CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-286

Pharmacology Review(s)

NDA 21-286
Benicar Tablets
(olmesartan medoxomil, Sankyo)

SUPERVISORY PHARMACOLOGIST'S ADDENDUM TO PHARM/TOX REVIEW

C.A. Resnick, Ph.D.
Supervisory Pharmacologist
Division of CardioRenal Drug Products

Introduction

The angiotensin II receptor antagonist Benicar (olmesartan medoxomil, Sankyo), if approved, will be the 7th member of this class to be approved (all for the indication of hypertension).

Olmesartan medoxomil (OM) has undergone the standard battery of preclinical tests required by the Agency for chronically administered drugs. It has, however, undergone a more extensive evaluation for mutagenic and carcinogenic potential because of positive results *in vitro* in a Chinese hamster lung chromosomal aberration assay and a mouse lymphoma assay (obtained relatively early in the preclinical testing program) and a non-significant increase in renal tubular neoplasia when the drug was administered for two years to rats (renal tubular neoplasia a relatively rare occurrence in the rat).

The potential for genetic toxicity and carcinogenicity (interrelated toxicities) has been considered by the division to be an approvability issue for an antihypertensive drug that has no unique clinical advantages over other currently marketed members of its class. This secondary review will deal exclusively with these areas of concern. There are no approvability issues associated with the other preclinical evaluations that have been conducted with OM and the reader is referred to the primary pharmacology review for descriptions of those evaluations and for comments and recommendations on the sponsor's proposed labeling.

The Carcinogenicity Studies

There were three carcinogenicity studies performed with OM, a standard two year study in the Fischer rat, a 6 month p53(+/-) mouse study and a 6 month Hras2 mouse study. Although there were no statistically significant OM-related tumor findings in any of these studies, there was a nominal increase in the incidence of renal tubular neoplasia in treated males in the two year rat study (adenomas and carcinomas which were not seen in the concurrent control rats, and are relatively rare on the basis of historical control data for the strain (0.8%)). Because an Executive Committee of the Center's Carcinogenicity Assessment Committee expressed concerns about the occurrence of renal tumors and renal tubular hyperplasia in OM-treated rats, the full CAC was asked to assess the evidence of carcinogenic potential for OM in the rat. A majority of the members of the committee felt that OM had tested positive in the rat carcinogenicity assay. There were no OM-associated increases in tumor incidence (renal or other) in the mouse studies. Because of a less than expected bladder tumor incidence in the positive control group in the p53(+/-) study, the committee was asked to assess the adequacy of that experiment and they found that study to be acceptable. In the sponsor's presentation to the CAC, they had stressed the absence of atypical hyperplasia in the rats and argued that the renal tubular hyperplasia which was seen should not be considered pre-neoplastic. On the other hand, they claimed that the bladder hyperplasia observed in the positive control (p-cresidine) group in the p53 (+/-) assay was atypical and should be considered pre-neoplastic.

A few weeks after the CAC meeting, office and division representatives met with the sponsor to explore what further actions they might take to strengthen their position that the increased incidence of renal tubular neoplasia in the Fischer rat was not related to treatment with their drug. The FDA representatives suggested that a kidney step-sectioning protocol be carried out and that the original study kidney slides be sent to NIEHS for peer review. It was also suggested that the sponsor perform additional in vivo assays to assess the mutagenic effect of OM on the kidney (mutamouse assay) and to assess the potential for DNA damage in the kidney (Comet Assay).

The peer review by NIEHS pathologists Gary Boorman and Bob Marinpot, and an independent peer review by the sponsor's expert consultant pathologist, [redacted] essentially confirmed the tumor findings of the original study pathologist. The original diagnosis of tubule hyperplasia was not confirmed by [redacted] who, instead, diagnosed renal tubule hypertrophy. The sponsor provided further support for this diagnosis with PCNA staining, which showed no greater proliferation in the kidney sections (of OM-treated rats) originally diagnosed as hyperplastic than in control rats. The NIEHS pathologists concluded that the tubular hyperplasia observed in the original study reflects tubular regeneration secondary to nephropathy. None of the peer reviewers saw evidence of the atypical hyperplasia that is considered evidence of preneoplastic activity. [redacted] asserted that one of the tumors in each of the OM-treated groups had a phenotype consistent with a spontaneous origin.

The step-sectioning of the kidneys (done blinded) resulted in four more tumor-bearing animals in comparison with the original (single section) evaluation. All of these additional occurrences were in OM-treatment groups. Whereas the single section evaluation resulted in incidences of 0, 2, 4 & 2 tumor bearing rats in the control, low dose, mid-dose and high dose groups, the step section evaluation resulted in corresponding incidences of 0, 3, 5 & 4 (all adenomas except for 1 carcinoma in the mid-dose group and 1 carcinoma in the high dose group). As with the single section evaluation, the step-sectioning did not result in a statistically significant increasing trend in tumor incidence. Although a pairwise comparison of the mid-dose group (not the high dose group) and the control group resulted in a p value <0.05, and although a pairwise comparison of the combined treatment groups with the control group also resulted in a p value <0.05, FDA statisticians use a p value of 0.01 to determine statistical significance when dealing with a common tumor and although renal tubular neoplasia is uncommon (about 0.8%) when detection is based on single-sectioning, it is common (about 4.5%) when detection is based on step-sectioning.

Genetic Toxicity

OM and olmesartan have been shown to induce chromosomal aberrations in cultured cells *in vitro* (Chinese hamster lung). OM was also positive for thymidine kinase mutations in the *in vitro* mouse lymphoma assay. Diacetyl, a side-chain cleaved by ester hydrolysis during the process of absorption from the gut, produced positive responses in both Ames and *in vitro* chromosomal aberration (Chinese hamster lung) assays[1]. (Olmesartan and diacetyl were not tested in the mouse lymphoma assay.) It was on the basis of these results that an executive committee of the Center's Carcinogenicity Assessment Committee (CAC) accepted the p53 (+/-) assay as an alternative to the standard 2 year carcinogenicity bioassay in the mouse (the p53 assay has been shown to be sensitive to genotoxic carcinogens). Additional testing has generally been limited to OM, which tested positive *in vivo* for damage to the LacZ gene in two of three studies and the CII gene (one study conducted) in the intestine of the MutaMouse. Negative results were obtained for effects on the LacZ gene in the kidney of the MutaMouse. Equivocal results were obtained in a test for DNA damage to the rat kidney (Comet Assay)[2]. OM tested negative for clastogenicity *in vivo* in the mouse bone marrow micronucleus test. Both OM and olmesartan tested negative *in vitro* in the Syrian hamster embryo cell transformation assay.

Current Status of the Application

On October 3rd, representatives of the Division and the Office again met with Sankyo. The company and their consultant, [redacted] outlined the reasons why they thought olmesartan medoxomil was not responsible for the renal tubular neoplasms that had been observed in the two year rat study. Some of the presentation (results of the PCNA staining, and the views of Drs. Boorman, Marinpot and [redacted]) constituted information that had not been available at the time of the CAC meeting and a decision was made to reconvene that committee. Before taking this drug back to the CAC, it was agreed that a pathology working group that includes one or more members chosen by the Agency, along with other members selected by the sponsor, should be asked to consider the relationship of OM to the renal tumors seen in the

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[1] Diacetyl occurs naturally in foods and drinks and is categorized as "Generally Regarded As Safe (GRAS)" by the FDA.

[2] Whether or not OM was positive in this assay is dependent on the statistical analysis that is applied. A decision on the most appropriate analysis is pending.

2-year rat study exclusively in animals exposed to the drug. The sponsor was told that an approvable letter would be issued but approval of their product would depend on the outcome of the CAC deliberations.

Evaluation

It is always difficult to rule out exposure to a drug as a factor in the increased incidence of a particular pathology associated with that exposure, especially when, as in the case of OM in rats, the incidence is higher than one would expect on the basis of historical data. But being unable to rule out a drug-relationship should not lead to the conclusion that such a relationship exists

Let's look at the strength of the evidence supporting a conclusion that the renal tubular neoplasms observed exclusively in OM-treated animals in the two year rat study are related to OM. Although OM has been shown to be genotoxic in some tests, and although the overall incidence of renal tubular neoplasms in OM-treated males in this study, based on the single section evaluation (5.3%), is almost 7 times historical control incidence (0.8%) and the highest OM group incidence (8%) is twice the highest incidence seen in any control group (4%),

- the overall incidence in OM-treated males, based on the more thorough step section evaluation (8%), is less than twice the historical control incidence (4.5%) and the highest OM group incidence (10%) is within the range of incidences seen in individual control groups (0-14%).

- there was no significant trend (not even a suggestion of a positive dose-response).

- there was no significant difference between any of the treated groups (alone or combined) and the control group.

- there were no preneoplasic lesions identified in the OM-treated rats.

Even if the renal tumors in the rat were a consequence of exposure to OM, there was no suggestion of any drug-related neoplasia in mice (transgenic models expected to detect genotoxic carcinogens) and the drug tested negative in a Syrian hamster cell transformation assay (which detects both genotoxic and nongenotoxic carcinogens). In the absence of a repeat of the 2 year rat study that results in a replication of the results of the original experiment, I consider the evidence for OM-related carcinogenicity in the rat as equivocal and lean to classifying OM as a genotoxic non-carcinogen.

Recommendation

Dr. Jagadeesh, in his review of the Benicar application, recommends that the package insert acknowledge the detection of renal tubular neoplasia exclusively in rats treated with olmesartan medoxomil, a recommendation consistent with the recommendation of the CAC. But if we are confident that this drug is a rodent carcinogen we should not be approving it for the treatment of hypertension. Because the issue of carcinogenic potential will be going back to the CAC for their reconsideration, it makes sense to me that labeling, or at least carcinogenesis labeling, not accompany the approvable letter that we have decided to issue for this application.

cc:
HFD-110/Jagadeesh
HFD-110/Lipicky
HFD-110/Throckmorton
HFD-110/Stockbridge
HFD-024/DeGeorge
NDA 21286_Secondary Review .doc 17 October, 2001

MEMORANDUM

To: Edward Fromm, Project Manager,
Division of CardioRenal Drug Products

Through: Douglas Throckmorton, M.D., Division Director,
Division of CardioRenal Drug Products

From: Charles Resnick, Ph.D., Supervisory Pharmacologist,
Division of CardioRenal Drug Products

Subject: Labeling for Benicar® Tablets (olmesartan medoxomil tablets, Sankyo)

Date: 23 April, 2002

In consideration of the recommendations conveyed by Jeri El-Hage's memorandum of 16 April 2002, please request that Sankyo make the following changes to their Benicar Tablet package insert at the next printing:

1. Under **PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility**, delete from the second paragraph the words "for DNA damage in the rat kidney (comet assay)."

2. Under **OVERDOSAGE**, delete the second paragraph, which makes reference to studies in mice, rats and dogs.

3. Under **WARNINGS, Fetal/Neonatal Morbidity and Mortality**, the next to last sentence notes, [redacted] The sentence should be modified to [redacted]

4. Under **PRECAUTIONS, Nursing Mothers**, the statement [redacted]

The sponsor's proposed wording for labeling modifications 3 and 4 should be cleared with the Division before being implemented.

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Charles Resnick
4/23/02 11:40:04 AM
PHARMACOLOGIST
Modifications to labeling to be made at next printing.
Changes recommended by ODE1.

MEMORANDUM

To: File, NDA 21-286

Through: Robert Temple, M.D., ODE I Office Director
Douglas Throckmorton, M.D., Division Director, Cardiorenal Drug Products
Charles Resnick, Pharmacology Supervisor, HFD-110
Gowra Jagadeesh, Ph.D, Pharmacology Reviewer, HFD-110
Edward Fromm, Project Manager, HFD-110

From: Jeri El-Hage, Ph.D., ODE I Associate Director for Pharmacology/Toxicology

Subject: NDA 21-286 , Benicar®, Olmesartan medoxomil
Tertiary Review of Pharmacology/Toxicology Data

Date: April 16, 2002

A complete toxicological evaluation of olmesartan medoxomil has been conducted and the toxicity profile supports the recommendation of the pharmacology reviewer and team leader for NDA approval. The Pharmacology/Toxicology review was completed in October 2001. Due to outstanding issues regarding the interpretation of the slight increase in renal tumor findings in the 2-year rat carcinogenicity study, the results of that study were taken to the full Carcinogenicity Assessment Committee(CAC) for review on January 31, 2002. The consensus of the CAC was that the non-statistically significant increase in renal tumor findings should not be included in the Benicar labeling. The minutes of the full CAC should be included in the action package.

The labeling for Benicar was reviewed in the Pharmacology /Toxicology policy group meeting today. The following recommendations regarding the labeling were made:

Regarding the preclinical reproductive findings in the last paragraph under **WARNINGS – Fetal/Neonatal Morbidity and Mortality**

1. [redacted]
Please describe the exposure relative to human exposure at this dose.

2. Same sentence continues [redacted] - Please specify what findings "milestones" represent.

3. Same sentence ". [redacted]
Again, please specify exposures in rats treated with 8 mg/kg/day relative to exposures with MRHD.

Regarding the **Carcinogenicity, Mutagenesis, and Impairment of Fertility** section-

1. P53 knockout mouse is jargon. Please replace the word knockout with [redacted]

2. The Syrian hamster embryo (SHE) cell transformation assay is not a mutagenicity assay. The results of this assay should be moved to the end of the first paragragh describing the results of the carcinogenicity studies.

3. Labeling convention is that the results of mutagenicity studies with positive findings are discussed first and then studies with negative results are discussed.

4. The policy group felt that the comet assay is not a validated method and that agreement was not reached by the division or the CAC regarding the acceptability of the results. Therefore, the wording " for DNA damage in the rat kidney (comet assay), " should be removed. The concern was that inclusion may lead other sponsors to conclude that this assay is generally accepted by FDA.

Regarding the **Nursing Mothers** section

Please give some indication of the meaning of "secreted at low concentration in the milk of lactating rats." For example, percent of total dose/radioactivity or percent of maternal drug concentration.

