Thesis for doctoral degree (Ph.D.) 2007

Corticosteroids in advanced cancer

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Karolinska Institutet

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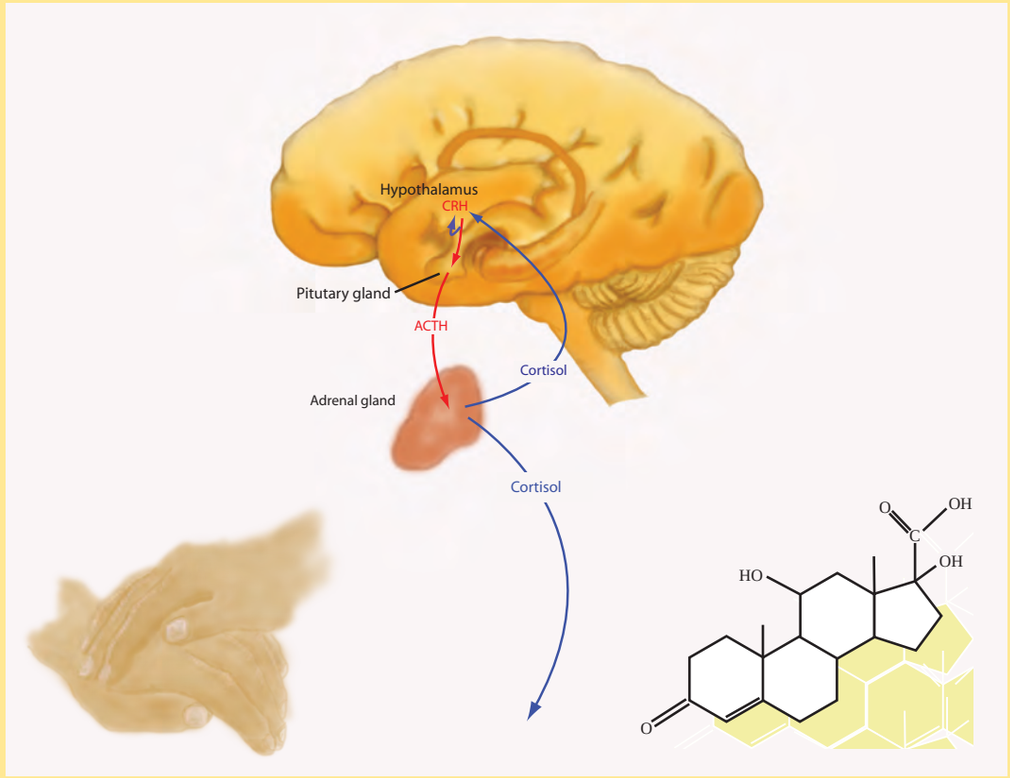
## epidemiology, symptom relief and patient experiences




Staffan Lundström

Karolinska Institutet

From the Department of Oncology-Pathology,
Karolinska Institutet, Stockholm, Sweden

# **Corticosteroids in advanced cancer:** epidemiology, symptom relief and patient experiences

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To Ingrid,

Anna and

Jonatan

*Soli Deo Honor et Gloria*

# ABSTRACT

Cortisol is the principal circulating glucocorticoid in man and has a wide variety of effects in the body. In advanced metastatic cancer, glucocorticoids are used to alleviate symptoms such as anorexia, poor strength and poor well-being. The mechanisms behind the symptom relieving effects are still unclear. The general aim of this thesis was to study endogenous cortisol in patients with advanced cancer and the usage and impact of exogenous corticosteroids in symptom relief.

Based on previous findings of impaired control of chemotherapy-related delayed nausea and vomiting in patients receiving single high-doses of dexamethasone, the recovery of the HPA-axis after a single dose of dexamethasone was examined in 10 healthy volunteers and compared with the recovery in 5 patients with gynaecological cancer receiving 8 or 20 mg of dexamethasone in conjunction with platinum-based chemotherapy (**paper I**). Analyses of urinary cortisol levels showed no differences in the recovery between patients and volunteers, indicating that corticosteroid-induced impairment in the control of delayed nausea was not dependent on the suppression and recovery of the HPA-axis.

In an explorative cross-sectional study, urinary cortisol levels were analysed in 23 patients with advanced predominantly gastrointestinal cancer who had rated symptom severity using EORTC QLQ C-30 (**paper II**). Significant correlations were found between levels of urinary cortisol and more pronounced appetite loss, fatigue and nausea/vomiting. The mean values of urinary cortisol were high, indicating a chronic stress condition in this patient group.

Attitudes and practice among physicians regarding treatment with corticosteroids in advanced cancer were examined in two cross-sectional surveys (**paper III**). The first survey collected answers from 338 physicians. In the second survey, data from 1292 patients enrolled in palliative care were registered. Corticosteroids were used in more than 50 % of the cancer patients and with high response rates when treating appetite loss, nausea, fatigue or poor well-being. The positive response came within the first week and was perceived as persisting beyond four weeks. Few physicians had guidelines on the use of corticosteroids in advanced cancer. Attitudes and examined practice were generally in good agreement with existing evidence.

Cortisol production and metabolism was analysed in 13 patients with advanced cancer using high performance liquid chromatography and gas liquid chromatography on 24-hour urine samples (**paper IV**). Symptom assessments were made with ESAS before and after five days of treatment with 4 mg of betamethasone. Normal cortisol production together with a metabolic shift from cortisone to cortisol in peripheral tissue was seen. This shift was more pronounced in patients with shorter survival, especially in those with an inferior response to corticosteroid treatment. The results support the view of a chronic stress condition and points towards possible interactions between the neuroendocrine system and the immune system in patients with advanced, metastatic cancer.

In a prospective observational study, qualitative content analysis was used to study the existential impact of corticosteroid treatment in 10 patients with advanced metastatic cancer (**paper V**). The patients were interviewed before and after one week of treatment with four milligrams of betamethasone. Prior to treatment patients' reported distressing symptoms, deterioration and diminished autonomy, symbolising threat and death. Corticosteroid treatment resulted in enhanced physical abilities and feelings of a more normalized life, symbolising health and hope. This transfer from threat to hope has important existential consequences in the end of life care and should be addressed when communicating goals of treatment and care with the patient and family.



**Keywords:** Corticosteroids, cancer, palliative care, anorexia, nausea, symptom assessment, existential

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# SAMMANFATTNING PÅ SVENSKA

Kortisol är ett hormon med många olika funktioner i kroppen. Det bildas i binjuren och har bland annat viktiga modulerande uppgifter i samband med kroppens stressreaktion, som kan vara utlöst av till exempel trauma, infektion eller inflammation. Vid avancerad metastaserad cancersjukdom används syntetiska glukokortikoider för att lindra besvärande symtom såsom aptitlöshet, trötthet och illamående. Mekanismerna bakom den symtomlindrande effekten är oklara.

Syftet med denna avhandling var att studera endogent, kroppseget kortisol vid avancerad cancersjukdom, samt hur kortisonbehandling används och vilken inverkan det har på den enskilda patienten.

De fem delarbeten som ingår belyser detta ur både ett epidemiologiskt perspektiv samt ett patientnära perspektiv, det sistnämnda med både en biokemisk och en existentiell vinkling.

I **delarbete I** studerades HPA-axelns (hypothalamus – hypofys – binjure) förmåga till återhämtning efter en engångsinjektion av dexametason hos 10 friska försökspersoner och 5 patienter med avancerad gynekologisk cancer. Analys av kortisol gjordes på 24-timmars urin. Patienterna fick 8 eller 20 mg dexametason i samband med cytostatikabehandling, och man hade tidigare funnit att 20 mg dexametason ledde till högre grad av fördröjt illamående efter behandlingen. Ingen skillnad i återhämtning sågs mellan patienter och försökspersoner, varför slutsatsen drogs att det inte var en förlångsammad återhämtning av HPA-axeln som låg bakom ett ökat fördröjt illamående efter den högre kortisondosen.

I **delarbete II** analyserades nivåer av urin-kortisol hos 23 patienter med avancerad cancersjukdom som hade skattat svårighetsgraden av olika symtom med ett frågeformulär (EORTC QLQ C-30). Förhöjda kortisolnivåer hittades, tydande på ett kroniskt stresstillstånd, och patienter med mer uttalad aptitlöshet, trötthet och illamående hade relativt sett högre kortisolnivåer.

Två olika enkätundersökningar utgjorde basen i **delarbete III**, den ena gjordes bland läkare som behandlade patienter med avancerad cancersjukdom, den andra bland patienter inskrivna i palliativ vård. Svar från 338 läkare och 1292 patienter registrerades och visade att kortisonbehandling gavs till drygt hälften av alla cancerpatienter. God effekt sågs vid behandling av aptitlöshet, illamående, trötthet och dåligt välbefinnande; effekten kom inom en vecka och upplevdes kvarstå längre än en månad. Behandlingen gavs i god överensstämmelse med existerande evidens, men många läkare saknade lokala riktlinjer för kortisonbehandling till dessa patienter.

I **delarbete IV** analyserades produktion och metabolism av kortisol hos 13 patienter med avancerad cancersjukdom. Analyser gjordes på 24-timmars urin. Symtomskattning med ESAS gjordes före, samt efter fem dagars behandling med 4 mg betametason. Patienterna hade en normal kortisolproduktion, men metabolismen var förskjuten från inaktivt kortison mot kortisol i vävnaden. Detta var mer uttalat hos patienter med kortare överlevnad, särskilt hos dem som inte hade ett tydligt positivt svar på kortisonbehandlingen. Även denna studie visar på betydelsen av ett kroniskt stresstillstånd hos patienter med avancerad cancersjukdom.

Kvalitativ forskningsmetodik användes i **delarbete V** för att studera den existentiella inverkan av kortisonbehandling vid avancerad cancersjukdom. Tio patienter intervjuades före och efter en veckas behandling med 4 mg betametason och kvalitativ innehållsanalys gjordes på materialet. Innan behandlingen beskrev patienterna besvärande symtom, successiv försämring och försämrad autonomi, symboliserande hot och död. Kortisonbehandlingen ledde till minskade symtom, ökad fysisk aktivitet och upplevelser av ett mer normaliserat liv, symboliserande hopp och liv. Detta skifte från hot till hopp har existentiella konsekvenser i livets slutskede och bör finnas med i diskussionen när vården planeras och målformuleringar görs tillsammans med patient och anhöriga.

# LIST OF PUBLICATIONS

This thesis is based on the following papers, which will be referred to by their Roman numerals:

I. **Lundström S.** Fürst CJ., Börjeson S., Steineck G., Åvall-Lundqvist E., Hursti TJ., Peterson C., Fredrikson M.: Aspects of delayed chemotherapy-induced nausea: dexamethasone and adrenal response patterns in patients and healthy volunteers.
*Supportive Care Cancer 2000;8:431-434.*

II. **Lundström S.** Fürst CJ.: Symptoms in advanced cancer: relationship to endogenous cortisol levels.
*Palliative Medicine 2003;17:503-508.*

III. **Lundström S.** Fürst CJ.: The use of corticosteroids in Swedish palliative care.
*Acta Oncologica 2006;45(4):430-7.*

IV. **Lundström S.** Axelson M., Fürst CJ.: Metabolic profiles of endogenous corticosteroids in advanced cancer. *Submitted*

V. **Lundström S.** Fürst CJ., Friedrichsen M., Strang P.: The existential impact of corticosteroid treatment in metastatic cancer. *Submitted*

# CONTENTS

# LIST OF ABBREVIATIONS

| | |
|---|---|
| $5\text{-}HT_3$ | 5-Hydroxytryptamine3 |
| ACTH | Adrenocorticotropic hormone |
| allo-THF | 3α,5α-tetrahydrocortisol |
| CBG | Corticosteroid-binding globulin |
| CRH | Corticotropin-releasing hormone |
| EORTC QLQ C-30 | European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire |
| ESAS | Edmonton Symptom Assessment Scale |
| GLC | Gas liquid chromatography |
| GR | Glucocorticoid receptor |
| HADS | Hospital Anxiety and Depression Scale |
| HPA-axis | Hypothalamic-pituitary-adrenal axis |
| HPLC | High performance liquid chromatography |
| HSD | Hydroxysteroid dehydrogenase |
| Il-1 | Interleukin 1 |
| Il-6 | Interleukin 6 |
| MPA | Medroxyprogesterone acetate |
| $NK_1$ | Neurokinin 1 |
| NSAID | Non-steroidal anti-inflammatory drug |
| PANIS | Palliative care research network in Sweden |
| RIA | Radioimmunoassay |
| STAI-T | Spielberger State Trait Anxiety Inventory-Trait |
| THE | 3α,5β-tetrahydrocortisone |
| THF | 3α,5β-tetrahydrocortisol |
| TNF-α | Tumour necrosis factor α |

# 1 BACKGROUND

Corticosteroids are often used for symptom relief in palliative care. There is much knowledge about biochemical and physiological characteristics of corticosteroids, but studies are lacking connecting this knowledge with the bedside situation in end of life care. The intention of this thesis is to contribute to our understanding of the symptom relieving effects of corticosteroids in patients with advanced cancer.

