REPRODUCTIVE MEDICINE: MEDICAL THERAPY

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PREFACE

The First International Symposium on Reproductive Medicine was held four years ago in San Juan, Puerto Rico. Its purpose was to integrate the different areas of Reproductive Medicine by bringing together specialists in the various disciplines dealing with both basic and clinical aspects of reproductive sciences. The Symposium was focused on pathophysiology and diagnosis as well as the socio-economic impact of reproductive system disorders and on the current status of training in Reproductive Medicine.

The Second International Symposium on Reproductive Medicine is focused on non-surgical therapy of reproductive system disorders and is dedicated primarily to clinical issues. Because of the rapid development of new therapeutic modalities during the past several years, e.g., Metrodin ("pure" human FSH), Lupron (GnRH analogue), widespread ovulation induction practices in the OB/Gyn community, a Reproductive Medicine Symposium addressing therapy was felt to be both timely and appropriate. The program committee made an effort to delineate the most commonly seen diagnostic categories and to provide an in-depth discussion by experts in each of the diagnostic areas. It is the hope of the organizers that the publication resulting from the deliberations at the Symposium will be of practical benefit to physicians treating reproductive system disorders.

We wish to express our gratitude to Ente Fiuggi without its assistance this symposium and resultant publication would not be possible and to the contributors who provided in a timely fashion excellent manuscripts.

The Editors

CONTENTS

THERAPY OF TESTICULAR DYSFUNCTION

THERAPY OF INFERTILITY

THERAPY OF MENOPAUSE

Reproductive medicine: medical therapy
G. Frajese et al., editors.

Clinical pharmacology of oestrogens and gestagens in post-menopausal women

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Abstract

Age-related changes in pharmacokinetics are briefly reviewed with possible relevance to the sex steroids. Little direct evidence is available for the steroids but it seems likely that the main effects result from the increase in volume of distribution for the lipid-soluble steroids due to the increase with age of the proportion of body fat and from enzyme induction in the liver on long-term therapy. These changes are probably of minor importance in most subjects, especially in comparison with the wide inter-subject variability in steroid metabolism. For many steroids, particularly ethynyloestradiol and norethisterone, a considerable first-pass effect occurs. The similarity of the inter-relationships between the administered oestrogens and their metabolites is described. Administered oestrogens are rapidly converted to their sulphate conjugates which are the major circulating form of the oestrogen and may determine their rates of metabolism. Of the three gestagens mainly used in hormone replacement therapy, only the pharmacokinetics of norethisterone, but not those of levonorgestrel or medroxyprogesterone acetate, have been studied in detail and little information is available regarding the steady-state concentrations of these steroids.

Whether the pharmacodynamic response to drugs changes with age is controversial and there is no information regarding the sex steroids. Information regarding the comparative potency of either the gestagens or oestrogens is meagre. Some of the deficiencies encountered are described and the problem is complicated by the interaction between the oestrogen and the gestagen. The type and degree of interaction cannot be extrapolated from one response to another, even when these responses are closely related, and this is illustrated by reference to changes in the serum concentrations of sex-hormone binding globulin and caeruloplasmin. The interaction depends not only on the relative doses of oestrogen and gestagen, but also on the structure of the gestagen.

Introduction

There are three reasons why the clinical pharmacology of oestrogens and gestagens may differ in the postmenopausal woman compared to the premenopausal one. Firstly, the physiological effects of aging; the physiological and clinical biochemistry of the older subject show considerable changes from those of younger subjects and although the differences are not marked over the period from the late premenopause to the immediate postmenopause, they do become increasingly important with advancing age. Secondly, the cessation of ovulation at the menopause and the marked decline in ovarian hormone secretion associated with a large increase in pituitary gonadotrophin production-changes which to a great extent are counteracted by the use of hormone replacement therapy. Thirdly the increasing incidence with age of pathology and/or drug treatment, whether the latter is prescribed or 'over-the-counter'. The older subject is likely to be using a number of drugs which will alter physiological processes and may interfere in the action of the oestrogens and gestagens. The effects of aging are complex and further complicated by the effects of disease and multiple drug use. The nutritional status of the older subject may also be inferior to that of the younger one and this may affect the clinical pharmacology of the oestrogens and gestagens. Many of these effects may have only a minor impact in the short-term but become very significant in the long-term.

