Review of Oxymetholone: A 17α-Alkylated Anabolic-Androgenic Steroid

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ABSTRACT

Background: Oxymetholone (17β-hydroxy-2-[hydroxymethylene]-17-methyl-5α-androstan-3-one) is a 17α-alkylated anabolic-androgenic steroid and a synthetic derivative of testosterone. It has been approved by the US Food and Drug Administration for the treatment of anemias caused by deficient red cell production.

Objectives: This review summarizes the pharmacokinetics, current and future clinical applications, and adverse effects of oxymetholone. Relevant studies were identified using a search of MEDLINE® through March 2001, supplemented by conference abstracts and presentations.

Results: Because of its anabolic properties, oxymetholone has been studied for the treatment of HIV-associated wasting, antithrombin III deficiency, pediatric growth impairment, and damaged myocardium, with varying degrees of success. Hepatotoxicity is a major adverse effect associated with the use of oxymetholone, with cholestatic jaundice the most important hepatic side effect. Less common hepatic side effects associated with the use of anabolic-androgenic steroids include peliosis hepatis and formation of hepatic tumors. All anabolic-androgenic steroids can cause androgenic side effects, including acne, hirsutism, hair loss, clitoral/phallic enlargement, vocal changes, erectile tissue stimulation, gynecomastia, amenorrhea, and changes in libido and sexual potency.

Conclusions: As is the case with many anabolic-androgenic steroids, few pharmacokinetic and tolerability studies were performed before oxymetholone's approval in the 1960s. It has proved, however, to be an appropriate treatment choice for selected patients with anemia, if carefully monitored.

Key words: oxymetholone, anabolic-androgenic steroid, testosterone, wasting, anemia.
(*Clin Ther.* 2001;23:789-801)

Accepted for publication March 27, 2001.

0149-2918/01/$19.00

INTRODUCTION

With the isolation of testosterone in 1935,[1] researchers began to explore potential applications of testosterone therapy based on its anabolic and androgenic properties. Early studies of orally or parenterally administered testosterone were unsuccessful, in part because rapid hepatic absorption and degradation via phase I metabolism resulted in subtherapeutic amounts of the hormone reaching target tissues. To overcome this limitation, testosterone analogues were developed that had slower hepatic metabolism and produced longer systemic exposure. Further modifications were aimed at altering the anabolic-androgenic ratio (for improved tolerability and efficacy), increasing in vivo half-life, and facilitating administration.[2,3] This work resulted in the development of >120 synthetic testosterone analogues. The effects of these compounds were similar to those of testosterone: they increased nitrogen retention, stimulated erythropoiesis, and improved skeletal calcium uptake. They also, however, possessed androgenic effects, including virilization.[4]

The 17α-alkyl derivatives of testosterone constitute an important class of anabolic-androgenic steroids (Figure 1). Introduction of the 17α-alkyl substituent into the testosterone molecule prevents metabolic inactivation through oxidation of the 17-hydroxy group to the 17-keto group. This change slows metabolism of these compounds, increasing their efficacy when administered orally.[3]

Oxymetholone (17β-hydroxy-2-[hydroxymethylene]-17-methyl-5α-androstan-3-one) is an orally active 17α-alkylated anabolic-androgenic steroid first described by Ringold et al.[5] It has a fully saturated A-ring structure, which may reduce the risk of hepatotoxicity (Figure 2).[6] Also, oxymetholone exhibits higher anabolic activity and lower androgenic ac-

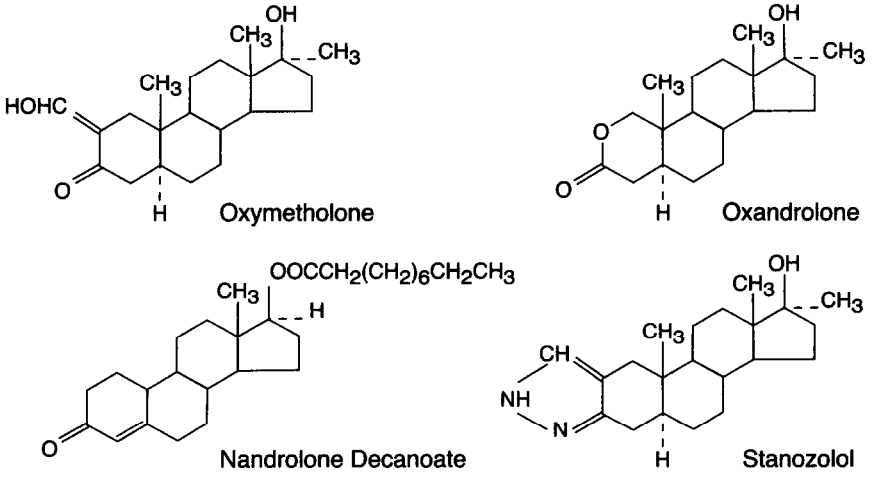

Figure 1. Structures of commonly used anabolic-androgenic steroids.