## *1.1 ADRENAL GLUCOCORTICOIDS*

Corticosteroids are a set of steroid hormones that are produced in the adrenal cortex. They are divided into two classes, glucocorticoids and mineralocorticoids, and both are fundamental for the function of the body.
Cortisol is the principal circulating glucocorticoid and is synthesized in the two inner zones of the adrenal cortex, the Zonae fasciculata and reticularis. Corticosterone, the other glucocorticoid in man, is secreted only in small amounts from the outer zone of the adrenal cortex, the Zona glomerulosa. It has weak glucocorticoid and mineralocorticoid potencies in humans, but constitutes the principal glucocorticoid in many species, including rodents. Aldosterone is the main mineralocorticoid and is synthesized in the Zona glomerulosa. This synthesis is predominantly under the control of the renin-angiotensin system. Aldosterone promotes sodium retention and potassium excretion and is important in maintaining fluid balance. Adrenal mineralocorticoids will not be addressed in this thesis.
Glucocorticoids and mineralocorticoids are derivates of cholesterol and the steroid synthesis occurs through a series of steps mainly involving enzymes from the cytochrome p450 family [1]. The synthesis of glucocorticoids is depicted schematically in Figure 1.

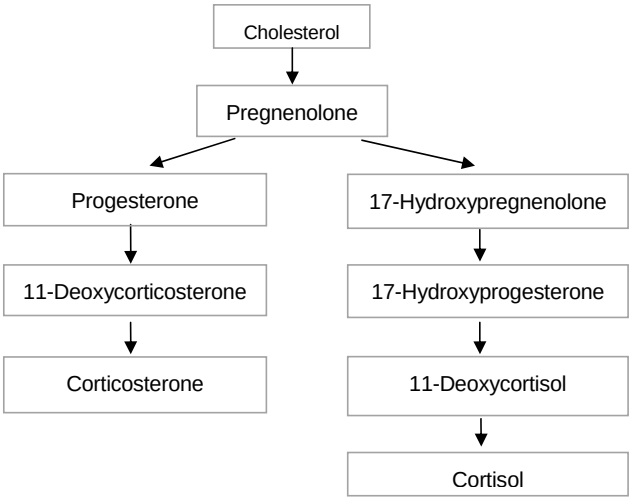


**Figure 1.** Synthesis of glucocorticoids in the Zonae fasciculata and reticularis of the adrenal cortex. Cortisol is the major secretory product.

### 1.1.1 Regulation of secretion:

Secretion of cortisol is controlled by the HPA-axis, see Figure 2. The neuroendocrine regulation of secretion consists of three different mechanisms: circadian rhythm, stress responsiveness and feedback inhibition.
ACTH from the anterior pituitary stimulates the formation of pregnenolone and its derivates in the adrenal cortex with subsequent secretion of cortisol. Prolonged ACTH stimulation also increases the synthesis of enzymes involved in the synthesis of glucocorticoids. ACTH is in turn regulated predominantly by CRH from the hypothalamus. CRH is secreted in a pulsatile manner during the day with a concordant diurnal rhyhtmicity in the secretion of ACTH and subsequently cortisol. This results in a peak in circulating cortisol levels early in the morning before awakening and a following decline during the day with the lowest levels after midnight.
Stress responsiveness is an important mechanism of neuroendocrine control. Within seconds after the onset of a stress stimulus, such as hypoglycaemia or trauma, CRH is released into the portal circulation and this is followed by an enhanced secretion of ACTH. Finally, within minutes, secretion of glucocorticoids is stimulated. The main actions of glucocorticoids are genomic and are not exerted until about an hour after the onset of the stressor. Parallel with this response of the HPA-axis, the sympathetic nervous system and the immune system are activated with actions that precede that of glucocorticoids. Proinflammatory cytokines like Il-1, Il-6 and TNF-α, which often are triggered in advanced cancer, activate the HPA-axis [2] and contribute to the neuroendocrine regulation during stress. In addition, nociceptive pathways can stimulate the activity in the HPA-axis [3]. Glucocorticoids are thought to be important in modulating the complex stress response in the body, showing permissive, suppressive and stimulating actions. This results in both enhancement of the body's ability to respond adequately to the stressor, and protection from overshooting by other defence mechanisms [4].
Feedback inhibition is the third regulator of cortisol secretion and occurs both at the pituitary level and the hypothalamus, see Figure 2. Cortisol exerts a negative feedback on the secretion of ACTH and CRH. Continuous administration of high doses of exogenous glucocorticoids results in reversible atrophy of the Zonae fasciculata and reticularis with consequent impairment or absence of stress responsiveness. There is also a short feedback loop of ACTH on the secretion of CRH. Daily secretion of cortisol under basal conditions ranges from 8 – 25 mg [1]. There is an increase in cortisol production with increasing age, accompanied by an attenuation of feedback inhibition [5].

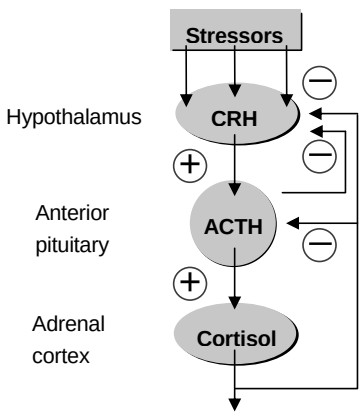


**Figure 2**. The hypothalamic-pituitary-adrenal axis, illustrating the negative feedback loops.

### 1.1.2 Circulation and metabolism

About 75 % of circulating cortisol is bound to CBG. Albumin binds normally about 15 % and the remaining 10 % constitutes the free, biologically active hormone. Synthetic glucocorticoids are extensively bound to albumin with the exception of prednisolone, which mainly binds to CBG. Cachexia and hypoalbuminaemia are often seen in patients with advanced cancer, leading to increased circulating levels of synthetic glucocorticoids when treatment is given. Total levels of plasma cortisol can vary due to varying CBG levels under different conditions, but through the neuroendocrine control the levels of free cortisol are maintained. The metabolism of glucocorticoids occurs mainly in the liver and the metabolites are subsequently conjugated with glucuronides or sulphate groups. Approximately 90 % of the cortisol and cortisone metabolites are conjugated and excreted through the urine [6]. Urinary free cortisol represents only 1 % of the total cortisol secretion rate [7]. The main steps in hepatic metabolism of cortisol and cortisone are shown in Figure 3. THF, allo-THF, THE, cortols and cortolones constitute approximately 80 % of total glucocorticoid metabolites [8]. Cortisol can be converted to the inactive glucocorticoid cortisone by the enzyme 11β-HSD which exists in two isoforms. The widely expressed 11β-HSD1 predominantly reactivates cortisone to cortisol, most notably in liver and adipose tissue. This facilitates glucocorticoid exposure to the glucocorticoid receptor (GR), mediating the intracellular effects. The other isoform, 11β-HSD2, catalyses dehydrogenation of cortisol to cortisone and is principally located in the kidney, colon, placenta and sweat glands where it protects mineralocorticoid receptors from inappropriate activation by cortisol [9, 10]. Pro-inflammatory cytokines, especially TNF-α and IL-1β, enhance the activity and expression of 11β-HSD1 [11, 12]. At the same time, they down-regulate 11β-HSD2 expression, thereby promoting local glucocorticoid availability [13].
The cortisol concentration in cells can be regulated both by secretion, controlled by the HPA-axis, and tissue metabolism, controlled by 11β-HSD. Intracellular cortisol levels can therefore differ from plasma cortisol levels depending on the expression and activity of 11β-HSD [11].

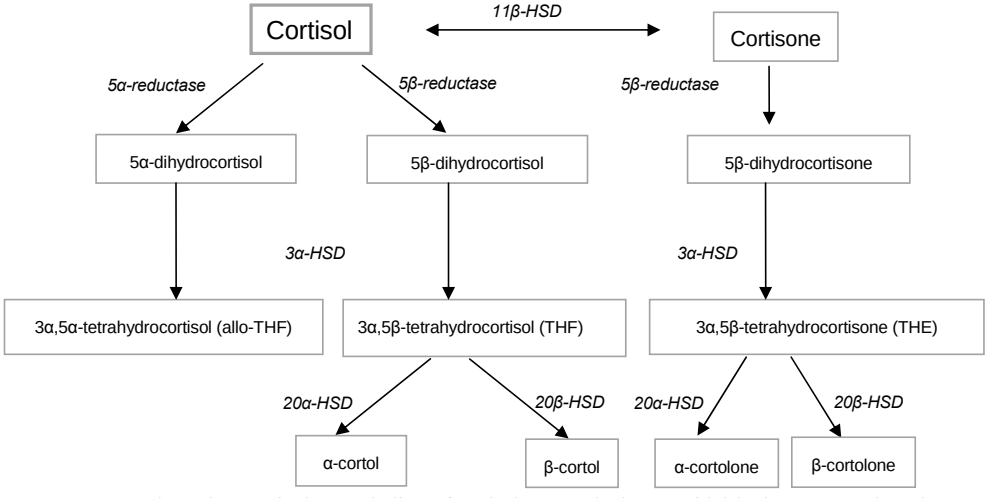


**Figure 3**. The main steps in the metabolism of cortisol. HSD = hydroysteroid dehydrogenase. Adapted from Andrews 2001 [8].

### 1.1.3 Biological effects of glucocorticoids

Glucocorticoids have a wide variety of effects in many organs in the body [1] and the important effects in modulating the stress response have already been mentioned. The biological activity of a glucocorticoid is dependent on the presence of a hydroxyl group at position C-11 of the steroid structure, see Figure 4. Whereas normal levels of glucocorticoids are important for maintaining organ functions, chronic excessive levels may prove detrimental for the body. On a molecular level, glucocorticoids interact with the intracellular glucocorticoid receptor forming a hormone-receptor complex, which is then translocated into the nucleus. Gene transcription is modulated, either resulting in synthesis of proteins which elicit the glucocorticoid response, or inhibition of gene transcription. Glucocorticoid receptors are widely distributed in the tissue, but the mechanisms by which glucocorticoids via one receptor modulates the diverse biological functions are largely unknown [14]. This modulation of gene transcription is thought to be responsible for most of the effects of glucocorticoids. However, new evidence indicates that membrane receptors mediate the rapid steroid effects, occurring within minutes [15, 16]. In general, glucocorticoids inhibit DNA, RNA and protein synthesis together with an accelerated protein catabolism. This provides substrates for the intermediary metabolism. In the liver, RNA and protein synthesis is stimulated. These effects on intermediary metabolism result under fasting conditions in increased hepatic gluconeogenesis and glycogen deposition. Another way of controlling carbohydrate metabolism is through inhibition of peripheral glucose uptake in muscle and adipose tissue. In states of glucocorticoid excess, this results in hyperglycaemia and increased insulin secretion which may contribute to increased insulin resistance. Lipolysis is stimulated in adipose tissue, but cortisol is also essential for adipocyte differentiation. An enhanced expression of 11β-HSD1 in human adipose tissue with increased autocrine generation of cortisol has been suggested to play a role in the pathogenesis of central obesity [7]. Taken together, the effects on metabolism serve to maintain or increase blood glucose levels.

