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Rationale and design of the CORE (COrticosteroids REvised) study: protocol

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ABSTRACT

Introduction Corticosteroids are an important pillar in many anti-inflammatory and immunosuppressive treatment regimens and are available in natural and synthetic forms, which are considered equipotent if clinical bioequivalence data are used. Current clinical bioequivalence data are however based on animal studies or studies with subjective endpoints. Furthermore, advancement in steroid physiology with regard to metabolism, intracellular handling and receptor activation have not yet been incorporated. Therefore, this study aims to re-examine the clinical bioequivalence and dose effects of the most widely used synthetic corticosteroids, prednisolone and dexamethasone.

Methods and analysis In this double-blind, randomised cross-over clinical trial, 24 healthy male and female volunteers aged 18–75 years, will be included. All volunteers will randomly receive either first a daily dose of 7.5 mg prednisolone for 1 week, immediately followed by a daily dose of 30 mg prednisolone for 1 week, or first a presumed clinical bioequivalent dose of 1.125 mg dexamethasone per day, immediately followed by 4.5 mg of dexamethasone per day for 1 week. After a wash-out period of 4–8 weeks, the other treatment will be applied. The primary study endpoint is the difference in free cortisol excretion in 24 hours urine. Secondary endpoints will include differences in immunological parameters, blood pressure and metabolic measurements.

Ethics and dissemination This study has been approved by the Medical Ethics Committee of the University Medical Center Groningen (METC 2020.398). The results of this study will be submitted for publication in peer-reviewed journals.

Trial registration number ClinicalTrials.gov (Identifier: NCT04733144), and in the Dutch trial registry (NL9138).

Strengths and limitations of this study

- Cross-over design limits high interindividual effect of exogenous glucocorticoids.
- State-of-the-art laboratory techniques, consisting of validated gas chromatography–tandem mass spectrometry and liquid chromatography–tandem mass spectrometry assays, which have superior specificity compared with immunoassays.
- Used doses reflect clinical practice.
- Absence of placebo intervention.
- Due to the COVID-19 pandemic and subsequent vaccination campaign wash-out could not always be maintained at 4–8 weeks.

INTRODUCTION

Since the first clinical use of cortisone in 1948, glucocorticoids have become a fundamental part in the treatment of many diseases, including autoimmune disorders, respiratory disorders and haematological malignancies.[1] Furthermore, corticosteroids have become a mainstay in the immunosuppressive treatment for solid-organ transplantation. Corticosteroids are available in various natural and synthetic forms.[2] In a clinical setting, different natural and synthetic forms are applied interchangeably, for which equipotent doses can be calculated according to established clinical bioequivalence data.[3] Although this is more or less thoughtlessly applied in daily practice, it is important to realise that the literature which provides the rationale for the current clinical bioequivalence data, consists of old, non-randomised studies.[4 5] In addition, these studies are limited by the use of subjective endpoints, outdated laboratory techniques and the use of animals or patients with rheumatoid arthritis as study participants.[4–6] Later, some attempts have been made to improve clinical bioequivalence data of corticosteroids, but these attempts were hampered by methodological imperfections.[7–9] Since then one pharmacological study, performed approximately twenty years ago, suggested that the current dosing tables reflect a reasonable dose equivalence relation, but this study included only five men and described only the effects of a single interventional dose.[10] Furthermore, recent decades have resulted in major advancements in our knowledge of corticosteroids, especially on intracellular handling and receptor transactivation or—repression but this has not yet resulted in a better understanding of their clinical bioequivalence.

