Eur. Neurol. *19*: 61–66 (1980)

Pial Arteriolar Reaction to Intravenous Administration of Bencyclane in the Cat

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Key Words. Bencyclane · Pial vessels · Optimal infusion rate

Abstract. In a series of 29 experiments in cats, the vasodilatory effect of Bencyclane on pial arterioles was investigated by means of the cranial window technique, using an image-splitting eyepiece, a photometric method or simple microscopic observation. Intravenous injection of 3 mg kg^{-1} led to vasodilatation in all experiments, yet decreased blood pressure within 30–40 sec until 5–6 min down to 70% of resting pressure. Mean maximal dilatation of arterioles with a 76-μm mean resting diameter was 53%. After normalization of blood pressure, arteriolar diameters remained increased by 5–10% for further 10 min, thus indicating increased cerebral blood flow for a total time of about 15 min. During intravenous infusion of 0.2–0.3 mg $kg^{-1}min^{-1}$ of the drug, pial arterioles dilated by about 10% with blood pressure remaining on resting levels. A higher dosage rate of infusion evoked further vasodilatation, yet parallel decrease of blood pressure.

Introduction

Cerebrovascular insufficiency is a very frequent diagnosis in the elderly patient. This justifies experimental efforts to find out possibilities of medical treatment. One approach would be to increase cerebral blood flow (CBF) by isolated cerebral vasodilatation.

Bencyclane (Fludilat®, Dr. Thiemann GmbH, Lünen, FRG; N-[(1-benzyl-cycloheptyloxy)-propyl]-N,N-dimethylamine) has been discussed in the last years as a vasoactive drug with special effectiveness on the cerebral resistance vessels (2, 4, 6, 9–11). Controversial data were reported by *Herrschaft* (8), showing Bencyclane ineffective in man. Thus it appeared of interest to reexamine pial vessel reactions in animal experiments. Special attention was drawn to separate the autoregulatory diameter changes during decrease of systemic blood pressure during medication from isolated drug action on the cerebral circulation. It is known from the first observations of *Forbes and Wolff* (5) that systemic blood pressure causes vasodilatation and -constriction with its decrease and increase, respectively. This 'myogenic cerebrovascular autoregulation' has been established in man and animal to keep CBF constant within a

range of 60–160 mm Hg of systolic blood pressure. Hypotensive cerebral vasodilatation would thus not be indicative for an increase in CBF. Therefore, drug action must either cause vasodilatation during constant blood pressure or maintain vasodilatation after transitory hypotension, the latter remaining above the level of hypoxia and reactive hyperemia.

Materials and Methods

29 experiments were performed in 24 cats with a body weight of 1.4–3.0 kg. They were anesthetized with 40 mg kg^{-1} sodium pentobarbital, intubated endotracheally and respirated with a 4:1 mixture of N_2O:O_2. After cannulating the left femoral vein and artery and fixation of the head into a stereotaxic head-holder, a right parietal cranial window was performed. As previously described in detail (1), the bony defect was covered with a glass shield and sealed with acrylic. Body temperature was continuously controlled with a Philips rectal thermosensor unit and maintained between 36.5 and 37.5 °C using a heating blanket. Brain surface temperature was continuously controlled with a YSI-thermosensor unit and maintained constant at 37 °C, irrigating the parietal glass window with thermostatically temperated (Thermomix®, Braun, Melsungen, FRG) Ringer's solution. Pial vessel reactivity was observed in a Leitz Intravital microscope; at the beginning of experiments, normal CO_2 reactivity of pial vessels was established by hypercapnia and hyperventilation, respectively (1). Mean arterial blood pressure (MABP) was continuously monitored via the femoral catheter connected to a Statham transducer P23dB and a Hellige

