the influence of tranexamic acid (amca) upon the level of serum transaminases (ldh, asat, alat) in patients with aneurysmal subarachnoid haemorrhage

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SUMMARY

In 46 patients with proven rupture of an intracranial aneurysm, 23 were, treated with tranexamic acid (AMCA) in a randomized controlled investigation, and venous blood samples were taken regularly for determination of LDH, ASAT, and ALAT. The results indicate that AMCA does not influence the serum levels of these enzymes.

KEYWORDS

Antifibrinolytic drugs; Cerebral aneurysm; Serum transaminases; Subarachnoid haemorrhage; Tranexamic acid (AMCA).

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INTRODUCTION

The aim of treating patients with ruptured cerebral aneurysms with antifibrinolytic drugs is to prolong the duration of the formed blood clot within and about the wall of the aneurysm before dissolution and thus decreasing the risk of rebleeding during the critical period of planned surgical delay. Tranexamic acid (trans-4-amino-methyl-cyclohexahe-carboxylic acid, AMCA) crosses the blood-brain barrier (Tovi and Thulin 1972, Fodstad et al 1981) and inhibits the local fibrinolytic activity in CSF (Tovi et al 1972, Fodstad and Nilsson 1981). An increased incidence of severe vasospasm with cerebral ischaemia, cerebral thrombosis, pulmonary embolism and myocardial infarction in patients receiving antifibrinolytic agents has been reported by several authors (Davies and Howell 1977, Farina et a! 1979, Fodstad 1980, Fodstad and Lilieqvist 1979, Fodstad et al 1981, Hoffman and Koo 1979, Kagström 1971, Kagström and Palma 1972,Rydin and Lundberg 1976, Shaw and Miler 1974, Someda et al 1977, Sonntag and Stein 1974, Tubbs et al 1979). There have also been reports on myopathy and myoglobinuria following treatment with epsilonamicocaproic acid (EACA) (Bennett 1972, Biswas et al 1980, Brodkin 1980, Erill et al 1972,Geronemus et al 1974,Gilligan 1973, Kennard et al 1980, Korsan-Bengtsen et al 1969, Lane et al 1979, MacKay et al 1978, Nibbelink et al 1975, Post et al 1977). To our knowledge no such reports have appeared using AMCA. The purpose of this study was to evaluate whether or not AMCA causes damage to the parenchymatous cells of the body through influence on the serum transaminases (ASAT-ALAT) and lactate-dehydrogenase (LDH) in patients with recently ruptured cerebral aneurysms in a controlled study.

MATERIALS AND METHODS

The material comprises a controlled clinical series of 46 patients admitted to the hospital within three days fo-

lowing a subarachnoid haemorrhage, SAH, due to a ruptured aneurysm. The diagnosis was verified by spinal fluid examination and cerebral angiography. The patients .were randomly assigned to conservative treatment (bedrest and sedation) or conservative treatment together with the administration of AMCA until operation. Not included in the trial were patients with life-threatening haematomas (who underwent an immediate operation) and patients with rheumatic diseases, liver diseases, renal diseases, diabetes and ischaemic heart diseases as well as elderly patients in poor clinical condition. AMCA was administered by slow i.v. injections in a dosage of 1 g six times daily for the first week, 1 g four times daily during the second through the fifth weeks and 1g three times daily during the sixth week of treatment. Hypotensive drugs, anticonvulsants and corticosteroids were used in approximately equal amounts in both groups. Those patients who were operated upon were given, in standardized doses, atropin and diazepam as premedication. Operation was performed under general anaesthesia using standardized technique and hyperventilation. Hypotension was induced during surgery with trimethaphan and in nine cases with halothane. The anaestethics used were fentanyli citrat, droperidol lactas, thiomebumal sodium, droperidolilactate and N2O2, in various standardized combinations.

Twelve hours prior to operation a short term steroid therapy was introduced. Mannitol was given half an hour prior to operation and maintained during and the first three days after operation. The parenteral water and electrolyte solutions used are listed in enclosure 1.

Alanine-aminotransaminase ALAT, aspartate-aminotransferase ASAT, and lactate-dehydrogenase LDH were analyzed repeatedly in serum. LDH in serum was determined according to Wróblewski and La Due (1953) with reagent manufactured by KABI, Diagnostica, Stockholm. Serum and NADH in buffer pH 8.0 is preinoculated in a 25° C water bath for 30 min and after adding pyruvic acid the NADH decrease per min. is measured, utilizing the extinction decrease at 340 nm.