Predniso(lo)ne and dexamethasone are the most commonly prescribed representatives of the synthetic corticosteroids and therefore provide an important focus to study clinical bioequivalence. When studying this, effects on the glucocorticoid receptor (GR) and the mineralocorticoid receptor (MR), metabolism or intracellular handling as well as tissue or system-specific transactivation or repression should be taken into account. Regarding the first, predniso(lo)ne and dexamethasone have divergent effects, because while both have GR effects (ie, anti-inflammatory and immunosuppressive properties), only predniso(lo)ne has MR effects.[11] Although these characteristics are known since their discovery, it may have important consequences for various organ systems relying on mineralocorticoid effects such as the brain and kidney, resulting in different (side) effects. Novel insights have also unveiled a difference in metabolism, for example, due to an alternative intracellular handling by both 11β-hydroxysteroid dehydrogenase type 1 and type 2.[12] It can therefore be hypothesised that currently presumed equipotent doses of prednisolone and dexamethasone have different effects on various organ systems for which these enzymes are important. Also, advancement in the understanding of the molecular mechanism of the GR has uncovered a wide range of system specific sensitivities to corticosteroids.[13 14] This indicates that the currently used approach of one conversion factor for all body systems may not be justified. Instead, it may be necessary to take this heterogenicity into account, by using system specific conversion rates. Finally, as studies have demonstrated that the pharmacokinetics of prednisolone are non-linear, while those of dexamethasone are, it may be postulated that the conversion factor between prednisolone and dexamethasone is dose-dependent.[15]

Therefore, we aim to re-examine the clinical bioequivalence and dosing effects of prednisolone and dexamethasone on various physiological systems, to provide reliable in vivo data in healthy volunteers and thus provide data to optimise systemic corticosteroid therapy to modern day standards.

METHODS AND ANALYSIS

Study design

The COrticosteroids REvised (CORE) study is an investigator-initiated, single-centre, randomised, double-blind, cross-over trial including healthy volunteers to receive two doses of prednisolone and two doses of dexamethasone. All volunteers will be randomly assigned to receive either first a daily dose of 7.5 mg prednisolone for 1 week, immediately followed by a daily dose of 30 mg of prednisolone for 1 week, or first a presumed clinical bioequivalent dose of 1.125 mg dexamethasone per day, immediately followed by 4.5 mg of dexamethasone per day for 1 week (figure 1). After awash-out period of 4–8 weeks, the other treatment will be applied. The duration of the wash-out period is at least 4 weeks, but can be extended to 8 weeks to prevent the influence of stressful periods such as exams and work deadlines. The primary outcomes of the trial is the difference in 24 hours urinary free cortisol excretion between lowest doses and highest doses of prednisolone and dexamethasone.

Study setting and population

All study visits will be performed in the outpatient clinic of the University Medical Center Groningen (UMCG), an academic hospital in the northern part of the Netherlands. A total of 24 healthy volunteers will be included in the study. As most of the outcomes are dependent on age and sex, the participants are subdivided into four groups, specifically 6 males aged 18–50 years, 6 females aged 18–50 years and using oral contraceptives, 6 males aged ≥50–75 years, and lastly six postmenopausal females aged ≥50–75 years. Next to the age and hormonal status mentioned above, volunteers need to have a body mass index between 18.5 and 30 kg/m^2, no relevant medical history and no dependency on any type of corticosteroid in any pharmaceutical form. All inclusion and exclusion criteria can be found in table 1. Participants will either be

