Primary care

Interaction of St John's wort with conventional drugs: systematic review of clinical trials

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Abstract

Objective To determine the methodological quality of clinical trials that examined possible interactions of St John's wort with conventional drugs, and to examine the results of these trials.

Design Systematic review.

Data sources Electronic databases from inception to April 2004, reference lists from published reports, and experts in the field.

Study selection Eligible studies were prospective clinical trials evaluating the pharmacokinetic effect of St John's wort on the metabolism of conventional drugs.

Data extraction Two reviewers selected studies for inclusion and independently extracted data.

Data synthesis 22 pharmacokinetic trials studied an average of 12 (SD 5) participants; 17 trials studied healthy volunteers and five studied patients. Most (17) studies used a "before and after" design; four studies used control groups other than the active group. Three studies randomised the sequence of administration or the participants to study arms or periods; three studies blinded participants or investigators. In 15 trials, investigators independently assayed the herb. Of 19 trials with available plasma data, three found no important interaction (change in area under the curve <20%) and 17 found a decrease in systemic bioavailability of the conventional drug; in seven studies the 95% confidence interval excluded a decrease of <20%.

Conclusion Clinicians and patients should beware of possible decreases in the systemic bioavailability of conventional drugs when taken concomitantly with St John's wort.

Introduction

Use of natural health products, including herbal medicines, vitamins, and supplements, is widespread.[1] With expanding use, clinicians and researchers are focusing their attention on the possibility that these products interact with prescribed drugs and alter their metabolism. Case reports and clinical trials have found that St John's wort (*Hypericum perforatum*), in particular, may cause important interactions, possibly leading to adverse events or drug resistance. The purposes of this systematic review were to identify all clinical trials examining drug interactions of St John's wort, assess these trials' methodological quality, and summarise their findings.

Methods

Data sources

We searched the following databases (from inception to April 2004): AMED, CINAHL, E-Psyche, CISCOM (to December 2002), Cochrane CENTRAL, Medline, the National Research Register (United Kingdom), ClinicalTrials.gov (United States), and bibliographies of retrieved articles; we also contacted experts in the field.

Study selection and quality assessment

Two reviewers (EM, PW), working independently and in duplicate, identified relevant abstracts and assessed eligibility after reading the full reports, resolving disagreements by consensus or arbitration. Eligible studies were prospective clinical trials examining the pharmacokinetic effect of St John's wort on the metabolism of a conventional drug.

We assessed the quality of each study by examining the study design, the mechanism to allocate patients, the inclusion of control patients, the use of placebo, and justification of sample size. In addition, we determined whether the trial used single dose pharmacokinetics or studied St John's wort at its steady state (continuous use of the herb increases the likelihood of an interaction). We also determined if the investigators assayed St John's wort in each preparation.

Statistical analysis

We measured inter-rater agreement (adjusted for chance) for eligibility using the κ statistic. We describe the magnitude of the interaction between St John's wort and the conventional drug by differences in the area under the curve (AUC) of the drug before and after challenge with St John's wort. We used the difference in AUC reported as a percentage of the AUC at baseline and 95% confidence interval around this change; if the difference was not reported, we estimated the confidence interval from reported measures of variance or P values for the change in AUC.[2] We

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P+ *A flow chart showing selection of studies for inclusion and a table with further details about the studies are on bmj.com*

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considered an interaction to be important when the confidence interval of the AUC difference was completely outside of the standard deviation (SD) 20% equivalence limits; we considered that no important interaction existed when the confidence interval of the AUC difference was entirely within the SD 20% equivalence limits.[3] Owing to statistical and methodological heterogeneity we did not pool results of the separate trials.

Results

Search results

The chance adjusted inter-rater agreement for inclusion of studies was $\kappa = 0.8$ (95% confidence interval 0.6 to 1.0); the 22 included trials (published between 1999 and April 2004) studied an average of 12 (SD 5) participants.[4–25] (For more details of selection and of the included studies, see the flow chart and table on bmj.com) Five studies enrolled patients who needed the drugs for health reasons[4–8]; all others enrolled healthy volunteers.

Pharmacokinetic details

Two studies investigated both single dose and steady state pharmacokinetics,[9 10] and 18 studies examined steady state pharmacokinetics. Two studies examined exclusively urine metabolites.[11 12] The mean duration of St John's wort dosing for steady state studies was 17 (SD 11.5, range 3-56) days. In seven studies, participants received St John's wort concurrently with the conventional drug for the post-exposure AUC assay.[4–6 13–16] Fifteen trials reported independent assays of the St John's wort preparation to determine whether the dosage of interest was truly contained in the product. Investigators assayed the serum concentration of the conventional drug for a mean of 37.5 (SD 47, range 7-216) hours to generate a "concentration over time" curve and the AUC.

