Arch. Psychiat. Nervenkr. 224, 351—360 (1977)

Archiv für Psychiatrie und Nervenkrankheiten
Archives of Psychiatry and Neurological Sciences

Effects of a New Diuretic on Cerebrospinal Fluid Pressure in Patients with Supratentorial Tumors

Alexander Hartmann[1], Hans-Jörg Schütz[1], Eckhart Alberti[1], Ferdinand Schreckenberger[1], Dieter Loew[2], and Jan Dýcka[2]

[1] Neurologische Universitätsklinik, D-6900 Heidelberg, Federal Republic of Germany
[2] Bayer AG, D-5600 Wuppertal, Federal Republic of Germany

Summary. The effect of a new, powerful diuretic on biochemical parameters, urine output, central venous pressure, blood pressure, and cerebrospinal fluid pressure in patients with supratentorial intracerebral tumors who showed signs and symptoms of increased intracranial pressure was tested. When compared to an untreated control group and to the steady-state data of each patient, CSF pressure was significantly reduced using a dose of 240 mg of the diuretic. The 120 mg dosage did not produce significant results. Normalization of increased cerebrospinal fluid pressure was not completely obtained using either dose. Used alone, this substance is not suitable for treatment of increased intracranial pressure due to brain edema in patients with intracerebral tumors. It might, however, be useful in combination with other medications.

Key words: Diuretics – Brain edema – Intracranial pressure – Tumors.

Zusammenfassung. Die Wirkung eines neuen Diuretikums auf biochemische Werte, Urinausscheidung, zentralen Venendruck, Blutdruck und den Liquordruck wurde bei Patienten mit supratentoriellen Tumoren und klinischen Zeichen erhöhten intrakraniellen Drucks untersucht. Im Vergleich zu einer unbehandelten Kontrollgruppe und den Ausgangsdaten der einzelnen Patienten kam es nach einer Einzeldosis von 240 mg BAY g 2821 zu einem signifikanten Absinken des Liquordrucks. Eine Dosis von 120 mg war ohne Wirkung. Keine der beiden Dosen führte zu einer Normalisierung des Drucks, so daß diese Substanz nicht als Einzelmedikation zur Behandlung des Hirnödems von Patienten mit Hirntumoren eingesetzt werden sollte. In Verbindung mit anderen Substanzen könnte es von Wert sein.

Schlüsselwörter: Diuretikum – Hirnödem – Hirndruck – Tumoren.

For offprints contact: Dr. A. Hartmann

Introduction

Treatment of increased intracranial pressure (ICP) in patients with cerebral tumors includes hyperventilation, administration of steroids, and intravenous infusion of hyperosmolar solutions. Since in these cases increased ICP is partially due to accumulation of fluid, diuretics are stated to have beneficial effects [8, 14]. However, only a limited number of direct observations of the diuretic's effect on ICP is published. In this study the effects of a new diuretic substance (BAY g 2821) on cerebrospinal fluid pressure (CSFP) and other parameters in patients with supratentorial intracerebral tumors are presented.

Method

Twenty-four patients with intracerebral neoplasms and clinical signs of increased ICP were examined. Diagnosis was achieved by clinical evaluation, scintigraphy, angiography, and pneumoencephalography and was confirmed in about 30% of the cases through biopsy or autopsy. The patients were randomized for the study.

Standard lumbar puncture was performed in the lateral recumbent position with the head of the patient slightly lower than the feet. The needle was bent at the tip (30°) allowing insertion of a thin gas-sterilized polyethylene catheter (inner diameter 0.5 mm) into the subarachnoid space. The needle itself was then withdrawn and the area of puncture covered with sterile cotton and tape. The catheter was connected to a transducer and both filled with sterile normal saline solution. CSFP was recorded on a 4-channel polygraph. Loss of CSF did not exceed 1 ml. CSFP, central venous pressure (CVP), and the pattern of respiration were continuously recorded for 25 h on the same polygraph. Blood pressure (BP) and heart rate (HR) were measured at first every ten min for four h and thereafter every 30 min. Urine was collected using a standard bladder catheter.