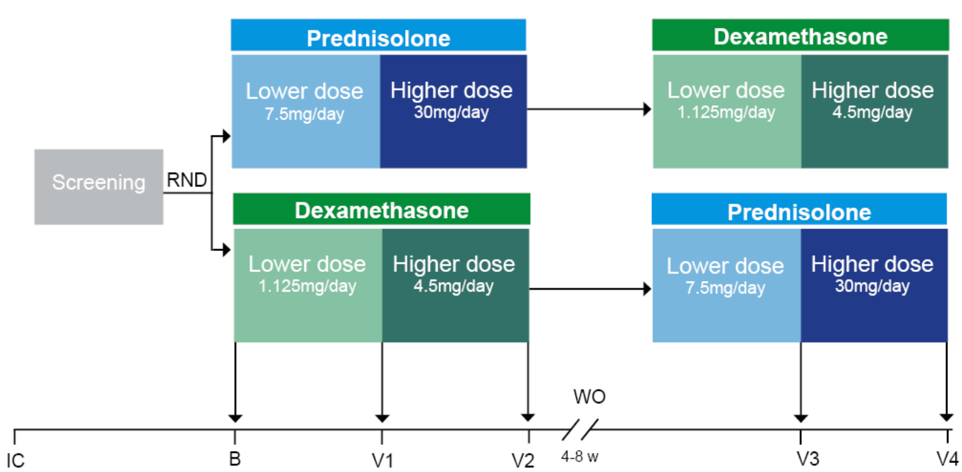

Figure 1 B, baseline; IC, Informed consent; RND, randomisation; WO, wash-out; w, weeks.

Table 1 Inclusion and exclusion criteria for the CORE study

Inclusion criteria	Exclusion criteria
1. Participants must have good command of the Dutch language	1. Potential participants with a medical history of:
2. Participants must provide written informed consent	A. Diseases affecting the HPA-axis, for example, primary and secondary adrenal insufficiency, pituitary tumours or Cushings' disease
3. Participants must have an age between 18 and 75 years	
4. Female participants aged 18–49 years must be using oral contraceptives and female participants age 50–75 years must be in the postmenopausal state	B. Chronic inflammatory diseases, for example, rheumatoid arthritis, polymyalgia rheumatica and asthma
5. BMI between 18.5 and 30 kg/m^2	C. Psychiatric diseases
6. Participants are not allowed to have a relevant medical history or use interfering medication	D. Diabetes mellitus
	2. Potential participants who have known contraindication to the study medication (eg, known peptic ulcer disease or active infectious disease).
	3. Night shift workers.
	4. Potential participants with a kidney function <60 mL/min/1.73 m^2, abnormalities in liver enzymes and/or abnormalities in thyroid function.
	5.Potential participants who are dependent on corticosteroids in any form, for example, asthmatic patients and transplant recipients
	6.Potential participants who use any medication which is likely to confound assessment of one the endpoints (eg, inhaled corticosteroids, hormone supplements, psychotropic drugs, carbamazepine or vaccination)
	7.Potential participants who intend to undergo significant lifestyle changes, for example, voluntary weight loss and discontinue smoking habits.
	8.Potential participants who are unlikely to adhere to the study medication (eg, volunteers with a history of substance abuse or non-adherence)

BMI, body mass index; CORE, COrticosteroids REvised; HPA, hypothalamic–pituitary–adrenal axis.

recruited through pamphlets placed in local public buildings or advertisement in the local newspaper.

Patient and public involvement

As this study is performed with healthy subjects, patients were not directly involved to the design of the study. Recruitment of participants was however updated based on input of the volunteers.

Intervention

This study is designed as a cross-over trial as previous studies have demonstrated a high interindividual variation for the effect of exogenous corticosteroids.[16 17] One intervention consists of two doses of prednisolone (11β,17,21-trihydroxy-1,4-pregnadieen-3,20-dion). To align the CORE study as much as possible with current clinical practice, the doses that were chosen were based on dosages which are often prescribed in clinical practice. In general, a distinction is made between maintenance doses, ranging from 5 to 20 mg prednisolone daily and active treatment doses, ranging from 30 to 80 mg prednisolone daily. To minimise potential side effects, we selected a low maintenance dose at a borderline physiological level, namely 7.5 mg prednisolone and a low active treatment dose namely 30 mg prednisolone, both for the duration of a week. To allow for comparison between prednisolone and dexamethasone, the currently presumed clinical bioequivalency data of dexamethasone (9-fluor-11β,17,21-trihydroxy-16α-methyl-1,4-pregn adieen-3,20-dion) were used, resulting in 1.125 mg dexamethasone and 4.5 mg dexamethasone, respectively.[18] All study medication was taken every day at eight o'clock in the morning after an overnight fast and provided to participants as capsules for oral ingestion. No tapering is applied as both intervention periods are no longer than 2 weeks.[19] To monitor interventional adherence, all remain drug capsules were counted on return during the study visit.