Regarding the **Overdosage** section

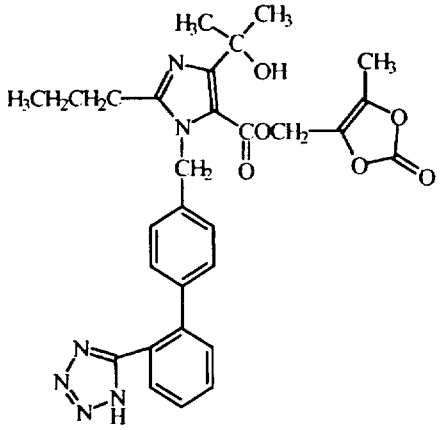
Please remove the [redacted] information from this section. This information would not be useful to the clinician in the event of an overdose.

NDA 21-286
Benicar® Tablets
(olmesartan medoxomil, Sankyo)

RESULTS OF *IN VITRO* AND *IN VIVO* GENETIC TOXICOLOGY STUDIES AND RESULTS OF MULTIPLE HISTOPATHOLOGIC EVALUATIONS OF KIDNEYS FROM A CARCINOGENICITY STUDY IN F-344 RATS

P/T REVIEWER(s): G. Jagadeesh, Ph.D.
DATE: January 25, 2002
NDA: 21-286
DRUG CODE#: CS-866, RNH-6334
CAS#: 144689-63-4
DIVISION(s): Cardio-Renal Drug Products, HFD-110
DRUG NAME(s): Olmesartan medoxomil (Benicar®)

CHEMICAL STRUCTURE:



THERAPEUTIC CATEGORY: Anti-hypertensive
PHARMACOLOGICAL/CHEMICAL CLASSIFICATION: Angiotensin II type 1 (AT-1) receptor antagonist
MUTAGENIC/GENOTOXIC: Yes

Olmesartan medoxomil (OM) is an angiotensin II receptor antagonist that has been shown to induce chromosomal aberrations in Chinese hamster lung (CHL) fibroblast cells and TK mutations in mouse lymphoma cells, both *in vitro* assays. OM tested negative in the MutaMouse kidney with equivocal results obtained in the MutaMouse intestine. Equivocal results were obtained in another *in vivo* test for DNA damage in the rat kidney (comet assay). Equivocal and negative results, respectively, were obtained for the active metabolite, olmesartan, in an *in vitro* chromosome aberration assay in CHL fibroblast cells and an Ames test (not tested in mouse lymphoma assay). Diacetyl, a side-chain cleaved by ester hydrolysis during the process of absorption from the gut, produced positive responses in both Ames and *in vitro* chromosomal aberration assays (Table 1). The latter result is said to be consistent with findings in the open literature. It should be noted that diacetyl occurs naturally in foods and drinks and is categorized as "Generally Regarded As Safe (GRAS)" by the FDA[1] and as "Category A: flavoring

[1] CFR report, Title 21, Vol 3, Part 184.1278, 2000.

substances which may be used in food stuffs" by Council of Europe's Committee of Experts on Flavoring Substances[2] and is not considered to pose a carcinogenic risk to humans. Based on the diacetyl content in various foods and drinks as reported in the literature, the sponsor estimates the daily intake of diacetyl in humans from food and drink to be more than 10 mg. This amount is larger than the amount of diacetyl (1.5 mg) produced from a maximum recommended daily dose of 40 mg OM (assuming 25% bioavailability).

Clastogenicity and mutagenicity with olmesartan medoxomil were concentration-related and the lowest concentration at which these responses were seen (124 µg olmesartan/ml, 10 µM) is much higher than encountered in human plasma (0.71 µg olmesartan/ml), suggesting that olmesartan medoxomil may pose little risk as a mutagen.

TABLE 1
SUMMARY OF GENETIC TOXICOLOGY DATA FOR OLMESARTAN MEDOXOMIL AND ITS METABOLITES

Assay		OM	OLM	Di-acetyl	HMPIC, MBT, Acetoin
Reverse mutation in bacteria (Ames assay)	-S9	-	-	-	-
	+S9	-	-	+	-
In vitro chromosome damage	-S9	+	-		-
(Chinese hamster lung)	+S9	-	+	+	-
In vitro mammalian cell gene mutation	-S9	+	NC	NC	NC
(Mouse lymphoma assay, TK locus)	+S9	+	NC	NC	NC
In vitro Morphological cell transformation (SHE)		-	-	NC	NC
In vivo Rat hepatocyte UDS		-	NC	NC	NC
In vivo micronucleus test		-	NC	NC	NC
In vivo gene mutation, transgenic mice (Muta™ mouse): intestine		±[1]	NC	NC	NC
In vivo gene mutation, transgenic mice (Muta™ mouse): kidney		-	NC	NC	NC
In vivo DNA damage in the kidney of 9 wk old rats (comet assay)		±[2]	NC	NC	NC
In vivo DNA damage in the kidney of 9 month old rats (comet assay)		-	NC	NC	NC

OM: olmesartan medoxomil, OLM: olmesartan, NC: not conducted
Responses are shown as: - negative, + positive, ± equivocal
1: Of the three studies, the first two were positive and the third negative for effects on the *LacZ* gene and equivocal for effects on the *CII* gene (only one of these studies in which effect on the *CII* gene was evaluated).
2: Ongoing discussion regarding adequacy of the analysis

[2] Flavoring substances and natural sources of flavoring. Vol 1. Chemically defined flavoring substances, Council of Europe, Maisonneuve, Strasbourg, 1992.

RAT CARCINOGENICITY STUDY

STUDY DURATION: 24 months
STUDY STARTING DATE: April 24, 1997
STUDY ENDING DATE: April 28, 1999
RAT STRAIN: F344/DuCrj [redacted]
ROUTE: Diet

NUMBER OF RATS:
- Control-1 (C1): 50/sex
- Control-2 (C2): NA
- Low Dose (LD): 50/sex
- Middle Dose (MD): 50/sex
- High Dose-1 (HD1): 50/sex
- High Dose-2 (HD2): NA

RAT DOSE LEVELS (mg/kg/day):
- Low Dose: 200
- Middle Dose: 600
- High Dose-1: 2000
- High Dose-2: NA

BASIS FOR DOSES SELECTED (MTD; AUC ratio; saturation; maximum feasible): MFD

PRIOR FDA DOSE CONCURRENCE (Div./CAC)? (y/n; Date): Yes

RAT KIDNEY TUMOR FINDINGS:

The most significant aspect of this study is in a nominal increase in the incidence of renal tubular neoplasia (adenomas and carcinomas) at all dose levels in treated males (2, 4, 2 in the low, mid and high dose groups, respectively). The tumor incidence is not statistically significant or dose-dependent. Renal tubular adenomas and carcinomas were not seen in the concurrent control rats, and are relatively rare on the basis of historical control data for the same strain (0.8%). The Executive Carcinogenicity Assessment Committee (CAC) at its meeting on March 20, 2001 expressed concerns about the occurrence of renal tubular cell tumors and renal tubular hyperplasia in only OM-treated animals. The full CAC was asked to assess the evidence of carcinogenic potential for OM in the rat. A full CAC meeting was held on May 4, 2001 and the participants included representatives and consultants for Sankyo Pharma. Twelve of the 20 CAC members felt that the drug had tested positive in the rat carcinogenicity assay, with 8 of these 12 saying that they could not conclude that the finding would have little or no relevance to human cancer risk. Seven of the 20 asked that a third party chosen by the agency redo the histopathology. An additional meeting was held with the sponsor on May 30th. At that meeting, the agency asked the sponsor to do additional evaluations to demonstrate that OM is not a carcinogen. In this context, the agency suggested that a kidney step-sectioning protocol be

carried out and that the original study kidney slides be sent to NIEHS for peer review. Sankyo performed all of the studies and submitted the study reports to the Division on August 30, 2001.

The peer review by NIEH pathologists and an independent expert review by [redacted] did not significantly alter the tumor findings of the original study pathologist (see Table 2). The step-section analysis of the kidneys resulted in four more tumor-bearing animals in comparison with the original (single section) evaluation. After step sectioning, the number of tumor bearing animals was 0, 3, 5 and 4 in the control, low, mid and high dose groups, respectively. Though the number of tumor bearing animals in the step-section analysis increased from 8 to 12, the sponsor still contends that the incidence is not significantly different from the concurrent control group incidence (0%) and that the incidence for each treated group is within the range of historical control group values for the step-section protocol (mean incidence, 4.5%; range, [redacted] %). The FDA analysis of the step-section data revealed no statistically significant increased trend in the incidence of adenomas and carcinomas that could be attributed to treatment with OM (p=0.12). Although, pair-wise comparisons (mortality adjusted or unadjusted) of the control and the mid dose group and of the control *versus* all treated males (combined) resulted in a p-value of 0.02, the Agency statisticians use a p value of 0.01 in determining statistical significance when dealing with common tumors (spontaneous rate <1%; background incidence for renal tubular neoplasia when detection is based on step-sectioning is 4.5%).

The firm requested a meeting to discuss the above test results and whether the toxicology issues associated with the drug were still an impediment to approval. The meeting was held on October 3, 2001. The firm presented their case in concluding that OM is not carcinogenic. At this meeting it was suggested to the firm that it might be helpful to have a Pathology Working Group (PWG) review carcinogenicity and nephrotoxicity issues. The group would be asked to answer the following questions:

Can the tumors be determined to be spontaneous in origin or drug-related? Is the nephrotoxicity spontaneous or drug-related? Are the tumors related to the nephropathy? Were all of the renal tumors considered primary renal tumors?

Sankyo agreed to a PWG to review the histopathology of male rat kidneys and to address the questions posed by the FDA. The PWG convened on November 26-28 and issued a report.

The PWG reports some degree of nephropathy in nearly all male rats including control. Unlike the findings by the study pathologist, the Panel did not find differences in the incidence of nephropathy between the control and treated groups. They did find an increase in the severity of nephropathy in treated male rats as compared to control male rats. But there was no dose response among treated groups. The Panel's observation is in concurrence with the Expert report by [redacted]

A summary of the incidence of proliferative lesions involving the renal tubules of the kidney diagnosed by the study pathologist (original results), the sponsor's expert consultant, [redacted] NIEH pathologists, step-section analysis by the sponsor, and the PWG are given in Table 2. The PWG review of kidney slides from 4 male rats from the step-section study that showed

additional tubular cell adenomas confirmed the presence of one tubular cell adenoma in each drug-treated group. After step-sectioning the sponsor's pathologist identified a total of 3, 5 and 4 tubular neoplasia bearing rats in the low, mid and high dose groups, respectively whereas, the PWG reports 3, 4 and 3 (Table 2).

TABLE 2
24-MONTH ORAL CARCINOGENICITY STUDY OF OLMESARTAN MEDOXOMIL IN RATS: COMPARISON OF THE INCIDENCE OF PROLIFERATIVE TUBULAR CELL LESIONS DIAGNOSED BY THE STUDY PATHOLOGIST AND PEER REVIEWERS

Dose mg/kg/ day	Animal #	Original results[1]	Expert report by [redacted]	NIEHS review[3]	After Step-sectioning Sponsor analysis[4]	PWG analysis[5]	
						Before step-sectioning	After Step-sectioning[6]
200	02M06				Adenoma		Adenoma
	02M21	Adenoma	**Carcinoma**	**Carcinoma**	Adenoma	Adenoma	Adenoma
	02M43	Adenoma[a]	Adenoma and **Carcinoma**[a]	Adenoma and **Carcinoma**[a]	Adenoma	Adenoma and **Carcinoma**[a]	Adenoma and **Carcinoma**[a]
600	03M10				Adenoma		Adenoma
	03M24	Adenoma	**Carcinoma**	Adenoma[b]	Adenoma	**Carcinoma**	**Carcinoma**
	03M26	**Carcinoma**[c]		**Carcinoma**[c]	**Carcinoma**[c]		
	03M30	Adenoma	Adenoma	Adenoma	Adenoma	Adenoma	Adenoma
	03M33	Adenoma	Adenoma	Adenoma	Adenoma	Adenoma	Adenoma
2000	04M02	Adenoma	Adenoma	Adenoma	Adenoma	Adenoma	Adenoma
	04M21				Adenoma		Adenoma
	04M24	**Carcinoma**	**Carcinoma**	**Carcinoma**	**Carcinoma**	**Carcinoma**	**Carcinoma**
	04M40				Adenoma		
Total of animals with adenoma or carcinoma (LD, MD, HD)		**2, 4, 2**	**2, 3, 2**	**2, 4, 2**	**3, 5, 4**	**2, 3, 2**	**3, 4, 3**

1: Original study #97-0022, Report #TR 146-570
2: At the request of the sponsor, [redacted] did unblinded review. Report prepared May 29, 2001
3: At the request of the FDA, Drs. G.A. Boorman and R.R. Marenpot of NIEHS reviewed 13 slides, 8 of them originally diagnosed as renal tubular neoplasia, the rest as renal tubular hyperplasia. Report dated July 25, 2001
4: At the request of the FDA, kidneys of all groups of male rats were evaluated using the NTP step-sectioning protocol at the sponsor's (Sankyo, Japan) laboratory (report #APR-148-080).
5: At the request of the FDA, a Pathology Working Group was constituted and the Panel was convened on 11/26.
6: PWG review of step-section tissue was limited to 4 male rats
[a]: multiple adenomas and carcinomas (diagnosed as multiple adenoma by the study pathologist)
[b]: characterized as carcinoma by Dr. Boorman and adenoma by Dr. Marenpot
c: diagnosed as metastatic carcinoma, uncertain primary (not primary renal tubular cell tumor) by [redacted]' and by PWG.

Subtle differences were seen in the observations made by the study pathologist and the PWG. There were differences in classifying the tumors as adenoma or carcinoma. Furthermore, the analysis of the PWG, like those of [redacted] and NIEH scientists, did not confirm the study pathologist's diagnosis of tubular cell hyperplasia. The PWG considered tubular cell hyperplasia

to be tubular cell hypertrophy associated with chronic nephropathy. It was characterized by them as "dilated cortical tubules lined predominantly by a single layer of enlarged eosinophilic cells. This lesion was not considered to be a proliferative lesion and is usually observed as an adaptive or compensatory change". The PWG observed one incidence of tubular cell hyperplasia in each of the control, low and high dose groups.