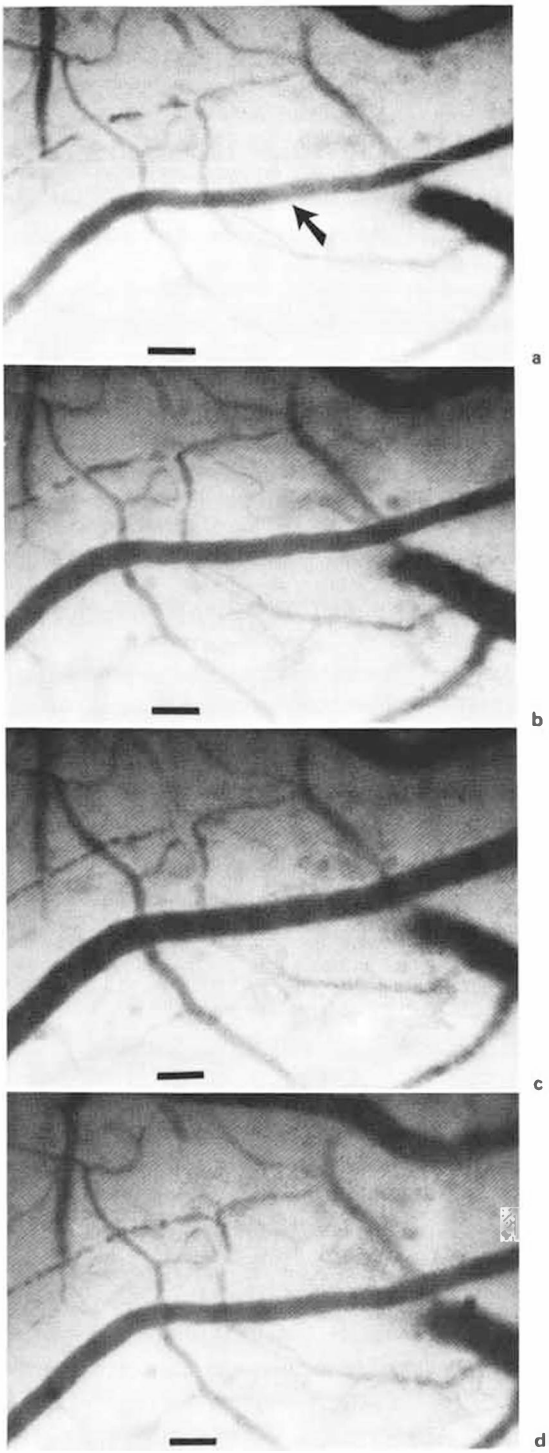

Fig. 1. Pial vessels seen through a cranial window. Bar = 66 μm. **a** Normal vessels before injection of Bencyclane; SAP = 115/85. Arrow: arteriole. **b** 30 sec after injection of 3 mg kg^{-1} Bencyclane. The arteriole is dilated; SAP = 100/80. **c** At 2 min after injection, maximal dilatation is achieved; SAP = 60/40. **d** 10 min after injection, the arteriolar vessels appear still somewhat wider than before administration of the drug, although blood pressure has returned to resting values.

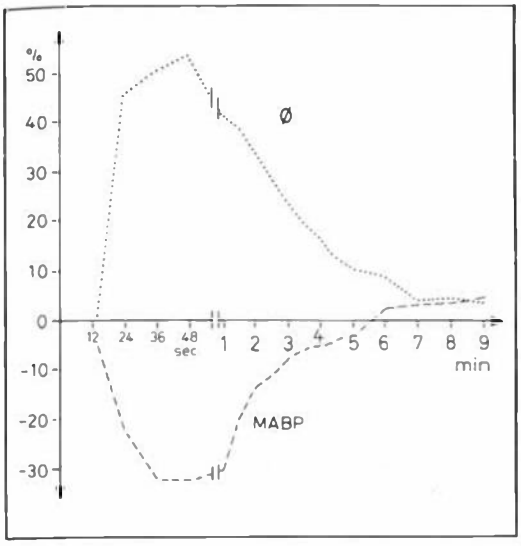

Fig. 2. Mean value curve of arteriolar diameters (ϕ) and mean arterial blood pressure (MABP) after intravenous injection of 3 mg kg^{-1} from 6 experiments: initial dilatation of more than 50% for about 1 min, paralleled by an MABP decrease of 30%; thereafter, MABP returns to normal, some 5% above resting values. Arteriolar diameters, however, remain 5–10% wider than before drug administration.

electromanometer. Blood gases were frequently checked in an AVL gas-check.

In the first 3 animals, arteriolar diameter changes were observed by eyeball control and photography (Leitz-Orthomat camera, Ectachrome high-speed film) after intravenous injection of 3 mg kg^{-1} Bencyclane.

In 13 experiments in 10 animals (one repetition in 3 animals), arteriolar diameter changes after intravenous injection of 3 mg kg^{-1} Bencyclane (6 experiments) or intravenous infusion of 0.1–0.8 mg $kg^{-1}min^{-1}$ (7 experiments) were measured with an image-splitting eyepiece, performing a measurement every 12 sec during the 1st min, every 30 sec during the next 4 min, and every minute until the end of experiments.