Primary outcome

Twenty-four-hour urinary cortisol excretion

The primary composite endpoint is the difference between the two lower doses and two higher doses of prednisolone and dexamethasone measured by 24 hours urinary free cortisol excretion as measure for hypothalamic–pituitary–adrenal axis (HPA-axis) suppression (24 hours free cortisol $Pred_{7.5mg}$ – $Dex_{1.125mg}$ and 24 hours free cortisol $Pred_{30mg}$ – $Dex_{4.5mg}$). For this endpoint, 24-hour urine is collected according to a strict protocol which is as follows: on the morning of the day before a study visit, participants are asked to discard a urine void and subsequently collect all urine for the next 24 hours including a urine void at exactly 24 hours after the first discarded urine void. Next to 24 hours urinary free cortisol excretion, urinary cortisone, tetrahydrocortisol, allo-tetrahydrocortisol, tetrahydrocortison, α-cortolon, and β-cortolon will be measured by using a validated gas chromatography–tandem mass spectrometry (GC-MS) and liquid chromatography–tandem MS assay (LC-MS/MS).[20 21]

Androsterone, etiocholanolone, dehydroepiandrosterone, 11-keto-etiocholanolone, 11-hydroxyandrosterone, 11-hydroxyetiocholanolone and estriol will also be measured using GC-MS as part of a complete urinary steroid profile, as well as allopregnanediol, pregnanediol, pregnanetriol and polone. Furthermore, 11-dehydrotetrahydrocorticosterone, tetrahydrocorticosterone, allo-tetrahydrocorticosterone, tetrahydrodeoxycortisol, pregnanediolone, pregnanetriolone, allo-pregnanediolone and 11-deoxytetrahydrocorticosterone will be measured in the same GC-MS/MS assay.[20] Additionally, plasma adrenocorticotropic hormone will be measured. More information on preanalytical handling can be found in table 2.

Secondary outcomes

Next to the interventional effect on the HPA-axis, the effects on the hypothalamic–pituitary–gonadal axis are studied, taking plasma levels of testosterone, dihydrotestosterone, progesterone, 17-hydroxyprogesterone, androstenedione, luteinising hormone, follicle stimulating hormone and sex-hormone binding globulin into account. Testosterone and dihydrotestosterone will be measured using LC-MS/MS according to a previously published protocol.[22] To study mineralocorticoid effects, plasma renin and aldosterone, serum potassium, 24-hour urine potassium and transtubular potassium gradient will be determined to assess the effects of prednisolone and dexamethasone on the renin–angiotensin–aldosterone system. The transtubular potassium gradient is used to gauge renal potassium secretion by the cortical collecting duct, providing a good measure of mineralocorticoid bioactivity. First, renin and aldosterone will be measured using an immunoradiometric renin assay (Renin III Generation, Cisbio) and by (LC-MS/MS), respectively, as previously described.[23] Second, both potassium and osmolality (potassium: ion-selective electrode, Roche. Osmolality: method of freezing point depression) will be measured in plasma and in 24-hour urine. These measurements may be taken together using the following

Table 2 Sample overview

Sample	Specifications	Centrifuge	Temporary storage on ice?	Tube size	N	Storage temperature
Serum	With gel	1885 g for 5 min on RT	No	500 µL	13	−80°C (−112 °F)
Serum	Without gel	1300 g for 10 min on 4°C–8°C	Yes	1 mL/500 µL	1/3	−80°C (−112 °F)
EDTA plasma		1300 g for 10 min on RT	No	1 mL/500 µL	1/7	−80°C (−112 °F)
EDTA plasma		1300 g for 10 min on 4°C–8°C	Yes	1 mL/500 µL	1/2	−80°C (−112 °F)
EDTA plasma*	For pharmacokinetics	1885 g for 5 min on RT	No	1 mL/500 µL	1/2	−80°C (−112 °F)
EDTA	With protease-inhibitors	1100 g for 10 min	No	500 µL	2	−80°C (−112 °F)
Whole blood†	CYP3A4 and CYP3A5	N.A.	No	4 mL	1	−20°C (−4 °F)
Sodium fluoride		1300 g for 10 min on 4°C–8°C	No	1 mL	1	−80°C (−112 °F)
Lithium-heparin		1885 g for 5 min on RT	No	500 µL	6	−80°C (−112 °F)
Lithium-heparin	For PBMC isolation		No	10 mL	1	−80°C (−112 °F)
PAXgene			No	2.5 mL	1	−20°C (−4 °F)
24-hour urine		1500 g for 10 min on RT	No	2 mL	9	−80°C (−112 °F)
Saliva†		N.A.	No	500 µL	1	−80°C (−112 °F)

