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The effects of dihydroergotamine in patients with head injury and raised intracranial pressure

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Abstract. In the first study 6 patients with raised intracranial pressure due to brain oedema following head injury were given dihydroergotamine because of low perfusion pressure. The intracranial pressure fell simultaneously with the increase in arterial pressure. The intracranial pressure fell from 24±2 mmHg by a maximum of 12±1 mmHg after a single intravenous injection of 0.25 mg of dihydroergotamine and remained at a low level for 35–70 min before stabilizing at a new level 5±1 mmHg below the baseline. The initial rapid and marked decrease in intracranial pressure may be the result of a reduced intracranial blood volume, due predominantly to constriction of the more voluminous venous capacitance vessels (by analogy with the corresponding vascular effect of dihydroergotamine on skeletal muscle and skin.) In the second study, experiments using sympathectomized cat skeletal muscle, showed that dihydroergotamine also reduced the hydrostatic capillary pressure, inducing absorption of fluid from the interstitial tissue to blood. It is suggested that a similar transcapillary absorption effect in the damaged brain may be an explanation for the observation that the intracranial pressure stabilized at a level below the initial one following dihydroergotamine.

Key words: Dihydroergotamine – Intracranial pressure – Vascular control – Head injury

High intracranial pressure due to cerbebral contusions and brain oedema after acute brain injury is frequently treated with hyperventilation and barbiturate infusion [1]. These are thought to reduce the intracranial pressure via constriction of the cerebral resistance vessels so causing a decrease in the blood volume. Theoretically, raised intracranial pressure should be reduced more effectively by constriction of the venous capacitance vessels as these hold a greater blood volume than the resistance vessels [2].

Dihydroergotamine is used clinically to treat orthostatic hypotension and other hypotensive states and from experiments on skeletal muscle and skin, is considered to exert its clinical effects mainly via constriction of the venous capacitance vessels [3, 4]. Provided such vascular responses also occur in the brain, administration of dihydroergotamine may transiently reduce the cerebral blood volume and so lower a raised intracranial pressure perhaps even to a greater extent than that induced by hyperventilation or by barbiturate infusion.

The hypothesis that a raised intracranial pressure may be reduced by the administration of dihydroergotamine in man was tested and confirmed in the present study. It is suggested that this may be due to an effect of reduced intracranial blood volume, predominantly on the venous side of the circulation. Experiments were also performed on the sympathectomized cat skeletal muscle in order to assess whether dihydroergotamine also may induce a slow but progressive decrease in tissue volume via the mechanism of fluid absorption due to reduced capillary pressure. This hypothesis was confirmed.

Material and methods

Studies in man

Observations were made on 6 previously healthy patients who had suffered traffic accidents with isolated severe head injuries on the basis of cerebral contusions and brain oedema. One of the patients (patient E in Table 1) also showed a small subdural haemorrhage demonstrated on the CT scan. All except two patients (patient B and E in Table 1), were simultaneously being treated with high doses of thiopental. In all cases the medical indication for treatment with dihydroergotamine was low cerebral perfusion pressure. Intracranial pressure was measured continuously via an intraventricular catheter using a Bentley transducer [5]. Dihydroergotamine (Orstanorm®,

Table 1. Individual data for the six patients. Patient C was given 2·0.25 mg i.v. and the other patients 0.25 mg i.v. of dihydroergotamine (see text). ΔICP denotes decrease in intracranial pressure

Patient	Sex	Age (years)	Days after the trauma	Thiopental treatment	ICP at control (mmHg)	ΔICP from control after 30 min (mmHg)	ΔICP from control after 120 min (mmHg)
A	F	54	2	Yes	24	9	4
B	F	13	3	No	27	16	8
C	F	20	7	Yes	53	33	3
D	F	17	5	Yes	19	10	8
E	M	60	8	No	26	14	5
F	M	22	6	Yes	24	10	4

Sandoz) was injected intravenously at a dose of 0.25 mg. The individual patient data are shown in the table.

