Emergency treatment of adrenal crisis with prednisone suppositories: a bioequivalence study in female patients with Addison’s disease

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Abstract

Objective: Patients with adrenal insufficiency (AI) need to adapt their glucocorticoid replacement under stressful conditions to prevent adrenal crisis (AC). Prednisone (PN) suppositories are used for emergency treatment. Pharmacokinetics of 100 mg PN suppositories after vaginal or rectal administration was evaluated.

Design: Single-center, open-label, sequence-randomized, cross-over, bioequivalence study.

Methods: Twelve females with primary AI were included. Comparison of pharmacokinetics after vaginal and rectal administration of 100 mg PN suppositories. Main outcome measures: bioequivalence ($C_{\text{max}}$: maximum plasma concentration of prednisolone; $AUC_{0-360}$: area under the plasma concentration curve of prednisolone from administration to 360 min), adrenocorticotropin (ACTH) levels, safety and tolerability. Comparison of ACTH-suppressive effect with subcutaneous and intramuscular administration of 100 mg hydrocortisone.

Results: Vaginal administration of PN suppositories was not bioequivalent to rectal administration: $C_{\text{max}}$ and $AUC_{0-360}$ were significantly lower after vaginal compared to rectal administration: 22 ng/mL (109%) vs 161 ng/mL (28%), $P < 0.001$; 4390 ng/mL * min (116%) vs 40,302 ng/mL * min (26%), $P < 0.001$; (mean (coefficient of variation), respectively). A suppression of ACTH by >50% of baseline values was observed 149 min (32%) after rectal PN administration; after vaginal PN administration, the maximum decrease within 360 min was only 44%. Adverse events were more frequent after vaginal administration and mainly attributable to the glucocorticoid deficit due to inadequate vaginal absorption. The ACTH-suppressive effect was more pronounced after parenteral hydrocortisone compared to rectal or vaginal PN.

Conclusion: Vaginal administration of PN suppositories in the available form is not useful for prevention of AC. Pharmacokinetics after rectal use of PN show inferiority compared to available data on parenteral glucocorticoids. In adrenal emergencies, hydrocortisone injection should be the first choice.

Key Words

- adrenal insufficiency
- adrenal crisis
- prednisone suppository
- vaginal
- rectal
- hydrocortisone injection

Introduction

Despite of established replacement therapy, an increased mortality of patients with adrenal insufficiency (AI) has been observed (1, 2, 3, 4). AI represented the second most frequent cause of death in a Norwegian cohort of patients with primary AI (3). The relative risk of death from infectious disease compared to the background population was 6.6 in a Swedish analysis (1). Patients with chronic AI are at risk of adrenal crisis (AC) which...
contributes to the increased mortality (5, 6, 7, 8, 9, 10, 11). An increase in cortisol secretion is an important adaptive mechanism to deal with stressful events. An AC, therefore, usually occurs under conditions of relative cortisol deficiency due to inadequate replacement at times of increased requirement. To avoid AC, patients are educated in adaptation of their glucocorticoid (GC) dose under stressful conditions (12, 13, 14). AC requires immediate initiation of parenteral administration of GCs (13, 14). As many health professionals are not familiar with this rare disease, intravenous GC replacement may be delayed (15, 16, 17). To enable patients to deal with emergency situations more independently, patients and relatives are educated in intramuscular (i.m.) hydrocortisone (HC) self-injection (18). Furthermore, off-label use of subcutaneous (s.c.) administration of HC appears to be a safe and efficient alternative (19). However, an easy to handle GC emergency set, for example, a ‘ready-to-use’ GC pen, is not available. Prednisone (PN) suppositories have been recommended by recent guidelines (14). However, the guidelines indicate that the level of evidence is low, as the rectal administration of PN (REC-PN), which is approved for the treatment of acute laryngotracheitis, croup and spastic bronchitis in children, has not been investigated in patients with AI to date. Rectal absorption in case of gastroenteritis and diarrhea is uncertain. Off-label vaginal administration of PN suppositories (VAG-PN) may be an alternative administration form. In an anonymous survey of 18 females with AI immediately following training in self-injection of GCs, 28% (n=5) preferred vaginal administration of a suppository over GC injection (own observations).

