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CLINICAL TRIAL REPORT

General theory of inflammation: patient self-administration of hydrocortisone safely achieves superior control of hydrocortisone-responding disorders by matching dosage with symptom intensity

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Objective: To determine if patient self-administration of hydrocortisone will safely achieve superior symptom control for all hydrocortisone-responding disorders as it does for Addison's disease and rheumatoid arthritis.

Methods: Two thousand four hundred and twenty-eight participants with hydrocortisone-responding disorders were brought to a minimum symptom state using daily administered hydrocortisone tablets in a 24-week, open study. Thereafter, participants used 5-day, low-dose hydrocortisone regimens to quench subsequent disorder exacerbations (flares) to maintain the minimum symptom state. Stressors such as emotional traumas, infections, allergies, and injuries were minimized to reduce disorder intensity, hydrocortisone consumption, and participant discomfort.

Results: Two thousand fifteen participants, 601 with fibromyalgia, 579 with osteoarthritis, 246 with rheumatoid arthritis, 226 with undifferentiated arthritis, 75 with back pain, 51 with Parkinson's disease, 44 with polymyalgia rheumatica, 25 with neuropathy, 25 with chronic fatigue syndrome, 25 with dementia, 21 with migraine headache, 19 with multiple sclerosis, and 78 with other disorders completed the 24-week study to achieve a composite average symptom improvement of 76% with equal response rates. The participants averaged ingesting 12 mg of hydrocortisone per day. No significant adverse reactions were observed.

Conclusions: Patient self-administration of hydrocortisone safely achieves superior symptom control for 38 hydrocortisone-responding disorders at equal rates and symptom improvements to confirm and amplify an earlier double-blind study finding on rheumatoid arthritis. These results are consistent with the body having an inflammation control system and chronic inflammation being a disorder unto itself with differing symptoms sets dependent on its location.

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Keywords: general theory of inflammation, chronic inflammation, inflammation control system, pain, osteoarthritis, fibromyalgia

Introduction

Patient self-administration of corticosteroids, wherein dosage is matched with symptom intensity, has proven effective to control the symptom variability of Addison's disease safely.

Later, patient self-administration of prednisone was proven effective to control the symptom variability of rheumatoid arthritis safely. In a double-blind trial, superior to standard-of-care treatment effectiveness was achieved with no significant adverse reactions.[1]

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A hypothesis has been proposed that hydrocortisone-responding disorders arise from a defect in an inflammation control system. The latter was defined as a minor modification in the operation of the hypthalamic–pituitary–adrenal (HPA) axis.[2] When the defect occurs, short-term, beneficial inflammation evolves unhindered into long-term, destructive inflammation. The hypothesis assumes the common denominator of hydrocortisone-responding disorders is chronic inflammation and the differing symptom sets observed are consequences of chronic inflammation existing in various locations. If this hypothesis were true, all hydrocortisone-responding disorders should respond with equal rates and efficacies to one effective chronic inflammation treatment.

This 24-week study is to determine if patient self-administration of hydrocortisone performs with equal rates and equal efficacies for all hydrocortisone-responding disorders safely.

Methods

The method of this study is that of the preceding double-blind study on rheumatoid arthritis[1] modified by adding stress management, increasing the induction period length and relating hydrocortisone dosages to body mass.

Two thousand four hundred and twenty-eight participants with hydrocortisone-responding disorders were continuously enrolled. Of the 2,015 participants completing the study, 1,635 were females of average age 66 and 380 were males of average age 67. The age range was 18–97. Disqualifying conditions were congestive heart failure, stomach ulceration, and unstable diabetes. Participants who were using a daily corticosteroid regimen prior to the study were maintained using the daily physiological dosage of that corticosteroid in addition to the study protocol.

The study protocol was: week 1) qualifying medical examination, food sensitivity laboratory test, daily monitoring of symptom intensities for establishing baseline; weeks 2-4) daily ingesting hydrocortisone tablets to achieve a minimum symptom state, monitoring symptom intensities for daily change from baseline and hydrocortisone response to dosage, laboratory-determined sensitive foods eliminated from diets, medical examination 2 at the end of week 4; and weeks 5-24) patient education, participant self-administration of hydrocortisone, monitoring of symptom intensities for daily change from baseline, laboratory-determined sensitive foods eliminated from diets, medical examination 3 at the end of week 24.

Hydrocortisone was administered daily for 3 weeks to achieve a minimum symptom state. This induction period (shower) consisted of ingesting hydrocortisone tablets at one time daily at 7–9 am according to the schedule given in Table 1.

Those who failed to attain significant symptom improvement during the induction period were disqualified from the study.

