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Anti-fertility activity of zafirlukast, a cysteinyl leukotriene receptor antagonist in female albino wistar rats

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ABSTRACT

The present research was to test zafirlukast, a cysteinyl leukotriene receptor antagonist in female albino Wistar rats, for antifertility activity. The matted female rats were divided into four classes of six separate animals each. Group I – provided 1 per cent w / v CMC- water suspension and acted as a regular monitor. Class II, III and IV- obtained Zafirlukast 1 percent w / v CMC in water at a dosage of 1, 10 and 20mg / kg body weight (e.g., daily). On the 10th day of pregnancy, in semiisterile condition, the animals underwent a laparotomy under a light ether anesthetic. The implants present on each ovary in both uterine horns and in the corpora lutea (CL) were counted. The animals were required to complete the gestation period (21-23 days), and they reported the number of litters born. The percentages of pre- and post-implantation failure were measured as well as the anti-fertility activities. As a result, the zafirlukast LOX inhibitor induced significant pre-implantation failure at dose levels of 20 mg / kg ($p<0.01$) and anti-fertility activity at dose levels of 10 mg / kg ($p<0.05$), 20 mg / kg ($p<0.01$) relative to control group. Zafirlukast, a receptor antagonist with cysteinylleukotrienes, has 100 per cent anti-implantation efficacy in Wistar albino rats. It suggests that zafirlukast can be used as an antifertility agent following confirmation of its protection and effectiveness in humans

Keywords: Anti-fertility activity, Zafirlukast, Cysteinylleukotrienes receptor, Anti-implantation activity

INTRODUCTION

Anti-fertility agents are the agents in both males and females which prevent fertility by interfering with different normal reproductive mechanisms. Development of new methods / agents for controlling fertility and research in this direction is imperative particularly for developing nations. If there was an ideal contraceptive, that contraceptive would be 100% effective, safe and easy to use; its effect would be reversible [1]. The growth of the world population has illustrated the need for new, inexpensive and secure contraception, or methods for maximum protection. Side effects of synthetics on normal and natural human bodies are far more

violent and unstable for extended use as long as they are supposed to be used by gender. Now time is disturbing to think of us as any alternative in the contraceptive field [2]. India will be the leading country in terms of population growth within a few years. Since the population is growing tremendously, this can have a dramatic impact on India's economic development. Family planning was encouraged by multiple contraception methods, but due to side effects caused by the use of steroidal contraceptives and the use of abortifacient drugs. There is a need for treatment that is safe with fewer side effects [3]. Around 48.2 per cent of couples aged 15 to 49 practice family planning strategies in India. Female sterilization constitutes 34.2%, with male sterilization dropping from 3.4% in 1992–93 to 1.9% in 1998–99. Condom use grew from 2.4 per cent to 3.1 per cent. Work is urgently required to develop new contraceptive modalities particularly for men and women, and to make existing methods safer, more effective and more acceptable [4].

Arachidonic acid, a fatty acid synthesized from linoleic acid in the diet, metabolizes the cyclooxygenase (COX) and lipoxygenase (LOX) pathways in the body. The arachidonic acid metabolites are called the eicosanoids. The COX track leads to the development of prostaglandin and thrombaxane, and the LOX track leads to the leukotrienes and hydroxyeicosatetraenoic acids [5]. The leukotrienes (LTs) are arachidonic acid metabolites of 5-lipoxygenase. The synthesis and release of (LTs) has been demonstrated in many cells and organs, and LTs are considered natural product of arachidonic acid's continuous metabolism [6]. Zafirlukast, a selective reversible cysteinyl leukotriene D4-receptor (LTD4 receptor) antagonist currently on the market for asthma care. Gastro-protective and antioxidant effects have been found on indomethacin-mediated gastric ulcer in rats [7], prophylactic ability against mild colitis caused by dextran sulphate sodium in rats [8], and protective effect on smoking-related lung injury in Wistar rats. [9] The lipoxygenase (leukotrienes) products have been seen in many mammalian tissues including humans. They are widespread in the lungs, intestines, uterus, kidneys, skin, back, and liver. They have become clinical targets for their functions as inflammation mediators. Potential use of lipoxygenase products in the management of primary dysmenorrhoea (especially in patients who do not react with PG synthetase inhibitors to the conventional treatment) and likely also in cases of endometriosis [10].