As patients with AI still die from AC, both improvement and simplification of emergency management has been postulated (10, 13, 20, 21, 22, 23, 24). We, therefore, aimed to systematically investigate the pharmacokinetic profile of PN after rectal and vaginal administration in patients with primary AI. In a sub-analysis, we compared the kinetics of ACTH plasma levels with data from a previous trial investigating HC after s.c. and i.m. administration.

**Subjects and methods**

**Study design**

The trial was conducted as a single-center, open-label, sequence-randomized, cross-over, bioequivalence study. Prednisolone levels after VAG-PN were compared to levels after REC-PN in the same patients over a period of 6 h. Secondary endpoints were the safety of VAG-PN and the response of ACTH levels to GC administration as an indirect measure of biological GC activity. Patient acceptance of the different modes of PN administration was assessed by a questionnaire. The study was approved by the Ethics Committee of the University of Wuerzburg (permit no. 185/16). In addition, approval was obtained by the federal institute for drugs and medical devices (EUDRACT-No.: 2016-000332-18). The study was registered at clinicaltrials.gov (clinicaltrials.gov identifier: NCT02689960) and complies with the Declaration of Helsinki. Written informed consent was obtained from all patients before study participation. In case of discontinuation after only one study visit, the data obtained from the first study visit was still included in the analysis.

**Patients**

Twelve patients with primary AI registered at the outpatient department of the University Hospital Wuerzburg agreed to participate. Key inclusion criteria were female sex, chronic primary AI due to autoimmune adrenalitis, age ≥18 years, ability to comply with the protocol procedures, stable replacement therapy, no anticipated change in medication during study period, negative pregnancy test and contraception (other than hormonal contraception) in premenopausal females. Postmenopausal status was defined as >12 months lasting amenorrhea in females aged above 50 years. Key exclusion criteria were diabetes mellitus, infectious disease with fever at the time of investigation, chronic infectious disease, known intolerance to the study drug (PN) or constituents (hydrogenated fat), hormonal contraception or hormone replacement therapy with estrogens, pregnancy or breast feeding, renal failure (creatinine >2.5 ULN (upper limit of normal)), liver failure, liver cirrhosis, hepatitis, elevated transaminases (ALAT or ASAT >3 ULN), disposition to vaginal mycosis (requiring treatment in the last 6 months or need of >2 antifungal therapies/year), recurrent urinary tract infections (need of antibiotic treatment more than twice/year), duodenal or gastric ulcer, increased propensity for thrombosis, active psychiatric disease, increased intraocular pressure, heart failure (NYHA>II), untreated hypothyroidism, vaccination with an attenuated vaccine <8 weeks prior study participation, insufficiently controlled arterial hypertension (documented elevation of systolic blood pressure >140mmHg and diastolic blood pressure >90mmHg in repeated ambulatory measurements), acute enteropathy and entero-anastomosis. In premenopausal women, study visit was postponed in case of menstruation.
Medical product

The investigational medical product (Rectodelt (Trommsdorf)) is officially registered in the European Union (approval number: 6329964.00.00). In this trial the investigational medical product was used without modification of the registered composition.

Pharmacokinetics studies

The patients were investigated in the morning. While the usual morning dose of HC was postponed and ingested after all study procedures, all further long-term medication (including fludrocortisone and levothyroxine) was ingested as usual by the patients. Six patients initially received the PN suppository vaginally and six patients rectally. The minimum time interval between study visits was 7 days. The median interval between VAG-PN and REC-PN was 8 days (7–21). The vaginal and rectal administrations were performed by the patients under supervision of an investigator to ensure correct administration. At every study visit, blood samples for the determination of serum prednisolone and plasma ACTH were collected at the following time-points: −10, 0, 10, 45, 75, 120, 180, 240, 300, 360 min and further processed within maximum 30 min after collection. A study flow chart is shown in Fig. 1.

Questionnaire and safety assessment

Patients received a diary to document any local or systemic adverse event during the following 7 days after intervention. In addition, patients were contacted by phone after VAG-PN (Fig. 1). At the end of the second study visit, patients received a questionnaire to collect general information on their adrenal disease and a personal rating of the different administration modes.

