CLINICAL CAPSULES

Calcium and Colorectal Cancer Risk

High intake of dietary calcium in women is significantly associated with reduction in the risk of colorectal cancer in a dose-response fashion, reported Andrew Flood, Ph.D., of the University of Minnesota, Minneapolis, and his colleagues.

In a prospective cohort of 45,354 women who completed dietary questionnaires over an average of 8.5 years, those in the highest quintile of calcium consumption (median of 985 mg /day) had a significant, 26% reduction in risk of colorectal cancer, compared with women in the lowest quintile (median of 337 mg/day), after adjustment for age. Supplemental calcium alone did not show the same dose-response relationship with colorectal cancer risk.

But women who had high intakes of calcium from their diet and supplements had a significant, 46% reduction in the risk of colorectal cancer after an adjustment was performed for age.

None of the associations changed after adjustment for other confounding factors (Cancer Epidemiol. Biomarkers Prev. 2005;14:126-32).

Predicting Fatal Alcoholic Hepatitis

The model for end-stage liver disease may offer a more practical method of predicting mortality from alcoholic hepatitis than the Maddrey discriminant function, despite similar accuracy between the two models, reported Winston Dunn, M.D., and his colleagues at the Mayo Clinic, Rochester, Minn.

With the optimal cut points for both models in a retrospective study of 73 patients with alcoholic hepatitis, the model for end-stage liver disease (MELD) had 75% sensitivity and specificity for both 30- and 90-day mortality. The discriminant function (DF) had 75% sensitivity and 69% specificity in predicting mortality at 30 days, and 88% sensitivity and 65% specificity at 90 days (Hepatology 2005;41:353-8).

MELD uses serum creatinine, serum bilirubin, and the international normalized ratio for prothrombin time, whereas DF uses prothrombin time in seconds and serum bilirubin. The investigators suggested that MELD may be more practical than DF because prothrombin time expressed as the international normalized ratio is comparable across all laboratories, unlike prothrombin time expressed in seconds. MELD also has been prospectively and retrospectively validated in heterogeneous cohorts of patients.

Lymph Nodes Missed in Colorectal Ca

Most patients with colorectal cancer who underwent radical surgery with no preoperative radiation during 1988-2001 did not receive adequate lymph node evaluation, according to findings from a population-based study of the National Cancer Institute's Surveillance, Epidemiology, and End Results cancer registry.

Of 116,995 patients, only 37% received adequate lymph node evaluation (at least 12 nodes), reported Nancy N. Baxter, M.D., of the University of Minnesota, Minneapolis, and her associates. The percentage of patients who received adequate lymph node evaluation was significantly higher among those who had stage II (41%) or III (46%) disease, compared with stage I (25%).

Patients with left-sided colon or rectal cancer had a significant, 50% lower likelihood of receiving adequate lymph node evaluation than those with right-sided colon cancer. Age of 71 years or older significantly reduced by 55% the likelihood of receiving adequate evaluation, compared with age of 50 years or younger (J. Natl. Cancer Inst. 2005;97:219-25). The investigators noted that a variety of factors influences the number of lymph nodes evaluated: number of nodes present in the patient, obesity, size of nodes and thickness of tumor penetration into the bowel, and underlying surgical and pathologic practice patterns.

Hepatitis B: Mono vs. Combo Therapy

In patients with hepatitis B e antigen–positive chronic hepatitis B, sustained viral response rates after discontinuing treatment were similar to those treated with pegylated interferon alfa-2b alone and those who received the interferon in combination with lamivudine, reported Harry L.A. Janssen, M.D., of Erasmus MC, Rotterdam (Netherlands), and his colleagues.

At the end of 52 weeks of treatment, hepatitis B e antigen was undetectable in significantly more patients in the combination therapy group (44%, 57 of 130) than in the monotherapy group (29%, 40 of 136). But 26 weeks after the end of treatment in the randomized, double-blind trial, the rate of sustained virologic response was similar in the monotherapy and combination-therapy patients (36% vs. 35%). The same trend in outcomes occurred when the investigators assessed hepatitis B virus DNA concentrations or alanine aminotransferase levels at the end of treatment and after follow-up (Lancet 2005;365:123-9).

—Jeff Evans

Diovan®
(valsartan)
Tablets
Rx only
BRIEF SUMMARY: Please see package insert for full prescribing information.

