

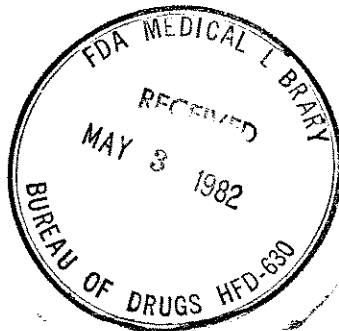
DEPARTMENT OF
HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration, HFI-22
Rockville, Maryland 20857

Official Business

THIRD CLASS BULK RATE
Postage & Fees Paid
PHS
Permit No. G29

Third Class Bulk Rate

FDA COLL



April 1982

Volume 12 Number 1

FDA Drug Bulletin

New Angina Drugs

Sucralfate Approved for Duodenal Ulcer

Ritodrine Update

Use of Approved Drugs for
Unlabeled Indications

Hepatitis B Vaccine for
Use in Selected Populations

Advice on Limiting Intake of Bonemeal

Bendectin PPI Available

Class I Recalls

New Angina Drugs

Two calcium channel blockers, nifedipine and verapamil, have been approved for treatment of vasospastic and classical effort-associated angina. These drugs are also referred to as "calcium entry blockers" or "calcium antagonists."

Drugs of this pharmacologic class have some common properties but also have important differences in clinical use.

Both agents inhibit transmembrane flux of extracellular calcium into cardiac and vascular smooth muscle, and produce, in isolated tissues, negative inotropic effects, depressed sino-atrial (SA) and atrio-ventricular (AV) node function, and vasodilation. At clinical

doses in humans, however, the vascular effects are usually predominant, causing reduced peripheral vascular resistance and lower blood pressure and preventing or reversing coronary spasm.

The effects on cardiac tissues are usually less prominent, probably because of afterload reduction and reflex sympathetic responses to vasodilation. In patients with normal cardiac function not on other negatively inotropic drugs, the negative inotropic effects of the drugs are not usually manifested.

In some cases, however, heart failure can be induced or worsened, and particular care must be paid to concomitant use of calcium channel blockers with beta blockers and to use in patients with aortic stenosis, where vasodilation would not be expected to produce significant afterload reduction.

Effects on AV and SA node function are also not prominent *in vivo* with nifedipine, although they can occur with verapamil.

Effectiveness

Verapamil, but not nifedipine, is an effective agent intravenously in interrupting supraventricular tachycardia and slowing the heart rate in atrial fibrillation.

Both drugs are effective in angina due to vasospasm and in chronic stable angina. Current labeling for nifedipine recommends it for use in stable angina only in patients "who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents." This reservation is based on the limited long-term evidence of safety and effective-

FDA Drug Bulletin

Information of Importance
To Physicians and
Other Health Professionals

Editorial Board

Arthur Hull Hayes, Jr., MD, *Commissioner*

Mark Novitch, MD, *Deputy Commissioner*

Stuart Nightingale, MD, *Acting Associate*

Commissioner for Health Affairs

Wayne L. Pines, *Associate Commissioner for*
Public Affairs

J. Richard Crout, MD, *Director, Bureau of Drugs*

Sanford A. Miller, PhD, *Director, Bureau of*
Foods

Marion J. Finkel, MD, *Associate Director,*
Bureau of Drugs

ness in people with stable angina.

Although the effectiveness of these agents in angina is documented, many aspects of their effectiveness remain to be defined. Uncontrolled reports¹ and studies in which these agents have been added to, or substituted for, organic nitrates that had proved insufficiently effective^{2,3} in vasospastic angina seem to indicate a special ability of the calcium antagonists to prevent vasospastic angina. In two well-controlled studies comparing nifedipine with isosorbide dinitrate, however,^{4,5} there was little difference between the two treatments. There are no similar direct comparisons of verapamil and organic nitrates.

Safety

The side-effect profile of these agents overlaps but is by no means identical. In general, nifedipine appears to have a somewhat greater tendency to decrease peripheral resistance and lower blood pressure than verapamil, and does not tend to inhibit SA or AV nodal conduction. There is often a small increase in heart rate, and typical symptoms and signs of vasodilation (dizziness, flushing, numbness and tingling of extremities, peripheral edema, or palpitations) are common but usually tolerable.