Experiments in cats

Five cats were used, their weights ranged from 3.9 to 4.4 kg. They were anaesthetized with α-chloralose at a dose of 50 mg/kg and urethane at a dose of 100 mg/kg. The cats were breathing spontaneously via a tracheal cannula. Body temperature was kept at 38±0.5 °C and the animals were heparinized (1000 IU/kg) to prevent clotting.

The experimental set-up is illustrated in Fig. 1. In summary the right hind leg gastrocnemius muscle was isolated from the body and autoperfused from the animal via a shunt circuit placed between the femoral and the popliteal arteries. The muscle was sympathectomized in order to increase the similarity with the brain circulation. Venous blood from the region was shunted back into the animal via the right external jugular vein. The blood flow (Q) to the muscle was continuously recorded in the arterial shunt with a pressure gradient flowmeter [6]. Arterial inflow pressure (AP) and venous outflow pressure (VP) were monitored from T-tubes close to the cannulated popliteal artery and vein. Using a special cannulation technique, small venous pressure (SVP) was recorded from venous microvessels [7]. This technique involves a small cannula (internal diameter of the tip = 0.3 mm) that was inserted into the sural vein pointing in a distal direction, at a site just distal to the adjacent fat pad. Pressure from communicating vessels in the venous capillary bed were now recorded via a stagnant column of blood. A previous study from this laboratory has shown that the recorded venous micropressure is closely related to the venous capillary pressure [8]. Differential pressure transducers and electronic divider circuits permitted continuous recordings of precapillary and postcapillary vascular resistances (R_a and R_v respectively) where: $R_a = (AP-SVP)/Q$ and $R_v = (SVP-VP)/Q$ [6].

The muscle preparation, with intact vascular connections was placed in a temperature-controlled (37 °C) plethysmograph filled with Tyrode solution and sealed from the atmosphere by the skin flap as shown in Fig. 1. The plethysmograph communicated via tubing with an open water-filled reservoir located on a force transducer. Volume changes of the muscle were recorded as change of weight of the reservoir [9]. The height of the reservoir was adjusted to a level giving an isovolumetric state in the control situation. Venous pressure was kept constant at about 7 mmHg. To ensure that the recorded volume changes were not caused by variations in arterial pressure during the dihydroergotamine infusion, arterial pressure was kept constant (~110 mmHg) by adjusting a screw clamp placed around the arterial shunt.

Statistics

All results are presented as mean±SEM and the statistical significances are calculated using Student's *t*-test for paired observations.

Results

Studies in man

Original recordings of the effects of dihydroergotamine on the raised intracranial pressure in four of the six patients are shown in Fig. 2. The patients represented in panels A, B and D were given one intravenous injection of 0.25 mg of dihydroergotamine and the patient in panel C was given two injections, each of 0.25 mg, the second dose was given about 10 min

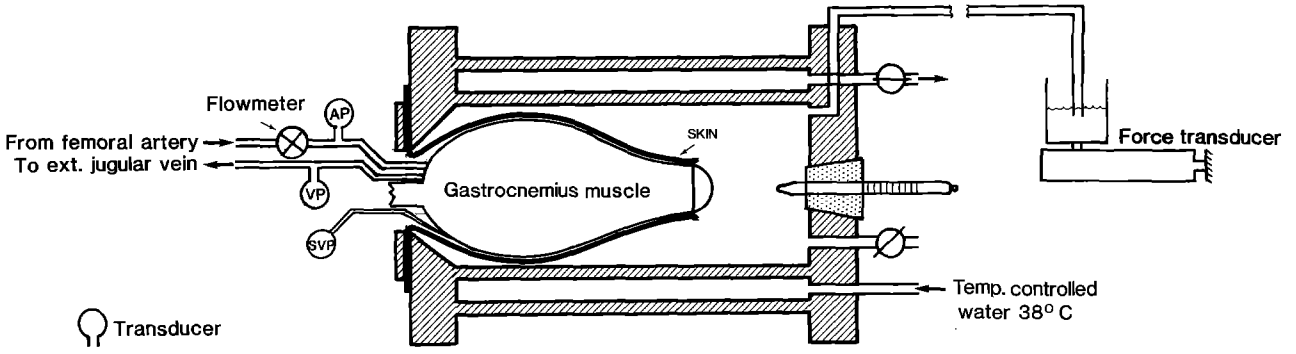

Fig. 1. The experimental set-up. The muscle is placed in a temperature-controlled plethysmograph filled with Tyrode solution. For details see text