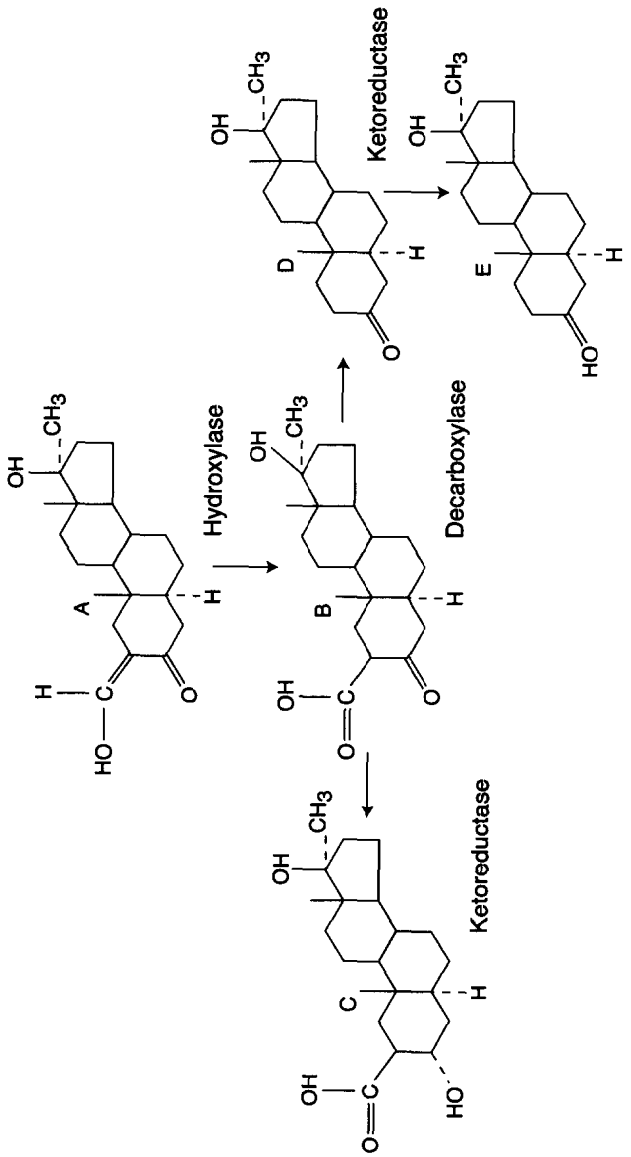

Figure 2. Hepatic metabolism of oxymetholone. Reprinted with permission, as modified, from Schänzer W.[3]

tivity compared with methyltestosterone, testosterone, and testosterone propionate (Table).[7]

Currently, oxymetholone is approved by the US Food and Drug Administration (FDA) for the treatment of anemias caused by deficient red cell production. In addition, acquired or congenital aplastic anemia, myelofibrosis, and hypoplastic anemias due to the administration of myelotoxic drugs often respond to this medication.[8] Researchers also have studied oxymetholone in the treatment of a variety of conditions, including HIV-associated wasting,[9] antithrombin III deficiency,[10] growth impairment in children,[11,12] and damaged myocardium in heart failure.[13]

This review summarizes the pharmacokinetics, current and future clinical applications, and adverse effects of oxymetholone. Relevant articles were identified using a search of MEDLINE® through March 2001, supplemented by conference abstracts and presentations.

PHARMACOKINETICS

Limited information is available on the pharmacokinetic profile of oxymetholone. Although uptake studies of oxymetholone have not been conducted, the structurally similar testosterone is completely absorbed when administered orally.[14] The structure-activity relationship and clinical experience with oxymetholone suggest that it is well absorbed after oral administration.