More serious reactions can also occur. Excessive hypotension occurs occasionally with the use of nifedipine, usually during the initial titration or at the time of upward dosage adjustment. It may be more likely in patients taking beta blockers concomitantly.

A few patients have developed increased frequency, duration, or severity of angina upon starting nifedipine or at

the time of dosage increases.⁶

Nifedipine dosage should be titrated over a 7 to 14 day period, if possible, to enable the physician to assess response at each dose level and monitor blood pressure before proceeding to higher doses.

There are isolated reports of patients recently withdrawn from beta blockers who have developed marked worsening of angina and even infarction.⁷

If possible, it is advisable to taper beta blockers before stopping them and beginning nifedipine. It does not appear that nifedipine can treat the increased angina sometimes associated with beta blocker withdrawal.

Concomitant use of nifedipine and beta blockers is usually well tolerated. However, there is little controlled experience with the combination, which is known to increase the likelihood of congestive heart failure and severe hypotension.

In rare instances, patients have developed heart failure after beginning nifedipine, usually when the drug was added to a beta blocker.⁸ Patients with tight aortic stenosis may also be at greater risk of developing heart failure with nifedipine.⁹

Nifedipine may be given concomitantly with nitrates, but there have been no controlled studies to assess the antianginal effectiveness of this combination.

Nifedipine has been reported to increase serum digoxin concentrations by about 50 percent and must be used with great caution with concomitant digoxin.¹⁰

Blood pressure falls with oral verapamil, but marked decreases appear unusual. There is usually a slight decrease in heart rate. Symptoms of vasodilation are not common. On the other hand, verapamil can inhibit SA node function and AV conduction, and cause sinus bradycardia, nodal escape rhythm, and/or AV block. It is, therefore, contraindicated in patients with pre-existing AV conduction abnormalities or sick sinus syndrome.

Verapamil has generally been avoided in patients with pre-existing

heart failure and is contraindicated in patients with severe left ventricular dysfunction because it can worsen heart failure.

There are few studies of verapamil given in combination with beta blockers, but it is clear that the combination can impair cardiac function in some patients,¹¹ even when cardiac function was initially good.¹²

Verapamil can cause constipation, which is usually mild.

In studies carried out in the United States, there were two reported instances of rechallenge-confirmed liver injury among the first 1,000 patients treated.¹³ The patients had a picture of predominantly hepatocellular injury (transaminases in the 1,000 unit range), although there were no liver biopsies to confirm this; there was prompt resolution on discontinuation of the drug. In nearly 4,000 patients treated since that time, only isolated instances of enzyme abnormalities have been reported. The world literature does not include any reports of liver injury similar to the one previously cited.¹³

Patients on verapamil should have periodic liver function tests. The drug should be stopped if abnormalities are seen. Physicians can help define the frequency and severity of this adverse reaction by reporting observed cases promptly to FDA.

In patients with impaired liver or kidney function, verapamil should be administered only with great caution. (Verapamil is highly metabolized by the liver and 70 percent of an administered dose is excreted as metabolites in the urine.)

Verapamil increases serum digoxin levels in patients on chronic digoxin therapy and must be used with caution in such patients. Maintenance digoxin doses should be reduced and the patient should be carefully monitored to avoid over- or under-digitalization when verapamil is administered.

Disopyramide should not be given within 48 hours before or 24 hours after verapamil due to the combined negative inotropic effects of the two

drugs.

Until further data are available, verapamil and quinidine should be used together cautiously, especially in patients with hypertrophic cardiomyopathy, because there have been a few reports of pulmonary edema in patients given the combination.¹⁴

As with nifedipine, verapamil may be given concomitantly with nitrates, although the effectiveness of the combination has not been evaluated.

More complete information for prescribing these drugs is available in the package inserts.

