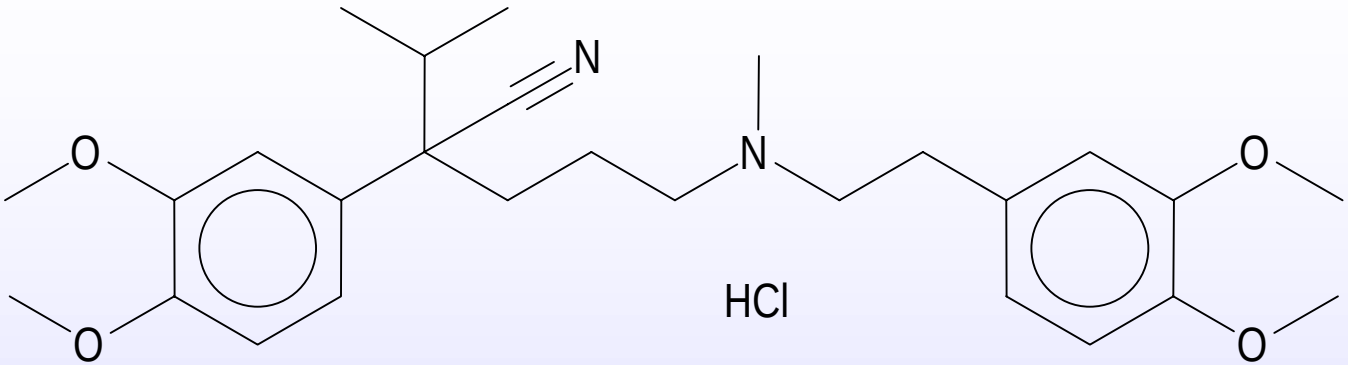
Verapamil



$C_{27}H_{38}N_2O_4 \cdot HCl$

Molecular Weight: 491.08 CAS Reg. No.: 152-11-4

What is verapamil?

- A calcium channel blocker used to treat hypertension, arrhythmia, and angina
- Verapamil and other calcium channel blockers are taken daily by millions of people worldwide

Epidemiologic Studies

- Eight cohort studies
  - Original study: Pahor *et al*., 1996a & b
  - Best study: Beiderbeck-Noll *et al*., 2003
  - More limited studies (6)
- Four case-control studies
  - 2 overall cancer
  - 2 specific cancer sites

Important Aspects of Study Design and Analysis

- Quality of exposure data
- Length of follow-up
- Comparison group(s)
- Control for confounding
  - Use of other drugs (other calcium channel blockers (CCBs), other hypertension drugs)
  - Smoking, body-mass index (BMI), other health indicators

Pahor *et al*., 1996a and 1996b

- Prospective cohort study in U.S.
  - 5052 elderly persons, 65% female, avg age 79 y, 94% white
- Separate analysis – hypertensives only
- Moderate follow-up
  - Avg 3.7 years, max 5 years
- Single interview exposure determination
  - Examination of prescription label
- Adjusted for smoking, BMI, number of hospital admissions not related to cancer

Pahor *et al*. Results

	Verapamil exposed cases	RR (95% CI)
Entire cohort Any exposure All cancer	18	2.49* (1.5-4.0)
Hypertensives Any exposure All cancer	10	2.46* (1.2-5.2)

Beiderbeck-Noll *et al*., 2003

- Prospective cohort study in the Netherlands
  - 3204 elderly persons, 65% female, avg age 79 y
- Longer follow-up
  - Avg 5.2 years, max 8 years
- Multiple interview exposure determination
  - Label examination
- Exposure duration data
  - Based on pharmacy database records

Beiderbeck-Noll *et al*. Analyses

- Model 1 – replicated Pahor analyses
  - Adjusted for smoking, BMI, number of hospital admissions not related to cancer
- Model 2 – basic exposure data, more factors
  - Adjusted for heart disease, diabetes, use of other drugs (ACE inhibitors, diuretiecs, beta-blockers)
- Model 3 – cumulative exposure data, adjusted as in model 2

Beiderbeck-Noll *et al.* Model 1 Results

Exposure & Outcome	Verapamil exposed cases	RR (95% CI)
Any exposure All cancer	9	2.1* (1.1-4.0)
Any exposure LHC	Not available (NA)	7.8* (1.7-37.0)

Beiderbeck-Noll *et al*. Dose Response Results

Exposure measure	Verapamil exposure	RR (95% CI) Any cancer
Duration of use (Model 3)	≤2 years	1.4 (0.8-2.5)
	>2 years	2.4* (1.2-4.9)
Daily dose (Model 1)	Low	1.7 (0.7-4.2)
	Medium	2.7*(1.02-7.4)
	High	No cases

