Perioperative analgesia and the effects of dietary supplements

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With over 50,000 dietary supplements available, resurgence in consumer interest over the past few decades has resulted in an explosion of use of these agents worldwide. Disillusionment with current medications and belief in “natural medicines” has resulted in a multibillion dollar industry. Active ingredients in a number of herbs are being tested for therapeutic potential, and some are...
kava kava
St. John’s wort
valerian
efficacious, so herbal medicines cannot be dismissed. The prevalence of herbology is further encouraged by a relatively relaxed policy of the FDA regarding these compounds, which they consider foods. As herbal products are included in the “supplement” category, there is no existing protocol for standardization of these products. There are numerous examples of herbs that can adversely affect patient recovery and outcomes in anesthesia. The prudent anesthesia provider will make sure to obtain correct information as to accurate herbal usage of each patient and attempt to discontinue these products two to three weeks prior to the delivery of an anesthetic. Postoperative analgesia, bleeding, and level of sedation can be negatively impacted related to herbal products and herbal–drug interactions. Over 90 herbal products are associated with bleeding and this can be a specific problem intraoperatively or when considering placement of a regional anesthetic for postoperative pain management.

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Practice points

- Owing to a number of factors, the use of herbal products has become common place worldwide in recent years.
- A number of these agents have important effects with regard to bleeding, to sedation, and herbal–drug interactions.
- A prudent anesthesia provider will obtain a good history of herbal product use and attempt to discontinue these agents two to three weeks prior to the induction of anesthesia.

Research agenda

- Standardization of herbal products and more effective preparation of these agents are critical for consumers.
- Improved education with regard to impact from herbals in surgery and in anesthesia at the level of medical and nursing schools is desperately needed.
- Randomized clinical trials comparing the effectiveness of different herbal products are needed.

Introduction

Dietary supplements, which include vitamins, minerals, fiber, fatty acids, or amino acids intended to provide nutrients that may otherwise not be consumed in sufficient quantities, are defined as foods, while others classify these agents as drugs or other products.

There are more than 50,000 dietary supplements available. Though there is little testing, often unsubstantiated therapeutic claims, and most of the time, lack of standardization, the use of dietary supplements in the United States and worldwide has remained consistently high over the past two decades [1]. In 2007, Americans spent $33.9 billion out-of-pocket dollars, which accounted for over 11% of total out-of-pocket expenses [2]. With over 55 million adults in the United States (U.S.) taking a dietary supplement at least once in their life, this multi-billion dollar dietary supplement industry will continue to be prevalent in the health care of patients [3,4]. As defined by the Dietary Supplement Health and Education Act (DSHEA) of 1994 by the U.S. Food and Drug Administration (FDA), a dietary supplement is any product which is taken by mouth and contains a dietary ingredient, such as a
vitamin, mineral, or herb, intended to supplement a person’s diet [5]. The majority of those who utilize a dietary supplement do so with the intent to improve or maintain overall health [6]. However, many do not realize the potential hazards of their use.

While dietary supplements are generally considered safe due to their natural origins, some components within these products are pharmacologically active and may adversely affect patients unaware of their effects. In general, these products are easy to access, inexpensive, do not require a prescription and thus are self-prescribed by the consumer. In this regard, therapeutic efficacy can be seen, and this may be related to the product itself or be seen through the placebo effect, which involves a physiological effect through a psychological mechanism.

It is important to note that from the 50,000 plus over the counter dietary supplements, currently there are over 120 which are commonly utilized pharmaceuticals derived from natural products [7]. These products have no requirement for efficacy and have no financial incentive to achieve “drug” status in the United States. Related to the 1994 Dietary Supplement Health & Education Law which created loopholes and deregulation of the industry, the FDA must prove that a dietary supplement is unsafe before it can be banned for sale and these agents are not considered drugs. Statements including, “Not been evaluated by FDA” and “This product is not intended to diagnose, treat, cure or prevent any disease” are required, emphasizing no proof of claims and effectiveness, assurance of quality, consistency of concentration or contaminants.