References:

1. Antman E, et al.: Nifedipine therapy for coronary-artery spasm. *N Engl J Med* 1980; 302: 1269-1273.
2. Waters DD, et al.: Provocative testing with ergonovine to assess the efficacy of treatment with nifedipine, diltiazem, and verapamil in variant angina. *Am J Cardiol* 1981; 48:123-130.
3. Johnson SM, et al.: A controlled trial of verapamil for Prinzmetal's variant angina. *N Engl J Med* 1981; 304: 862-866.
4. Hill JA, et al.: Randomized double-blind comparison of nifedipine and isosorbide dinitrate in patients with coronary arterial spasm. *Am J Cardiol* 1982; 49:431-438.
5. Ginsburg R, et al.: Randomized double-blind comparison of nifedipine and isosorbide dinitrate therapy in variant angina pectoris due to coronary artery spasm. *Am Heart J* 1982; 103:44-48.
6. Jariwalla AG, Anderson EG: Production of ischemic cardiac pain by nifedipine. *Brit Med J* 1978; 2:1181-1182.
7. Meinertz T, et al.: Beta blocker withdrawal syndrome. *Lancet* 1979; 1 (8110):270.
8. Robson RH, Vishwanath MC: Nifedipine and beta blockade as a cause of cardiac failure. *Brit Med J* 1982; 284:104.
9. Gillmer DJ, Kark P: Pulmonary edema precipitated by nifedipine. *Brit Med J* 1980; 284:1420-1421.
10. Belz GG, et al.: Digoxin plasma concentrations and nifedipine. *Lancet* 1981; 1:844.
11. Bala Subramanian V, et al.: Combined therapy with verapamil and propranolol in chronic stable angina. *Am J Cardiol* 1982; 49:125-132.
12. Chew C, et al.: Influence of severity of ventricular dysfunction on hemodynamic responses to intravenously administered verapamil in ischemic heart disease. *Am J Cardiol* 1981; 47:917-922.
13. Brodsky SJ, et al.: Hepatotoxicity due to treatment with verapamil. *Annals of Int Med* 1981; 94(4):490-491.
14. Epstein S, Rosing D: Verapamil: its potential for causing serious complications in patients with hypertrophic cardiomyopathy. *Circ* 1981; 64:437-441.

Sucralfate Approved for Duodenal Ulcer

Sucralfate (Carafate), a basic aluminum salt of polysulfated sucrose, has been approved for short-term (up to 8 weeks) treatment of duodenal ulcer. The drug is chemically unlike any other drug used for treatment of duodenal ulcer.

Sucralfate exerts its effect through local rather than systemic action, and there is little systemic absorption. Although the mechanism of sucralfate's anti-ulcer activity has not been fully defined, studies suggest that, with extracellular protein, it forms an ulcer-adherent complex that covers the ulcer site and protects it against further attack by acid, pepsin, and bile salts. The medication has negligible acid-neutralizing capacity and its anti-ulcer effects cannot be attributed to neutralization of gastric acid.

In two U.S. multicenter, placebo-controlled studies with endoscopic evaluation at 2 and 4 weeks, sucralfate was more effective than placebo in promoting complete healing, and statistically significantly better at 4 weeks. In the first study, the ulcer healing rate at 4 weeks was 75.2 percent for sucralfate and 63.6 percent for placebo. In the second study the 4-week ulcer healing rate was 92 percent for sucralfate and 58 percent for placebo.

The better result in the second study may be attributable to the dosage schedule used. In the first trial, sucralfate was given 2 hours after meals and at bedtime rather than as now recommended, 1 hour before meals and at bedtime. The latter regimen was used in several foreign studies and in the second U.S. study.

There are no known contraindications to the use of sucralfate. Adverse reactions in clinical trials involving more than 2,400 patients were minor and only rarely led to the discontinuation of the drug. The most frequent complaint was constipation, which was reported by 2.2 percent of patients. Other adverse effects reported in no

more than 1 of every 350 patients were diarrhea, nausea, gastric discomfort, indigestion, dry mouth, rash, pruritus, back pain, dizziness, sleepiness, and vertigo.

No long-term studies have been carried out and there is no recognized reason for long-term use of sucralfate. Specifically, it is not known whether sucralfate can prevent ulcer recurrence. Long-term studies will be needed to assess the possibility of adverse effects associated with long-term use, e.g., effects on absorption of fat-soluble vitamins.

The recommended adult dosage is 1 g four times a day on an empty stomach. Antacids may be prescribed as needed for relief of pain but should not be taken within 30 minutes before or after administration of sucralfate.

While healing with sucralfate may occur during the first week or two, treatment should be continued for 4 to 8 weeks unless healing has been confirmed by X-ray or endoscopy.