In concluding remarks, the PWG report observes that *"the morphologic appearance of the neoplasms observed in this study are similar to spontaneously occurring tubular cell adenoma and carcinoma which have been reported in control male F344 rats, and it is not possible to determine whether these neoplasms are spontaneous or drug induced based only on morphology. The relatively low incidence, the lack of a dose response and the absence of an increased incidence of hyperplastic lesions suggestive of preneoplastic changes indicates that the few tubular cell neoplasms observed in this study are not related to treatment with CS-866 when the overall weight of the evidence is considered."*

NDA #21,286

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

G. Jagadeesh, Ph.D.

October 15, 2001

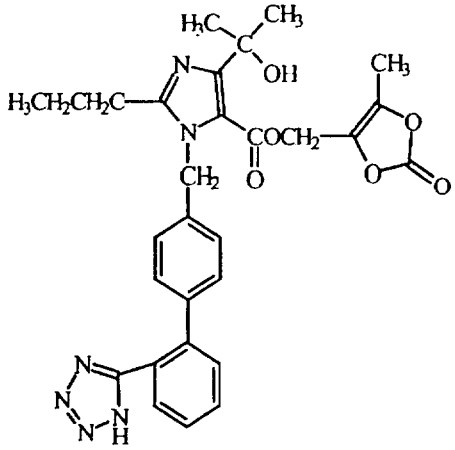
ORIGINAL SUBMISSION DATE July 25, 2000
CENTER RECEIPT DATE July 25, 2000
REVIEWER RECEIPT DATE July 28, 2000

SPONSOR Sankyo Pharma Inc.
780 Third Avenue, 47th Floor
New York, NY 10017

DRUG PRODUCT BENICAR™ (Olmesartan medoxomil) Tablets

DRUG CHEMISTRY

Code Names: CS-866, RNH-6334
Chemical Name: (5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl 4-(hydroxy-1-methylethyl)-2-propyl-1-[[2'-(1H-tetrazol-5-yl)-1,1'-biphenyl-4-yl]methyl]-1H-imidazole-5-carboxylate
CAS Registry No.: 144689-63-4



Molecular Weight 558.59

PHARMACOLOGICAL CLASS Angiotensin II receptor antagonist

INDICATION Treatment of hypertension

FORMULATION Film-coated tablets containing 20 mg or 40 mg of olmesartan medoxomil and the following inactive ingredients: microcrystalline cellulose, hydroxypropylcellulose, lactose, low-substituted hydroxypropylcellulose, magnesium stearate, titanium dioxide, talc, and

PROPOSED DOSAGE REGIMEN The usual recommended starting dose of BENICAR™ is 20 mg once daily when used as monotherapy. For patients requiring further reduction in blood pressure, the dose may be increased to 40 mg once daily or 20 mg twice daily.

IND UNDER WHICH CLINICAL TRIALS WERE CONDUCTED

TABLE OF CONTENTS

1. PHARMACODYNAMICS

1.1. Studies Related to Proposed Therapeutic Indication

Olmesartan medoxomil (OM) is a new orally active angiotensin II (AII) receptor antagonist, that binds selectively to the AT_1 receptor. It is a prodrug hydrolyzed rapidly and completely to olmesartan, an active metabolite, during absorption from the gastrointestinal tract. OM is practically insoluble in water and sparingly soluble in methanol. Multiple *in vitro* and *in vivo* animal studies using rats, mice, rabbits, guinea pigs, and dogs have been conducted to elucidate the pharmacology of OM and olmesartan. The results of these studies are summarized here and categorized according to effects on the various body systems.

1.1.1. Angiotensin II Antagonistic Action

1.1.1.1. Receptor Specific Studies (Report #FR 140-902)

The selectivity of olmesartan for angiotensin II receptors was evaluated by receptor binding techniques using the AT_1 receptor predominant bovine adrenal cortical and AT_2 receptor predominant bovine cerebellar membranes. OM and olmesartan were dissolved in ethanol and $NaHCO_3$ solution, respectively. Unlabeled angiotensin II displaced bound ^{125}I-angiotensin II from both the cortical and cerebellar membranes with similar affinities (IC_{50} values, 1.5 and 0.57 nM, respectively). On the other hand, olmesartan markedly inhibited ^{125}I-angiotensin II binding to the cortical membrane with high affinity (IC_{50}, 8.0 nM), but did not inhibit ^{125}I-angiotensin II binding to the cerebellar membrane, demonstrating high selectivity for AT_1 receptors (Fig. 1.1.1.1). The parent compound, OM, was tested for its AII antagonistic activity. Based on the IC_{50} values, OM had about one-fourth of the antagonistic activity of olmesartan. Additionally, the receptor binding activity of olmesartan was compared to other AII receptor antagonists, losartan and its active form EXP3174; CV-11974 (the active form of candesartan); saralasin, a peptidic non-selective antagonist; and PD123177, an AT_2-selective antagonist (Table 1.1.1.1). Based on the IC50 values, olmesartan was 11-, 2-, and 1.5-fold more potent as an AT_1 receptor antagonist than losartan, EXP3174, and CV-11974, respectively.

TABLE 1.1.1.1
INHIBITORY EFFECTS OF OLMESARTAN AND OTHER AII RECEPTOR ANTAGONISTS ON SPECIFIC BINDING OF ^{125}I-ANGIOTENSIN II

Test compound	Adrenal Cortex (AT_1)	Cerebellum (AT_2)
AII	1.5 ± 0.1	0.57 ± 0.04
OLMESARTAN	8.0 ± 0.8	>100,000
OM	33.0 ± 8	Not Tested
Losartan	92.0 ± 5	>100,000
EXP3174	16.0 ± 1	>100,000[a]
CV-11974	12.0 ± 1	>100,000[a]
Saralasin	5.0 ± 0.2	1.5 ± 0.1
PD123177	>100,000	150 ± 20

Values represent the concentrations of the test compound (nM) that displace the specific binding of ^{125}I-AII by 50% (IC_{50}) (mean ± SEM); n=3 to 10. [a]: n=2.

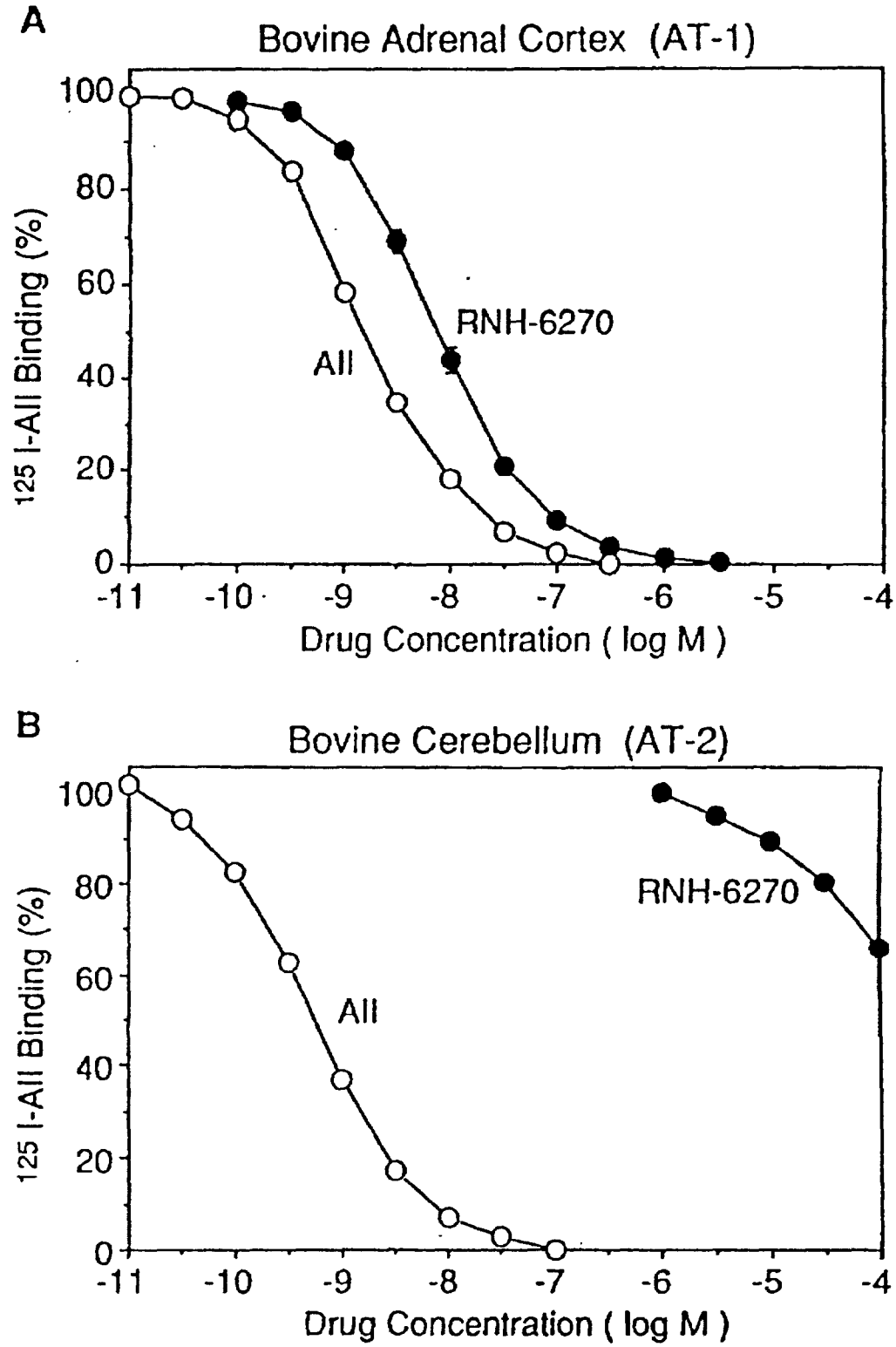
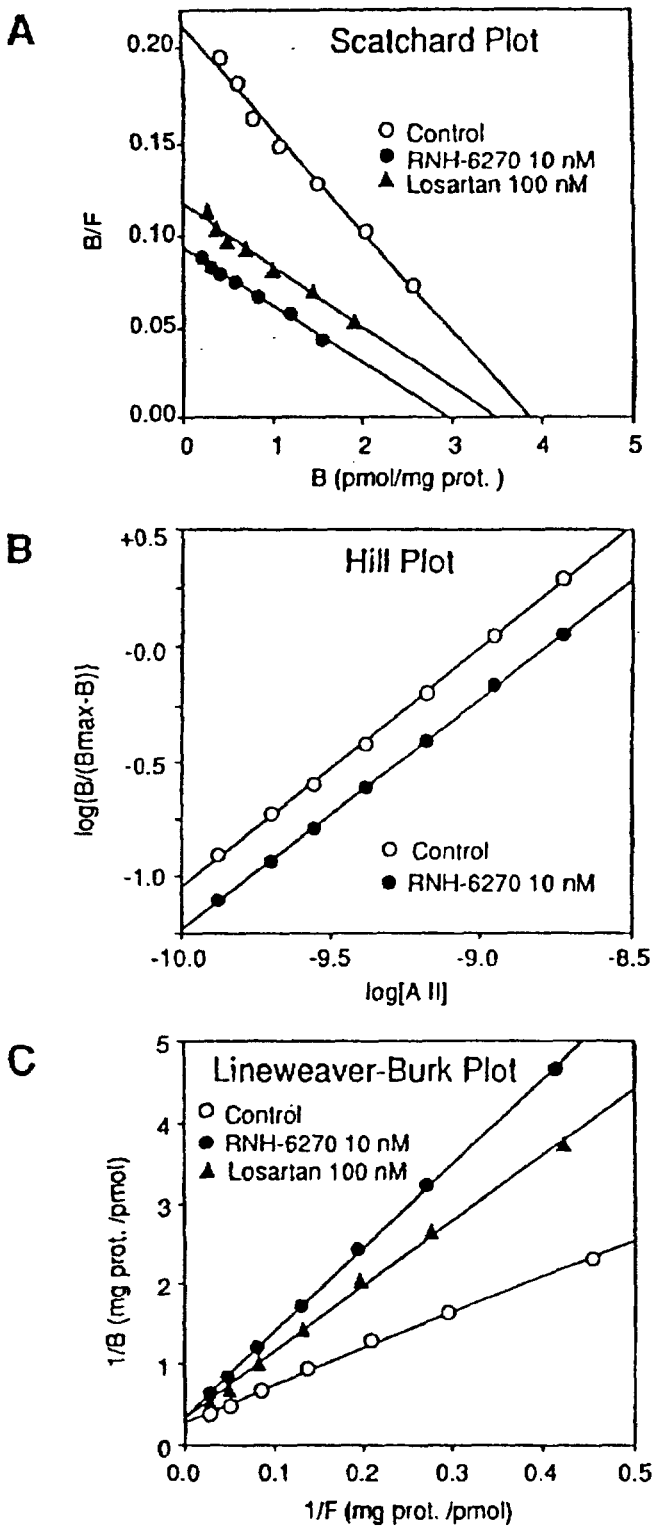


Fig. 1.1.1.1.: Displacement of specific binding of ^{125}I-angiotensin II to bovine adrenal cortical (A) and bovine cerebellar membranes (B) by unlabeled AII and olmesartan (RNH-6270). Data are means ± SEM (n=4 to 6).



The effect of olmesartan on the binding of ^{125}I-angiotensin II to AT_1 receptors was further investigated in saturation experiments in bovine adrenal cortical membranes at one concentration level only (10 nM). In a Scatchard plot of the binding data, olmesartan reduced the slope of the line ($-1/K_D$) from 0.055 to 0.032 or increased the K_D (dissociation constant)). The corresponding B_{max} (maximum number of binding sites) was also reduced, suggesting a non-competitive antagonism. However, The results from Hill and Lineweaver-Burk plots suggested that olmesartan was a competitive antagonist at the AT_1 receptor (Fig. 1.1.1.2).