The concentrations of PGE, PGF, LTB, and LTC4/D / E increase in the ovary of PMSG-primed immature rats after hCG administration has begun the ovulatory cycle. Since variations in patterns of temporal changes of the different eicosanoids are seen during ovulation, we propose that each eicosanoid plays a distinct role in the follicular rupture process [11]. An alternative lipoxygenase (LOX) pathway has been shown to induce pharmacological inhibition to induce defective ovulation. The expression of ALOX5 and ALOX12 in the preovulatory follicle and that inhibiting LOX activity in the early phase led to a reduction in preovulatory induction of PTGS2 and development of PGE2 and thus to a defective ovulation. These findings can help to understand the mechanism in rats for involving the LOX pathway, at least the induction of PTGS2 activity, in LH-triggered ovulatory response [12]. LTB4 can play a role in rat ovary ovulation pathways, and LTB4 can execute its effects via MMP-2 [13].

In rats, NDGA tends to be an ovulation inhibitor. LTB 4 reversed NDGA's inhibition of ovulation, indicating a role for this LT in intraovarian ovulatory changes [14]. LTs in uterine functions during implantation and decidualization have been reported.[15, 16] The involvement of lipoxygenase pathways in the pre-implantation rabbit uterus and blastocyst, and their differential activity in different compartments of the uterus on different days of early pregnancy indicate an integrated role for these mediators in embryo-uterine interaction during implantation [1]. For both fertilisation and oocyte penetration, mouse and human spermatozoa need cysteinyl leukotriene activity [18].

Metabolites of lipoxygenase may be involved in human parturition. An earlier involvement in pregnancy [19] also suggests role for 5-LOX and FLAP in regulating parturition at term. HSD11B2 is decreased by progesterone in human placental trophoblasts and increased by inhibition of endogenous LOX metabolites, and a portion of the impact of LOX metabolites on HSD11B2 is mediated by stimulation of endogenous progesterone output [20]. The induction and

progression of decisiondualization includes LTs [21]. All the details above suggested that leukotrienes are involved in normal reproduction. If these leukotrienes are blocked or their receptor is blocked it can have a negative reproductive effect. In this study, based on this hypothesis, we evaluated the anti-implantation efficacy of zafirlukast a cysteinyl leukotriene receptor antagonist in female Wistar albino rats.

MATERIALS AND METHODS

Animals

Inbred female (100-150 g) and male (150-250 g) albino Wistar rats were obtained from SwamyVivekanandha College of pharmacy, animal house and maintained under standard conditions at 21±1^{o} C and 50-60% relative humidity with a photoperiod of 12 h light: 12 h dark. The animals were fed with standard pellet diet and water *ad libitum*. The protocols received prior approval from the Institutional Animal Ethical Committee and experiments were conducted in accordance with guidelines set by the CPCSEA (Committee for the purpose of control and supervision of experiments on animals), India.

Drugs

A gift sample of Zafirlukast obtained from (Ranbaxy Labs Ltd., Mumbai) was used for the study.

Chemicals

- Carboxy methyl cellulose (LobaChemie Pvt. Ltd., Mumbai).
- Betadine (G.S.Pharmbutor Pvt. Ltd., Rudrapur).
- Neosporin (GlaxoSmithkline Pharmaceutical Ltd. Bangalore).

Anti-Implantation Activity

The female's vaginal smears were taken regularly to determine their oestrus process. Adult female Wistar albino rats of proven pro-oestrus and oestrus fertility were housed with mature male rats of proven fertility (three females for one male). On mating days, females of the required weight were put in male cages for around 14 h. In the early morning vaginal smears each female was tested for the existence of spermatozoa. The first appearance of sperm in the vaginal smear has been taken as pregnancy day one. Implantation in rats happens on day 5 of pregnancy.

The female rats which had mated were then separated and caged singly. They were divided into four different groups consisting of six animals each.

The various groups were treated as follows:

The drug were administered orally once daily through gastric gavage from 1-7 days of pregnancy and 7-21 days of pregnancy

- Group I – received the 1% w/v CMC- water suspension and served as control (p.o. daily).
- Group II - received Zafirlukast 1mg/kg body weight in 1%w/v CMC in water (p.o. daily).
- Group III- received Zafirlukast 10mg/kg body weight 1%w/v CMC in water (p.o. daily).
- Group IV- received Zafirlukast 20mg/kg body weight 1%w/v CMC in water (p.o. daily).