Ritodrine Update

Since the approval of ritodrine (Yutopar) for use in premature labor (see November 1980 and July 1981 *Drug Bulletins*), FDA has been monitoring several areas of concern about the drug's known cardiovascular effects. In light of a number of adverse reaction reports, the labeling of ritodrine has been updated to warn about:

- the need to monitor the patient's state of hydration;
- the possibility of pulmonary edema with or without the concomitant use of corticosteroids, many cases of which seem to be related to overhydration;
- the possible unmasking of occult cardiac disease, the first sign of which may be chest pain.

Ritodrine, a beta₂-sympathomimetic drug, may be useful in preterm labor in pregnancies of at least 20 weeks gestation when contraindications have been ruled out.

However, in pregnancies of more than 32 weeks, physicians should care-

fully weigh the risks and benefits before administering the drug.

When gestational age is in doubt, intrauterine growth retardation should be considered in the differential diagnosis of preterm labor. Among low birth weight infants, about 9 percent may be growth retarded for gestational age. Prolongation of labor beyond term will not correct the growth retardation of these babies.

Initial administration of ritodrine is intravenous. To minimize the risk of hypotension, the patient should be maintained in the left lateral position during infusion and careful attention should be given to her state of hydration. The amount of i.v. fluids administered should be monitored to avoid either circulatory fluid overload (overhydration) or inadequate hydration. An excess sodium load should be avoided in hydrating the patient.¹

The boxed warning for ritodrine has been amended to read:

Maternal pulmonary edema has been reported in patients treated with Yutopar, sometimes after delivery. While occurring infrequently, it has occurred more often when patients were treated concomitantly with corticosteroids. Maternal death from this condition has been reported with or without corticosteroids given concomitantly with drugs of this class.

Patients so treated must be closely monitored in the hospital. The patient's state of hydration should be carefully monitored. (See Dosage and Administration.) If pulmonary edema develops during administration, the drug should be discontinued. Edema should be managed by conventional means.

Because cardiovascular responses are common and more pronounced during intravenous administration of Yutopar, cardiovascular effects, including maternal pulse rate and blood pressure and fetal heart rate,

should be closely monitored. Observe for premonitory or actual maternal signs and symptoms of pulmonary edema. A persistent high tachycardia (over 140 beats per minute) and/or persistent tachypnea (respiratory rate over 20 per minute) may be signs of impending pulmonary edema with drugs of this class.

Occult cardiac disease may be unmasked with the use of Yutopar. If the patient complains of chest pain or tightness of chest, the drug should be temporarily discontinued and an ECG should be done as soon as possible.

The drug should not be administered to patients with mild to moderate preeclampsia, hypertension, or diabetes unless the attending physician considers that the benefits clearly outweigh the risks.

Reference:

1. Philipsen T, et al.: Pulmonary edema following ritodrine-saline infusion in premature labor. *Ob Gyn* 1981; 58(3): 304-7.

Use of Approved Drugs for Unlabeled Indications

The appropriateness or the legality of prescribing approved drugs for uses not included in their official labeling is sometimes a cause of concern and confusion among practitioners.

Under the Federal Food, Drug, and Cosmetic (FD&C) Act, a drug approved for marketing may be labeled, promoted, and advertised by the manufacturer only for those uses for which the drug's safety and effectiveness have been established and which FDA has approved. These are commonly referred to as "approved uses." This means that adequate and well-controlled clinical trials have documented these uses, and the results of the trials have been reviewed and approved by FDA.

lir
ma
pro
ing
use
tie
in
pro
bel
tio
ma
the
por
son
var
stu
use
on
con
cut
suc
pro
tial
reg
ma
Thi
init
who
occ
ical
tha
lab
V
pra
tior
pre
pac
flec
ness
He
Us
as
re
He
in
t
sele
quit
form

The FD&C Act does not, however, limit the manner in which a physician may use an approved drug. Once a product has been approved for marketing, a physician may prescribe it for uses or in treatment regimens or patient populations that are not included in approved labeling. Such "unapproved" or, more precisely, "unlabeled" uses may be appropriate and rational in certain circumstances, and may, in fact, reflect approaches to drug therapy that have been extensively reported in medical literature.