Hormone measurements

Since PN is converted to the biologically active metabolite prednisolone by hepatic 11beta-hydroxysteroid dehydrogenase type 1 (25), prednisolone levels were measured in serum. For the determination of serum prednisolone ultra-performance liquid chromatography (UPLC (Acquity) with PDA (UV)-detector; MVZ Dr. Eberhard & Partner, Dortmund, Germany) was used. Intra- and inter-assay variations given by MVZ Dr. Eberhard & Partner, Dortmund, Germany were <15%. Intra-assay coefficients of variation (CVs) during measurements were as follows (n=20): 1.63, 2.05 and 2.96%. Inter-assay CVs were as follows: 6.8, 6.3 and 5.3%. Samples with values below 7 ng/mL (= lower limit of quantitation) were rated as 0 ng/mL for calculations. ACTH levels were determined from EDTA plasma with a solid-phase, two site sequential automated chemiluminescent immunometric assay (IMMULITE 2000 ACTH (PIL2KAC-18, 2018-03-15), Siemens Healthcare Diagnostics). Statistics for intra-assay precision given for the ACTH assay from Siemens Health Care Diagnostics IMMULITE 2000 ACTH ranged from 6.7 to 9.5% (mean values). Inter-assay precision ranged from 6.1 to 10%. Measurements from our study had been performed in a certified clinical routine laboratory regularly participating in ring trials. An assay from the same batch was used for all measurements.

Pharmacokinetic analysis

Pharmacokinetic data for assessment of bioequivalence: $C_{\text{max}}^\text{PN/HC}$ (maximum plasma concentration of prednisolone) and $\text{AUC}_{0-360}^\text{PN/HC}$ (area under the plasma concentration curve of prednisolone from administration to last observed concentration at time). Further pharmacokinetic data: $C_{\text{av}}$, $t_{\text{max}}$, (average plasma concentration of prednisolone), $t_{\text{max}}$ (time interval between administration and maximum plasma concentration of prednisolone), MRT (mean residence time of prednisolone) and $t_{50}$ (serum concentration half-life of prednisolone). $C_{\text{max}}$ and $t_{\text{max}}$ were obtained directly from the observed values. $C_{\text{av}}$ was calculated as mean of all values between 10 and 360 min. $\text{AUC}_{0-360}^\text{PN/HC}$ was assessed by the trapezoidal rule. MRT was calculated as the area under the moment curve divided by the $\text{AUC}_{0-360}^\text{PN/HC}$. Elimination half-life was calculated using the formula: $t_{50} = \ln (2)/ke$. The elimination rate constant was calculated as follows: $ke = (\ln (C1) − \ln (C2))/\Delta t$. The biological efficacy was evaluated by the decrease of ACTH levels. Kinetic data: $C_{\text{BASELINE}}$ (baseline ACTH level, mean of values at −10 min and 0 min), $C_{\text{MIN}}$ (minimal ACTH concentration after administration of PN/HC), $\Delta C_{\text{BASELINE-MIN}}$ (difference between baseline and minimal ACTH level after administration of PN/HC), $t_{50}$ (time to a 50% decrease of the baseline ACTH level), $t_{2\text{ULN}}$ (time to a decrease of the ACTH level <92 ng/L (= upper limit of normal multiplied with 2)), $\text{AUC}_{0-360}^\text{MIN}$ and $\text{AUC}_{0-240}^\text{MIN}$ (area under the concentration-time curve (ACTH) from zero to last sampling time). $C_{\text{MIN}}$, $t_{50}$ and $t_{2\text{ULN}}$, were obtained directly from the observed values. $C_{\text{BASELINE}}$, $\Delta C_{\text{BASELINE-MIN}}$ and the AUC were calculated. $\text{AUC}_{0-360}^\text{MIN}$ and $\text{AUC}_{0-240}^\text{MIN}$ were assessed by the trapezoidal rule.
Recruitment of patients and prearrangement
- 6 pre- and 6 postmenopausal women
- Patient information and examination of inclusion and exclusion criteria
- Block randomization (ratio 1:1) to the order of the two different modes of administration

First study visit
- Intervention: vaginal* PN administration
- n=6

Second study visit
- Intervention: rectal PN administration
- Questionnaire
- n=6