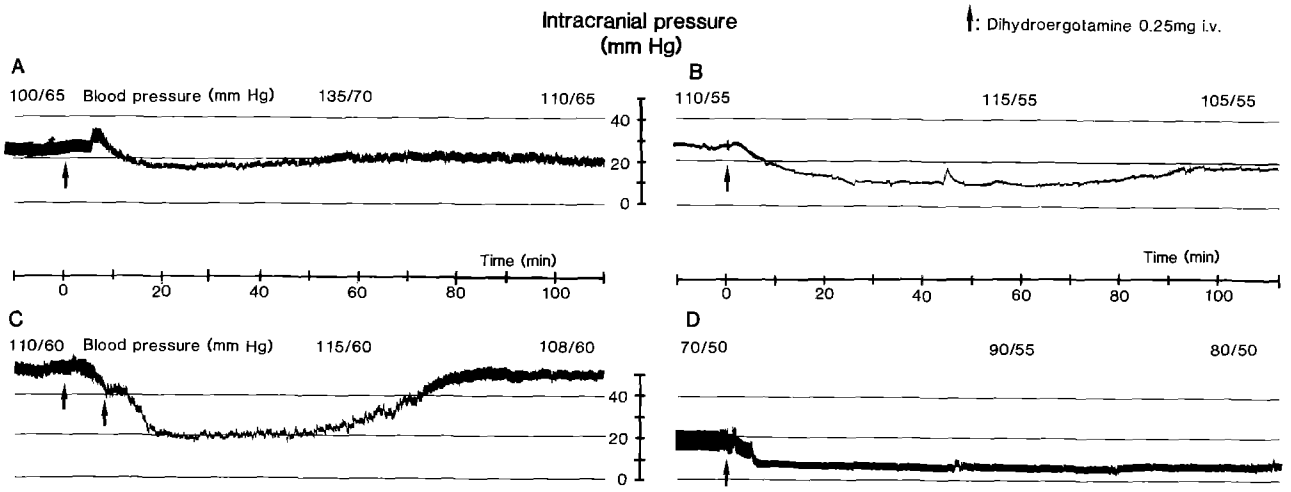

Fig. 2. The effects of dihydroergotamine on intracranial pressure in four patients (represented by *panels A, B, C* and *D*). The *panel C* patient was given two doses and the other patients one dose of the drug. Notice the marked decrease in intracranial pressure in all patients despite an increase in perfusion pressure. For details see text

after the first one. The patients represented in panels A, B and C were simultaneously being treated with a continuous high infusion rate of thiopental in order to cause a 'burst suppression pattern' on the EEG [10]. The patient in panel D had previously been treated with thiopental but this treatment had been discontinued 3.5 days earlier.

As seen from Fig. 2 the intracranial pressure began to fall 3–5 min following the injection, after a small and transient increase in intracranial pressure. Arterial pressure, as expected, increased simultaneously in all patients though more markedly in patient A. The patterns of response were similar for the two patients not illustrated in Fig. 2. Individual data for all the six patients are presented in the table. The mean intracranial pressure fell from 24±2 mmHg by as much as 12±1 mmHg, for the five patients given a single dose of dihydroergotamine and remained at a low level for 35–70 min (mean ≈ 40 min), followed by a slow return towards the pretreatment levels, but stabilizing at a mean level 5±1 mmHg below the initial one. In patient C, who was given two doses of dihydroergotamine, the intracranial pressure fell by 33 mmHg, but the pretreatment level was extremely high at 53 mmHg.

Whether a single dose of dihydroergotamine is beneficial for this category of patients cannot be determined from the present study. Note, however, that the intracranial pressure in patient B, which was recorded at greater than 25 mmHg before the administration of dihydroergotamine, never exceeded 20 mmHg following treatment.