Glucocorticoids have multiple effects on the immunologic and inflammatory response including enhanced mobilization of leukocytes, inhibition of prostaglandin and leukotriene production, and decreased production of proinflammatory cytokines like Il-1, Il-6 and TNF-α [17-19]. The immunosuppressive and anti-inflammatory properties are particularly prominent when pharmacological doses are administered.

In the brain, glucocorticoids modulate memory function, sleep and mood which are most apparent in states of glucocorticoid excess or deficit. Appetite and food intake is increased after glucocorticoid administration [20, 21] and this is probably centrally mediated via lowered levels of CRH with subsequent decreased inhibition of appetite stimulating peptides [22]. Glucocorticoids increase cardiac output and peripheral vascular tone, the latter probably due to a permissive role for catecholamine action [23]. Water and electrolyte balance is affected by glucocorticoids through increased glomerular filtration rate and mineralocorticoid effects, resulting in sodium retention and potassium excretion. In addition, excessive levels of glucocorticoids results in inhibition of fibroblasts and bone formation, decreased calcium absorption and increased urinary calcium excretion. To maintain serum calcium levels, bone resorption is accelerated and together with decreased bone formation this ultimately leads to osteoporosis.

### 1.1.4 Adrenal glucocorticoids in advanced metastatic cancer

Studies on secretion of endogenous cortisol in patients with advanced, metastatic cancer have shown elevated plasma cortisol levels [24-28]. Further enhancement of cortisol levels in more advanced diseases was demonstrated. Enlargement of the adrenal gland with impaired dexamethasone-induced suppression of the HPA-axis have also been shown [29]. Adding further to the findings of disturbances in the function of the HPA-axis, circadian rhythm alterations associated with poor prognosis have been reported in cancer patients [30-34].

## *1.2 SYNTHETIC GLUCOCORTICOIDS*

Glucocorticoids and their synthetic derivates are grouped according to their relative effects on carbohydrate metabolism and their antiinflammatory effects. In general, potencies based on effects on glucose metabolism closely parallel those for antiinflammatory effects [35]. There is also a difference in the duration of the antiinflammatory effect, based on the duration of suppression of the HPA-axis after a single dose [36]. The increased activity of synthetic glucocorticoids is due to increased affinity to the glucocorticoid receptors and delayed plasma clearance, which increases tissue exposure. Many of the synthetic glucocorticoids have negligible mineralocorticoid effects [1]. The chemical structure of some glucocorticoids is presented in Figure 4. Table 1 shows the relative potencies, biological half-life and equivalent doses of these compounds.

**Table 1**. Relative potencies and equivalent doses of representative glucocorticoids [35, 36].

| *Compound* | *Antiinflammatory potency* | *Biological half-life (h)* | *Equivalent dose (mg)* |
|---|---|---|---|
| Cortisol | 1 | 8 – 12 | 20 |
| Cortisone | 0.8 | 8 – 12 | 25 |
| Prednisolone | 4 | 18 – 36 | 5 |
| Betamethasone | 25 – 30 | 36 – 54 | 0.6 – 0.75 |
| Dexamethasone | 25 – 30 | 36 – 54 | 0.75 |

Dexamethasone and prednisolone are the most commonly used synthetic glucocorticoids in cancer patients. In Sweden, by tradition, betamethasone is used instead of dexamethasone.
Because of their broad effects, the clinical use of glucocorticoids is complicated by a number of serious side effects. The most common adverse effects encountered in cancer patients are listed in Table 2.

**Table 2**. Potential side effects of treatment with glucocorticoids in advanced cancer [36].

| | | | |
|---|---|---|---|
| Cushingoid appearance with moon-face | Glucose intolerance or aggravated diabetes mellitus | Susceptibility to infections | Impaired wound healing |
| Proximal myopathy | Fluid retention with oedema | Dyspepsia | Suppression of the HPA-axis |
| Psychiatric disturbances (euphoria, depression) | Sleep disturbances | Oropharyngeal candidosis | Thin fragile skin with ecchymoses |

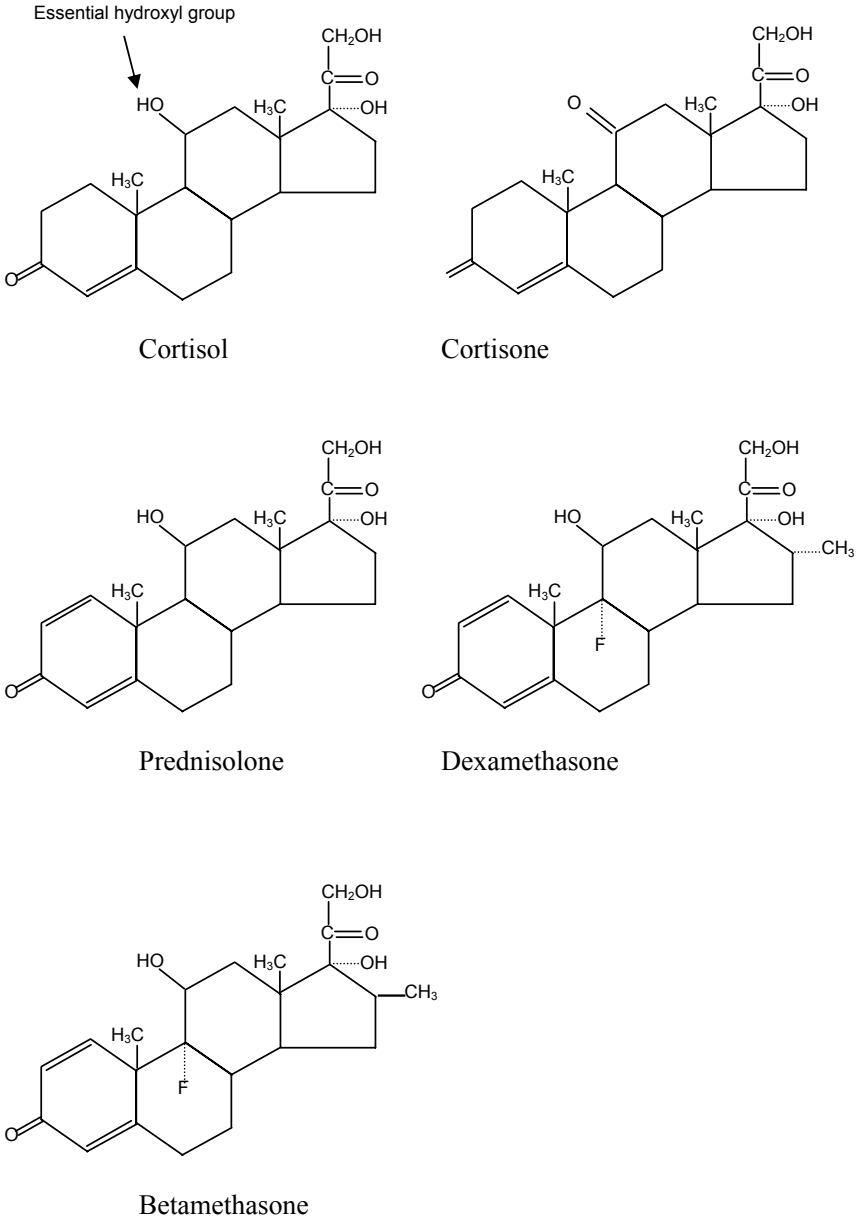


**Figure 4**. Structure of glucocorticoid products and selected synthetic derivates.

### *1.3 TREATMENT WITH GLUCOCORTICOIDS IN CANCER*

Glucocorticoids induce apoptosis in cells of the haematopoietic system and this has since long been taken advantage of in the treatment of leukaemia, multiple myeloma and other haematological malignancies [37]. For many years, glucocorticoids have also been used to treat different solid tumours, such as carcinoma of the prostate and breast, and to manage tumour and treatment related symptoms. While apoptosis is induced in cells that provoke and sustain inflammation, glucocorticoids protect the resident cells of the inflamed tissue by arresting apoptotic signals [38]. Several in vitro studies on cell lines from different solid tumours have shown corticosteroid-induced resistance to cytotoxic therapy [39-42]. Studies have also shown that immunosuppression can exacerbate the metastatic process in animals, but few clinical studies have so far addressed these potentially negative effects of glucocorticoids in cancer treatment [43]. At the same time, the role of chronic inflammation in the development and progression of cancer have attracted an increasing attention during the last years [44, 45], adding to the complexity when considering the use of these potent antiinflammatory drugs. Glucocorticoids are used to reduce the oedema of cranial and spinal metastases [46, 47], to alleviate pain [48-51] and to reduce symptoms in patients with intestinal obstruction [52] or respiratory manifestations [53, 54].

Most importantly, glucocorticoids are used in the treatment of both acute and delayed chemotherapy-induced nausea and vomiting. Acute symptoms occur within the first 24 hours after chemotherapy administration whereas the concept of delayed nausea and vomiting is applied on symptoms appearing from day 2. Delayed nausea and vomiting can persist for several days or even weeks after completed treatment. Glucocorticoids are known to reduce both acute and delayed symptoms [55-58] and endogenous cortisol also appears to serve as an antiemetic [59, 60]. However, relatively higher doses of glucocorticoids do not enhance the effect on acute symptoms [61], and may even impair the control of delayed symptoms [62]. The mechanisms by which glucocorticoids exert their antiemetic effect are largely unknown.

In advanced metastatic cancer, glucocorticoids have been used for approximately 40 years on non-specific indications such as anorexia, poor strength and poor well-being [63, 64]. Due to potentially serious adverse effects, close monitoring of the patient using the lowest effective dose and discontinuing if no benefit is obtained is recommended [65, 66]. Six controlled studies report positive effect on appetite, pain or sense of well-being after treatment with dexamethasone, methylprednisolone or prednisolone [20, 48, 67-71]. Four uncontrolled studies demonstrate positive effect on appetite, strength or sense of well-being after treatment with dexamethasone or prednisolone [49, 66, 72, 73]. One retrospective study reports effect on appetite after treatment with prednisone [74]. Two of these studies show that the positive effects rarely exceed four weeks [48, 68]. Studies in palliative care units on the clinical use of glucocorticoids in advanced cancer show that approximately between one third and a half of all palliative patients being enrolled in palliative care are treated with corticosteroids for symptom control. Dexamethasone is the drug of choice and the doses varies between 0.5 mg on alternate days to 16 mg daily [65, 66, 72, 73, 75-77]. Table 3 summarizes the available studies on corticosteroid treatment in advanced

cancer. Phase II and phase III trials using glucocorticoids for antitumoral treatment of solid tumours are not included.

Despite the evident positive effects that treatment with glucocorticoids often brings about in this patient group, there are no studies exploring the existential impact of this treatment in the individual patient. Existing studies have focused on the degree of symptom control and frequency of side effects. Considering the profound existential impact on both patients and families from the cancer diagnosis and from the knowledge about being in the terminal phase [78, 79], little is known regarding subjective consequences of improved symptom control in this patient group.