In Europe, in 2003, an agreement by the European Parliament was made regarding traditional herbal medicinal products and the key components include: committee overseeing herbal products, labeling, definition of herbal Products, pharmacy authorities to determine which herbs are generally recognized as safe and what cautions should be pursued. Nowhere are these quality control efforts more intensively pursued than in Europe, where herbs have remained a part of the health care system throughout the 20th century, when the stringent drug standards were developed. All European member states have implemented national laws for herbals directive, which allow for significant regulation and standards.

One area in particular which warrants concern is the use of dietary supplements in patients who require anesthesia, as they can cause sedation, have drug–drug interactions, and are linked to untoward effects, including bleeding, which can be a specific problem during surgery or if a regional technique is being employed for postoperative analgesia. This issue of dietary supplement use in anesthesia has been previously discussed [8–10]. However in general, little guidance or best practices strategies have evolved for health care professionals. This article will address the use of dietary supplements vis-à-vis postoperative analgesia.

**Concerns with dietary supplement use in anesthesia**

Dietary supplements react to medications through the exact same mechanisms as other drug–drug interactions. Our own research demonstrated a decade ago that approximately one in three (32%) of patients admitted to self-administering one or more dietary supplement. Nearly 70% of patients who were taking one or more dietary supplement did not state as such when asked in the course of a routine anesthetic assessment [11]. While there are multiple pathways of interaction, these interactions can be classified into either a pharmacokinetic or pharmacodynamic interaction.

**Pharmacokinetic interactions**

Pharmacokinetic interactions are described as those which impact the absorption, distribution, metabolism, or excretion of dietary supplements [12]. The most commonly noted pharmacokinetic interactions involve the cytochrome P450 (CYP450) pathway. Many drugs used in anesthesia may be metabolized through the CYP450 pathway, therefore it is important to identify and address the usage of dietary supplements which may interact with this pathway (Table 1). Dietary supplements can inhibit or induce the metabolic action of CYP450 isoenzymes. A dietary supplement which inhibits CYP450 isoenzymes may decrease the metabolism of active drugs, which may then lead to increased drug levels and an increased duration of action. Conversely, a dietary supplement which induces CYP450 isoenzymes may increase the metabolism of active drugs, which may then lead to decreased
drug levels and a decreased duration of action. Because pharmacokinetic interactions affect metabolic action of CYP450 isoenzymes, the magnitude of effect may be manifold rather than additive or oppositional. Dietary supplements which either inhibit or induce CYP450 isoenzyme 3A4 (CYP3A4) warrant the most concern. This is because greater than half of all marketed drugs are metabolized to a certain degree by this CYP3A4 [8]. Commonly used dietary supplements that induce this isoenzyme include St. John's wort and garlic.

St. John's wort, which annually has approximately twenty million packages sold in Europe and the U.S., interacts with medications including anticoagulants, opiates, antifungals, and immunosuppressive agents. A specific example is documented case reports of a pharmacokinetic reaction between St. John's wort and cyclosporine. Levels of cyclosporine have been shown to decrease as much as 70% in patients who are concurrently on this dietary supplement, which may then lead to sub-therapeutic cyclosporine levels and eventually organ rejection [14]. Another example of an interaction is St. John's wort and meperidine, which in theory can result in serotonin syndrome [15]. A third example is St. John's wort with methadone, which can increase its rate of absorption and lead to opioid withdrawal through a CYP3A4 inducer mechanism [16].

This high potential for drug-dietary supplement interactions makes it difficult to determine a safe and effective dose of drugs taken concurrently with St. John's wort and garlic. Garlic has also shown to induce CYP3A4. Unlike St. John's wort, some clinical evidence has suggested that garlic may also inhibit CYP2E1 activity by almost 40% [18]. This is important to note because some anesthetics such as the older agents enflurane and halothane, as well as isoflurane, are metabolized by this isoenzyme [13].