As shown by Kaufman and Clark [10] and by Garretson and Brindle [3], ICP equals CSFP unless cerebral or tonsillar herniation blocks the intraventricular CSF pulse wave. In some patients we have performed combined intraventricular and lumbar CSF-pressure measurements and identical values were found. In the patients of this study herniation was excluded by clinical evaluation. Further methodological information has been published elsewhere [6].

Prior to the administration of the diuretic and in two 12-h intervals following initiation of therapy the following parameters were measured: total blood count, hematocrit, serum potassium, serum sodium, serum calcium, serum glucose, serum urea, serum creatinine, and potassium and sodium concentration in the CSF.

Using levulose and Ringer's solution, intravenous fluid substitution was adjusted according to urine output and CVP.

The following groups were evaluated:

1. *Control Group.* Eight patients did not receive any antiedematous substances for 25 h.
2. *Group 120 mg.* After recording all parameters for one h (steady state) 120 mg of the diuretic BAY g 2821 were given orally to eight patients. Data were monitored for 24 h.
3. *Group 240 mg.* The same procedure as in group 120 mg was performed but 240 mg BAY g 2821 were given to eight patients.

Statistical evaluation of the results was performed as follows: a 3-factorial, variance-analytical method was used for blood pressure, CVP, HR, urine output, and all biochemical parameters. Regarding CSFP the values from one-min intervals of the monitor record were taken and the mean calculated from five values. A polynomial orthogonal regression of the second degree was calculated for each patient ($\hat{y} = B'_o + B'_1\zeta_1 + B'_2\zeta_2$). ζ is the orthogonal function of x (5). B'_i as the regression coefficient is an independent variate. B'_0 is a measure for the level, B'_1 for the linearity and B'_2 for the nonlinear effect. B'_1 and B'_2 reflect the profile.

All three groups were analyzed using a 1-factorial variance analysis with the variable B'_i. This method furnishes a combined time-response curve as a polynomial function of the nth degree. The degree of the function was calculated according to the proposal of Weber [16].

Results

There were no complications or deaths within four days following completion of the study. Clinical signs and symptoms were not changed by the diuretic.

Table 1 lists the mean steady-state data for all groups. Except for serum calcium and platelet count, there were no significant differences among the three groups. In the control group, significant changes in cardiovascular parameters, respiration, and metabolic data during 25 h were not found.

The effect of 120 mg and 240 mg BAY g 2821 on BP, HR, CVP, and respiration is shown in Figure 1. In both groups slight reduction of the systolic BP occured but never exceeded 13 mm Hg within 24 h. The reduction of systolic BP was statistically significant, but changes of diastolic values were statistically not significant.

CVP fell by 2 mm Hg at the most in the 120 mg group and by 1 mm Hg in the 240 mg group (Fig. 1). There was no relevant change in HR and respiration in either group.

Figure 2 indicates the effect of both dosages on urine output as compared to the control group. Sixty min after administration of BAY g 2821, output reached its peak and remained at this level for about two more h. Thereafter it began to decline and reached the steady-state value eight h following administration in the 120 mg group and more than twelve h after application in the 240 mg group.

Table 2 indicates the effect of BAY g 2821 on biochemical parameters. Mean values, SD, and deviation from the steady-state data are listed. Sodium, potassium, and blood urea were reduced after 12 and 24 h. These and the other parameters, however, did not change dramatically.

Table 1. Steady-state data of the cardiovascular system, blood count, and blood and CSF biochemistry