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Fig. 1.1.1.2.: Scatchard (A), Hill (B) and Lineweaver-Burk (C) plots of ^{125}I-angiotensin II binding to bovine adrenal cortical membranes in the absence and presence of olmesartan (RNH-6270) or losartan. Data from a typical experiment are shown. B/F: bound/free

1.1.1.2. Studies in Isolated Tissues (Report #FR 140-903)

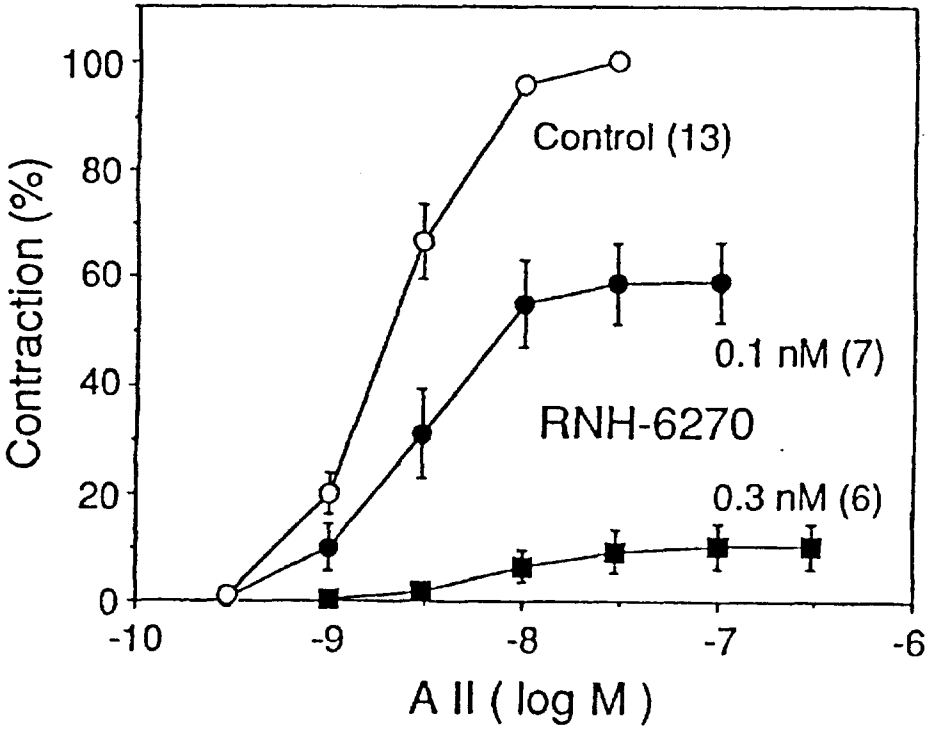
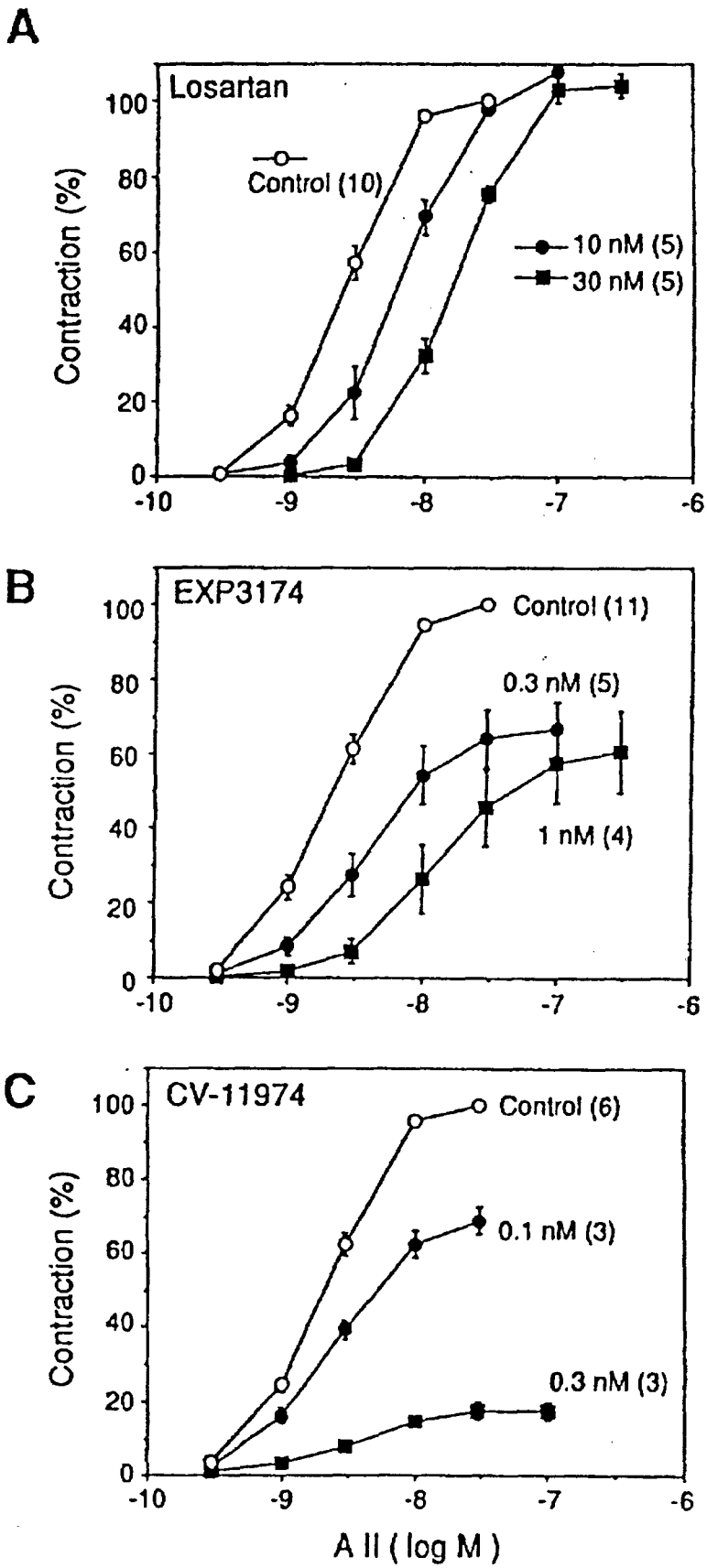


Fig. 1.1.1.3.: Effects of olmesartan (RNH-6270) on concentration-contractile response curves for angiotensin II in guinea pig aortic strips. Data are means ± SEM.

Angiotensin II-induced contractions of isolated guinea pig thoracic aortic strips were markedly reduced by olmesartan in a concentration-dependent manner (studied at two concentration levels, 0.1 and 0.3 nM). The rightward shift did not occur in a parallel fashion due to intense reduction in the maximal contractile response. At a concentration of 0.3 nM, olmesartan reduced the maximal contractile response by approximately 90% (Fig. 1.1.1.3). This is a characteristic of non-competitive, insurmountable antagonism. The pD_2' value (an index of reduction in the maximal contractile response) was estimated to be 9.91. It may be recalled that radioligand saturation binding studies showed reduction in angiotensin II binding sites, providing evidence that olmesartan non-competitively interacts with AT_1 receptors.

Though losartan is a prototype competitive, surmountable antagonist (producing a parallel rightward shift of the agonist dose response curve with no diminution of maximal response, Fig. 1.1.1.4A), its active metabolite, EXP-3174, like olmesartan, produced a nonparallel rightward shift and a diminution of maximal response (Fig. 1.1.1.4B), characteristics of a noncompetitive, insurmountable antagonist. CV-11974 (the active metabolite of candesartan cilexetil) also produced a non-parallel rightward shift and a diminution of maximal response (Fig. 1.1.1.4C). Insurmountable, but *not* non-competitive antagonism (diminution of maximal response with a parallel rightward shift) has been demonstrated by other angiotensin II receptor antagonists, telmisartan and irbesartan (refer to this reviewer's reviews of NDA 20,850 and NDA 20,757). This type of behavior could be related to the kinetics of binding to the AII receptors. According to the sponsor, the onset of AII inhibition during treatment and the disappearance of inhibition after removal were slower for olmesartan than for losartan. (The inhibitory action of olmesartan peaked at 90 minutes and was long lasting, persisting for 90 minutes after removal of the drug by repeated washing.) Additionally, the presence of allosteric sites to which an antagonist can bind,



the coupling between receptors and effectors, the desensitization of receptors, etc. may result in insurmountable antagonism.

The mean IC_{50} values (the concentrations causing 50% inhibition of the response to AII) were 0.12, 19, 0.40, 0.14 and 1.4 nM for olmesartan, losartan, EXP-3174, CV-11974 and saralasin, respectively. Accordingly, olmesartan was estimated to be 160, 3.4, 1.2 and 12 times more potent in inhibiting AII-induced contractions of isolated artery than the respective comparator antagonists.

The inhibitory effects of olmesartan on the AII-induced contraction appeared specific as the same concentrations had no antagonistic activity against phenylephrine- or potassium-induced contractions and, thus, olmesartan does not have a non-specific suppressive action against vascular contraction.

Fig. 1.1.1.4.: Effects of losartan (A), EXP-3174 (B), and CV-11974 (C) on concentration-contractile response curves for angiotensin II in guinea pig aortic strips. Data are means ± SEM. The number of experiments is shown in parentheses.

1.1.1.3. Studies in Rats (Report #FR 140-909)

The ability of OM and olmesartan to selectively antagonize an angiotensin II-induced pressor response was evaluated in conscious male Wistar [redacted] rats (300 to 400 g body weight). Animals had indwelling cannula for determination of blood pressure (from femoral artery) and for drug administration (into femoral vein). Experiments were performed 24 hr after surgery, with animals in a conscious, non-restrained and fasted condition. The pressor responses to AII (50 ng/kg, i.v. administered repeatedly at a 15-20 min interval) were observed before dosing (baseline), at 30 minutes and 1 hour after dosing, and at 1-hour intervals thereafter for up to 8 hours after administration. Test compounds were solubilized in DMSO for intravenous administration, and in 50% dimethylformamide for oral administration.

Olmesartan was administered I.V. to rats at doses of 0.01 and 0.03 mg/kg (5 rats/dose). Both dose levels produced a significant inhibition of AII-induced pressor responses with a maximum inhibition of approximately 88% at a dose of 0.01 mg/kg and 91% at a dose of 0.03 mg/kg within 0.5 to 1 hour after administration. There was a gradual decline in the inhibitory effect over time; however, the pressor response did not fully recover within 8 hours after administration. The mean inhibitory effects of doses of 0.01 mg/kg and 0.03 mg/kg were 31% and 55%, respectively, at 8 hours (Fig. 1.1.1.5).

Studies done simultaneously with other AII receptor antagonists indicated that CV-11974 was slightly weaker than olmesartan, while EXP3174 was approximately 10-fold less potent than olmesartan.

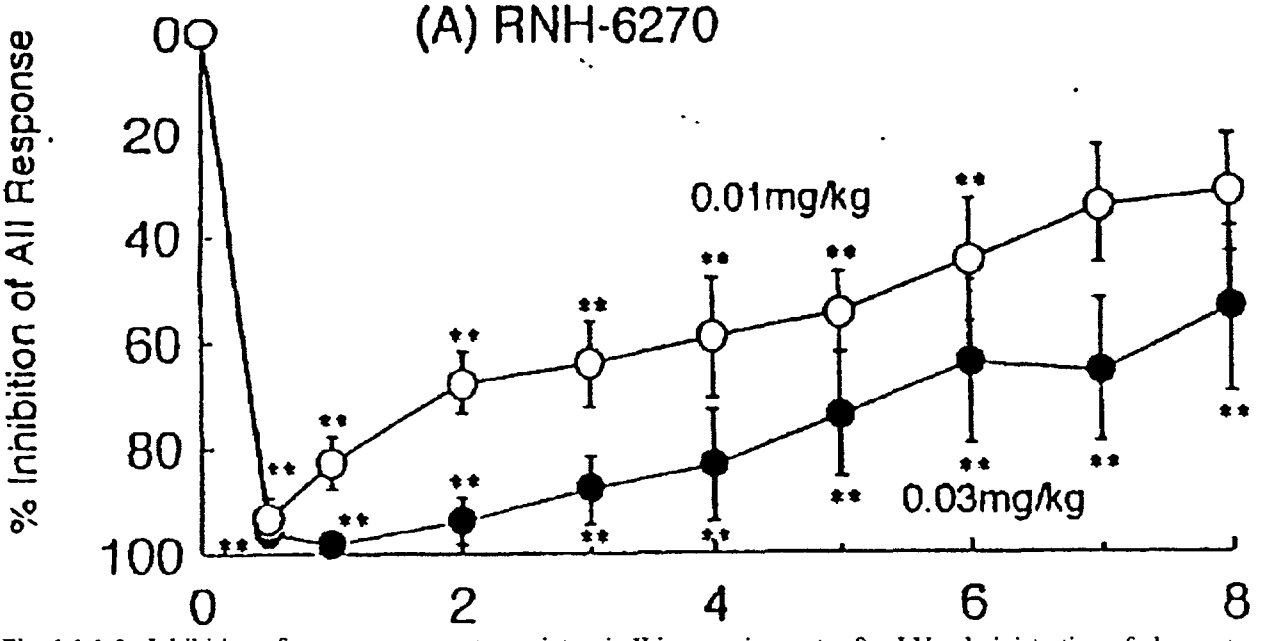


Fig. 1.1.1.5.: Inhibition of pressor response to angiotensin II in conscious rats after I.V. administration of olmesartan (RNH-6270). X-axis shows time in hours. Values are means ± SEM. N = 3-5. * $p < 0.05$, ** $p < 0.01$ compared with time 0 value.

