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Review Article

Levormeloxifene - a non-hormonal woman-centric oral contraceptive under development: a comprehensive review

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ABSTRACT

The drugs controller general of India (DCGI) has granted permission to Cipla Limited, an Indian pharmaceutical company, to conduct Phase-I clinical trial of levormeloxifene for development as oral contraceptive for women as joint collaboration with CSIR-Central Drug Research Institute, Lucknow, India (CSIR-CDRI). Levormeloxifene is laevorotatory enantiomer of ormeloxifene, a benzopyran Selective Estrogen Receptor Modulator (SERM). Ormeloxifene is racemic mixture in equal quantities of levo- and dextro-enantiomers (compounds having same chemical composition but mirror-image 3-dimensional structures). In rats, levormeloxifene [Minimum Effective Dose (MED): 0.15 mg/kg/day] prevented pregnancy at almost half the dose than ormeloxifene (MED: 0.25 mg/kg/day) when administered orally covering the entire pre-implantation period. Levormeloxifene is equally effective as single 1 mg/kg dose when administered within 24 hours of coitus. In accordance with its higher relative binding affinity (RBA: 15.7±3.1 percent of estradiol-17β), levormeloxifene exhibited more potent estrogenic and antiestrogenic activities than the d-ormeloxifene (RBA: 2.10±0.9) or dl-ormeloxifene (RBA: 5.24±1.45). Besides, it shows promise in prevention of increased bone turnover and destructive joint diseases, and beneficial effect on serum lipids. This is the first comprehensive review providing relevant published information on structure, pharmaceutical properties, preparation, safety, pharmacokinetics and pharmacodynamics of levormeloxifene.

Keywords: Benzopyran SERM, Health effects, Levormeloxifene, Pharmaceutical properties, Preparation, Pharmacokinetics, Pharmacodynamics, Structure, Safety

INTRODUCTION

Levormeloxifene (INN; Developmental Code Name: NNC 46-0020; Figure 1) is laevorotatory enantiomer/isomer of ormeloxifene, a benzopyran SERM, that has been identified for development as oral contraceptive for women as joint collaboration between CSIR-CDRI and Cipla Limited.[1-3] The DCGI permission for randomised, single dose (levormeloxifene: 15 mg tablet; ormeloxifene/Saheli: 30 mg tablet as reference product), oral, open label, Phase-I clinical trial in healthy adult female subjects under fasting conditions with parallel pharmacokinetic study was based on recommendations of the Subject Expert Committee (SEC) at its 36th meeting held on 5 June 2023, which reviewed data generated by CSIR-CDRI and Cipla Limited. Based on request from Cipla Limited, SEC agreed to waive non-clinical studies of levormeloxifene as ormeloxifene had already been approved by Central Drugs Standard Control Organisation, the national regulatory body for cosmetics, pharmaceuticals and medical devices.[1-4]

Rationale for developing pure enantiomer is based on the fact that in preclinical studies, contraceptive efficacy of ormeloxifene was driven by levo-form and to reduce overall chemical burden for women of reproductive age.[5] Interestingly, bone-preserving effect and antiatherogenic activity of ormeloxifene are also confined primarily to its l-enantiomer; d-enantiomer being much less effective.[6,7] In in vitro Ames Salmonella assay aimed to identify potential

antimutagenic/anticarcinogenic activity, too, l-enantiomer showed more protective effects in Salmonella strains TA97a, TA98, TA100 and TA102 against known bacterial mutagens than d-enantiomer.[8]

CHEMICAL STRUCTURE

(-) -3R,4R-trans-7-methoxy-2,2-dimethyl-3-phenyl-4-[4-(2-(pyrrolidin-1-yl)ethoxy}phenyl] chromane; CAS No.78994-23-7; chemical formula: $C_{30}H_{35}NO_3$; molar mass: 457.614 g.mol^{-1}; molecular weight: 457.6038; melting point (hydrochloride salt): 197ºC; IUPAC name: l-(2-(4-((3R,4R)-7-methoxy-2,2-dimethyl-3-phenyl-3,4-dihydro-2H-chromen-4-yl)phenoxy)ethyl)pyrrolidine.[1]

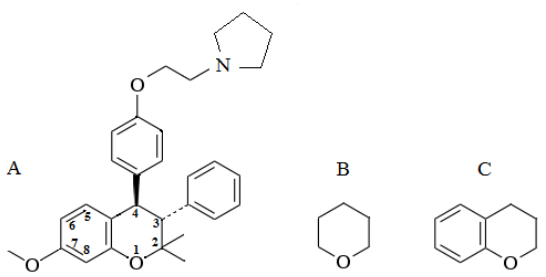

Figure 1: Chemical structure of (A) levormeloxifene (free base) with numbered carbon atoms, (B) Pyran ring, and (C) Benzopyran (Chroman) ring.

Levormeloxifene and ormeloxifene though earlier referred to as triphenylethylenes along with tamoxifen, structurally they are triphenylethane derivative with closed-ring-rigid-scaffold and peripheral functional groups that interact with estrogen receptors (ER) resulting in tissue-specific estrogen-agonistic or antagonistic effects of varying magnitudes.[9,10] These have now been classified under benzopyrans, separately from triphenylethylenes (clomiphene, tamoxifen, toremifene, droloxifene, idoxifene, ospemifene, fispemifene, afimoxifene, miproxifene), indoles (bazedoxifene, zindoxifene, pipendoxifene), tetrahydronaphthalenes (lasofoxifene, nafoxidine) and benzothiophenes (raloxifene, arzoxifene).[11,12] Benzopyrans are polycyclic organic compounds that result from fusion of benzene ring to heterocyclic pyran ring.[13]

