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In depth study of Adrenocorticosteroid Drugs: A milligram level determination

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Abstract: *The adrenocorticosteroids drugs are an important group of therapeutic compounds used for a variety of clinical purposes. It is estimated that annually at least 5 million patients in the United States receive adrenocortical steroids. In depth study of these drugs are important for various diseases. A well-founded appreciation for the pharmacological characteristics of these drugs provides the basis for the rational and safe use of this important group of drugs.*

Background*: Adrenocorticoids are synthesized in the cortex (shell) of adrenal glands. They are named as glucocorticoids (hydrocortisol, cortisone) arid mineralocortieoids (aldosterone) on the basis of their activity. Addison's disease, Cushing's disease and Conn's syndrome are pathologic conditions related to adrenal cortex and the hormones produced in them. Importance of adrenocorticoids is most dramatically observed in adrenalectomized animals. There is an increase of urea in blood, muscle weakness, decreased liver glycogen and decreased resistance to insulin, lowered resistance to trauma (cold, chemical shock) (glucocorticoid activity) and electrolyte disturbances (mineralocorticoid activity).*

Materials and Methods*: Aliquots containing 1-5 mg of the sample were taken in 100 ml stoppered conical flask followed by the addition of 5ml AHC (0.1 M) reagent, prepared in 0.5N HNO_3. The reaction mixture was shaken well and allowed to react for required reaction time at room temperature (25-30ºC). The unconsumed Ce(IV) was titrated against 0.025M FAS solution using two drops of ferroin indicator (0.001M). A blank experiment was also performed under identical conditions using all the reagents except the sample. The amount of AHC consumed for the sample was calculated with the difference in the titre values of ferrous ammonium sulphate solution for blank and actual experiments.*

Results*: The adrenocorticosteroids drugs are an important group of therapeutic compounds used for a variety of clinical purposes. It is estimated that annually at least 5 million patients in the United States receive adrenocortical steroids. In depth study of these drugs are important for various diseases. A well-founded appreciation for the pharmacological characteristics of these drugs provides the basis for the rational and safe use of this important group of drugs.*

Conclusion: *The adrenocorticosteroids drugs are an important group of therapeutic compounds used for a variety of clinical purposes. It is estimated that annually at least 5 million patients in the United States receive adrenocortical steroids. In depth study of these drugs are important for various diseases. A well-founded appreciation for the pharmacological characteristics of these drugs provides the basis for the rational and safe use of this important group of drugs.*

Key Word*: Milligram Level Determination, Adrenocorticosteroid Drugs*

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I. Introduction

Adrenocorticoids are synthesized in the cortex (shell) of adrenal glands. They are named as glucocorticoids (hydro cortisol, cortisone) arid mineralocorticoids (aldosterone) on the basis of their activity. Addison's disease, Cushing's disease and Conn's syndrome are pathologic conditions related to adrenal cortex and the hormones produced in them. Importance of adrenocorticoids is most dramatically observed in adrenalectomized animals. There is an increase of urea in blood, muscle weakness, decreased liver glycogen and decreased resistance to insulin, lowered resistance to trauma (cold, chemical shock) (glucocorticoid activity) and electrolyte disturbances (mineralocorticoid activity).

Mineralocorticoids control salt and water balance in the renal tubes. They cause retention of Na^+, Cl^+, and water and reduce levels of K^+ (increase its elimination). Glucocorticoids produce increased glucogenesis (formation of glucose from protein) and exert a lesser but not significant effect on salt and water balance. Glucocorticoids regulate biosynthesis and metabolism of carbohydrates, proteins and lipids. In addition, glucocorticoids are affecting the immune system and are used as anti-inflammatory agents.

Classical steroid hormone mechanism wherein cortisol (aldosterone) diffuses into the nucleus of cell, binds to its specific receptor, resulting in the transcription of specific Proteins. Hydrocortisone leads to

lipocortin, which is an inhibitor of phospholipase A2. This enzyme is involved in the mediation of inflammatory signal wherein it releases Prostaglandins, leukotrienes from cell membrane. By inhibiting phospholipase A2