After oral administration of OM (0.03 and 0.1 mg/kg; 5 or 6 rats/dose) to conscious rats, a dose-dependent AII antagonistic effect with a maximal effect of 85% was observed within 2 hours at 0.1 mg/kg and remained at 81% at 8 hours. At 0.03 mg/kg, a mean maximal effect of 66% could be reached only after 8 hr of dosing. As with I.V. administration of olmesartan, the inhibitory effect of OM lasted for more than 8 hours after oral administration (Fig. 1.1.1.6). In this study, candesartan cilexetil had a similar time course and potency; the maximal inhibitory effect of losartan did not develop until 6 hours after administration and losartan was significantly less potent than OM.

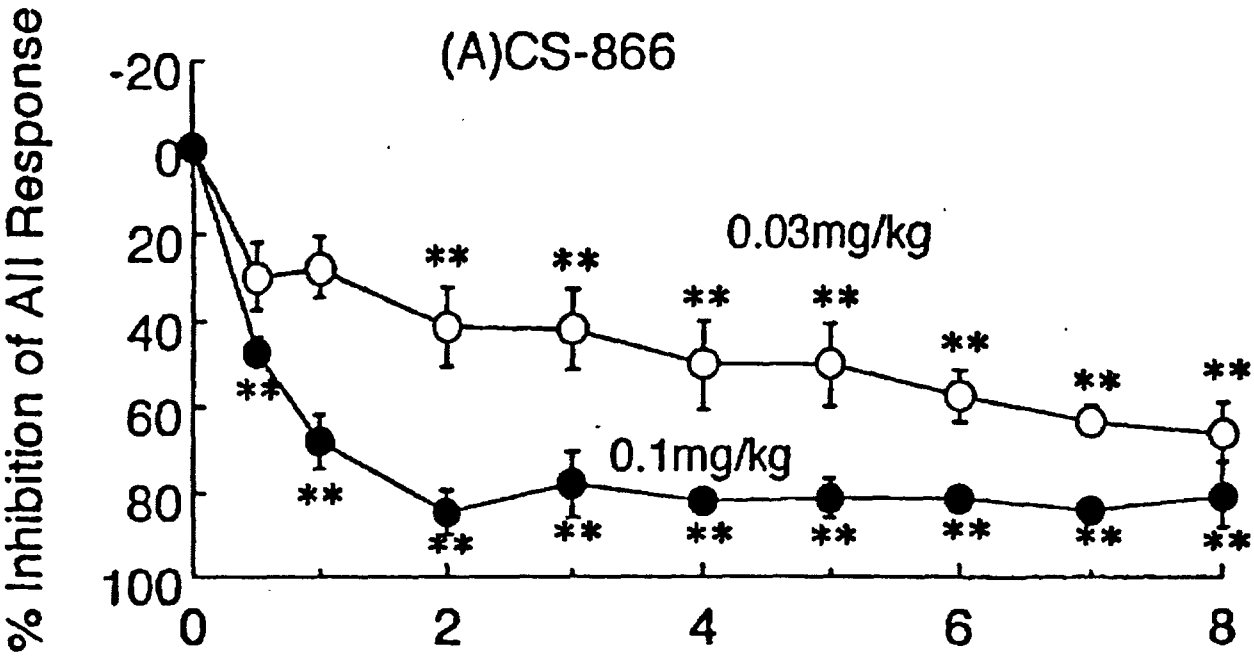


Fig. 1.1.1.6.: Inhibition of pressor response to angiotensin II in conscious rats after oral administration of olmesartan medoxomil (CS-866). X-axis shows time in hours. Values are means ± SEM. N = 3-6. * $p < 0.05$, ** $p < 0.01$ compared with time 0 value.

1.1.1.4. Studies in Dogs (Report #FR 140-909)

The ability of OM to selectively antagonize an angiotensin II-induced pressor response was evaluated in conscious male Beagle dogs (9 to 15 kg body weight). Animals had indwelling cannula for determination of blood pressure (from left femoral artery) and for drug administration (into left femoral vein). Experiments were performed 3 to 4 days after surgery, with animals in a conscious, non-restrained and fasted condition. The pressor responses to AII (200 ng/kg, i.v. administered repeatedly at about 30 min intervals) were observed before dosing (baseline), at 30 minutes and 1 hour after dosing, and at 1-hour intervals thereafter for up to 8 hours and then 24 hr after administration. The effects were compared to those obtained with candesartan and losartan. Test compound was administered orally by capsule containing lactose, low substituted hydroxypropylcellulose (—) and sodium lauryl sulfate , —

As in rats, the peak inhibition occurred at 2 hours after oral administration (65% and 88% at doses of 0.3 mg/kg and 1 mg/kg, respectively). The inhibition at 8 hours was 63% and blood pressure had not fully recovered 24 hours after administration of 1 mg/kg OM (Fig. 1.1.1.7). Candesartan cilexetil, at the same doses as OM, had a slower onset of action (7 hours) and was slightly weaker; losartan at a dose of 30 mg/kg caused only about 50% inhibition of the AII pressor response. The results of this study indicate that OM is a long-lasting and potent AII receptor antagonist in the dog. With oral administration, the inhibitory effect of OM was equivalent to that of candesartan cilexetil and about 100 times greater than that of losartan, while the onset of action was more rapid than with candesartan cilexetil and comparable to losartan.

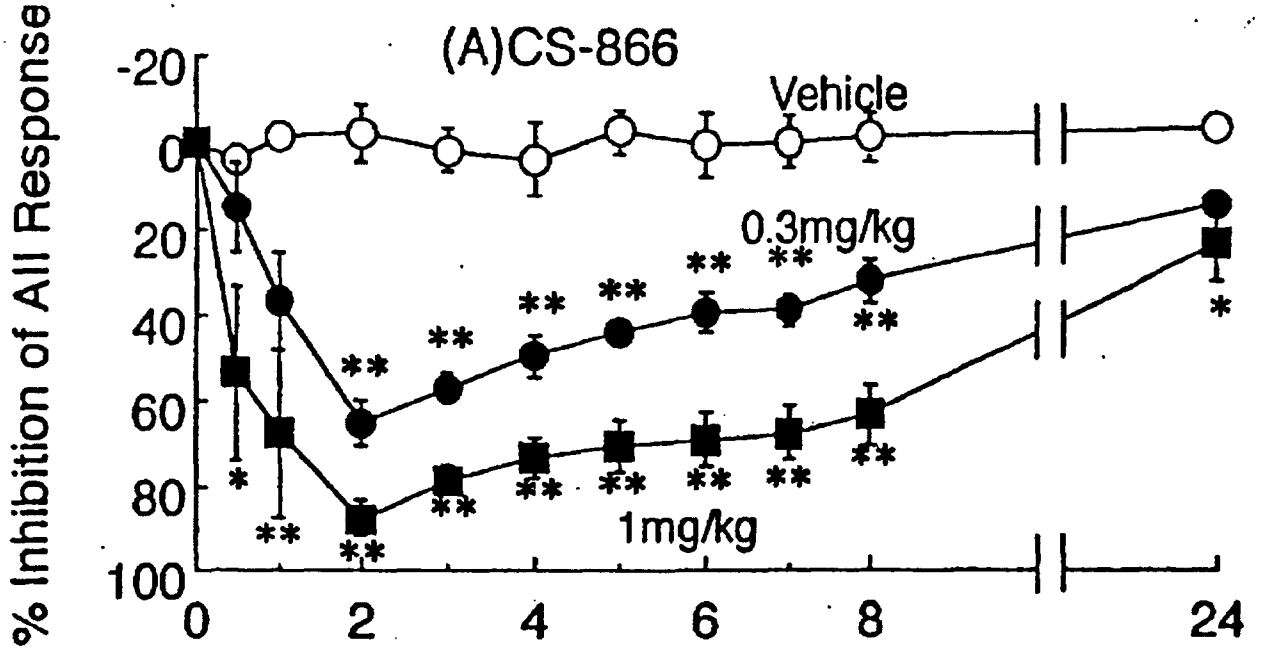


Fig. 1.1.1.7.: Inhibition of pressor response to angiotensin II in conscious dogs after oral administration of olmesartan medoxomil (CS-866). Values are means ± SEM. N = 3-4/dose. * $p < 0.05$, ** $p < 0.01$ compared with vehicle group.

1.1.2. **Antihypertensive Effects**

The antihypertensive effects of OM were determined in normotensive rats and in four models of hypertension: the spontaneously hypertensive rat (SHR), the 2-kidney-1-clip renal hypertensive rat (RHR), the desoxycorticosterone acetate-salt hypertensive rat (DOCA-salt), and the renal hypertensive dog.

1.1.2.1. Normotensive Rats (Report #FR 140-924)

The effect of OM on blood pressure of normotensive animals was determined in conscious male Wistar [redacted] rats (280 to 440 g body weight) and compared to the effects of the two AT_1 receptor antagonists, losartan and candesartan. Blood pressure was determined via an indwelling catheter in the femoral artery. Experiments were performed, 1 to 3 days after surgery, with animals in a conscious, non-restrained and fasted (18 hr) condition. OM was administered orally

at doses of 1, 3, 10, and 30 mg/kg (six or seven animals per dose); losartan was administered orally at doses of 3, 10, 30, and 100 mg/kg (four to nine animals per dose); and candesartan cilexetil (CC) was administered orally at doses of 1, 3, 10, and 30 mg/kg (five to eight animals per dose). Control groups received the respective vehicles orally. Blood pressure and heart rate were monitored continuously for 24 hours after drug administration. OM was dissolved in a mixture of 30% DMSO and 20% ethanol and diluted with water for low doses. CC was dissolved in a mixture of 40-55% DMSO and 20% ethanol, and losartan was dissolved in distilled water.

The hypotensive effects of the three compounds were compared by calculating 24 hour-hypotensive areas (area under the curve of blood pressure versus time) for each dose. All three compounds increased the hypotensive area in a dose-dependent manner (Table 1.1.2.1, Fig. 1.1.2.1). OM and CC were equipotent, while losartan was approximately 10 to 15 times less potent.

TABLE 1.1.2.1
DOSE-RESPONSE RELATIONSHIPS FOR HYPOTENSIVE ACTION OF OM, LOSARTAN, OR CANDESARTAN CILEXETIL IN NORMOTENSIVE RATS (MEAN ± SEM)

	Hypotensive Area (% • Hour)		
Dose (mg/kg)	**OM**	**Losartan**	**CC**
1	87 ± 27		103 ± 22
3	156 ± 59	27 ± 13	205 ± 62
10	185 ± 21	71 ± 13	206 ± 28
30	245 ± 29	134 ± 51	281 ± 42
100		245 ± 62	

OM decreased blood pressure at doses of 1 or more mg/kg; the maximal responses were 15%, 18%, and 20% reductions from pre-dose values at doses of 3, 10, and 30 mg/kg, respectively. Maximal responses were observed 4 to 6 hours after dosing and returned to pretreatment levels within 24 hours after treatment. An increase in heart rate was also observed at these doses, with an increase in the duration of the response observed with increasing dose. Losartan also decreased blood pressure at doses of 10 or more mg/kg with maximal responses of 11%, 12%, and 18% at doses of 10, 30, and 100 mg/kg, respectively; maximal responses were seen 6 to 7 hours after administration. Blood pressure returned to pretreatment levels within 20 hours after dosing. Heart rate was significantly increased after administration of 30 and 100 mg/kg. CC decreased blood pressure at all doses administered. The maximal responses occurred 4 to 7 hours after administration and were 13%, 18%, 20% and 22% lower than control values at 1, 3, 10, and 30 mg/kg, respectively. Heart rate was increased at all dose levels.

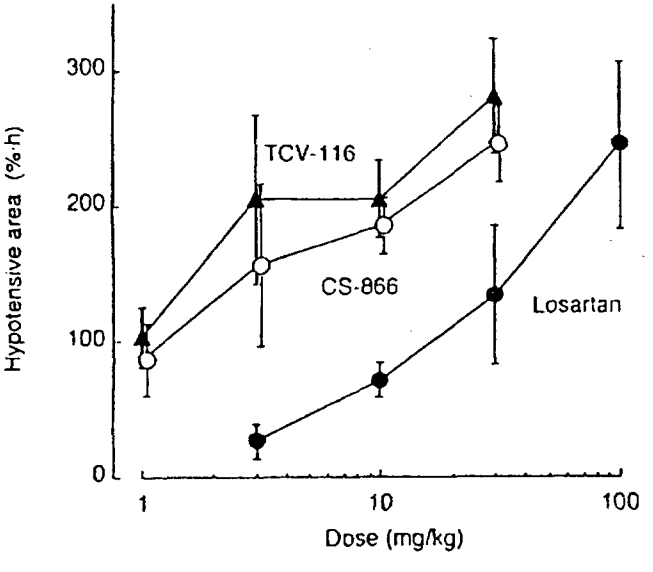


Fig. 1.1.2.1.: Dose-response relationships for antihypertensive actions of OM (CS-866), candesartan (TCV-116) and losartan in normotensive rats. The hypotensive area was calculated as explained in the text. Values are mean ± SEM.

1.1.2.2. Spontaneously Hypertensive Rats

A. Acute Study (Report #FR 140-916, 142-031): The antihypertensive effect of OM was determined in conscious male SHR (21-25 weeks of age and 300 to 470 g body weight) after a single oral administration of 0.03, 0.1, 0.3, or 1 mg/kg (4 to 9 rats/group). The effects of OM were compared to those of losartan (1, 3, 10, and 30 mg/kg; 3 to 7 rats/group) and candesartan cilexetil (0.03, 0.1, 0.3, and 1 mg/kg; 4 to 7 rats/group). Two to four days before the experiment, each rat was anesthetized and a catheter was implanted in a femoral artery for recording arterial b.p. On the day of the experiment, after measuring arterial b.p. and heart rate for 2 hrs, either a test substance or its vehicle was administered orally, followed by continuous measurement of b.p. and heart rate for 24 hr. Animals were fasted for 18 hr before and until 6 hr after test drug or vehicle administration. OM was dissolved in DMSO, losartan in water and CC in a mixture of 30% DMSO and 20% ethanol.

