Herbals and the heart

Baltimore, MD – When investigators found an ephedrine-containing supplement in the locker of Baltimore Orioles pitcher Steve Bechler, who died suddenly in February 2003 of apparent heat stroke, some people quietly, no doubt sheepishly, rejoiced. With a high-profile death believed by a medical examiner to implicate ephedra, advocates hoarse from years of calling for a ban on the agent and for an overhaul of the system that led to its availability finally had something that might galvanize change. They were right.

Unhappily, you need to line up a whole lot of coffins to make Congress change.

Within weeks, the FDA released a statement announcing that it was proposing a new regulation to establish more rigorous manufacturing and labeling standards for dietary supplements in the US. According to existing legislation, dating back to 1994, supplements are not subject to the same stringent rules that apply to food, over-the-counter medications, or prescription drugs. A dietary supplement must adhere to specific labeling restrictions, but manufacturers do not need to provide information to the FDA to put a product on the market, nor do they need to conduct any postmarketing surveillance.

Dr Drummond Rennie

Dr Drummond Rennie, deputy editor of the *Journal of the American Medical Association* (*JAMA*), is quick to make the connection. "It's no accident at all that the Department of Health and Human Services suddenly takes action immediately after the death of the pitcher taking ephedra, which got a huge amount of publicity. It's tragic that it had to take that, but that's what it takes. Unhappily, you need to line up a whole lot of coffins to make Congress change."

Herbal help for the heart

Certainly, not everyone will welcome any changes the FDA proposes. Depending on the survey, anywhere from one tenth to as many as one half of the US population has used a herbal, vitamin, or mineral supplement in the past year, and many do so at least once a week. A World Bank study, commissioned in 1997, estimated that four billion people, primarily in the developing world, depend on herbal remedies for their primary healthcare.

An impact on cardiovascular health is inevitable. A recent study showed that more than 70% of patients discharged from hospital following admission for acute coronary syndrome (ACS) were using some kind of complementary or alternative medicine.

A search on the Internet brings up a medicine cabinet's worth of herbal and dietary supplements, or "nutraceuticals," which purport to benefit the heart. Topping the list are the omega-3 fatty acids, which recently crossed over the bridge to legitimacy when the **AHA** released a statement asserting that certain omega-3 fatty acids, taken as supplements at specified doses, could help lower triglycerides. In parts of Europe and Asia, hawthorn is a well-accepted and regularly prescribed vasodilator, although in most countries it is regulated as a prescription medication in much the same way that digoxin (originally from foxglove) is regulated as a drug in North America.

The bulk of supplements being marketed as heart healthy, however, have limited or equivocal science backing them up. These include coenzyme Q10 (or CoQ10), garlic, fenugreek, gugulipid, magnesium, L-carnitine, ginger, grape seed extract, B vitamins, flax seed oil, and ginkgo biloba.

Herbal supplements in cardiology practice

Dr Mehmet Oz

Their disputed benefits have not prevented them from infiltrating mainstream cardiology practices. **Dr Mehmet Oz** (Columbia University, NY), a cardiovascular surgeon and medical director of the Complementary Medicine Center at Columbia Presbyterian hospital, told **heart*wire*** that almost one in three of his patients are already taking dietary supplements of some kind and that he himself "routinely" prescribes CoQ10 and "offers" L-carnitine.

> Tylenol is much worse than ephedra: it's a killer! And it's still on the market.

Likewise, **Dr Stephen Sinatra** (New England Heart and Longevity Center, Manchester, CT), a former chief of cardiology at Manchester Memorial Hospital, CT, says nutritional supplements are fundamental to his work. "I couldn't practice effective cardiology without my dependence on traditional supplements and herbals," he assured **heart*wire***. In fact, Sinatra sells his own line of nutritional supplements called **Advanced BioSolutions**, each product formulated for specific disease conditions, with names like "Cholesterol Solutions"™ and "Daily BP Support"™.

