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Review

Use of medroxyprogesterone acetate for hormone therapy in postmenopausal women: Is it safe?

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ABSTRACT

Medroxyprogesterone acetate (MPA) has been in clinical use for over 30 years, and was generally considered to be safe until the results of long-term studies of postmenopausal hormone therapy (HT) using treatment with conjugated equine estrogens (CEE) combined with MPA and CEE alone suggested that MPA, and perhaps other progestogens, may play a role in the increased risk of breast cancer and cardiovascular diseases. This review examines critically the safety of MPA in terms of breast cancer and cardiovascular disease risk, and its effects on brain function. Research into mechanisms by which MPA might cause adverse effects in these areas, combined with the available clinical evidence, suggests a small increase in relative risk for breast cancer and stroke, and a decline in cognitive function, in older women using MPA with an estrogen for postmenopausal HT. However, short-term (less than 5 years) use of MPA with an estrogen in the years immediately after the onset of menopause for the management of vasomotor symptoms does not appear to be associated with any increased risk of these disorders.

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1. Introduction

Medroxyprogesterone acetate (MPA) is a synthetic progestogen (progestin) that is related in chemical structure to progesterone. Its structure differs from progesterone only in that it has a methyl group at carbon 6 and an acetate group at carbon 17. These structural differences result in a higher progestational activity and bioavailability of MPA than progesterone when given orally.

The most common use of MPA is for contraception and HT. However, it is also used to treat abnormal uterine bleeding, secondary amenorrhea, dysmenorrhea and endometriosis. Prior to use of MPA for HT and contraception, MPA in massive doses (grams) had been used extensively for the treatment of hormone-dependent cancers, particularly breast cancer [1]. Discussion of these important aspects of MPA use is outside the scope of the current review. However, a detailed review [1] has identified several independent studies. The studies indicated in this publication show that even at very high doses administered for an extended period of time, MPA was relatively safe to use therapeutically for those indications.

MPA began its history of prescriptive use for postmenopausal women in the late 1970s, after it was shown that addition of a progestin to estrogen therapy in women with an intact uterus could prevent estrogen-induced endometrial changes, including adenocarcinoma. Because of its anti-proliferative effects on the endometrium and its accepted use for other clinical applications, MPA for more than 25 years was generally considered safe for use in postmenopausal hormone therapy (HT). Its use rose steadily and remained high throughout the late 1980s and 1990s. However, this changed with the well-publicized findings of the Women's Health Initiative (WHI) trial in which the conjugated equine estrogen (CEE)/MPA arm of the study was prematurely stopped in 2002. The data Safety Monitoring Board of the trial concluded that the evidence for breast cancer harm, along with evidence for some increase in coronary heart disease, stroke and pulmonary embolism outweighed the evidence of benefit for fractures and possible benefit for colon cancer after a mean of 5.2 years of follow-up in postmenopausal women [2]. Since the CEE-alone arm of that trial showed no increase in breast cancer and the health benefits/risk ratio was more balanced [3], a number of investigators speculated that continuous use of MPA in the CEE/MPA trial may have played a role in the increased risk of breast cancer.

The purpose of the present article is to review critically some of the most important publications that address the safety of MPA, not only regarding breast cancer risk, but also risk of cardiovascular disease and its effects on the brain when used in conjunction with estrogens. Detailed review of the vast body of epidemiological studies is outside the scope of this review, but a substantial number of these studies are discussed in several articles in this special issue of the journal.

2. Metabolism and pharmacokinetics of MPA

The relative binding affinity profile of MPA shows that MPA binds with high affinity to the progesterone receptor (PR) [4]. In addition, it binds substantially to both the androgen receptor (AR) and glucocorticoid receptor. Furthermore, MPA does not bind significantly to either the mineralocorticoid receptor or estrogen receptor (ER).

Considering the wide use of MPA for a considerable number of years, it is surprising that relatively little is known about the metabolism and pharmacokinetics of MPA. The 6-methyl and 17-acetoxy groups on the MPA molecule make it more resistant to hepatic metabolism than progesterone. Based on in vitro studies, three main hydroxylation sites of MPA were proposed to be 6β, 2β and 1β positions, generated by CYP3A [5]. One would also expect the double bond and ketone group in ring A to undergo reduction, forming dihydro and tetrahydro metabolites of MPA.

Following its administration, MPA is bound weakly to albumin in blood; it does not bind to SHBG. However, MPA appears to have a suppressive effect on SHBG, probably due to its androgenic properties. In one study, it was shown that MPA decreased SHBG levels by 14–18% following oral administration of 10 mg MPA daily for 14 days to postmenopausal women receiving 4 mg oral estradiol valerate [6].

When a single dose of 10 mg of MPA was administered orally to each of 3 postmenopausal women, mean peak serum MPA levels ranged from 3.4 to 4.4 ng/ml and were attained between 1 and 4 h after its ingestion [7]. The MPA levels then fell precipitously until 6–12 h after dosing, and subsequently declined gradually until 24 h post-treatment, at which time the MPA levels ranged from 0.3 to 0.6 ng/ml.

Serum levels of MPA were measured in a single-blind, triple cross-over study, in 12 postmenopausal women who received 1 of 3 different formulations containing MPA on each of 3 study days separated by 1 week [8]. One of the formulations contained 5 mg of MPA combined with 2 mg of estradiol. The second formulation also contained 5 mg of MPA, but was administered separately in combination with 2 mg of estradiol. The third formulation contained 10 mg of MPA combined with 2 mg of estradiol valerate. The initial objective was to administer the medications using a pre-determined randomized scheme with a balanced design to include 5 participants who ingested each drug on each study day. However, due to unexpected exclusion of some participants, the number of women treated with the medications was 3–6 on the first treatment day and 3–5 on the next two treatment days. The results showed that there was a significant increase in MPA levels between study days 1 and 3 with each formulation. After adjusting for inter-subject variability and period effect, the maximum concentration (C_{max}) and area under the concentration curve from 0 to 32 h ($AUC_{0-32\,h}$) values (geometric means) for the two 5-mg MPA treatments were 4.2–4.4 ng/ml and 30.6–30.8 ng h/ml, respectively. For the 10-mg MPA dose, the corresponding values were 6.0 ng/ml and 46.7 ng h/ml, respectively. No linear-response effect of MPA was observed in either of the two pharmacokinetic parameters studied. Similar findings were observed in a study in which 5 normally cycling women received a 10 mg oral dose of MPA [9]. The elimination half-life of MPA was found to be about 30 h.

It is well recognized that aging is associated with altered pharmacokinetics of drugs. Elderly postmenopausal women are a different population compared to younger postmenopausal women due to age-associated changes. Pharmacokinetic differences between those age groups can be attributed to decreased hepatic and renal function, reduced cardiac output, impaired pulmonary function, reduction in body weight and muscle mass, and changes in body composition. It has been shown that following oral administration of 2.5 or 5 mg of MPA combined with 1 or 2 mg of estradiol valerate to postmenopausal women daily for 12 or 14 days, the AUC was, on average, 1.6–1.8 times higher in the oldest group of women (>65 years) compared to the youngest group (<60 years) [10]. This increased MPA exposure in elderly postmenopausal women may have adverse effects, especially if the women have preexisting conditions.

3. Effect of MPA on breast cancer risk

3.1. Androgen signaling in the breast

A number of studies carried out by Wayne Tilley and Steven Birrell and their co-workers have focused on the disruption of AR signaling by MPA in breast tissues. These researchers believe that