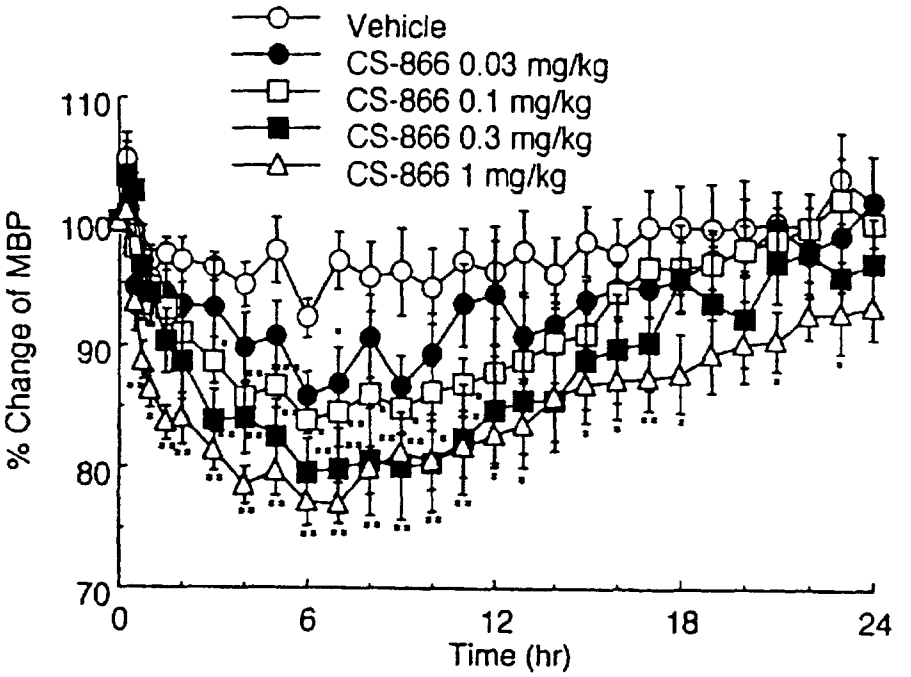


Fig. 1.1.2.2.1.: Changes in mean blood pressure after single oral administration of OM (CS-866) in conscious male SHR. Values are mean ± SEM. * $p < 0.05$, ** $p < 0.01$ compared with vehicle group. Baseline = 100.

All three compounds decreased blood pressure in a dose-dependent manner, with a similar pattern. Blood pressure started to fall gradually, reaching a maximal response at approximately 6 to 9 hours, and then recovered slowly. The maximal responses for the highest dose levels were 23% for OM (Fig. 1.1.2.2.1), 26% for losartan, and 24% for CC. Significant increases in heart rate were observed at some time points after administration of all three compounds. All three compounds increased the 24-hour hypotensive area (% •hour) in a dose-dependent manner. The dose calculated to result in a 300%•hour hypotensive area was about 0.3 mg/kg for OM, about 0.5 mg/kg for candesartan, and about 10 mg/kg for losartan (Fig. 1.1.2.2.2 and Table 1.1.2.2.1). The data thus suggest that OM and CC are approximately equipotent, whereas losartan is nearly 20 to 30 times less potent on a mg/kg basis.

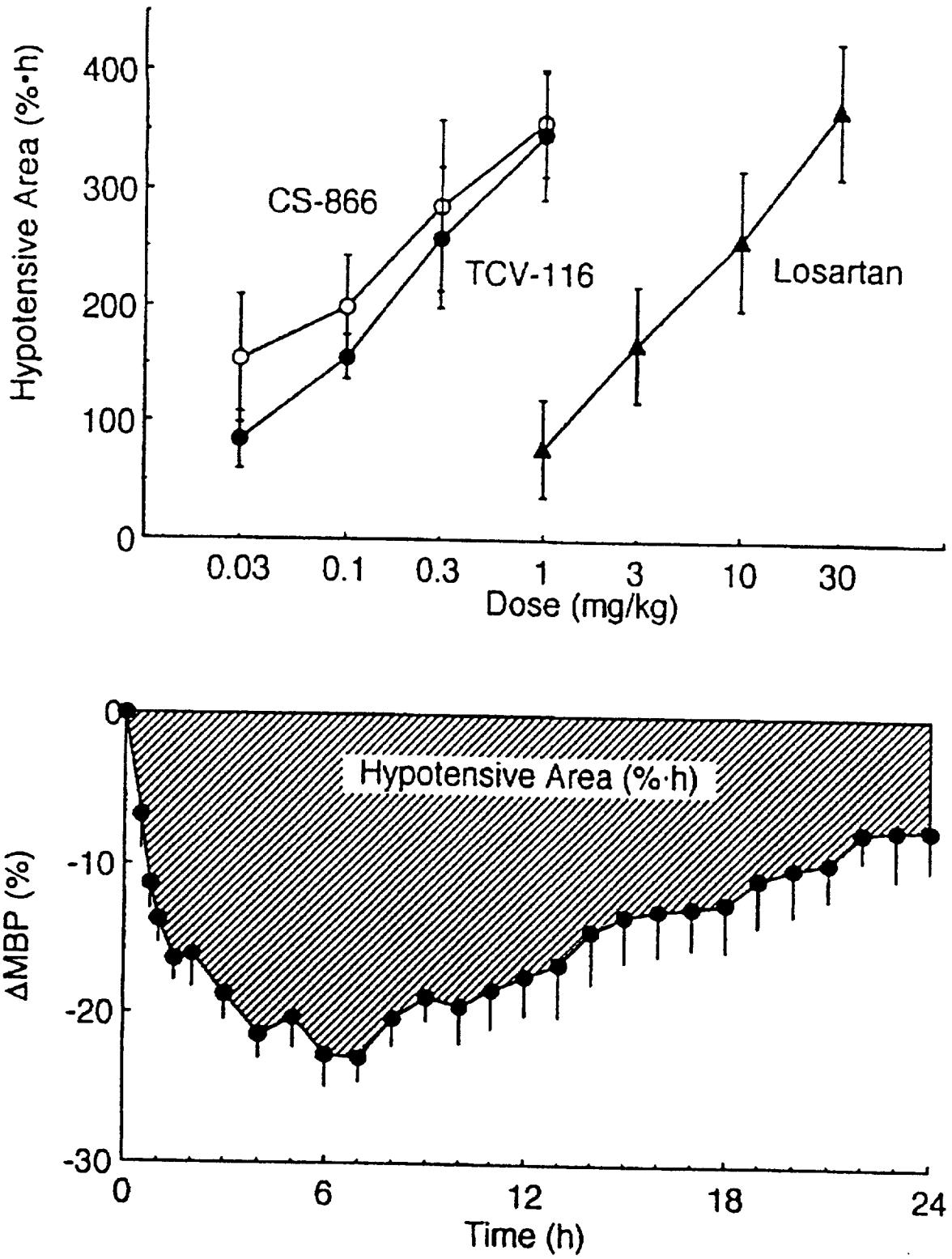


Fig. 1.1.2.2.2.: Dose-response relationships for antihypertensive action of OM (CS-866), candesartan (TCV-116), and losartan in SHR (upper panel). The hypotensive area for OM was calculated as the area above the b.p. curve during the 24 hr observation period (lower panel). Values are mean ± SEM.

TABLE 1.1.2.2.1
DOSE-RESPONSE RELATIONSHIPS FOR ANTIHYPERTENSIVE ACTION OF OM, LOSARTAN, AND CANDESARTAN CILEXETIL IN SHR (MEAN ± SEM)

	Hypotensive Area (%•h)		
Dose (mg/kg)	OM	Losartan	CC
0.03	154 ± 55		121 ± 43
0.1	198 ± 44		156 ± 19
0.3	286 ± 73		259 ± 60
1	357 ± 45	78 ± 42	347 ± 54
3		169 ± 50	
10		254 ± 63	
30		370 ± 57	

B. Chronic Study (Report #FR 140-911): The antihypertensive effect of OM was determined in conscious male SHR (27-29 weeks of age, body weight not given) after oral administration of 0.1, 0.3, and 1 mg/kg/day for 2 weeks (6 rats/group). About a week before the experiment, each rat was anesthetized and a catheter was implanted in its abdominal aorta for recording arterial b.p. OM was administered orally, daily at 11 AM to animals in a non-fasted condition. Blood pressure was measured during and after the cessation of drug treatment. OM was suspended in 0.3% SCMC and administered in a volume of 2 ml/kg. A control group (8 rats) was treated with the vehicle.

OM decreased blood pressure in a dose-dependent manner and the maximal response was unchanged throughout the 2-week treatment period compared with the response on the first day of treatment. The maximal responses were between 10 and 19 mm Hg at 0.1 mg/kg, 20 and 37 mm Hg at 0.3 mg/kg, and 35 and 44 mm Hg at 1 mg/kg (Fig. 1.1.2.2.3). Minimal effects on heart rate (increases) were observed. After cessation of treatment with 1 mg/kg OM, the blood pressure returned to pretreatment levels over 4 days; a rebound effect was not observed. The results of this study demonstrate that tolerance does not develop to the antihypertensive effects of OM.

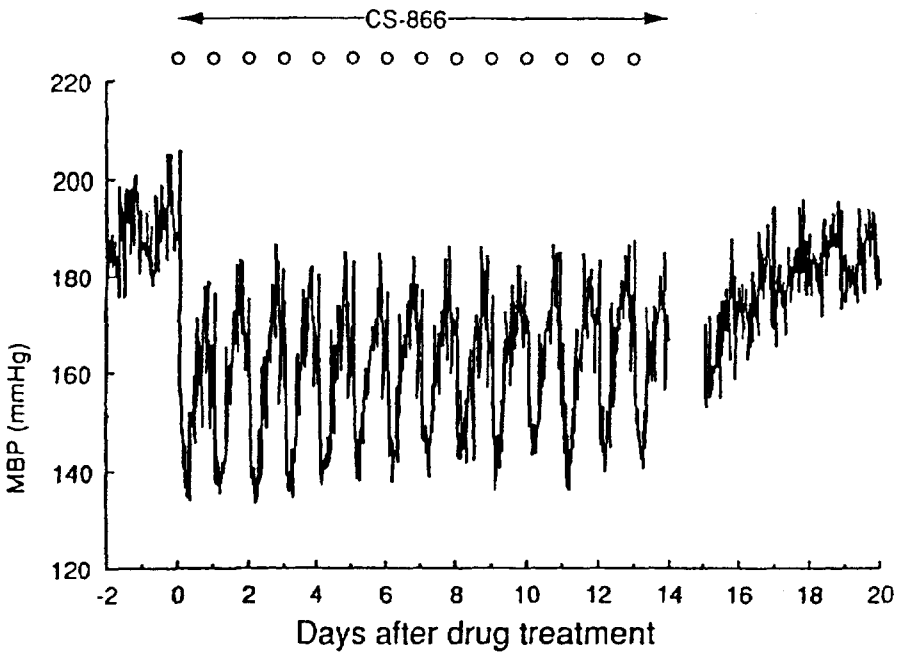


Fig. 1.1.2.2.3.: Changes in mean blood pressure during repeated oral administration of OM (CS-866, 1 mg/kg, p.o.) for 14 days and after the cessation of treatment in conscious male SHR. Values are expressed as mean.

1.1.2.2.2. Renal Hypertensive Rats (RHR) (Report #FR 141-001)

The dose-response effects of OM, administered orally, on b.p. and heart rate were evaluated in the 2-kidney, 1 clip, high-renin model of hypertension (Goldblatt model). Male Wistar [redacted] rats (7 weeks of age, body weight not given) were anesthetized with pentobarbital and a silver clip was applied to the proximal part of the left renal artery adjacent to the branching of the artery. Six weeks after the surgery, indwelling catheters were inserted into a femoral artery and 2 to 4 days later the animals were used for experimentation.

Animals were treated orally with OM at doses of 0, 0.01, 0.03, 0.1 or 0.3 mg/kg (5 or 6 rats/dose). Blood pressure and heart rate were continuously monitored for 24 hours after administration. OM reduced blood pressure in RHR in a dose-dependent manner. The maximal response, at a dose of 0.3 mg/kg, was observed 3 hours after administration; mean blood pressure decreased from 178 mm Hg pretreatment to 119 mm Hg. At doses of 0.1 mg/kg or less the maximum effect was observed 6 hours after administration. The calculated 24-hour hypotensive areas were 71, 248, 412, and 439 %•hour at 0.01, 0.03, 0.1 and 0.3 mg/kg, respectively. An increase in heart rate was observed during the first 2 hours of administration, but no significant differences from vehicle control values were noted thereafter.