Not surprisingly, Sinatra sees no reason to change the FDA's current hands-off attitude to herbal supplements. "I think the current FDA approach is okay," he told **heart*wire***. "You look at the fourth leading cause of death in the US today and that's properly prescribed drugs in the hospital environment, whereas I can't think of a single major side effect I've had prescribing supplements, and I've been using and prescribing supplements for 20 years. Most supplements are safe; yes, there are some bad ones out there, like ephedra, and I agree with the FDA here. But look at Tylenol. Tylenol is much worse than ephedra: it's a killer! And it's still on the market."

FDA seeks an alternative strategy

The FDA claims to have set the changes in motion after analyses of dietary supplements in private sector laboratories showed that "a substantial number" of dietary supplements did not actually contain the amount of dietary ingredients promised by their labels. The new regulation the FDA is proposing would require current good manufacturing practices (CGMPs) for the manufacturing, packing, and holding of dietary supplements.

"Under the CGMP proposal, manufacturers would be required to evaluate the identity, purity, quality, strength, and composition of their dietary ingredients and dietary supplements," the statement reads. "If dietary supplements contain contaminants or do not contain the dietary ingredient they are represented to contain, the FDA would consider those products to be adulterated. Some product quality problems the CGMPs would help prevent include products that are superpotent or subpotent; that contain the wrong ingredient, a drug contaminant, or other contaminants (eg, bacteria, pesticide, glass, lead); that contain foreign material; and that are improperly packaged and mislabeled."

As of May 2003, the FDA was still in the process of soliciting comments from the public and industry on how this proposed new regulation "can best achieve the goals of promoting accurate labeling information and preventing adulteration without imposing unnecessary regulatory burdens."

Contacted by **heart*wire***, an FDA spokesperson said that the agency authorities, including **Dr Mark B McClellan**, commissioner of food and drugs, would not be granting interviews about the proposed changes until the period of public commentary had ended.

Dr Robert Califf

Dr Robert Califf (Duke Clinical Research Institute, Durham, NC) points out that the FDA's changes can only go so far. "The FDA is prohibited by law from regulating supplements in the same way that it does pharmaceuticalsthat's really a question for Congress, and not the FDA. What the FDA *can* do is if there's evidence of unsafe outcomes in people who take herbal supplements, it can then act to require that the advertising or labeling of the supplement include that information. But it can't go out and require that a company collect that information if there is no indication of a problem."

The other place the FDA can act is if there's evidence that the quality of manufacturing is not producing what's in the label or being advertised. "I don't know the details of what this FDA announcement really means, but I suspect it's working within the constructs of current law to try to safeguard the public."

In current legislation, however, "the law says supplements are presumed safe unless proven unsafe, kind of the opposite of the laws for drugs: they're really presumed not safe until proven safe."

Any changes to the current US regulatory approach will likely bring the US closer to the positions of regulatory bodies in other countries, many of which have overhauled their approach to supplements in recent years. The European Union now classifies vitamins as medical drugs rather than food supplements. Canada, where supplements have previously been regulated as foods or drugs, is revising legislation to create a separate "natural health products" classification subject to controlled definitions, product licensing, adverse-reaction reporting, site licensing, GMPs, clinical trials, labeling, and packaging. In Australia, the Therapeutic Goods Administration tests for quality and safety but not efficacy, although manufacturers must have information to support their claims.

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Sinatra agrees the FDA can play a role in improving labeling warnings for certain nutraceuticals known to interact with prescription drugs, particularly garlic, fish oil, St John's wort, and vitamin E, all of which he believes raise bleeding risk in patients on warfarin. "But I don't think we should go and regulate the industryit's a question of personal freedom. What it boils down to is, do you want the government telling you what you can put into your mouth? I would rather people decide on their own."