lipocortin (and hence cortisol) behaves as an anti-inflammatory agent. Aldosterone in them leads to release dustmen-induced protein, which regulates Na'-K'-ATPase pump, thereby revaluating electrolyte balance. It is white to almost white, odorless, hygroscopic powder, Keely soluble in water, slightly soluble in ethanol, practically insoluble in chloroform, dichloromethane and ether. Betamethasone is a moderately potent glucocorticoid steroid with anti-inflammatory and immunosuppressive properties. Unlike other drugs with these effects, Betamethasone does not cause water retention, it is applied as a topical cream, ointment, foam, lotion or gel to treat itching (e.g., from eczema). Betamethasone sodium phosphate is sometimes prescribed as an intramuscular injection (IM.) for itching from various

ailments including allergic reactions to poison ivy and similar plants. The compound is available as a number of ester derivatives: Betamethasone dipropionate, sodium phosphate and valerate. Due to its anti-inflammatory and immunosuppressive properties, its analysis was done by many researchers. Tamvakopoulos, C.S., and co-workers reported analysis of Betamethasone in rat plasma using automated solid-phase extraction coupled with liquid, chromatography tandem mass spectrophotometry. Samtani, M.N., and co-workers, eprted Stabilization and HPLC analysis of Betamethasone sodium phosphate in plasma. Graham, R.E., and co-workers reported Analysis of Betamethasone and its organic esters in pharmaceutical products. Samtani, M.N., and co-workers reported Stability of Dexamethasone sodium phosphate in rat plasma. Arthur, K.E., and co-workers reported Analysis of Betamethasone, Dexamethasone and related compounds by liquid chromatography electrospray mass spectrometry. Rotmens K S., and co-workers reported effect of Betamethasone administration on fetal heart rate tracing: a blinded longitudinal study. Schepens, A., and co-workers reported a single course of prenatal Betamethasone in the rat alters postnatal brain cell proliferation but not apoptosis. Moss, T., and co-workers reported Pharmacokinetics of Betamethasone after maternal or fetal Mtramuscular administration. Samtani, M.N., and co-workers reported Betamethasone Pharmacokinetics after two prodrug formulations in sheep, implications for antenatal corticosteroid use. Van Indexing, B., and coworkers reported visual interpretation of the effect of maternal Betamethasone administration on the fetal heart rate pattern. Roghair, R.D., and co-workers reported late-gestation Betamethasone enhances coronary artery responsiveness to angiotensin II in fetal sheep.

II. Material and Methods

Aliquots containing 1-5 mg of the sample were taken in 100 mL stoppered conical flask and 5 mL of the $3x10^{-2}$ N PFC reagent, prepared in glacial acetic acid and 10 mL of 5N H_2SO_4 was added to it. The reaction mixture was shaken thoroughly and allowed to excel for required reaction time at room temperature (25-30°C). After the reaction is over 5mL of 10% potassium iodide was added to stand for one minute. The unconsumed PFC was determined iodometrically. A blank experiment was also run under identical conditions using all the reagents except the sample. The amount of PFC consumed for the sample was calculated with the difference in the titer values of sodium thiosulphate solution for blank and actual experiments. The recovery of the sample was calculated with the amount of PFC consumed for the sample. For every sample percentage error, coefficient of variation and standard deviation were calculated.

To evaluate the authenticity of the method recovery experiments were also carried out by standard drug addition method. For such experiments a known amount of the pure drug is taken and varying amounts of the pharmaceutical preparations of that compound are added and the total amount of the sample was find out with titration and calculations.

III. Result and Discussion

As described in the survey of literature, the PFC reagent has not been used for the estimation of adrenocorticosteroid drugs. Therefore, I described a simple method for the determination of following adrenocorticosteroid drugs, such as Betamethasone sodium phosphate, Dexamethasone sodium phosphate, Hydrocortisone sodium succinate, Prednisolone sodium succinate and Triamcinolone in pure form and in their pharmaceutical preparations such as Betnesol (Inj), Cortil (Tab), Decdon (Inj), Dexasone (Tab), Primacort (Inj), Wycort (Inj), Wysolone (Tab), Predone Fone (Syrup), Tricort (Inj) and Ledercort (Tab) have been studied.