Study design

The table shows the study design and methodological quality of the 22 included trials. Eighteen did not have a control group—that is, a group treated equally but not receiving the active drug concomitantly. Of the four studies with control groups, three were randomised (procedure to generate the randomisation sequence not described)[13 17 18]; three control groups received placebos (placebo used not described).[13 15 18]

Effects of St John's wort

The figure shows the effect of St John's wort on the plasma AUC of the conventional drug; it uses a forest plot with studies grouped by study design. In three studies, the 95% confidence interval excluded a reduction in AUC of $>20\%$.[8 14 19] Of the 16 other studies, point estimates of 15 indicated a decrease of $>20\%$ in availability of the conventional drug. Of these 15, the confidence interval excluded a reduction of $<20\%$ in AUC in seven. One study assessed primary mechanisms of interactions and did not report AUC data.[20]

Discussion

Our review shows that St John's wort has the potential to reduce systemic bioavailability of many conventional drugs. However, the studies had several shortcomings. Firstly, they were small: in 10 of the 22 trials the 95% confidence interval overlapped the 20% threshold for an important reduction in the area under the curve (AUC), so the results were inconclusive, and no study was large enough to examine subgroups meaningfully. Secondly, they contained few safeguards against bias (such as random and concealed allocation of participants, inclusion of controls, and blinding. Thirdly, their methods varied widely, with inadequate use of widely accepted standards of research practice.

Characteristics of methods used in 22 reviewed studies

Name and year	Study design	Herb assayed	Control group	Blinding	Randomisation	Sample size discussed
Mathijssen, 2002[5]	Before and after	No	No	No	No	No
Markowitz, 2000[16]	Before and after	Yes	No	No	No	No
Burstein, 2000[14]	Before and after	Yes	No	No	No	No
Durr, 2000[20]	Before and after	No	No	No	No	No
Piscitelli, 2000[21]	Before and after	Yes	No	No	No	No
Mai, 2003[7]	Before and after	Yes	No	No	No	Yes
Hebert, 2004[23]	Before and after	Yes	No	No	No	No
Bauer, 2003[6]	Before and after	Yes	No	No	No	Yes
Hall, 2003[8]	Before and after	Yes	No	No	No	Yes
Jiang, 2004[22]	Before and after	Yes	No	No	Yes	Yes
Johne, 2002[4]	Before and after	Yes	No	No	No	Yes
Wang, 2001[10]	Before and after	Yes	No	No	No	Yes
Wang, 2002[9]	Before and after	Yes	No	No	No	No
Markowitz, 2003[24]	Before and after	No	No	No	No	Yes
Dresser, 2003[25]	Before and after	No	No	No	No	No
Roby, 2001[11]	Before and after	Yes	No	No	No	No
Wenk, 2004[12]	Before and after	No	No	No	No	No
Sugimoto, 2001[15]	Crossover	No	Yes (placebo)	Yes	Yes	No
Pfrunder, 2003[17]	Crossover	Yes	Yes	No	Yes	No
Wang, 2004[18]	Crossover	No	Yes (placebo)	Yes	Yes	No
Morimoto, 2004[19]	Crossover	Yes	No	No	No	No
Johne, 1999[13]	Parallel	Yes	Yes (placebo)	Yes	No	Yes

The variable effect of St John's wort on different conventional drugs may be related to the variety of metabolic pathways that these drugs use. We could not, however, discern a clear relation between the nature of the conventional drug being tested or its posited metabolism and the magnitude of the interaction.

Our study is the first systematic review of St John's wort that examines the methodological quality of the clinical trials. Previous reviews have described the findings of clinical trials but have not assessed the trial validity or effect sizes.[26-28]

Our review uncovers several threats to the validity of pharmacokinetic studies that examine herb-drug interactions. A serious concern about conducting any research with herbs is the correspondence of the herb studied with the products that are available to and preferred by consumers. Assaying the herb is critical, as the product's content can differ from the dosage reported on the label and the composition varies from batch to batch.[29] Only 15 of the 22 studies reported that they assayed the St John's wort content of the preparations they used. Furthermore, the duration of dosing used in these trials was highly variable, and few studies reported their rationale for the dosing regimen tested.

The methodological quality of the included studies was limited. Most studies used a "before and after" design that lacked contemporary controls or randomisation of order of administration, in particular to control for carryover effects, time dependent metabolic variability, and co-ingestions. When investigators used controls, they did not clearly describe how they allocated participants, how they generated the allocation sequence, and how they concealed this sequence from investigators enrolling participants. The US Food and Drug Administration's guidance on conducting pharmacokinetic trials,[3] a commonly used guide, may consider these important safeguards against bias in future recommendations.

What is already known on this topic

Some research has suggested decreased systemic bioavailability of conventional drugs when St John's wort is taken concomitantly

What this study adds

Studies examining drug interactions of St John's wort are limited in scope and methodological quality, particularly in the areas of controls and randomisation

Clinicians and patients do not currently have high quality information to guide their decisions to use herbal products, particularly in conjunction with conventional drugs

We used a somewhat arbitrary threshold (20%) in AUC change to identify important changes in systemic bioavailability of the conventional drug after exposure to St John's wort; we could not identify clearly established drug specific thresholds beyond which reductions in AUC might lead to important reductions in drug effect. Lack of such thresholds may seriously hinder the clinical interpretation of pharmacokinetic trials.