*Study visits 1–4.
†Only on baseline.
N, amount of tubes in storage; NA, not available; PBMC, peripheral blood mononuclear cell; RT, room temperature.

formula to calculate the transtubular potassium gradient:

$$TTPG = \frac{[K^+]urine}{[K^+]blood} \times \frac{Osmblood}{Osmurine}.$$ [24]

Immune system

To investigate the effect of prednisolone and dexamethasone on the immune system, multiple entities will be investigated. First, absolute leucocyte, granulocyte and monocyte counts will routinely be performed using flow cytometry. Second, during each study visit peripheral blood mononuclear cells will be isolated using Leucosep tubes (227288, Greiner Bio-one, Kremsmünster, Austria). After isolation peripheral blood mononuclear cells will be aliquoted and placed into isopropanol containers and put into liquid nitrogen for long-term storage. Lastly, to assess the influence of corticosteroids on a gene expression level, 10mL PAXgene tubes will be collected each visit. PAXgene tubes allow for immediate stabilisation of intracellular RNA, thereby facilitating reproducible and accurate gene expression data.

Pharmacokinetic measurements

Population-specific pharmacokinetic models and limited sampling strategy were developed to assess the pharmacokinetic parameters of both prednisolone and dexamethasone (MwPharm V.3.81 (Mediware, Zuidhorn, The Netherlands)). MWPharm parameterised a population pharmacokinetic model, originating from literature values.[25] Population pharmacokinetic models of prednisolone and dexamethasone were described with the following parameters (±SD): bioavailability of 82%±13% and 86%±5%, absorption constant of 1.6±0.1h-1 and 0.6±0.0h-1, volume of distribution of 1.5±0.2L/kg and 2.0±0.5L/kg, and elimination constant of 0.169±0.033h-1 and 0.154±0.026h-1, respectively. Furthermore, Monte Carlo analyses were used to develop the limited sample strategy. In these analyses, 1000 patients were simulated for both dosages of prednisolone and dexamethasone. The area under the curve (AUC) was estimated based on four points sampling protocol. Performance criteria were set at a R value of >0.95 and a relative root mean squared error of <15% (table 3).[26]

As a result of these calculations, blood samples will be drawn at three time points, namely before, 3hours after and 4hours after ingestion of the study medication on the seventh day. Furthermore, participants are asked to collect saliva at four time points, with the first three time points corresponding to the blood samples and the fourth 7–11hours after ingestion of the last study medication. Plasma cortisol measurements will be performed using validated LC-MS/MS method.[27] Prednisolone and dexamethasone levels in both plasma and saliva will be measured by isotope dilution LC–MS/MS. Cortisol binding globulin (CBG) will be determined by a radioimmuno-assay, and albumin will be measured using the brome cresol green method on a Roche Modular ISE/P. Individual pharmacokinetic parameters will be calculated by maximum a posteriori Bayesian estimation, essentially performed as described by Werumeus Buning.[16] Total body clearance, volume of distribution, $t_{1/2}$, maximum concentration and AUC will be calculated for all interventions in each individual. Lastly, CYP3A4 and CYP3A5 polymorphisms will be taken into account, as these genetic variations have an important contribution to inter-individual pharmacokinetic variability.