Califf points out that people have the freedom to choose only if they have all the appropriate information in front of them. "My interpretation of the freedom of the consumer is that it really comes down to truth in

advertising, and if you look at the polls that have been done on consumersand there's not that many of themmost consumers absolutely do not understand that these supplements have not been tested. They presume that because they're on the shelves and they *are* labeled that the FDA has given some assurances that they're safe. So there's a lot of ignorance among the public about what it is they're consuming. I'm completely for freedom of consumers, as long as the information is provided allowing them to make a reasonable choice."

Rennie returns to the ephedra example and Bechler's death, pointing out that people taking ephedrine-containing products were likely not aware of any problems with ephedra.

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"When you see supplements killing people, you say, this is outrageous. Fundamentally these people had no warning, and they were killed. We don't allow that with pharmaceuticals: we have a system in place, and this is what is completely and utterly lacking in the chemicals, sometimes very powerful ones, that are called 'supplements,'" he argues. "And supplement is a wonderful word because it means you live an ordinary life, but if you take a supplement you can live a better life, but in fact for this poor pitcher and for many other people, you live a dead life, and that's a tragedy."

Powerful lobby resists tougher legislation

Sinatra's opinions, however, are shared by a hefty slice of the US citizenry who has been vocal in its concerns over tougher regulations for herbal and nutritional supplements. A year ago, when the 15 European Union countries passed the *EU Directive on Dietary Supplements*, which classifies vitamins as medical drugs rather than food supplements, a worldwide online petition demanding that the bill be overturned boasted that it had garnered more than 600 million signatures.

Defenders of "soft" legislation for herbal products fear that stricter regulation will limit availability of certain supplements or ban them altogether, limit allowable doses of supplements without prescription, send prices soaring, or result in a pharmaceutical company monopoly over vitamins and nutritional supplements.

This last worry is one of the most oft-cited warnings from lobbyists wanting to preserve the status quo. In fact, the status quo already involves substantial pharmaceutical company ownership of many of the major brands of dietary supplements, a fact that helps in part to explain the powerful influence lobby groups have had in keeping supplements out of regulatory red tape.

Roche of Switzerland is the world's largest vitamin producer, while **Abbott** and **Wyeth** are both major players, the latter owning Centrum®, one of the most popular vitamin brands in North America, as well as the **Solgar Vitamin and Herb** company. **GlaxoSmithKlein** owns **Abtei**, the leading provider of vitamins, minerals, and herbal supplements in Germany, as well as brands marketed elsewhere in the world, including a cod liver oil product marketed primarily in the developing world. **Johnson & Johnson** has a product line called "nutritionals" such as its soft supplemental calcium "chews," while **Pfizer** is rumored to have invested heavily in studies of traditional Chinese medicinal herbs.

Let's have a little science

At the root of the issue is the science behind the supplements. Rennie agrees that certain supplements undoubtedly confer some sort of benefit, but he is uncomfortable with the lack of science proving efficacy and safety. "If I'm a pharmaceutical company and I want to claim that my drug has beneficial effects on the heart, guess what? I need to show it in a clinical trial. That's all that I'm asking for with these supplements, just show me. Let's have a little science here."


Dr John A Sutherland

Dr John A Sutherland (Arizona Heart Institute, Phoenix, AZ), a cardiologist who has researched the role of herbal and other complementary medicines in the treatment of cardiovascular diseases, points out that compared with the substantial literature on most of the major heart drugs, the amount of information on supplements is still fairly limited. Studies that do exist use different brands of supplements, for which the purity or composition of the product may be variable, making it difficult to compare or pool results between studies.

"Garlic, for example," says Sutherland. "We have mixed reports on whether garlic does or does not help cholesterol or blood pressure. Many of the studies in the US use one active ingredient of garlic called allicin, which is thought to be a biologically active substance, but are we *positive* that that's the substance? No. And like tobacco, garlic is very busy making all sorts of interesting chemicals. So should we be taking deodorized garlic capsules? Should we take allicin the chemical? Is it better to eat raw or cooked garlic, because raw and cooked garlic are different substances? It's a terribly complex set of issues, chemically speaking."