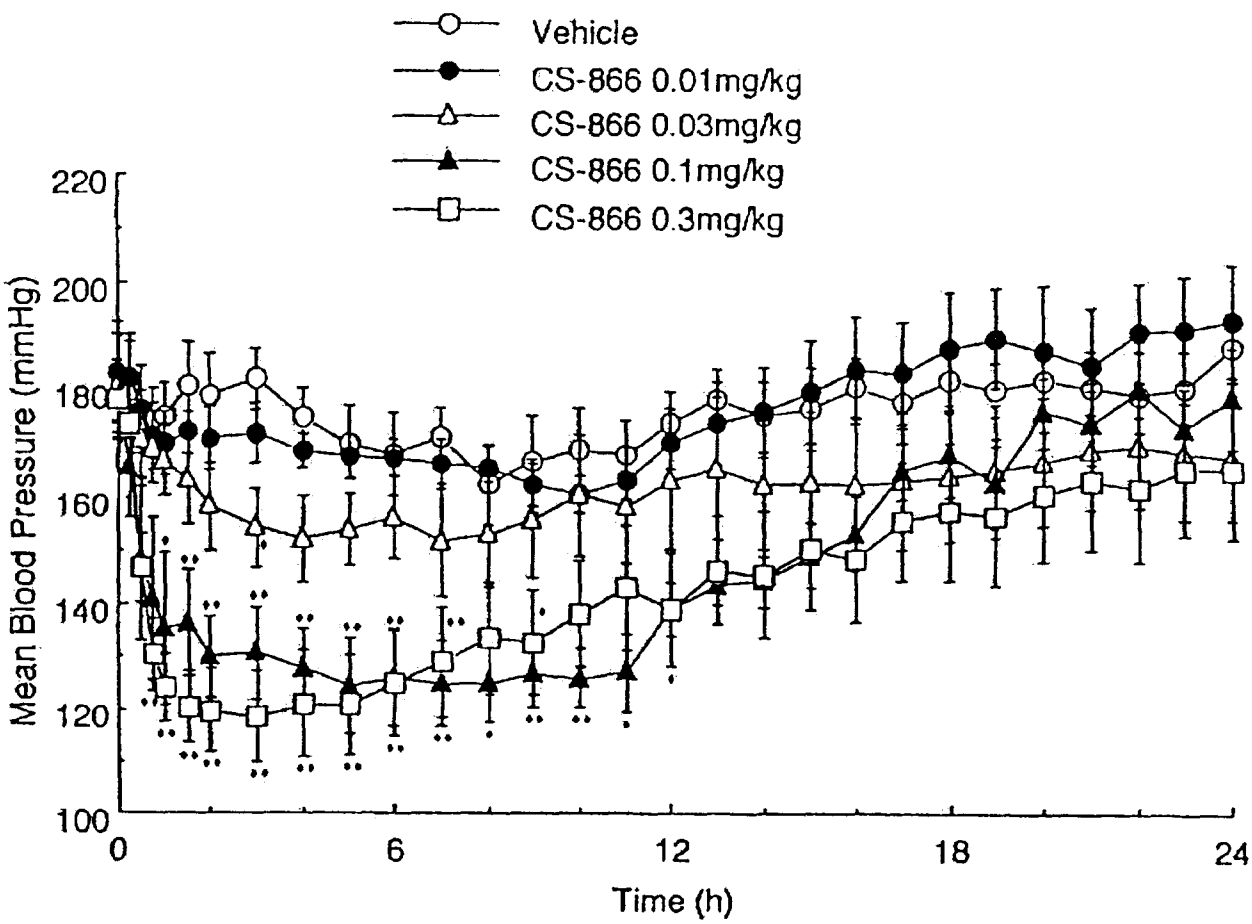


Fig. 1.1.2.2.4.: Changes in mean blood pressure after single oral administration of OM (CS-866) in conscious 2-kidney, 1 clip renal hypertensive rats. Values are mean ± SEM (n=5 to 6).

1.1.2.2.3. DOCA-salt Hypertensive Rats (Report #FR 142-026)

The antihypertensive effect of OM was evaluated in conscious desoxycorticosterone acetate-salt (DOCA-salt) hypertensive rats, a non-renin-dependent or low-renin model of hypertension. Male Wistar — rats (WKY, 7 weeks of age) were made hypertensive by removing the left kidney followed by treatment once a week with DOCA (20 mg/kg, S.C.) in combination with 0.9% saline as drinking water (treatment begun 1 week after nephrectomy). Eight weeks after nephrectomy (two to four days before the study), rats were anesthetized and catheters implanted for recording arterial b.p. from the left femoral artery. OM was administered as single oral doses of 30 mg/kg and blood pressures and heart rates were measured for 24 hours after administration and compared to those of vehicle-treated animals (n=5 or 6 rats). OM was solubilized in DMSO. OM did not lower blood pressure in DOCA-salt hypertensive rats; the calculated 24-hour hypotensive area was 56 %•hour which did not differ from vehicle control. The hypotensive activity of OM in DOCA rats was at least 100 times less than that in SHR. This suggests that the hypotensive action of OM results from blockade of the renin-angiotensin system.

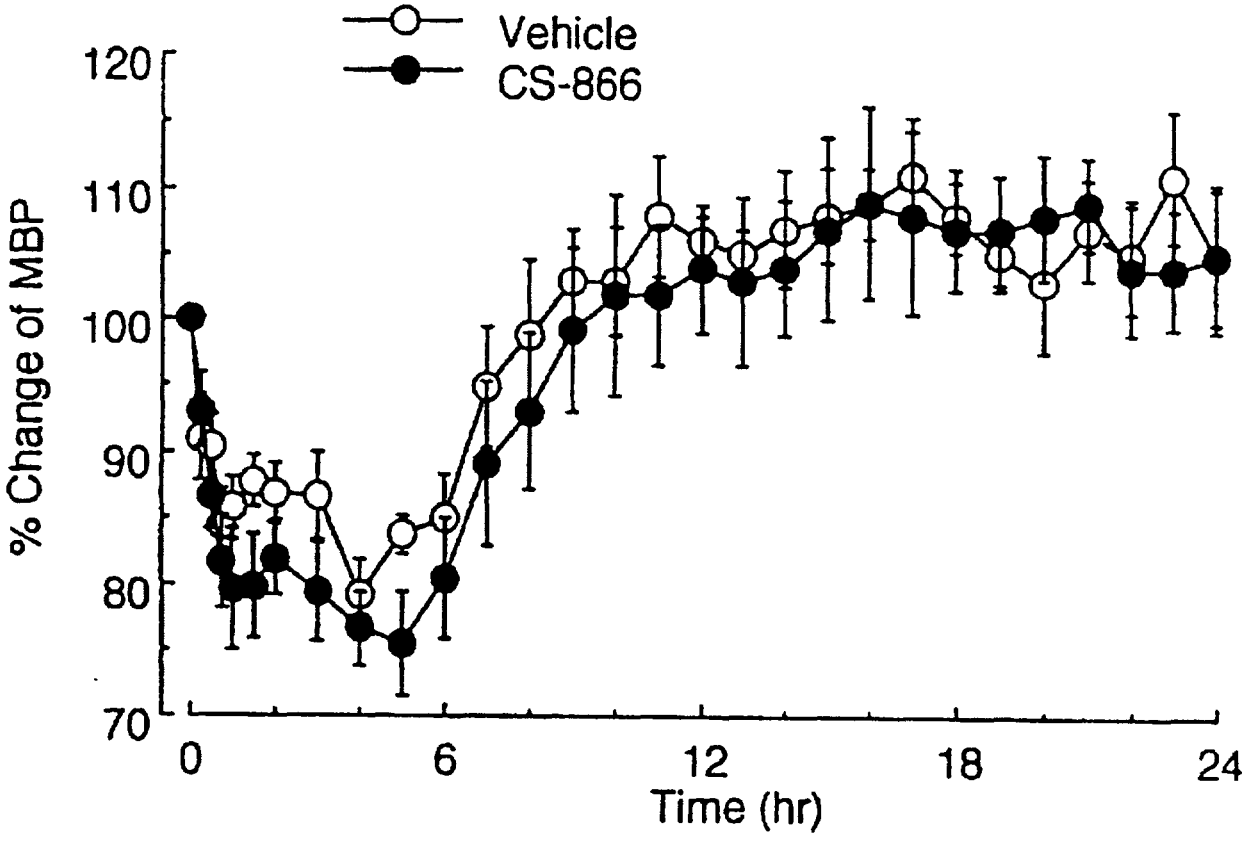


Fig.: 1.1.2.2.5.: Changes in mean blood pressure after single oral administration of OM (CS-866) in conscious DOCA-salt hypertensive rats. Values are mean ± SEM (n=5 to 6).

1.1.2.2.4. Renal Hypertensive Dogs (Report #FLS 93-4787)

The antihypertensive effect of OM was determined in birenal Goldblatt-type hypertensive dogs (2K1C). Male Beagle dogs (7 to 8 months old, 7.9 to 9.6 kg) were made hypertensive by constriction of the left renal artery with a hemostatic clip, resulting in a decrease in blood flow of approximately 20% to 30%. Two to three weeks after the stenotic surgery, an indwelling catheter was inserted into a femoral artery for recording blood pressure. OM (lot #NH001C3 and NH004C1) was mixed with lactose, low substituted hydroxypropylcellulose and sodium lauryl sulfate and administered by capsule once a day at dosages of 0 (vehicle), 1, 3, or 10 mg/kg/day for 14 days (4 to 7 dogs/group). Only animals whose mean b.p. steadily exceeded 115 mm Hg were selected for treatment, which began four weeks after surgery.

The parameters determined included general condition, body weight, water intake, blood pressure, and heart rate. The effects on the renin-angiotensin system were determined by measuring plasma renin and angiotensin I converting enzyme (ACE) activities, plasma aldosterone, angiotensin I and II, and serum sodium, potassium, and creatinine concentrations. Effects on the sympathetic nervous system were determined by measuring plasma epinephrine and norepinephrine. In addition, plasma atrial natriuretic peptide (ANP) was determined. The blood was collected from the radial cutaneous vein of the foreleg. A urinalysis was conducted that included urine volume, specific gravity, sodium, potassium, and creatinine. Parameters were determined predosing, at various time during the dosing period, and during a 7-day withdrawal period.

There were no treatment-related changes in the general condition of animals treated with OM. Body weights decreased gradually for dogs in all groups, but there were no significant differences from the control group weights. Significant decreases from mean control blood pressure were observed in the groups treated with 3 or 10 mg OM/kg/day. The maximum hypotensive response and 24-hour hypotensive area values were calculated for each group (Table 1.1.2.2.3). No rebound effect was observed in any of the treated groups during the withdrawal period.

TABLE 1.1.2.2.3
MAXIMUM HYPOTENSION AND 24-HOUR HYPOTENSIVE AREA IN RENAL HYPERTENSIVE DOGS TREATED ORALLY WITH OM FOR 14 DAYS (MEAN VALUES)

	Maximum Hypotension (mm Hg)			24-Hour Hypotensive Area (%·hour)		
Group	Day 1	Day 7	Day 14	Day 1	Day 7	Day 14
Control	10.4	12.6	8.6	-33.5	-108.3	-11.6
OM						
1 mg/kg	13.8	17.0	14.8	160.2	-4.7	25.4
3 mg/kg	28.5[a]	29.2[a]	21.5[b]	317.7[a]	386.4[a]	277.9
10 mg/kg	22.1	18.9	19.9	142.5	434.0[a]	404.8[b]

[a] : p =0.01 compared to control group
[b] : p=0.05 compared to control group

Compared with the control group, no significant change in heart rate was observed in the drug treated groups, except for a significant decrease at 24 hour after administration on day 14 in the

high dose group. Renin activity was increased above concurrent control on days 1, 7 and 14 in all groups treated with OM with a significant increase noted at 4 and 8 hours after administration on day 14 in the 10 mg/kg/day group. Plasma concentrations of angiotensin I and II were generally increased non dose-dependently at all dose levels. Concentrations of angiotensin I were statistically significantly increased on day 14 in the groups receiving 1 or 3 mg OM/kg/day but not in the group receiving 10 mg OM/kg/day. Angiotensin II concentrations were statistically significantly increased on day 14 in the high dose group. ACE activity tended to be decreased in all treated groups compared to the control group; however, the decrease was statistically significant only in the high dose group. There were no effects on plasma aldosterone concentration. Serum sodium, potassium, and creatinine concentrations were unaffected. There were no apparent treatment-related effects on plasma norepinephrine, epinephrine or ANP in any of the treated groups indicating no influence of the drug on the sympathetic nervous system. The urinary excretion of sodium and creatinine on days 6 to 8 during the dosing period and the excretion of creatinine and creatinine clearance on days 5 to 7 during the withdrawal period were significantly higher in animals receiving 10 mg OM/kg/day.

1.1.3. **Effects on Cardiac Hypertrophy and Nephropathy**

1.1.3.1. Cardiac Hypertrophy in Rats (Report #FR 140-920)

The heart weight of the SHR is heavier than that of normotensive WKY rat. This increase reflects hypertrophy of the heart, possibly due to such factors as increasing activity of the sympathetic nervous system and renin-angiotensin system, some growth factors, and pressure overload due to hypertension. To determine whether OM would affect the hypertrophy observed in hypertensive rats, OM was administered orally to 16-week old male SHR at doses of 0.3 and 1 mg/kg/day (9 rats/group) for 6 weeks. A group of control animals received the vehicle (0.3% CMC, 2 ml/kg). Systolic blood pressure was measured before the start of the treatment and 18 hours after the administration of the last dose (tail-cuff plethysmographic method). At the end of 6 weeks, the rats were anesthetized, exsanguinated to death and hearts were removed and weighed. The heart weights were compared to those of age-matched WKY rats.

Administration of 1 mg/kg of OM significantly decreased systolic blood pressure at the end of the treatment period, while the dose of 0.3 mg/kg had no effect; heart rate was significantly decreased at both dosages. The heart:body weight ratio in the vehicle-treated SHR was much greater than that in WKY (3.754 g/kg vs. 2.727 g/kg, respectively). Chronic treatment with OM reduced the heart:body weight ratio in a dose-dependent manner. The ratio after treatment with 0.3 mg/kg was 3.454 g/kg and after 1 mg/kg was 3.418 g/kg, both statistically significantly lower than in vehicle-treated SHRs (Table 1.1.3.1). These results suggest that OM may ameliorate the cardiac hypertrophy due to hypertension. It is suggested that inhibition of the sympathetic nervous system mediated *via* angiotensin II receptor antagonism may be responsible in preventing hypertensive cardiac hypertrophy.

TABLE 1.1.3.1
MAXIMUM HYPOTENSION AND 24-HOUR HYPOTENSIVE AREA IN SHR TREATED ORALLY WITH OM FOR 14 DAYS (MEAN VALUES)

Parameter	Interval	SHR			WKY
		Vehicle	OM, 0.3 mg/kg/day	OM, 1 mg/kg/day	
Body Weight (g)	0 week	327 ± 6	324 ± 3	326 ± 3	348 ± 6**
	6 week	365 ± 7	372 ± 5	378 ± 4	409± 9**
Heart Rate (beats/min)	0 week	388 ± 6	395 ± 6	394 ± 11	348 ± 10**
	6 week	431 ± 12	395 ± 8*	392 ± 11*	388 ± 9*
Systolic Blood Pressure (mmHg)	0 week	229 ± 3	225 ± 5	225 ± 4	150 ± 5**
	6 week	231 ± 6	213 ± 7	207 ± 5*	132 ± 3**
Heart Wt/Body Wt (g/kg)	6 week	3.75 ± 0.06	3.45 ± 0.08*	3.42 ± 0.09**	2.73 ± 0.03**

Values are mean ± SEM from 9 rats.
* $p < 0.05$, ** $p < 0.01$ compared with vehicle-treated SHR group by Dunnett's test.