On the 10th day of pregnancy, in semiisterile condition, the animals underwent a laparotomy under a light ether anesthetic. The implants present on each ovary in both uterine horns and in the corpora lutea (CL) were counted. The animals were required to complete the gestation period (21-23 days), and they reported the number of litters born. The pre- and post-implantation loss percentages and the anti-fertility operation were determined using the following formula [22].

$$\% \text{ Pre- implantation loss} = \frac{\text{Number of CL} - \text{number of implants}}{\text{Number of CL}} \times 100$$

$$\% \text{ Post- implantation loss} = \frac{\text{Number of implants} - \text{number of litters}}{\text{Number of implants}} \times 100$$

$$\% \text{ Anti-fertility activity} = \frac{\text{Number of CL} - \text{number of litters}}{\text{Number of CL}} \times 100$$

Procedure for laparotomy

The animal was lightly anesthetized with ether and limbs were tied to a rat board (waxed) with the ventral side up. The hairs on the area around the midline abdominal region were clipped with curved scissor and the region was cleaned with 70 % alcohol. An incision of 2 cm length was made along the midline to expose the viscera. The superficially lying coils of ileum were lifted to expose the two uterine horns. The horns were examined for implantation sites. Implants were visible as clear swellings on the uterine horns giving the uterine tube a beaded appearance. Embryos with bright red dish aspect and a clear margin were considered to be healthy. Resorbing was considered for those with a dull blue color with no strong margin and orientation with some exudates [23]. The number of implants per horn was counted as well as the resorption sites. The ovaries that sit on the upper end of the uterine horns reveal corpora lutea over the surface as reddish yellow spots. Also noted was the amount of corpora lutea present at each ovary.

The organs were replaced again, after counting. To avoid any infection a small amount of Neosporin powder was sprayed over the organs. Using absorbable catguts and skin layer with continuous sutures using silk thread, incision through muscular layer was closed with continuous suture. After wiping with 70 per cent alcohol, an antiseptic, povidone iodine solution was applied to the sutured region. Throughout the experiment the animal was placed on mild ether anesthesia. The rats were moved to a warm position after laparotomy until they recovered from anaesthesia.

Statistical analysis

The values are expressed in mean ± SEM. One way ANOVA followed by Tukey's multiple comparison Test was used to analyse the effect of different dose of drug when compared to control, with the help of Graph Pad Instat software, version 3.01. $P<0.05$ considered as significant.

RESULTS

The Effect of Zafirlukast on Implantation

Anti-implantation activity of zafirlukast when treated with 1-7 days of pregnancy

The LOX inhibitor zafirlukast elicited significant pre-implantation loss at dose levels of 20 mg/kg ($p<0.01$) and the anti-fertility activity, at dose levels of 10 mg/kg ($p<0.05$), 20 mg/kg ($p<0.01$), when compared to control group (Table: 1, Figure: 1).

Table 1: anti-implantation activity of Zafirlukast treated for 1-7 days of pregnancy at different dose levels of 1, 10 and 20 mg/kg body weight

S. NO	TREATMENT	% PRE-IMPLANTATION LOSS	% POST-IMPLANTATION LOSS	% ANTI-FERTILITY ACTIVITY
1	Control	29.986 ± 4.839	22.696 ± 6.182	44.845 ± 7.461
2	Zafirlukast (1 mg/kg)	58.588 ± 17.014	33.773 ± 18.325	74.605 ± 13.900
3	Zafirlukast (10 mg/kg)	46.088 ± 15.977	61.615 ± 15.042	83.165 ± 7.853*
4	Zafirlukast (20 mg/kg)	100 ± 0.000**	00 ± 0.000	100 ± 0.000**

n=6; The values are expressed as mean ± SEM; *P< 0.05, **P<0.01 when compared to control groups (One way ANNOVA followed by Tukey's multiple comparison Test).

