Intracranial Bleeding Associated With Urokinase Therapy for Acute Ischemic Hemispheral Stroke

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SUMMARY Four patients undergoing urokinase infusion therapy for acute occlusive cerebrovascular disease had intracerebral hemorrhage in the ischemic hemisphere. Three patients died during the acute phase of their illness and an autopsy was performed on two. The pathogenesis of cerebral bleeding in these case reports is discussed.

Introduction

THE CHEMICAL and clinical observations on our series of 31 patients treated with urokinase for acute ischemic stroke have been discussed in another publication. In this report we provide detailed clinical and pathological observations on four patients in this series who had cerebral hemorrhage during or within 24 hours of urokinase (UK) treatment.

Case Reports

CASE 1: RZ (BH-567288)

A 66-year-old woman was well before admission except for complaints of occasional intermittent tingling of the fingers of the left hand and left foot for six months and more recently of recurrent occipital headaches. She had not seen a physician for years and was not known to have hypertension or diabetes. On January 13, 1974, she was found at 09:00 in a disarrayed bed having difficulty speaking and moving her left arm and leg.

On admission to the Neurology Service of the St. Louis City Hospital, her blood pressure was 210/95, pulse 94 and regular, and respirations 18 per minute. She was arousable but she gave her name, age, name of her son and sister, the president of the United States, the day, month and year.

Bilateral cataracts obscured her fundi but she could count fingers on visual field testing despite a left homonymous hemianopia. Her eyes were deviated to the right of the midline and, on request, could not be moved fully to the left. The corneal reflexes and the pupils were equal bilaterally. The left side of her face was weak and the left arm and leg could not be moved. Tendon reflexes were hyperactive on the left and the left plantar reflex was extensor. Her response to pinprick was diminished on the left in the face and limbs.

The initial laboratory tests were normal including: complete blood count (CBC), electrolytes, BUN, blood sugar, blood gases, skull and chest x-rays. A lumbar puncture revealed a opening pressure of 110 mm H2O with clear and colorless spinal fluid. The first and fourth tubes contained 42 and 14 RBCs, considered traumatic in origin. She was transfused to Barnes Hospital where her initial coagulation studies showed plasma fibrinogen 240 mg %, one-stage prothrombin time 14.4 seconds, thrombin clotting time 10.1 seconds, plasma recalcification time 62 seconds, euglobulin clot lysis greater than four hours, euglobulin on fibrin plate 52 mm2 and plasminogen 2.1 CTA units per milliliter. Intravenous urokinase was started at 21:15 (1:15 P.M) and the dose was 1,500 units per pound per hour for a calculated total dose of 2.2 million units over eight hours. Coagulation moieties were monitored at 30 minutes, two and four hours, and at the end of infusion.

Seven hours after urokinase was started, she suddenly vomited, became comatose and had reactive extensor posturing. Her respirations were Cheyne-Stokes, the pupils were small and reactive, and the eyes responded to the doll's eye maneuver. The drug was stopped. The post-treatment coagulation studies were not significantly altered. A few hours after the onset of coma, her pupils were fixed and small, the right greater than the left. She was decerebrate and spastic, and had bilateral Babinski signs. An emergency right brachial angiogram was performed revealing stenosis of the right internal carotid at the bifurcation and virtual occlusion in its supraclinoid portion. There was no filling of the right anterior cerebral artery and minimal filling of the middle cerebral branches. The patient remained comatose with no change in her clinical status and died a few hours after the procedure.

Neuropathology Report

Gross. The brain was swollen, and the right hemisphere was softer than the left. Examination of the base of the brain revealed moderate bilateral uncal herniation, greater on the right, and a deviation of the brain stem to the left. Extensive atheromatous disease was found in the right internal carotid artery which had a slit-like lumen above the bifurcation from the common carotid. A similar severe stenosis was found a few centimeters below the carotid siphon. The walls of the right middle and anterior cerebral arteries showed extensive atheromatous thickening with recent thrombotic occlusion of the proximal middle cerebral artery. Coronal sections of the brain revealed hemorrhagic infarction of the deep structures of the right hemisphere extending from the rostral end of the caudate nucleus to the caudal end of the thalamus. The infarction involved the caudate, putamen, pallidium and internal capsule but spared the diencephalon. The right lateral ventricle was compressed to a slit by the mass and there was no blood in the ventricular system. There was an area of necrosis in the middle of the left cerebral peduncle which had impinged on the free edge of the tentorium as the brain stem was deviated to the left. Midline Duret hemorrhages were found in the midbrain.
Microscopic. There were extensive atheromatous degeneration and severe stenosis of the right internal carotid artery at its origin and several centimeters below the carotid siphon. Both sites were almost occluded by recent antemortem thrombus (fig. 2). The middle cerebral artery showed moderate atheromatous changes and a recent occluding thrombus in the proximal portion. The basal ganglia in the area of the hemorrhagic infarction showed fresh perivascular hemorrhages with dissection into the tissue and eosinophilic ghost-like neuronal remnants. The adjacent cortex in the middle cerebral distribution revealed congested vessels with perivascular hemorrhages and moderate edema, particularly in the insula. The neurons in this area were shrunken and poorly stained, suggesting early ischemic necrosis. The midportion of the left cerebral peduncle was infarcted (Kernohan's notch) and typical Duret hemorrhages were in the midbrain tegmentum extending into the tegmentum of the pons.