For those who responded to hydrocortisone administration but failed to achieve the objective 75% symptom improvement, the induction period was repeated with the daily addition of adult dosage doxycycline to optimize symptom control. The latter was continued for 30 days beyond the end of the repeated induction period.

To maintain the minimum symptom state after the induction period, participants were taught for what reasons and when to ingest 5-day hydrocortisone regimens (boosters) for quenching disorder flares.

The 5-day flare-quenching regimen consisted of ingesting hydrocortisone tablets during day 1 immediately upon flare recognition and during days 2–5 at 7–9 am. The booster hydrocortisone dosages are given in Table 2.

Stress management was necessary for some participants to achieve and maintain a satisfactory minimum symptom state. For this study, stressors were defined to be emotional traumas, allergies, infections, and injuries.

Education principles were: restrict total hydrocortisone available to within its safe use limit per month;[4] limit booster use to four times a month; implement boosters at the early onset of a flare; ingest hydrocortisone between 7 and 9 am except for the first day dose of the booster that is to be taken immediately upon flare recognition; take the daily hydrocortisone dosage at one time and do not spread it out throughout the day; minimize emotional traumas; restrict each participant's diet to exclude participant-specific, laboratory-determined sensitive foods; and minimize strenuous work and exercise of inflamed areas.

Table 1 Hydrocortisone dosages of the induction period

Body mass	Week 1	Week 2	Week 3
>68 kg	60 mg/day	40 mg/day	20 mg/day
68 to 114 kg	80	60	40
>114 kg	100	80	60

Table 2 Hydrocortisone of the 5-day flare-quenching booster

Body mass	Day 1	Day 2	Day 3	Day 4	Day 5
<68 kg	30 mg	20 mg	20 mg	20 mg	10 mg
150 to 250 kg	40	30	20	20	10
>114 kg	50	40	30	20	10

If a participant experienced significant symptom enhancement during days in which no hydrocortisone was ingested, that is, hydrocortisone holidays, an am/pm blood hydrocortisone test was performed. If the homeostasis hydrocortisone blood levels were significantly below average, daily hydrocortisone supplementation was administered in addition to patient self-administration of hydrocortisone of the study.

Short-term hydrocortisone overdosage warnings were the appearance of a moon face and a hyper state. When observed, patient compliance was reviewed and appropriate action taken.

Eighty-one physicians from 20 states performed the required medical examinations, provided the diagnoses, prescribed the medicine, and monitored participant progress.

Outcome was determined by having participants rate each symptom intensity that characterizes the disorder being treated at the same time daily using a defined 0–10 scale.[1] The assigned numbers for each symptom were added to give the total score daily. The total score was plotted vs time. A second graph line of hydrocortisone ingested vs time was superimposed upon the total score graph to evaluate dose-response relationship.

Results

Two thousand four hundred and twenty-eight participants were enrolled into the study. Four hundred and thirteen participants were discontinued due to unsatisfactory outcome. Two thousand fifteen participants completed the study. For the participants who completed the study, the average symptom improvement was 76%, see Table 3. No significant adverse reactions were reported. Participants averaged ingesting 12 mg hydrocortisone per day. For the disorders where n is >50 excluding undifferentiated arthritis, the mean average symptom improvement from baseline was 73% with a sigma of 6%.

Participants where n>245 diagnosed with fibromyalgia, osteoarthritis and rheumatoid arthritis who completed the study achieved an overall 77% average symptom improvement. The 601 participants with fibromyalgia averaged 77% symptom improvement; the 579 with osteoarthritis, 77%; and the 246 with rheumatoid arthritis, 78%.

The response rate to treatment was identical for all disorders.

Table 3 The average symptom improvement (efficacy) of participants arranged by decreasing number of participants (n)

Disorder	n	Efficacy, %
Fibromyalgia	601	77
Osteoarthritis	579	77
Rheumatoid arthritis	246	78
Arthritis, undifferentiated	226	76
Back pain	75	70
Parkinson's disease	51	62
Polymyalgia rheumatica	44	80
Chronic fatigue syndrome	25	78
Neuropathy	25	74
Dementia, Parkinson's disease	22	67
Headache, migraine	21	86
Multiple sclerosis	19	67
Asthma	11	68
Systemic lupus erythematosis	9	60
Bursitis	6	79
Irritable bowel syndrome	6	71
Psoriatic arthritis	6	63
Crohn's disease	5	92
Carpal tunnel syndrome	5	86
Spinal stenosis	4	78
Headache	3	84
Nervous system symptoms	3	63
Ankylosing spondylitis	3	60
Urinary tract inflammation	3	58
Post traumatic stress disorder	2	71
Acid reflux	1	100
Bowel inflammation	1	100
Scoliosis	1	100
Dementia, rheumatoid arthritis	1	92
Dementia	1	86
Eye inflammation	1	85
Eczema	1	77
Myofacial syndrome	1	73
Meniere's disease	1	69
Sjogren's syndrome	1	69
Dementia, multiple sclerosis	1	67
Restless leg syndrome	1	47

