INTERNATIONAL CONGRESS AND SYMPOSIUM SERIES

TREATMENT OF HYPERTENSION WITH URAPIDIL

PRECLINICAL AND CLINICAL UPDATE

EDITED BY

A. AMERY

ROYAL
SOCIETY OF MEDICINE
SERVICES

LONDON NEW YORK

International Congress and Symposium Series
Number 101

Treatment of hypertension with urapidil:
preclinical and clinical update

Edited by
A. Amery

Royal Society of Medicine Services
London New York
1986

Royal Society of Medicine Services Limited
1 Wimpole Street London W1M 8AE
7 East 60th Street New York NY 10022

These proceedings are published by Royal Society of Medicine Services Ltd with financial support from the sponsor. The contributors are responsible for the scientific content and for the views expressed, which are not necessarily those of the Royal Society of Medicine or of Royal Society of Medicine Services Ltd. Distribution has been in accordance with the wishes of the sponsor but a copy is available to any Fellow of the Society at a privileged price.

British Library Cataloguing in Publication Data
Treatment of hypertension with urapidil: preclinical and clinical update, proceedings of a symposium sponsored by Byk Gulden Pharmaceuticals, held in Gottlieben, Switzerland, 3–4 June 1985.—
(International congress and symposium series, ISSN 0142–2367; no. 101)
1. Hypertension—Chemotherapy 2. Urapidil—Therapeutic use
I. Amery, A. II. Royal Society of Medicine
III. Series
616.1'32061 RC685.H8

ISBN 0-905958-29-2

Editorial and production services by Fisher Duncan Ltd, 10 Barley Mow Passage, London W4 4PH
Phototypeset by Dobbie Typesetting Service, Plymouth, Devon
Printed in Great Britain at the University Press, Oxford

Contributors

Editor

A. Amery
Inwendige Geneeskunde – Cardiologie, U.Z. Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium

C. Amodeo
Department of Internal Medicine, Section on Hypertensive Diseases, Ochsner Clinic, New Orleans, 1514, Jefferson Highway, Louisiana 70121, USA

M. Ampelas
Clinique des Maladies de l'Appareil Digestif, Hôpital St Eloi, Rue Bertin Sans, F-34059 Montpellier, France

K. Arakawa
Fukuoka University, Japan

L. M. Atkinson
Cardiac Department, King's College Hospital, Denmark Hill, London SE5 9RS, UK

S. Bacher
Abteilung für Klinische Pharmakologie der 1. Medizinischen Universitätsklinik Wien, Lazarettgasse 14, A-1090 Vienna, Austria

P. Bauret
Clinique des Maladies de l'Appareil Digestif, Hôpital St Eloi, Rue Bertin Sans, F-34059 Montpellier, France

H. Behr
Byk Gulden Research Centre, P.O. Box 6500, D-7750 Konstanz, FRG

P. Bories
Clinique des Maladies de l'Appareil Digestif, Hôpital St Eloi, Rue Bertin Sans, F-34059 Montpellier, France

W. Burkart
Department of Gynaecology, Universitäts-Frauenklinik, Albert-Schweitzer-Strasse 33, D-4000 Münster, FRG

M. Chiariello
I Clinica Medica, II Facoltà di Medicina e Chirurgia, Università degli Studi di Napoli, Via S. Pansini 5, I-80131 Naples, Italy

S. K. Choraria
George Eliot Hospital, College Street, Nuneaton, Warwickshire CV10 7DJ, UK

M. Condorelli
I Clinica Medica, II Facoltà di Medicina e Chirurgia, Università degli Studi di Napolo, Via S. Pansini 5, I-80131 Naples, Italy

A. Cuocolo

I Clinica Medica, II Facoltà di Medicina e Chirurgia, Università degli Studi di Napoli, Via S. Pansini 5, I-80131 Naples, Italy