PHARMACEUTICAL PROPERTIES

Levormeloxifene (free base) is very poorly soluble in water. Its hydrochloride salt is hygroscopic, has some pharmaceutically undesirable properties and forms solid gel in aqueous suspension.[14]

Its hydrogen fumarate salt (CAS No.: 199583-01-2; chemical formula: $C_{34}H_{39}NO_7$/$C_{30}H_{35}NO_3.C_4H_4O_4$; molar mass: 573.2727 g.mol^{-1}; molecular weight: 573.686; IUPAC name: 1-(2-(4-((3R,4R)-7-methoxy-2,2-dimethyl-3-phenylchroman-4-yl)phenoxy) ethyl) pyrrolidine fumarate) is non-hygroscopic with good stability characteristics, bioavailability, handling properties and reproducible crystalline form; solubility: soluble in DMSO; storage conditions: dry, dark place at 0-4ºC for days-weeks, -20ºC for months-years; shelf life: >3 years if stored properly (Table 1).[14,15]

PREPARATION OF ENANTIOMERS OF DL-ORMELOXIFENE

Preparation of optically active levo- and dextro-enantiomers of dl-ormeloxifene involves synthesis of dl-ormeloxifene and then processing to resolve its enantiomers as free base or hydrogen fumarate salt.[14,16] Process for preparation of dl-ormeloxifene has been described (Indian Patent No. 129187; US Patent No. 3322237) and subsequently published.[2]

To stirred, 50°C warm solution of (+/-)-trans-7-methoxy-2,2-dimethyl-3-phenyl-4-(4-(2-(pyrrolidin-1-yl)ethoxy) phenyl) chromane (1.00 kg; 2.19 mol) in methanol (10 l) is added (+)-ditoluoyltartaric acid (464 g; 1.20 mol) and stirred until solution becomes homogenous.[14,16]

Formic acid (73 g; 1.59 mol) is then added and temperature is allowed to drop to 30-40°C. If crystallization does not start, solution is seeded and temperature is allowed to drop to 20°C. Suspension is stirred for two hours at 20°C and cooled to 5-10°C for two hours and crystals are collected by filtration. Recrystallization from refluxing methanol (26 l) after cooling to 5-10°C and filtration give pure crystals of levormeloxifene (+)-ditoluoyltartrate salt (yield: 556 g; melting point: 136-138°C).[14,16]

Levormeloxifene (+)-ditoluoyltartrate (500 g) is suspended in a mixture of toluene (2.5 l), water (2 l) and sodium carbonate (157 g) at ambient temperature and stirred until salts dissolve. Aqueous phase is separated. Toluene phase is washed with water (2 l) and evaporated to oil. The oil is dissolved in ethanol (1 l) at 40-60°C and solution is added to solution of fumaric acid (69g; 0.59 mol) in ethanol (2 l). Mixture is stirred for an hour at 40-60°C and then cooled to 5°C. Levormeloxifene fumarate crystals are collected by filtration and dried at 50°C (321g; yield: 57%).[14,16]

Process for preparation of crystalline d-ormeloxifene fumarate is essentially same, except for use of di-p-toluoyl-d-tartaric acid.[14,16]

SAFETY, PHARMACOKINETICS, PHARMACO-DYNAMICS

Safety, pharmacokinetics and pharmacodynamics of levormeloxifene fumarate were investigated in two randomized, double-blind, placebo-controlled studies in healthy postmenopausal women (47-66 years of age; n=104; having ≥1 year history of physiological/surgical amenorrhea and not receiving hormone replacement treatment (HRT) for last 3 months) after oral administration in ascending single (2.5, 10, 20, 80, 160,

320 mg; n=8/group) or multiple (20, 80, 160 mg/day x5 weeks; n=6/group; 40 and 80 mg/day x8 weeks; n=12/group) doses.[17] In single dose trial, levormeloxifene was given as 1 mg ml^{-1} solution using hydroxypropyl-β-cyclodextrin as solubiliser and subjects were fasted from 8 hours before until 4 hours after dosing. In multiple dose trial, levormeloxifene was administered as tablets of 10 mg (20 mg dose) and 40 mg (other doses) in the morning after overnight fast and fasting was continued until 0.5 hour after dosing.

Safety

Levormeloxifene in single or multiple doses was well tolerated and no maximum tolerated dose was achieved.[17] Adverse events (headache, lower abdominal pain, pharyngitis, fatigue, nausea, hot-flushes, leukorrhea, leg cramps, myalgia, rhinitis) were generally mild-moderate in severity and were resolved completely. In single dose study, there were no differences between adverse event profiles even after highest (320 mg) dose of levormeloxifene or placebo. There also was no evidence of increase in frequency/type of adverse events with increasing dose of levormeloxifene. Most frequent adverse events after multiple dosing were headache, abdominal pain and leukorrhea with highest frequency (almost double than that at lower doses) occurring after highest (160 mg/day) dose. Vaginal bleeding after levormeloxifene withdrawal was observed in 1-2 subjects in all groups. No clinically significant changes of safety variables (blood pressure, heart rate, body temperature, electrocardiogram, routine haematology, clinical chemistry, urinalysis) or adverse events listed above were observed.[17]

Levormeloxifene is contraindicated in those hypersensitive to it or ormeloxifene and in those with history of thromboembolism (viz., pulmonary embolism or deep vein thrombosis).[18] Ormeloxifene is not recommended for women suffering from recent history of hepatitis, liver disorders, polycystic ovarian disease, chronic cervicitis, cervical hyperplasia, known/suspected pregnancy and lactation.[2,3]