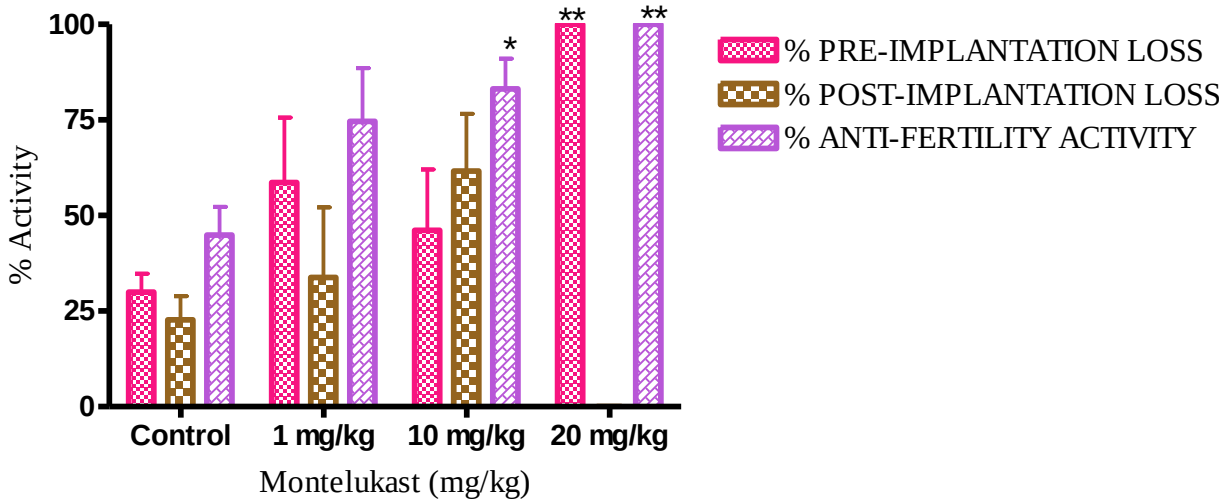

Figure 1: Pre- and post-implantation loss (%) and anti-fertility activity (%) of zafirlukast when administered orally at various dose levels to female albino *Wistar* rats from days 1 to 7 of pregnancy. Values are expressed as mean ± SEM; *P<0.05, **P<0.01 when compared to control group (n=6).

Anti-implantation activity of zafirlukast when treated 7-21 days of pregnancy

The LOX inhibitor zafirlukast elicited significant pre-implantation loss at dose levels of 1 mg/kg (p<0.05), 10 mg/kg (p<0.001), 20 mg/kg (p<0.001) and the anti-fertility activity, at dose levels of 1 mg/kg (p<0.001), 10 mg/kg (p<0.001) and 20 mg/kg (p<0.001), when compared to control group (Table: 2, Figure: 2).

Table 2: Anti-implantation activity of zafirlukast treated for 7-21 days of pregnancy at different dose levels of 1, 10 and 20 mg/kg body weight

S. NO.	TREATMENT	PRE-IMPLANTATION LOSS	POST-IMPLANTATION LOSS	ANTI-FERTILITY ACTIVITY
1	Control	18.199 ± 1.558	37.031 ± 3.347	48.701 ± 2.096
2	Zafirlukast (1 mg/kg)	56.03 ± 14.233*	56.711667 ± 18.287	92.909283± 3.493***
3	Zafirlukast (10 mg/kg)	96.15833 ± 3.846***	11.1111 ± 11.111	98.717933± 1.282***
4	Zafirlukast (20 mg/kg)	93.93667± 3.835***	33.333 ± 21.082	100 ± 000***

n=6; The values are expressed as mean ± SEM; *P< 0.05, ***P<0.001 when compared to control groups (One way ANNOVA followed by Tukey's multiple comparison Test).

