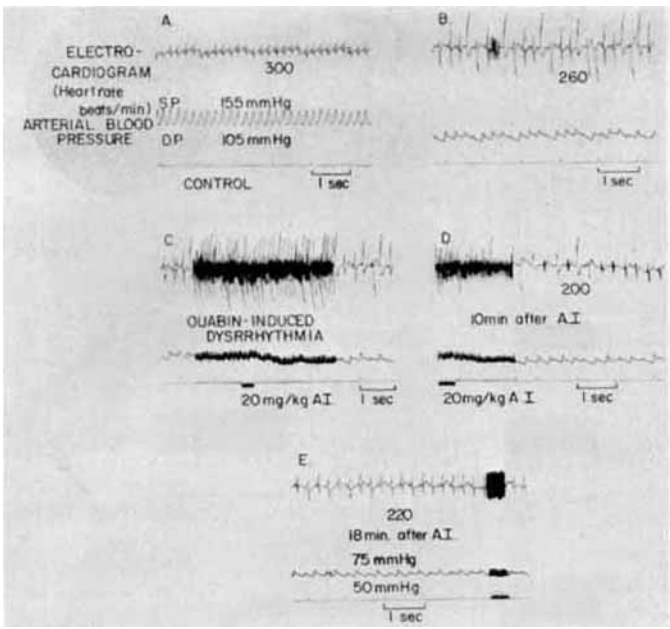

Figure 3—*Antiarrhythmic action of* A. indica *extract. Key: A, control before ouabain-induced dysrhythmia; B, 10 min after sustained dysrhythmia; C, after first dose (20 mg/kg) of extract; D, after second dose (20 mg/kg) of extract; and E, normal sinus rhythm 18 min after initial dose of extract.*

rise to a somewhat persistent vasodilation due to a reduction in arteriolar tone.

Heart rate remained nearly constant in the guinea pig, whereas there was a slight but progressive decrease in the rabbit. A direct depressant action of the compound is an untenable explanation of the mechanism of cardiac slowing in view of the observed increases in both pulse width and ECG amplitude, which may be evidence of a positive inotropic effect.

The extract of *A. indica* possessed weak antiarrhythmic activity against ouabain-induced cardiac dysrhythmias. The present experiments did not provide a satisfactory explanation of the mechanism involved, but the negative chronotropic effect of the drug appears to be beneficial in this respect.

REFERENCES

(1) B. Oliver, "Medicinal Plants in Nigeria," Nigerian College of Arts and Technology, Zaria, Nigeria, 1959, p. 48.

(2) A. Tella, *West Afr. J. Pharmacol. Drug Res.*, **3**, 80P (1976).

(3) S. O. Arigbabu and S. G. Don-Pedro, *Afr. J. Pharmacol. Pharm. Sci.*, **114**, 181 (1971).

(4) L. R. Klevans, J. L. Kovacs, and R. Kelly, *J. Pharmacol. Exp. Ther.*, **196**, 389 (1975).

(5) E. B. Thompson, *J. Pharm. Sci.*, **62**, 1638 (1973).

ACKNOWLEDGMENTS

The authors thank the Drug Research Unit of the University of Ife, Ile-Ife, Nigeria, for use of their facilities, Dr. O. O. Odebiyi who assisted in the phytochemical extraction of the plant material, and Mr. Toni Sanni for assistance.

This study was undertaken when E. B. Thompson was on a Sabbatical leave at the Drug Research Unit, University of Ife, Ile-Ife, Nigeria.

Use of Guinea Pigs as Model to Study Galactose-Induced Cataract Formation

DAVID C. KOSEGARTEN ˣ and TIMOTHY J. MAHER

Received December 5, 1977, from the *Department of Pharmacology, Massachusetts College of Pharmacy, Boston, MA 02115.* Accepted for publication February 10, 1978.

Abstract □ Because the dietary requirement for ascorbic acid is similar in humans and guinea pigs, galactose-induced cataract research with the guinea pig as an experimental model instead of the rat might be appropriate and may represent a closer analogy to galactosemic cataract formation in humans. In this study, dietary ascorbic acid was found in all guinea pigs to have a retarding or delaying effect on the development of galactose-induced cataracts.