	Controls	120 mg BAY g 2821	240 mg BAY g 2821	$P \leqq$
Blood pressure, systolic (mm Hg)	135.7 ± 28.5	150.6 ± 18.0	146.3 ± 18.7	0.40
Blood pressure, diastolic (mm Hg)	78.8 ± 8.8	88.8 ± 8.8	88.1 ± 10.7	0.08
Heart rate (min^{-1})	88 ± 16	84 ± 19	77 ± 13	0.37
Respiration (min^{-1})	18 ± 4	16 ± 4	14 ± 1	0.10
Central venous pressure (mm Hg)	2.9 ± 2.5	5.6 ± 2.2	5.5 ± 2.4	0.07
Urine output (ml/min)	59.4 ± 32.7	59.4 ± 24.3	53.1 ± 34.2	0.90
Sodium in blood (mEq/l)	142.9 ± 5.7	139.7 ± 2.9	140.4 ± 3.7	0.32
Potassium in blood (mEq/l)	3.8 ± 0.60	3.8 ± 0.58	3.9 ± 0.47	0.91
Calcium (mEq/l)	4.4 ± 0.31	4.7 ± 0.19	4.9 ± 0.30	0.01
Blood urea (mg/100 ml)	41.9 ± 19.1	35.5 ± 10.6	44.4 ± 19.2	0.56
Uric acid (mg/100 ml)	5.0 ± 2.2	5.3 ± 1.3	5.7 ± 1.6	0.74
Blood creatinine (mg/100 ml)	1.0 ± 0.42	1.1 ± 0.22	1.0 ± 0.13	0.96
Fasting blood glucose (mg/100 ml)	119.0 ± 30.5	133.7 ± 63.8	138.1 ± 55.4	0.74
Hemoglobin (g/100 ml)	13.2 ± 1.28	13.8 ± 1.26	14.5 ± 1.26	0.16
Hematocrit (%)	39.3 ± 3.0	40.8 ± 2.7	42.1 ± 3.5	0.21
White blood count (mm^{-3})	10,138 ± 1436	10,675 ± 3251	9487 ± 2055	0.61
Platelets (mm^{-3})	233,500 ± 114,594	275,750 ± 73,647	198,875 ± 64,239	0.05
CSF Sodium (mEq/l)	150.5 ± 15.1	141.8 ± 7.2	146.1 ± 9.8	0.31
CSF Potassium (mEq/l)	2.9 ± 0.86	3.1 ± 0.33	3.1 ± 0.7	0.88

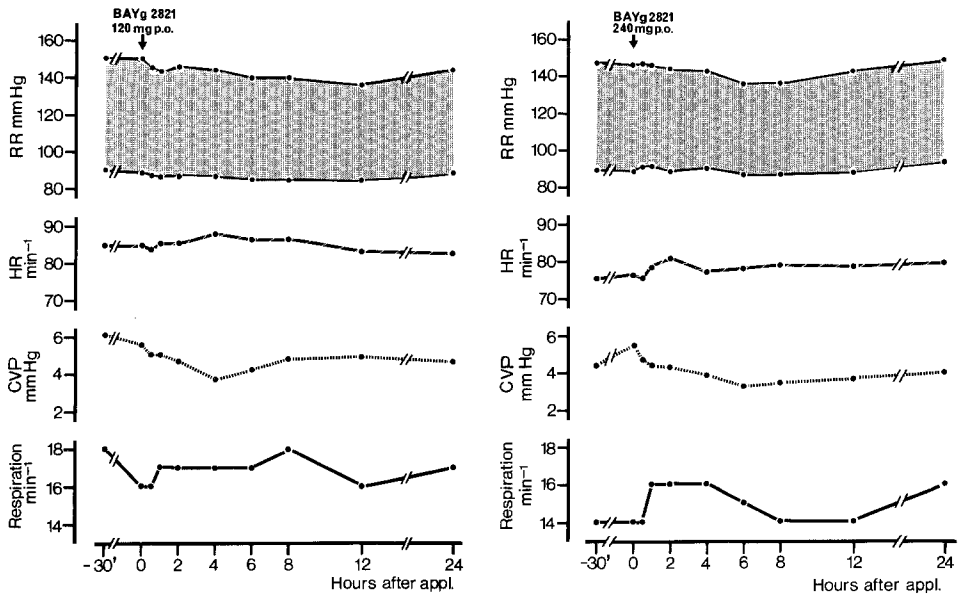

Fig. 1. Effect of BAY g 2821 on hemodynamic parameters. CVP = central venous pressure; HR = heart rate; RR = blood pressure

