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Cerebral Vasoconstriction by Indomethacin in Intracranial Hypertension

An Experimental Investigation in Pigs

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Background: **Uncontrolled increase in intracranial pressure is the most significant cause of mortality in patients with severe traumatic brain lesions, and the efficacy of common nonsurgical treatments has been questioned. Pharmacologically induced cerebral vasoconstriction aiming at a decrease of cerebral blood volume and brain edema has recently been suggested as an alternative. Limited clinical experience with indomethacin as a cerebral vasoconstrictor has been reported but dose- or concentration-effect relationships were not investigated. In particular, there is a lack of data showing whether a therapeutic window exists in which risk of cerebral ischemia is minimized.**

Methods: **In a porcine model of intracranial hypertension induced with two epidural balloons to a level of 26–28 mmHg, 18 animals were randomized into three groups receiving 0.1, 0.3, and 3.0 $mg \cdot kg^{-1} \cdot h^{-1}$ indomethacin, respectively, as an infusion during 80 min. Intracranial pressure, mean arterial blood pressure, and electrocortical activity were recorded continuously and measurements of cerebral blood flow, arteriovenous difference in oxygen content and cerebral venous pH were performed at 5, 20, 40, 60, and 75 min during and 10 min after the indomethacin infusion. Baseline measurements, performed before the indomethacin infusion, were used as an internal control. The infusions were pharmacokinetically designed to mimic the reported clinical conditions.**

Results: **An 11% mean decrease in intracranial pressure during the infusion, but no effects on cerebral blood flow, arteriovenous difference in oxygen content, venous pH, and electrocortical activity were observed in the group of animals receiving 0.1 $mg \cdot kg^{-1} \cdot h^{-1}$. When the rate of infusion was 0.3 and 3.0 $mg \cdot kg^{-1} \cdot h^{-1}$, the decrease in intracranial pressure was 20 and 25%, respectively, but this was accompanied by a decrease in cerebral blood flow and venous pH, an increase in arteriovenous difference in oxygen content, and a slowing of the electrocortical activity. All changes were statistically significant.**

Conclusions: **Indomethacin, which is known to constrict precapillary resistance vessels, caused a decrease in intracranial pressure during experimental intracranial hypertension. This was accompanied by signs of cerebral ischemia when indomethacin was used in a dose that has previously been suggested for the treatment of increased intracranial pressure in patients. (Key words: Analgesics, nonsteroidal: indomethacin. Brain: cerebral blood flow; cerebral ischemia; intracranial pressure. Monitoring: electroencephalogram. Species: pigs.)**

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AN uncontrollable increase in intracranial pressure (ICP) is the final common pathway in many serious intracranial conditions and the main cause of death in patients with severe head injuries.[1,2] Increased ICP always implies a volume expanding process within the rigid skull cavity and therapy must aim to reduce one or more of the intracranial volumes. Because in many cases surgical evacuation or drainage of cerebrospinal fluid is insufficient, other means to reduce intracranial volume must be taken.

Controlled hyperventilation is commonly used to treat patients with increased ICP. During physiologic conditions, hyperventilation rapidly induces cerebrovascular vasoconstriction with a concomitant reduction of intracranial blood volume and ICP.[3,4] However, this treatment is of limited value: patients with severe head

injuries may have an impaired or abolished cerebrovascular reactivity to changes in Pa_{CO_2},[5–7] the effects of hyperventilation appear to be relatively short lasting[8,9] and adverse effects of short-term as well as prolonged hyperventilation have been reported.[10,11] The efficacy of therapies that primarily aim at reducing cerebral water content (corticosteroids, osmotherapy) has also been questioned.[12,13]

Increased ICP can be counteracted by pharmacologic vasoconstriction.[14,15] This therapy may also be effective in patients with impaired cerebrovascular reactivity to changes in Pa_{CO_2}, and the effects may be long lasting. However, the risk for adverse effects of pharmacologic vasoconstriction may be greater than when hyperventilation is employed. We previously presented experimental[16] and clinical[17] data showing that dihydroergotamine (DHE) reduces increased ICP.

Indomethacin causes cerebral vasoconstriction in animals[18,19] and humans[20] and may therefore be potentially useful for the treatment of increased ICP. In a limited number of patients with uncontrollable intracranial hypertension, a continuous infusion of indomethacin reduced ICP to less than 20 mmHg for the duration of the treatment.[15] It was not clear, however, whether the chosen dose of indomethacin was the optimal one, or whether a dose-response relationship can be established for this action of indomethacin on the cerebral circulation. The current series of experiments was performed to explore the effects of three infusion rates of indomethacin on cerebral hemodynamics and energy metabolism during intracranial hypertension. The experimental model has recently been shown to produce steady-state conditions of cerebral physiologic parameters during the time needed for the current experiments.[21] To closely mimic the reported clinical conditions[15] in the pig model, the pharmacokinetics of indomethacin in the pig were briefly explored and infusion schedules were designed that would cause similar exposure of the porcine brains as that of the patients' brains to active concentrations of the drug.

Material and Methods

The experiments were performed at the Department for Experimental research, Malmö University Hospital, Malmö, Sweden after obtaining approval of the Ethics Committee for Animal Studies of Lund University.