Clinical pharmacology encompasses two aspects; clinical pharmacokinetics and pharmacodynamics. The former is concerned with the fate of the drug after administration – absorption, distribution, blood and tissue concentrations, metabolism and elimination – and ideally seeks to relate these processes to the drug's biological activity and side-effects. Pharmacodynamics assesses the responses of the tissues to the drugs presented to them and how these responses may be modified under changing conditions. The intensity and duration of drug effects depend on both pharmacokinetics, which will determine the concentration and duration of the active moiety of the drug at the target organ, and pharmacodynamics, determined by the sensitivity and the magnitude of the response of the target organ.

General pharmacokinetic considerations in relation to oestrogens and gestagens

Age-related changes in drug absorption undoubtedly occur; decreases in splanchnic blood flow and a decrease in mucosal surface area would both tend to impair absorption but as far as the steroids are concerned the effects seem to be minor. In most subjects the steroids are rapidly and efficiently absorbed

after oral administration, mainly in the upper small intestine, with the peak concentration in blood usually occurring within 2 hours. Small decrements in intestinal function as a result of age would probably have little effect. Two factors are important, however, in the rate and extent of absorption: one is the pharmaceutical formulation of the steroid and the other the rate of intestinal transit. Thus vomiting or excessively rapid transit through the intestine as a result of diarrhoea or use of laxatives result in deficient absorption. Other drugs may also affect gastro-intestinal motility. An interesting aspect of the absorption of steroids such as ethynyloestradiol which undergo sulphation in the gastro-intestinal tract is that their absorption may be increased by concomitant administration of other compounds, for example paracetamol or Vitamin C, which are also sulphated. Oral administration of antibiotics may, by affecting the intestinal bacteria, interfere with the enterohepatic circulation of the steroids. For some steroids, for example ethynyloestradiol and norethisterone, the first-pass effect (metabolism in the intestinal wall and liver) leads to a considerable (40%–60%) reduction in their bioavailability.

In blood only a small proportion (less than 5%) of the steroid circulates in the unbound state and in most tissues it is this fraction which exerts the biological activity. Considerable binding to albumin occurs and for some gestagens, for example norethisterone and levonorgestrel, binding to sex hormone binding globulin (SHBG) is important so that a complex dynamic equilibrium may exist between the three forms of the circulating steroids. The binding to albumin is relatively weak but that to SHBG is much stronger. The dynamics of the binding, particularly to SHBG, is complicated by the constantly changing concentrations of the steroids in blood after intermittent oral administration and changes in serum SHBG concentrations resulting from administration of the steroids. Serum SHBG concentrations may be influenced by other drugs and in some pathological conditions. There is little change in SHBG with age; there is a negative correlation with body size and this may account for the tendency of SHBG levels to be slightly lower in postmenopausal women.[1] Serum albumin concentrations decrease with advancing age and this is sufficient to reduce the binding of many drugs despite the high binding capacity of albumin; however, for the sex steroids, which are given in very small doses, the effect is likely to be insignificant. The low binding affinity of the steroids for albumin also means that small changes in serum albumin concentrations do not affect the distribution of the steroids between the different fractions. Other sex steroid-binding proteins have been claimed to be present in blood but their influence on the distribution of the sex steroids would appear to be insignificant. Methods for determining the percentage of steroid in the circulation in the unbound state are unsatisfactory and the results which have been published must be accepted only as approximations. The estimation of the sex steroids in saliva has been suggested as a simple means

of determining the unbound fraction since it is only this fraction which diffuses from blood into saliva. However, although there is a good correlation between the concentration of unbound fraction in blood and the concentration in saliva when groups of subjects are considered, the correlation is less good in individual subjects.

