BASIS OF MEDICAL TREATMENT MODALITIES AND THEIR CLINICAL IMPLICATIONS FOR PROSTATIC DISORDERS.

Essay

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By

Abdel Nasser Mohamed Abdel Halim

M.B , B. Ch.

Supervisors

Prof. Dr. Farouk Moustafa Fahmy

Prof. of Urology

Ain Shams University.

Dr. Ismail Othman Abdel-Hafiz

Lecturer in Urology.

Ain shams University

Faculty of Medicine
Ain Shams University.
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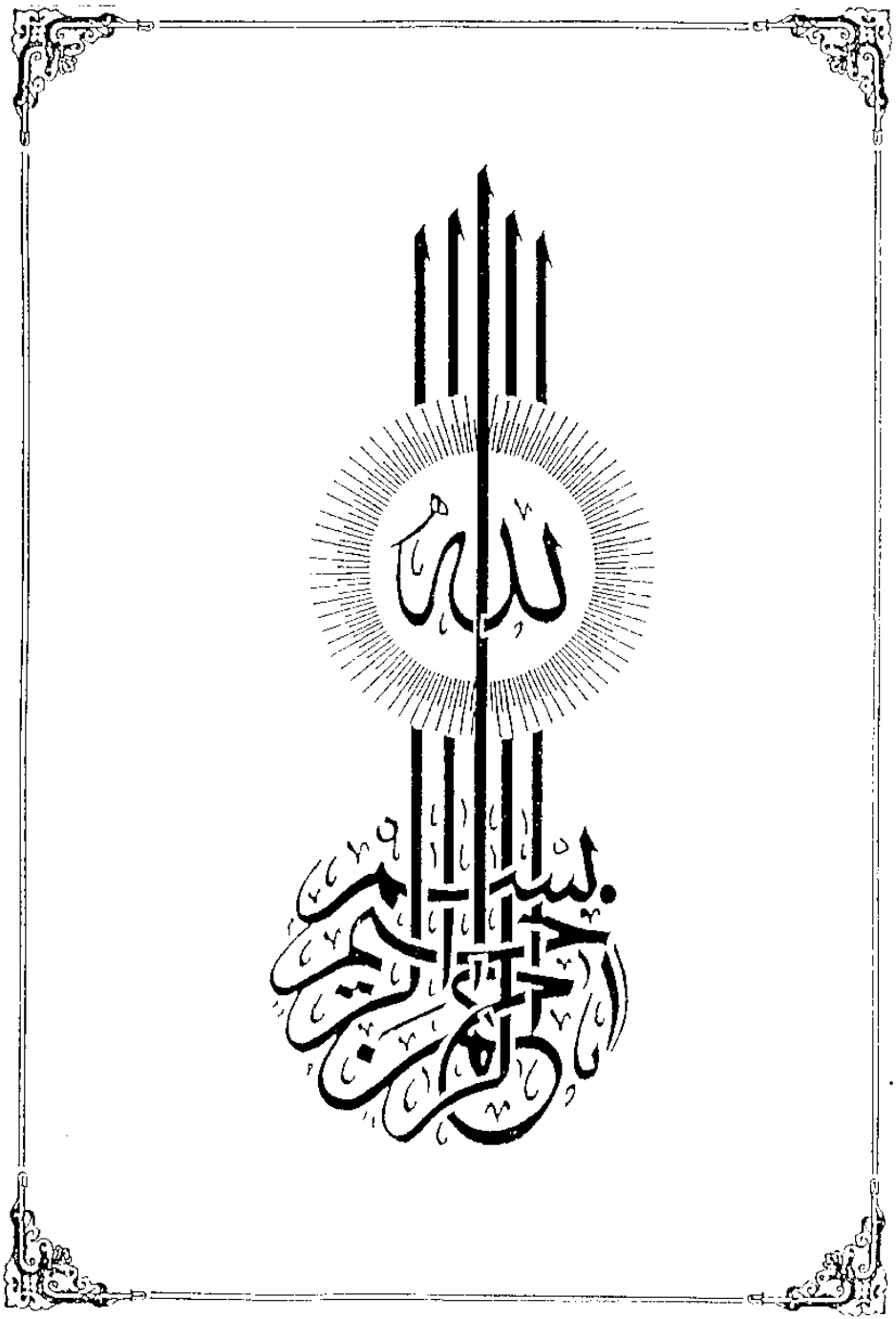

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INTRODUCTION

Of the various prostatic diseases, there are 3 of importance from the thereapeutic point of view as they represent much difficulty in their management. These diseases are chronic bacterial prostatitis, benign prostatic hyperplasia and carcinoma of the prostate.