W. R. Dame

Department of Gynaecology, Universitäts-Frauenklinik, Albert-Schweitzer-Strasse 33, D-4000 Münster, FRG

N. de Luca

I Clinica Medica, II Facoltà di Medicina e Chirurgia, Università degli Studi di Napoli, Via S. Pansini 5, I-80131 Naples, Italy

J. Downer

Anaesthetics Unit and Anaesthetics Department, The London Hospital, Whitechapel, London E1 1BB, UK

A. Ebihara

Department of Clinical Pharmacology, Oita Medical School, 1506, I-Chome, Idaigaoka, Hazama-Cho, Oita-Gun, Oita-Ken, 879-56 Japan

E. D. Frohlich

Department of Internal Medicine, Section on Hypertensive Diseases, Ochsner Clinic, 1514 Jefferson Highway, New Orleans, Louisiana 70121, USA

A. Fujimura

Department of Clinical Pharmacology, Oita Medical School, 1506, I-Chome, Idaigaoka, Hazama-Cho, Oita-Gun, Oita-Ken, 879-56 Japan

E. Godehardt

Institut für Medizinische Dokumentation und Statistik der Universität zu Köln, Joseph-Stelzmann-Strasse 9, D-5000 Cologne 41, FRG

R. Gradnik

Centro di Fisiologia Clinica e Ipertensione, Università di Milano, Via F. Sforza 35, 20122 Milan, Italy

E. Guffanti

Servizio Cardiologia, INRCA, Via Montereggio 25, I-22064 Casatenovo (Como), Italy

K.-D. Haehn

Medizinische Hochschule, Department of General Medicine, Karl-Wichert-Allee 9, D-3000 Hannover 61 (Kleefeld), FRG

R. Haerlin

Byk Gulden Research Centre, P.O. Box 6500, D-7750 Constance, FRG

W. Heitz

Institut für Medizinische Dokumentation und Statistik der Universität zu Köln, Joseph-Stelzmann-Strasse 9, D-5000 Cologne 41, FRG

L. Hessel

Hôpital Jean Rebeyrol, Avenue du Buisson, F-87031 Limoges Cedex, France

N. Hino

Department of Clinical Pharmacology, Oita Medical School, 1506, I-Chome, Idaigaoka, Hazama-Cho, Oita-Gun, Oita-Ken, 879-56 Japan

Y. Inagaki

Chiba University, Japan

M. Ishii

University of Tokyo, Tokyo, Japan

D. E. Jewitt

Cardiac Department, King's College Hospital, Denmark Hill, London SE5 9RS, UK

Y. Kaneko
Second Department of Internal Medicine, Yokohama City University Hospital, 3-46 Urafune-Cho, Minami-Ku, Yokohama, 232 Japan

W. Kaufmann
Medizinische Klinik, Ostmerheimerstrasse 200, D-5000 Cologne 91, FRG

T. Kokubu
Ehime University, Ehime, Japan

K. Kondo
Department of Clinical Pharmacology, Jichi Medical School, Jichi, Japan

I. Kobrin
Department of Internal Medicine, Section on Hypertensive Diseases, Ochsner Clinic, New Orleans, 1514 Jefferson Highway, Louisiana 70121, USA

J. Lalor
Anaesthetics Unit and Anaesthetics Department, The London Hospital, Whitechapel, London E1 1BB, UK

R. Lang
Medizinische Klinik II, Ostmerheimerstrasse 200, D-5000 Cologne 91, FRG

G. Leonetti
Centro di Fisiologia Clinica e Ipertensione, Università di Milano, Via F. Sforza 35, 20122 Milan, Italy

H. Liebau
Allgemeines Krankenhaus Heidberg, Department of Nephrology, Tangstedter Landstrasse 400, D-2000 Hamburg 62, FRG

A. E. Lison
Department of Internal Medicine, Universitäts-Frauenklinik, Albert-Schweitzer-Strasse 33, D-4000 Münster, FRG