Pharmacokinetics

Pharmacokinetic analysis of levormeloxifene in postmenopausal women showed rapid absorption (mean t_{max}: 2-3 hours), slow elimination (mean $t_{½}$: 4.8-8.4 days), considerable drug accumulation (RA: 3-5) and plasma half-life of approximately one week.[17] According to Kiehr et al who evaluated levormeloxifene pharmacokinetics after single 40 mg dose in young (50-58 years of age; n=15) versus elderly (66-79 years; n=13) postmenopausal women, no significant differences were observed between two groups in any pharmacokinetic parameter, except that its mean elimination half-life was longer in elderly (151 hours) than younger (126 hours) postmenopausal women by 25 hours.[19] In rats, Mountfield et al observed plasma C_{max} six hours after oral administration of levormeloxifene and long (24 hour) half-life of elimination.[20]

Chauhan et al have reported enhanced bioavailability of levormeloxifene by use of its nano emulsion based on pharmacokinetic profiling of free drug as compared with that of nano formulation in female rats and higher in vitro cellular uptake of nano formulation as compared with free fluorescein isothiocyanate solution.[21]

Whole body autoradiography following oral administration of ^{14}C-levormeloxifene to rats showed that levormeloxifene was absorbed from gastrointestinal tract and widely distributed into tissues. Peak radioactive concentrations were generally observed four hours after administration in intestine, liver, lung, kidney, spleen, pancreas, adrenals and ovaries.[20] Fecal elimination was the major excretion route. Majority of drug was excreted as desmethylnorlevormeloxifene, the 7-desmethyl metabolite of levormeloxifene, besides two monohydroxy levormeloxifene species and a pyrrolidinone ring-opened metabolite. Unchanged drug (6-12%) was also excreted.[20]

In another study, ^{14}C-levormeloxifene administered to rat, cynomolgus monkey and a postmenopausal woman showed similar metabolic pathways in the three species, with demethylation forming major metabolite in rat and woman volunteer, while in monkey major metabolite involved oxidative opening of pyrrole ring. Main site of metabolism was liver and majority of drug and its metabolites were excreted via fecal route.[22]

Pharmacodynamics

Bone preserving, antiatherogenic effects

Levormeloxifene prevented increased bone turnover and bone loss in all trabecular-rich bone sites (vertebrae, distal femur, proximal tibia) following ovariectomy and showed beneficial effect on serum lipids with preventative effect on atherosclerosis in ovariectomized rats and cholesterol-fed rabbits.[7,9,23] In cynomolgus monkeys, levormeloxifene (0.5, 1, 5 mg/kg x12 months) inhibited loss of lumbar spine bone mineral density (BMD) following ovariectomy, but, unlike estradiol, it did not prevent loss of BMD at femoral neck and whole body Bone Mineral Content or exhibit dose-related effect.[24]

Clinically, levormeloxifene has been evaluated by the Danish Pharmaceutical Company Novo Nordisk as an alternative to conventional HRT for treatment and prevention of postmenopausal bone loss.[2,9,10,14] In 12-month randomized, double-blind, placebo-controlled Phase-II study in healthy postmenopausal women (n=50/group), levormeloxifene (1.25, 5, 10, 20 mg/day) decreased bone turnover and increased BMD comparable to that observed during HRT (0.5 mg norethisterone acetate+1.0 mg estradiol-17β).[9,10,14] Levormeloxifene also decreased total cholesterol (13-20% versus ~8% with HRT) and low density lipoprotein (LDL) cholesterol (22-30% versus 12% with HRT), but high density lipoprotein cholesterol remained unaffected.[6] In 12-month follow-up period without any treatment after 12 months of treatment,

spine BMD measured at 6-month intervals returned to baseline at the same rate in all levormeloxifene-treatment groups.[6,9,25] According to Bloch-Thomsen et al, who conducted exploratory, post-hoc analysis of data from above trial, there was significant correlation between increased BMD of spine and hip and decreased total cholesterol and LDL cholesterol and women with greatest response in BMD were those with most favorable response in lipid profile.[6,26]

In Phase-III studies, too, effect on bone turnover and BMD was similar for each dose of levormeloxifene. Study was unable to differentiate between effects of different doses of levormeloxifene and MED was never established, as also observed in other studies.[9,17,24] This, according to Alexandersen et al, might indicate that lowest dose (1.25 mg/day) used in this trial may be sufficient or even too high and that levormeloxifene with its many positive characteristics could be of value for prevention of postmenopausal bone loss at considerably lower than the doses used in this trial.[6] MED for prevention of bone loss was never established before taking it into Phase-III trial.[9,17,24] Since in Phase-II trial, dose-response relationship was observed in bone markers at 0.25-1.25 mg/day doses (but not at higher doses), 0.5 and 1.25 mg/day doses were chosen for Phase-III trial.[9]

Skrumsagar et al have also reported estrogen-like bone-preserving (as evidenced by decrease in collagen-I C-terminal telopeptide, a biomarker of bone turnover) and antiatherogenic (decrease in serum total and LDL-cholesterol) effects of levormeloxifene in two randomized, double-blind, placebo-controlled studies in healthy postmenopausal women.[17] Reduction again was not dose dependent.