The term "unapproved uses" is, to some extent, misleading. It includes a variety of situations ranging from unstudied to thoroughly investigated drug uses. Valid new uses for drugs already on the market are often first discovered through serendipitous observations and therapeutic innovations, subsequently confirmed by well-planned and executed clinical investigations. Before such advances can be added to the approved labeling, however, data substantiating the effectiveness of a new use or regimen must be submitted by the manufacturer to FDA for evaluation. This may take time and, without the initiative of the drug manufacturer whose product is involved, may never occur. For that reason, accepted medical practice often includes drug use that is not reflected in approved drug labeling.

With respect to its role in medical practice, the package insert is informational only. FDA tries to assure that prescription drug information in the package insert accurately and fully reflects the data on safety and effectiveness on which drug approval is based.

Hepatitis B Vaccine for Use in Selected Populations

An inactivated hepatitis B vaccine (Heptavax-B) has been licensed for use in the United States. It is intended for selected populations at high risk of acquiring hepatitis B, one of three known forms of viral hepatitis. (The others are

hepatitis A and non-A non-B hepatitis.)

The vaccine is the first to be made from human blood. Noninfectious antigen is purified from the plasma of asymptomatic human carriers of hepatitis B. After a series of chemical treatments, followed by the addition of alum adjuvant, the vaccine is administered in three intramuscular injections over a 6-month period.

Vaccination is not intended for the general population, but is recommended for persons older than 3 months of age who are at increased risk of hepatitis B virus infection. These persons will include health care workers, institutionalized patients, laboratory workers, hemodialysis staff and patients, family contacts of carriers, some military personnel, and persons with numerous sexual partners.

There continues to be a dialogue among government agencies, industry, and the medical community about use of the vaccine in selected high-risk groups. The Advisory Committee on Immunization Practices (ACIP) of the U.S. Centers for Disease Control (CDC), with assistance from representatives of FDA, the National Institutes of Health, and the medical community, has met several times to discuss specifically which population groups should receive this vaccine. The ACIP will meet once more in May of this year to draft final guidelines for use of this vaccine.

Efficacy

In clinical trials, 85 to 96 percent of persons receiving three doses of either 20 mg or 40 mg of vaccine were immune to infection. The duration of protection is presently unknown. However, in clinical trials, vaccine-induced antibodies, shown to provide protection against infection, persisted for at least 24 months in those receiving all three doses and will probably last for at least 5 years. After this time, a booster may be necessary to maintain immunity.

Side effects have been mainly local, mild, and transitory.

Availability

Due to the complexity of the methods used for producing the vaccine, it will be summer or fall of 1982 before the product is generally available from Merck, Sharp & Dohme. This manufacturer can supply complete physician information.

Advice on Limiting Intake of Bonemeal

Due to the unknown but often substantial lead content of individual samples of bonemeal and dolomite, FDA advises practitioners that these substances should be used as little as possible in infants, young children, and pregnant or lactating women.

Bonemeal is used primarily as calcium and/or phosphorus supplements. Bonemeal supplements are usually composed of finely crushed, processed bone and are packaged in powder, capsule, tablet, or wafer form. The source of bone is usually cattle but sometimes also horses. Bone marrow may also be added to this product. All bonemeal products contain lead which originates primarily from the diet of the animals from which the bone is taken. Bone serves as a repository for lead in the body and, in general, the older the animal the more lead in its bones.

Dolomite is a mineral deposit, consisting of calcium-magnesium carbonate with traces of other elements, including lead. Dolomite is used as a calcium and magnesium supplement and, like bonemeal, may be purchased in powder, capsule, tablet, or wafer form.

While a large portion of the small amounts of dietary lead ingested by humans is excreted, some is deposited in the mineral fabric of bone and some goes into soft tissue. Infants and children tend to absorb lead more efficiently than adults. When it is consumed in excess, lead may produce toxic reactions including central nervous system damage, anemia, and abdominal pain. As in animals, the accumulation of lead in human bone increases with age. Additionally, studies with

adult volunteers have shown that over a long time, the accumulation of lead in the body is proportional to the level of intake.

FDA Surveys

FDA has undertaken limited surveys to identify the extent of lead contamination of bonemeal and to determine whether the problem is limited or industry-wide.

One survey by FDA's Division of Consumer Studies of approximately 3,000 persons, 16 years of age and older, determined that about 1 percent of the population surveyed consumed bonemeal as a calcium source. More than 90 percent of the individuals consuming bonemeal were women, 50 years of age or older. The available information suggests that the average intake of bonemeal does not usually exceed 10 g/day.