USE IN PREGNANCY: When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, Diovan should be discontinued as soon as possible.
See ***WARNINGS: Fetal/Neonatal Morbidity and Mortality.***

INDICATIONS AND USAGE: Hypertension: Diovan® (valsartan) is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.
Heart Failure: Diovan is indicated for the treatment of heart failure (NYHA class II-IV) in patients who are intolerant of angiotensin converting enzyme inhibitors. In a controlled clinical trial, Diovan significantly reduced hospitalizations for heart failure. There is no evidence that Diovan provides added benefits when it is used with an adequate dose of an ACE inhibitor. *(See CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects, Heart Failure in the full prescribing information for details.)*
CONTRAINDICATIONS: Diovan® (valsartan) is contraindicated in patients who are hypersensitive to any component of this product.
WARNINGS: Fetal/Neonatal Morbidity and Mortality: Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin-converting enzyme inhibitors. When pregnancy is detected, Diovan® (valsartan) should be discontinued as soon as possible.
The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.
These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should advise the patient to discontinue the use of valsartan as soon as possible.
Rarely (probably less often than once in every thousand pregnancies), no alternative to a drug acting on the renin-angiotensin system will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra-amniotic environment.
If oligohydramnios is observed, valsartan should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a nonstress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.
Infants with histories of *in utero* exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.
No teratogenic effects were observed when valsartan was administered to pregnant mice and rats at oral doses up to 600 mg/kg/day and to pregnant rabbits at oral doses up to 10 mg/kg/day. However, significant decreases in fetal weight, pup birth weight, pup survival rate, and slight delays in developmental milestones were observed in studies in which parental rats were treated with valsartan at oral, maternally toxic (reduction in body weight gain and food consumption) doses of 600 mg/kg/day during organogenesis or late gestation and lactation. In rabbits, fetotoxicity (i.e., resorptions, litter loss, abortions, and low body weight) associated with maternal toxicity (mortality) was observed at doses of 5 and 10 mg/kg/day. The no observed adverse effect doses of 600, 200 and 2 mg/kg/day in mice, rats and rabbits represent 9, 6, and 0.1 times, respectively, the maximum recommended human dose on a mg/m^2 basis. (Calculations assume an oral dose of 320 mg/day and a 60-kg patient.)
Hypotension: Excessive hypotension was rarely seen (0.1%) in patients with uncomplicated hypertension treated with Diovan alone. In patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients receiving high doses of diuretics, symptomatic hypotension may occur. This condition should be corrected prior to administration of Diovan, or the treatment should start under close medical supervision.
If excessive hypotension occurs, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.
Hypotension in Heart Failure Patients: Caution should be observed when initiating therapy in patients with heart failure. Patients with heart failure given Diovan commonly have some reduction in blood pressure, but discontinuation of therapy because of continuing symptomatic hypotension usually is not necessary when dosing instructions are followed. In controlled trials, the incidence of hypotension in valsartan-treated patients was 5.5% compared to 1.8% in placebo-treated patients.
PRECAUTIONS: General: ***Impaired Hepatic Function:*** As the majority of valsartan is eliminated in the bile, patients with mild-to-moderate hepatic impairment, including patients with biliary obstructive disorders, showed lower valsartan clearance (higher AUCs). Care should be exercised in administering Diovan® (valsartan) to these patients.
Impaired Renal Function - Hypertension: In studies of ACE inhibitors in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen have been reported. In a 4-day trial of valsartan in 12 hypertensive patients with unilateral renal artery stenosis, no significant increases in serum creatinine or blood urea nitrogen were observed. There has been no long-term use of Diovan in patients with unilateral or bilateral renal artery stenosis, but an effect similar to that seen with ACE inhibitors should be anticipated.
Impaired Renal Function - Heart Failure: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar outcomes have been reported with Diovan.
Some patients with heart failure have developed increases in blood urea nitrogen, serum creatinine, and potassium. These effects are usually minor and transient, and they are more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or Diovan may be required. In the Valsartan Heart Failure Trial, in which 93% of patients were on concomitant ACE inhibitors, treatment was discontinued for elevations in creatinine or potassium (total of 1.0% on valsartan vs. 0.2% on placebo). Evaluation of patients with heart failure should always include assessment of renal function.
Concomitant Therapy in Patients with Heart Failure: In patients with heart failure, concomitant use of Diovan, an ACE inhibitor, and a beta blocker is not recommended. In the Valsartan Heart Failure Trial, this triple combination was associated with an unfavorable heart failure outcome *(see CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects, Heart Failure in the full prescribing information).*
Information for Patients: ***Pregnancy:*** Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to drugs that act on the renin-angiotensin system, and they should also be told that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.
Drug Interactions: No clinically significant pharmacokinetic interactions were observed when valsartan was coadministered with amlodipine, atenolol, cimetidine, digoxin, furosemide, glyburide, hydrochlorothiazide, or indomethacin. The valsartan-atenolol combination was more antihypertensive than either component, but it did not lower the heart rate more than atenolol alone.