Eighteen pigs (plus 1 in a pilot study, see Appendix) of Swedish mixed domestic breed weighing an average of 20.3 kg were included in the study. The animals had free access to water but were fasted from food for 24 h before the experiments. The anesthetic procedures and surgical preparations have been described in detail previously.[21] Briefly, the pigs received 7.5 mg midazolam intramuscularly 20 min before anesthetic induction with 100 mg propofol and 1.0 mg fentanyl. After tracheal intubation, the lungs were ventilated to normocapnia with 70% N_2O in oxygen. Anesthesia was continued with infusion of fentanyl (0.1 $mg \cdot kg^{-1} \cdot h$ during the preparations, then decreased to 0.0 $mg \cdot kg^{-1} \cdot h^{-1}$), and neuromuscular blockade was achieved with 10 mg intravenous alcuronium followed by infusion of 0.6 $mg \cdot kg^{-1} \cdot h^{-1}$. Repeated measurements of blood gases (Pa_{O_2}, Pa_{CO_2}) were performed to adjust the level of ventilation.

A branch of the femoral artery was catheterized for blood sampling and pressure recordings. Cerebrovenous blood was obtained *via* retrograde cannulation of the right internal jugular vein with the tip of the catheter at the base of the skull.[21] Cervical tributaries were ligated. For injection of isotope (^{133}Xe) for cerebral blood flow (CBF) measurements, a catheter was placed in the right common carotid artery with the tip proximal to the carotid bifurcation. The external carotid artery and the occipital artery were ligated to avoid extracranial isotope accumulation.

Parietal burr holes were drilled bilaterally and balloons were inserted extradurally, covering a major part of the parietal region.[21] A microtransducer for ICP monitoring was introduced 5 mm into the brain parenchyma of the right occipital lobe through a separate burr hole.[22]

Measurements

Cerebral blood flow was measured after injection of 2–4 MBq (54–108 μCi) ^{133}Xe dissolved in 0.1–0.2 ml isotonic saline into the internal carotid artery followed by a flush of 1.2 ml saline. Clearance of the tracer substance was measured by an extracranial lead-shielded NaI scintillation detector (Novo Cerebrograph 10a, Randers, Denmark) and cerebral arteriovenous oxygen difference (Cav_{O_2}) was calculated from the blood hemoglobin concentration and from arterial and internal jugular vein oxygen tensions and saturations.[23] Cerebral venous pH (vpH) was measured in blood sampled from the internal jugular vein. Cerebrovascular resistance (CVR) was calculated as CVR = (mean arterial blood pressure [MAP] − ICP)/CBF.

Bipolar electrocortical activity (EEG) was recorded with two pairs of electrodes inserted subcutaneously in the frontal and occipital regions. The signals were recorded (high pass filter: 0.5 Hz; low pass filter 30 Hz) *via* an analog-digital converter (PCM-2 A/D VCR, Adaptor, Medical Systems Corp., Greenvale, NY) and a compressed spectral array program was used for computerized fast Fourier transform analyses (sampling frequency: 64 Hz), using a Biologic Brain Atlas III system (Biologic Systems Corp., Mundelein, IL) over 2-min periods corresponding to the CBF measurements. Absolute and relative amplitudes of δ (0.5–3.75 Hz), τ (4–7.75 Hz), α (8–12.75 Hz), $\beta 1$ (13–23.75 Hz), and $\beta 2$ (24–31.75 Hz) bands were computed. Increase in δ activity and decreases in the sum of α, $\beta 1$, and $\beta 2$ activities[24,25] were used as indicators of cerebral ischemia.

Experimental Design

The experimental protocol is illustrated in figure 1. Approximately 3.5 h after induction of anesthesia, CBF was measured during normocapnia (38 mmHg) as well as hyperventilation (30 mmHg) (measurements 1 and 2) to investigate whether cerebral vasoreactivity was preserved before ICP was increased. Intracranial pressure was then increased by incremental injections of in total approximately 3.5 ml of saline into each epidural balloon over a period of 45–55 min until a steady-state concentration was established,[21] after which a new set of measurements (measurement 3) was performed. Infusion of indomethacin was then started at a constant rate and maintained for 80 min, during which ICP was recorded every 10 min and CBF and Cav_{O_2} were measured at 5, 20, 40, and 60 min after start of the infusion (measurements 4–7). At 75 min, another set of measurements was performed during hyperventilation (measurement 8). Ten minutes after the end of indomethacin infusion the final measurements were performed (measurement 9). Controlled ventilation was maintained for another 50 min during which ICP was continuously monitored. The animals were then killed with an overdose of pentobarbital, and correct position of the catheters was verified at necropsy.

Infusion Rates of Indomethacin

The pigs were randomized to receive either 0.1, 0.3, or 3.0 $mg \cdot kg^{-1} \cdot h^{-1}$ (low, medium, and high infusion rates, respectively) indomethacin during an 80-min infusion period. The pharmacokinetic rationale for this dosing is given in the Appendix. Indomethacin (Confortid, Dumex, Helsingborg, Sweden) was diluted in physiologic saline and infused into a superficial vein of a hind leg by means of a syringe pump. The actual rate of each infusion was determined by assay of the solution and weighing of the syringe before and after the infusion. Arterial blood samples for determination of the indomethacin plasma concentration were drawn before the infusion and at 2, 5, 10, 20, 30, 40, 50, 60, 70, 80, and 90 min.