Other common dietary supplements which have notable pharmacokinetic interactions include kava, which inhibits CYP2E1 similarly to garlic and inhibits CYP3A4, and valerian which also inhibits CYP3A4 [19]. While kava and valerian have been shown to interact with drugs metabolized by CYP3A4 in vitro, no strong evidence supports this interaction in human patients [13,20]. It should be noted that clinically, both have dose-dependent sedative and anxiolytic effects, and therefore, can act additively or synergistically with benzodiazepines, opiates, and adjuvant medications postoperatively.

**Pharmacodynamic interactions**

In contrast to pharmacokinetic interactions, pharmacodynamics reactions do not involve an interaction with the CYP450 system, and result in either an additive or oppositional pharmacological effect [12]. An additive pharmacodynamic interaction occurs when two or more substances have similar pharmacological effects, which results in the addition of those similar effects. Conversely, an oppositional pharmacodynamic interaction occurs when two or more substances affect similar pharmacological effects, but with opposite vectors of action which may result in the cancellation of pharmacological effects. Compared to a pharmacokinetic interaction where the resultant interaction

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**Table 1**

Selected dietary supplements that interact with CYP450 from Ref. [13].

<table>
<thead>
<tr>
<th>CYP3A4</th>
<th>Inhibition</th>
<th>CYP1A2</th>
<th>Induction</th>
<th>CYP2C19</th>
<th>Inhibition</th>
<th>CYP2C9</th>
<th>Induction</th>
<th>CYP2E1</th>
<th>Inhibition</th>
<th>CYP2D6</th>
<th>Inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cat's claw, chamomile, danshen, Devil's claw, evodia, feverfew, ginkgo, b goldenseal, grapefruit, Hu Zhang, kava, quercetin, red clover, Shisandra, b Siberian Ginseng, valerian</td>
<td>Chamomile, ginkgo, b St. John's wort, Shisandra b</td>
<td>Evodia, indole-3-carbinol, St. John's wort</td>
<td>Devil's claw, feverfew, grapefruit, kava, red clover</td>
<td>Devil's claw, feverfew, ginkgo, grapefruit, ipriflavone, kava, quercetin, red clover, Siberian Ginseng</td>
<td>Devil's claw, feverfew, ginkgo, grapefruit, ipriflavone, kava, quercetin, red clover, Siberian Ginseng</td>
<td>Garlic, kava</td>
<td>Garlic, kava, goldenseal, kava, quercetin, Siberian Ginseng</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* b Not a complete list.
  b Conflicting evidence regarding CYP3A4 induction/inhibition.
may be manifold greater, a pharmacodynamic interaction may be less extreme because their effects may be additive or oppositional.

Additionally, these interactions can often be predicted based on the pharmacological effects of a dietary supplement, both desired and undesired (e.g. adverse reactions). The more pertinent and significant pharmacodynamic interactions to be aware of in patients with anesthesia are those whose pharmacological affects include blood clotting (e.g. antiplatelet/anticoagulant effects), central nervous system (CNS) depression, hypoglycemic effects, blood pressure, stimulant effects, and those which may affect serotonin levels (Table 2). There are over 90 dietary supplements which may interact with blood clotting alone and this can be a significant issue intraoperatively or when considering a regional technique for postoperative analgesia [13].

Current practice

Currently, there are no concise guidelines regarding the use of dietary supplements in anesthesia. However, because many of these products have significant pharmacological effects, there is a possibility that these dietary supplements may interact with anesthesia or other medications associated with anesthesia. Discontinuation of the supplements prior to admission to a hospital or anesthesia is considered an appropriate option [13]. If a dietary supplement is discontinued prior to anesthesia, the American Society of Anesthesiologists recommends at least two weeks prior to any procedure [8,21]. For the majority of dietary supplements, abrupt discontinuation poses little to no harm. However, there are no concise recommendations when to start or to restart dietary supplements in postsurgical anesthesia. It would be prudent to stop all dietary supplements until all medications are discontinued for a duration of at least five half-lives of the discontinued medications. A duration lasting five half-lives of a drug is generally considered enough time for approximately 97% of the drug to be eliminated from the body [19]. Therefore, a drug–dietary supplement interact would be less likely to occur.