Coadministration of valsartan and warfarin did not change the pharmacokinetics of valsartan or the time-course of the anticoagulant properties of warfarin.
CYP 450 Interactions: The enzyme(s) responsible for valsartan metabolism have not been identified but do not seem to be CYP 450 isozymes. The inhibitory or induction potential of valsartan on CYP 450 is also unknown.
As with other drugs that block angiotensin II or its effects, concomitant use of potassium sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium and in heart failure patients to increases in serum creatinine.
Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no evidence of carcinogenicity when valsartan was administered in the diet to mice and rats for up to 2 years at doses up to 160 and 200 mg/kg/day, respectively. These doses in mice and rats are about 2.6 and 6 times, respectively, the maximum recommended human dose on a mg/m^2 basis. (Calculations assume an oral dose of 320 mg/day and a 60-kg patient.)
Mutagenicity assays did not reveal any valsartan-related effects at either the gene or chromosome level. These assays included bacterial mutagenicity tests with *Salmonella* (Ames) and *E coli;* a gene mutation test with Chinese hamster V79 cells; a cytogenetic test with Chinese hamster ovary cells; and a rat micronucleus test.
Valsartan had no adverse effects on the reproductive performance of male or female rats at oral doses up to 200 mg/kg/day. This dose is 6 times the maximum recommended human dose on a mg/m^2 basis. (Calculations assume an oral dose of 320 mg/day and a 60-kg patient.)
Pregnancy: ***Pregnancy Categories C (first trimester) and D (second and third trimesters):*** *See WARNINGS, Fetal/Neonatal Morbidity and Mortality.*
Nursing Mothers: It is not known whether valsartan is excreted in human milk, but valsartan was excreted in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.
Pediatric Use: Safety and effectiveness in pediatric patients have not been established.
Geriatric Use: In the controlled clinical trials of valsartan, 1,214 (36.2%) of hypertensive patients treated with valsartan were ≥ 65 years and 265 (7.9%) were ≥ 75 years. No overall difference in the efficacy or safety of valsartan was observed in this patient population, but greater sensitivity of some older individuals cannot be ruled out.
Of the 2,511 patients with heart failure randomized to valsartan in the Valsartan Heart Failure Trial, 45% (1,141) were 65 years of age or older. There were no notable differences in efficacy or safety between older and younger patients.
ADVERSE REACTIONS: Hypertension: Diovan® (valsartan) has been evaluated for safety in more than 4,000 patients, including over 400 treated for over 6 months, and more than 160 for over 1 year. Adverse experiences have generally been mild and transient in nature and have only infrequently required discontinuation of therapy. The overall incidence of adverse experiences with Diovan was similar to placebo.
The overall frequency of adverse experiences was neither dose-related nor related to gender, age, race, or regimen. Discontinuation of therapy due to side effects was required in 2.3% of valsartan patients and 2.0% of placebo patients. The most common reasons for discontinuation of therapy with Diovan were headache and dizziness.
The adverse experiences that occurred in placebo-controlled clinical trials in at least 1% of patients treated with Diovan and at a higher incidence in valsartan (n=2,316) than placebo (n=888) patients included viral infection (3% vs. 2%), fatigue (2% vs. 1%), and abdominal pain (2% vs. 1%).
Headache, dizziness, upper respiratory infection, cough, diarrhea, rhinitis, sinusitis, nausea, pharyngitis, edema, and arthralgia occurred at a more than 1% rate but at about the same incidence in placebo and valsartan patients.
In trials in which valsartan was compared to an ACE inhibitor with or without placebo, the incidence of dry cough was significantly greater in the ACE-inhibitor group (7.9%) than in the groups who received valsartan (2.6%) or placebo (1.5%). In a 129-patient trial limited to patients who had had dry cough when they had previously received ACE inhibitors, the incidences of cough in patients who received valsartan, HCTZ, or lisinopril were 20%, 19%, and 69% respectively ($p < 0.001$).
Dose-related orthostatic effects were seen in less than 1% of patients. An increase in the incidence of dizziness was observed in patients treated with Diovan 320 mg (8%) compared to 10 to 160 mg (2% to 4%).
Diovan has been used concomitantly with hydrochlorothiazide without evidence of clinically important adverse interactions.
Other adverse experiences that occurred in controlled clinical trials of patients treated with Diovan (> 0.2% of valsartan patients) are listed below. It cannot be determined whether these events were causally related to Diovan.
Body as a Whole: Allergic reaction and asthenia; ***Cardiovascular:*** Palpitations; ***Dermatologic:*** Pruritus and rash; ***Digestive:*** Constipation, dry mouth, dyspepsia, and flatulence; ***Musculoskeletal:*** Back pain, muscle cramps, and myalgia; ***Neurologic and Psychiatric:*** Anxiety, insomnia, paresthesia, and somnolence; ***Respiratory:*** Dyspnea; ***Special Senses:*** Vertigo; ***Urogenital:*** Impotence
Other reported events seen less frequently in clinical trials included chest pain, syncope, anorexia, vomiting, and angioedema.
Heart Failure: The adverse experience profile of Diovan in heart failure patients was consistent with the pharmacology of the drug and the health status of the patients. In the Valsartan Heart Failure Trial, comparing valsartan in total daily doses up to 320 mg (n=2,506) to placebo (n=2,494), 10% of valsartan patients discontinued for adverse events vs. 7% of placebo patients.
The table shows adverse events in double-blind short-term heart failure trials, including the first 4 months of the Valsartan Heart Failure Trial, with an incidence of at least 2% that were more frequent in valsartan-treated patients than in placebo-treated patients. All patients received standard drug therapy for heart failure, frequently as multiple medications, which could include diuretics, digitalis, beta-blockers, or ACE inhibitors.