**Table 3**. Characteristics of studies related to corticosteroids in advanced cancer.

| *Reference* | *Study design* | *No. of patients* | *Drug* | *Dosage (mg)/route* | *Symptomatic outcome* | *Assessment tool* |
|---|---|---|---|---|---|---|
| Moertel et al. 1974 [68] | Placebo-controlled | 116 | Dexamethasone | 0.75 or 1.5 PO qid | Appetite ↑ | Self-report assessment |
| Willcox et al. 1984 [20] | Placebo-controlled, crossover | 61 | Prednisolone | 5 PO tid | Appetite ↑<br>Well-being ↑ | VAS |
| Bruera et al. 1985 [48] | Placebo-controlled, crossover | 40 | Methylprednisolone | 16 PO bid | Appetite ↑<br>Pain control ↑ | VAS |
| Twycross, Guppy 1985 [70] | Placebo-controlled | 56 | Prednisolone | 5 PO tid | Trend for effect on appetite, mood | VAS |
| Della Cuna et al. 1989 [67] | Placebo-controlled | 403 | Methylprednisolone | 125 IV od | Appetite ↑ Vomiting ↓<br>Well-being ↑ Pain ↓ | LASA |
| Popiela et al. 1989 [69] | Placebo-controlled | 173 | Methylprednisolone | 125 IV od | Appetite ↑ vomiting ↓<br>Well-being ↑ | LASA |
| Laval et al 2000 [52] | Placebo-controlled | 58 | Methylprednisolone | 240 or 40 IV od | Symptoms of bowel obstruction ↓ | Caregiver assessment |
| Hanks et al. 1983 [72] | Prospective observational | 218 | Dexamethasone<br>Prednisolone | 4 – 16 (dex. start dose)<br>10 – 30 (prednisolone start dose) | Appetite ↑ Mood↑<br>Strength ↑ Nerve pain ↓ | Caregiver assessment |
| Farr 1990 [74] | Retrospective | 143 | Prednisone | 5 – 10 PO tid | Appetite ↑ Radicular pain ↓ | |
| Needham et al. 1992 [65] | Prospective observational | 100 | Steroids at time of admission recorded | Varying | 29 % of patients reported beneficial effects | Survey of current practice |
| Mercadante et al. 2001 [73] | Prospective observational | 50 | Dexamethasone | 4 – 16 PO daily | Appetite ↑ Nausea/vomit ↓<br>Strength ↑ Pain ↓ | Caregiver assessment |
| Hardy et al. 2001 [66] | Prospective observational | 106 | Dexamethasone | 4 – 16 PO daily | Appetite ↑ Nausea/vomit ↓<br>Strength ↑ Pain ↓ Mood ↑ | NRS |
| Gannon et al. 2002 [76] | Retrospective | 90 | Dexamethasone<br>Prednisolone | N/A | N/A | |

**Abbreviations:** bid = twice daily; od = once daily; qid = four times daily; tid = three times daily; PO = oral; IV = intravenous; VAS = visual analog scale; LASA = linear analog self-assessment scale; NRS = numerical rating scale; N/A = not available.

# 2 AIMS

The overall aim of this thesis was to study endogenous cortisol in patients with advanced cancer and the usage and impact of exogenous corticosteroids in symptom relief. The specific aims were:

- To study whether the recovery of the HPA-axis differs between patients and healthy volunteers after a single dose of dexamethasone (I).
- To investigate the relationship between levels of endogenous cortisol and symptom severity in advanced cancer (II).
- To study attitude and practice among physicians regarding treatment with corticosteroids in advanced cancer, and how corticosteroids are used in palliative care (III).
- To explore in detail endogenous glucocorticoid production and metabolism in patients with advanced cancer and relate this to symptom relieving effects of exogenous corticosteroids (IV).
- To study the deeper meaning and implication of corticosteroid treatment in patients with advanced metastatic cancer (V).

# 3 MATERIAL AND METHODS

## 3.1 DESIGN OF STUDIES

This thesis comprises one case-control study (paper I), one explorative cross-sectional study (paper II), two cross-sectional survey studies (paper III) and two prospective observational studies (papers IV and V). Table 4 summarizes the characteristics of these studies.
A total of 1343 patients, 10 healthy female volunteers and 338 physicians participated in the five studies.

**Table 4**. Characteristics of studies included in the thesis.

| *Design* | *Year* | *No. of participants* | *Median age (year)* | *Questionnaires/ assessment* | *Urinary analyses* |
|---|---|---|---|---|---|
| I Case-control | 1994 (pts)<br>1997 | 5 patients<br>10 volunteers | 51 (patients)<br>51 (volunteers) | Self-report assessment | Urinary cortisol (RIA) |
| II Cross-sectional | 1998 – 2000 | 23 patients | 76 | EORTC QLQ C-30, STAI-T, HADS | Urinary cortisol (RIA) |
| III Cross-sectional survey | 2000 (s1)<br>2004 (s2) | 338 physicians<br>1292 patients | <br>69 | Questionnaire (s1)<br>Caregiver assess-ment (s2) | None |
| IV Observational | 2003 – 2004 | 13 patients | 74 | ESAS, global question | Urinary cortisol, cortisone (HPLC), metabolites (GLC) |
| V Observational (qualitative methodology) | 2005 – 2006 | 10 patients | 79 | Interview | None |

**Abbreviations:** pts = patients; s1 = survey 1; s2 = survey 2; EORTC QLQ C-30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; STAI-T = Spielberger State Trait Anxiety Inventory-Trait; HADS = Hospital Anxiety and Depression Scale; ESAS = Edmonton Symptom Assessment Scale; RIA = radioimmunoassay; HPLC = High performance liquid chromatography; GLC = Gas liquid chromatography.

## 3.2 THE TYPICAL PALLIATIVE CARE PATIENT

The typical palliative care patient encountered in the present studies had a non-curable cancer disease, most often with local or distant metastases. He or she had previous to enrolment received oncological treatment with surgery, chemotherapy or radiotherapy and had short expected survival. Multiple symptoms like pain, anorexia, fatigue and nausea were common, but symptom severity varied over time and between patients. Psychosocial and existential issues added to the complexity often seen in these patients.

## 3.3 THE PALLIATIVE CARE UNIT AT STOCKHOLMS SJUKHEM FOUNDATION:

All patients in study II, IV and V were enrolled at the palliative care unit of Stockholms Sjukhem Foundation. The unit also participated in study III. This unit has 38 beds distributed on two wards and 25 patients in advanced home care. Patients are referred

from the whole county of Stockholm with approximately 2 million inhabitants. Over 600 patients are referred every year. The median survival is 14 days at the wards and approximately one month in advanced home care. A specialized multidisciplinary team forms the basis of the daily work.

### *3.4 STUDY POPULATION*

*Paper I:* In this case-control study 10 healthy female volunteers where recruited at the Karolinska University hospital in Stockholm, and they were age-matched with five patients with gynaecological cancer reported in a previous study [62]. These five patients had received, in two consecutive cycles, single doses of 20 mg or 8 mg dexamethasone in conjunction with platinum-based combination chemotherapy at the department of gynaecological oncology, Radiumhemmet, Stockholm. The volunteers were given 8 mg of dexamethasone. 24-hour urinary collections were carried out in both patients and volunteers and subsequently analysed for urinary free cortisol.

*Paper II:* All patients with advanced cancer who were admitted to the palliative care unit during October 1998 – October 2000 and did not have ongoing treatment with corticosteroids were screened for inclusion. Twenty three patients with predominantly gastrointestinal cancer were included in this explorative study where symptom assessments were performed and demographic data, concurrent illness, medication, tumour burden, nutritional status, blood parameters and endogenous cortisol levels in 24-hour urine collections were analysed. Major reasons for exclusion were ongoing oncological treatment or cognitive impairment.

*Paper III:* Physicians' attitudes and practice regarding treatment with corticosteroids for anorexia, nausea, fatigue and poor well-being in patients with advanced cancer were studied during the autumn 2000 using a questionnaire with 18 questions, see Appendix. All members of the Swedish Society of Oncology (SOF) and the Swedish Association for Palliative Care (SFPM) were invited to participate, in total 573 physicians. Answers were received from 338 physicians all over the country representing different medical specialities. In a second step, all units in the Swedish palliative care research network (PANIS) [80, 81] received during the autumn 2004 a questionnaire with 10 questions on the use of corticosteroids in patients enrolled in palliative care, see Appendix. Thirty out of 37 (81 %) invited units participated, and 1292 patients were registered. In this cross-sectional survey 86 % of the patients had cancer, with breast-, lung-, prostate-, colorectal-, pancreatic- and ovarian cancer being the most frequent diagnoses. The most common non-malignant diagnoses were chronic pulmonary disease, chronic heart failure, chronic gastrointestinal disorder and amyotrophic lateral sclerosis.

*Paper IV:* In this prospective observational study we screened all patients with advanced cancer being referred to the in-patient unit during October 2003 – December 2004 and who were not using corticosteroids. Thirteen out of 133 patients were included, the major reasons for exclusion being cognitive impairment or short expected survival. Symptom assessments were performed at the study inclusion and after five respectively 10 days of treatment with four milligrams of betamethasone. Demographic data, concurrent illness, medication, tumour burden and blood parameters were

analysed. Urinary excretion of cortisol, cortisone and their metabolites were analysed in 24-hour urine collected before corticosteroid treatment.

*Paper V:* To study the existential impact of corticosteroid treatment, ten patients at the unit being considered for corticosteroid treatment were recruited during autumn 2005 to autumn 2006. The patients were recruited in order to achieve variation in gender, age, level of education, cancer diagnosis and expected time of survival. Demographic data and data on disease location, received treatment and concurrent illness were collected from the patient records. A semi structured interview guide was constructed and each patient was interviewed twice; before and after one week of treatment with four milligrams of betamethasone. One patient died within one week from beginning treatment; in total 19 interviews were performed. Three patients were interviewed in their homes, the rest in the palliative care unit. The material was analysed using qualitative content analysis.

### *3.5 SYMPTOM ASSESSMENTS AND QUESTIONNAIRES*

Data on health related quality of life in clinical research is generally collected with questionnaires or instruments containing items organized into scales. Due to the subjectivity of health related quality of life, self-assessment is preferred when using these instruments [82, 83].

*Paper II:* On admission, the patients were assessed for symptoms and other quality of life dimensions using EORTC QLQ C-30 (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire) [84]. Scores were calculated according to the scoring manual of the instrument [85]. This instrument incorporates nine multi-item scales: five functional scales (physical, role, cognitive, emotional and social); three symptom scales (fatigue, pain and nausea and vomiting); and a global health and quality of life scale. Single-item symptom measures are also included (dyspnoea, insomnia, appetite loss, constipation and diarrhoea). There is also a question addressing the perceived financial impact of the disease. A total of 30 items are covered which deals with health and well-being during the last week. Symptoms are rated on 4-point scales ranging from (1) “Not at all”, (2) “A little”, (3) “Quite a bit” to (4) “Very much”. Two items in “global health status” range from (1) “Very poor” to (7) “Excellent”, see Appendix. The questionnaire has been validated and found to be reliable in cancer patients [86-89].

In order to consider the association between individual differences in anxiety proneness and levels of cortisol, patients filled out the STAI-T (Spielberger State Trait Anxiety Inventory-Trait) which assess the level of anxiety a person reports as generally characteristic of him or herself [90]. The instrument consists of 20 statements, and feelings of apprehension, tension, nervousness, and worry are evaluated on 4-point Likert-type scales ranging from “Almost never” to “Almost always”. A total score is calculated. The Hospital Anxiety and Depression Scale (HADS) [91, 92] was used to screen for the separate dimensions of anxiety and depression in 16 of the patients in this study. The instrument is divided into an anxiety subscale and a depression subscale, both containing seven intermingled items. Respondents can score 0 – 21 points on each of the subscales; 0 – 7 points on a subscale represents a “non-case”, 8 – 10 points a “doubtful” or possible case, and 11 – 21 points a “definite case” of anxiety or depression [91].