Table 3 Results of the Monte-Carlo analyses for the proposed scheme of four sampling points

	% RMSE
Prednisolone—7.5mg	3.34
Prednisolone—30mg	2.60
Dexamethasone—1.125mg	14.1
Dexamethasone – 4.5mg	4.66

% RMSE, relative root mean squared error.

Anthropometrical and metabolic parameters

Anthropometry measurements will include body length, body weight, waist circumference and hip circumference. Body weight (kg) will be measured without shoes and outer clothing using a calibrated digital measuring scale (seca 877, seca, Hamburg, Germany). Height (cm) will be measured using a wall-secured stadiometer. Waist and hip circumference (cm) will be calculated using a measuring tape roll with standardised retraction mechanism. Waist circumference will be measured mid-way between the lowest rib and the iliac crest with the participant in standing position. Hip circumference will be determined at the maximum circumference over the trochanter major. All anthropometry measurements will be assessed twice after which the average will be used in further analyses.

To assess metabolic function and potential changes during corticosteroid use, we will perform an in-depth analysis of the glucose metabolism and lipid profiles. First, fasting glucose levels will be measured using the Roche P Analyzer and fasting insulin levels and c-peptide levels will be measured using a luminescence-immunoassay (Alinity, Abbot, Abbott Park, Illinois, USA). For glucagon-like peptide-1 (GLP-1) special blood collection tubes will be used containing K_2EDTA and a proprietary cocktail which includes esterase inhibitors, dipeptidyl peptidase-4 and other protease-inhibitors (P800 Blood Collection Tube, BD Vacutainer, Franklin Lakes, New Jersey, USA). To measure active GLP-1 concentrations, commercially available ELISA kit (IBL International (Hamburg, Germany) JP27784) will be used.

To further investigate the glucose metabolism, a 75g oral glucose tolerance test will be performed during all study visits. Venous blood samples will be collected before ingestion and at 30, 60, 90 and 120min after ingestion for measurements of glucose, insulin, C-peptide and GLP-1. All glucose samples will be transported to the clinical laboratory immediately after collection to prevent a decay in the glucose levels due to a delay in preanalytical handling (see table 2).[28]

Furthermore, all samples used to determine lipid levels will be collected after an 8-hour overnight fast. The measurement of total cholesterol, low-density lipoprotein, high density lipoprotein and triglyceride levels will be performed by our in-hospital routine laboratory. Similarly, for measurement of non-esterified fatty acids, fasting blood samples will be collected and will be analysed using an enzymatic endpoint method (Diasys kit, Roche, Rotkreuz, Switzerland).

Neurocognitive function

A battery of six standardised cognitive tests, as provided by CanTab Cognitive and Psychological test ((Cognitive assessment software) Cambridge Cognition 2019), covering attention, memory and executive functions will be used. We will use the One Touch Stockings of Cambridge for planning, Paired Associates Learning for visual episodic memory, rapid visual information processing to test sustained attention, reaction time to assess processing and psychomotor speed, and the motor screening task to measure sensorimotor function and comprehension. Practice effects are minimised because this test battery provides parallel modes and stimuli randomisation.

Questionnaires

At each study visit participants are asked to complete following questionnaires. The 36-Item Short Form Health Survey is a generic and reliable instrument reflecting 8 domains of health, namely physical functioning, physical role, pain, general health, vitality, social function, emotional role and mental health.[29 30] The Patient Health Questionnaire-15 will be used to assess the presences and frequency of adverse events as it is a valuable tool for the detection of somatoform disorders.[31] The Medication Adherence Report Scale (MARS-5) is a short questionnaire measuring participants adherence to the study medication and demonstrates acceptable reliability and validity.[32] The Short Questionnaire to Assess Health-enhancing physical activity is a valid and reliable questionnaire to assess physical activity levels and contains questions about habitual activities with respect to occupation, leisure time, household, transportation means and other daily activities.[33] Lastly, as food intake, specifically salt intake, can have an influence on blood pressure and other secondary outcome measures, participants will be asked to complete a 3-day food diary.[34]

Biomarkers and other endpoints

Due to the difference in mineralocorticoid effects of prednisolone and dexamethasone, it can be hypothesised that this difference may translate into a difference in blood pressure between prednisolone or dexamethasone treatment. Therefore, blood pressure (mmHg) will be measured according to a standardised clinical protocol using an automated device (Omron M2 Basic, Hoofddorp, The Netherlands). Participants will be seated for at least 15 min before blood pressure is measured. Then blood pressure and heart rate are measured three times with a 30 s interval.