D. Magometschnigg
Abteilung für Klinische Pharmakologie der 1. Medizinischen Universitätsklinik Wien, Lazarettgasse 14, A-1090 Vienna, Austria

E. Major
Department of Anaesthetics, Morriston Hospital, Heo Maes Eglwys, Cwmrhydyceirw, Swansea SA6 6NL, UK

C. Mazzola
Servizio Cardiologia, INRCA, Via Montereggio 25, I-22064 Casatenovo (Como), Italy

A. F. Mele
I Clinica Medica, II Facoltà di Medicina e Chirurgia, Università degli Studi di Napoli, Via S. Pansini 5, I-80131 Naples, Italy

F. Messerli
Department of Internal Medicine, Section on Hypertensive Diseases, Ochsner Clinic, 1514 Jefferson Highway, New Orleans, Louisiana 70121, USA

J. M. Metcalfe
Cardiac Department, King's College Hospital, Denmark Hill, London SE5 9RS, UK

K. A. Meurer
Institut für Medizinische Dokumentation und Statistik der Universität zu Koln, Joseph-Stelzmann-Strasse 9, D-5000 Cologne 41, FRG

H. Michel
Clinique des Maladies de l'Appareil Digestif, Hôpital St Eloi, Rue Bertin Sans, F-34059 Montpellier, France

J.-P. Michel
Hôpital Jean Rebeyrol, Avenue du Buisson, F-87031 Limoges Cedex, France

C. Mion
Department of Nephrology, University Hospital, F-34059 Montpellier, France

Y. Mizuno
Fujita-Gakuen University, Japan

M. M. Monaghan
Cardiac Department, King's College Hospital, Denmark Hill, London SE5 9RS, UK

R. J. M. Morgan
Anaesthetics Unit and Anaesthetics Department, The London Hospital, Whitechapel, London E1 1BB, UK

G. Mourad
Department of Nephrology, University Hospital, F-34059 Montpellier, France

K. Ohashi
Department of Clinical Pharmacology, Jichi Medical School, Jichi, Japan

T. Omae
National Cardiovascular Centre, Japan

H. Pozenel
Herz- und Kreislaufzentrum der Bauern, Parkstrasse 12, A-4540 Bad Hall, Austria

H. W. Radtke
Byk Gulden Research Centre, P.O. Box 6500, D-7750 Konstanz, FRG

B. Ricciardelli
I Clinica Medica, II Facoltà di Medicina e Chirurgia, Università degli Studi di Napoli, Via S. Pansini 5, I-80131 Naples, Italy

C. Rosendorff
Departments of Physiology and Medicine, University of the Witwatersrand Medical School, 7 York Road, Johannesburg 2193, South Africa

G. Rosiello
I Clinica Medica, II Facoltà di Medicina e Chirurgia, Università degli Studi di Napoli, Via S. Pansini 5, I-80131 Naples, Italy

L. Rupoli
Centro di Fisiologia Clinica e Ipertensione, Università di Milano, Milan, Italy

A. Slingeneyer
Department of Nephrology, University Hospital, F-34059 Montpellier, France

P. Smyth
Cardiac Department, King's College Hospital, Denmark Hill, London SE5 9RS, UK

V. W. Steinijans
Byk Gulden Research Centre, P.O. Box 6500, D-7750 Konstanz, FRG

T. Takeda
Osaka City University, Osaka, Japan

K. Taniguchi
Tokyo Medical and Dental University, Tokyo, Japan

L. Terzoli
Centro di Fisiologia Clinica e Ipertensione, Università di Milano, Milan, Italy

B. Trimarco
I Clinica Medica, II Facoltà di Medicina e Chirurgia, Università degli Studi di Napoli, Via S. Pansini 5, I-80131 Naples, Italy