*Paper III:* The questionnaire on physicians' attitudes and practice regarding treatment with corticosteroids in advanced cancer (survey 1) was initially presented to six physicians working in different parts of the country. They all had long experience of treatment with corticosteroids in cancer and adjustments to the questionnaire were done according to their comments. The questionnaire focused on treatment of appetite loss, fatigue, nausea and poor wellbeing and comprised 18 questions on the availability of local guidelines, the number of patients being treated, preferred drugs and doses, estimation and evaluation of effect, tapering of doses, gastroprotection and side effects, see Appendix. Most of the questions were of single or multiple choice models. The respondents answered anonymously but were asked to state their medical speciality. They were explicitly requested to answer the questions out of their daily practice, avoiding looking for answers in textbooks. The questionnaire on the use of corticosteroids in palliative care (survey 2) was constructed in collaboration with the members of the steering committee of the palliative research network. It comprised 10 questions on age, gender, diagnosis, whether the patient had ongoing treatment with systemic corticosteroids, drug and dosage, indication for treatment, effect, gastroprotection and side effects, see Appendix. In four questions, the respondent had the answering alternative "I don't know". The registration of the individual patient was based on the patient record, and evaluation of treatment effect and side effects was based on the clinical impression of the physicians and/or nursing staff caring for the patient. There were no individual self-assessments made by the patients. All registered data were subsequently entered into a web based survey generator by the local participant.
*Paper IV:* ESAS (Edmonton Symptom Assessment Scale) [93] was used on admission (ESAS 1) and after five (ESAS 2) respectively ten days (ESAS 3) of corticosteroid treatment. This instrument consists of ten numeric rating scales ranging from 0 to 10 on nine different items, see Appendix. ESAS is extensively used in palliative care and has been validated in this setting [94, 95]. In addition, corticosteroid treatment was evaluated after five days using a self-constructed single global question on perceived improvement or deterioration: "Please indicate with a cross on the line how you feel after you have started with corticosteroid treatment." This global question consisted of a numeric rating scale from -7 to +7 combined with a verbal scale ranging from "I feel a great deal of deterioration" to "I feel a great deal of improvement", see Appendix.

### *3.6 BIOCHEMICAL ANALYSES*

Blood samples for analyses of haematological (papers II and IV), liver (II, IV) and thyroid (II) parameters as well as electrolytes (II, IV) were collected and subsequently analysed at the routine hospital laboratory using standard methods. Analyses on 24-hour urine collections were performed as follows:
*Paper I:* 24-hour urine collections were carried out on the day before dexamethasone injection and for four (volunteers) respectively five (patients) days thereafter. The night and day urinary samples were analysed separately. Urinary free cortisol was analysed by an automated method based on fluorescence measurement using kits from Wallac, Stockholm, Sweden (today PerkinElmer Sweden). The same method was used for both patients and volunteers.
*Paper II:* 24-hour urine collections were carried out within 48 hours of completion of the questionnaires. Urinary free cortisol was analysed by radioimmunoassay using kits

from Orion Diagnostica (Espoo, Finland). The results in paper II are based on absolute excretion of cortisol expressed as nmol/24 hours. In addition, we normalized cortisol excretion to urinary creatinine excretion taking into account possible incompleteness in urine collection. The results based on creatinine correction are presented in the result section of this thesis.
*Paper IV:* 24-hour urine collections were carried out within 48 hours of completion of the first assessment with ESAS. The urinary excretion of free cortisol and cortisone was determined by high performance liquid chromatography (HPLC) and UV-detection (254 nm) following extraction and purification on a small octylsilane-bonded silica column. The urinary cortisol/cortisone ratio was used as an estimation of renal 11β-HSD2 activity [96]. The excretion of conjugated metabolites of cortisol and cortisone, including THF, allo-THF, cortols, THE and cortolones, was measured by using a simplified version of the gas liquid chromatography (GLC) method [97]. This method was also used to analyse the excretion of testosterone metabolites, i.e. androsterone, etiocholanolone, 11-hydroxy-androsterone and 11-hydroxy-etiocholanolone. The latter two can be derived from both glucocorticoids and testosterone [98]. Total cortisol excretion was calculated from the sum of THF, allo-THF, THE, cortols and cortolones [99]. The ratio of urinary metabolites of cortisol and cortisone (THF+ allo-THF+ α-cortol)/(THE + α-cortolone) was used as an estimation of 11β-HSD1 activity [6, 96]. Reference values from healthy controls previously examined at the laboratory were used for all urinary analyses. Urinary creatinine secretion was used as a quality measurement of the collection process. Creatinine-clearance was calculated using the Cockroft-Gault formula.

### *3.7 QUALITATIVE ANALYSIS*

In paper V, a qualitative methodology was used to study the existential impact of corticosteroid treatment in advanced cancer. A semi structured interview guide was constructed by the authors and discussed with colleagues in the multi professional palliative care team at the unit. Nineteen interviews were analysed using qualitative content analysis with no predetermined categories using both a manifest (descriptive) and a latent (interpretative) focus [100, 101]. The following stages of analysis were performed by the first and last author of the paper: (1) the material was read through repeatedly to obtain an overall impression and to identify themes relevant to the study. (2) The interviews were then reread carefully to identify significant text segments (meaning units) and to develop codes and preliminary categories. (3) All authors joined and agreement was obtained on preliminary categories and the central component. The final categories were compared to avoid overlapping. Quotations were used to exemplify the categories.

### *3.8 STATISTICAL METHODS*

Descriptive statistics were used in all papers. The usage of symptom assessments (paper II and IV) and questionnaires (paper III) rendered mainly ordinal data in these studies, implying that the predominant statistical methods used were non-parametrical. These methods do not assume a particular family of distributions for the data [102]. Several non-parametric tests are based on ranks with the inherent weakness of difficulties in calculating confidence intervals. Modern computationally intensive procedures known as bootstrapping offers methods of computing confidence intervals

for statistics with inconvenient or unknown sampling distributions. The Monte Carlo method, using resampling with replacement to estimate the statistic's sampling distribution, can be used to estimate confidence intervals [103]. This method was applied to the data in study II in addition to standard non-parametrical methods. The results from the Monte Carlo method (calculated with StatXact.4, Cytel Statistical Software & Services) were not reported in the paper, but they are reported in the result section of this thesis.

The raw scores of the EORTC QLQ C-30 questionnaire were linearly transformed into a 100-point scale according to the guidelines in the EORTC scoring manual [85]. A high score for a symptom scale/item represented a high level of symptomatology, whereas a high mean score fore functional scales and global health status reflected a better level of functioning. All scales were analysed, but we choose beforehand to focus on three symptom scales (fatigue, pain and nausea and vomiting) and the single item appetite loss, as this was considered to be of particular interest in this group of patients with advanced disease and short survival.

When using ESAS for symptom assessments there are no standardized methods of calculating changes between two different assessments in the individual patient. Both absolute and relative changes are used, with the latter being the most common [104]. In paper IV we calculated a "centred relative change" for each symptom from ESAS 1 to ESAS 2, which ensured all effects to be in the interval [-100%; +100%] and turned down unreliably large effects for those starting on a low score. Furthermore it meant that the possible outcome space was the same for all patients, though the outcome probabilities might differ between patients. Finally, a total sum of centred relative changes for all items was calculated for each patient. In concordance with study II, when analysing correlations between urinary cortisol levels and single items in ESAS, we focused on nausea, appetite loss, tiredness and well-being.

*Missing data:*

Missing data in EORTC QLQ C-30 was not imputed due to the importance of individual self-assessment. Missing data in the questionnaire in survey 1 (paper III), i.e. questions where answers were left out by the respondent, were handled as a separate answering entity for each question. The relative distribution of answers between different given alternatives were not corrected due to missing data. The design of the questionnaire in the survey generator in survey 2 (paper III) was made so that single questions could not be left out by mistake, thereby ensuring full completion of each individual questionnaire.

The statistical package SPSS version 11 (SPSS Inc.) was used in paper II, whereas STATISTICA version 7.1 (StatSoft Inc.) was used in paper III and IV.

Statistically significant differences and correlations in all studies were defined to be those with a p-value $< 0.05$. All tests were considered two sided.

*Paper I:* Student's t-test was used to compare the values of urinary free cortisol between day 1 and day 3, respectively day 3 and 5 in each treatment group, i.e. healthy volunteers and patients after receiving 8 respectively 20 mg of dexamethasone.

*Paper II:* To study correlations between urinary free cortisol and the severity of different symptoms, Spearman rank order correlation was used in order to test for significance.

*Paper III:* Comparing statistical analyses were performed on data from survey 2 to detect differences in treatment effect of corticosteroids on symptoms between two different cancer diagnoses (Mann-Whitney U test), and to test for correlations between

assessments of two (Spearman rank order correlation) respectively multiple (Friedman ANOVA) different symptoms.
*Paper IV:* Correlations between biochemical data, survival and symptom assessments were performed with Spearman rank order correlation. The Mann-Whitney U test was used to test for differences in biochemical data between the two groups of patients categorized by the value 3 of the global evaluation question.

### *3.9 ADDITIONAL ASPECTS ON METHODOLOGY*

There are problems with patient recruitment into studies in palliative care due to short survival, cognitive impairment and ethical considerations. It is therefore important to find a broader study base to increase enrolment. The Swedish palliative care research network (PANIS) was established by the researcher in 2002 in order to gain more knowledge about symptom prevalence, treatment traditions and current problems in palliative care [80, 81]. The idea was to collect data from patients in several palliative care units to overcome the problem with small patient materials in research related to advanced disease and end of life care. The national network has grown continuously and comprises today 64 palliative care units in 43 cities all over the country. It reaches over two thirds of all patients enrolled in specialised palliative care in Sweden. The network is led by a steering committee with six members. One objective of the network is to identify questions of interest in research and within the framework of the network facilitate the recruitment of patients into studies.
*Present network research method:*
Each participating unit receives twice a year a questionnaire by e-mail on a specific topic decided upon by the steering committee. All patients at each participating unit are registered on a specific day, and the registering physician or nurse has the opportunity to choose the day most appropriate for registration within a time interval of four weeks. The registration is based on the patient record. If required, an evaluation of treatment effect or side effects is based on the clinical impression of the physicians and/or nursing staff caring for the patient. All registrations are entered into a web based survey generator by the local participant. The design of the questionnaire in the survey generator is made so that single questions cannot be left out by mistake, thereby ensuring full completion of each individual questionnaire. Reports for analyses are generated within the survey generator by the network coordinator after the survey is closed and are subsequently transferred to an Excel database for descriptive statistical analyses. Further statistical analyses are performed within specialized statistical packages. Results and feedback are transferred to all units in the network within weeks after the survey has closed. The web based survey generator also enables the local participants to have online access to the evolving results during the whole study period. These results are presented as graphs and mean/median figures.
All participating units are explicitly told to register all patients at their unit regardless of ongoing specific treatment or not. However, there is no monitoring at the units ensuring adherence to this. An accompanying letter with detailed instructions on the specific survey and how to use the web based survey generator is enclosed with the questionnaire. These instructions are also available on the network website. All participants are asked to inform the network coordinator by e-mail when they have completed the survey or whether they will not participate in the ongoing survey.
So far, eight surveys have been conducted within the network and data from over 9100 patients have been collected. Survey 2 in paper III was performed within this network.

# 4 RESULTS

## 4.1 PAPER I:

In this study the recovery of the HPA-axis after a single dose of dexamethasone was examined in 10 healthy volunteers by analysing urinary free cortisol in 24-hour urine collections. The results were compared with those obtained after dexamethasone injection in 5 patients with gynaecological cancer receiving platinum-based combination chemotherapy, reported in a previous study by Peterson [62].
A pronounced and significant ($p < 0.05$) decline in urinary free cortisol levels relative to baseline was seen in the volunteers as a function of dexamethasone administration. This was similar to the decline in the patients. The values had normalised in both patients and volunteers within two days after the dexamethasone injection. There were no significant differences in cortisol levels after injections of 8 mg and 20 mg dexamethasone. Control of chemotherapy-induced delayed nausea was impaired in the patients when they received 20 mg as compared to 8 mg of dexamethasone, but the differences were not statistically significant.
The conclusion was that the pattern of recovery of the HPA-axis was similar in patients and healthy volunteers, and corticosteroid-induced impairment in the control of delayed nausea was not dependent on the suppression and recovery of the HPA-axis.