These experiments were assessed to find out the optimal drug infusion rate that dilates pial arterioles without lowering blood pressure, e.g., to find out the dosage leading to an isolated effect on the cerebral vessels. Infusion rate was started at 0.1 mg $kg^{-1}min^{-1}$ and increased by 0.05 mg $kg^{-1}min^{-1}$ every 10–20 min until MABP began to fall.

13 more experiments were performed in 11 animals (one repetition in 2 cases) to observe the time-course of blood pressure and arteriolar diameter changes after intravenous injection of 3 mg kg^{-1} Bencyclane in 6 cases and infusion of 0.6 mg $kg^{-1}min^{-1}$ in 5 cases, respectively. Therefore, a photometric measurement unit was connected to the Intravital microscope (1). The photometric light intensity curve was, together with blood pressure, documented on a Rikadenkie 2-channel writer.

Results

In all three experiments of the first group, vasodilatation was observed qualitatively; here, small arterioles below 30 μm resting diameter dilated markedly more than larger arterioles up to 200 μm. After injection of Bencyclane, MABP decreased in all animals within 20–50 sec 27–44% below resting values. After blood pressure had returned to pretreatment levels – which occurred after 2 min 5 sec, 2 min 14 sec and 13 min, respectively – arterial vessels seemed still to be somewhat wider than their pretreatment diameters were (fig. 1).

In the second group, the extent of arteriolar dilatation was established using the image-splitting technique. After injection of 3 mg kg^{-1} in 6 experiments, mean maximal dilatation was observed after 48 sec to +53%. The mean resting diameter of the investigated arterioles was 76 μm. The curves of MABP and arteriolar changes during the first 9 min after injection are depicted in figure 2: this shows an initial blood pressure decrease down to 70% of normal in parallel with vasodilatation. After 5.5 min, blood pressure has settled back to normal; however, the observed arteriolar diameters remain 5–10% above resting levels for about further 10 min, indicating slightly increased CBF.

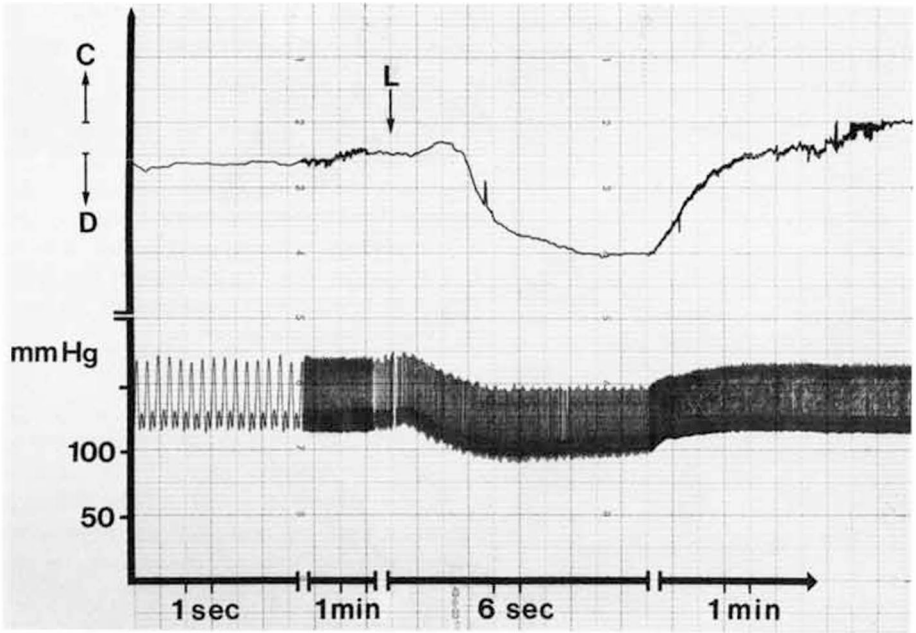

Fig. 3. *Upper curve:* Semiquantitative documentation of arteriolar diameter changes by photometry after intravenous injection of 3 mg kg^{-1} Bencyclane (arrow). D = Dilatation; C = constriction. *Lower curve:* Blood pressure. After injection, MABP decreases from 140 to only 120 mm Hg; nevertheless, the arteriole dilates markedly.

During a 0.2–0.3 mg $kg^{-1}min^{-1}$ infusion of Bencyclane, pial arterioles dilated by 7.2–11% (mean 9.6%), MABP remaining unchanged.