On entering the bloodstream, oxymetholone undergoes both phase I and phase II metabolism.[3] Although oxymetholone interacts with the cytochrome P450 (CYP) system in vitro, it is not metabolized by these enzymes.[15] Its interaction with CYP2D6, CYP3A, CYP1A2, or CYP2C19 results in weak inhibition and seems to have little clinical significance.[15] Further clinical studies are required to rule out all possible CYP-related drug interactions.[15]

The primary phase I metabolic reactions involve oxidation at C2, reduction at C3, and hydroxylation at C17.[16] Approximately 5% of oxymetholone has been recovered in urine as conjugates of glucuronic acid.[17] Two major unconjugated acidic metabolites were later isolated in urine, and 5 minor acidic metabolites, 4 of them unusual seco steroids, have been characterized.[18,19] The effects of these metabolites have not been determined, but they are unlikely to be related to hepatotoxic effects in humans.[19]

In humans, renal excretion of nitrogen during metabolic homeostasis can predict the anabolic activity of anabolic-androgenic

Table. Anabolic-androgenic ratios of commonly used anabolic-androgenic steroids in animal models.[7,39]

Androgen	Androgenic Activity	Anabolic Activity
Oxymetholone	0.45	3.2
Oxandrolone	0.24	3.22
Nandrolone decanoate	0.31–0.41	3.29–4.92
Stanozolol	0.3	2.0–3.2

Values are relative to methyltestosterone, testosterone, or testosterone propionate.

steroids. Oxymetholone has been shown to be superior to methyltestosterone in terms of nitrogen retention.[20] Interpatient and intrapatient variability make it difficult to determine a dose-response curve. Oxymetholone has been shown to increase urinary erythropoietin levels up to 5-fold.[20]

CLINICAL USES

Acquired and Congenital Anemia

Oxymetholone has been most thoroughly studied in the treatment of aplastic anemia. Many of the effects of oxymetholone, however, were originally reported in published case studies involving small numbers of patients; some of these are discussed in this section. Because of small patient numbers, some of these case studies did not arrive at statistically significant conclusions. Nonetheless, they demonstrate the variety of uses of oxymetholone that have been explored.

Remission of anemia, as indicated by increases in hemoglobin to >12 g/dL, increases in reticulocyte count, and improvement in numbers of neutrophils and platelets, has been demonstrated after treatment with oxymetholone. Increases in bone marrow cellularity during remission have been observed. Permanent remissions, as well as remissions lasting up to 5 years after cessation of therapy, have been documented.[21]

The response to oxymetholone administered for ≥3 months was studied in 45 patients with hypoproliferative or aregenerative anemia.[22] Patients with hypocellular marrow had the best response, with 13 partial or full remissions in 18 cases. A complete remission was noted only in patients who did not have pancytopenia. Of 7 patients with myelofibrosis, 4 had thrombocytopenia. Improvement after treatment with oxymetholone occurred in all 4 of these patients.

The benefit of androgen therapy was seen in 3 patients with acquired aplastic anemia,[23] in whom a direct relationship was observed between oxymetholone dose and blood cell counts. The number of erythrocytes, neutrophils, and platelets varied with oxymetholone dosage, with the exception of the platelet count in 1 patient.

The use of oxymetholone in 5 children with aplastic anemia was described in another set of case reports.[24] All 5 children, including 2 who were refractory to testosterone treatment, had a satisfactory bone marrow and clinical response. Oxymetholone appeared to have greater erythropoietic-stimulating effect than testosterone, an observation that agreed with previous data.[25,26]

In a randomized, crossover clinical trial involving 143 patients,[27] oxymetholone was 1 of 4 anabolic-androgenic steroids used to treat anemia in patients receiving hemodialysis. The men were treated with nandrolone decanoate, fluoxymesterone, oxymetholone, or testosterone enanthate, whereas the women received all drugs except testosterone enanthate. In all, 17% of the men responded to treatment with oxymetholone (increase in hematocrit of ≥5%), compared with 4% of women having such an increase. Parenteral anabolic-androgenic steroid therapy was better tolerated than oral therapy. Whereas the oral preparations were easier to administer and had fewer side effects (eg, hematoma, pain), they also were associated with a significantly higher incidence of liver toxicity and virilizing effects ($P < 0.05$). (Oral preparations such as oxymetholone demonstrate higher hepatotoxicity than parenteral therapies because higher drug

concentrations are presented to the liver on first pass.) The investigators concluded that oral anabolic-androgenic steroids should be reserved for use in dialysis patients who are unable to tolerate parenteral preparations.