Hand grip strength will be measured using a Jamar Hydraulic Hand Dynamometer (Patterson Medical JAMAR 5030J1, Warrenville, Canada) as describe previously.[35 36] To measure total body muscle mass, 24 hours urinary creatinine excretion rate will be used as it is an excellent and inexpensive measure of muscle mass.[37] Lastly, osteocalcin will be assessed using electrochemiluminescence immunoassay (Cobas E, Roche, Rotkreuz, Switzerland) as it has been linked to physiological processes such as the glucose metabolism.[38]

Assignment of interventions

After enrolment by the study physician (SPS or AV), the participant is randomised to start with either prednisolone or dexamethasone in a 1:1 ratio. Randomisation will be done by the trial pharmacist of the UMCG in accordance with a pre-specified allocation sequence. Randomisation is done using a four-block randomisation without stratification. The allocation sequence is stored on a secure network station of the pharmacy of the UMCG.

As the CORE study is designed as a double-blind trial, study participants, study physicians, and principle investigators will be blinded. The blinding is guaranteed by the use of identical study medication capsules and medication labels (Apotheek A15, Gorinchem, The Netherlands). The trial pharmacist who will perform the randomisation, will be aware of the intervention assignment. Unblinding will only be done when a serious adverse event (SAE) occurs, which requires the specific knowledge of the used study medication or when the entire trial is completed. Outcomes will be assessed in a unblinded manor.

Data collection, management and analysis

Once a participant has given written informed consent, the study will consist of a screening visit and five study visits. The latter are a baseline visit, after the low dose of the first intervention, after the high dose of the first intervention, and after the low dose and after the high dose of the second intervention. In principle, all study visits are identical with the exception of the baseline visit where no pharmacological endpoints will be assessed. All data will be collected by two trained study physicians (SPS and AV).

All data, including the questionnaires, will be stored using REDCap (Research Electronic Data Capture, Vanderbilt University Medical Center, Nashville, Tennessee, USA). All entered data are double checked by both study physicians. Due to the low risk associated with the study interventions no data monitoring safety board was required. The study will however be intensively monitored, according to the guideline 'Quality Assurance of research involving human subjects 2.0' of 'The Netherlands Federation of University Medical Centers'.[39] The safety will be assessed in two ways. First, as it is undesirable to use exogenous corticosteroids while having an active infection, all participants will be checked for any symptoms (including vital signs, physical examination and laboratory infection parameters) of an active infection during all study visits. Second, all adverse events, including potential SAE, will be documented and the frequency of all adverse events will therefore be deemed a safety measure.

To ensure confidentiality, all participants will receive a unique identification code, which can only be decoded with a separately stored identification file. As in accordance with the trial information and consent form, participant information is only accessible to the study physician and study monitor, and in case of an SAE may be provided to the trial pharmacist.

Sample size and statistical analyses

To date, no modern day randomised cross-over trials investigating the effects prednisolone and dexamethasone on the HPA-axis (or other endpoints) in healthy individuals are available. Hence, the number of participants which will be included in the CORE study, is based on the scientific guideline of the European Medicines Agency regarding bioequivalency studies which states that bioequivalence studies should not include less than 12 subjects.[40] Because males and females clinically differ in terms of circulating levels of oestrogens and corresponding CBG levels, we deemed it necessary to included 12 male and 12 female participants. If drop-out cannot be prevented, new volunteers will be included to ensure adherence to the scientific guideline of the European Medicines Agency.