Study visit / Pharmacokinetic studies
- START in the morning (8:00–11:00), usual morning dose of HC was postponed
- Blood sampling after rectal/vaginal administration of 100 mg PN (suppository): -10, 0, 10, 45, 75, 120, 180, 240, 300, and 360 min
- Quick and cooled transport of blood samples to the laboratory within maximum 30 min
- Centrifugation of blood samples 4000 rpm for 5 min
- Hormone measurements: prednisolone – UPLC; ACTH – chemiluminescent immunometric assay
- *Phone contact 3 (±1) and 7 (±1) days after vaginal administration of prednisone
- Return of diary 7 days after the second study visit

Primary and secondary endpoints
- Bioequivalence ($C_{\text{max}}$ and AUC$_{0-360}$ after vaginal compared to rectal administration of PN)
- ACTH suppressive effects, patients’ preference, safety

Results

Study cohort

Twelve female patients with primary AI caused by autoimmune adrenalitis were included. Six patients were premenopausal and six postmenopausal. Eleven patients completed all study visits, and one patient discontinued before completion and only received VAG-PN. Additional autoimmune thyroid disease was documented in 11 patients; one patient was diagnosed with premature ovarian failure. Median age was 51 years (range: 31–63) and median duration of primary AI was 12 years (2–33). BMI was 26 kg/m² (18–33). All patients were on stable steroid replacement therapy with HC (20 mg (10–30)) and fludrocortisone (0.05 mg (0.05–0.15)). Ten patients received levothyroxine replacement (81 μg (50–138)). No patient received any medication known to induce GC-metabolizing hepatic cytochrome P450 3A4 (26).

Pharmacokinetics of vaginal and rectal administration of prednisone

Prednisolone serum concentrations after VAG-PN compared to REC-PN are displayed in Fig. 2. After VAG-PN, no serum prednisolone levels could be detected at any time point during 360 min in five patients while after REC-PN, prednisolone levels were measurable in all patients. Pharmacokinetic parameters after PN administration are given in Table 1. Maximum serum prednisolone levels as well as the AUC$_{0-360}$ significantly differed after rectal...
and vaginal administration of 100 mg PN suppositories with lower values after VAG-PN (Table 1). The 90% CI for AUC$_{0-360}$ and C$_{max}$ (test/reference ratio) were not within the bioequivalence bounds (80–125%): AUC$_{0-360}$: 0.1–4.8% and C$_{max}$: 2.8–13%.

No significant correlation could be observed between BMI and the pharmacokinetic data (C$_{max}$, C$_{av}$, AUC$_{0-360}$ and MRT) after either administration. Furthermore, no significant correlation between the day of menstrual cycle and C$_{max}$, C$_{av}$, AUC$_{0-360}$ and the MRT was detected. The patient cohort was further divided into a pre- (n=6) and postmenopausal (n=6) group of women to investigate the potential influences on vaginal absorption of PN. Pharmacokinetic parameters did not differ between both groups. Moreover, no difference of pharmacokinetic parameters was observed in case of self-reported vaginal dryness. ACTH levels continuously decreased from 790 ng/L (54%) to 448 ng/L (68%) after VAG-PN and from 767 ng/L (47%) to 26 ng/L (67%) after REC-PN. The decrease in ACTH levels was significantly more pronounced after REC-PN compared to VAG-PN (Fig. 3). Minimal ACTH levels and the AUC$_{0-360}$ were significantly lower after REC-PN (Table 2). Pharmacokinetic parameters are provided in Table 2.

### Patient questionnaire

The questionnaire was completed by eleven patients (92%). In general, the patients rated their coping with the disease as ‘very good’ (n=1) or ‘good’ (n=9); one patient gave no answer. History of AC was reported by four patients (reported causes of AC: 66.7% gastroenteritis, 33.3%...
other febrile infections). All patients were equipped both with an emergency card and set (at least consisting of a 100 mg hydrocortisone ampoule for parenteral injection). Three patients already had self-injected HC in case of emergency; none of the patients had previously used a PN suppository. All study participants indicated that the opportunity to use PN suppositories as an alternative to HC self-injection would make them feel safer. Eight patients would use vaginal PN suppositories after study participation. Regarding the mode of GC administration in case of gastroenteritis (possible answers within this multiple-choice question were vaginal PN administration, s.c. or i.m. HC injection), one patient preferred i.m. injection of HC, three patients s.c. injection of HC and seven patients preferred vaginal administration of a PN suppository.