Discussion

General theory of inflammation

The inflammation control system of the body[2] terminates acute inflammation at its due time. In normal operation, an inflammation-initiating event causes acute inflammation to occur which in turn activates the HPA axis to make an approximate 12-fold, 4 hrs, hydrocortisone surge concentration in the blood (surge). This surge then terminates the very inflammation that activated the HPA axis in the first place much as an electrical switch turns off a light.

As the surge weakens with age, injury, and heredity, acute inflammation evolves into chronic inflammation proportionately while being manifested as bad days (flares) for patients.

Resolution of chronic inflammation

The solution is teaching patients to ingest hydrocortisone tablets on the bad days and not on the good ones to manually restore the pulse to its effective concentration in the blood. In this way, only the missing hydrocortisone is replaced thereby avoiding overdosing adverse effects. Patient self-administration is mandated since only patients experience the bad days.

Flares should be terminated during their earliest stages to minimize hydrocortisone consumption and patient discomfort since the amount of hydrocortisone required to terminate inflammation is related to inflammation intensity.[3]

Patients must be brought to a minimum symptom state before employing patient self-administration. If they were not to do this, they would be unable to judge flare occurrences from background symptom intensities satisfactorily.

Patients are expected to experience 3.3 flares each month.[1] The hydrocortisone amount in each booster is 25% of the monthly safe use limit.[4] With the restriction of using a maximum of 4 boosters per month, this limits hydrocortisone use to its safe use limit. If patients were to use 3.3 boosters per month, there would be a comfortable 17.5% margin of error.

Adrenal suppression is avoided by incorporating hydrocortisone holidays. Participants using the maximum 4 boosters per month would have 8–11 hydrocortisone holidays irregularly interspersed throughout a month during which natural production of hydrocortisone by the adrenal glands is exercised.

Participants incapable of judging early stage flares used a simpler, yet effective plan, whereby the 5-day booster was ingested during the week days thereby leaving Saturdays and Sundays as hydrocortisone holidays.

Inflammation-initiating and enhancing events, such as emotional traumas, allergies,[5] infections,[6,7] and injuries, must be minimized for optimum success. In implementation, participants excluded laboratory-determined allergenic foods from their diets, took a broad-spectrum antibiotic, and avoided strenuous exercise of inflamed tissues. Slow hydrocortisone-responding participants ingested a broad-spectrum antibiotic during the repeated induction period and for 1 month thereafter to suppress occult infections.

The 3-week induction period left 21 weeks of this 24-week study to learn if patients were capable of maintaining the minimum symptom state using patient self-administration of hydrocortisone. Patients were expected to average 17.3 flares during the 21 weeks at the rate of 3.3 flares per month. This number of flares was judged adequate for judging patient capability.

Educators contacted the participants weekly to monitor compliance, total score improvement from baseline, adverse effect occurrence, and train and retrain as needed. Educators contacted the attending physicians monthly to solicit adverse event occurrence data and provide them with participant compliance, hydrocortisone consumption, and symptom improvement from baseline data.

Outcome measurement

The monitoring process was designed to encourage patient compliance, allow computer-assisted data analyses, and facilitate communication among participants, physicians, and educators. An average of sequential day measurements avoided 1-day measurement risk error. Daily outcome monitoring enabled educators to learn of participant quantitative progress in the less stressful environment of their homes without travel, illustrate the consequences of applying principles taught, evaluate compliance, assist participants to identify the early stage of flares, and compile study statistics.

This digital monitoring system gave participants a numerical value as to when to treat a flare. It removed much of the guesswork out of the patient self-administration of hydrocortisone and gave participants confidence to initiate treatment quickly with less hydrocortisone.

The outcome measurement method was validated during the preceding double-blind clinical trial[1] to be equivalent to physician global assessment and number of tender joints, the most accurate disease measurements of rheumatoid arthritis intensity.

The ultimate test

Self-administration if hydrocortisone symptom improvements observed during this study approximately doubled that of standard treatments. Patient self-administration of hydrocortisone achieved an average symptom improvement of 76% for the 38 hydrocortisone-responding disorders of the study with a narrow sigma value of 6% for those disorders where n>50, see Table 3.

The 601 participants of this study with fibromyalgia averaged 77% symptom improvement whereas fibromyalgia patients treated by milnacipran achieved 35–42% symptom improvement; by pregabalin, 26–31%; and by duloxetine, 17–30%.