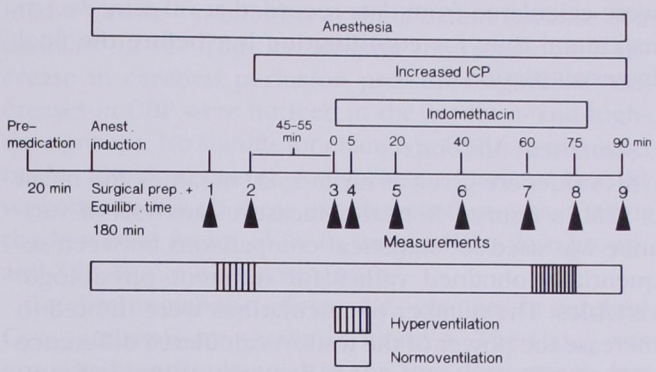

Fig. 1. Summary of the experimental protocol. After evaluation of the cerebral vasoreactivity to hyperventilation (measurements 1 + 2) and induction of increased ICP, a control measurement was performed (measurement 3). After start of the indomethacin infusion, repeated measurements were performed after 5, 20, 40, and 60 min (measurements 4 – 7). Measurement 8 was made to evaluate cerebral CO_2 reactivity during increased ICP. Ten minutes after termination of the infusion, measurement 9 was performed.

Assay of Indomethacin

Indomethacin was assayed in the plasma samples by high-performance liquid chromatography,[26] using diclofenac as the internal standard and ultraviolet UV detection at 260 nm. The within-day coefficient of variation was 5.4% at 0.026 μg/ml, 1.1% at 0.11 μg/ml, and 0.8% at 3.0 μg/ml (n = 8 in all cases). The between-day coefficient of variation was 1.5% at 0.10 μg/ml (n = 6) and 3.8% at 1.0 μg/ml (n = 11).

The unbound fraction (f_u) of indomethacin in porcine plasma was determined by equilibrium dialysis against isotonic phosphate buffer, pH 7.4, with 8 h incubation at 37°C. Assay of the plasma and dialysate was by high-performance liquid chromatography. Duplicate determinations were performed on plasma from four different pigs, spiked to 1.0 and 10 μg/ml. For comparison, f_u was also determined in plasma from six human volunteer donors, spiked to 10 μg/ml of indomethacin.

Concentration-effect relationships for the action of indomethacin on ICP, Cav_{O_2}, vpH, and EEG parameters

were calculated from data recorded at 60 min, *i.e.*, at maximum time for equilibration but before the final hyperventilation.

Statistical Methods

All values are given as mean ± SD in tables and mean ± SEM in figures. Repeated-measures analysis of variance was used for statistical comparisons between sequentially obtained values for different physiologic variables. The number of calculations were limited to increase the power of the tests. A calculated difference of $P < 0.05$ was considered to be statistically significant.

Results

The total clearance of indomethacin in the pilot experiment (Appendix) was 13.7 ml · min^{-1} · kg^{-1} and the estimated terminal half-life was 17 min. The steady-state plasma concentration (C_{ss}) of indomethacin was 0.078 ± 0.018 μg/ml in the low infusion rate group, 0.28 ± 0.05 μg/ml in the medium infusion rate group, and 2.95 ± 0.47 μg/ml in the high infusion rate group of pigs. On the average, 88% of C_{ss} had been reached by 40 min of infusion. The calculated steady-state clearance was 16.9 ± 4.0 ml · min^{-1} · kg^{-1}, with no difference between the three groups of pigs. The f_u of indomethacin in porcine plasma was 2.9 ± 0.3% at 1 μg/ml and 3.4 ± 0.6% at 10 μg/ml total concentration, and in human plasma 0.46 ± 0.07% at 10 μg/ml. Using the f_u value of 2.9%, the mean C_{ss} of unbound indomethacin consequently would be 0.0022 ± 0.0005 μg/ml, 0.0082 ± 0.0013 μg/ml, and 0.086 ± 0.014 μg/ml in the three groups.

After surgical preparation and equilibration time (measurement 1) CBF was 49 ± 3 ml · 100 g^{-1} · min^{-1}, Cav_{O_2} 3.1 ± 0.6 ml · 100ml^{-1}, and CVR 2.0 ± 0.3 mmHg · 100g^{-1} · min^{-1} · ml^{-1} with no differences among the three experimental groups. During the hyperventilation test before infusion of indomethacin, all animals showed a decrease in CBF (43 ± 3 ml · 100 g^{-1} · min^{-1}) and increases in Cav_{O_2} (3.7 ± 0.7 ml · 100 ml^{-1}) and CVR (2.3 ± 0.3 mmHg · 100 g^{-1} · min^{-1} · ml^{-1}). No differences were observed among the three experimental groups. During the second hyperventilation test (measurement 8), the increase in ventilation produced only a slight decrease in ICP, and CBF and Cav_{O_2} remained virtually unchanged, indicating an impaired cerebral vasoreactivity to changes in p_{CO_2} (figs. 2–4).