Keyphrases □ Models, experimental—guinea pig for study of galactose-induced cataract formation, effect of ascorbic acid □ Galactose-induced cataract formation—studied in guinea pigs, effect of ascorbic acid □ Ascorbic acid—effect on galactose-induced cataract formation in guinea pigs

Galactose fed in high enough concentration causes cataracts in experimental animals (1–3). In humans, cataract formation is a prevalent complication of galactosemia, an inborn error of metabolism associated with impaired galactose biotransformation.

BACKGROUND

Classic galactosemia results from a deficiency of the enzyme galactose 1-phosphate uridyl transferase, which leads to tissue accumulation of galactose 1-phosphate and galactose. Once inside the lens, galactose is reduced by aldol reductase to galactitol, to which the lens is impermeable. A high concentration of galactitol within the lens of the galactosemic rat leads to an osmotic overhydration, which ultimately causes the formation of mature cataracts (4–6).

The early observation that scorbutic guinea pigs showed a decline in lens ascorbic acid content led to the production of cataracts in a small percentage of guinea pigs by feeding them a scorbutic diet (7). Galactose cataracts also developed in guinea pigs maintained on a scorbutic diet that included 30% casein (8).

There is a scarcity of literature on the use of the guinea pig as an animal model for the study of galactose cataracts, but a large number of studies used the rat. Of particular importance in this regard is the renewed interest in the use of flavonoids (9) or vitamin diets (10) to delay the formation of galactose-induced cataracts in the rat.

Unlike the rat, however, humans and guinea pigs cannot synthesize their own daily requirements of ascorbic acid, which is essential in the daily diet to prevent scurvy. Because of this similarity and because of the infrequent use of the guinea pig as an experimental model for the study of galactosemic cataracts, the present study was undertaken to determine if ascorbic acid could effectively delay the onset of galactosemic cataracts in the guinea pig.

EXPERIMENTAL

Fifteen Hartley strain guinea pigs, approximately 300 g, were housed in three gang cages, five per cage. The dietary protocol is shown in Table

0022-3549/78/1000-1478$01.00/0

Table I—Protocol, Mean Animal Weight, and Food and Fluid Daily Intake

Group	Protocol	Animal Weight, g (*LSD* = ±86.9)	Food Intake, g/animal/day (*LSD* = ±4.72)	Fluid Intake, ml/animal/day (*LSD* = ±26.1)
I	Scorbutic, no galactose	363.1	53.44[a]	190.8[a]
II	Scorbutic with galactose	395.0	47.36	67.6[a]
III	Ascorbic acid with galactose	462.7[a]	48.16	111.8[a]

[a] Significant at $p = 0.05$.

I. All animals were fed a diet[1] lacking ascorbic acid. Group II animals received galactose as a 10% solution as their drinking supply, while the drinking supply of Group III animals contained both galactose (10%) and ascorbic acid (1%). Group I animals received tap water. Fresh solutions were prepared each day, and daily food and fluid consumption were recorded.

Throughout the 25 days, the animals were weighed and examined with an ophthalmoscope every other day. One drop of 0.25% atropine sulfate ophthalmic solution was applied to the ocular conjunctiva as a mydriatic. The presence or absence of cataract formation was recorded. When cataract formation was present, appropriate drawings were made to depict their extent and rate of change. Food and fluid consumption and animal weight data were subjected to least significant difference analysis of variance.

RESULTS AND DISCUSSION

By Day 7 of the study, two animals from Group II had faint rings on the periphery of both lenses. By Day 9, all animals in Group II had rings on the periphery of the lens, indicative of marginal cataracts (Fig. 1A). At the end of 25 days, these peripheral rings had progressed slightly to a more coarse and thicker opacity (Fig. 1B). At Day 25, none of the animals from Group I or III showed any signs of cataract formation (Fig. 1C). The daily food and fluid intake of Group II guinea pigs was less than that of the other two groups, yet their mean weight was not significantly different.

The appearance of cataracts in both eyes of all animals fed galactose and placed on a scorbutic diet and the absence of cataracts in any of the control groups indicate that ascorbic acid has a retarding or delaying effect on the development of galactose cataracts in the guinea pig.