No reliable information is available on the use of bonemeal as a calcium source for young children or infants. However, it is possible that bonemeal has been used as a calcium supplement for infants who have an intolerance for milk.

Although levels are usually lower, FDA scientists have found some samples of bonemeal containing lead at concentrations as high as 17 to 20 parts per million (ppm). Comparably high levels of lead have also been detected in some samples of dolomite.

It is known that the consumption of bonemeal containing 5 to 10 ppm lead by infants and children may result in lead intakes that clearly exceed the FDA recommended tolerable or maximal daily intake from all sources. For the infant, lead intake should be as low as possible and less than 100 micrograms/day, and for children between 6 months and 2 years the intake of lead should be no more than 150 micrograms/day.

Special Risk

Individuals at special risk of lead toxicity from the consumption of bonemeal or dolomite include infants, children, women of childbearing age, and

possibly the elderly. Others who ingest bonemeal at the recommended doses (usually not more than 5 to 10 grams/person/day) would not ordinarily exceed the WHO/FAO (World Health Organization/Food and Agriculture Organization) guideline for a tolerable daily adult intake of 430 micrograms of lead. However, individuals who consume more than two to three times the recommended dose would be at greater risk if the lead content of the bonemeal is high.

Pregnant or lactating women taking bonemeal or dolomite to meet increased calcium needs may have sufficient increased lead intake and absorption to present a health hazard to the developing fetus, via placental transfer of lead, or to the nursing infant from its mother's milk.

Bendectin PPI Available

A patient package insert (PPI) for Bendectin, an antiemetic combination of doxylamine and vitamin B₆ used in pregnancy, has been issued by the manufacturer, Merrell Dow Pharmaceuticals.

Pads of the PPIs are being distributed to retail pharmacies and physicians who are high prescribers of the drug, and are available to other health professionals from the manufacturer, upon request.

A Spanish language version of the PPI will be available upon request from the manufacturer.

In its summary section, the PPI explains: "Bendectin is used to treat the nausea and vomiting that may occur during the first few weeks of pregnancy. You should take this drug only if nausea and vomiting interfere with your eating or daily activities and if other treatments prescribed by your doctor do not relieve your symptoms. These other treatments include eating soda crackers or dry toast, or drinking hot or cold liquids as soon as you wake up in the morning.

"There is no way to prove that any

substance taken by pregnant women does not cause birth defects on rare occasions. For this reason, no drug, including Bendectin, should be taken during pregnancy unless it is clearly necessary."

As was discussed in the March 1981 issue of the *Drug Bulletin*, the revised physician labeling for Bendectin cautions physicians that the drug should be used only when more conservative treatment for nausea and vomiting in pregnancy has failed and when symptoms are sufficiently distressing to require drug intervention.

Class I Recalls

As a special service to health professionals, the *Drug Bulletin* is publishing information on recent Class I recalls. The following products have been withdrawn voluntarily in firm-initiated Class I recalls because they pose serious health hazards:

Infant Formula

Nursoy Concentrated Liquid, 13-ounce cans, coded A26M, B2M, and B9M, and Nursoy Ready-to-Feed 32-ounce cans coded A28M and B11M. Codes may be preceded by a number such as 1, 2, or 3, which can be ignored. Example: 2A26M. Formula lacks vitamin B₆, which can result in serious health effects ranging from irritability to convulsions. Cans may be returned to the retailer for refund or replacement. Recall date: March 3, 1982.

SMA powder and liquid with code numbers A25M through A31M, and B1M through B15M. Code numbers may be preceded by a number such as 1, 2, or 3, which can be ignored. Example: 2A25M. Formula is deficient in vitamin B₆, which can result in serious health effects ranging from irritability to convulsions. Cans may be returned to the retailer for refund or replacement. Recall date: March 12, 1982.

Defibrillator

Safeguard 3, serial numbers 290, 374, 379, 380, 1001, 1002, 1006. The storage capacitor may fail, resulting in low discharge energy and consequent failure to defibrillate. The manufacturer, Safeguard Medical Systems, Inc., Beltsville, Md., will replace faulty condensers. Recall date: Dec. 14, 1981.

as
fer