H. van Aken
Department of Anaesthesiology, Universitäts-Frauenklinik, Albert-Schweitzer-Strasse 33, D-4400 Münster, FRG

P. A. van Zwieten
Laboratorium voor Farmacie der Universiteit van Amsterdam, Plantage Muidergracht 24, NL-1018 TV Amsterdam, Netherlands

A. Vaccarella
Servizio Cardiologia, INRCA, Via Montereggio 25, I-22064 Casatenovo (Como), Italy

A. Veniero
I Clinica Medica, II Facoltà di Medicina e Chirurgia, Università degli Studi di Napoli, Via S. Pansini 5, I-80131, Naples, Italy

H. O. Ventura
Department of Internal Medicine, Section on Hypertensive Diseases, Ochsner Clinic, New Orleans, 1514 Jefferson Highway, Louisiana 70121, USA

M. Volpe
I Clinica Medica, II Facoltà di Medicina e Chirurgia, Università degli Studi di Napoli, Via S. Pansini 5, I-80131 Naples, Italy

G. Wambach
Medizinische Klinik, Ostmerheimerstrasse 200, D-5000 Cologne 91, FRG

W. Wurst
Byk Gulden Research Centre, P.O. Box 6500, D-7750 Konstanz, FRG

D. J. M. Williams
Department of Anaesthetics, The Intensive Care Unit, Broomfield Hospital, Chelmsford, Essex.

E. R. Williams
George Eliot Hospital, College Street, Nuneaton, Warwickshire CV10 7DJ, UK

H. Yasuda
Hokkaido University, Hokkaido, Japan

K. Yoshinaga
Tohoku University, Tohoku, Japan

A. Zanchetti
Centro di Fisiologia Clinica e Ipertensione, Università di Milano, via F. Sforza 35, 20122, Milan, Italy

K. Zech
Byk Gulden Research Centre, P.O. Box 6500, D-7750 Konstanz, FRG

Contents

Chronic treatment of hypertensive patients

Pharmacological and haemodynamic profile of urapidil

P. A. VAN ZWIETEN

Division of Pharmacotherapy, University of Amsterdam, Amsterdam, Netherlands

Summary

A survey is given of the pharmacological profile of urapidil, underlying its antihypertensive activity. Urapidil mainly causes arteriolar vasodilatation, although a venous dilator effect may occur as well. As a rule, vasodilatation and the lowering of blood pressure are not accompanied by reflex tachycardia. The hypotensive effect of urapidil is mainly attributed to the following mechanisms.

(1) Blockade of vascular postsynaptic α_1-adrenoceptors;

(2) A central hypotensive effect of an unknown mechanism, obviously different from that of clonidine and similarly acting α_2-adrenoceptor agonists. Central α_2- and α_1- adrenoceptors are not involved in the effect of urapidil and neither are the following receptors: histamine (H_1 and H_2); dopamine (DA_2); muscarine (M_1); serotonin (5-HT_2); opioid.

Blunting of the baroreceptor reflex by urapidil occurs possibly as a result of the blockade of central α_1- and peripheral cardiac β-adrenoceptors. In contrast to earlier views, the involvement of urapidil with peripheral presynaptic α_2-adrenoceptors appears negligible.

The molecule of urapidil does not contain any stereoisomers. Accordingly, all of the mechanisms discussed above are incorporated in one and the same molecule.

Introduction

The uracil derivative urapidil (Fig. 1) was recognized as an antihypertensive drug with a combined mode of action nearly a decade ago. The drug has been recently introduced into the treatment of hypertensive disease and its position in comparison with other antihypertensives remains to be established. Older pharmacological data suggested that urapidil owes its hypotensive activity mainly to peripheral α-adrenoceptor

Treatment of hypertension with urapidil: preclinical and clinical update, edited by A. Amery, 1986: Royal Society of Medicine Services International Congress and Symposium Series No. 101, published by Royal Society of Medicine Services Limited.