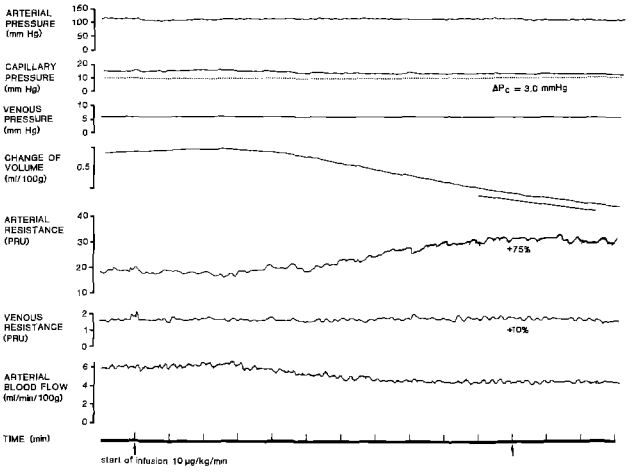

Fig. 3. An original recording of the effects of a continuous intraarterial dihydroergotamine infusion on circulatory parameters (listed as ordinates). Notice the marked increase in arterial resistance and decrease in venous capillary pressure as well as the simultaneous and continuous decrease in muscle volume. Calculations are made during steady-state (> 10 min after start of the infusion), marked on the figure by an *arrow* on the time scale

Experiments in cats

Original recordings from one of the experiments showing the 7 circulatory parameters, arterial pressure, venous capillary pressure, venous pressure, change of muscle volume, arterial resistance, venous resistance and arterial blood flow are shown in Fig. 3. About 3 min after start of the continuous intraarterial infusion of dihydroergotamine (10 µg/kg/min) the arterial resistance (R_a) and the venous resistance (R_v) starts to increase. There is a relatively greater increase in R_a than R_v, which causes a fall in the venous capillary pressure and absorption of fluid from tissue to blood occurs. During steady-state, reached within 10 min of commencing the infusion, R_a increased by about 75%

and R_v by only 10% producing a fall in venous capillary pressure (P_c) of 3.0 mmHg and an absorption rate of 0.04 ml/min/100 g.

The averaged results from five such animal experiments are shown in Fig. 4. Panel A shows the relative changes in pre- and postcapillary resistances, panel B shows changes in venous capillary pressure and panel C shows the muscle volume changes. All the parameters were measured >10 min after the start of the dihydroergotamine infusion. Arterial resistance (R_a) increased on average by 47±8% and venous resistance (R_v) by 9±4% (panel A). Capillary pressure was significantly reduced, by 2.8±0.4 mmHg (panel B) giving an absorption rate of 0.037±0.007 ml/min/100 g (panel C). The tissue volume change can be classified as a change in net transcapillary fluid flux or a change in regional blood content (capacitance response). As the calculations in these experiments are made during steady-state conditions (>10 min after start of the drug infusion) they represent only transcapillary fluid fluxes since the capacitance response will be seen only in the initial period of the infusion [2].

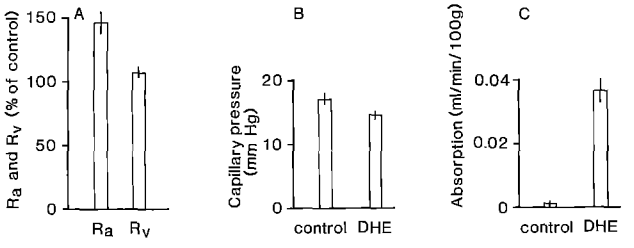

Fig. 4. Averaged data from 5 experiments are shown. The calculations are made about 10 min after start of the infusion. *Panel A* shows relative changes of precapillary resistance (R_a) and postcapillary resistance (R_v), *panel B* shows changes of venous hydrostatic capillary pressure ($p<0.025$), and *panel C* the net transcapillary absorption rate during an intra arterial infusion of dihydroergotamine (DHE). All data displayed as mean±SEM

Discussion

From the present study it is clear that dihydroergotamine lowers raised intracranial pressure in man, despite a simultaneous increase in arterial perfusion pressure.