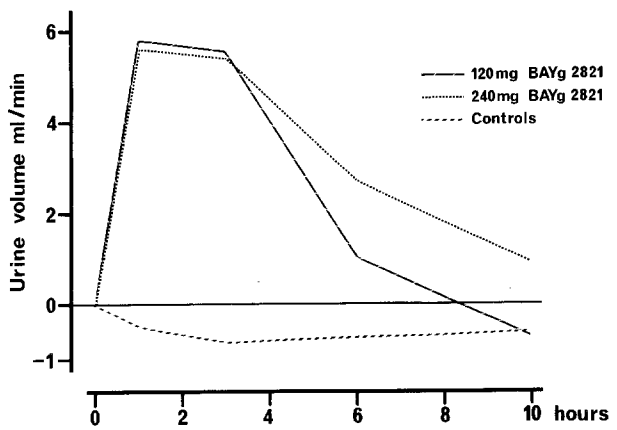

Fig. 2. Effect of BAY g 2821 on urine output, expressed in deviation from the steady-state volume in ml/min

Under steady-state condition, mean CSFP in the control group was 31 mm Hg (± 10.0), in the 120 mg group 33.1 mm Hg (± 3.3), and in the 240 mg group 36.6 mm Hg (± 5.1). In the control group mean CSFP after 24 h was 33.1 mm Hg (± 11.6) (Fig. 3).

The effect of BAY g 2821 on CSFP may be seen in Figure 3, expressed also as deviation from the mean steady-state value. Mean reduction after 24 h was 2.5 mm Hg in the 120 mg group and 6 mm Hg in the 240 mg group. In both groups

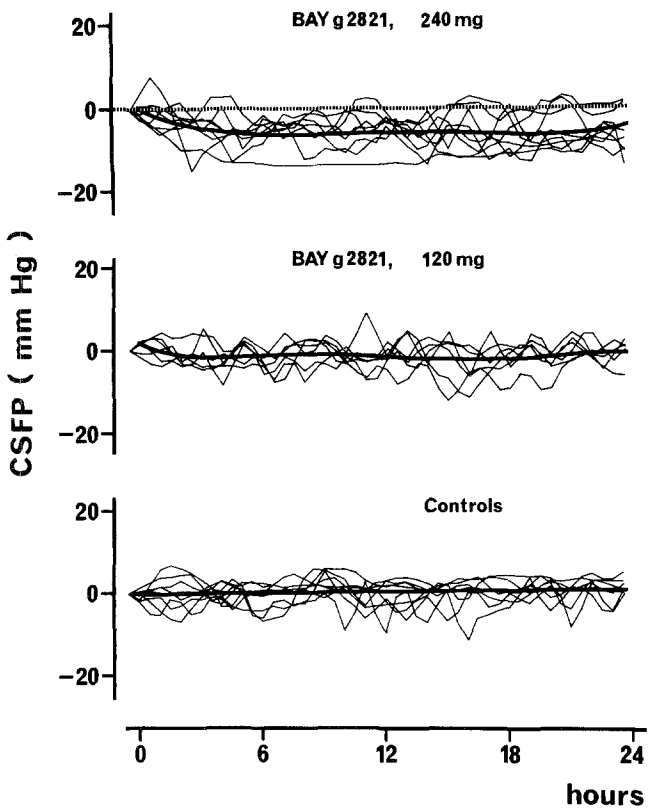

Fig. 3. Effect of BAY g 2821 on cerebrospinal fluid pressure (CSFP). Each line represents the course of CSFP over 24 h, expressed in deviation from the steady-state value. The *thick lines* indicate the mean CSFP course for each group. Only BAY g 2821 in a dosage of 240 mg has a statistically significant effect: CSFP decreases by approximately 6 mm Hg within three hours after start of therapy and remains at this level for the rest of the study. The *dotted line* represents the zero-line (steady-state value)

the drug took effect approximately 60 min after administration and lasted for the rest of the study (Fig. 4). The effect was statistically significant for the 240 mg group ($P < 0.001$), but not for the 120 mg group. In two cases of the 120 mg group, CSFP reacted differently compared to the other six patients. These two cases were not included in Figure 3 but are described here.