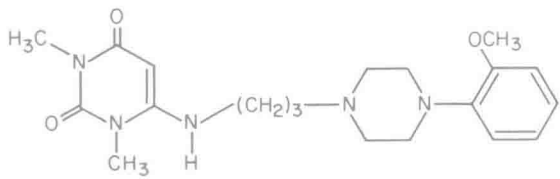

Figure 1. Chemical structure of urapidil = 6-{3-[4-(0-methoxyphenyl) piperazinyl]-propylamino}-1,3-dimethyluracil.

blockade (1). In addition, it has been claimed that urapidil induces a presynaptic inhibition of noradrenaline release from the sympathetic nerve endings, as well as a central hypotensive effect somewhat comparable to that of clonidine and related α_2-adrenoceptor agonists. This rather unusual combination of pharmacological mechanisms has led to the claim that urapidil includes the effects of both prazosin and clonidine in one and the same molecule. As is discussed in this paper, this view has proved erroneous. The combination of hypotensive mechanisms together with the fairly positive clinical judgement of the drug's value in antihypertensive treatment, however, has led to a renaissance of interest in urapidil's pharmacological profile. Accordingly, many new data have significantly changed the general opinion on urapidil's mode(s) of action. The older literature on this drug has been reviewed extensively by Schoetensack and co-workers (1). This paper deals in particular with the recently acquired experimental data on urapidil and their interpretation.

Haemodynamic profile

All animal studies so far performed suggest that urapidil mainly causes arteriolar dilatation, a reduction in total peripheral resistance (TPR), and, hence, a fall in blood pressure, in particular in hypertensive animals and patients (1–11). The drug induced such haemodynamic changes both in acute experiments (2–4,7) and upon prolonged treatment (6,8,10). The hypotensive effect was observed in rats, cats and dogs, both in conscious animals (6,8,10,11) and during anaesthesia (2,3,7,11). The hypotensive effect was as to be expected — more pronounced in spontaneously hypertensive rats (SHR) than in WKY-control animals (9,10). Acute treatment of SHR with urapidil induced a reduction of TPR through all circulations, including those in the skin, skeletal muscle, brain, heart, kidneys and splanchnic organs (9,10) and caused modest reflex tachycardia in conscious SHR (10,13) but in all other animal models no increase in heart rate was induced by urapidil, in spite of its hypotensive effect (1–12). In normotensive human volunteers the intravenous administration of urapidil caused a reduction in TPR and blood pressure (1), whereas prolonged oral treatment of hypertensive patients with urapidil is not usually accompanied by changes in heart rate; in several studies even *brady*cardia has been reported (1). Apart from a general reduction in TPR, urapidil caused obvious renal arterial dilation in conscious Goldblatt-hypertensive rats and dogs (14,15).

In contrast to dihydralazine, which upon prolonged treatment rapidly loses its hypotensive potency as a result of reflex activation of the sympathetic nervous system and the renin–angiotensin–aldosterone system, no tachyphylaxis was observed for urapidil, either in conscious dogs (6) or in human hypertensives (1). Prolonged treatment of conscious SHR with urapidil did not prevent cardiac hypertrophy (8,10,13).

It is generally agreed that the hypotensive/antihypertensive effect of urapidil is predominantly (or solely) caused by a reduction in TPR, reflecting arteriolar dilatation. Dilatation of the *venous* vascular bed by urapidil might be anticipated because of the drug's α-adrenoceptor blocking activity, but the importance of such an effect has not been systematically studied. A certain degree of preload reduction, caused by intravenously administered urapidil in normotensive human volunteers would suggest that venous dilatation indeed occurs (16). This matter remains to be studied in more detail.

Mode of action

Radioligand binding studies — affinity of urapidil for receptors

Radioligand binding studies have been carried out to establish the affinity of urapidil for a number of relevant receptors. So far all studies have been performed with homogenates of rat brain (2,11). The results of the two main receptor binding studies (2,11) show satisfactory mutual agreement and may be summarized as follows.

