release, and induced anti-natriuresis and anti-diuresis, but did not aggravate the renal response to submaximal exercise. Inhibition by indomethacin of renin-mediated angiotensin II generation and cyclo-oxygenase-1-mediated thromboxane A₂ synthesis may, during exercise, counterbalance renal vasoconstriction produced by blockade of vasodilatory prostaglandins. Nabumetone had no effect on the renin–aldosterone system or on overall renal function at rest or during exercise. Under resting conditions, nabumetone did not change renal prostaglandin synthesis, but during exercise nabumetone decreased the rate of formation of PGI₂. This may have been caused either by an inhibition of cyclo-oxygenase-1 or by inhibition of specific exercise-induced activation of cyclo-oxygenase-2, or both.

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