In one patient CSFP during steady-state was 60 to 80 mm Hg. Approximately two h after administration of the drug, CSFP rose to 90—110 mm Hg. At the same time a moderate increase of the pressure amplitude was observed (Fig. 5). Four h after initiation of therapy CSFP began to fall and reached a level of 80 to 90 mm Hg four h later. Shortly afterward therapy with hyperosmolar solutions was started since the patient complained of headache and nausea. CSFP fell rapidly and subjective discomfort disappeared within one h.

In the other patient steady-state CSFP was recorded as being 30 to 45 mm Hg. CSFP amplitude was enlarged. One h after administration of BAY g 2821 CSFP decreased and reached normal values six h later (Fig. 6), where it remained for the rest of the study.

Table 2. Effect of BAY g 2821 on biochemical parameters, hemoglobin, and hematocrit. For each parameter the measured value, SD, and deviation from the steady state are indicated. Δ = deviation

	Controls				BAY g 2821 (120 mg)				BAY g 2821 (240 mg)			
	12 h	Δ	24 h	Δ	12 h	Δ	24 h	Δ	12 h	Δ	24 h	Δ
Sodium (mEq/l)	143.0 ± 7.1	+ 0.1	143.5 ± 6.1	+0.6	137.3 ± 3.3	−2.5	137.0 ± 5.2	− 2.7	138.6 ± 3.6	−1.8	135.9 ± 6.6	− 4.5
Potassium (mEq/l)	3.7 ± 0.4	− 0.1	3.9 ± 0.4	+0.1	3.4 ± 0.4	−0.4	3.4 ± 0.4	− 0.4	3.5 ± 0.5	−0.4	3.4 ± 0.3	− 0.5
Calcium (mEq/l)	4.5 ± 0.5	+ 0.1	4.5 ± 0.4	+0.1	4.8 ± 0.2	+0.1	4.8 ± 0.4	+ 0.1	4.9 ± 0.4	0	4.6 ± 0.3	− 0.3
Blood urea (mg/100 ml)	38.9 ± 15.4	− 3.0	37.3 ± 14.1	−4.6	31.5 ± 8.6	−4.0	30.9 ± 7.4	− 4.6	38.1 ± 17.7	−6.3	36.9 ± 19.6	− 7.5
Uric acid (mg/100 ml)	5.1 ± 2.3	+ 0.1	5.1 ± 2.0	+0.1	6.1 ± 1.7	+0.9	5.8 ± 1.3	+ 0.5	5.5 ± 2.1	−0.2	5.3 ± 2.1	− 0.4
Creatinine (mg/100 ml)	0.9 ± 0.3	− 0.1	1.0 ± 0.3	0	1.1 ± 0.2	0	1.0 ± 0.1	− 0.1	1.0 ± 0.3	0	1.0 ± 0.2	0
Fasting blood glucose (mg/100 ml)	113.6 ± 27.3	− 5.4	123.8 ± 27.5	+4.8	127.0 ± 28.5	−6.8	116.1 ± 12.1	−17.6	129.0 ± 59.0	−9.1	153.8 ± 54.6	+15.7
Hemoglobin (g%)	13.0 ± 1.3	− 0.2	13.4 ± 1.2	+0.2	14.2 ± 1.4	+0.4	14.2 ± 1.3	+ 0.4	15.1 ± 1.5	+0.6	14.9 ± 1.4	+ 0.4
Hematocrit (%)	38.5 ± 1.8	− 0.8	39.6 ± 2.4	+0.3	42.0 ± 3.2	+1.2	41.4 ± 3.8	+ 0.6	43.5 ± 4.1	+1.4	42.8 ± 4.2	+ 0.7
CSF Sodium (mEq/l)	169.2 ± 15.9	+18.7	150.4 ± 10.2	−0.1	135.7 ± 15.6	−6.1	133.2 ± 23.9	− 8.6	149.0 ± 6.7	+3.1	144.0 ± 6.9	− 2.1
CSF Potassium (mEq/l)	2.6 ± 0.7	− 0.3	2.8 ± 0.4	−0.1	2.7 ± 0.3	−0.4	2.8 ± 0.4	− 0.3	2.7 ± 0.4	−0.4	2.7 ± 0.4	− 0.4