Increasing of the dosage rate up to 0.6 mg $kg^{-1}min^{-1}$ led to a further dilatation up to 24%; in this situation, however, MABP decreased by 9–28% (mean 10.6%). Arterial pCO_2 was kept between 29 and 35 mm Hg (mean 30.0 mm Hg), pO_2 between 93 and 112 mm Hg (mean 101 mm Hg) during these experiments.

Vasodilatation was observed in all experiments using the photometer technique for qualitative determination of pial arteriolar dilatation. In 2 cases, blood pressure remained unchanged despite vasodilatation; in 9 cases, MABP decreased by an average of 41.7%, ranging from −18 to −70%. A typical pattern of arteriolar behavior after Bencyclane injection is depicted in figure 3 which shows marked vasodilatation during and still after minimal fall in blood pressure. During these experiments, arterial pCO_2 was maintained between 28 and 40 mm Hg (mean 33.3 mm Hg) and pO_2 between 80 and 122 mm Hg (mean 110.4 mm Hg).

Control measurements under steady state conditions, normocapnia and normotension before beginning of drug administration revealed no pial arteriolar diameter variations as measured with the image splitter. In a larger control series, diameter variations had run up to a mean value of 0.83% (1).

Discussion

The blood pressure decreasing effect of Bencyclane has already been observed in several experimental series (6, 7) and is known from clinical experience. This fact undoubtedly complicates the proof of a direct cerebral vasodilatory action after bolus injection since normal myogenic cerebrovascular autoregulation implies vasodilatation during blood pressure decrease and vice versa to maintain global CBF on a constant level. In our experiments, arterioles under investigation remained dilated by 5–10% after blood pressure normalization for about 10 min. This observation fits with other experiments (6, 7), where CBF remained increased after the same medication of 3 mg kg^{-1} and normalization of initially decreased blood pressure. In those experiments, 1 mg kg^{-1} did not increase CBF to the same extent as 3 mg kg^{-1}. On the other hand, 5 mg kg^{-1} did not increase CBF more than 3 mg kg^{-1}, thus indicating the optimal dosage to be around 3 mg kg^{-1}. A comparison of the initial mean maximal arteriolar dilatation of +53% from our own investigations with other published data is not possible. The time-course of pial arteriolar reactions becomes especially evident from continuous diameter observation with the photometer technique: it shows the quick initial vasodilatation to a maximum within 20–40 sec, which is in good correlation with an investigation of *Hutten and Vaupel* (9): these authors measured cerebrovascular resistance during Bencyclane infusion and found a minimal resistance after 30–60 sec, using an arterial drug concentration of 0.94 mg/ml of blood. The decrease in resistance of 21–25% resulted in a 27.1–33.5% global CBF increase.

Regarding the clinical use of the drug, intravenous infusion is undoubtedly preferable to bolus injection, and the dosage must be known not to lower blood pressure during therapy. The effective dosage rate dilating cerebral resistance vessels of 20–50 μm for some 10% has been demonstrated to range between 0.2 and 0.3 mg $kg^{-1}min^{-1}$. This dosage seems to affect isolated dilatory action on brain vessels, vascular resistance elsewhere in the body thus remaining unchanged. The dosage is also very near to data evaluated by *Kohlmeyer* (10) in man: global flow was increased by 11–57% during infusion of 0.1 mg $kg^{-1}min^{-1}$ Bencyclane, patients with decreased resting flow reacting more than patients with normal flow.

Two observations support the assumption of true drug action directly on the resistance vessels: the first is an increase of CBF and arteriolar diameters in experiments lacking a drop in blood pressure (6, 7; own experiments). The second observation concerns the local effect of Bencyclane, which unequivocally shows a vasodilatory effect (2, 4, 6). Reactive hyperemia as a consequence of 'prolonged transitory flow increase following pressure rises within the normotensive pressure range' (3), which could also be called 'delayed autoregulation' (1), cannot have influenced our diameter measurements after bolus injection of Bencyclane, since mean posthypotensive dilatation was identical to the dilatation during infusion and steady blood pressure.

In conclusion, experimental data available on the cerebrovascular effect of Bencyclane show an increase of CBF for at least 15 min after injection of the dosage of 3 mg kg^{-1}. The optimal drug application is an intravenous infusion of 0.2–0.3 mg $kg^{-1}min^{-1}$.

Acknowledgements

This work was supported by the 'Österreichischer Fonds zur Förderung der wissenschaftlichen Forschung'.

We acknowledge the kind support of Dr. *Neuhold* and the technical assistance of *S. Schreiner.*

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Received: February 13, 1979
Accepted: May 3, 1979

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