Twenty-eight patients with chronic refractory anemia from bone marrow failure were studied before and after treatment with oxymetholone.[20] Erythropoietin excretion was enhanced >5-fold above the expected hematocrit level in 70% of patients. In 23% of patients, red cell mass was increased by ≥20%. Oxymetholone, however, did not improve the condition of patients who required frequent red cell transfusions. The investigators recommended that the use of oxymetholone be reserved for patients with more moderate degrees of bone marrow failure and symptomatic anemia.

Oxymetholone was administered for ≥2 months to 7 patients with sickle cell anemia.[28] Six patients showed a >5-fold increase in urinary erythropoietin, with an increase in red cell mass ranging from 17% to 75% above the control value. The authors suggested that oxymetholone might be useful in selected adult patients with sickle cell disease in whom severe anemia was contributing to the morbidity of the disease.

In another study, 134 patients with acquired aplastic anemia were randomized to receive antilymphocyte globulin and methylprednisolone with or without oxymetholone.[29] The response rate at 4 months was significantly greater in the patients receiving oxymetholone (57% [39/69] vs 40% [26/65]; $P < 0.04$). The improvement in response rate was more pronounced in women with low neutrophil counts than in comparable men (78% vs 27%; $P < 0.03$). Addition of oxymetholone, however, did not improve either the quality of response or short-term survival.

Myelofibrosis

Eleven patients with advanced myelofibrosis were studied in a multicenter prospective study.[30] Normalization of the peripheral blood or substantial improvement (>3 g hemoglobin/dL) was observed after 9 of 15 courses of oxymetholone. The need for blood transfusions ceased completely in all 5 patients who had required them before the trial. When oxymetholone treatment was reduced or interrupted, 4 patients relapsed, although 2 of them responded to a renewed course of oxymetholone. Based on these findings, oxymetholone may be of value in advanced cases of myelofibrosis with anemias requiring transfusion.

Myelosuppression

Lithium carbonate plus oxymetholone was compared with lithium alone in the treatment of chemotherapy-induced myelosuppression.[31] Seventy-one patients were included in the lithium group, 63 in the combined-treatment group, and 79 in the control group. Although the addition of oxymetholone did not substantially lessen myelosuppression in most patients, it improved patients' appetite and body weight. The majority of patients in the lithium and control groups lost weight, whereas those receiving oxymetholone gained weight (median body weight gain, 1.25 kg; $P < 0.001$).

HIV-Related Wasting

Although anabolic-androgenic steroids have been used for years in wasting con-

ditions such as nephrotic syndrome, chronic liver disease, and cancer,[32,33] their use in HIV infection is relatively new. Oxymetholone was administered alone and in combination with ketotifen (a histamine$_1$ antagonist with anti–tumor necrosis factor–alpha activity) to patients with HIV-related wasting in an open-label, prospective trial.[9] Thirty patients were randomly assigned to oxymetholone monotherapy (n = 14) or oxymetholone plus ketotifen (n = 16), and the results were compared with those in a group of 30 untreated individuals who met the inclusion criteria. In addition to body weight, the Karnofsky scale (a measure of quality of life) was used to further evaluate the response to therapy.

The mean gain in body weight was 8.2 kg (14.5%) in the oxymetholone group ($P < 0.001$), 6.1 kg (10.9%) in the combination-therapy group ($P < 0.005$), and −1.8 kg (weight loss) in untreated controls. The mean time to peak body weight was 19.6 weeks with oxymetholone monotherapy, compared with 20.8 weeks with combination therapy. The mean Karnofsky score, which measures the ability to perform activities of daily living on a scale from 0% (lowest) to 100% (highest), improved equally in both groups, from 56% before treatment to 67% after 20 weeks of treatment ($P < 0.05$). Findings on other quality-of-life measures were positive as well. The activities-of-daily-life score improved in 68% of patients in both treatment groups ($P < 0.05$), whereas appetite/nutrition scores improved by 91% in both groups ($P < 0.01$). The investigators reported that oxymetholone was well tolerated and promoted weight gain in cachectic patients with advanced HIV infection. The addition of ketotifen did not produce further weight gain.

In a 12-week pilot study,[34] 32 HIV-positive men received oxymetholone in addition to ongoing intramuscular injections of testosterone. Patients' mean body weight increased slightly from 100% to 104% of ideal body weight. Liver function test results, blood lipid levels, HIV RNA titer, and CD4+ counts were monitored, and no significant adverse effects were observed. At follow-up visits, patients reported significantly less anorexia, depression, and fatigue than before treatment ($P < 0.05$).