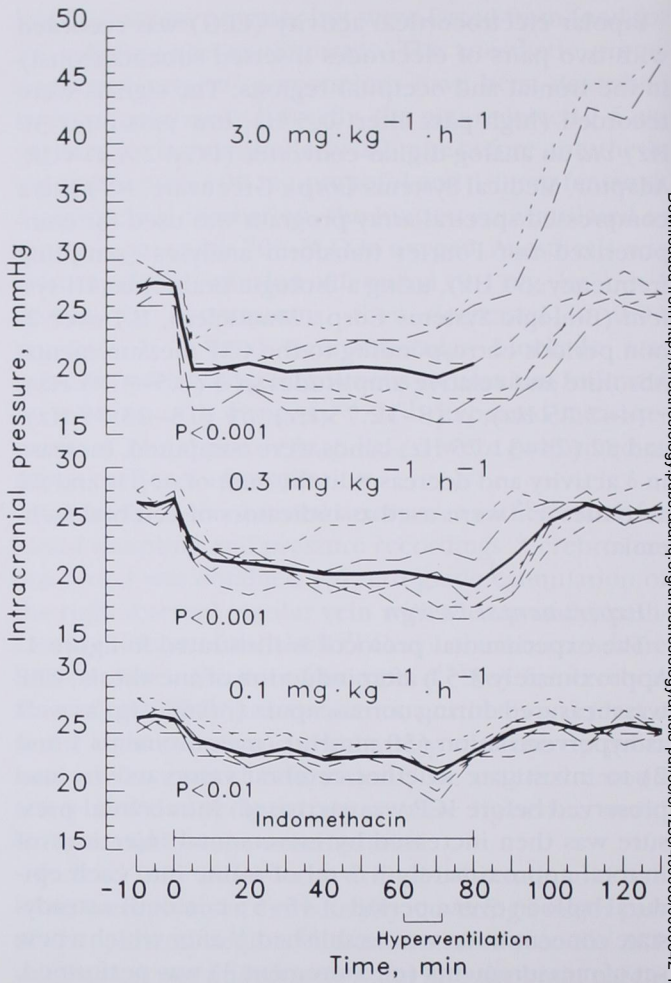

Fig. 2. Effects of three different infusion rates of indomethacin (0.1, 0.3, and 3.0 mg · kg^{-1} · h^{-1}) on intracranial pressure after induction of intracranial hypertension in 18 anesthetized pigs. The heavy lines are the mean curves. The *P* values refer to the effects of the treatment between 0 and 60 min evaluated by repeated-measures analysis of variance.

Figure 2 shows ICPs in the three groups of animals before and during continuous infusion of indomethacin and up to 50 min after the end of infusion. The decrease in ICP was significant in all groups. The initial decrease (at 5 min) was 6% in the low-dose group, 15% in the medium-dose group, and 26% in the high-dose group. The mean decrease in ICP during the entire period was 11%, 20%, and 25%, in the three groups, respectively. After termination of the indomethacin infusion, ICP increased and reached the baseline level within 30 min in all but two pigs. In these animals in the high infusion rate group, ICP continued to increase and after 50 min reached 48 and 47 mmHg, respectively.

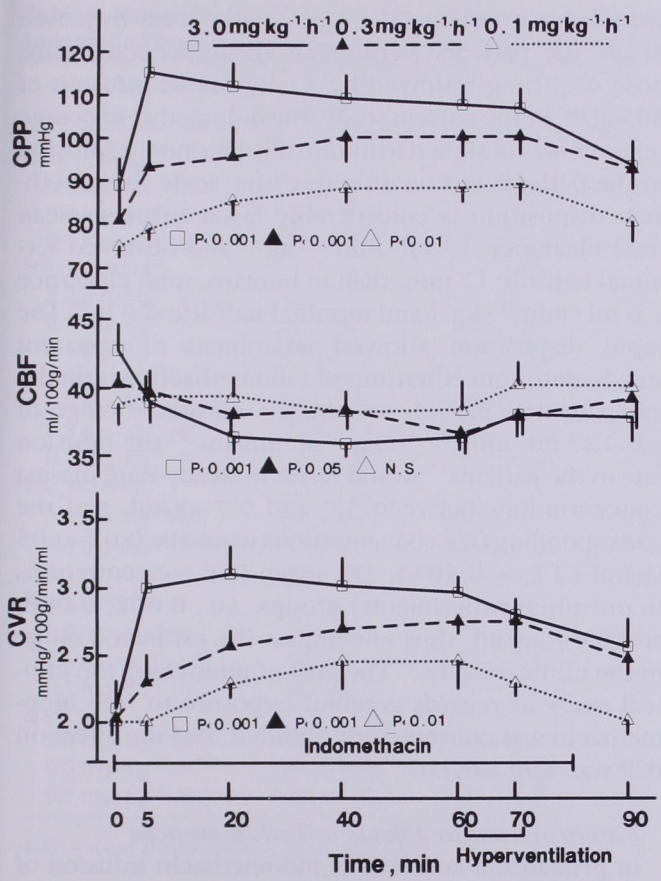

Fig. 3. Effects of three different infusion rates of indomethacin (0.1, 0.3, and 3.0 mg · kg^{-1} · h^{-1}) on cerebral perfusion pressure, cerebral blood flow, and cerebral vascular resistance in 18 anesthetized pigs with induced intracranial hypertension. The *P* values refer to the effects of the treatment between 0 and 60 min, evaluated by repeated-measures analysis of variance.

Systemic physiologic variables are given in table 1. During baseline conditions (measurement 3), no important differences were noted among the three groups of animals. In all groups, infusion of indomethacin was accompanied by a significant increase in MAP. No changes in rectal temperature, arterial Pa_{O_2}, Pa_{CO_2} or pH occurred during the indomethacin infusion. A slight increase in heart rate was observed in the high-dose group.

The effects of indomethacin on cerebral perfusion pressure, CBF, and CVR are shown in figure 3. During baseline conditions (measurement 3) no significant differences were noted among the three experimental groups. During indomethacin infusion, a significant and concentration-related increase in cerebral perfusion pressure was obtained, mainly because of an increase in MAP (table 1), but also to some extent because of a decrease in ICP (fig. 2). Despite the pronounced increase in cerebral perfusion pressure, significant decreases in CBF were noticed in the medium- and high-dose groups. No significant change in CBF was obtained in the low-dose group. A significant increase in CVR was obtained in all three experimental groups: 19% in the low-dose group, 27% in the medium-dose group, and 32% in the high-dose group.