## 4.2 PAPER II:

Urinary free cortisol levels were analysed in 23 patients with advanced cancer who had rated symptom severity using different assessment instruments.
For the group in whole, the mean and median values for cortisol were high as compared to the reference values. Significant positive correlations were found between levels of urinary free cortisol and appetite loss, fatigue and nausea/vomiting. Patients with relatively higher cortisol levels had more pronounced symptoms. These findings were even more pronounced when cortisol levels were normalized to urinary creatinine excretion, see Table 5. The Monte Carlo estimate of p-value with 99 % confidence interval based on 10 000 sampled tables are also shown in Table 5. These values were calculated from the non-normalized urinary cortisol levels. There were no significant correlations between cortisol levels and total STAI-T score or HADS score for depression or anxiety. An additional finding was a significant inverse correlation between cortisol levels and levels of serum albumin. There were few missing data in the study; two item scores for pain in EORTC QLQ C-30 were missing as well as one item score for nausea. One patient refrained from filling out STAI-T.
To conclude, we found correlations between high levels of endogenous cortisol and aggravated symptoms in advanced cancer.

**Table 5**. Spearman rank order correlation between urinary analyses and different parameters in EORTC QLQ C-30 (study II).

| *Parameter* | *No. of pairs* | *$r_s$ for UFC* | *p-value* | *$r_s$ for UFC/Crea* | *p-value* | *99 % CI for p-value* |
|---|---|---|---|---|---|---|
| Appetite loss | 23 | 0.59 | 0.003 | 0.62 | 0.002 | 0.0019 – 0.0049 |
| Nausea/vomiting | 23 | 0.44 | 0.04 | 0.46 | 0.03 | 0.033 – 0.043 |
| Fatigue | 23 | 0.51 | 0.01 | 0.73 | < 0.001 | 0.011 – 0.017 |

**Abbreviations:** UFC = urinary free cortisol; Crea = creatinine

### *4.3 PAPER III:*

Physicians' attitudes and practice regarding treatment with corticosteroids for anorexia, nausea, fatigue and poor well-being in patients with advanced cancer were studied in survey 1. In survey 2, the actual usage and perceived effects of corticosteroids in palliative care was studied.

#### 4.3.1 Survey 1:

The first survey was answered by 338 physicians (59 %). Thirty-six answers were excluded due to incomplete answering (n= 12) or statements from the respondents that they lacked experience of the actual treatment (n= 24). The remaining 302 completed questionnaires were collected from all over the country. Almost half of the respondents were oncologists. Together with geriatricians, surgeons, internists and general practitioners they constituted 85% of all the respondents. One third of the physicians reported that they had local guidelines on treatment with corticosteroids in advanced cancer at their unit. Two thirds answered that they prescribed corticosteroids to more than 50% of their cancer patients with appetite loss, fatigue, nausea or poor wellbeing. Eighty-three percent stated that more than 50 % of their patients had a positive effect of the treatment and 97% of the respondents experienced that the positive effect was seen within five days. Sixty-three percent answered that the positive effect usually lasted between 3-6 weeks.
Betamethasone was the most commonly prescribed drug followed by prednisolone. The mean starting daily dose for treating anorexia, fatigue or low mood was 3.5 mg of betamethasone or 17 mg of prednisolone respectively. The mean starting dose for treating nausea was 4.8 mg or 19 mg daily respectively. Poor well-being was seen as the symptom that showed the most positive response on corticosteroid treatment. Twenty-seven percent of the respondents answered that they prescribed gastroprotectors to 75-100 % of their patients treated with corticosteroids. The corresponding figure for patients treated concomitantly with corticosteroids and non steroidal anti-inflammatory drugs (NSAID) was 65 %. Sixty eight percent of all respondents used preferably proton pump inhibitors (PPI) for gastroprotection. Two thirds of the respondents did not see side effects related to treatment with corticosteroids as a problem. The side effects most often seen were oral candidosis, aggravated or triggered diabetes mellitus, moon face and fragile skin/purpura. The mean value of missing data for all questions was six percent, ranging from 1 to 14 %. Doses used when commencing treatment with corticosteroids (question 4), was only possible to assess in 50 % of the answers, since it was not possible to separate single from multiple doses.

#### 4.3.2 Survey 2:

Thirty palliative care units (81%) participated in the study. A total of 1292 patients were registered and a majority was enrolled in advanced home care. The mean age was 67 years and there was a predominance of women. 1116 patients had cancer. A total of 608 patients (47%) had ongoing treatment with systemic corticosteroids, 582 (96%) of them had a cancer diagnosis. More than 60 % of the patients with lung or prostate

cancer used corticosteroids whereas only 28 % of the patients with ovarian cancer had ongoing treatment.
Eighty-five percent of the cancer patients on corticosteroids used betamethasone. Oral administration was used in more than 90 % of the cancer patients and 85 % received a single daily dose of their corticosteroid. Two thirds of the cancer patients on betamethasone had a daily dose below 3.5 mg, whereas only 33 patients had a daily dose over 8 mg. Two thirds of the cancer patients had used corticosteroids for more than four weeks. Table 6 summarizes the details on drugs and dosage of corticosteroids in the cancer patients.

**Table 6.** Drugs and dosage in cancer patients treated with corticosteroids in survey 2 of study III.

| | ***Number of patients (%)*** |
|---|---|
| Betamethasone | 497 (85) |
| Prednisolone | 75 (13) |
| Prednisone | 8 (1) |
| Other corticosteroid | 2 |
| Oral administration | 549 (94) |
| Intravenous administration | 28 (5) |
| Subcutaneous administration | 3 |
| Daily dose of betamethasone < 3.5 mg | 327 (66) |
| Daily dose of betamethasone > 8 mg | 33 (7) |
| Daily dose of prednisolone < 25 mg | 67 (89) |
| Single daily dose of corticosteroid | 497 (85) |
| Ongoing corticosteroid treatment since 7 days or less | 57 (10) |
| Ongoing corticosteroid treatment since more than 4 weeks | 387 (66) |

The non-specific indications for corticosteroid treatment dominated with appetite loss, fatigue and poor wellbeing being the most frequent. Figure 5 shows the effect in the five most common indications for all cancer patients treated with corticosteroids. Most patients with non specific indications had a positive response to corticosteroids with less than 10 % of the patients assessed as having no effect of the treatment. There was a statistically significant difference in treatment effect on fatigue between patients with lung cancer and prostate cancer. When analyzing the treatment effect over time for all cancer patients using corticosteroids for either appetite loss, fatigue, nausea or poor wellbeing, the results showed that the positive response came within a week and the response was stable over time. Patients treated for more than 4 weeks retained the positive effect.
Gastroprotection was used in 75 % of the patients treated with corticosteroids. Proton pump inhibitors constituted 95 % of all prescribed gastroprotectors. In approximately one third of the cancer patients treated with corticosteroids the respondent experienced troublesome side effects. Eighty-one percent of these patients had used corticosteroids for more than four weeks. The five most common side effects among patients judged as having troublesome side effects were moon face, myopathy/muscle weakness, skin purpura, oral candidosis and aggravated/triggered diabetes mellitus. Due to the construction of the web based survey generator, there were no missing data, but in 29 cancer patients (5 %) the respondents did not know for how long the corticosteroid treatment had been going on. In 48 cancer patients (8 %) the respondents could not assess if there were troublesome side effects.
In conclusion, we found that corticosteroids were commonly prescribed in Swedish palliative care, often without access to guidelines. High response rates to the treatment were seen.

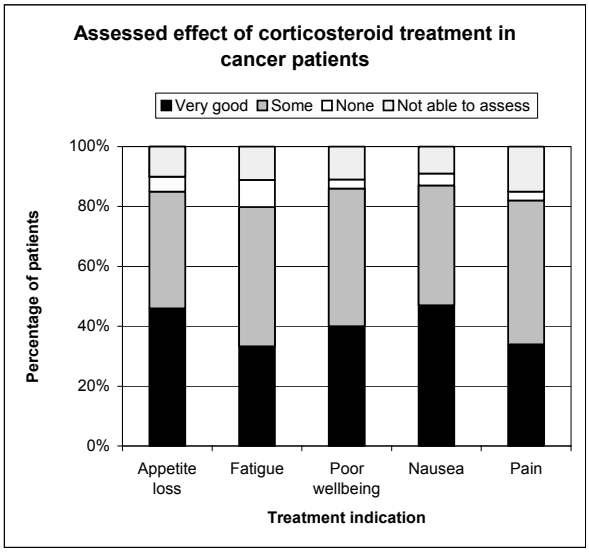


**Figure 5**. Assessment of effect on different symptoms for cancer patients treated with corticosteroids (survey 2 of study III).

### *4.4 PAPER IV:*

The endogenous corticosteroid production and metabolism in 13 cortisone-naive patients with advanced cancer was analysed. Correlations with symptom relieving effects of daily treatment with four milligrams of betamethasone were examined. Five patients had levels of urinary cortisol above the reference interval. The sum of urinary cortisol and cortisone was normal in 10 patients, two patients had lowered values whereas one patient, the one with shortest survival, had a higher than normal value. Cortisol production, estimated by the sum of cortisol and cortisone metabolites, was normal in all but one patient, a male with hepatocellular cancer who had lowered production. The ratio of urinary metabolites of cortisol and cortisone was raised in six patients, indicating an increased conversion from cortisone to cortisol by 11β-HSD1 in the tissue. The urinary cortisol/cortisone ratio was raised in a majority of the patients, suggesting an impaired activity of renal 11β-HSD2. There was a significant negative correlation between survival from the day of urine collection and the cortisol/cortisone metabolite ratio. This correlation was strengthened when analysing the subgroup of seven patients scoring three or less on the global evaluation question, see Figure 6. In this subgroup there was also a positive correlation between cortisol production and ratio of urinary metabolites of cortisol and cortisone, as well as a significant inverse correlation between cortisol production and survival. The median age in the group of patients scoring three or less was 76 years compared to 56 years in the group with better response to corticosteroid treatment. The Spearman correlation coefficient for age versus value of the global evaluation question was -0.58 ($p = 0.04$). There were no correlations between age and the calculated metabolic ratios.

The levels of androsterone and etiocholanolone were low in all patients compared to the reference values. The mean ratio of (11-hydroxy-androsterone + 11-hydroxy-etiocholanolone)/(THF + allo-THF + THE + cortols + cortolones) was 14 %, ranging from 4 – 31 %. This ratio was indicative of the fraction of urinary metabolites which could have been derived from either glucocorticoids or testosterone.
Four patients with short survival were not able to fill out ESAS 3; it was therefore left out from the analyses for the whole study group. There were no missing data for ESAS 1 or ESAS 2, neither for the global evaluation question. We found a significant correlation between severity of nausea on ESAS 1 and cortisol production, but we were not able to show this for appetite loss, tiredness or well-being.
All but one patient experienced an improvement during the corticosteroid treatment as assessed by the global evaluation question, with values ranging from 1 to 7. The total sum of centred relative changes for all items on ESAS correlated strongly with the global evaluation question, see Figure 7. Results of blood analyses showed an inverse relationship between U-cortisol and level of serum albumin as previously reported in paper II. Table 7 summarizes the correlations found in this study.
To conclude, normal cortisol production together with a metabolic shift from cortisone to cortisol in the tissue was seen. This shift was more pronounced in patients with shorter survival, especially in those with an inferior response to corticosteroid treatment.

**Table 7.** Spearman rank order correlation between different parameters in study IV.

| ***Parameter*** | $r_s$ | ***p-value*** |
|---|---|---|
| Cortisol/cortisone metabolite ratio vs survival | -0.71 | < 0.01 |
| Cortisol/cortisone metabolite ratio vs survival in pts with inferior response | -0.93 | < 0.01 |
| Cortisol production vs severity of nausea | 0.68 | < 0.01 |
| Cortisol production vs survival in pts with inferior response | -0.82 | < 0.05 |
| Cortisol production vs cortisol/cortisone metabolite ratio in pts with inferior response | 0.86 | 0.01 |
| Urinary cortisol vs serum albumin | -0.66 | 0.01 |
| Total sum of centred relative changes on ESAS vs score on global evaluation question | 0.76 | < 0.01 |
| Age vs score on global evaluation question | -0.58 | < 0.05 |

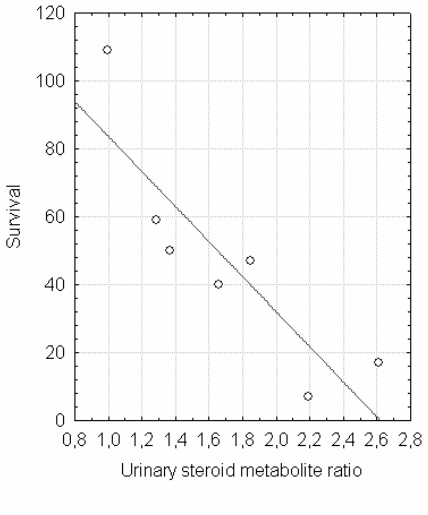


**Figure 6**. Urinary corticosteroid metabolite ratio [(THF+ allo-THF+ α-cortol)/(THE + α-cortolone)] versus survival from the day of urinary collection in patients scoring three or less on the global evaluation question (study IV).