The literature on the subject of the cerebral vascular effects of dihydroergotamine is sparse and there are only a few studies dealing with the effects of dihydroergotamine on cerebral blood flow [11, 12]. The present study is the first to analyse the effects of dihydroergotamine on intracranial pressure in man. Possible mechanisms of action of dihydroergotamine on the intracranial pressure certainly cannot be established from these human studies nor can the effects of dihydroergotamine on cat skeletal muscle directly be applied to the cerebral circulation. The observed patterns of response of the raised intracranial pressure after one intravenous injection of dihydroergotamine, however, are similar to those which might be predicted from the vascular effects of dihydroergotamine on the skeletal muscle. Although there are some differences, there are also similarities between vascular control in the brain and in the sympathectomized skeletal muscle. Both have a high basal vascular tone at rest and an effective autoregulatory capacity. The adrenergic influence is slight and myogenic and metabolic control are important mechanisms for local vascular regulation in both tissues [2, 16]. It is therefore suggested that skeletal muscle experiments in this specific situation may well be a reliable tool, providing a tentative explanation for the effect of dihydroergotamine on raised intracranial pressure.

Our knowledge of the vascular effects of dihydroergotamine arises mainly from studies on skeletal muscle and skin in man and animals [3, 4], from which it has been proposed that dihydroergotamine exerts its circulatory effects predominantly via constriction of the venous capacitance vessels. The present cat experiments on the autoperfused vascular bed, however, clearly show that intraarterial infusions of dihydroergotamine also induce vasoconstriction in the resistance vessels in the sympathectomized skeletal muscle. This increase in resistance is more pronounced on the arterial side (Fig. 4A) which will reduce the capillary hydrostatic pressure (Fig. 4B) and induce a net transcapillary fluid movement from tissue to blood (Fig. 4C).

The effects of dihydroergotamine on the intracranial pressure as illustrated in Fig. 2 are in agreement with the hypothesis that dihydroergotamine reduces both the intracranial blood and tissue volume, analogous to the effects seen in skeletal muscle. The initial pressure decrease, which may be an effect of a reduced blood volume, starts 3—5 min after the injection, a time delay which is also seen in the skeletal muscle experiments. This pressure decrease lasts for about 35–70 min, a reasonable time on the basis of the half-clearance time of the drug [4]. After clearance of the drug the intracranial pressure stabilizes at a level below the initial one, indicating a reduction of the brain oedema.

From a theoretical point of view the use of a combination of these two physiological mechanisms seems to be ideal when treating raised intracranial pressure: one 'protective' mechanism inducing a fast and powerful pressure decrease to prevent further damage of brain tissue due to the increased intracranial pressure per se and a 'treating' mechanism which induces a simultaneous but slower reduction of brain oedema. It can be argued, however, that transcapillary absorption in the brain is unlikely to be due to the very low

capillary permeability in this tissue compared to skeletal muscle. Certainly this is the case in the normal brain, but there is much data to suggest that the capillary permeability is markedly increased after head trauma with damage of the blood-brain barrier [14].

According to the studies previously mentioned [11, 12], the cerebral blood flow is unaltered by dihydroergotamine, indicating that the vasconstrictor effect of this drug on cerebral blood flow is counteracted by the simultaneous increase in arterial blood pressure. This also indicates that the nutritional state of the brain is not significantly altered.

The mode of action of dihydroergotamine on smooth muscle is still unclear in spite of thorough analysis [15]. Dihydroergotamine seems to exert its local vasoconstrictor influence via a direct excitatory effect on the vascular smooth muscle, perhaps mediated through stimulation of 5-HT and alpha receptors [4].

This type of comparative analysis between different tissues, if made with caution, can be a useful instrument to explain phenomena which are diffficult or impossible to analyse directly. We are reduced to this type of comparative study for detailed analysis of cerebral vascular control as no other organ of the body is less adapated to experimental study of its circulation than the brain [16].

This study suggests that dihydroergotamine is a drug which can reduce raised intracranial pressure. Further studies are required to precisely define the mechanisms behind this effect and before dihydroergotamine is used clinically for the treatment of raised intracranial pressure.

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