Body weight tends to decrease with age with associated decreases in total body water, intracellular water and lean body mass. For water soluble drugs such as the steroid conjugates the apparent volume of distribution (Vd, the volume of fluid in which the drug appears to distribute at a concentration equal to that of plasma) will decrease but since these conjugates are usually biologically inactive and are rapidly cleared by the kidney, the decrease in Vd is of little importance. However, the proportion of body fat tends to increase with age and for the lipid-soluble steroids the Vd will increase leading to a lowered blood concentration which would be accentuated by the localisation of the steroids in adipose tissue which is claimed to occur. These changes in Vd may be one of the more important physiological changes in regard to the effect of aging on drug metabolism.

The liver is the main organ responsible for the metabolism of the sex steroids although both the lungs and the gastrointestinal tract may contribute significantly. Both hepatic mass in proportion to body weight and liver blood flow decrease with age and may therefore lead to a decreased rate of drug metabolism. The decline in drug metabolising capacity with age is evidenced by the significant increase in bromsulphthalein retention and in the half-life of antipyrine although the crude hepatic function tests used in clinical biochemistry do not show any change. With the low doses of the sex steroids used therapeutically the changes in hepatic function are unlikely to be severe enough to reduce the rate of metabolism of the steroids. Metabolism of the steroids, as well as many other drugs, occurs in the smooth endoplasmic reticulum of the liver cell and the activity of the enzyme system is influenced by both steroids and many other drugs. Most drugs increase the activity of this drug metabolising system thus leading to an increased rate of their own metabolism and also that of other drugs, although some drugs may inhibit this system. Interactions between the metabolism of the steroids and other drugs can, and do, occur.[2] This interaction is particularly important in the older subject since it is more likely that they are already using other prescribed or 'over-the-counter' drugs. Older subjects are known to take more drugs than younger ones. These drug interactions will not always be of such a magnitude as to interfere seriously with the therapeutic effectiveness of the drugs but in a minority of subjects they are. It has been suggested that for the same dose of drug, enzyme induction occurs to a lesser extent in the older subject than in the young and drug interactions may therefore have a lower incidence in older subjects.

In many instances drug metabolism follows first-order reaction kinetics, whereby a constant proportion of the drug is metabolised per unit time and this applies to many of the steroids. The rate of metabolism of the drug or steroid is commonly assessed by measuring its half-life of elimination ($t^1/2$, the time required for its serum concentration to decrease by 50%). However, although widely used, since it is easy to understand and to estimate, $t^1/2$ is a derived parameter and is determined by the clearance of the drug (Cl, the volume of blood cleared of the drug in unit time by all processes) and by Vd. The relationship is $t^1/2 = 0.693.Vd/Cl$. Thus if Cl and Vd changed proportionately, $t^1/2$ would not change although the effects on drug metabolism would be very marked; if both Cl and Vd increased, the serum concentration of the drug and hence its biological activity would decrease although this would not be reflected in $t^1/2$. Since age-related changes in body composition affect Vd and therefore $t^1/2$, clearance provides a better indication of the rate of drug disposal. Clearance can, under simple conditions, be calculated from the dose divided by the area under the serum drug concentration-time curve and is thus not influenced by Vd. Since the sex steroids used in hormone replacement therapy are administered uninterruptively over a period of days or weeks, steady-state conditions will be achieved even though there will be fluctuations in the serum concentrations during any 24-hour period when the steroids are administered orally. The reduced ability of the liver to metabolise drugs in the elderly subject will lead to a decrease in clearance and since the dose administered (D) remains the same, the steady-state concentration (Css) in serum will increase (Css = D/Cl). Little information is available regarding steady-state concentrations of the steroids.

The sex steroids are metabolised mainly by reduction and/or hydroxylation and the metabolites are rendered more water soluble by the formation of glucuronide and, to a lesser extent, sulphate conjugates which are excreted in the urine. For some steroids however, for example ethynyloestradiol, the faecal route may be important and up to 30% of a dose of EE may be excreted in the faeces. Renal function, as assessed by creatinine clearance but not by serum creatinine or urea levels, decreases with age due mainly to a reduction in glomerular filtration rate. Although this is quite marked, it probably has little effect on excretion of the steroid glucuronides which are efficiently cleared. The reduction in renal function is unlikely to affect the biological activity of the steroids, since the conjugates are biologically inactive and only small amounts, if any, of the active steroid are excreted unchanged in the urine.