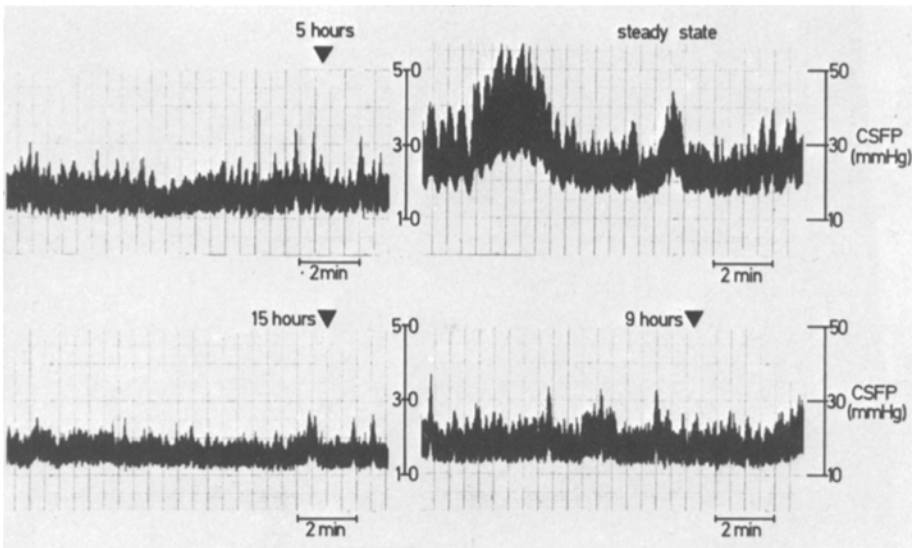

Fig. 4. Effect of 240 mg BAY g 2821 in one patient. Curve reads from right to left. Increased steady-state CSFP decreases after start of therapy and remains low. At the same time the CSFP amplitude decreases. 'Hours' indicates time after administration of the drug

Discussion

BAY g 2821 (generic: Muzolimine; chemically: 3-amino-1-(3,4-dichlor-α-methyl-benzyl)-2-pyrazolone) is a new potent diuretic that will be produced for clinical use soon. It exerts strong influence on urine output when given orally. Output increases a short time after administration and remains high for several h (Fig. 2). The loss of fluid is associated with excretion of sodium and potassium from the blood but not to a significant degree from the CSF (Table 2). Intravenous substitution is capable of compensating for the fluid loss. Under the influence of the drug, systemic blood pressure does not drop to a critical level (Fig. 1), nor does an increase of hematocrit occur indicating serious hypovolemia (Table 2). Judging from the parameters measured and from our clinical observations BAY g 2821 seems a safe compound to enhance diuresis [1].

In patients with intracerebral tumors, pathological accumulation of fluid is due to damage to the blood-brain barrier with increased migration into and reduced absorption from the extracellular space [11]. The increased amount of fluid within the skull causes elevation of ICP, which might be followed by a reduction of cerebral blood flow and thus further development of brain edema. The monitoring of eight untreated patients with tumors of the central nervous system and clinical signs and symptoms of increased ICP indicated that this vicious cycle results in most of the cases in an unerring increase of CSFP by approximately 2.1 mm Hg/24 h (Fig. 3). This observation suggests that immediate therapy is necessary to reduce ICP and prevent further complications.