Different treatment modalities have been proposed for these diseases.

In this study the medical treatment modality will be dealt with. The basis upon which drugs can be suggested for these conditions are given.

For the prolblem of chronic bacterial prostatitis, review of the factors governing the diffusion of antimicrobials from plasma into the focus of infection and the most applicable agents for this disease are given.

On dealing with the problems of benign prostatic hyperplasia and carcinoma of the prostate an initial insight into the factors controlling normal and abnormal prostatic growth is necessary.

Finding a medical treatment alternative for benign

prostatic hyper-plasia is still a hope, and a trial for this is evaluated carcinoma of the prostate accounts for the third leading cause of death from all malignancies in men and at the time such cases are diagnosed, about 75 per cent of patients will be found to have metastatic disease.

These patients therefore, are candidates for systemic medical treatment.

For convenience the medical treatment modality for advanced carcinoma of the prostate is divided into three lines : Endocrine therapy, cytotoxic chemotherapy and combined hormone-cytotoxic agents. These lines will be dealt with as regards the mode of action of individual drugs and their clinical efficacy in carcinoma of the prostate.

Three items recently introduced into the field of advanced carcinoma of the prostate. These are : Gonadotrophin-releasing hormone analogues, Estramustine phosphate and androgen receptors assays. A cover for these subjects is given in this study.

Finally we hope that this study can provide the

reader with simple, satisfactory and useful insight into the medical treatment modalities for prostatic disorders.

BACTERIAL PROSTATITIS

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Bacterial infections of the prostate gland causing acute and chronic bacterial prostatitis are commonly met with in urological practice.

The pathogens responsible for bacterial prostatitis are similar in type and prevealance to those causing urinary tract infections (Stamey, 1980). Strains of Eschericia coli clearly predominates although infections due to species of proteus, Klebsiella, Enterobacter, Pseudomanas, Serratia and other less common gram-negative organisms are found occasionally. Although most prostatic infections are caused by a single pathogen, at times, mixed infections involving two or more types of bacteria are involved. Most agree that gram-positive Enterococci can cause chronic bacterial prostatitis and its associated recurrent bacteruria. Whether other gram-positive bacteria such as coagulase-negative Staphylococci, Streptococci, Micrococci and Diphtheroids are important pathogeus in prostatitis is questionable.

In bacterial infections of the prostate two items are of importance :-

1- Bacteria present in prostatic acinar fluid are separated from drugs present in the plasma by a layer of epithelial cells (prostatic barrier), so that for any particular antimicrobial to be effective

against such pathogeus it has first to cross the prostatic barrier.

2- In cases of acute bacterial prostatitis, because the infection is in the stroma as well as in the prostatic acini and the barrier for penetration by antimicrobials is breached by the acute inflammatory process, there will be no difficulty in the management of such condition provided the proper antimicrobial is used in optimal doses. However, in chronic bacterial prostatitis there is evidence of cryptic colonization of the prostatic acini by the pathogens and hence the blood/prostatic fluid barrier assumes importance. (Stamey, 1968)

* BASIS OF ANTIMICROBIAL THERAPY IN CHRONIC BACTERIAL PROSTATITIS :-

As mentioned before for any drug to pass from the blood into the prostatic fluid it has first to cross the prostatic barrier. The prostatic barrier is an epithelial membrane, the later being a biological membrane so it is lipid in nature. The factors that affect diffusion of antimicrobial agents through this barrier are :

[1] Lipid Solubility :-

For a drug to penetrate an epithelial membrane readily it should be in a lipid soluble state if it has a molecular

radius more than 4 Å. What determines the lipid solubility of a drug is the presence of lipophilic (hydrophobic) or non-polar groups in the structure of the drug molecule, for example the alkyl groups (Ch_3, CH_3 (CH_2)..etc) are non-polar and increase the lipid solubility of a compound in which they are found. Structural elements that allow for hydrogen bonding with water decrease the lipophilicity of a molecule. Polarity is high for ionized molecules, including the ionized form of a dissociable molecule. Many functional groups (e.g. COOH, OH, NH_2 .. etc), thus increase the hydrophilic properties of a drug.

It follows then that the prostatic barrier, being a biological membrane is only permeable to the unionized form of a drug molecule and is relatively impermeable to the ionized form.