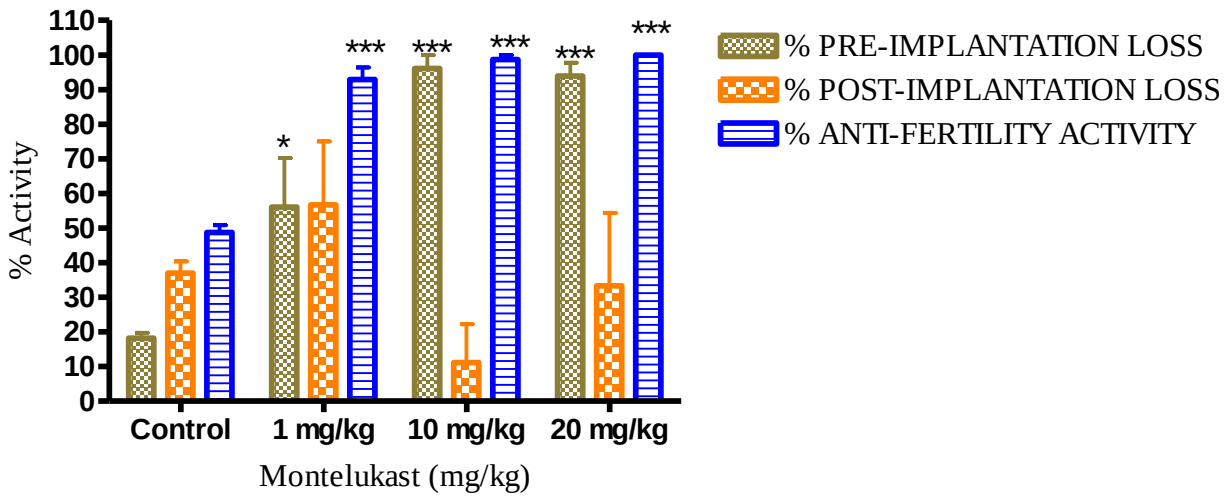

Figure 2: Pre- and post-implantation loss (%) and anti-fertility activity (%) of zafirlukast when administered orally at various dose levels to female albino *Wistar* rats from days 7 to 21 of pregnancy. Values are expressed as mean ± SEM; *P<0.05, ***P<0.001 when compared to control group (n=6).

DISCUSSION

India controls 16 per cent of the world's population over 2.4 per cent of the world's land area. Thus the most significant problem facing India today is its population size and growth. The 2001 census has shown that India's population as of 1 March 2001 was 102.70 crores. The country's population rose from 36.11 crores to 102.70 crores in the 50 years since 1951. The population of India is increasing quite rapidly the burden of numbers on the country's natural resources is expected to increase. Population density has risen from 117 people per sq.km in 1951 to 324 people in 2001, which may exacerbate the still very bad social and demographic indicators in this country [24]. Arachidonic acid is primarily metabolized by lipoxygenases (LOX including 5-LOX, 12-LOX, and 15-LOX) and cyclooxygenase (COX including COX-1, COX2). 5-lipoxygenase is the first dedicated enzyme in the LOX pathway to generate 5-hydroperoxyeicosatetraenoic acid (5-HPETE) followed by 5-HETE and leukotrienes, including LTA4, LTB4, LTC4, LTD4 and LTE4 [25]. Targeting upstream enzymes affects several downstream pathways, which can cause adverse effects by disrupting the equilibrium between various pathways that metabolize AA. Aiming at downstream enzymes or receptors may be more appropriate [26]. The lipoxygenase (leukotrienes) products have been shown in many mammalian tissues, including humans [10]. Leukotrienes are involved in various reproductive stages including ovulation [11-14], implantation [17, 27, 28], decision [21], parturition [19]. Pakrasi et al. (1985) reported that the presence of lipoxygenase pathways in the pre-implantation rabbit uterus and blastocyst, their differential operation in different uterus compartments on different days of early pregnancy, suggests that these mediators play an integrated role in embryo-uterine interaction during implantation [17]. Leukotrienes may be essential for uterine implantation and/or implantation preparation [26]. The product Lipoxygenase may play a role in implantation [28].

For both fertilisation and oocyte penetration, mouse and human spermatozoa need cysteinyl leukotriene activity [18]. Metabolites of lipoxygenase may be involved in human parturition. An earlier involvement in pregnancy [19] also suggests role for 5-LOX and FLAP in regulating parturition at term. The induction and progression of decisiondualization includes LTs [21]. If this role of leukotriene is blocked in normal implantation it may have an adverse effect on implantation. We selected zafirlukast, a cysteinyl leukotriene receptor antagonist for evaluating anti-fertility activity in albino Wistar rats, based on this hypothesis. Zafirlukast sodium is primarily used in the treatment of asthma, chronic obstructive pulmonary disease (COPD), and in the relief of

allergic rhinitis symptoms. It is an orally active agent, which binds to the CysLT1 receptor with high affinity and selectivity. Zafirlukast inhibits LTD4's physiological actions at the receptor CystLT1 [29].