Pharmacokinetics of oestrogens

Three formulations of oestrogens have been mainly used in the postmenopausal woman; 1) ethynyloestradiol orally, 2) oestrone sulphate and preparations

Table 1. Mean values for pharmacokinetic parameters derived from measurement of unconjugated (column A) and total (column B) ethynyloestradiol

Pharmacokinetic parameter	A	B
Slopes (h^{-1})		
Ka	2.07	2.88
ß	0.07	0.05
α	0.42	0.42
Peripheral rate constants (h^{-1})		
K_{12}	0.22	0.17
K_{21}	0.18	0.11
Elimination rate constant (h^{-1})	0.22	0.18
Half lives (h)		
Ka	0.33	0.28
α	1.87	1.77
ß	10.4	14.3
Fraction in central compartment		
(F)	0.33	0.30
Area under curve (pg/ml/h)	941	10,040

(Original data from references 4 and 5).

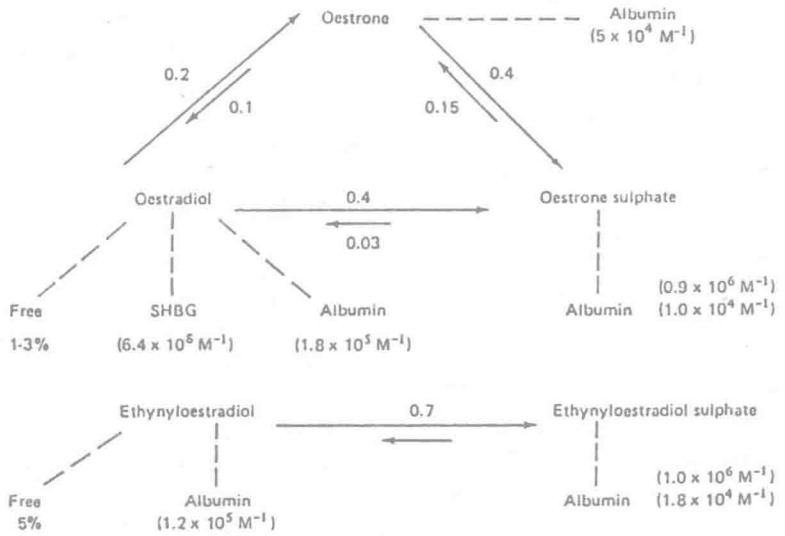

Fig. 1. Comparison of metabolism of ethynyloestradiol and oestradiol. (Broken lines denote binding. Values in parentheses are equilibrium association constants and values attached to arrows are transfer constants. Data from reference 3).

containing mainly oestrone sulphate; and 3) oestradiol including micronised oestradiol orally, oestradiol esters orally which are readily hydrolysed to oestradiol, and percutaneous oestradiol using a gel, creme or patch which give a slow continuous delivery of the steroid into the circulation. More pharmacokinetic data is available for ethynyloestradiol because of its use in oral contraceptives than for the other formulations. The information for ethynyloestradiol has been extensively reviewed[3] and accordingly only selected aspects are presented.

After oral administration ethynyloestradiol is rapidly absorbed with peak concentrations in serum occurring within 2 hours in 95% of subjects. However, in spite of this rapid absorption less than half of the dose is usually bioavailable due to extensive metabolism in the intestinal wall and liver. After a 30 µg dose serum levels of the unconjugated steroid are low, less than 150 pg/ml (0.5 nmol/l) at the peak and usually almost undetectable, less than 30 pg/ml (0.1 nmol/l), at 24 h. With the smaller doses (10 to 20 µg daily) used as hormone replacement therapy, the serum levels will be correspondingly lower. However, values for serum total ethynyloestradiol are about ten times higher due to the rapid conversion of ethynyloestradiol to its 3-sulphate conjugate. After a 50 µg dose, peak concentrations are from 400 to 2000 pg/ml (1.33 – 6.7 nmol/l) with a considerable decrease to less than 250 pg/ml (0.8 nmol/l) at 24 h. The concentration of the conjugated steroid was always higher than that of the unconjugated, the ratio between the two from about 12:1 at 1 h after administration to about 3:1 at 24 h.