### Adverse events

In total, 23 mild or moderate adverse events were documented in ten patients. After REC-PN, one patient reported increased fatigue and flushing and another patient reported dizziness. After VAG-PN, ten patients reported adverse events: four patients reported fatigue and two patients reported dizziness. Collapse, cephalgia, flushing, exertional dyspnea and nausea were reported by one patient, respectively. Local adverse events were reported by 50% of the patients: three patients developed

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**Table 2** Effect of vaginal (n = 12) and rectal (n = 11) administration of 100 mg prednisone suppositories on ACTH values; kinetic parameters.

<table>
<thead>
<tr>
<th></th>
<th>Mean (CV %)</th>
<th>CI 95 %</th>
<th>MIN</th>
<th>MAX</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_BASELINE (ng/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal</td>
<td>790 (54)</td>
<td>520–1060</td>
<td>34</td>
<td>1254</td>
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</tr>
<tr>
<td>Rectal</td>
<td>767 (47)</td>
<td>527–1007</td>
<td>87</td>
<td>1250</td>
<td></td>
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<tr>
<td>C_MIN (ng/L)</td>
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<td></td>
<td></td>
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<tr>
<td>Vaginal</td>
<td>448 (68)</td>
<td>255–641</td>
<td>21</td>
<td>844</td>
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</tr>
<tr>
<td>Rectal</td>
<td>26 (67)</td>
<td>14–138</td>
<td>12</td>
<td>75</td>
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<tr>
<td>ΔC_BASELINE–MIN (ng/L)</td>
<td></td>
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<tr>
<td>Vaginal</td>
<td>342 (63)</td>
<td>204–479</td>
<td>13</td>
<td>747</td>
<td>0.001</td>
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<td>Rectal</td>
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<td>502–980</td>
<td>72</td>
<td>1224</td>
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<tr>
<td>ΔC_BASELINE–MIN (%)</td>
<td></td>
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<tr>
<td>Vaginal</td>
<td>47 (44)</td>
<td>34–60</td>
<td>11</td>
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<td>Rectal</td>
<td>95 (5)</td>
<td>92–98</td>
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<td>99</td>
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<tr>
<td>AUC0–360min (ng/L * min)</td>
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<td></td>
<td></td>
<td>0.033</td>
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<tr>
<td>Vaginal</td>
<td>207457 (67)</td>
<td>108,528–306,386</td>
<td>11,641</td>
<td>353,735</td>
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</tr>
<tr>
<td>Rectal</td>
<td>95949 (43)</td>
<td>68,152–123,746</td>
<td>16,512</td>
<td>168,042</td>
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</table>

Analyses were performed by one-way ANOVA. Bold indicates statistical significance, P < 0.05.

AUC0–360min, area under the concentration-time curve (ACTH) from zero to last sampling time; C_BASELINE, baseline ACTH (mean of values −10 min and 0 min); ΔC_BASELINE–MIN, difference between baseline and minimal ACTH levels after administration of prednisone; CI, confidence interval; C_MIN, minimal ACTH concentration after administration of prednisone; CV, coefficient of variation; MAX, maximum; MIN, minimum.
vaginal discharge, one patient developed a urinary tract infection as well as a vaginal mycosis and one patient reported local feeling of heat directly after administration. No severe adverse events occurred.

The symptoms after REC-PN lasted maximum 24 h and did not require any intervention. The general symptoms after VAG-PN were most likely caused by inadequate absorption of PN resulting in GC deficiency. Additional HC administration during the study procedures in one patient (values after HC administration were not included in analysis). General symptoms lasted 14 days in one patient; in all other patients 24–72 h. The urinary tract infection was treated by systemic antibiotic therapy and vaginal mycosis by local antifungal therapy.

**Comparison of PN suppositories versus subcutaneous and intramuscular injection of hydrocortisone**

Plasma ACTH levels were compared to data obtained in 12 patients with primary AI (five men, seven women) after i.m. and s.c. administration of 100 mg HC investigated in another pharmacokinetic study (19). Six participants of the current trial also had participated in the former study. The mean BMI of both study cohorts did not differ significantly (26 kg/m² vs 26 kg/m² in the current trial; \( P = 0.715 \)). The decline in mean ACTH levels, as a measure of the biological efficacy of the respective GCs, was slower both after REC-PN and VAG-PN (100 mg PN) compared to i.m. and s.c. injection of 100 mg HC (Fig. 3).