For testing the quantitative validity of reaction, Betamethasone sodium phosphate was taken as test sample. Different amount of sample (1-5mg) was allowed to react with varying concentrations of pyridinium fluorochromate (PFC) at room temperature (25-30°C) for different intervals of time. The unconsumed PFC was back titrated iodometrically. A blank experiment was also run under identical conditions using all the elements except the sample. The difference in the titre values of sodium thiosulphate consumed for blank and actual experiments were used to calculate the amount of the simple present in a particular experiment. The stoichiometry of the reaction was established for each sample and a possible course of reaction was also

suggested. On the basis of the reaction conditions developed for Betamethasone sodium phosphate, the determination of other compounds in the pure form and in their pharmaceutical preparations were done.

In order to develop suitable reaction condition for the determination of above Adrenocorticosteroids with PFC agent, the effect of different variables was studied.

Keeping the amount of Betamethasone sodium phosphate and concentration of PFC reagent as constant, the reaction time was varied from 1-25 minutes. Aliquots containing 5 mg of Betamethasone sodium phosphate were taken in 100 mL stoppered conical flask and 5 mL PFC reagent prepared in glacial acetic acid was added to it. Now the reaction mixture was shaken well and allowed to react at room temperature for 1-25 minutes. After the reaction was over the unconsumed PFC was determined by kick titrating the reaction mixture against standardized sodium thiosulphate (0.01 N) solution using potassium iodide and starch as indicator. The percentage recovery of the sample does not change after a proper reaction time. Therefore, estimation was done on the same reaction time. Similar experiments were performed with other samples as well. It was observed that all the Admnocorticostemids require same reaction time (10 min) to complete the reaction except Triamcinolone which takes 15 minutes to complete the reaction.

Keeping the reaction time, amount of Betamethasone sodium phosphate and concentration of PFC (3 x 10^{-2}N) constant, the concentration of sulphuric acid was varied from (1-7 N) and the results were noted. Result given in the table shows that the best recovery of the samples was obtained at 5N concentration of sulphuric acid. 'I o ascertain the exact amount of SN sulphuric acid needed for the reaction, some deviations, were done in the volume, accurate results were obtained at 10 mL of the acid. Similar results were obtained in case of other Adrenocorticosteroids. Thus, for completing the reaction and getting accurate results 10 mL of 5N sulphuric acid was recommended or the experiment.

Keeping the reaction time, amount of Betamethasone sodium phosphate and concentration of sulphuric acid as constant, the effect of varying concentration of PFC was studied. 5mg of the sample was allowed to react with 5mL of varying concentration (0.01-0.1 N) of PFC. The unconsumed PFC was back titrated iodometrically and the recovery of the sample was calculated. It was found that the best results were obtained at 0.03N concentration of PFC. The concentration of reagent less than 0.03 N gives higher percentage error and low recovery. The reason for this is due to incomplete reaction of the reagent with the sample. The higher concentration than 0.03 N gives no significant advantage in percentage recovery. Therefore, the higher concentration of the reagent was avoided. Variation in the volume of $3x10^{-2}$ N PFC was also studied (Table- 11). It was observed that 5mL of $3x10^{-2}$ N PFC gives accurate result. Thus, for completing the reaction, getting accurate results and also avoiding the wastage of the reagent, 5 mL of $3x10^{-2}$ N PFC was recommended for the experiment. In the similar way the studies of different variables were also done with Betamethasone sodium phosphate.

Keeping all other conditions constant, the reaction temperature was varied from 5°C onwards and the recovery of Betamethasone sodium phosphate was calculated. It was observed that the reaction was completed within 15 minutes at room temperature (25-30°C). The heating of the reaction mixture gives inaccurate results. It may be due to decomposition of reagent at high temperature, Although the reaction is completed at room temperature, but the experiment was also carried out at lower temperature up to 5°C. In this case also El decrease in recovery of the sample was noted. It shows that the reagent does not react properly at lower temperature. Thus, for the estimation of Betamethasone sodium Phosphate a reaction temperature of 25-30°C was maintained. Such experiments were carried out with all other samples and the recovery was noted. It was observed that the reaction at room temperature was suitable for all other Adrenocorticosteroids e.g. Dexamethasone sodium phosphate, Hydrocortisone sodium succinate, Prednisolone sodium succinate and Triamcinolone.

IV. Conclusion

The adrenocorticosteroids drugs are an important group of therapeutic compounds used for a variety of clinical purposes. It is estimated that annually at least 5 million patients in the United States receive adrenocortical steroids. In depth study of these drugs are important for various diseases. A well-founded appreciation for the pharmacological characteristics of these drugs provides the basis for the rational and safe use of this important group of drugs.

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