ASAT converts with the aid of added 2-oxoglutarate, existing 1 -aspartate into oxalacetate. Oxalacetate is reduced to malate in the presence of an auxiliary enzyme, MD, with an associated co-enzyme in reduced form, NADH, and NADH is oxidiced simultaneously to NAD*. The oxidation if followed spectrophotometrically at 340 nm. It progresses at the same rate as the formation of oxalacetate in the aminotransferase reaction and is directly proportional to the ASAT activity in the serum sample (KABI Diagnostica, Stockholm).

ALAT converts, with the aid of added 2-oxoglutarate, existing 1 -alanine into pyruvate, which is then reduced to lactate in the presence of the auxiliary enzyme, LDH, with an associated co-enzyme in reduced form. The oxidation of NADH to NAD* is followed spectrophotometrically in the same manner as in the ASAT assay (KABI Diagnostica, Stockholm).

TABLE 1

PATIENT-GROUP		+ AMCA	- AMCA	TOTAL
LDH	1.Preoperative	12	12	24
	2.Postoperative	9	7	16
	3.Discharge	11	9	20
	4.Follow-up	2	2	4
ASAT	1.Preoperative	14	11	25
	2.Postoperative	9	9	18
	3.Discharge	13	10	23
	4.Follow-up	3	1	4
ALAT	1.Preoperative	17	12	29
	2.Postoperative	13	10	23
	3.Discharge	11	11	22
	4.Follow-up	2	3	5

LDH, ASAT and ALAT in serum were analyzed on the day of admission and thereafter continually for three days. During hospitalization venous blood samples were taken once a week until the patient was discharged from the hospital. If operation was undertaken, the blood samples for enzyme analyses were taken immediately before surgery and then for three days postoperatively. A control blood sample for analyses of transaminases in serum and a complete neurological examination, including echo-encephalography, EEG and neuro-ophthalmologic examination, was performed three months or later after the onset of the bleeding. The highest obtained enzyme value was chosen at the four following different stages of hospitalization, and set up in a scheme for comparison and statistical analysis (Table 1):

Group 1) The highest enzyme level during hospitalization in patients not operated upon. In operated patients the highest preoperative level was chosen.
Group 2) No values for non-operated patients. The highest postoperative level in patients operated upon.
Group 3) The enzyme level taken.before the patient was discharged from hospital.
Group 4) The enzyme level on the day of control examination.

The material thus comprises approximately 2000 enzyme values, of which 700 were chosen, as explained above, for comparison. In the four groups of patients enzyme levels above normal range were summarized, firstly from the patients treated with AMCA, secondly from patients not treated with AMCA.

TABLE 2

PATIENTS	+ AMCA	- AMCA	TOTAL
Number	23	23	46
Males	11	12	23
Females	12	11	23
Operation	19	16	35
Deaths	5	5	10

RESULTS

Of the 46 patients, 23 were treated with AMCA and 23 were controls (Fodstad et al 1978). There was no difference between the groups regarding sex or patients' condition on admission. Mean age for the AMCA-treated patients was 45 years (range 23 to 68 years) and for control patients 52 years (range 34 to 68 years). Nineteen AMCA-treated patients and 16 controls were operated upon, usually with obliteration of the aneurysm at an average of 16 and 18 days respectively after the primary bleed (Table 2). In the AMCA-treated group one patient had a fatal rebleeding 32 days after the primary bleed. In the control group nine patients rebled 3 to 34 days after the primary SAH. Three patients rebled twice and three died from their rebleedings. In the AMCA-treated group two additional patients died from cerebral infarction, one of them after operation which was performed while having symptoms of ischaemia. Deep venous thrombosis in the legs diagnosed clinically developed in two AMCA-treated patients and in one control patient. Two control patients had myocardial infarction. Five patients in each group died during the six week's observation time. At the mean follow-up time of 18 months (range 3 to 34 months) a total of six AMCA-treated patients and 10 controls died from causes related to their primary aneurysm disease and its management. The morbidity was similar in the two groups of patients on discharge as well as on the follow-up examinations. The result of measurements of serum enzymes as shown in Fig. 1 -3.