Pharmacokinetic parameters for ACTH levels after REC-PN compared to s.c. and i.m. injection of HC are shown in Table 3. ACTH levels were significantly lower after s.c. (17 ng/L (51%); \( P = 0.022 \)) and i.m. (14 ng/L (64%); \( P = 0.018 \)) injection of HC compared to REC-PN (79 ng/L (78%)). The time to a 50% decrease of baseline ACTH values was significantly longer after REC-PN compared to s.c. (\( P < 0.001 \)) and i.m. (\( P < 0.001 \)) injection of HC, while there was no significant difference between s.c. and i.m. administration of HC (\( P = 0.971 \)). After VAG-PN, the maximum decline of ACTH levels compared to baseline values was 44% after 360 min. A similar pattern of decline of ACTH levels was found for all investigated routes of administration when only ACTH levels of the six female patients that participated in both studies were compared (Supplementary Fig. 1, see section on supplementary data given at the end of this article). Again, the time to a 50% decrease of baseline ACTH values was significantly longer after REC-PN compared to s.c. and i.m. injection of HC.

**Discussion**

Our study documents the pharmacokinetic profile of a commercially available PN suppository after both vaginal and rectal administration in female patients with AI. After REC-PN, drug levels were seen in every patient and the pharmacokinetic results are comparable to available data from healthy subjects (27). In contrast, insufficient bioavailability is observed after VAG-PN, clearly demonstrating that this administration route should be avoided at least when using the currently available galenic formulation. Maximum serum prednisolone concentrations and the AUC\(_{0-360}\) were significantly lower after VAG-PN compared to REC-PN. Five patients did not achieve any measurable prednisolone levels during 360 min. In addition, there were more adverse events after VAG-PN, which were most likely due to the insufficient absorption and the resulting GC deficiency as the patients had to postpone their morning GC dose. Local adverse events were also more frequent after VAG-PN.

The used PN suppository was established for rectal use. Therefore, the vaginal pH value and anatomy might have impaired the vaginal absorption of the suppository. The composition of the PN suppository with a high ratio of hydrogenated fat may have contributed to the reduced vaginal absorption. Furthermore, sphincter tone better prevents an uncontrolled passing after rectal use. After VAG-PN three patients described vaginal discharge during the study visit. Since relevant drug levels are achieved after vaginal administration of other medications (e.g. misoprostol) (28, 29), it cannot be generally assumed that this mode of administration is associated with an impaired absorption. In an emergency situation, however, rapid GC availability must be ensured.

It remains to be defined which time intervals and GC levels may be considered as safe. In a previous study, we postulated that the time needed to reach cortisol levels of >36 µg/dL (>1000 nmol/L) does not exceed 30 min (19). This value is twice the cutoff level required to pass the short Synacthen test, representing a maximum ACTH stimulus. The cut-off was achieved both after i.m. and s.c. HC (19). Median prednisolone levels 45 min after rectal administration in our current study were 4.9 µg/dL (2–9.6) (136 nmol/L (56–266)). The relative GC potency between prednisolone and HC has been calculated as 1:4–8 (30, 31). The suppressive effect on ACTH secretion was delayed and less pronounced after administration of PN suppositories compared to s.c. and i.m. administration of 100 mg HC (19) and the minimal ACTH levels (\( C_{\text{MIN}} \)) achieved after REC-PN remained significantly higher compared to those
Table 3  Effect on ACTH values after rectal (n = 11) administration of 100 mg prednisone versus subcutaneous (n = 12) and intramuscular (n = 12) administration of 100 mg hydrocortisone; kinetic parameters.