Cerebral metabolic effects, *i.e.*, changes in cerebral Cav_{O_2} and vpH are shown in figure 4. The Cav_{O_2} was not significantly changed in the low-dose group, but in the medium- and high-dose groups the increases in Cav_{O_2} were highly significant. Significant decrease in vpH also occurred in these two groups.

Further indications of the cerebral metabolic effects of indomethacin were obtained from the computerized analysis of the EEG changes (fig. 5). The percent changes in voltage were calculated for low (δ; fig. 5A) and summed high (α-, β1, and β2; fig. 5B) frequencies. The observed changes were not significant in the low infusion rate group, but significant decrease in high frequencies were observed in the medium infusion rate group, and a significant decrease in high frequencies as well as an increase in δ voltage were found in the high infusion rate group.

Figure 6 summarizes the effects of three infusion rates of indomethacin on the percent changes in ICP, Cav_{O_2}, venous hydrogen ion activity and high and low EEG frequencies. The figure illustrates that with indomethacin treatment of increased ICP no "therapeutic window" could be found, *i.e.* when an effect was observed on ICP there were simultaneous changes indicating cerebral ischemia.

Discussion

This study explored the effects and the potential risks of cerebral vasoconstriction induced by three different infusion rates of indomethacin during increased ICP. Following is a discussion of (1) the relevance of the experimental model; (2) the possible mechanisms underlying the cerebrovascular effects of indomethacin; (3) the observed effects of indomethacin in the current experimental situation; and (4) the effects of indomethacin during intracranial hypertension as compared to the effects induced by dihydroergotamine.

The Experimental Model

Recent clinical experience indicates that conventional nonsurgical therapies of increased ICP are inef-

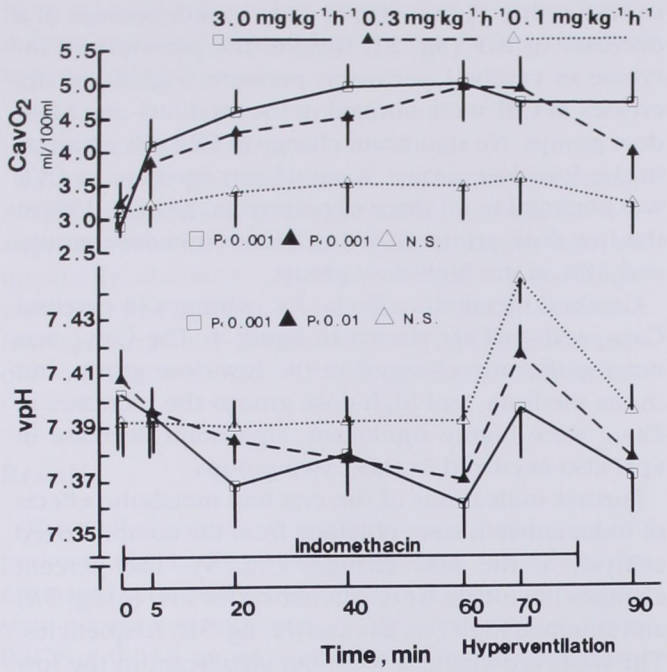

Fig. 4. Effects of three different infusion rates of indomethacin (0.1, 0.3, and 3.0 mg · kg^{-1} · h^{-1}) on cerebral arteriovenous difference in blood oxygen content and jugular venous pH in 18 anesthetized pigs with induced intracranial hypertension. The *P* values refer to the effects of the treatment between 0 and 60 min, evaluated by repeated-measures analysis of variance.

fective in patients with cerebral vasoparalysis (as indicated by an impaired cerebral CO_2-vasoreactivity)[27,28] and that the prognosis for these patients is very poor.[7] We have previously shown that the current model provides the possibility of increasing ICP to a level that is generally considered dangerous, *i.e.*, >20 mmHg, producing stable physiologic parameters during the experimental time period necessary for evaluation of a pharmacologic treatment, and producing a brain lesion characterized by an impaired or abolished cerebral vascular CO_2 reactivity. Some differences between this experimental situation and the clinical situation do, however, exist. Under clinical conditions, focal intracranial mass lesions are rapidly evacuated and any subsequent elevation of ICP is generally caused by brain edema. Although it might be possible to experimentally mimic this clinical situation, it would have been difficult to obtain the steady-state conditions for ICP and other physiologic parameters necessary for the current study. The discrepancy should, however, be kept in mind.

Indomethacin has been used for the treatment of patients with posttraumatic intracranial hypertension resistant to conventional therapy.[15] In the study by Jensen *et al.*, the patients were given an intravenous bolus dose of 30 mg followed by a continuous infusion of 30 mg/h. In the current study, the indomethacin dosage regimen was designed to mimic the continuous infusion in the patients but on a shorter time scale. Indomethacin disposition is considerably faster in pigs, mean total clearance 17 ml · min^{-1} · kg^{-1} and observed terminal half-life 17 min, than in humans, total clearance 1.6 ml · min^{-1} · kg^{-1} and terminal half-life 6.0 h.[29] The rapid disposition allowed attainment of apparent steady-state concentrations of indomethacin within the experimental period. Assuming a clearance range of 51–127 ml · min^{-1} · 70 kg^{-1} in humans,[29] the infusion rate in the patients[15] would result in steady-state plasma concentrations between 3.9 and 9.7 μg/ml, and the corresponding free concentrations would be 0.02–0.05 μg/ml (if f_u = 0.46%). The mean free concentrations in our three experimental groups, *i.e.*, 0.002, 0.008, and 0.09 μg/ml, thus encompass the estimated range in the clinical study.[15] The goal of mimicking the clinical study as regards cerebral exposure to free indomethacin was consequently fulfilled, and the effect on ICP was very similar.