In view of the concern over its tendency to cause highly significant increase compared to placebo in gynecological disorders during clinical trials viz., leukorrhea, endometrial thickness, edema, vascularization and cysticity of endometrium, enlarged uterus, uterovaginal prolapse, urinary incontinence, micturition frequency and vaginal bleeds several days or weeks after study termination and failure to demonstrate significant long-term efficacy, its development was halted after 10 months (in September 1999) of the planned 3-year Phase-III osteoporosis-treatment trial, was not approved for clinical use and was never marketed.[1,6,9,18,25,27]

Prevention of destructive joint diseases, osteoarthritis

According to Christgau et al levormeloxifene suppressed cartilage degradation, as evidenced by significant decrease in urinary excretion of cartilage-specific collagen type-II degradation products (CTX-II) both in six-month-old ovariectomized rats (0.2, 5 mg/kg/day ×9 weeks; n=60) and postmenopausal women (1.25, 5, 10, 20 mg/day; n=301; participating in Phase-II study of this SERM) and prevention of ovariectomy-induced increase in surface erosion as assessed by histological analysis of hind knee articular cartilage in rats, suggesting its potential therapeutic benefits in prevention of destructive joint diseases such as osteoarthritis.[9,28]

Garnero, who evaluated urinary CTX-II in stored samples from randomized placebo-controlled clinical trials in postmenopausal women, has reported that bone-effective doses of oral and transdermal levormeloxifene (as also estradiol-17β and bisphosphonates alendronate and ibandronate) significantly decreased urinary CTX-II within 3-6 months, suggesting indirect effects of these drugs on subchondral bone turnover and/or direct action on cartilage metabolism.[29] Several observational studies have indicated that estrogen-deficiency increases incidence of osteoarthritis in postmenopausal women.[28] Expression of ER in articular cartilage in animals and ERα and ERβ in humans, beneficial effects of estrogen on cartilage in animal models of osteoarthritis, reduced risk of radiographic osteoarthritis in postmenopausal women, significant protective effect of HRT for osteoarthritis of knee and hand joints in women and reduction in hip and knee joint replacement in women, too, suggest significant benefit of estrogen replacement therapy in osteoarthritis.[30-32]

Anticancer and thrombin-modulating activity

Using PC-3 (prostate cancer) cell line, both ormeloxifene and levormeloxifene caused more than 90% cell death, but did not show any thrombin inhibitory/enhancing activity or exhibit any effect on endogenous thrombin generation potential in rat plasma in vitro, suggesting its positive effect on cardiovascular system.[33] Cancer associated thrombosis is well established in clinical settings and thrombin has been found to induce angiogenesis at cancer sites, thus establishing link between cardiovascular diseases and cancer.[33]

Contraceptive efficacy, relative binding affinity, hormonal profile

Levormeloxifene (MED: 0.15 mg/kg; Table 2) exhibited 33- and about 2-fold higher anti-implantation activity than d-ormeloxifene (MED: 5.0 mg/kg) and dl-ormeloxifene (MED: 0.25 mg/kg), respectively when administered orally to rat on days 1-7 post-coitum.[34] Levormeloxifene is equally effective at 0.15 mg/kg/day dose administered orally on days 1-5 post-coitum or as single 1 mg/kg dose within 24 hours of coitus.[35] Ormeloxifene, in comparison, prevents implantation when administered as single 1.25 mg/kg dose until secretion of nidatory estrogen (secreted between 21:00 hours on day 4 and 10:00 hours on day 5 post-coitum), which is responsible for induction of endometrial receptivity to blastocyst signals for decidual transformation in this species.[2,3] RBA (percent of estradiol-17β) for immature (21-25 days old) rat uterine cytosol ER determined by competitive inhibition assay showed that levormeloxifene is more potent ER binder (RBA: 15.7±3.1; Table 2) than d-ormeloxifene (RBA: 2.10±0.9) or dl-ormeloxifene (RBA: 5.24±1.45), as its 3R,

4R absolute configuration with axial methyl group at C-2 diverted downwards along C-7α axis of estradiol is well tolerated by ER and makes the best fit.[34,36]

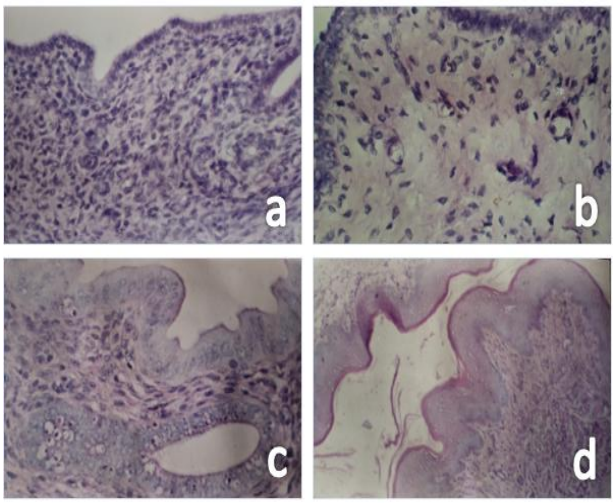

Figure 2: Transverse sections of mid-piece of uterus (a, c) and vagina (b, d) of ovariectomized immature rats treated with the vehicle (a, b) or 17α-ethinylestradiol (1.0 µg/day; c, d) orally once daily for 3 consecutive days and autopsied 24 hours after the last treatment. In vehicle control rats, uterus (a) as well as vagina (b) were lined with low cuboidal luminal epithelium. Uterine stroma was compact and fibroblastic with leucocytic infiltration into the stroma and epithelium; 17α-Ethinylestradiol treatment induced marked increase in uterine luminal epithelial cell height, loose endometrial stroma and endometrial glandular proliferation (c), and pseudostratification of vaginal epithelium (d). There was increase in uterine and vaginal epithelial folding and presence of sloughed cornified luminal epithelial cells in vaginal lumen in 17α-ethinylestradiol-treated rats. These cornified cells were observed in vaginal smear of these rats at autopsy.