One obstacle in providing optimal patient care in regards to dietary supplements and anesthesia is the voluntary disclosure of dietary supplement use by a patient to their physician. As noted, our research demonstrated that only about one-third of patients disclose their history of dietary supplement use to their physician without being specifically asked to do so and similar data has been demonstrated in more recent years [11,22]. Therefore, it is essential that all dietary supplements taken by a patient are identified and appropriately addressed prior to initiation of anesthesia. These discussions can take place at the Surgeon’s clinic and certainly during anesthesia pre-operative evaluation, allowing for time to discontinue the herbal products (s) well before surgery. Health care practitioners should use multiple specific terminologies describing dietary supplements when assessing dietary supplement use by the patient as many patients will not connect your question of what medicines are being taken with the use of these agents. Examples of these terms include but are not limited to

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Selected dietary supplements with notable pharmacological effects in patients undergoing anesthesia, modified from Ref. [13].</th>
</tr>
</thead>
<tbody>
<tr>
<td>Notable pharmacological effect</td>
<td>Dietary supplements&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Antiplatelet/anticoagulant</td>
<td>Andrographis, black tea, boldo, chondroitin, danshen, dong quai, fenugreek, fish oil, garlic, ginger, ginkgo, glucosamine, green tea, guarana, horse chestnut, policosanol, resveratrol, saw palmetto, turmeric, vitamin E, willow bark</td>
</tr>
<tr>
<td>CNS depression</td>
<td>Chamomile, hops, kava, L-tryptophan, lavender, lemon balm, melatonin, passionflower, skullcap, theanine, valerian</td>
</tr>
<tr>
<td>Hypoglycemic effects</td>
<td>Agaricus mushroom, alpha-lipoic acid, American ginseng, banaba, bitter melon, cinnamon, chromium, fenugreek, glucomannan, gymnema, panax ginseng, prickly pear cactus, vanadium</td>
</tr>
<tr>
<td>Blood pressure effects</td>
<td>Andrographis, casein peptides, coenzyme Q10, horny goat weed, garlic, L-arginine, licorice, pycnogenol, theanine</td>
</tr>
<tr>
<td>Stimulant effects</td>
<td>Bitter orange, dimethylamylamine (DMAA), ephedra, higenamine, raspberry ketone, yohimbe</td>
</tr>
<tr>
<td>Serotonergic effects</td>
<td>5-HTP, L-tryptophan, phosphatidylserine, SAMe, St. John’s wort, theanine</td>
</tr>
</tbody>
</table>

<sup>a</sup> Not a complete list.
“dietary supplements,” “fortified foods,” “herbal supplements,” “herbal tea,” “natural extracts,” “minerals,” “natural products,” “natural supplements,” “vitamins,” etc. Utilization of different specific terminology should help patients recognize and identify supplements. If possible, patients should also bring in all containers of any dietary supplement taken [8,21]. This will help to ensure that the list of dietary supplements taken is as complete as possible. Many herbal data-bases exist and can serve as valuable reference guides for the anesthesia team.

Discussion

In summary, use of dietary supplements is widespread and the anesthesia provider is required to obtain information as to the intake of these agents well prior to the induction of anesthesia. Though thousands of these products are marketed worldwide, many of them have important side effects and dietary supplement—drug interactions that can lead to morbidity and to mortality. It should be noted that over 90 dietary supplement products are associated with bleeding and this can be a specific problem intraoperatively or when considering placement of a regional anesthetic for postoperative pain management. While knowledge of all dietary supplement—drug interactions is not a reasonable expectation for any health care professional, assessing each patient for dietary supplement use is imperative to provide adequate patient care. Knowledge of the pharmacokinetics or pharmacodynamics (pharmacological effects) of a dietary supplement product may also help to anticipate potential interactions with medications. Additionally, an appreciation for some of the most common dietary supplements and their associated effects is warranted, especially in the area of postoperative analgesia management and anesthetics.

Conflict of interest

None.

References