Cerebrovascular Effects of Indomethacin

In primates, a continuous indomethacin infusion of 0.2 mg · kg^{-1} · min^{-1} was found to reduce CBF by approximately 40% and the cerebrovascular CO_2 reactivity by 80%.[18] Similar effects have also been observed in humans, nonhuman primates, dogs, and rats whereas some uncertainty remains regarding the effects in cats and rabbits.[19] Although the measurements in the current were not performed during normal physiologic conditions, our results indicate that indomethacin induces cerebral vasoconstriction also in the pig.

The decrease in hyperemia induced by indomethacin during hypercapnia appears to be quite specific to this situation. Thus, it has been shown that indomethacin has no effect on cerebral autoregulation[30] or on the hyperemia caused by hypoxia,[31] hypoglycemia,[32] bicuculline induced seizures,[33] or by transient cerebral ischemia.[34] Because indomethacin is a cyclooxygenase inhibitor it has been speculated that the hypercapnic vasodilation is caused by the release of some eicosanoid whose synthesis is blocked by indomethacin. Currently, there is no direct evidence that hypercapnia is associated with altered prostaglandin production.[19] The cerebral hemodynamic effects of indomethacin are not shared by other cyclooxygenase inhibitors such as ibu-

Table 1. Values for Systemic Physiologic Parameters during Administration of Three Different Infusion Rates of Indomethacin (0.1, 0.3, and 3.0 mg·kg^{-1}·h^{-1}) in 18 Normoventilated Pigs with Induced Intracranial Hypertension

	Baseline	5 min	20 min	40 min	60 min	*P* values	10 min after indomethacin
MAP (mmHg)							
3.0 mg·kg^{-1}·h^{-1}	114 ± 14	136 ± 15	133 ± 15	129 ± 17	126 ± 15	<0.001	116 ± 14
0.3 mg·kg^{-1}·h^{-1}	110 ± 18	116 ± 20	118 ± 19	121 ± 17	121 ± 16	<0.001	99 ± 49
0.1 mg·kg^{-1}·h^{-1}	102 ± 8	104 ± 8	110 ± 10	111 ± 10	110 ± 9	<0.01	105 ± 10
HR (beats/min)							
3.0 mg·kg^{-1}·h^{-1}	159 ± 20	148 ± 28	151 ± 27	163 ± 21	169 ± 15	—	174 ± 14
0.3 mg·kg^{-1}·h^{-1}	165 ± 28	162 ± 27	158 ± 23	170 ± 21	174 ± 22	—	180 ± 12
0.1 mg·kg^{-1}·h^{-1}	168 ± 23	166 ± 26	164 ± 27	164 ± 28	164 ± 27	—	165 ± 23
Temperature (°C)							
3.0 mg·kg^{-1}·h^{-1}	38.0 ± 0.6	38.1 ± 0.5	38.1 ± 0.5	38.1 ± 0.5	38.1 ± 0.5	—	38.1 ± 0.5
0.3 mg·kg^{-1}·h^{-1}	38.0 ± 0.5	38.0 ± 0.6	38.0 ± 0.6	38.0 ± 0.5	38.0 ± 0.5	—	38.0 ± 0.5
0.1 mg·kg^{-1}·h^{-1}	37.5 ± 0.3	37.5 ± 0.3	37.5 ± 0.3	37.5 ± 0.4	37.5 ± 0.4	—	37.5 ± 0.4
Pa_{O_2} (mmHg)							
3.0 mg·kg^{-1}·h^{-1}	116 ± 8	115 ± 12	113 ± 11	113 ± 11	113 ± 9	—	113 ± 9
0.3 mg·kg^{-1}·h^{-1}	117 ± 5	115 ± 7	113 ± 8	113 ± 10	114 ± 7	—	115 ± 4
0.1 mg·kg^{-1}·h^{-1}	107 ± 8	105 ± 8	107 ± 8	107 ± 6	108 ± 7	—	108 ± 6
Pa_{CO_2} (mmHg)							
3.0 mg·kg^{-1}·h^{-1}	38 ± 1	38 ± 1	39 ± 1	39 ± 1	39 ± 1	—	38 ± 1
0.3 mg·kg^{-1}·h^{-1}	38 ± 1	37 ± 1	38 ± 1	38 ± 1	38 ± 1	—	38 ± 1
0.1 mg·kg^{-1}·h^{-1}	38 ± 1	38 ± 2	38 ± 1	38 ± 1	38 ± 1	—	38 ± 1
apH							
3.0 mg·kg^{-1}·h^{-1}	7.46 ± 0.03	7.46 ± 0.03	7.44 ± 0.03	7.45 ± 0.02	7.45 ± 0.04	—	7.45 ± 0.03
0.3 mg·kg^{-1}·h^{-1}	7.45 ± 0.02	7.46 ± 0.01	7.45 ± 0.03	7.45 ± 0.02	7.44 ± 0.02	—	7.45 ± 0.02
0.1 mg·kg^{-1}·h^{-1}	7.43 ± 0.01	7.43 ± 0.02	7.43 ± 0.02	7.43 ± 0.02	7.44 ± 0.01	—	7.44 ± 0.02

MAP = mean arterial pressure; HR = heart rate.

profen, diclofenac, naproxen, or sodium salicylate.[19] It is also apparent from our data as well as those of others[18] that the effect of indomethacin on ICP and CBF is very rapid in onset and dissipation, closely following the plasma concentration curve. This suggests a direct, reversible drug effect rather than a biochemical modulation such as cyclooxygenase inhibition. In the current study it is possible that the impaired CO_2 reactivity during the last hyperventilation test (measurement 8) was partly caused by the effects of indomethacin. However, it should be emphasized that in our experimental model CO_2 reactivity is impaired also when no drug is given.[21]

Effects of Indomethacin during Intracranial Hypertension

In the medium and high infusion rate groups, a rapid and pronounced decrease in ICP was observed after start of indomethacin infusion whereas the decrease in ICP in the low infusion rate group was far less pronounced. In the clinical study,[15] it was speculated that part of this effect could be caused by a decrease in body temperature. In the current study, temperature was kept constant, consequently the decrease in ICP is in all probability due to a direct vasoconstrictor effect of indomethacin.