Estrogenic activity has been assayed by uterine weight gain in immature rats (25-30 g; ovariectomized 7 days earlier) treated subcutaneously for three days with ascending (0.05, 0.5, 5, 50, 100 µg/day) doses of each compound or estradiol-17β (0.05, 0.1, 0.2, 0.5, 1 µg/day).[34] Levormeloxifene, in accordance with its higher RBA, exhibited more potent uterotrophic activity than dl-ormeloxifene, while its d-enantiomer exhibited nearly half the uterotrophic activity than dl-ormeloxifene. At nearly 200-times the dose of estradiol-17β, both levormeloxifene and ormeloxifene increased uterine weight to almost same extent as estradiol-17β. However, even at 1000 times the dose of estradiol-17β, d-ormeloxifene failed to induce similar uterine weight gain. Fact that uterotrophic activity was related to RBA was clearly evident at 5 µg dose, where levormeloxifene was most active followed by dl-ormeloxifene, while d-ormeloxifene did not produce any uterine weight gain.[34]

When administered orally (once daily x3 days; Table 3) at respective contraceptive dose in ovariectomized immature rats, levormeloxifene (0.15 mg/kg) exhibited significantly higher uterotrophic (178%) activity than ormeloxifene (142%; 0.25 mg/kg).[35] Histologically, too, while levormeloxifene (0.15 mg/kg) induced marked increase in uterine luminal epithelial cell height and pseudo stratification of vaginal epithelium similar to that after 17α-ethinylestradiol (1.0 µg/day), effect after ormeloxifene (0.25 mg/kg) was much milder with cuboidal uterine luminal epithelium and lower order of vaginal epithelial pseudo stratification. Even at higher (1.25 mg/kg) dose of ormeloxifene, while uterine luminal epithelium remained low columnar, vaginal epithelium exhibited marked pseudo stratification. There was no endometrial glandular stimulation or sloughing of cornified vaginal epithelial cells into the lumen after levormeloxifene or dl-ormeloxifene as observed in 17α-ethinylestradiol-treated rats (Figures 2,3).[34,35]

According to Bain et al while 17α-ethinylestradiol (0.2 mg/kg) treatment (3x/week for 5 weeks; oral) produced pseudostratified uterine epithelium and glandular proliferation in ovariectomized rats, levormeloxifene (0.5 mg/kg) induced significant increase in endometrial thickness with cell volumes equivalent to ethinylestradiol-treated rats without any evidence of proliferation, glandular stimulation or activity and reduced gland numbers.[9,23,37] According to Holm et al levormeloxifene treatment for up to 13 weeks produced no noticeable estrogenic effect on uterine or testicular tissue in cholesterol-fed rabbits.[7] In comparison, in adult ovariectomized micropigs fed with atherogenic diet, levormeloxifene (37.5 mg/day x26 weeks), besides increasing uterine weight and epithelial and endometrial thickness, also increased glandular hyperplasia, cystic changes, stromal edema and stromal fibrosis and significant incidence of lobuloalveolar epithelial hyperplasia in mammary tissue.[38] According to Goodrich et al, these marked uterine effects of levormeloxifene in micropigs are probably highly predictive of adverse events that would be encountered in clinical trials and have suggested value of micropig model of menopause in assessment of benefits and risks of postmenopausal therapies for cardiovascular and reproductive tissues.[38]

Skrumsagar et al have reported ~50% reduction in plasma concentration of follicle-stimulating and luteinizing hormones in randomized, double-blind, placebo-controlled study in postmenopausal women after oral administration in multiple (20, 80, 160 mg/day x5 weeks; n=6/group or 40, 80 mg/day x8 weeks; n=12/group) doses of levormeloxifene.[17] Effect was similar to that of estrogen, indicating an estrogen agonist-like action of levormeloxifene on hypothalamus-pituitary-ovarian axis. No effect on plasma estradiol concentrations was, however, reported.[17]

In antiestrogenicity assay in immature rats, all the three compounds administered subcutaneously at 100 µg/day

dose inhibited estradiol (0.5 µg/day)-induced uterine weight gain. At lower doses (5, 50 µg/day), varying degree of antagonism was evident with levormeloxifene and dl-ormeloxifene, while d-ormeloxifene had no inhibitory effect.[34]

Administered orally (once daily ×3 days) at respective contraceptive dose, levormeloxifene (0.15 mg/kg) exhibited significantly higher antiuterotrophic activity (27% inhibition in 17α-ethinylestradiol (1.0 µg/day)-induced uterine weight gain) than ormeloxifene (20%; 0.25 mg/kg). Significantly, at single day contraceptive (1 mg/kg) dose, too, levormeloxifene exhibited much greater antiuterotrophic response (44%) than ormeloxifene (26%; 1.25 mg/kg ×3 days) (Table 3, Figures 2,3).[35]