Fig. 5

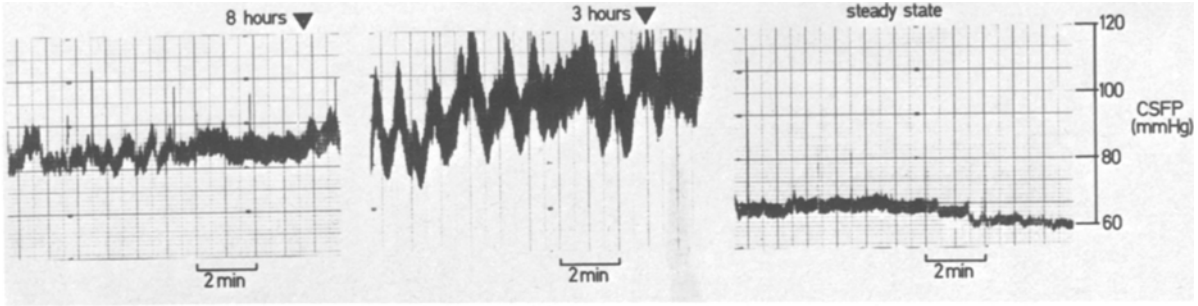

Fig. 6

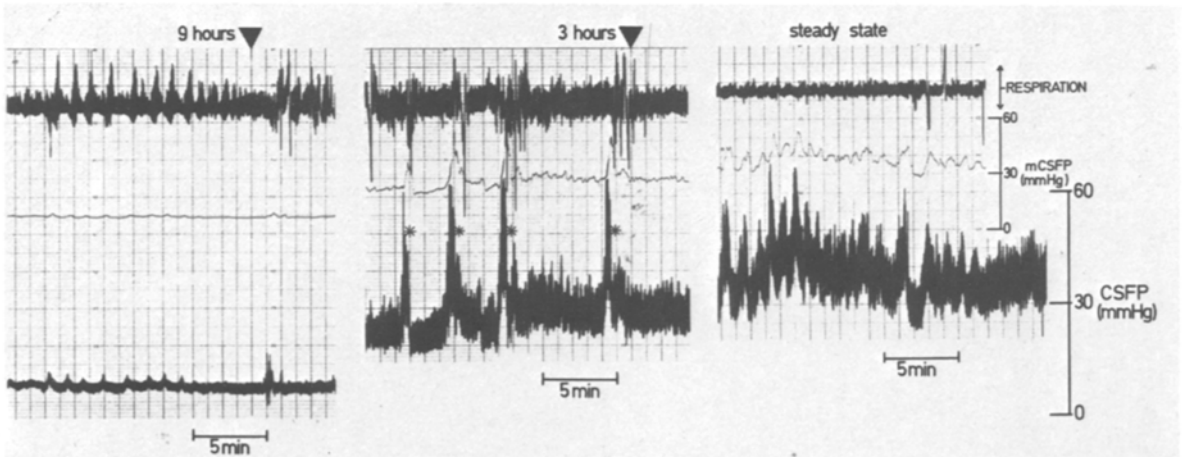

Fig. 5. Example of inefficiency of 120 mg BAY g 2821 on CSFP. Curve reads from right to left. After administration of the drug CSFP increases and reached a level above the steady state. 'Hours' indicate time after administration of the drug

Fig. 6. Positive effect of 120 mg BAY g 2821 on CSFP. Curve reads from right to left. The *upper curve* shows the respiration pattern, the *lower* the cerebrospinal fluid pressure (CSFP), and the *middle* one mean CSFP. In this case CSFP fell after administration of BAY g 2821 down to normal levels. 'Hours' indicates time after administration of the drug

The basic principle in the use of diuretics in treatment of brain edema is the removal of fluid from the intravascular space with simultaneous transport of fluid from the extracellular space to the vascular system. However, the results from direct CSF-pressure recording under the influence of fast-acting diuretics are not uniform [4, 7, 9, 13].

BAY g 2821 causes a reduction of CSFP, which is dependent on the dosage. 120 mg reduce CSFP by 2.5 mm Hg within 24 h, compared to steady state (which is 4.6 mm Hg compared to the relative change of CSFP in the control group). 240 mg decrease CSFP by 6 mm Hg within 24 h (8.1 mm Hg compared to the control group). In both groups the effect starts to appear at about the same time as the increase of urine output. Rebound phenomena were seen in none of our cases. From this study it might be concluded that BAY g 2821 is capable of partial interruption of the vicious cycle between increased ICP and reduced cerebral blood flow.

The desired aim in therapy for brain edema and increased ICP is pressure normalization. This was achieved in only one case using 120 mg BAY g 2821 (Fig. 6). In another patient ICP did not drop following administration of the diuretic and it was necessary to infuse hyperosmolar solutions (Fig. 5). In all other 14 cases studied here CSFP dropped somewhat but did not reach physiological levels (Fig. 3).