[1] Charles River rabbit diet.

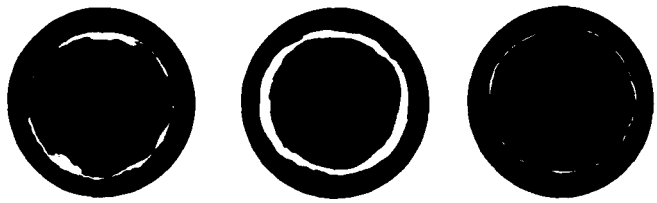

Figure 1—*Drawings of lenses illustrating the effect of ascorbic acid on the formation of galactose cataracts in the guinea pig.*

While it has been shown that rats have ample galactose 1-phosphate uridyl transferase (11), there have been no reports on the level of galactose 1-phosphate uridyl transferase in the guinea pig. Moreover, lens aldol reductase activity has been studied in rats (12, 13) but not guinea pigs.

Further investigations are being conducted in these laboratories on guinea pig galactose 1-phosphate uridyl transferase and lens aldol reductase activity in relation to galactosemic cataract formation. The present study demonstrates that the guinea pig is a suitable model for galactosemic cataract investigations, which is desirable considering the similarity between humans and the guinea pig with regard to the dietary requirement for ascorbic acid.

REFERENCES

(1) H. S. Mitchell and W. M. Dodge, *J. Nutr.*, **9**, 37 (1935).
(2) J. W. Patterson, *Am. J. Ophthalmol.*, **36** (6)II, 143 (1953).
(3) Z. Dische and E. Borenfreund, *ibid.*, **38**, 165 (1954).
(4) R. van Heyningen, *Nature (London)*, **184**, 194 (1959).
(5) J. H. Kinoshita, *Invest. Ophthalmol.*, **13**, 713 (1974).
(6) S. D. Varma and J. H. Kinoshita, *Exp. Eye Res.*, **19**, 577 (1974).
(7) N. K. Monjukowa and M. J. Fradkin, *Arch. Ophthalmol.*, **133**, 328 (1935).
(8) H. Tojo, *Acta Soc. Ophthalmol. Jpn.*, **58**, 556 (1954).
(9) S. D. Varma, E. Mikuni, and J. H. Kinoshita, *Science*, **188**, 1215 (1975).
(10) J. D. Heffley and R. J. Williams, *Proc. Natl. Acad. Sci. USA*, **71**, 4164 (1974).
(11) S. Kelly and L. DesJardins, *Proc. Soc. Exp. Biol. Med.*, **138**, 545 (1971).
(12) S. D. Varma and J. H. Kinoshita, *Biochem. Pharmacol.*, **25**, 2505 (1976).
(13) A. B. Segelman, F. P. Segelman, S. D. Varma, H. Wagner, and O. Seligman, *J. Pharm. Sci.*, **66**, 1358 (1977).

Quinazolinylformamidines and Quinazolinediylbisformamidines as Antihypertensive Agents

J. D. WARREN ˣ, S. A. LANG, Jr., P. S. CHAN, and J. W. MARSICO

Received October 12, 1977, from the *Chemical Research Department, Lederle Laboratories, American Cyanamid Co., Pearl River, NY 10965.* Accepted for publication February 9, 1978.

Abstract □ Eleven quinazolinylformamidines and quinazolinediylbisformamidines were synthesized and investigated for antihypertensive activity in spontaneous hypertensive rats. Several compounds showed moderate antihypertensive activity at 100 mg/kg po. The same compounds were not hypotensive in the normotensive dog.

Keyphrases □ Quinazolinylformamidines, substituted—synthesized, evaluated for antihypertensive activity in rats □ Antihypertensive activity—various substituted quinazolinylformamidines evaluated in rats □ Structure–activity relationships—various substituted quinazolinylformamidines evaluated for antihypertensive activity in rats

In an investigation of the potential antihypertensive activity of 2,4-diaminoquinazoline derivatives, the quinazolinediylbisformamidine (III) was observed to be a moderately active (25 mg/kg) antihypertensive agent when orally administered to spontaneously hypertensive rats (1). Further evaluation of III revealed it to be free of

0022-3549/78/1000-1479$01.00/0