1.1.3.2. Nephropathy in Rats (Report #FR 143-023)

The effect of OM and olmesartan on hypertensive nephropathy was studied in male SHR. OM was administered orally to 38-week old SHRs at dosages of 0, 3 or 10 mg/kg/day for 6 weeks (9 or 10 rats/group). The active metabolite, olmesartan was administered orally to 32-week old SHRs at a dose of 0 or 100 mg/l in the drinking water (neither body weight nor water consumption data is given in the report) for 23 weeks (three rats in the vehicle control group and seven treated rats). Blood pressure, urinary protein excretion, urinary N-acetyl-ß-D-glucosaminidase (NAG) activity (an index of tubular injury), blood creatinine, and blood urea nitrogen (BUN) were determined during the study. After 6 or 23 weeks of treatment, animals were sacrificed and the kidneys were examined histologically and the glomerular sclerosis and the tubular injury indices were determined. Treated and untreated SHRs were compared to WKY rats.

High blood pressure and increased urinary protein excretion were observed in SHRs compared to WKY of the same age (32 weeks). OM lowered blood pressure in a dose-dependent manner and decreased urinary protein excretion in SHRs. OM also lowered urinary NAG activity, an index of proximal tubule injury. Plasma creatinine, BUN, and the histologic indices of renal dysfunction, which were elevated in SHR (44 weeks old) compared with age-matched WKY (Table 1.1.3.2.1), were lower, though not significantly lower, than vehicle control.

Treatment of SHR with olmesartan in the drinking water for 23 weeks, significantly decreased plasma creatinine and BUN, with values similar to those observed in WKY. Olmesartan also significantly reduced the glomerular sclerosis index and non-significantly reduced the tubular injury index compared to untreated SHR (Table 1.1.3.2.2). The results of these two experiments indicate that OM may be effective against the renal injury produced by hypertension.

TABLE 1.1.3.2.1
EFFECT OF OM ON SYSTOLIC BLOOD PRESSURE AND OTHER PARAMETERS ASSOCIATED WITH HYPERTENSIVE NEPHROPATHY IN SPONTANEOUSLY HYPERTENSIVE RATS TREATED ORALLY FOR 6 WEEKS (MEAN VALUES)

	WKY	SHR		
		Dose of OM (mg/kg/day)		
Parameter		0 (Vehicle)	3	10
Blood pressure (mm Hg)	137.20[a]	218.30	205.20	168.50[a]
Urinary protein excretion (mg/day/100g bw)	1.34[a]	25.43	8.94[a]	6.01[a]
NAG activity (mU/day/100g bw)	44.44[a]	95.74	50.25[a]	35.35[a]
Plasma creatinine (mg/dL)	0.27	0.31	0.30	0.29
BUN (mg/dL)	15.78[a]	20.34	18.67	17.62
Glomerular sclerosis index	205.90	218.10	212.80	207.90
Tubular injury index	0.25[a]	2.67	2.00	1.70

[a] $p<0.01$ compared to SHR vehicle control group

TABLE 1.1.3.2.2
EFFECT OF OLMESARTAN ON SYSTOLIC BLOOD PRESSURE AND OTHER PARAMETERS ASSOCIATED WITH HYPERTENSIVE NEPHROPATHY IN SPONTANEOUSLY HYPERTENSIVE RATS TREATED ORALLY (IN THE DRINKING WATER) FOR 23 WEEKS (MEAN VALUES)

	WKY	SHR	
		Dose of olmesartan	
Parameter		0 (Vehicle)	100 mg/l
Plasma creatinine (mg/dL)	0.60[a]	0.81	0.59[b]
BUN (mg/dL)	14.83[b]	27.66	15.71[b]
Glomerular sclerosis index	195.40[b]	230.70	203.90[a]
Tubular injury index	0.89[b]	3.67	2.57

[a] $p<0.05$ compared to vehicle control
[b] $p<0.01$ compared to vehicle control

1.2. Safety Pharmacology

1.2.1. *Cardiovascular, Hemodynamic and Autonomic Effects*

1.2.1.1. In Vitro Studies (Report #BR 139-010)

Olmesartan was evaluated for its agonist or antagonist effects on a variety of isolated tissue preparations to elucidate its secondary activities in relation to its desired therapeutic indication.

The following table (Table 1.2.1.1.1) summarizes the results on isolated tissue preparations in which the effect of olmesartan *per se* and its interactions against standard agents were studied.

TABLE 1.2.1.1.1
EFFECTS OF OLMESARTAN ON ISOLATED TISSUE PREPARATIONS FROM GUINEA PIG AND RABBIT

Tissue preparation	Olmesartan, concentration	*per se*	Interactions against standard agents
Guinea pig atria: contractile force & beating rate	1 to 100 µg/ml	No effect	None studied
Guinea pig trachea	1 to 100 µg/ml	No effect	No effect on the dose-response curve of 5-HT, bradykinin, histamine, ACh, barium Cl.
Guinea pig ileum	0.01-1 ng/ml against AII; 1 to 100 µg/ml against other agents	Not studied/reported	No effect on the dose-response curves of 5-HT, bradykinin, histamine, ACh, or barium Cl. Significantly inhibited AII-induced contractions by 27, 39 and 82%, respectively, at 0.01, 0.1 and 1 ng/ml.
Rabbit ileum	1 to 100 µg/ml	No effect on spontaneous movement	Not studied

1.2.1.2. In Vivo Studies (Report #FR 142-055)

The cardiovascular and autonomic effects of olmesartan were determined in three male anesthetized Beagle dogs (10 to 12 kg body weight) given 0.1, 1 and 10 mg/kg (bolus) doses IV at 30 to 60 min intervals. Anesthesia was induced by an IV injection of 40 mg/kg pentobarbital and maintained throughout the experiment by continuous infusion of pentobarbital at a rate of 5 to 8 mg/kg/hr. Respiratory rate, blood pressure, heart rate, carotid blood flow, femoral blood flow, and apex-base lead electrocardiogram (ECG) were monitored for 30 minutes after IV administration of 0.1 or 1 mg olmesartan/kg and for 60 minutes after the administration of 10 mg olmesartan/kg. In addition, the effect of each dose of olmesartan was determined on the blood pressure responses to norepinephrine (1.0 to 1.4 µg/kg), acetylcholine (0.7 to 1.5 µg/kg) and bilateral carotid occlusion (for 1 minute).

Five minutes after a dose of 0.1 mg olmesartan/kg, mean blood pressure was statistically significantly decreased and remained decreased for the duration of the observation period; higher doses decreased mean blood pressure to the same extent (approximately 7%) as the lowest dose. Heart rate showed a tendency to decrease but the change was not statistically significant. There was no effect on carotid blood flow, femoral blood flow, or respiratory rate at any dose. There were no changes in the ECG of any of the dogs. The depressor response to ACh and the pressor response to carotid occlusion showed a tendency to be depressed by administration of olmesartan, but again these effects were not statistically significant. The pressor response to NE was not affected by administration of olmesartan. The results of this study indicate that OM would have no influence on the cardiovascular system other than the hypotensive effect due to its effects on the AT_1 receptor.

1.2.2. ***CNS Effects*** (Report #BR 139-010)

The pharmacological effects of OM on the central nervous system were determined by measuring general behavior (Irwin method), locomotor activity, analgesic activity and muscle relaxation activity in mice, effects on the duration of thiopental anesthesia and electroshock- and

pentylenetetrazol-induced convulsions in mice, and EEG and body temperature in rats. The results of these studies are summarized in Table 1.2.2.1. The oral administration of 300 mg OM/kg was associated with a significant increase in locomotor activity in mice between 30 and 60 minutes after administration; no increase was observed after 60 minutes. There were no other CNS effects observed. The results of these studies suggest that OM induces neither excitatory nor inhibitory effects on the CNS at doses below 300 mg/kg.

TABLE 1.2.2.1
EFFECTS OF OLMESARTAN MEDOXOMIL ON THE CNS

Tests	OM, Dose mg/kg	Animal Species	Results
General behavior	30-1000	mouse	no effect
Locomotor activity	30-300	mouse	significant increase in activity at 300 mg/kg between 30 and 60 minutes of obsvn.
Duration of thiopental anesthesia	30-300	mouse	no effect
Convulsions	30-300	mouse	no effect
Analgesic activity	30-300	mouse	no effect
Muscle relaxation	30-300	mouse	no effect
Spontaneous EEG	100	rat	no effect
Body temperature	30-300	rat	no effect

1.2.3. ***Effects on the Gastrointestinal Tract*** (Report #BR 139-010)

The potential effect of OM on intestinal transit was assessed in mice using the charcoal meal test. Groups of 5 male ddY mice (20 to 22 g bw) received oral doses of vehicle (0.5% CMC at a volume of 0.1 ml/10 g) or 30, 100 or 300 mg/kg OM by gavage. One hour later, they were administered a 10% charcoal suspension containing 0.5% CMC at a volume of 0.1 ml/10 g orally. The mice were sacrificed 30 minutes later. The intestinal propulsive ratio was measured as the ratio of the distance covered by the charcoal meal (from pylorus to end of charcoal band) to the total length of the intestine. OM up to a dose of 300 mg/kg did not modify intestinal propulsive ratio in mice.

To study the effects on defecation, male ddY mice (23 to 25 g bw) were given oral doses of 0, 30, 100 or 300 mg OM/kg (5 mice/dose); immediately thereafter a 10% charcoal suspension (0.1 ml/10 g) was administered. Beginning 30 minutes later, defecation of charcoal-containing feces was monitored and recorded every 30 minutes for 6.5 hours. Administration of OM did not affect defecation time as compared to controls.

The effect of OM on gastric acid secretion was determined in male Sprague-Dawley rats (200 to 210 g bw). Animals were fasted for 24 hr with free access to water. The pylorus was ligated under anesthesia. OM was administered intraduodenally at a dose of 0, 30, 100, or 300 mg/kg (5 rats/dose) immediately after the ligation and the abdomen was closed. Animals were sacrificed 4 hours later and the stomach removed and gastric juice collected. OM-treated rats showed reduced gastric secretion and acidity (tendency to inhibit) relative to control animals; however, the differences were not statistically significant.

1.2.4. ***Effects on Renal Function*** (Report #BR 139-010)

The effects of OM on urinary volume and excretion of electrolytes were determined in male Sprague-Dawley rats (210 to 230 g bw) treated orally with 10, 30, 100 or 300 mg/kg (9 rats/dose). Animals were housed in metabolic cages and urine was collected for periods of 0 to 6 and 6 to 24 hours after drug administration. Urinary volume and osmolarity and the urinary electrolytes (sodium, potassium, and chloride) were determined. OM tended to decrease urine volume and increase urine osmolarity significantly at doses 30 or more mg/kg. Urinary sodium excretion increased significantly during 0-6 hr at 300 mg OM/kg. OM had no effect on potassium and chloride excretion (Table 1.2.4.1).

TABLE 1.2.4.1
EFFECTS OF OLMESARTAN MEDOXOMIL ON URINE VOLUME, ELECTROLYTES AND OSMOTIC PRESSURE IN RATS

Drug	Dose (mg/kg)	Time (h)	Volume (ml)	Total Electrolyte (μEq)			Osmotic pr. (mOsm)
				Na^+	K^+	Cl^-	
Control	-	0-6	9.2 ± 1.3	1085 ± 107	776 ± 97	1484 ± 195	819 ± 83
		6-24	10.7 ± 1.0	1946 ± 158	1661 ± 119	1684 ± 107	1704 ± 151
		0-24	19.9 ± 2.3	3030 ± 262	2437 ± 145	3167 ± 300	-
OM	10	0-6	8.3 ± 0.6	937 ± 25	787 ± 100	1289 ± 54	810 ± 33
		6-24	9.9 ± 0.2	2045 ± 112	1777 ± 141	1850 ± 118 .	1898 ± 115
		0-24	18.2 ± 0.5	2982 ± 108	2563 ± 41	3140 ± 74	-
	30	0-6	6.7 ± 0.7	877 ± 99	785 ± 47	1226 ± 51	999 ± 126
		6-24	9.1 ± 0.6	1947 ± 199	1892 ± 82	1687 ± 208	2125 ± 90*
		0-24	15.8 ± 0.7*	2824 ± 199	2677 ± 105	2913 ± 201	-
	100	0-6	6.7 ± 0.3	1021 ± 53	573 ± 27	1281 ± 43	896 ± 10
		6-24	8.6 ± 0.4*	1681 ± 29	1906 ± 135	1467 ± 36	2202 ± 93*
		0-24	15.3 ± 0.5*	2701 ± 65	2478 ± 109	2748 ± 58	-
	300	0-6	8.6 ± 0.3	1374 ± 87*	776 ± *20*	1134 ± 135	919 ± 46
		6-24	8.6 ± 0.3*	1782 ± 111	1769 ± 82	1350 ± 92	2111 ± 70*
		0-24	17.2 ± 0.6	3156 ± 155	2544 ± 96	3083 ± 128	-

Each value represents mean ± SE. from three experiments.

1.2.5. ***Effects on Coagulation*** (Report #BR 139-010)

Olmesartan medoxomil (0, 30, 100 or 300 mg/kg, 5 mice/dose) did not significantly affect bleeding times in ddY male mice (22 to 25 g bw) 1 hour after oral administration.

Prothrombin time (PT) and activated partial thromboplastin time (APTT) in male Sprague-Dawley rats (210 to 240 g bw) were measured 1 hour after administration of OM at oral doses of 0, 30, 100 or 300 mg/kg (5 rats/dose). Both PT and APTT values for OM-treated rats were comparable to control values.

Olmesartan at concentrations of 0, 1, 10 and 100 μg/ml (5 samples/concentration) did not induce hemolysis in male Japanese White rabbit blood.