BAY g 2821 probably inhibits reabsorption of sodium in the renal tubule [12]. It has been stated that furosemide might reduce the relative specific activity of sodium in the cerebral cortex, but not in the white matter [15]. From the results presented here it cannot be concluded whether BAY g 2821 in the dosages used influences the extracellular concentration of sodium and potassium in the brain or whether it influences the specific activity of these electrolytes. The level of sodium and potassium in the CSF did not change significantly ($P > 0.05$). The strong effect on sodium excretion in the kidney [1] and the lack of a significant effect on sodium concentration in the CSF might explain the mild effect on CSF pressure, since the development of a sodium gradient between CSF and blood inhibits the movement of water from the brain to the vascular system. Further investigations, including measurements of alterations of electrolytes in CSF, blood, and urine, will be necessary to answer this question.

The mild effect on CSFP indicates that BAY g 2821, like other diuretics, should not be used alone in the therapy of brain edema. It might, however, be useful in conjunction with slow-acting steroids.

We are grateful to Mr. Trtinjak for his substantial help.

References

1. Berg, K. J., Jørstad, S., Tromsdal, A.: Studies on the clinical pharmacology of a new potent diuretic, BAY g 2821. Pharmatherapeutica **1**, 319—332 (1975)
2. Fuhrmeister, U., Berndt, S. F.: Pathophysiologie, Klinik und Therapie des Hirnödems. Deutsches Ärzteblatt **73**, 1601—1607 (1976)
3. Garretson, H. D., Brindle, G. F.: Effects of ventriculoatrial shunting on CSF dynamics. In: Cisternography and Hydrocephalus (C. Harbert, ed.), pp. 323—334. Springfield, Ill.: Ch. C. Thomas Publ. 1972

4. Girke, W., Lieske, V.: Pathophysiologie und Therapie des Hirnödems. Med. Klinik **69**, 1—11 (1974)
5. Guest, P. G.: Numerical methods of curve fitting. Cambridge-London: Cambridge University Press 1961
6. Hartmann, A., Alberti, E.: Eine einfache Methode zur kontinuierlichen Messung des Liquordrucks. Acta Neurochir. (Wien) **36**, 201—214 (1977)
7. Hartmann, A., Alberti, E., Schütz, H.-J., Schreckenberger, F.: Die Wirkung von Furosemid und Dexamethason auf den Liquordruck beim Hirntumor. Med. Welt **27**, C. N. F., 884—886 (1976)
8. Hemmer, R.: Konservative Therapie bei erhöhtem Hirndruck. Deutsche Med. Wochenzeitschrift **91**, 770—772 (1966)
9. Hayakawa, I.: Klinische Untersuchungen über ein neues Hirndruckminderungsmittel. Zentralbl. Neurochir. **28**, 17—25 (1967)
10. Kaufmann, G. E., Clark, K.: Continuous simultaneous monitoring of intraventricular and cervical subarachnoid cerebrospinal fluid pressure to indicate development of cerebral or tonsillar herniation. J. Neurosurg. **33**, 145—150 (1970)
11. Klatzo, I.: Pathophysiological aspects of brain edema. In: Steroids and brain edema (H. J. Reulen and K. Schürmann, eds.), pp. 1—8. Berlin-Heidelberg-New York: Springer 1972
12. Loew, D., Meng, K.: The renal mechanism of BAY g 2821. Pharmatherapeutica **1**, 333—340 (1977)
13. Schmidt, K.: Hirndurchblutung bei intrakranieller Drucksteigerung und beim Hirnödem. In: Der Hirnkreislauf (H. Gänshirt, ed.), pp. 715—729. Stuttgart: G. Thieme 1972
14. Thilmann, J., Zeumer, H.: Untersuchungen zur Behandlung des Hirnödems mit hohen Dosen Furosemid. Deutsche Med. Wochenzeitschrift **99**, 932—935 (1974)
15. Tutt, H.-P., Pappius, H. M.: Studies on the mechanisms of action of steroids in traumatized brain. In: Steroids and Brain Edema, (H. J. Reulen and K. Schürmann, eds.). pp. 147—151. Heidelberg-Berlin-New York: Springer 1972
16. Weber, E.: Grundriß der biologischen Statistik. 7. Aufl. Stuttgart: G. Fischer 1972

Received May 26, 1977