As the anticipated duration of the trial is expected to be limited no interim analyses will be performed. The newest versions of IBM Statistics SPSS (IBM, version 23), GraphPad Prism (La Jolla, California, USA), STATA (STATA, version 14) and/or R (Vienna, Austria) will be used for statistical analyses. Demographic data will be presented as median (IQR). To compare paired outcomes, Wilcoxon signed-rank test will be used. To compare unpaired data, a Mann-Whitney U-test will be performed. The two-tailed alpha level of <0.05 will be considered statistical significant.

Trial status

The CORE study has started on the 4 March 2021. On 1 January 2022, 15 participants have concluded the study. A total inclusion time of 1 year and 3 months was anticipated, however, due to the COVID-19 pandemic the complementing vaccination campaign, the study inclusion is delayed. The extent of the delay is at this moment still unclear.

Ethics and dissemination

The CORE study is conducted according to the principles of Helsinki and in accordance with the Medical Research Involving Human Subjects Act (WMO, The Netherlands). This study has been approved by the Medical Ethical Committee of the UMCG, The Netherlands (METC 2020.398) on the 18 January 2021. Potential protocol amendments will be submitted to the Medical Ethical Committee for review and subsequently distributed to volunteers. Potential participants need to actively seek contact with the investigators and when interested will receive written information. Prior to obtaining informed consent, research staff will explain the aim of the study and all study procedures to the volunteers. Additionally, the research staff will explain that participation is voluntary and that participants are able to withdraw their consent at any given point in time. If the potential participant has no further questions, written informed consent will be obtained from all volunteers by a study physician (SPS or AV). Simultaneously, participants are asked if collected data may be used for ancillary studies and if in agreement provide written informed consent. Participants will receive a financial compensation of €500. A full SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement checklist can be found in online supplemental material.

This study will be submitted for publication in peer-reviewed journals and oral presentations at (inter) national conferences. Authorships will be determined based on the International Committee of Medical Journal Editors guidelines. Raw data will be available on reasonable request in deidentified form.

Discussion

This article describes the rationale and design of the CORE study which is a randomised, double-blind, cross-over trial investigating the clinical bioequivalence and dose response of prednisolone and dexamethasone with regard to various physiological systems of the human body. Within this design, the CORE study will include 12 healthy men and 12 healthy women, to receive 7.5 mg prednisolone/1.125 mg dexamethasone and 30 mg prednisolone/4.5 mg dexamethasone all for 1 week in random order. Data will be collected to evaluate hormonal axes, immunological status, metabolic pathways, pharmacokinetic parameters and other organ systems with state-of-the-art laboratory techniques.

Although prednisolone and dexamethasone are already widely used in clinical practice, well-validated clinical bioequivalence data are lacking. The CORE study will help to gain new insight into the comparability between the two medications and improve the existing pharmacodynamic data. By investigating outcome measurements in a cross-over and double-blind fashion, in-depth information regarding the system specific effects of prednisolone and dexamethasone will be gained while taking inter-individual differences into account. Another strength of the CORE study the selected dosage and treatment duration reflect clinical practice. This will aid translating the outcomes of the CORE study to routine clinical practice. A limitation of the current study is the absence of a placebo arm. Inclusion of a placebo intervention, however, may result in a substantial increase of the study duration, and may subsequently result in negative effect on the inclusion rate. As a result, a baseline study visit was implemented to serve as reference point. Another limitation could be the relative low number of participants. Nevertheless, the number of included participants is in concordance with current guidelines of bioequivalence study of the European Medicines Agency and is even double the number of minimal requirement of subjects, to allow for subgroup analyses based on age and sex.

Lastly, this study investigates the effects of prednisolone and dexamethasone in healthy volunteers. However, in various disease states some aspects of glucocorticoid action could change in a disease specific manner. In order to draw conclusions on glucocorticoid action in specific disease states, further research is needed.

In conclusion, the CORE study has the potential to improve the current understanding of the most widely used corticosteroids and may therefore aid various clinicians in clinical decision making, including general practitioners, endocrinologists, nephrologists, rheumatologists and many more.

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