Treatment of Intracranial Hypertension with Indomethacin

To the Editor.—Recently, Nilsson et al.1 concluded that intravenous infusion of indomethacin in doses of 0.3 and 3 mg/kg/h, but not 0.1 mg/kg/h, caused a constriction of precapillary resistance vessels that resulted in a substantial decrease in cerebral blood flow (CBF) accompanied by a progressive increase in cerebral arteriovenous oxygen difference, a decrease in jugular venous pH, and slowing of electroencephalographic activity, indicating cerebral ischemia. In addition, they found a progressive increase in intracranial pressure (ICP) during and after indomethacin infusion in two pigs, suggesting that the vasodilatation was so pronounced that ischemic lesion had developed. The authors did not find that their studies supported the clinical use of indomethacin in the treatment of intracranial hypertension due to head injury.

The authors analyzed our article,2 in which we studied the effect of indomethacin (30 mg intravenously, followed by 30 mg/h for 7 h) in five patients with severe head injury with resistant intracranial hypertension. All patients had focal cerebral contusion and edema, with compression of the ventricular system and basal cisterns. On average, we found an instantaneous decrease in ICP from 28 to 17 mm Hg (mean value) accompanied by a decrease in CBF, an increase in the arteriovenous oxygen content difference (AVDO2) at 2 h of indomethacin administration, and a decrease in arteriovenous lactate difference (at 15 min). At conclusion of the study, 1–6 months after head trauma, all patients had regained consciousness. We concluded that the effect of indomethacin on intracranial hypertension in patients with severe head injury was promising, but the cerebral vasodilator effect of indomethacin was potentially dangerous because it might provoke cerebral ischemia. However, subsequent followup of these patients revealed nothing that could obviously be linked to indomethacin use. Our preliminary result was confirmed recently in another clinical study.3 Since then, we compared the effect of indomethacin with that of acute hyperventilation in patients with severe head injury, and found that 30 mg indomethacin as a bolus injection caused a decrease in ICP comparable with a decrease in PaCO2 of 0.88 kPa. In the same study, the degree of change in AVDO2, jugular venous saturation, arteriovenous lactate difference, and lactate/oxygen index did not differ between hypoxia and indomethacin.4 These studies were supplemented with other studies of healthy volunteers, in which hypoxia and hypercapnia restored the indomethacin-induced CBF decrease,5 and a dose–response study in which 0.1 mg/kg/h indomethacin reduced CBF significantly.6 In another clinical study, the effects of 30 mg indomethacin during cranio-
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In Reply:—The comment by Cold et al. to our article “Cerebral Vasocostriction by Indomethacin in Intracranial Hypertension” addresses important problems within neuro-intensive care: Should post-traumatic brain swelling be treated with pharmacologic vasocostriction? If so, what drug and dosage should be chosen? In our study of induced intracranial hypertension in piglets, we found that indomethacin reduced intracranial pressure (ICP) by constriction of precapillary resistance vessels only when cerebral blood flow (CBF) was reduced to a level where progressive changes in CavO₂, vph, and electroencephalography occurred, indicating ischemia. We concluded that our data did not support the use of indomethacin in patients with intracranial hypertension due to head injury. In their comment, Cold et al. refer to clinical publications not available at that time. Some of these are still in press, but we had the opportunity to review the manuscripts.

The study by Biestro et al. included 10 patients with severe head injuries and raised ICP. The patients were given a bolus of indomethacin bolus (50 mg) followed by a continuous infusion (21.5 ± 11.4 mg/h). The authors measured significant decreases in ICP and increases in cerebral perfusion pressure (CPP) during the treatment, but no data were given regarding CBF, CavO₂, vph, electroencephalography, or other physiologic parameters. Four of the ten head-injured patients were reported dead, but no data regarding the cause or the time of death were presented.

In the study by Dahl et al., physiologic parameters that included ICP, CPP, CBF, and CavO₂ were studied in 14 patients with head injuries (mean ICP 14.8 mmHg before treatment). The study compared the effect of a bolus of indomethacin (30 mg intravenously) with that of induced hypocapnia. Indomethacin was found to decrease ICP and CBF and increase CavO₂ significantly. It is remarked by the authors that: “Although ischemia evaluated from CBF, SvO₂, and LOI (lactate/oxygen index) were indicated in individual cases after both hyperventilation and indomethacin, it was not reflected in outcome.” However, the increase in ICP before treatment was very modest, and “patients in poor clinical condition indicating transientorial herniation were excluded.” There is no indication in the study that a bolus injection of indomethacin had any beneficial effect on outcome.

In their letter, Cold et al. claimed that, during continuous intravenous indomethacin treatment, “the ICP-reducing effect is sustained and the increase in AVO₂, the jugular venous lactate and EEG are transitory” and that they “find a low mortality of 10% in indomethacin treated severe head injury.” We have been unable to find the data supporting these statements. In the report by Jensen et al., indomethacin was administered intravenously throughout a 7-h period. During this period, the decrease in global CBF and the increase in CavO₂ remained. At 7 h after start of infusion, ICP seemed to have returned close to pretreatment level (28 ± 3 mmHg vs. 25 ± 11 mmHg). There is a lack of information regarding physiologic parameters in patients with severe head injuries when indomethacin infusion is continued beyond 7 h. Cold et al. also said that “results in an experimental model of a focal mass expanding lesion in pigs cannot rightly be transferred to the pathophysiologic events of severe human head injury.” Although this is obviously true, it seems to us that the clinical experiences by Biestro et al. and Dahl et al. are in good agreement with our experimental study: indomethacin reduces increased ICP, but at the expense of decreased CBF and impending cerebral ischemia. We agree with Cold et al. that indomethacin is contraindicated in patients suffering from cardiac ischemia, renal insufficiency, gastric bleeding, and coagulation disorders. Unfortunately, patients with severe head trauma may, quite often, experience multi-organ failure, which may limit the clinical use of indomethacin even further.

In our opinion, cerebral vasoconstriction is only one of the components, though important, in the treatment of posttraumatic brain swelling. Our treatment concept was published recently. The concept aims at a reduction of ICP through decreased CBF and increased absorption of cerebral interstitial fluid. The latter is accomplished through reduction of intracapillary pressure by a combination of moderate precapillary vasoconstriction (DHE) and reduction of mean arterial blood pressure. We are currently reviewing our clinical results since 1989 that show that mortality in patients with closed head injuries has been almost eliminated, with no increase in the number of patients surviving in a vegetative state (Eker et al., in preparation).

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