Hengge et al[35] conducted an analysis of the hepatotoxicity of oxymetholone in 30 patients with advanced HIV disease undergoing long-term oxymetholone treatment. In the study's initial phase, which lasted 30 weeks, 2 nonblinded groups received either oxymetholone alone or oxymetholone plus ketotifen. After the initial phase, 25 of the original 30 patients were followed in an open-label phase. Twenty patients continued treatment for ≥1 year at an average oxymetholone dose of 50 mg/d. The most common laboratory abnormality during the initial phase was a slight elevation in γ-glutamyltransferase (GGT) in 37% (11) of patients; after controlling for confounding variables, this amounted to an elevation of GGT in 17% (5) of oxymetholone-treated patients. Significant elevations in total bilirubin were noted in 10% (3) of patients. One patient developed a liver tumor that could have been peliosis hepatis. Serum albumin concentrations were increased in 20% (6) of patients.

Antithrombin III Deficiency

There have been several case reports of the resolution of thrombi in patients treated with oxymetholone in combination with anticoagulant therapy.[10] To the

best of our knowledge, there have been no studies of oxymetholone treatment for antithrombin III deficiency. The results of the case reports, however, may warrant further investigation.

Impaired Growth in Children

The effects of oxymetholone in growth-retarded, underweight children were investigated in a double-blind, placebo-controlled study.[11] Twenty-five children were randomized to oxymetholone and 29 to placebo. After 12 months of treatment, a statistically significant difference in mean height increase was observed in the oxymetholone group compared with the placebo group (8.2 vs 5.6 cm; $P < 0.02$). Similarly, a statistically significant difference in body weight gain was noted between the oxymetholone group compared with the placebo group (2.81 vs 1.75 kg; $P < 0.01$). There were no significant between-group differences in bone age effects. In this study, low doses (0.11–0.29 mg/kg/d) of oxymetholone produced a slight but significant increase in growth in undersize children without causing a significant increase in skeletal age versus height age.

The effect on bone growth of oxymetholone with and without fluoride was studied in nonambulatory osteoporotic children.[12] Twenty patients received combination therapy with oxymetholone and fluoride, and 20 received oxymetholone monotherapy. After 18 months, the mean rate of bone growth (determined by radiographic scaling of the long axis of the os calcis) with the combination therapy was 8.7%, whereas oxymetholone monotherapy increased the rate of bone growth by 7.0%. This difference was not statistically significant. During a 12-month follow-up phase, there was a statistically significant difference in growth rate between the monotherapy and combination-therapy groups (4.7% vs 8.1%; $P < 0.05$). These results indicate that it is possible to increase bone mineralization rapidly in nonambulatory osteoporotic children with intermittent oxymetholone and fluoride therapy.

Damaged Myocardium in Heart Failure

A small study reported the effects of oxymetholone on the residual myocardium of the dilated failing heart.[13] Twelve patients received oxymetholone for 3 months. Changes in left ventricular (LV) performance were evaluated based on echocardiography and plasma concentrations of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP). Improvements in LV dimensions without diastolic dysfunction were observed. Unexpectedly, LV mass decreased with oxymetholone. In addition, significant reductions in mean plasma ANP (–28 pg/mL) and BNP (–52 pg/mL) were seen ($P < 0.001$). The reductions in LV mass and plasma BNP levels reflected reduction in LV strain and improvement in LV myocardial function. The effects of oxymetholone were similar in patients with cardiomyopathy and volume overload, suggesting the applicability of oxymetholone to both categories of patients.

ADVERSE EFFECTS

Hepatotoxicity

Hepatotoxicity is a serious adverse effect associated with the use of 17α-alkylated anabolic-androgenic steroids. Cholestatic jaundice is the major hepatic side effect and is both dose and duration de-

pendent. A small number of case reports have been published documenting the occurrence of cholestatic jaundice in patients treated with oxymetholone.[36,37] Functional liver failure and hepatic necrosis have not been observed with 17α-alkylated anabolic-androgenic steroids when a single agent was used, although FDA labeling regulations require a class statement about these risks. In addition, oral preparations such as oxymetholone have higher hepatotoxicity than parenteral anabolic-androgenic steroids, because higher drug concentrations are presented to the liver on first pass.