Other Predominately Female, Elderly Cohorts

- Fitzpatrick *et al*., 1997: U.S. Breast cancer
  - 3198 women, avg age 72 y, 33% black
  - Moderate follow-up, max 5 y
  - Drug formulation (immediate vs. Sustained release)
  - Increased crude rates for immediate release form; RRs for verapamil not calculated
- Cohen *et al*., 2000: North Carolina
  - 3511 persons, avg 73 y, 65% female, 57% black
  - Moderate follow-up, max 6 y
  - Adjusted for smoking, BMI, other drugs: RR=1.3 (0.8 - 2.2)
  - Verapamil risk highest among CCBs examined

Predominately Male Cohorts

- Braun *et al*., 1998 – Israel
  - 11,575 persons, avg age 60 y, 78% male
  - Short follow-up, avg 2.8 y, 3.8 y max
  - Single interview exposure determination
  - Adjusted for smoking, RR = 1.2 (0.6-2.4) all cancer
- Sajadieh *et al*., 1999 – Denmark
  - 878 verapamil users who had suffered heart attack
  - Most (64%) were <65 y at start of study, 80% male
  - Longer follow-up, max 8 y; Only 1¼ y verapamil use
  - Compared to general population, despite clinical trial origin of study group. No adjustment for smoking.
  - Increased lung ca risks in women, SIR=3.9* (1.3-9.1)

Other Cohorts

- Olsen *et al*., 1997a – Denmark
  - 17,911 persons, 49% male, 32% age <59 y
  - Short follow-up, avg 1.8 y, 3 y max (20% had < 1 y)
  - Exposure based on 1 prescription in database
  - No adjustment for smoking, other drugs
  - Compared to general population, SIR = 1.09 (0.9-1.3)
- Hole *et al*., 1998 – Scotland
  - 2297 hypertensives; 51% male, avg 56 y
  - Longer follow-up. avg 5 y, 15 y max
  - Exposure based on 1 prescription given in clinic, 1980-1995
  - Comparison to longitudinal cohort from 1970s
  - Adjusted for smoking, RR=1.2 (0.8-1.6)

Case-Control Studies

- All cancer, 2 studies
  - Jick *et al*., 1997
  - Rosenberg *et al*., 1998
- Site-specific cancer, 2 studies
  - Meier *et al*., 2000
  - Hardell *et al*., 1996

Jick *et al*., 1997

- Nested case-control study
  - UK cohort of hypertensives in medical database
  - 446 cases, 1750 controls
  - Avg age 72 y, 51% male
- Exposure based on physician report
  - Based on database, use >1 year before diagnosis
  - Information on duration of use
  - Subjects had at least 4 y history in database
- Adjusted for smoking, other drugs, BMI: OR=1.8 (0.94 – 3.6)

Rosenberg *et al*., 1998

- Hospital admission-based study
  - Average age 56 y, 41% male, in U.S.
  - 9513 cases, 1st cancer diagnosis
  - 6492 controls admitted for other causes, excluded admissions for cardiovascular disease
- Exposure data self reported in hospital interview
  - Subjects had begun use at least 1 y prior to admission, average duration of use, 3.8 y
- Adjusted for smoking & BMI: OR=1.2 (0.9 – 1.5)
  - Not other CCBs or other hypertensive meds

Meier *et al*., 2000

- Nested case-control study
  - U.K. cohort of post-menopausal women in medical database, 42% were > 70 y
  - 3706 breast cancer cases, 9809 age-matched controls
- Exposure data based on physician report
  - Subjects had at least 4 y history in database
  - Information on duration of use for 80%
- Adjusted for smoking, BMI
  - Analyses limited to those using single drug therapy
  - Comparison to those using no anti-hypertensive medications

Meier *et al*. Results

Outcome	Exposure duration	Verapamil exposed cases	OR (95% CI)
Breast cancer	1-2 y	8	1.6 (0.7-3.7)
	3-4 y	4	4.0* (1.0-16.1)
	≥ 5 y	7	1.0 (0.4-2.4)

Hardell *et al*., 1996

- Case-control study of colon cancer
  - Hypothesis-generating design, 50% female
  - 301 cases, 621 population-based controls, Sweden
- Self reported exposure information
  - Via mailed questionnaire
  - No information on initial exposure or duration
- No adjustment for smoking, BMI, or other factors
  - Comparison to all not using verapamil

Hardell *et al*. Results

Outcome	Exposure	Verapamil exposed cases	OR (95% CI)
Colon cancer	Any use	10	22* (2.4-480)