CASE 2: EM (BH-7000095)

A 70-year-old man had a history of coronary artery disease with a myocardial infarction in 1969 and coronary insufficiency in 1970. In addition, he had congestive heart failure and mild diabetes and had been operated on in 1969 for a Grade 2 transitional cell carcinoma of the bladder. During the year prior to admission, he had had two transient episodes of right hemiparesis and more recently recurrent right-sided headaches. On March 29, 1972, he was admitted to Barnes Hospital in the early afternoon because of the sudden onset of difficulty speaking and moving his right arm and leg.

Physical examination revealed a cooperative man with a nonfluent aphasia who could follow simple commands. His blood pressure was 180/100, pulse 80 and respirations 16 per minute. A cataract obscured the right fundus and the left was unremarkable. Although visual fields and eye movements were normal, the right pupil was unreactive to light. The right side of his face drooped and the strength of the right arm and leg was markedly decreased. His right arm was hyperreflexic but the reflexes were equal in the lower limbs. The right plantar reflex was extensor. His perception of pin and touch was impaired on the right. A bruit was heard over the right carotid artery.

Initial laboratory results including CBC, electrolytes, BUN and glucose were normal. Skull x-rays showed a calcified midline pineal and the chest x-rays revealed cardiomegaly with no evidence of congestive heart failure.

At lumbar puncture, the opening pressure was 110 mm H2O, the fluid was clear and colorless, the protein 38 mg % and the glucose 76 mg %. Pretreatment blood coagulation findings were: plasma fibrinogen 400 mg %, one-stage prothrombin time 14 seconds, thrombin clotting time 20 seconds, plasma recalcification time 100 seconds, plasminogen 2.4 CTA units per milliliter and euglobulin clot lysis time greater than three hours.

Urokinase infusion was started two hours after admission. He received a loading dose of urokinase of 1,750 units per pound of body weight and an infusion of 1,750 UK units per pound per hour. At 11:00 P.M., two and one-half hours after starting the urokinase, he was more lethargic, his left pupil had become fixed and dilated, and he vomited. Bigeminal rhythm was noted on the EKG and intravenous lidocaine was started. Urokinase was stopped. Three hours later, his condition had deteriorated and his blood pressure rose to 218/112. He had a tachycardia of 108 and a respiration rate of 36 per minute. He was unresponsive with fixed, dilated pupils and had become decerebrate. An echoencephalogram revealed a left to right shift of 4 to 5 mm compatible with a mass in the left hemisphere. He died 19 hours after admission to the hospital.

Neuropathology Report

Gross. There was patchy, fresh subarachnoid blood over both hemispheres and on the base of the brain. The brain was swollen and gyral flattening was more on the left than right. There was moderate transtentorial herniation of the
left medial temporal lobe. The terminal portion of the left internal carotid artery was occluded by nonadherent atheromatous material that did not extend into the circle of Willis. Coronal sections of the brain revealed a large fresh hematoma in the left basal ganglia region which had ruptured into and filled the entire ventricular system. The hematoma also extended caudally from the diencephalon into the midbrain.

**Microscopic.** There were marked atheromatous degeneration and stenosis of the internal carotid artery and an organizing thrombus virtually occluded its terminal portion. Sections of the diencephalon and tissues surrounding the large hematoma revealed fresh blood invading the surrounding white matter and beyond. Perivascular hemorrhages and extensive edema characterized the surrounding cerebral tissue. The neurons in the insular cortex showed shrinkage and eosinophilic staining indicative of early infarction but there was no evidence of a significant macrophage or glial response. Duret hemorrhages were found in the midbrain and extended caudally into the tegmentum of the pons.