Peliosis hepatis, an unusual cystic lesion of the liver, is a rare side effect associated with oxymetholone use.[38,39] The occurrence of peliosis hepatis is of greater clinical concern after discontinuation of treatment than before. Peliosis hepatis is a life-threatening adverse event; for this reason, the FDA mandates inclusion of appropriate warnings in the prescribing information for all anabolic-androgenic steroids.

Benign and malignant hepatic tumor formation has been associated with the use of 17α-alkylated anabolic-androgenic steroids. The incidence of tumorigenesis appears to increase with the duration and extent of exposure. Tumor regression has occurred after cessation of anabolic-androgenic steroid therapy.[40,41]

Physicians prescribing anabolic-androgenic steroids should be alert to symptoms of hepatotoxicity with long-term use and monitor liver function periodically.[42]

Decreased Anticoagulant Tolerance

Suppression of clotting factors II, V, VII, and X by anabolic-androgenic steroids is a well-known and clinically significant side effect. Anabolic-androgenic steroids with 17α-alkylation (including oxymetholone) have been shown to produce significant increases in plasma plasminogen factor, leading to fibrinolytic activity.[43] Based on 1 case report,[44] the use of oxymetholone with anticoagulants may not be absolutely contraindicated, but their use requires careful testing with small doses of anticoagulant to determine the maximum tolerated dose of oxymetholone in individual patients.

Hyperlipidemia

Reversible hyperlipidemia has been reported after 5 1/2 weeks of oxymetholone therapy in a patient receiving long-term hemodialysis.[45]

Common Side Effects of Anabolic-Androgenic Steroids

All anabolic-androgenic steroids may cause androgenic side effects such as acne, hirsutism, hair loss, clitoral/phallic enlargement, vocal changes, erectile tissue stimulability, gynecomastia, amenorrhea, and changes in libido and sexual potency. In addition, anabolic-androgenic steroids may interfere with measures of thyroid function and impair carbohydrate metabolism. They may accelerate bone maturation, resulting in growth impairment. Although many of these side effects are reversible on drug discontinuation, certain effects, such as growth impairment, hirsutism, and clitoral or phallic enlargement, may be irreversible.[8]

DOSAGE

Oxymetholone is indicated for the treatment of anemias caused by deficient red cell production, including acquired aplas-

tic anemia, congenital aplastic anemia, myelofibrosis, and the hypoplastic anemias associated with administration of myelotoxic drugs. The recommended daily dose of oxymetholone is 1 to 5 mg/kg body weight per day in children and adults with anemias caused by deficient red cell production. The usual effective dose is 1 to 2 mg/kg per day, but higher doses may be required, and the dose should be individualized. The response may not be immediate, and therapy should be given a minimum trial of 3 to 6 months. After remission, some patients may require no further oxymetholone therapy, whereas others may require a reduced maintenance dose. A maintenance dose is usually required in patients with congenital aplastic anemia.[8]

CONCLUSIONS

Oxymetholone is an orally active anabolic-androgenic steroid that has been studied clinically in various diseases since the 1960s. As is the case with many anabolic-androgenic steroids, much of the data on oxymetholone was published in the 1960s, and few pharmacokinetic and tolerability studies were performed before the drug's approval by the FDA. In addition, many publications have been case reports in small numbers of patients, which precluded attainment of statistically significant results. Oral anabolic-androgenic steroid preparations such as oxymetholone have demonstrated higher hepatotoxicity than parenteral preparations, because higher drug concentrations are presented to the liver on first pass. Our review of the literature, however, suggests that oxymetholone may be an appropriate therapy in certain patients who are carefully selected and monitored.

Additional clinical applications of oxymetholone are currently being investigated, and research continues in those areas in which the drug has shown promise. The possible benefit in patients with HIV-associated wasting is being further evaluated. Anabolic steroid therapy may facilitate bone growth and myocardial repair. However, future clinical applications of oxymetholone will depend on thorough evaluation of its tolerability and efficacy and assessment of its risks versus benefits.

Oxymetholone is appropriate in many patients with anemias associated with red cell deficiency, and it may be an option for the treatment of other conditions. Although other agents, such as erythropoietin, may be preferred for the treatment of anemia, oxymetholone may be useful in certain patient populations, particularly those who are unable to tolerate standard therapies.

ACKNOWLEDGMENT

This paper was supported by an educational grant from Unimed Pharmaceuticals, Inc, Deerfield, Illinois.

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