It has been suggested that patients with severe traumatic brain lesions do not show an impaired autoregulation of the cerebral perfusion, but that the pressure-perfusion curve is shifted to the right.[35] In accordance with this hypothesis, it has been suggested that increased ICP should be treated with an elevation of MAP.[36] Should this hypothesis be correct it might be speculated that the decrease in ICP in the current experiments is in fact an autoregulatory effect caused by the increase in MAP. There is, however, no reason to believe that cerebral autoregulation is intact in the current experimental situation. Autoregulation is generally thought to be a more vulnerable regulator of cerebral perfusion than CO_2-vasoreactivity[5,37] and in the current experimental model CO_2 reactivity is impaired also when no drug is given.[21] In accordance

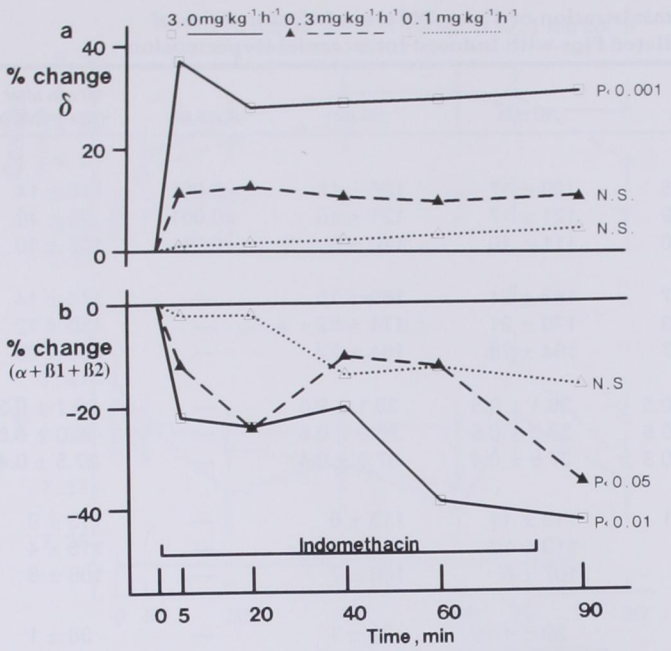

Fig. 5. Effects of three different infusion rates of indomethacin (0.1, 0.3, and 3.0 mg·kg^{-1}·h^{-1}) on low (δ) (*A*) and high ($\alpha + \beta_1 + \beta_2$) (*B*) frequences of electroencephalogram during induced intracranial hypertension. The *P* values refer to the effects of the treatment between 0 and 60 min, evaluated by repeated-measures analysis of variance.

with several recently reviewed studies[19] we conclude that indomethacin acts directly as a vasoconstrictor also in this experimental situation.

In the high rate infusion group, two pigs showed a progressive increase of the ICP during and after the indomethacin infusion. This suggests that the vasoconstriction was so pronounced that ischemia lesion had developed. A similar effect was observed in some patients in the clinical study.[15] The effects of indomethacin on Cav_{O_2}, vpH, and EEG all suggest a risk of cerebral ischemia. These changes did not result from a decrease in cerebral perfusion pressure: the decrease in ICP and, in particular, the increase in MAP actually caused an increase in cerebral perfusion pressure.

It has recently been shown that a single oral dose of 100 mg indomethacin in healthy males causes a decrease in power in the α band and a decrease in mean and peak α frequency of the EEG.[38] These changes are similar to those found in patients with minor ischemic cerebral disorders,[39] and, based on these data, administration of indomethacin was suggested as a mode to induce transient cerebral hypoperfusion in humans.[38] It is thus probable that indomethacin may induce cerebral ischemia during intracranial hypertension.

Indomethacin Versus *Dihydroergotamine as Treatment for Intracranial Hypertension*

We recently reported the effects of DHE in the current experimental model.[16] Low-dose (0.15 mg intravenous followed by 0.03 mg/h) and high-dose (1.0 mg intravenous followed by 0.2 mg/h) DHE treatment induced a similar and lasting reduction of ICP. In contrast to the group given low-dose DHE, the group treated with high-dose DHE disclosed a decrease in global CBF, a progressive increase in Cav_{O_2}, a decrease in jugular venous pH, and an increase in EEG delta activity indicating global cerebral ischemia. It was concluded that low-