	Valsartan (n=3,282)	Placebo (n=2,740)		Valsartan (n=3,282)	Placebo (n=2,740)
Dizziness	17%	9%	Back Pain	3%	2%
Hypotension	7%	2%	Dizziness, postural	2%	1%
Diarrhea	5%	4%	Hyperkalemia	2%	1%
Arthralgia	3%	2%	Hypotension, postural	2%	1%
Fatigue	3%	2%			

Other adverse events with an incidence greater than 1% and greater than placebo included headache NOS, nausea, renal impairment NOS, syncope, blurred vision, upper abdominal pain and vertigo. (NOS = not otherwise specified).
From the long term data in the Valsartan Heart Failure Trial, there did not appear to be any significant adverse events not previously identified.
Post-Marketing Experience: The following additional adverse reactions have been reported in post-marketing experience:
Hypersensitivity: There are rare reports of angioedema; ***Digestive:*** Elevated liver enzymes and very rare reports of hepatitis; ***Renal:*** Impaired renal function; ***Clinical Laboratory Tests:*** Hyperkalemia; ***Dermatologic:*** Alopecia.
Clinical Laboratory Test Findings: In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of Diovan.
Creatinine: Minor elevations in creatinine occurred in 0.8% of patients taking Diovan and 0.6% given placebo in controlled clinical trials of hypertensive patients. In heart failure trials, greater than 50% increases in creatinine were observed in 3.9% of Diovan-treated patients compared to 0.9% of placebo-treated patients.
Hemoglobin and Hematocrit: Greater than 20% decreases in hemoglobin and hematocrit were observed in 0.4% and 0.8%, respectively, of Diovan patients, compared with 0.1% and 0.1% in placebo-treated patients. One valsartan patient discontinued treatment for microcytic anemia.
Liver Function Tests: Occasional elevations (greater than 150%) of liver chemistries occurred in Diovan-treated patients. Three patients (< 0.1%) treated with valsartan discontinued treatment for elevated liver chemistries.
Neutropenia: Neutropenia was observed in 1.9% of patients treated with Diovan and 0.8% of patients treated with placebo.
Serum Potassium: In hypertensive patients, greater than 20% increases in serum potassium were observed in 4.4% of Diovan-treated patients compared to 2.9% of placebo-treated patients. In heart failure patients, greater than 20% increases in serum potassium were observed in 10.0% of Diovan-treated patients compared to 5.1% of placebo-treated patients.
Blood Urea Nitrogen (BUN): In heart failure trials, greater than 50% increases in BUN were observed in 16.6% of Diovan-treated patients compared to 6.3% of placebo-treated patients.
Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F)
[see USP Controlled Room Temperature].
Protect from moisture.
Dispense in tight container (USP).

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