[2] PH and PKa :-

As mentioned before, lipid solubility of a drug depends mainly on the degree of ionization so that the amount of the drug present in a lipid soluble state will correspond to the amount of unionized part of this drug.

The degree of ionization of a dissociable drug will in turn depend upon its PKa (S) and the ambient PH.

The PKa of a drug is its acidic dissociation constant and determines the degree of dissociation at any particular Ph. An acid drug becomes increasingly ionized, and thus less lipid soluble, at higher PH values, while at lower PH values a greater proportion is unionized. The reverse is true for basic drugs. When 50 per cent of the drug is ionized, the PH is at the PKa of the drug.

Relatively small shifts in PH at or near the PKa of a drug will give disproportionally large changes in the relative proportions of the ionized or unionized species.

In the general tissues in the body (Blood, Extracellular fluid, Cells ... etc), there is slight,if any, difference in PH (7.4) and a drug will be in the same degree of ionization wherever it is. This is not true for secretions, however, and the prostatic fluid of humans under normal conditions has a PH of about 6.6. Thus it is clear that there is a difference in PH on either side of the prostatic barrier, being 7.4 on the plasma side and 6.6 on the secretory side. Such a difference may have profound consequences on the relative concentrations of drugs on either side of this lipid membrane. For example, if a drug which is a weak base passes from the plasma into a more acidic environment such as the prostatic fluid,it will become more highly ionized,

the degree of alteration of ionization depends on its Pka relative to the actual PHs. Since only the lipid soluble, unionized portion of the drug is able to penetrate readily the membrane, the increasing ionization of this basic drug on the secretory side (having a lower PH) of the prostatic membrane will lead to a "trapping" of the drug on this side, and at equilibrium there will be an increase in its total concentration at the lower PH. For an acidic drug the reverse will occur and the ion trapping phenomenon will occur on the more alkaline side that is the plasma side and the drug will never concentrate in the prostatic fluid.

On the basis of these considerations it is possible to state that "For an antibacterial substance to be optimally concentrated in the prostatic fluid, it should be basic with a PKa of at least 7.4 . An antibacterial acid can never achieve a concentration in the prostatic fluid exceeding that in the plasma so long as the PH of prostatic fluid is acidic relative to that of plasma. However, the foregoing description applies only for normal men without previous prostatic infection and according to most investigators, the PH of prostatic fluid in these conditions is 6.6 (Blacklock, 1974).

This is not true in cases of chronic bacterial prostatitis in which the prostatic acinar fluid becomes alkaline, about 8.1.

(White, 1975 and Pfau et al., 1978). Such a difference in the PH of prostatic fluid in normal and diseased prostates is of utmost importance as it explains the failure of some basic antimicrobials to concentrate in the prostatic fluid.

[3] Plasma Protein Binding :-

The blood plasma contains proteins to which antimicrobials bind to some extent. The extent of protein binding varies with different drugs. Thus protein binding can be as high as those of Fusidic acid (97%) and Cloxacillin (95%) and be as low as that of gentamycin (less than 10%).

As these binding proteins are only confined to the blood plasma, these bounded fraction of drugs are not available for diffusion into the extracellular fluid, and hence accross the prostatic barrier. Therefore the only available fraction for diffusion accross the lipid membrane is that non-protein bound fraction of drug.

The protein concentration in the prostatic fluid is low, and therefore, most drugs in it are vertually completely unbound. It is apparent that binding to plasma proteins will limit the amount of drug available for diffusion into the prostatic fluid.

* EXPERIMENTAL STUDY OF ANTIMICROBIAL CONCENTRATIONS IN THE PROSTATIC FLUID :-

The use of an animal model to study the secretion of different antimicrobials into the prostatic fluid is easy to perform since the anatomy can be modified in the dog so as to avoid urine contamination of prostatic fluid samples. Isolation of the prostatic outflow can be achieved by diverting the urine by means of canulated ureterostomies or cystostomy and ligating tightly the bladder neck above the prostate, sometimes with division. Under these circumstances The animal can remain in good health for a long time Using this animal model it is possible to measure accurately the plasma levels of the different antimicrobials with their corresponding concentrations in the prostatic fluid. See the table.

As observed in the table, only the basic macrolide drugs erythromycin and oleandomycin are found the the prostatic fluid in significant concentrations. The explanation for this lies in the physico-chemical characteristics of these drugs.

The results concerning diffusion of sulfonamides into the prostatic fluid (PF) deserves a special mention since a clear relationship between the PKa and the PF/plasma concentrations of the individual sulfonamides has been shown.