Urapidil has a stronger affinity for α_1- than for α_2-adrenoceptors, but is rather less selective for the α_1-subtype than is prazosin, the prototype of selective α_1-adrenoceptor antagonists. It should be realized, however, that urapidil's absolute affinity for α_2-adrenoceptors is even lower than that of prazosin because of the higher potency of prazosin on a molar base.

Apart from its well established affinity for α-adrenoceptors, urapidil possesses some modest affinity for dopaminergic receptors (2), but no affinity whatsoever for muscarinic cholinergic receptors. Urapidil's affinity for dopaminergic receptors is lower than that of clonidine (2).

A modest affinity of urapidil for β-adrenoceptors was found in a cardiac ventricular membrane preparation (17). A non-selective radioligand was used, hence no conclusions could be drawn with respect to a preference for β_1- or β_2-receptors.

Antagonism towards vascular postsynaptic α_1-adrenoceptors

The α_1-adrenoceptor antagonistic properties of urapidil have been described by several authors in different animal models and species. α-Adrenoceptor antagonism of urapidil had already been detected by Schoetensack *et al.* (1) using the non-selective α-adrenoceptor antagonist dihydro-ergotamine. In later studies, when selective agonists and antagonists for the α_1- and α_2-adrenoceptor subtypes had become available, it became clear that urapidil is a selective antagonist of postjunctional α_1-adrenoceptors in the following animal models: anaesthetized cats or dogs (2,9,15), conscious SHR and normotensive rats (7,9,11,14,18); anaesthetized intact rats (11); pithed rats (3,11,19); conscious dogs (5,15); isolated rat aorta and caudal artery preparations (7,11). An example is shown in Fig. 2. Some α_2-adrenoceptor antagonism of urapidil has also been described, but this effect is very much weaker than the blockade of α_1-adrenoceptors (11,19).

In conclusion, urapidil is a selective α_1-adrenoceptor antagonist, as should be expected from the radioligand binding studies discussed above. Urapidil is less potent than prazosin. As already discussed previously, the selectivity for α_1-adrenoceptors

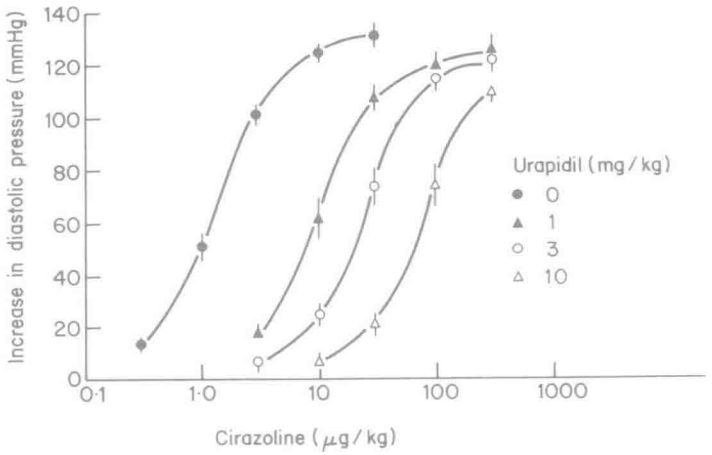

Figure 2. Competitive antagonism of urapidil towards vascular postsynaptic α_1-adrenoceptors in pithed rats. Dose–response curves for the increase in diastolic pressure by intravenous administration of the selective α_1-adrenoceptor agonist cirazoline in pithed normotensive rats after intravenous pretreatment (15 min previously) with various doses of urapidil. Symbols represent mean values ± SE (n = 5–6). Data from ref. 11.

of urapidil is somewhat lower than that of prazosin, but the extremely weak absolute affinity of urapidil for α_2-adrenoceptors probably rules out any relevant participation in postsynaptic α_2-adrenoceptor blockade of the drug's vasodilator effect.