**CASE 3: EJ (BH-357701)**

An 84-year-old man was chronically ill with renal disease and mild azotemia and had an ileal loop bladder. He was also being treated for hypertension, congestive heart failure and atrial fibrillation. On the morning of admission, August 31, 1973, he was found sitting on his bed unable to speak properly but able to understand.

On admission to Barnes Hospital, his blood pressure was 200/100, pulse 88 per minute and respirations 18 per minute. He was alert and able to follow commands with the left arm and leg, but his speech was unintelligible though fluent. Funduscopic examination was normal. The pupils were equal and reactive. He had a mild right lower facial weakness and a mild right hemiparesis. The reflexes were symmetrical except for a right Babinski sign. Sensory examination revealed decreased sensation in the right half of the body and the carotids were palpable with no bruits.

Normal laboratory tests on admission were: electrolytes, blood sugar, CPK, LDH, SGOT, BUN, urinalysis and a urine culture. The creatinine was 1.7, cholesterol 325, and Ht 34.3. The chest x-ray revealed marked cardiomegaly and normal lung fields and skull films were normal. The EKG showed atrial fibrillation and VDRL was reactive. A lumbar puncture done on admission revealed an opening pressure of 225 mm H2O. The fluid was clear and colorless with no cells. The initial pretreatment blood coagulation studies were performed at 30 minutes and three, six and nine hours and his head and eyes tended to look to the left. He could, however, move his eyes to the right on command. The mild right-sided weakness became marked and the right palmar extensor response more definite. Pretreatment blood coagulation studies showed plasma fibrinogen 404 mg %, one-stage prothrombin time 11 seconds, thrombin cloting time 10.1 seconds, and plasma recalcification time 150 seconds.

Urokinase infusion began five hours after admission. He was given 1,200 units per pound per hour for eight hours. His neurological status was unchanged during and immediately after the first infusion, but the following morning he was found comatose, responding only to pain. His blood pressure was 165/113 and the respirations 40 per minute and Cheyne-Stokes. The left pupil was 4 mm and the right 2.5 mm and they were unreactive to light. There was bilateral extensor posturing, right greater than left. A repeat lumbar puncture on September 1, 1973, showed grossly bloody fluid with an opening pressure of 420 mm H2O. He remained deeply comatose and died on September 3, 1973. Autopsy was refused.

**CASE 4: FF (BH-542989)**

A 71-year-old man had a history of high blood pressure controlled by hydrochlorothiazide, 50 mg per day. There was a vague story of a small stroke in the past from which he made a virtually complete recovery with some residual difficulty with his gait. He was otherwise in good health and on no other medications up to a month prior to admission. During this month, the patient and his family complained of decreased memory and ability to concentrate, particularly in his business dealings. He was well on October 19, 1972, the morning of admission, but while at lunch, suddenly had difficulty speaking and rightsided weakness for which he was brought to the hospital.

At physical examination on admission to Barnes Hospital the blood pressure was 130/90 mm Hg. The pulse was 100 per minute and the respirations 60 per minute. He was awake and alert and could follow simple commands, i.e., raise his right and left arm and open and close the mouth. He had a fluent aphasia. Funduscopic and visual field testing was within normal limits. The left pupil was 0.5 mm larger than the right, but both were reactive. The extraocular movements were normal and there was no nystagmus. No abnormalities were noticed in the examination of the rest of the cranial nerves. There were increased tone in the right arm and leg and mild rightsided weakness. Sensory examination revealed hypesthesia on the right side with decreased vibration and joint position sense. The reflexes were symmetrical in the arms and legs and there were no ankle jerks. There was a right Babinski sign. Carotid pulsations were more prominent on the right and there were no carotid bruits.

The initial laboratory examinations were normal including urinalysis, CBC with a platelet count of 164,000, electrolytes, BUN, blood sugar, x-rays and a brain scan. An EEG showed high voltage delta and diffuse theta slowing in the left central posterior region. A lumbar puncture revealed an opening pressure of 150 mm H2O and clear, colorless fluid with no cells. The initial pretreatment coagulation findings were: plasma fibrinogen 320 mg %, one-stage prothrombin time 10.4 seconds, thrombin time 11.5 seconds, and plasma recalcification time 94 seconds.