Site-Specific Findings: Any Calcium Channel Blocker Use

- Studies reported site-specific results only for all CCB use (includes verapamil)
- Elevated risks for same sites found for verapamil-only exposures:
  - Lymphohematopoietic cancers
  - Breast cancer
  - Colon cancer

Site-Specific Cancer and Any CCB: LHCs

Cancer site	Study	CCB exposure	RR estimate (95% CI)
LHC (all)	Pahor *et al*.	Any use	2.6* (1.1-5.8)
Non-Hodgkins Lymphoma	Olsen *et al*.	Any use	1.4 (0.8-2.2)

Site-Specific Cancer and Any CCB: Breast Cancer

Cancer site	Study	CCB exposure	RR estimate (95% CI)
Breast	Pahor et al.	Any use	1.7 (0.5-5.5)
	Fitzpatrick *et al*.	Any use	2.6* (1.5-4.5)
		Estrogen & CCB	4.5* (1.6-12.8)
	Hole *et al*.	Any use	1.5 (NA)

Site-Specific Cancer and Any CCB: Colon Cancer

Cancer site	Study	CCB exposure	RR estimate (95% CI)
Colon	Pahor *et al*.	Any use	2.0 (0.9-4.4)
	Rosenberg *et al*.	Any use	0.9 (0.7-1.3)
		≥ 5 y use	1.7* (1.0-2.8)

Summary of Epidemiologic Evidence

- Approximate doubling of risk for all cancers
  - Original cohort study (Pahor *et al*.)
  - Best cohort study to date (Beiderbeck-Noll *et al*.)
- Increased site-specific risks for verapamil users
  - LHC in best cohort study (Beiderbeck-Noll *et al.*)
  - Breast cancer in well-designed nested case-control study (Meier *et al*.)
  - High risks of colon cancer in a weaker study
- Studies of any CCB use provide support for increased risks at these same sites

Animal Studies

- No carcinogenicity studies of verapamil (alone) in animals are available in the published literature
- Physicians' Desk Reference (PDR) reports results of two relevant studies in rats
  - 18-month toxicity study (6-fold human dose)
  - 2 year diet study (up to 12-fold human dose)
  - "…no evidence of carcinogenic potential"
- Requests made to U.S. FDA failed to yield more information on these studies

Other Relevant Data

- Genotoxicity studies in nonhuman cells
- Genotoxicity studies in human cells
- Synergy with genotoxic agents
- Modulation of tumorigenicity
- Effects on cellular growth
- Pharmacokinetics and metabolism

Genotoxicity Data: Non-Human Cells

- *In vitro* studies
  - No evidence of mutagenicity
  - No increased chromosome damage in Chinese hamster ovary cells
- *In vivo* studies
  - No increased chromosome damage in mouse bone marrow cells

Genotoxicity Data: Human Cells

- Chromosomal aberrations
  - *In vitro* studies:
    - No increased aberrations in human lymphocytes in early study
    - Increased aberrations in human lymphocytes stimulated with phytohemagglutinin
  - *In vivo* study: increased aberrations in human lymphocytes of persons taking verapamil

Synergy with Genotoxic Agents

Increases in:

- Chromosomal aberrations
  - Human lymphocytes (*in vitro*): bleomycin and peplomycin
- Clastogenicity
  - Mouse bone marrow cells (*in vivo*): acrylamide, cyclophosphamide, and dioxidine
- Micronuclei formation
  - CHO cells (*in vitro*): arsenite
- Mutations
  - *Salmonella* (*in vitro*): several classes of known mutagens

Modulation of Tumorigenicity and Effects on Cellular Growth

- Reduced tumor development in animals
  - Administered with known carcinogens in several studies
- Showed no consistent effect on cellular apoptosis
  - *In vitro* and *in vivo* studies

Pharmacokinetics

- Bioavailability
  - Low
  - Slightly higher in women than in men
  - Increased in older (> 60 y) individuals
- Elimination half-lives
  - Longer in older individuals and in women
- Tissue distribution studies
  - Limited data
  - May accumulate in the lung

Metabolism

- Extensively metabolized
  - <5% excreted unchanged
  - At least 6 urinary metabolites
- Cytochrome P450 isozymes have been identified
- Large interindividual differences
  - Some clearly related to cytochrome P450 mediated biotransformation
  - Women have higher levels of P450 3A4
  - Older subjects have decreased activities of isozymes

Summary

- Epidemiologic evidence supportive of an effect
  - With longer exposures or higher doses
  - In studies of elderly and/or female subjects
- Animal studies provide no evidence
  - May be inadequately tested
- Genotoxicity results are mixed
  - Human lymphocyte chromosomal aberrations
  - Mechanism of action is unknown
- Pharmacokinetic and metabolism data suggest possible age and gender differences