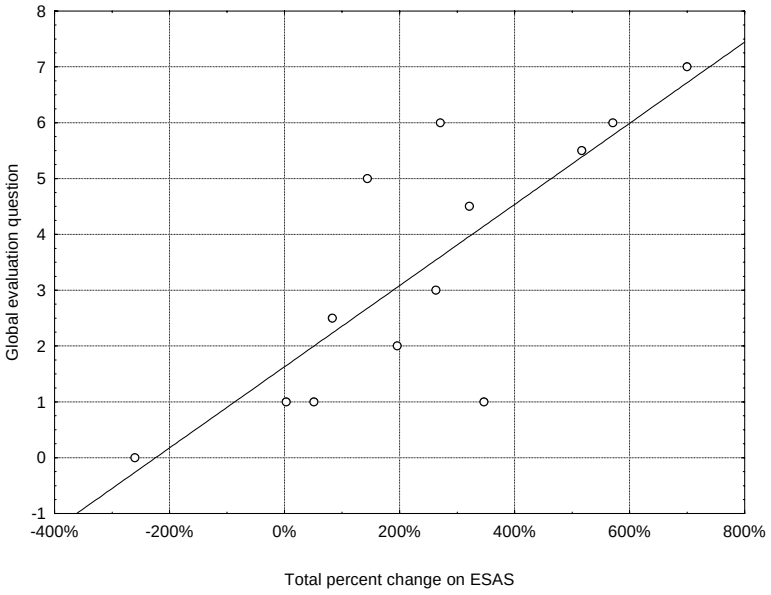


**Figure 7**. Total sum of centred relative changes on ESAS (Edmonton Symptom Assessment Scale) versus score on the global evaluation question (study IV).

### *4.5 PAPER V:*

In this study we used a qualitative methodology to explore the existential impact of corticosteroid treatment in 10 patients with advanced metastatic cancer. The patients were interviewed both before and after one week of treatment with four milligrams of betamethasone.

Both physical symptoms and anxiety were reported before treatment. Expectations on the treatment mainly concerned relief from physical symptoms. Eight out of ten patients experienced positive effects of the treatment. As expected, these patients reported prompt improvement of several symptoms, resulting in senses of a more normalised life. Enhanced abilities also resulted in increased expectations and the timeline was extended. On an interpretative level, rapid deterioration with aggravated symptoms and diminished autonomy symbolised threat and death. Perceived improvements, even in one single symptom, withdrew the immediate threat. This change from deterioration to improvement was interpreted as the return of hope, a revived link to life.

In conclusion, symptom relief brought about with corticosteroid treatment had profound existential consequences in patients with advanced cancer.

# 5 DISCUSSION

In this discussion, the general findings and interpretations are first presented. This is followed by a discussion on methodological considerations. Finally clinical implications and suggestions for future research are presented.

## *5.1 FINDINGS AND INTERPRETATIONS*

### 5.1.1 Endogenous cortisol in advanced cancer

The results presented in this thesis support the view of a chronic stress condition in patients with advanced metastatic cancer. Raised levels of endogenous cortisol were seen in study II and a metabolic shift from cortisone to cortisol was seen in study IV. During severe illness, surgery, trauma or infection, there is an activation of the HPA-axis and a subsequent elevation of cortisol levels as an adaptation to stress [105]. Inflammation is a key factor in these conditions, and the pro-inflammatory cytokines TNF-α, Il-1 and Il-6 account for most of the HPA-axis stimulating activity [17, 106]. Inflammation is also a critical component of tumour progression [44, 45] and systemic inflammation is linked with adverse prognosis in patients with cancer [107]**.** Antiinflammatory treatment with indomethacin has been shown to prolong survival in patients with advanced disease [138]. Studies on secretion of endogenous cortisol in patients with cancer show elevated plasma cortisol levels [24-26, 108], and these elevations are further enhanced in more advanced disease [25, 27, 28, 109]. Our findings of raised levels of urinary cortisol in patients with advanced cancer in study II were in accordance with these studies. However, the covariation between high levels of endogenous cortisol and more pronounced symptoms found in this study has not been shown before. We found a significant correlation between severity of nausea on ESAS 1 and cortisol production, but we were not able to show this for appetite loss, tiredness or well-being (study IV). The small number of subjects in study IV is one possible explanation. This covariation between cortisol levels and symptom severity raises the question whether high levels of cortisol in itself mediates symptoms or whether other factors, e.g. pro-inflammatory cytokines, are more likely to mediate cancer-related symptoms. Research within the field of cancer cachexia points at the pivotal role of cytokines in this syndrome [110], and symptoms as anorexia, fatigue and nausea are thought to in part be mediated by pro-inflammatory cytokines [111, 112]. It is therefore likely to believe that cytokines play a more important role than cortisol in the mediation of cancer-related symptoms.

We could demonstrate correlations between cortisol metabolism and survival in study IV. Increased activity in 11β-HSD1 was associated with shortened survival. This was accentuated in patients with an inferior effect of corticosteroid treatment. This subgroup also showed a negative correlation between survival and cortisol production, although age could have been a confounder when doing the subgroup analyses. Other research groups have found correlations between alterations in cortisol circadian rhythms and poor prognosis in patients with metastatic breast cancer [33, 34]. Measurements of systemic levels of cortisol have not been shown to correlate with survival [113].

The generally low levels of testosterone metabolites found could be seen as a shift away from androgen synthesis towards increased cortisol production. Although the

median value of urinary cortisol was higher in patients than in controls, and five patients had values of urinary cortisol exceeding the reference interval, cortisol production estimated by the total sum of metabolites remained normal (study IV). The raised cortisol levels we found suggest a shift in metabolism from cortisone to cortisol, and the findings of raised ratios of cortisol metabolites and urinary cortisol/cortisone points towards enhanced activity of 11β-HSD1 and diminished activity of 11β-HSD2. Pro-inflammatory cytokines enhance the activity and expression of 11β-HSD1 [11, 12]. At the same time, they down-regulate 11β-HSD2 expression [13] and have also been found to suppress testosterone production [114, 115].
Taken together, our findings of raised levels of endogenous cortisol, enhanced metabolic shift towards cortisol in patients with short survival and diminished testosterone production support the impression of chronic stress, with an important influence of cytokines in the regulation of the HPA-axis in advanced cancer. The levels of urinary cortisol and cortisone reflects the levels in plasma [116], and it is interesting to note that most of the patients retained normal systemic levels together with normal cortisol production, even if their metabolism in peripheral tissue shifted towards cortisol (study IV). Intracellular cortisol levels are regulated both by secretion, controlled by the HPA-axis, and tissue metabolism, controlled by 11β-HSD. These levels can therefore differ from plasma cortisol levels depending on the expression and activity of 11β-HSD [11]. Our findings give the impression of a peripheral, possibly cytokine mediated stress response, rather than a systemic stress response reflected in enhanced cortisol production. This implies that measurement of metabolites and assessment of 11β-HSD activity is required for a correct estimation of the cortisol-mediated stress response in patients with advanced cancer.

### 5.1.2 Endogenous cortisol and delayed nausea

We found a rapid recovery of the HPA-axis in healthy volunteers after an injection of dexamethasone (study I). This was similar to the recovery in patients given dexamethasone in connection with platinum-based chemotherapy. The pattern of recovery did not differ in the patients when they were given either 8 or 20 mg of dexamethasone [62]. Other studies on the recovery of the HPA-axis in both patients and healthy volunteers have also found a rapid recovery after single high doses of corticosteroids [117, 118]. An interpretation of this is that corticosteroid-induced impairment in the control of chemotherapy-induced delayed nausea does not depend on the suppression and recovery of the HPA-axis.
The pathophysiology behind delayed nausea and vomiting is still unknown and the symptoms remain a challenge in the clinic [119]. There are studies indicating that endogenous cortisol can serve as an antiemetic. Relatively higher excretion rates of endogenous cortisol are associated with relatively lower levels of chemotherapy-induced nausea and vomiting [59, 60]. On the other hand, relatively higher doses of glucocorticoids administered as antiemetics do not enhance the effect on acute symptoms [61, 120]. Platinum containing chemotherapy has been shown to cause an immediate reduction in serum cortisol levels following infusion [121], but the data from our previous study [62] do not support the possibility of this being a persistent state during several days, and a possible cause of delayed symptoms. Cisplatin has a long half-life and there is a possibility that the pattern of delayed nausea and vomiting had been different if the patients had been given dexamethasone for several days. Also,

other possible causes of nausea were not examined. The serotonergic system mediates in part nausea and vomiting, and differences in the modulation of serotonergic ($5\text{-}HT_3$) and/or peptidergic ($NK_1$) transmission by low as opposed to high doses of corticosteroids could be interesting to evaluate when searching for possible mechanisms of corticosteroid-induced impairment in the control of chemotherapy-induced delayed nausea.

### 5.1.3 Treatment with corticosteroids

In study IV and V the patients were treated with four milligrams of betamethasone daily and evaluations of the treatment effect were performed after five (study IV) respectively seven (study V) days. The response rate was high in both studies; 12 out of 13 patients experienced an improvement in study IV and the corresponding figures in study V were 8 out of 10 patients. The methodology to assess these improvements differed between the two studies, but the results resemble those reported in the large patient cohort examined in survey 2 of study III. This magnitude of response to corticosteroid treatment on non-specific indications such as anorexia, nausea and low mood has been reported in an earlier study [66], but exceeds those reported by other authors [65, 72, 73]. The difference could not be explained by the usage of higher doses of corticosteroids in the patients reported in study III, IV and V. Both surveys in study III showed that a positive effect of corticosteroid treatment could be expected within a week, and in survey 2 the respondents experienced that this effect persisted beyond four weeks. This result could be questioned due to the design of the study with ratings performed by caregivers, but nevertheless it is interesting as it is in contrast to previous findings where symptomatic benefits are reported to rarely extend for more than four weeks [48, 68].

The mechanisms behind the positive effects of exogenous corticosteroids on non-specific symptoms are still unclear. Glucocorticoids inhibit the production of proinflammatory cytokines like Il-1, Il-6 and TNF-α [17]. Medroxyprogesterone acetate (MPA) can inhibit the actions of Il-1, Il-6 and TNF-α [122] and high-dose treatment with MPA in advanced cancer resulted in improvements of quality of life together with suppression of raised levels of cortisol [123]. An interpretation of this based on present knowledge is that a deranged balance between the neuroendocrine system and the immune system contributes to symptoms in advanced cancer. Chronic stress due to tumour burden, psychological and psychosocial factors results in raised levels of cytokines which in turn stimulate the HPA-axis to ultimately produce cortisol to counteract the actions of the cytokines. An imbalance between these different actions could be temporarily balanced by sufficient doses of exogenous corticosteroids that would suppress the cytokine activity.

The results of study III showed that few physicians had local guidelines on treatment with corticosteroids in advanced cancer. Corticosteroids were prescribed to more than 50 % of the patients in palliative care on a wide range of indications. The proportion of patients on corticosteroids was in accordance with earlier studies from other countries [72, 75, 76]. In general, there was a good agreement between reported practice and existing evidence, indicating that prescribing physicians in palliative care are familiar with this class of drugs.