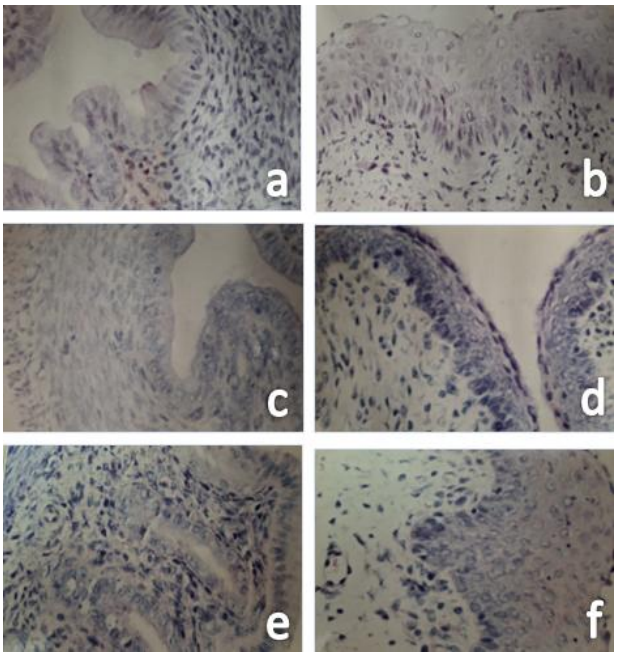

Figure 3: Transverse sections of mid-piece of uterus (a, c, e) and vagina (b, d, f) of ovariectomized immature rats treated with levormeloxifene (0.15 mg/kg; a, b) or dl-ormeloxifene (0.25 mg/kg; c, d, or 1.25 mg/kg, (e, f) orally once daily for 3 consecutive days and autopsied 24 hours after the last treatment. Levormeloxifene induced marked increase in uterine luminal epithelial cell height (a) and pseudostratification of vaginal epithelium (b), similar to that in 17α-ethinylestradiol-treated rats (Figure 2c, d). The effect after 0.25 mg/kg dose of dl-ormeloxifene was much milder with cuboidal uterine luminal epithelium (d) and lower order of vaginal epithelial pseudostratification (e). Even in rats treated with the higher (1.25 mg/kg) dose of dl-ormeloxifene, while uterine luminal epithelium remained low columnar (e), vaginal epithelium exhibited marked pseudostratification (f). There was no endometrial glandular stimulation or sloughing of vaginal epithelium into the lumen after levormeloxifene or dl-ormeloxifene treatment as observed in 17α-ethinylestradiol-treated rats (Figure 2d).

PELVIC ORGAN PROLAPSE AND URINARY INCONTINENCE

Pelvic organ prolapses and urinary incontinence in postmenopausal women treated with other SERMS

In a randomized, double-blind, placebo-controlled study, healthy postmenopausal women treated with tamoxifen (20 mg; n=14), raloxifene (60 mg; n=15), conjugated equine estrogen (0.625 mg; n=15) or placebo (n=13) and evaluated at baseline and 20 weeks after drug therapy, 75% patients who received raloxifene, 60% patients who received tamoxifen and 22% patients in conjugated equine estrogen group had increases in prolapse by any measure (POP quantitation or cotton swab or clinical assessment) compared with 18% in placebo group.[39] Triphenylethylene SERMs idoxifene, droloxifene and miproxifene, though exhibited beneficial actions including prevention of bone loss and fractures in preclinical and early phase clinical studies, failed during development due to increased risk of POP and UI and stimulatory effect on uterine endometrium with increased risk of endometrial hyperplasia, polyps and cancer and were not considered as viable options for prevention and treatment of postmenopausal osteoporosis.[9,40] According to Hendrix and McNeeley, higher proportion of surgery for pelvic organ prolapse in treated versus untreated women were noted during levormeloxifene and idoxifene trial.[40]

POP in one perimenopausal patient with dysfunctional uterine bleeding receiving ormeloxifene therapy

In a prospective randomized study conducted in Out Patient Department of Obstetrics and Gynaecology in a tertiary-care hospital over two-year period in perimenopausal Indian women with DUB (41-50 years of age), of the 100 women treated with ormeloxifene (60 mg twice-a-week for 12 weeks followed by 60 mg once-a-week for next 12 weeks, which is twice its recommended contraceptive dose), genital prolapse was observed in one case.[2,10,11]

According to these investigators, while ormeloxifene was better drug than commonly used steroidal progestin norethisterone in management of patients with DUB and that they recommend its use only in patients who have completed child-bearing in perimenopausal age group after thorough investigations, further trials on ormeloxifene should be conducted in younger age group to confirm/refute side effects of genital prolapse and stress UI before it is universally recommended for use.[11] Prolonged unsupervised ormeloxifene therapy has also been reported to cause harmful effects such as enlarged uterus, endometrial hyperplasia, micro glandular cervical hyperplasia and menorrhagia.[41-43] These investigators have emphasized need to educate patients about possible side effects, medical surveillance of all patients and evaluation of long-term effects of ormeloxifene therapy.[41-43]

Table 1: Comparison of chemical nature and pharmaceutical properties of levormeloxifene and dl-ormeloxifene.[2,3,10,13-15]

Parameter	Levormeloxifene, Hydrogen fumarate salt	dl-Ormeloxifene, Hydrochloride salt
Chemical nature	Triphenylethane	Triphenylethane
	Benzopyran SERM	Benzopyran SERM
	l-Enantiomer	Racemic mixture in equal quantities (1:1, w/w) of l- and d-enantiomers
Physical nature	White crystalline, non-hygroscopic	White crystalline, non-hygroscopic
Molecular weight	573.686	493.5
Solubility	DMSO, poorly soluble in water	Chloroform, acetone, methanol, ethanol Almost insoluble in water, isobutanol, hydrochloric acid or sodium hydroxide
Shelf life	>3 Years	3 Years
Storage conditions	Dry, dark place, 0-4°C for days-weeks, -20°C for months-years	Colourless/amber glass containers or aluminium strips at room temperature

Table 2: Comparison of contraceptive activity of dl-ormeloxifene and its l- and d-enantiomers.[2,3,10,34,36,57,58]

Parameter, species	dl-Ormeloxifene Hydrochloride salt	Levormeloxifene Hydrogen fumarate salt	d-Ormeloxifene
Relative binding affinity[a]	5.24±1.45[b]	15.7±3.1[b]	2.10±0.9[b]
Contraceptive efficacy[c] Rat (mg/kg, oral)			
Days 1-5 post-coitum[d]	0.25	0.15	5.0
Day 1 post-coitum[e]	1.25[f]	1.0	
Mouse (mg/kg, oral)			
Days 1-5 post-coitum[d]	0.25		
Day 1 post-coitum[e]	1.25		
Beagle dog (mg/kg) 24 hours after coitus			
Oral	2.5, 5.0		
Intramuscular	1.5, 2.5		
Rhesus monkey (mg/kg, oral) 24 hours after coitus	2.5		
Human (oral) Regular contraception	30 mg biweekly followed by 30 mg weekly		
Post-coital/ emergency contraception within 24 hours of unprotected coitus	60 mg single dose or 30 mg twice at 12-hour interval		

Blank spaces indicate relevant information not available. [a]Immature (21-25 days old) rat uterine cytosol ER using Competitive Inhibition Assay. [b]Percent of estradiol-17β. [c]MED: Minimum Effective Dose. [d]Covering entire pre-implantation period. [e]Within 24 hours of coitus. [f]Equally effective when administered until secretion of nidatory estrogen.