The 579 with osteoarthritis of this study averaged 77% symptom improvement whereas osteoarthritis patients

treated by celecoxib achieved an estimated 25% symptom improvement.

The 246 with rheumatoid arthritis of this study averaged 78% symptom improvement whereas rheumatoid arthritis patients treated by adalimumab achieved 41–61% symptom improvement; by etanercept, 8–51%; and by infliximab 23–47%.

The 51 with Parkinson's disease of this study averaged 62% symptom improvement whereas Parkinson's disease patients treated with levodopa achieved 7–29% symptom improvement. Parkinson's disease dementia improved by 67% whereas levodopa exhibited no effect on dementia.

The 19 with multiple sclerosis of this study averaged 67% symptom improvement whereas multiple sclerosis patients treated with glatiramer acetate achieved 16% symptom improvement.

No significant hydrocortisone adverse effects were observed. Participants averaged ingesting 12 mg hydrocortisone per day during self-administration. This consumption rate is less than the 15 mg hydrocortisone per day that gives rise to hydrocortisone adverse effects in the most sensitive adults.[4] The adverse effects were weight gain, hypertension, gastrointestinal symptoms, insomnia, muscle pain or spasms, and hyperglycemia as reported to occur during the preceding study employing an identical protocol.[1]

Salient features

Compatibility of the protocol of this study with other medicines is inherent. All medicines are designed to be compatible with hydrocortisone that is ever present in the blood.

The increased vasopermeability of inflammation[8] allows extra plasma and immune cells to enter inflaming tissues from the pressurized blood system to cause swelling and the immune response. The HPA axis hydrocortisone surge re-establishes normal vasopermeability to terminate inflammation.

Once the surge is weakened, the patients become overly sensitive to all inflammation-initiating and exacerbating events.

Patient self-administration of hydrocortisone features dosage flexibility. Pharmacological and physiological doses of hydrocortisone are mingled with hydrocortisone holidays to provide the needed flexibility to counteract the dynamic exacerbation and remission character of chronic inflammation.

The resistance of Parkinson's disease, multiple sclerosis, dementia, and fibromyalgia to other treatments and their positive responses to hormone hydrocortisone treatment can be attributed to the responsible chronic inflammation being located within the brain protected by the blood-brain barrier.

Patient self-administration of hydrocortisone eliminates most chronic pain by extinguishing chronic inflammation. The efficacies are similar to that of narcotic treatment but without addiction and mental disturbance. With the permission of the surgeon and anesthesiologist, one participant successfully used patient self-administration of hydrocortisone as the only anesthetic to recover from a knee replacement surgery.

The HPA axis has been reported dysfunctional in certain circumstances.[9–12] Reported consequences of the dysfunction were brain-immune interactions, disease susceptibility, allergies, inflammatory/autoimmune diseases, fibromyalgia, rheumatoid arthritis, post-traumatic stress syndrome, depression, burnout, chronic fatigue syndrome, inflammatory bowel disease, multiple sclerosis, attention deficit hyperactivity disorder, and alcoholism. These are consistent with the hydrocortisone treatment results for these disorders portrayed in Table 3.

Chronic inflammation is probably the first step on the pathway to Addison's disease. After the body production of the hydrocortisone pulse fails to produce the extra hydrocortisone required for the surge, the production of hydrocortisone will likely deteriorate further to not being able to maintain the normal homeostasis hydrocortisone concentration in the blood.

Patient self-administration of hydrocortisone is FDA-compliant for hydrocortisone use applied to corticosteroid-responding disorders.

Bone and joint destruction are reduced during low-dose administration of corticosteroids.[13]

Patients desire to take control of their disorder rather than let it control their lives. They honor physicians who will train and trust them to use hydrocortisone.

Conclusions

Patient self-administration of hydrocortisone safely achieves superior symptom control for 38 hydrocortisone-responding disorders at equal rates and efficacies. These results are consistent with the body having an inflammation control system and chronic inflammation being a disorder unto itself with differing symptoms sets dependent on its location.

Informed consent

All participants signed a written informed consent form. This study was performed as a research study planned by an appointed committee from within the University of North Dakota School of Medicine with the protocol and informed consent form preapproved by the Institutional Review Boards of the University of North Dakota, North Dakota State University, and the Dakota Medical Center.

Data Sharing

The computer deidentified participant data containing graphic progress reports with total symptom scores and daily hydrocortisone consumption vs time are in computer/electronic form and will be accessible from June l, 2019 to August 31, 2019. The data are located at 2579 Movil Bay Lane NE, Bemidji, MN 56601.

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Disclosure

The authors report no conflicts of interest in this work.

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