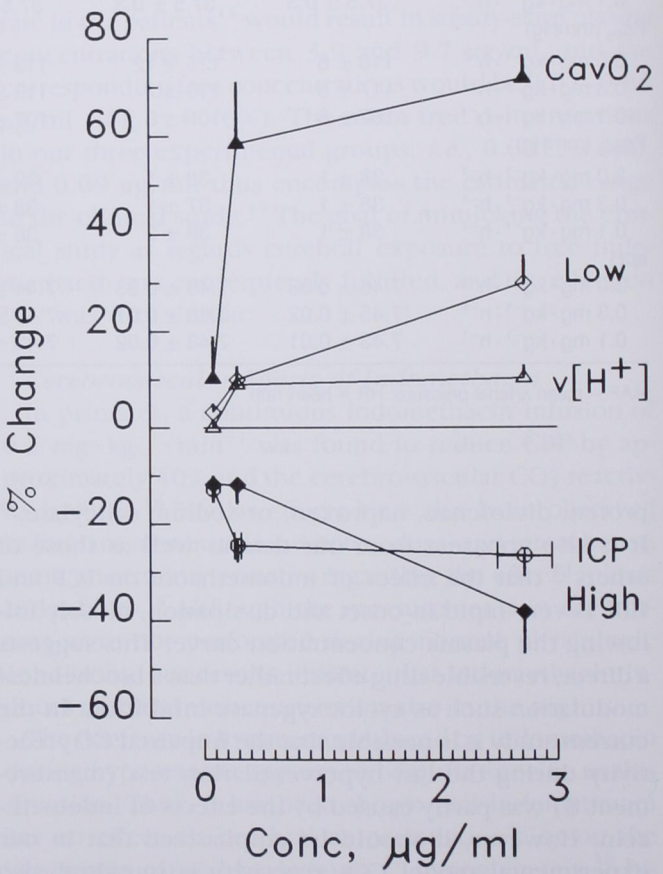

Fig. 6. Relationships at 60 min of infusion between mean plasma concentration of indomethacin and mean values of cerebral effects. Changes *versus* baseline of intracranial pressure, cerebral arteriovenous oxygen difference, and jugular venous hydrogen ion activity (v[H$^+$]) were approximately the same at a mean concentration of 2.7 µg/ml as at 0.3 µg/ml, showing that nearly maximal effects had been reached. Electroencephalographic changes, as sum of α, β1, and β2 voltage (High) and as δ voltage (Low), were still on the rising part of the concentration—effect curve. Plasma concentrations of indomethacin are shown as mean ± SEM on the intracranial pressure curve.

dose DHE might be useful in the treatment of increased ICP and that this treatment appeared to be effective also when cerebral CO_2 reactivity was impaired. In contrast, the current study indicates that with indomethacin a decrease in ICP to 20 mmHg or less (a level which is often considered as suitable in patients with severe head injuries) is obtained only when Cav_{O_2}, vpH, and EEG indicate impending cerebral ischemia.

The mechanisms by which the effects of indomethacin and DHE are accomplished are presumably different. The vasoconstriction induced by indomethacin is probably limited to the precapillary resistance vessels,[19] whereas DHE is a rather nonspecific drug exerting its effect mainly as a noncompetitive agonist at vascular 5-HT (5-hydroxytryptamine) receptors.[40] It is also a potent agonist at several 5-HT as well as dopamine$_2$, α_1-, and α_2-adrenergic binding sites in homogenized brain tissue.[41] Dihydroergotamine causes a constriction mainly of venous capacitance vessels,[42] but a contractile effect on precapillary resistance vessels has also been shown.[14] Both effects are probably also obtained in the human cerebral vasculature.[17,43] These differences may explain why a decrease of ICP to 20 mmHg or less was obtained with indomethacin only when regional CBF was reduced to a dangerous level while an appropriate dose of DHE may decrease ICP without the risk of inducing cerebral ischemia.

In summary, the current study shows that indomethacin can reduce ICP in an experimental model with an extradural focal mass causing secondary brain damage. The decrease in ICP is obtained by a constriction of precapillary resistance vessels but only when CBF was reduced to a level where progressive changes in Cav_{O_2}, vpH, and EEG occurred. This study does not support the clinical use of indomethacin in patients with intracranial hypertension due to head injury.

Appendix

Pharmacokinetic Calculations

An estimate of the pharmacokinetics of indomethacin in the pig was obtained by infusion of 4.1 mg/kg over 10 min in one animal (21 kg) with arterial blood sampling at 1, 2, 4, 6, 8, 10, 12, 14, 16, 20, 30, 50, 70, 100, 130, 190, and 250 min after the start of infusion. A three-compartment model was fitted to the plasma concentration data by standard methods (RSTRIP software, MicroMath, Salt Lake City, UT). Total clearance (CL) was calculated as Dose/AUC, where AUC is the area under the curve. The dose-normalized (to 1 mg/kg) bolus disposition function of indomethacin in the pilot animal was $C = 55.9 \cdot e^{-2.60 \cdot t} + 7.1 \cdot e^{-0.22 \cdot t} + 0.65 \cdot e^{-0.040 \cdot t}$ (units: μg/ml and min^{-1}).

The obtained intravenous bolus disposition function was used to simulate plasma concentration curves with various putative infusion schemes. The MLTIDOSE software[44] was used. Simulations indicated that 90% of a steady-state concentration (C_{ss}) would be reached 22 min after the start of a zero-order infusion. This mode of administration was consequently chosen.

For each constant rate infusion experiment, the actual C_{ss} of indomethacin was estimated by fitting the equation

$$C = C_{ss} \cdot (1 - e^{-k \cdot t})$$

to the concentration data using RSTRIP. The rate constant, k, is that of a monoexponential disposition function. The apparent steady-state clearance (CL_{ss}) was then calculated as CL_{ss} = (rate of infusion)/C_{ss}. The steady-state concentrations of unbound indomethacin were calculated as $C_{ss} \cdot f_u$, using the mean value of f_u obtained in the *in vitro* incubations.

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