<table>
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<th>Mean (CV %)</th>
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<td><strong>C_{BASELINE}</strong> (ng/L)</td>
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<td>s.c.</td>
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<td>415–1033</td>
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<td><strong>C_{MIN}</strong> (ng/L)</td>
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<td>Dunnett-T3: (1) rectal versus s.c.: <strong>P = 0.022</strong>; (2) rectal versus i.m.: <strong>P = 0.018</strong>; (3) s.c. versus i.m. 0.883</td>
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<td>∆C_{BASELINE-MIN} (%)</td>
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<td>97</td>
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<td>Dunnett-T3: (1) rectal versus s.c.: <strong>P = 0.030</strong>; (2) rectal versus i.m.: <strong>P = 0.031</strong>; (3) s.c. versus i.m. 0.995</td>
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<td>t_{50} (min)</td>
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</tr>
<tr>
<td>Dunnett-T3: (1) rectal versus s.c.: <strong>P &lt; 0.001</strong>; (2) rectal versus i.m.: <strong>P &lt; 0.001</strong>; (3) s.c. versus i.m. 0.971</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t_{2ULN} (min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rectal</td>
<td>193 (35)</td>
<td>137–249</td>
<td>45</td>
<td>240</td>
</tr>
<tr>
<td>s.c.</td>
<td>132 (40)</td>
<td>99–166</td>
<td>10</td>
<td>180</td>
</tr>
<tr>
<td>i.m.</td>
<td>116 (34)</td>
<td>92–141</td>
<td>45</td>
<td>180</td>
</tr>
<tr>
<td>Dunnett-T3: (1) rectal versus s.c.: <strong>P = 0.134</strong>; (2) rectal versus i.m.: <strong>P = 0.041</strong>; (3) s.c. versus i.m. 0.787</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>AUC_{0–240min} (ng/L * min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rectal</td>
<td>90,419 (43)</td>
<td>64,146–116,693</td>
<td>13,899</td>
<td>156,720</td>
</tr>
<tr>
<td>s.c.</td>
<td>56,078 (62)</td>
<td>33,895–78,261</td>
<td>3826</td>
<td>122,719</td>
</tr>
<tr>
<td>i.m.</td>
<td>40,993 (62)</td>
<td>24,864–57,121</td>
<td>10,040</td>
<td>104,757</td>
</tr>
<tr>
<td>Dunnett-T3: (1) rectal versus s.c.: <strong>P = 0.063</strong>; (2) rectal versus i.m.: <strong>P = 0.005</strong>; (3) s.c. versus i.m. 0.549</td>
<td></td>
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</tbody>
</table>

Analyses were performed by one-way ANOVA. *Post hoc* tests: Scheffé procedure and Dunnett-T3. Bold indicates statistical significance, *P < 0.05.*

The superiority of parenteral GC administration, however, only holds true if treatment is initiated within similar time intervals. Delays may result from the time-consuming preparation of injections and fear to self-inject (17). A patient-friendly ready-to-use HC syringe is unavailable (15, 17). Most of the patients in our study (64%) preferred the use of suppositories over GC injection in case of emergency provided that safety is similarly guaranteed. However, the patients’ preference was only assessed within a small number of female patients and might vary in a larger and more heterogeneous cohort. It has furthermore not been investigated if suppositories are administered in a shorter period of time in case of incipient AC. Nevertheless, all study participants stated that the option of using suppositories would make them feel safer and increase their general well-being.

As PN is converted to prednisolone by hepatic 11beta-hydroxysteroid dehydrogenase type 1 (25), it may be assumed that use of prednisolone or HC suppositories might vary in a larger and more heterogeneous cohort. It has furthermore not been investigated if suppositories are administered in a shorter period of time in case of incipient AC. Nevertheless, all study participants stated that the option of using suppositories would make them feel safer and increase their general well-being.

In conclusion, vaginal administration of PN suppositories in the investigated available galenic composition is not sufficient for prevention or treatment of AC. Although sufficient drug levels were observed over...
time after REC-PN, it cannot be regarded as equivalent to parenteral administration of GC for treatment of adrenal emergencies. On the background of the available data, GC injection should be recommended to the patients as the first choice to prevent or treat AC until adequate professional medical care is available.

Supplementary data
This is linked to the online version of the paper at https://doi.org/10.1530/EC-19-0024.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement
S Burger-Stritt was involved in the design of study, preparation of study protocol and applications for authorities, conduct of the study, data analysis and preparation of the manuscript. L Bachmann was involved in the preparation of applications for authorities, conduct of the study, laboratory measurements and data analysis. M Kurfaß was involved in pharmacokinetic analysis and preparation of the manuscript. S Hahner was involved in design of study, preparation of study protocol and applications for authorities, data analysis and preparation of the manuscript.

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