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Co-administration of St. John's wort and hormonal contraceptives: a systematic review☆,☆☆,★

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Abstract

Objectives: St. John's wort (SJW) is a known strong inducer of the cytochrome P450 (CYP) 3 A4 enzyme, and both the ethinyl estradiol and progestin components of hormonal contraceptives are substrates of CYP3A4. This systematic review examined whether the co-administration of SJW and hormonal contraceptives leads to significant safety or efficacy concerns.
Study design: Systematic review.
Methods: PubMed and Cochrane Library databases were searched for articles of any comparative study design (clinical or pharmacokinetic) that examined potential interactions between SJW and hormonal contraceptives in women of reproductive age.
Results: Of the 48 identified articles, four studies met inclusion criteria and compared use of combined oral contraceptives (COCs) alone to the use of COCs co-administered with SJW. Two studies demonstrated no change in markers of ovulation, but one study demonstrated increased follicular growth and probable ovulation when COCs were co-administered with SJW. Three studies demonstrated an increased risk of breakthrough bleeding with COCs and SJW. Three studies showed changes in at least one pharmacokinetic parameter that suggested a significantly decreased exposure to hormone concentrations when COCs were co-administered with SJW. The only study that did not demonstrate any significant pharmacokinetic differences examined a SJW product containing a low amount of hypericin.
Conclusion: Limited evidence showing increased risk of ovulation and breakthrough bleeding raises concern for decreased contraceptive efficacy when COCs are co-administered with SJW. The pharmacokinetic evidence is mixed but suggests that SJW administration may be associated with weak to moderate induction of the metabolism of COCs.

Keywords: St. John's wort; *Hypericum perforatum*; Hormonal contraception; Drug interactions; Depression

1. Introduction

Use of complementary and alternative medicine (CAM) has been growing in the United States for decades [1–3]. Surveys of US adults report that 42% to 63% of respondents use some form of CAM therapy [2–5], and about 18% reported use of at least one herbal product in the previous 12 months [1]. Use of herbal preparations and CAM therapies is more common in women than men [1–4]. Approximately 20% of reproductive-age women in the United States report taking herbal products [1,3]. The herbal product known as St. John's wort (SJW) (*Hypericum perforatum)* has become a common therapy for the treatment of depression in the United States and around the world [6]. However, SJW has been associated with numerous adverse drug interactions, likely due its ability to induce the cytochrome P450 (CYP) enzyme 3 A4 [7]. The US Food and Drug Administration classifies SJW as a strong inducer of CYP3A4 and weak inducer of CYP2C9 enzymes. A strong inducer for a specific CYP is defined as one that decreases the area under the curve (AUC) of a substrate for that CYP by ≥80% and a weak inducer translates to a 20–50% decrease in AUC [8].

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SJW is commonly used along with prescription medications [9]. One study found that, for nearly 28% of office visits in which the use of SJW was documented by the provider, at least one other drug was prescribed that could lead to a potentially harmful combination, including oral contraceptives [9]. Contraceptive steroids are metabolized by both CYP3A4 and CYP2C9 enzymes [10]. Thus, coadministration with CYP3A4 and/or CYP2C9 inducers, such as SJW, may lead to rapid metabolism of steroid hormones, potentially leading to decreased steroid hormone concentrations and increased risk for unintended pregnancy.

Case reports have linked the use of SJW in users of combined oral contraceptives (COCs) with breakthrough bleeding [11] and unintended pregnancy [12]. In addition, the Medicines and Healthcare Products Regulatory Agency of the United Kingdom released a drug safety update about SJW in March 2014 describing 19 reports of potential drug interactions between SJW and hormonal contraceptives. The reporting physicians suspected that 15 cases of unintended pregnancies (4 with etonogestrel implants and 11 with oral contraceptives) and 4 cases of breakthrough bleeding (all with oral contraceptives) were linked to co-administration of the contraceptive and SJW [13]. Although previous published reviews have looked at some of the evidence around SJW and drug interactions, none focused solely on SJW and hormonal contraception [7,14]. Thus, given the theoretical concerns and case reports of potentially significant interactions, this systematic review was conducted to examine the evidence on interactions between SJW and hormonal contraception. We were interested in interactions in both directions, that is, does use of SJW increase or decrease steroid hormone concentrations (from the hormonal contraceptive), possibly leading to decreased contraceptive efficacy or increased risk for adverse events? Additionally, does use of hormonal contraception increase or decrease SJW concentrations, possibly leading to SJW toxicity or decreased SJW efficacy?

The United States *Medical Eligibility Criteria for Contraceptive Use, 2010* (US MEC) does not include recommendations for the safe use of contraception with SJW [15]. This systematic review was conducted to prepare for a meeting held at the Centers for Disease Control and Prevention in August 2015 to update the US MEC.

2. Methods

A systematic review was conducted according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [16].

2.1. Search strategy

We searched PubMed and Cochrane Library databases from database inception through December 8, 2015 (Appendix A).

2.2. Selection criteria

We searched for studies that addressed two research questions:

#1: Among women using hormonal contraception, does use of SJW increase adverse outcomes (due to increased concentrations of the hormonal contraception) or decrease contraceptive efficacy (due to decreased concentrations of the hormonal contraception) compared with non-use of SJW?
#2: Among women taking SJW, does use of hormonal contraception increase adverse mental or physical health outcomes (e.g., due to decreased or increased concentrations of SJW) compared with non-use of hormonal contraception?

Articles were included if they examined the co-administration of SJW (of any dose) with any type of hormonal contraceptive (COCs, transdermal patches, or vaginal rings; progestin-only implants, injectables, or pills; emergency contraceptive pills; or levonorgestrel intrauterine devices) among women of reproductive age. Articles in any language and of any comparative study design were included; however, case reports and case series, abstracts, and unpublished data, such as theses or dissertations, were excluded. Clinical outcomes of interest were pregnancy, ovulation, breakthrough bleeding, and adverse events. As we anticipated limited availability of clinical data, we also included articles that examined pharmacokinetic (PK) outcomes of either SJW or hormonal contraceptive steroid hormones. All PK parameters measured were included.

A common method for assessing potential clinical significance of significant changes in PK parameters is to calculate geometric mean ratios for various parameters (e.g., geometric mean ratio for area under the curve$_{\text{drug A}}$ [AUC]=AUC$_{\text{drug A}}$ in users of drug B/AUC$_{\text{drug A}}$ in non-users of drug B ×100), construct 90% confidence intervals (CIs) around that ratio, and set a predefined range that would suggest a lack of interaction (bioequivalent). For this review, the predefined range was a 90% CI of 80–125%. Geometric mean ratios with 90% CIs falling outside that range were said to suggest bioinequivalence. We excluded CYP genotyping outcomes and studies that examined the effects of a third co-administered drug.

2.3. Study selection and quality rating

One author (E.B.B.) searched all titles and abstracts and identified articles that required full-text review. Two authors (E.B.B. and K.M.C.) identified full-text articles that met inclusion criteria. Clinical studies were assigned a quality rating according to the US Preventative Services Task Force rating system. Because a standard rating system for PK studies has not been established, we developed and applied one (Appendix B). Two authors (E.B.B. and K.C.) independently assigned a quality rating to each article. The