Clinicians and patients should beware of possible reductions in systemic bioavailability of conventional drugs when taken concomitantly with St John's wort. Higher quality research is necessary to provide reliable information to guide clinical practice. In particular, trials that include adjustments in the dose of the conventional drug to achieve optimal AUC in the presence of herbs that reduce bioavailability of that drug may provide clinicians and patients with an approach to their concomitant use.
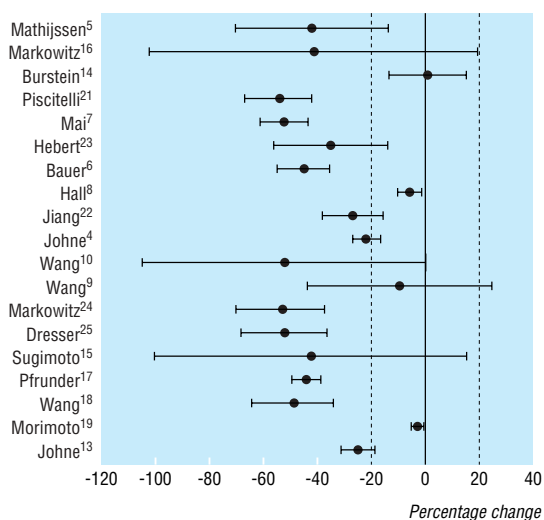
Mean percentage reported change (with 95% confidence intervals) in systemic bioavailability of drugs in plasma, after exposure to St John's wort. Trials are ordered according to study design (Mathijssen to Dresser are "before and after," Sugimoto to Morimoto are crossover, and Johne is a parallel design)

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3 Food and Drug Administration. In vivo drug metabolism/drug interaction studies—study design, data analysis, and recommendations for dosing and labeling. 1999. www.fda.gov/cber/gdlns/metabol.pdf (accessed 20 May 2004)
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When I use a word

Balancing benefits and harms in health care

Some drugs yield more than one benefit. For instance, β blockers have antihypertensive, antianginal, and antiarrhythmic effects. They also have more than one adverse effect. So we can talk about their benefits and harms. It's all to do with how you count.

The Danish philologist Otto Jespersen expounded the concept of count and non-count nouns in an unpublished lecture to the Copenhagen Academy of Sciences in 1911. As he explained in *The Philosophy of Grammar* (1924), you can form plurals if you can collect two things alike. For example, two bananas (two of the same thing). Or two fruits, an apple and an orange (two of the same kind). But we have no plural word for a journal plus a stethoscope, except to call them two objects, and certainly no plural word for a journal plus health care.

Music, traffic, and tact cannot be counted; arm, leg, and eye can—at least in English; in Hungarian the word for any pair of body parts is singular; one eye is referred to as a half eye. Then "you" in English denotes both singular and plural ("ye" having disappeared), while the French have "tu" and "vous." "Peut-on tutoyer?" a student asked her supervisor; the reply was stony: "Si vous voulez." Some nouns have it both ways, depending on meaning. Chocolates in a box are countable—two chocolates, a few chocolates, many chocolates (but who's counting?). Chocolate in a bar is not—much chocolate, little chocolate, less chocolate. Morbidity (sickness) is not countable, but comorbidities means diseases; competency (ability) is not countable, but "competencies" means things people can do. Both plurals are relatively new uses.

Now "harm" has two meanings, injury and an injury. And the countable sense has as long a pedigree as the uncountable one. Harms are referred to in a 10th century poem, *Genesis*, wrongly attributed to Caedmon: "Ealle synt uncre hearmas gewrecene." Shakespeare uses the noun harm about 90 times, and 14 of those are plural. In *The Taming of the Shrew*, a messenger tells Christopher Sly that his doctors "thought it good you hear a play / And frame your mind to mirth and merriment, / Which bars a thousand harms and lengthens life." And Shakespeare knew his count from his non-count: "She hath more hair than wit and more faults than hairs," says the Veronese clown, Lance, about his sweetheart. However much hair she had, she doesn't sound like a great catch.

Drugs are prescribed because of their potential benefits, but in every case there are risks of harms; before prescribing, the former should be weighed against the latter. This is commonly called assessing the "benefit to risk ratio." But benefit and risk are non-comparable: one is an actual outcome, the other a chance of one. Benefits are properly balanced by harms. However, the two are incommensurate and cannot be combined into a ratio. One should therefore talk about the benefit to harm balance, which is a complex function of the seriousness of the problem to be treated, the efficacy and safety of the drug to be used, and the efficacy and safety of other available drugs.

And that is why we have called this special issue of the *BMJ* "Balancing benefits and harms in health care."

Jeff Aronson *clinical pharmacologist, Oxford*

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