In this study, the oral administration of leukotrienes receptor antagonist zafirlukast was tested for anti-fertility properties in three doses of 1mg / kg (adult human dose conversion to animal dose), 10mg / kg, and 20 mg / kg rat body weight [30, 31]. 1 to 7 days of pregnancy and 7 to 21 days. Treatment Days 1-7 were chosen as they span the entire implantation cycle. Days 1-3 are the days of endometrium preparation for blastocyst implantation, when the uterine blood flow increases rapidly as a result of increased endometrial capillary permeation [32]. It is suspected that afternoon of day 4 is the time of the "estrogen explosion," which may be responsible for the implantation on day 5. Days 6-7 reflect very early post-implantation stages [33]. Days 7-21 are time of post-implantation. In 1 to 7 days as compared to control group, the rats treated with zafirlukast 10 mg / kg showed substantial ($p<0.05$) percent anti-fertility activity. The animal treated with 20 mg / kg zafirlukast showed substantial ($p<0.01$) percent loss of pre-implantation and percentage of anti-fertility activity as compared to control group (Table: 1-5, Figure: 1). During this 1-7 day study procedure, zafirlukast demonstrated substantial dose-dependent antifertility activity.

In 7 to 21 days, as compared to control group, the rats treated with zafirlukast 1 mg / kg showed substantial ($p<0.05$) percent loss of preimplantation. In contrast to control group, the animals treated with zafirlukast 10 mg / kg, 20 mg / kg showed substantial ($p<0.001$) percent loss in preimplantation. In contrast to control group, the experimental group treated with zafirlukast 1 mg / kg, 10 mg / kg, 20 mg / kg showed substantial ($p<0.001$) percent anti-fertility activity (Table: 6-10, Figure: 2). In this 7-21 day study treatment zafirlukast showed major dose-dependent anti-fertility activity.

Pakrasi, (1997) stated that a selective 5-lipoxygenase enzyme inhibitor does not impede mice's implantation, suggesting a question about the involvement of 5-lipoxygenase products in implantation [11]. But in our study results a cystenylleukotrienes receptor antagonist in female albino Wistarrats demonstrated dose-dependent anti-implantation activity of the zafirlukast. It would be 100% effective, safe and easy to use if an ideal contraceptive is available and its effect would be reversible [1]. We found that in both 1-7 days and 7-21 days of study therapy, the LOX-inhibitor zafirlukast 20 mg / kg achieved 100 per cent anti-fertility activity.

Our analysis revealed that zafirlukast meets the one of ideal contraceptive requirements. Our findings also suggest leukotriene is involved in the implantation process. We interpret our findings as confirmation that rat implantation involves leukotrienes formed in the endometrium and that the drug that we administered works at the endometrial stage. In order to validate this interpretation, it would be necessary to record that the treatments did not cause endocrine changes which interfere with pregnancy implantation. An increase in oestradiol, for example, would speed up transportation of eggs through the oviduct and reduce the number of implanted embryos. Inhibition of prolactin secretion and subsequent luteolysis with decreased progesterone production would also cause pre and post implantation loss. An additional approach could consist of demonstrating that exogenous progesterone does not reverse the action of drugs.

We consider that strength of our anti-fertility study includes that results were obtained by direct observation. Anti-implantation research is a promising field of WHO contraceptive research and development programmes. Since we studied the anti-implantation activity of zafirlukast, it may add good scientific knowledge to the contraceptive research. Further studies will be required to evaluate the anti-ovulatory effect of zafirlukast and to find out its reversible nature in anti-fertility activity.

Our study suggested that zafirlukast can be used as an anti-fertility agent, since it produced 100% anti-fertility activity. Further research however needed to determine the safety and efficacy of zafirlukast in pregnant animals. If the efficacy and safety is established in animals, we may further proceed by appropriate clinical trials to evaluate its effectiveness and safety in humans. Our research also indicated that in pregnant women and people with reproductive age groups the cysteinyl leukotriene receptor antagonist zafirlukast could be

avoided. It is also suggested that adequate pharmacovigilance studies can be performed in zafirlukast to establish its safety in pregnant women and that proper warning can be given on the label.

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