At 6:30 P.M., treatment was begun with a urokinase loading dose of 1,700 units per pound of body weight. The same dosage per hour was continued. Blood coagulation studies were performed at 30 minutes and three, six and eight hours. The greatest deviation from normal was seen at six hours. Plasma fibrinogen was 240 mg %, one-stage prothrombin 16.5 seconds, thrombin cloting time 19 seconds, plasma recalcification time 160 seconds, and...
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euglobulin on fibrin plate 370 mm². During the infusion, the patient’s blood pressure began to rise, and by 12:15 A.M. on October 20, 1972, it reached 200/130 mm Hg. The patient was given hydralazine hydrochloride (5 mg) and then had sudden atrial fibrillation with a ventricular rate of 150 which responded to 100 mg IV of lidocaine. A lidocaine drip was then administered and the following morning urokinase was stopped. The blood pressure was 210/110 mm Hg. The patient was more lethargic but still able to follow simple commands. A right homonymous hemianopia was noted and on October 21, 1972, he was in coma. The eyes were deviated to the left and there was a dense right hemiparesis with bilateral Babinski signs. A lumbar puncture revealed an opening pressure of 330 mm H₂O and grossly bloody spinal fluid with a hematocrit of 32. The diagnosis of a left hemispheric bleed was made. The patient remained essentially unchanged for the remainder of his hospitalization and was discharged to a nursing home on November 16, 1972.

Discussion

All four patients had rapidly progressive symptoms of dysfunction compatible with intracerebral hemorrhage during or within 24 hours of urokinase infusion. The initial diagnosis of cerebral infarction was confirmed in the first two patients at autopsy but not in the latter two. It is possible, though improbable, that Cases 3 and 4 had primary cerebral hemorrhages which were misdiagnosed; but if so, catastrophic exaggeration of the lesions by urokinase seems to be an inevitable inference. Cases 1 and 2, however, had premortem occlusions of internal carotid arteries and ischemic infarction in the cortex of the appropriate hemisphere which suggests that ischemic necrosis was the underlying pathological process on admission to the hospital. Furthermore, because hemorrhagic infarction and cerebral hemorrhage are such unusual findings associated with internal carotid artery occlusion, we conclude that it is highly probable that the urokinase therapy is responsible for these consequent hemorrhagic events.

A certain number of patients with extensive infarction may progress spontaneously to death in the first day or two but this is a rare occurrence. Indeed, one patient of this sort is included in a portion of the present urokinase study where randomized controls were used. Following infusion of saline solution, he suddenly had a unilaterally dilated pupil and unresponsiveness. Emergency angiography showed occlusion of the appropriate internal carotid artery, confirmed at autopsy, with associated massive ischemic infarction of the cerebral hemisphere.

Bleeding complications have been reported with urokinase therapy and are not unique with our series.⁹ The most reliable data have been reported in the statistically controlled Urokinase Pulmonary Embolism Trials⁸ which revealed a significant incidence of hemorrhagic complications during and within 24 hours of therapy. Bleeding, however, was closely related to the invasive procedures necessary to investigate the patients for diagnosis and for hemodynamic control of the therapy. Although some of the bleeding secondary to vascular punctures was rated “severe” by the authors, none was fatal that could be directly related to urokinase therapy. One patient had a questionable intracerebral bleed but the patient had had a stroke one month prior to treatment and the bleeding was not proved. Another patient had a fatal intracerebral hemorrhage during treatment but because this patient was excluded from the randomized trial the drug administered was not specified (either urokinase or streptokinase).

Two other controlled therapeutic trials of thrombolytic agents (thrombolysin and streptokinase) in occlusive cerebrovascular disease have been published⁹,¹⁰ and hemorrhagic complications were significant in the streptokinase trial.¹¹ Because the patients also received anticoagulants in this study, the incidence of hemorrhagic complications cannot be compared with other studies.

Our experience suggests several factors that might diminish the risk of thrombolysis in future studies. The most important initial diagnostic problem is to exclude the small intracerebral hemorrhage that may mimic infarction. Noninvasive computed tomography, not available during the present study, has improved the early diagnosis of cerebral hemorrhage with such certainty that it is now the definitive diagnostic procedure for this condition.

A second significant problem is the state of the ischemic cerebral tissue at the time of therapy. Irreparable infarction of the brain with necrosis of the vessels would be a contraindication to treatment but ischemic brain without infarction might not. Both result in the same clinical picture initially when therapy must be considered. Recent developments in nucleotide brain scan tomography offer a more reliable assessment of the metabolic state of cerebral tissue and the state of infarction. When this investigative development is perfected and the results correlated with pathological findings, a more precise evaluation of the reversibility of ischemic brain tissue will be available on which to base therapeutic decisions.

Carotid angiography, in our experience, is still hazardous at present dosage levels of urokinase. Although the femoral catheterization route may offer an acceptable risk, the diagnosis of major cerebrovascular occlusion must still be based primarily upon clinical findings and noninvasive studies.

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