Table 3: Estrogenic and antiestrogenic activities of levormeloxifene and dl-ormeloxifene in immature female rats.[34,35]

Treatment	Daily dose, oral	Days of treatment	Estrogenic activity		Antiestrogenic activity[b]	
			Uterine weight[a]	Percent gain[c]	Uterine weight[a]	Percent inhibition[d]
Vehicle	-	1-3	17.00±0.81			
17α-Ethinylestradiol	1.0 µg	1-3	136.00±11.43[e]	700		
Levormeloxifene	0.15 mg/kg	1-3	47.33±1.85[e,f]	178	99.66±5.78[f]	27
	1.0 mg/kg	1	42.33±1.76[e,f]	149	76.33±7.21[f,g]	44

Treatment	Daily dose, oral	Days of treatment	Estrogenic activity		Antiestrogenic activity[b]	
			Uterine weight[a]	Percent gain[c]	Uterine weight[a]	Percent inhibition[d]
Vehicle	-	1-3	17.00±0.25			
17α-Ethinylestradiol	1.0 µg	1-3	107.50±2.80[e]	532		
dl-Ormeloxifene	0.25 mg/kg	1-3	41.13±3.87[e,f,k]	142	85.60±6.50[f]	20
	1.25 mg/kg	1-3	49.25±6.65[e,f]	190	79.16±5.11[f,h]	26

[a]Mean±SEM at autopsy on day 4. [b]For antiestrogenic activity, each rat received 1.0 µg daily dose of 17α-ethinylestradiol in addition to the test agent. [c]Percent uterine weight gain over vehicle control group (rounded off to the nearest digit). [d]Percent inhibition in 17α-ethinylestradiol-induced uterine weight gain (rounded off to the nearest digit). [e]P<0.01 versus corresponding vehicle control group. [f]P<0.01 versus corresponding 17α-ethinylestradiol-treated group. [g]P<0.01, [h]P<0.05 versus corresponding preceding value. [k]P<0.05 versus corresponding levormeloxifene (0.15 mg/kg) treated group. All other relevant comparisons were statistically nonsignificant (Student's t-test).

Incidence of POP in perimenopausal women

In another one-year hospital-based cross-sectional study on incidence of POP in perimenopausal and menopausal Indian women (>40 years of age; n=150), Ansari et al, analyzed POP by stage (early stages: I, II; advanced/higher stages: III, IV) according to Pelvic Organ Prolapse Quantification (POP-Q) System and have reported that while age can predict severity of POP, all stages of POP were present mostly in 41-50 years age group rather than in >50 years age group as reported by Wang et al.[44,45] Stage I POP was found mostly in premenopausal women, whereas in menopausal women stages II, III and IV were common.[44,45] Prevalence of POP was 4.8%; asymptomatic and symptomatic POP being in the proportion of 2:3.[44]

Pathophysiology of POP and UI

Pelvic floor disorders including POP and UI are debilitating conditions, with major impact on quality of life (QoL), QoL being worse than age-standardized population. According to existing studies, POP prevalence varies widely, ranging from 3-50% in different regions of the world due to multiple socio-cultural facts.[45-47] POP is often asymptomatic and becomes symptomatic in menopausal age with symptoms of pelvic pressure, vaginal bulge, difficulty in micturition and defecation and sexual dysfunction.[44,45] UI, too, is not an inevitable result of aging and can occur at any age, but is more common in older people, especially women>50 years of age.[48] Worldwide, POP is defined as descent of pelvic organs from normal anatomic position usually to or beyond hymenal remnants, owing to loss of support from connective tissues, muscles or both.[45] UI, also known as overactive bladder, is accidental loss of urine and is classified as urgency, stress, functional and overflow incontinence.[48]

It is not clear whether increased incidence of POP observed in levormeloxifene clinical trials was result of increased weight or size of uterus or whether factors such as modification of elasticity of pelvic floor tissues had an influence.[6,9,25] According to Ravn et al relationship between increased uterine weight and increased frequency of POP and UI is plausible.[9] Endometrial edema observed in levormeloxifene-treated women could also be a generalized problem in female pelvic floor.[9,25]

According to Hsu and DeLancey, uterine prolapse arises because of injuries and deterioration of muscles, nerves and connective tissues that support and control normal pelvic function.[46] Importance of elastin fibrils to maintain structural and functional integrity of pelvic floor and marked decrease and fragmentation of elastin fibers in patients with POP and abnormal elastin homeostasis in patients with UI have been reported.[47] Using primary smooth muscle cell (SMC) cultures from anterior vaginal wall biopsies from women undergoing abdominal hysterectomy, Takacs et al have demonstrated that levormeloxifene inhibits elastin secretion by inhibiting TGF-β1 production, which in turn may contribute to development of POP and UI.[47] According to Ewies et al, levormeloxifene disturbed ability of fibroblasts to maintain cytoskeleton architecture resulting in disruption of ligamentous integrity causing POP.[49] Postpartum ovariectomized rats treated with levormeloxifene show considerably more uretheral relaxation and decreased intercellular matrix composition, known to play role in development of UI. Reports on effect of estrogen, raloxifene and levormeloxifene on expression of alpha1A-adrenergic receptors and Rho-kinase signalling molecules in rat urethral SMCs, suggesting possible molecular mechanisms through which these agents differentially affect UI are available.[50,51]