Effects on presynaptic α-adrenoceptors

In older studies a presynaptic α_2-adrenoceptor agonistic effect of urapidil had been believed to exist (1,3), but this effect could not be confirmed by several authors (7,11,19). The weak α_2-adrenoceptor antagonistic activity of urapidil does not lead to any significant presynaptic release of noradrenaline (19). For these reasons presynaptic effects of urapidil should be regarded as practically irrelevant. This view is in accordance with the extremely weak absolute affinity of urapidil for α_2-adrenoceptors observed in radioligand binding studies (see p. 3).

Cardiac β-adrenoceptors

Modest β-adrenoceptor blockade by urapidil has been described by a few authors (11,17,20). The stimulation of adenylate cyclase in a guinea-pig ventricular membrane preparation was reduced by urapidil via a competitive mechanism at the level of β-receptors. Both in guinea-pig and rat isolated atria urapidil proved a competitive antagonist of the chronotropic response to isoprenaline (11,20). Urapidil also blunted the tachycardiac response to noradrenaline in pithed rats. Pharmacological analysis with selective antagonists has revealed that urapidil is a selective antagonist of

β_1-adrenoceptors, β_2-receptors not being involved. The β_1-adrenoceptor antagonistic activity of urapidil, however, is rather modest and it remains unclear whether this effect is relevant in oral treatment of hypertensive patients. The β_1-antagonistic effect of urapidil is characterized by a modest degree of intrinsic sympathomimetic activity (ISA) (11). In other words, urapidil should be characterized as a modest β_1-selective adrenoceptor blocking agent with moderate ISA.

Central effects

Central hypotensive activity Earlier studies as reviewed by Schoetensack (1) had already suggested the existence of a central component in the hypotensive activity of urapidil, although the evidence from these experiments was not conclusive (2). Several later studies largely confirmed that urapidil possesses considerable hypotensive activity in various models. The drug was injected by different techniques into brain cavities or into a vertebral artery (2–4,11). Comparing the hypotensive effect of urapidil when injected into various brain regions it could be demonstrated that the strongest hypotensive activity was observed upon injection into the cat's hind-brain region via the IVth ventricle (2). In this respect there was a significant difference with respect to clonidine, which is known to be more active when injected into several other brain areas, in particular the pontomedullary region in the brain-stem (21). Furthermore, the clonidine-induced central hypotensive effect, which is known to be mediated by central α_2-adrenoceptors remained unchanged after pretreatment with urapidil (2).

A further discrepancy of urapidil's effect with respect to the central hypotensive activity of clonidine was demonstrated by studying the influence of yohimbine on

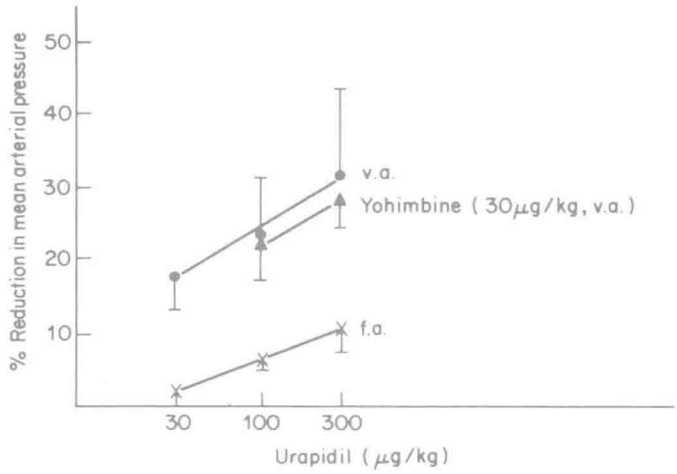

*Figure 3. Demonstration of the central hypotensive activity of urapidil. After infusion into the left vertebral artery, inducing perfusion of the brain-stem with the drug, the hypotensive effect is much stronger than after systemic administration via a femoral artery. The central hypotensive effect of urapidil is not reduced by prior treatment with the α_2-adrenoceptor antagonist yohimbine. Dose–response curves for the reduction in mean arterial pressure of chloralose-anaesthetized cats by urapidil after infusion via the vertebral artery (v.a.) or via the femoral artery (f.a.) and after infusion via the vertebral artery 15 min after v.a. infusion of yohimbine (30 μg/kg). Symbols represent mean values ± SE (n = 4–5). * $p < 0{\cdot}05$. Data from ref. 11.*