In these patients with far advanced cancer, it can be difficult to discern side effects clearly related to corticosteroid therapy. Two thirds of the physicians in survey 1 did

not see side effects as a problem, and in one third of the patients in survey 2 troublesome side effects were reported. The five most common side effects in survey 2 were seen in between five and thirteen percent of all treated cancer patients, while the figures in the literature varies between 5 and 36 % [68, 74]. Length of treatment and size of the dose are important factors when studying the prevalence of side effects, and the variance in these factors between different studies makes it difficult to analyse the figures. However, despite the difficulties in discerning side effects and the weakness in study design, the interpretation of our findings is that physicians have a tendency to underestimate side effects related to corticosteroid treatment.
Gastroprotection with proton pump inhibitors was often used according to study III. The notion that advanced cancer is a condition of chronic stress supports this extensive use, and especially the combination of NSAID and corticosteroids should result in prophylactic treatment due to the increased risk of gastric irritation [124].
The extensive response rates on corticosteroid treatment in non-specific indications represent a major benefit in terms of symptomatic improvement in this group of patients with advanced disease and short expected survival. Good symptom control is important in palliative care [125] and has been shown to foster hope [126]. This was confirmed in study V where treatment with corticosteroids was found to have profound existential implications. Corticosteroid treatment reduced symptoms and increased strength, thereby strengthening autonomy and fostering hope. Hope was not only limited to symptom control issues. Good symptom control created hope on a deeper level, as absence of symptoms gave the patients a perception of a more normalized life. On the other hand, aggravated symptoms, reduced strength and diminished physical abilities resulted in reduced autonomy which was perceived as an ultimate threat by the patients. The interviews in study V indicated that it was the change in itself towards improvement or deterioration rather than the absolute level of symptom distress prior to treatment which determined the patients' experience of hope or threat in association with corticosteroid treatment. An interpretation of this is that corticosteroid treatment can in many patients create respite and give them possibilities to finish "unfinished business". This is important to address when communication goals of treatment and care with the patient and family.

## *5.2 METHODOLOGICAL CONSIDERATIONS*

Some methodological aspects of the studies described in this thesis deserve particular attention.

### 5.2.1 Internal validity – systematic errors

Internal validity is defined as the absence of systematic errors within studies, in this section divided into bias and confounding [127].

#### *5.2.1.1 Selection bias*

This refers to error in choosing the individuals or groups to take part in a study. High participation rates and response rates normally preclude severe selection bias.

The healthy female volunteers in study I were recruited through a notice at the Karolinska University Hospital in Stockholm. They were mainly hospital staff and were checked for ongoing medical treatment that could interfere with the analyses.
In study II, IV, and V, inclusion and exclusion criteria were tight due to the explorative nature of these studies. This made inclusion of patients difficult, a well known problem in palliative care research. All patients entering the palliative care unit were screened by research nurses for inclusion according to a protocol in study II and IV, so the risk for random biased selections into these studies was small.
In survey 1 of study III, 59 % of the invited physicians answered the questionnaire. There was a satisfactory mix between different medical specialities involved in palliative care and answers were collected from all over the country. As the respondents answered anonymously, the gender distribution was not possible to assess. In survey 2 of study III, 81 % of the units in the network participated representing all parts of the country. All units were explicitly told to register all enrolled patients in concordance with the working method of the network. However, there was no monitoring at the units ensuring adherence to this. Recruitment was limited to specialised palliative care units, affecting the external validity of the results.
Patients in study V were recruited after the physician in charge had decided to start treatment with corticosteroids. This meant that the physician had estimated that treatment could be of benefit in the individual patient. This study was based on a qualitative research method and a purposeful sampling. Therefore the term selection bias, which refers to quantitative studies, is not applicable for this study. In conclusion, selection bias is of concern in study II and IV.

#### *5.2.1.2 Information bias*

This refers to problems related to misclassification. The present studies rely on information from patient records, questionnaires, interviews and biochemical analyses. Data from patient records were collected using standardized data sheets in study II and IV. This ensured patient data that was important to the research question to be collected uniformly from the records. In study II and IV self-assessment using validated questionnaires were utilized, minimizing information bias. The research nurse handed the questionnaires to the patients and they were completed in the patient room. If the patients were unable to read the questions or write the answer, the research nurse assisted when necessary. In study IV a non-validated global evaluation question was used to evaluate the effect of corticosteroid treatment. The results showed a strong correlation between the sum of relative changes on ESAS and the value of the evaluation question. ESAS has been validated [94, 95] and this correlation points towards validity also of the evaluation question, but this has to be confirmed in a larger study.
The use of non-validated questionnaires in both surveys in study III is more crucial. However, the questionnaire in survey 1 was adjusted according to the comments from six experienced physicians with background in research. Three experienced researchers and clinicians participated in the construction of the questionnaire in survey 2. This strategy tested the face validity. Both questionnaires were used in a descriptive, cross-sectional setting.
Patients were assessed by physicians or nurses concerning response to corticosteroid treatment and occurrence of side effects in survey 2, no self-assessments were made by

the patients. Assessments made by the staff in patients with advanced cancer are generally inconsistent and the accuracy is dependent on the type of symptom. It is generally agreed that the patients are the most valid source of information about their quality of life [128]. However, in patients with advanced disease there are significant problems of missing data in clinical studies that measure quality of life [129]. Selection biases would result if only those patients well enough to complete questionnaires were left in the study sample [128]. There is a substantial agreement in the literature regarding more accurate assessments by physicians and nurses on physical-functional symptoms than on psychological and social symptoms [129, 130]. Also, nurses seem to rate patient symptoms better than physicians [131, 132]. Still, a recent study advises against using physicians' assessments as a substitute for patient self-assessment in palliative care [133]. In survey 2 of study III physicians and/or nurses rated treatment effect on primarily physical symptoms together with occurrence of side effects. Selection bias was avoided, but information bias cannot be ruled out.
The rationale for using measurements of urinary cortisol in 24-hour urine samples as an estimation of cortisol secretion rate in study I and II was based on previous findings [116]. Based on more extensive literature studies, the total sum of urinary cortisol and cortisone metabolites was used as an estimation of cortisol production in study IV [99]. In study I and II urinary cortisol was analysed using radioimmunoassay (RIA), while the highly specific HPLC method was used in study IV. When using RIA, less than half of "urinary cortisol" is really cortisol; the rest is often assumed to consist of cortisol metabolites. This could give an incorrectly high value for urinary cortisol in patients [134, 135]. The values of urinary cortisol in study II were probably incorrectly high, nevertheless the values reflected cortisol-related products. RIA was used in both patients and healthy volunteers in study I, and comparison between these groups concerned relative changes from baseline levels of cortisol, excluding systematic errors that weighted differently between the groups.

#### *5.2.1.3 Recall bias*

This refers to the problem of retrospectively relating information regarding the period before treatment, where effects related to the treatment may influence answers. In survey 1 of study III, physicians were asked to state their attitudes and practice, which opened up for recall bias. Due to the prospective design used in study IV and V, where collected information referred to the actual study period, recall bias was avoided.

#### *5.2.1.4 Confounding*

Confounding means finding an association for the wrong reason. A confounder is a factor associated both with the exposure and the outcome under study, and is best dealt with in randomized studies. In studies comparing groups, potential confounding factors can influence the comparison. Comparisons in study III were made between treatment responses in patients with different cancer diagnoses, and in study IV between patients with different treatment responses to corticosteroids. Equal distribution of known risk factors and characteristics, such as age, between groups can prevent apparent confounding, but unknown confounders can still influence the results. There was a difference in age between patients with lung cancer and prostate cancer who responded differently to corticosteroid treatment concerning fatigue in survey 2 of study III. The mean age of the lung cancer patients was 66 years as compared to 76 years for patients

with prostate cancer, who were perceived as having an improved response to the treatment. In this study, age could not explain the higher level of fatigue observed. In study IV, age was a confounding factor when doing the analyses on the subgroups with different responses to treatment. However, age did not correlate with the calculated metabolic ratios used when estimating metabolic activity.

### 5.2.2 Statistical variation – random errors

Random error, the influence of chance, affects the precision of a study. This can be estimated with confidence intervals and tested with analyses of significance. Small sample sizes in study II and IV caused less precision and enhanced the risk of random error. Apart from using the Monte Carlo method in study II, confidence intervals were not calculated in the studies. Analyses based on ranks make calculation of confidence interval difficult. The risk of type I errors due to multiple testing and comparison was considered low in the studies, and no adjustments were made.

### 5.2.3 External validity

This refers to the possibility to generalize the findings to other populations than the one under study. Small sample sizes with participants from a single geographic location threaten the external validity. Patient inclusion was difficult in study II and IV resulting in small sample sizes. There was a predominance of gastrointestinal cancer in both studies and the gender distribution was skewed in study IV. All patients lived in an urban area. Therefore, generalization to the palliative care population is difficult in these studies. Study III presented two large study samples with participants from all over the country. Provided that there were internal validity and adequate precision, the results would be representative of palliative care physicians and the palliative care population in Sweden.

### 5.2.4 Trustworthiness

Within qualitative research, the concept of trustworthiness is used instead of validity when evaluating the research. Two strategies were used in study V to promote trustworthiness. A dialogical validation [136] was made with the patients, as similar questions were addressed several times during the interview, to ensure the patients' genuine perception. Secondly, a dialogical intersubjectivity [137] was used, according to which the interviews were analyzed separately by the first and last author and then compared for similarities and differences. The material was discussed until agreement was reached. Also, the construction of the semi structured interview guide was discussed with colleagues in the multi professional palliative care team to enhance face validity. With a sample size of ten, most patients presented a similar picture, indicating a relative saturation of data. However, it cannot be ruled out that an increased number of patients would have given further variation and insight.

## 5.3 CONCLUSIONS, CLINICAL IMPLICATIONS AND FUTURE PERSPECTIVES

This thesis supports the view of chronic physiological stress in advanced cancer. Alterations in the metabolism of cortisol indicative of an enhanced stress response were seen, and a covariation between symptom severity and levels of endogenous cortisol were found. The results pointed towards a preserved function of the HPA-axis with normal cortisol production and a normal pattern of recovery of the HPA-axis after single dose treatment with dexamethasone. In an epidemiological perspective, we found that corticosteroids were frequently prescribed to cancer patients in Swedish palliative care, often without access to guidelines. High response rates to the treatment were seen. This positive response to corticosteroid treatment were found to have profound existential consequences in the patients, with feelings of normalized life, strengthened autonomy and a revived hope.

There are several clinical implications that can be based on the findings presented in this thesis.

- The presence of a chronic physiological stress condition in patients with advanced cancer should be considered when pharmacological treatment and other interventions are planned.
- Written guidelines on the use of corticosteroids in advanced cancer could assist clinicians in choosing adequate therapy to assure patients an optimal effect and a reduced risk for adverse effects.
- It is important that physicians and nurses do not underestimate the occurrence of side effects in patients treated with corticosteroids.
- There are good chances of improvement when corticosteroid treatment is initiated, and this should be addressed when communicating goals of treatment and care with the patient and family.

Based on the findings of this thesis, future studies of patients with advanced metastatic cancer could focus on some of the following topics:

- Finding possible differences in the modulation of serotonergic ($5\text{-}HT_3$) and/or peptidergic ($NK_1$) transmission by low as opposed to high doses of corticosteroids when searching for potential mechanisms of corticosteroid-induced impairment in the control of chemotherapy-induced delayed nausea.
- The interactions between the neuroendocrine system and the immune system, especially the impact of corticosteroid treatment on levels of pro-inflammatory cytokines.
- To find the optimal corticosteroid dose for symptom relief and the optimal dose regimen, i.e. continuous vs. pulsed treatment, for maintenance of the positive effect.
- Validation of a single, global question in the evaluation of treatment effect.
- Examine the existential impact of symptom control in general in the palliative care population.

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# 8 APPENDIX

1. EORTC QLQ C-30 (study II)
2. Questionnaire in survey 1, study III
3. Questionnaire in survey 2, study III
4. ESAS (study IV)
5. Global evaluation question (study IV)