It has also been long assumed that pelvic floor dysfunction is related to changes in menopause and is influenced by hormones.[46] While little is understood about precise role of hormonal status on pelvic support pathology, lack of estrogen following menopause causes thinning of vagina and is thought to reduce strength of supporting connective tissues.[52] Obgynket.com have hypothesized that SERMs enhance hypoestrogenic effects of menopause and may reduce tensile stiffness in uterosacral ligaments (USLs) and impact of SERMs on biomechanical properties may be correlated to changes in estrogen (ER) and progesterone (PR) receptor density and collagen type ratio, which may elucidate hormonal factors that impact POP in

postmenopausal female.[52] USLs are primary pelvic supportive structures of vagina, cervix and uterus and are located between vagina and rectum, connecting proximal vagina to sacrum. Little, however, is understood about potential clinical effects of SERMs on urogenital system, with the exception of effect on endometrium.[52] There also are no preclinical studies showing mechanistic basis for SERMs induction of POP.[52] Any stimulatory effect on uterus observed in preclinical trials should thus infer specific focus on urogenital system in imminent clinical trials.[9]

Several studies have looked at hormone receptors in tissues involved in pelvic organ support.[46] According to Shahryarinejad et al, ER in USLs may be responsible for changes in tissue elasticity.[53] Using monoclonal antibodies, Mokrzycki et al showed presence of both ER and PR in nuclei of SMCs of USLs, regardless of variations in age, race, menopausal status, parity, Body Mass Index (BMI) and medications affecting serum steroid hormone levels in all women undergoing hysterectomy for non-malignant conditions.[54] Significantly, hormone receptors were not found in collagen, vascular or neuronal components. Based on these observations, authors have suggested that USLs may be target for estrogen and progesterone and that steroid hormones may have role in pelvic support.[54] Banie et al have reported expression of ERα and ERβ in urethral SMCs in post-partum rats, former predominantly in cytoplasm and latter in nucleus.[50] According to Chen et al, while mRNA transcripts for ERα were present in vaginal wall and USLs of both pre- and post-menopausal women, ERβ mRNA was detected in vaginal wall and USLs from premenopausal women only.[55] According to Hsu and DeLancey, any supposition that hormones play major role in POP must be based on human studies that actually prove differences in prolapse occurring with and without hormonal supplementation or hormonal antagonist administration.[46]

POP and UI are generally associated with ageing and hormonal changes after menopause.[45] However, recently reported incidence of POP in normal pre-/peri-menopausal women, with all stages present mostly in 41-50 year age group (who technically are within the fertile range requiring family planning services) rather than in >50 years age group, occurrence of POP in one (out of 100) perimenopausal patient with DUB receiving ormeloxifene therapy, harmful genital effects (enlarged uterus, endometrial hyperplasia, microglandular cervical hyperplasia, menorrhagia) following prolonged unsupervised ormeloxifene therapy in young women and increased incidence of POP and UI during levormeloxifene clinical trials for treatment and prevention of postmenopausal bone loss and certain other SERMs (idoxifene, droloxifene and miproxifene), which exhibit beneficial actions including prevention of bone loss and fractures in preclinical and early phase clinical studies but are stimulatory on endometrium with increased risk of endometrial hyperplasia, polyps and cancer, may caution against prolonged unsupervised clinical use of SERMs.[6,9,11,25,40-44,56] According to Hendrix and McNeeley, identification and assessment of impact of current and future SERMs on pelvic floor and other genital tissues will be important to understand their potential long-term application in disease treatment and prevention.[40]

THE WAY FORWARD

Based on literature discussed above, there appears to be a need to:

Evaluate contraceptive efficacy of levormeloxifene as regular as well as emergency contraceptive using suitable safe and effective marketed oral contraceptive as reference standard in imminent clinical trials.[57] Significantly, need for emergency contraception is increasing globally because of changing lifestyle, fear of unwanted pregnancies and complications from pregnancy termination.[58]

Systematically analyse all participants, especially those over 40 years of age, using parallel placebo group comparable at baseline in terms of confounding and other risk factors for POP and UI, in study design in imminent clinical trials of levormeloxifene as contraceptive to rule out incidence and extent of any such health effects, including stimulatory effect on uterus/endometrium.[9,11,40,44,59,60] According to Hendrix and McNeeley, while higher proportion of surgery for POP in treated versus untreated women was noted during levormeloxifene and idoxifene trial, treated groups were not necessarily similar for confounding and risk factors that might make it challenging to preclude definitive association between effect of these agents and POP.[40]

Assess therapeutic benefits (including prevention or delay) following prolonged administration during imminent clinical trials of levormeloxifene as contraceptive in fertile-age pre-/peri-menopausal women. Pertinently, while levormeloxifene has shown promise in prevention of increased bone turnover and destructive joint diseases and beneficial effect on serum lipids, ormeloxifene is considered useful in the management of DUB, abnormal uterine bleeding, menorrhagia, cancer breast in women and men non-responsive to conventional therapy, mastalgia, fibroadenoma, ovulation-induction in women with ovulatory failure and protection against pulmonary hypertension.[2,3,10,11]

CONCLUSION

Need for orally active contraceptive that is pharmacologically and toxicologically safe, devoid of local/systemic side effects over prolonged periods of application, acting at peripheral target site (i.e., beyond hypothalamus-pituitary-gonadal axis), stable under wide range of environmental conditions, self-centric, self-applicable, socially-acceptable, financially-feasible and above all reversible at will can never be overemphasized.

Suggestions based on discussed literature and those from other investigators might be of value in the development of levormeloxifene or any other agent for human use and welfare, as developing lead molecule into clinically viable product involves enormous time, effort and financial commitment.[9,11,40-44,46,57,58]

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