In his practice, Califf suggests a multivitamin with "plenty of vitamin B" and says an omega-3 fatty acid supplement would be "a reasonable thing to recommend" if a patient weren't eating fish. "But beyond that, there's not a single supplement that I know of that could be recommended in providing a health benefit that's been adequately measured," he told **heart*wire***.

Sinatra, by contrast, refutes the idea that the existing studies for the most commonly used supplements are inadequate. He says that studies that failed to show a benefit for a particular product were "doomed from the start" because the investigators did not know how to up-titrate the supplement to the right level or were unfamiliar with drug-supplement interactions that would have limited or nullified the effects of the supplement. For example, he says, statins, beta blockers, antidepressants, and diabetic drugs all reduce endogenous CoQ10 levels, something that has not always been considered in CoQ10 studies. "The people who should be doing these studies are ones who use these supplements in their day-to-day practice of cardiology. The problem is these studies are designed by university centers and none of the physicians doing these studies have ever used these supplementsthey don't know how to use them, they don't even know how to choose them!" Sinatra argues.

> I think the really good cardiologists out thereand there are a lot of themreally combine the best of both worlds and they really can reduce a lot of the suffering they see.

He believes any cardiologist who has tried some of the products will stand by their effects. "I see people suffering who can't walk from one side of the room to another, and they're on all sorts of drugs, they've been given the best conventional cardiology has to offerbypass surgery, stents, implantable defibrillatorsand then you give them CoQ10, hawthorn, and magnesium, and all of a sudden they come into your office and give you a big hug, because they feel so much better. You've really done something for these people," he says. "I think the really good cardiologists out thereand there are a lot of themreally combine the best of both worlds and they really can reduce a lot of the suffering they see."

Debating the FDA's role

Rennie, for one, doesn't buy it. He points out that if a product is truly biologically active to the extent that it provides powerful benefits, it would be impossible for it to be harmless. "You can't have one without the other.

You don't have to be a rocket scientist or even a pharmacologist to know that that's nonsense. And people swallow thatliterallyand that's unbelievable."

Rennie, along with *JAMA* editors **Drs Phil B Fontanarosa** and **Catherine D DeAngelis**, listed what they believe is required for an overhaul of the current FDA regulation of herbal and nutritional supplements in a recent *JAMA* editorial, as reported by **heart*wire***.[1] They say supplements should be regulated at least as much as over-the-counter medications and that the FDA should regulate identity, purity, quality, and compositional strength of the products. "Right now, you haven't a clue what you're getting. It's a complete crapshoot," Rennie says.

The FDA should also require manufacturers to conduct postmarketing surveillance and put restrictions on advertising claims, where necessary, suggests Rennie. Under current legislation, he notes, "the benefit of a particular supplement is established by gossip and television. It's rather like watching Popeye eating spinach."

Whereas pharmaceutical products aiming to combine more than one drug in a single pill are subject to even greater regulatory hurdles, supplements frequently combine multiple products. "These are concoctions that are often mixtures of multiple pharmacologically active agents, and they're not tested in the same way, under any circumstances, that drugs are tested," Califf explains. "Every vial may be a little bit different when it comes to a herbal concoction, and [according to current regulations] the FDA can't test this. People just need to understand, and I don't think they do, that when they take a herbal supplement they're taking something that has not been proved to be safe."

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Establishing purity standards and regulating labeling claims are two areas where even Sinatra concedes the FDA could have a role. "Whenever you have a nutraceutical that can interact with a drug, this needs to be clarified in the label," he states. He also agrees that the closing the gap between stated label strength and assay strength will be essential for supplements to receive wider acceptance. "This is where good manufacturing practices come into play, and that is a place where the FDA should get involved. That needs to be better regulated," he admits.