A comparison of the pharmacokinetic data for the unconjugated and conjugated fractions in serum is shown in Table 1. It is of interest that the two sets of parameters show a remarkable similarity suggesting that ethynyloestradiol and its sulphate are metabolised in a similar fashion. The ten-fold difference in area under the curve (bioavailability) reflects the much higher concentration of the sulphate in blood compared to the unconjugated steroid. One interpretation of the data is that ethynyloestradiol sulphate acts as a reservoir or slow release form for the free, biologically active steroid. This interpretation has been questioned recently based upon investigations in which the 3-sulphate and the 17-sulphate were administered both orally and intravenously to women.[6] Although the 17-sulphate and also the 3,17-disulphate can be formed *in vivo*, the 3-sulphate appears to be the major conjugate.[7]

There is a close similarity between the metabolism of ethynyloestradiol and oestradiol (Fig. 1). Ethynyloestradiol is rapidly converted to the sulphate which binds to two sites on serum albumin and from which the free steroid can be slowly regenerated. For oestradiol conversion to oestrone and to oestrone sulphate is also rapid and the latter also binds to two sites on serum albumin with similar binding constants to those for ethynyloestradiol sulphate suggesting that the two conjugates may bind to the same sites on the protein. The

binding constants for oestradiol and ethynyloestradiol to albumin are also similar. One important difference is that whereas ethynyl-oestradiol does not bind to SHBG (sex hormone binding globulin), oestradiol does and this may be one mechanism regulating the level of free oestradiol in blood. The lack of any specific binding of ethynyloestradiol in blood might result in its rapid metabolism unless it were 'protected' and one mechanism for achieving this may be by sulphate conjugation. Probably no more than 1% of oestradiol exists in the free state in the circulation. The value of 5% for ethynyloestradiol was determined by equilibrium dialysis and would be a maximum value, probably under *in vivo* conditions the value is less than 2%.

The interrelationships for orally administered oestradiol and oestrone sulphate are also indicated by the scheme in Fig. 1. A number of studies have shown that when oestradiol is administered percutaneously, much of the metabolism to oestrone and its sulphate which occurs after oral administration on the first passage through the liver is avoided and an oestradiol:oestrone ratio similar to that of premenopausal women is achieved.

Conjugated equine oestrogen formulations contain oestrone sulphate as the major component with about 25% of equilin sulphate and 15% dihydroequilin sulphate. The interrelationships between these ring B unsaturated oestrogens are similar to those for oestrone and oestradiol.[8] Evidence suggests that equilin sulphate also binds to albumin and, as for oestradiol and ethynyloestradiol, the major circulating forms are the sulphates whereas the main urinary metabolites are glucuronides.

It is of interest that the 'natural' oestrogens appear to be absorbed more slowly after oral administration than the synthetic sex steroids; thus whilst in most women peak concentrations of ethynyloestradiol occur within 2 h of dosing, after oral administration of micronised oestradiol or conjugated oestrogens, the peaks occur at 3 to 6 h. The concentration of oestrone sulphate in postmenopausal women is usually from 100 to 450 pg/ml (0.8–1.23 nmol/l) and does not change with time postmenopause. One of the major determinants of the serum concentration appears to be body weight. Presumably the increased proportion of fat in the heavier subject enhances the production of oestrone from androstenedione.[9] The proportion of oestrone sulphate to total oestrogens in the postmenopausal woman and after administration of oestradiol appears to be higher than premenopause. Oestrone sulphate levels in serum are still elevated three days after a 2 mg dose of micronised oestradiol[10] suggesting that it would be important to determine the concentrations in women on long-term treatment and to ascertain steady-state concentrations; such information does not appear to exist.

Another aspect of the pharmacokinetics of ethynyloestradiol which is relevant to hormone replacement therapy is the wide inter-subject variation.[11] Such wide variations have been shown to occur with orally administered