the centrally initiated depressor response to urapidil, injected into the cat's vertebral artery. This classical technique, which has been employed, for instance, to demonstrate the central hypotensive activity of clonidine, guanfacine and α-methyldopa (21,22), did indeed reveal a potent centrally induced depressor effect of urapidil (11) (see Fig. 3).

However, in contrast to the effect of clonidine (22,23), the central hypotensive activity of urapidil could not be antagonized by yohimbine (injected into the vertebral artery prior to urapidil), a selective α_2-adrenoceptor antagonist. This finding, which proves that the central hypotensive activity of urapidil is *not* mediated by central α_2-adrenoceptors could be confirmed by others in a different experimental model (2). Furthermore, the hypotensive effect of urapidil, induced upon injection of the drug into the left vertebral artery of cats (11,12), could not be suppressed by the blockade with selective, appropriate antagonists of the following receptors: histamine (both H_1 and H_2); dopamine (DA_2); serotonin ($5\text{-}HT_2$); muscarine (M_1); α-adrenoceptor and opioid-receptors. These findings clearly indicate that the central hypotensive effect of urapidil is different from that of clonidine, no central α_2-adrenoceptors being involved (12). This discrepancy between the central effects of the two drugs is accentuated by the different brain regions where their effects are initiated (2,21). As discussed above, none of the better known receptor types appears to be playing a role in the central hypotensive activity of urapidil. The mechanism of urapidil's central effect thus remains unclear and it obviously deviates from that of well known centrally acting antihypertensives.

It was recently demonstrated that reduced sympathetic impulse outflow from the central nervous system is provoked by urapidil, not involving central α- or β-adrenoceptors (9).

The absence of reflex tachycardia, in spite of the vasodilator effect of urapidil, should also be interpreted as a basically central mechanism, although an inhibitory effect of the blockade of cardiac β_1-receptors by urapidil may also be considered. The central mechanism has recently been studied in more detail (5). Accordingly, the reflex tachycardia induced by the vasodilator activity of bradykinin (intravenous) was suppressed by intravenously injected urapidil, but not by prazosin. Guanethidine, a peripheral adrenergic neuron blocker, abolished the centrally induced effect of urapidil, thus suggesting the involvement of peripheral sympathetic neurons as effectors (5). Furthermore, it may be speculated that similarly, as shown for prazosin, the blockade of central α_1-adrenoceptors may contribute to the blunting of baroreceptor reflex activity by urapidil (24).

In conclusion, there is ample evidence available in animal models for a rather potent central hypotensive effect of urapidil. It is initiated in other brain regions than that of clonidine and it does not involve central α_2-adrenoceptors or any other of the better known receptor types. The central effect of urapidil is thus rather different from that of clonidine and other well known centrally acting antihypertensives. The central mechanism of urapidil initiates reduced sympathetic outflow and blunting of the baroreceptor reflex tachycardia.

Sedation Although under clinical conditions sedation may occur, it is not a prominent side-effect of urapidil (1). A modest prolongation of the hexobarbitone-induced sleeping time was observed in mice. The effect, however, was much weaker than that of clonidine and, in obvious contrast to that of clonidine (11), it could not be reduced by the α_2-adrenoceptor antagonist yohimbine. This finding once more accentuates the discrepancy between the central activities of urapidil and clonidine.