Oz agrees. "The FDA needs to play a role since we do not know what we are really getting in the pills and this must be addressed or we will have unreliable results," he says.

Good for the brain, bad for the heart?

Quite separate from the variable efficacy of herbal supplements in treating heart diseases are the unwanted, often ill-understood cardiovascular effects of supplements taken for totally unrelated health concerns. Ephedra, taken primarily for weight loss or "enhanced athletic performance," may forever top the notorious-supplements list for the MIs, arrhythmias, seizures, and sudden deaths linked to ephedrine-containing products. Other herbal and nutritional products, however, also have an impact on the cardiovascular system.

Consumers typically take ginkgo biloba as "brain food" and to enhance memory, ginseng to improve energy and reduce stress, garlic to improve circulation and prevent yeast infections, cancers, colds, and flu. Yet all of these agents are believed by many Western medicine physicians to increase bleeding risk. Oz, for example, tells his patients to stop taking all of these supplements before undergoing surgery at his institution.

In 2001, **Dr Michael K Ang-Lee** (Pritzker School of Medicine, University of Chicago, IL) and colleagues published a paper in *JAMA* listing possible cardiovascular side effects of the most commonly used supplements that they say must be halted preoperatively.[2]

St John's wort

They note that both kava, a herbal antidepressant, and valerian, a pain reliever and sedative, can increase the tranquilizing effects of anesthesia; St John's wort, taken for depression, can increase the metabolism of many perioperative drugs, while echinacea, a popular cold remedy, may activate cell-mediated immunity, produce allergic reactions, and decrease effectiveness of immunosuppressants. Of course, as with the extolled benefits of all herbal and nutritional supplements, the research supporting their possible harmful effects on the heart is equally patchy.

Questions, answers and an open mind

Sutherland isn't taking any chances. In his practice at the Arizona Heart Institute, Sutherland has added a page to the typical patient information questionnaire that patients fill out in his waiting room. The page lists the most common herbal supplements and asks patients to tick off any that they may be taking and provides a blank line for them to add any not listed.

"The practice of taking supplements is now so widespread and so common that the best way to get people to tell you what they're taking is to give them cues. They may not think of saw palmetto as being something that a cardiologist might be interested in," he says.

Sutherland believes that patients may also be wary of telling their doctors that they are taking herbal products. He goes out of his way to make sure they are comfortable mentioning any alternative remedies they are trying. He also provides half-page fact sheets explaining to patients how certain herbal products may interact with their cardiovascular medications or procedures.

"We are a fairly high-tech center here, we do all these fancy interventions, and so we make a point of asking questions about supplements because people sometimes assume that we are so far toward one pole of allopathic medicine that we must be somehow exclusive of any other approach, and the answer is no," he explains. "I'm a physician, but I'm not close-minded. I tell my patients, if you're going to take product *X*, here's what you need to know about it, and here's what I need to know about what you're taking so we can calculate that into the equation."

In the meantime, Rennie is keeping a close watch on the FDA as it revises its supplement regulations. "The proposed changes will go through the hoops, and I know that this will be passionately opposed by all sorts of manufacturers and all sorts of people will come forward and say 'I lost 10 pounds,' or whatever, and other people will say there should be no regulation in a free country. But I believe that it *will* grind forward, the FDA will take action, and it will do it in a way that seems to be open and democratic. Whether it will go far enough is anybody's guess."

Sources

1. The need for regulation of dietary supplements--lessons from ephedra.2003 Mar 26; 289(12) :1568-70 PUBMED
2. Herbal medicines and perioperative care.2001 Jul 11; 286(2) :208-16 Available at: http://www.jama.com PUBMED

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- Researchers hope to boost performance, structure of failing hearts with nutritional supplement
  [*HeartWire* > *News*; Jul 11, 2000]
- Cardiotoxic effects of "detoxifying" herbal cleanses: A case report

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