Group 1) It-was found, that on the day of hospitalization 24 patients had LDH enzyme values above the normal level, which has been set to 450 U/L. Twelve of these patients then received treatment with AMCA, whereas 12 patients were not treated.
Twenty-five patients had ASAT enzyme values above the normal level, which has been set to 40 U/L. Fourteen patients were then given AMCA, the remaining 11 patients received no treatment.
Twentynine patients had ALAT enzyme values above the normal level, which has been set to 40 U/L. Seventeen patients were treated with AMCA, 12 patients were not treated.

Group 2) Of 35 operated patients, 16 showed postoperative rise in LDH values, of which nine were treated with AMCA.
In 18 patients half of which were treated with AMCA, ASAT values above the normal range were found.
Twenty-three patients showed ALAT values above the normal range, 13 of them were treated with AMCA, the other 10 patients received no treatment. Twelve of the patients had values within normal range preoperatively.
Group 3) On the day before discharge from the hospital 20 patients had LDH values above normal range. Eleven patients were treated with AMCA and nine patients were not.

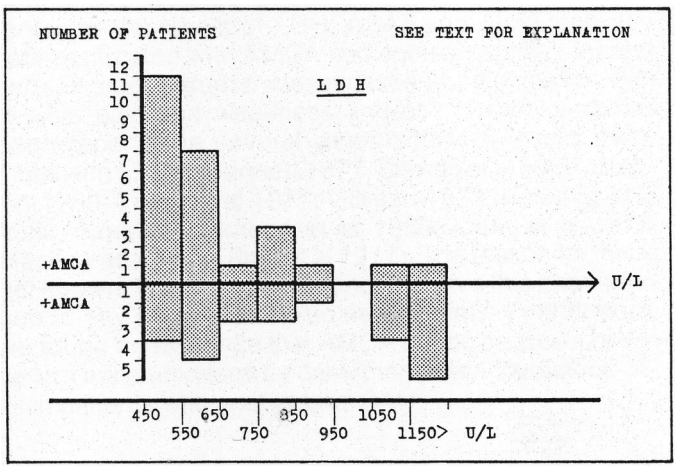

Fig. 1

Twenty-three patients had ASAT values above the normal range. Thirteen of the patients were treated with AMCA, the remaining 10 were not. Sixteen of these patients underwent operation; seven of them had been treated with AMCA.
Twenty-two patients showed a rise in ALAT, half of them were treated with AMCA. Eight of the AMCA-treated patients had been operated upon.
Group 4) At follow-up 24 patients had normal enzyme values, 10 patients had values slightly above normal range and three patients had high values. Six of the patients with raised values had been treated with AMCA.

Altogether, 40 patients showed a rise in serum transaminases during hospitalization. Twenty were treated with AMCA out of which 16 were operated upon. Thirteen patients (65%) had normal values at the follow-up. In the

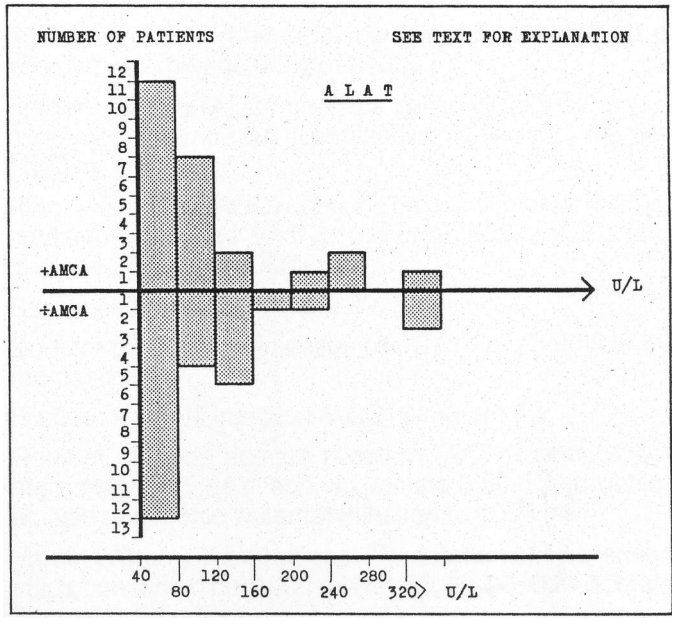

Fig. 2

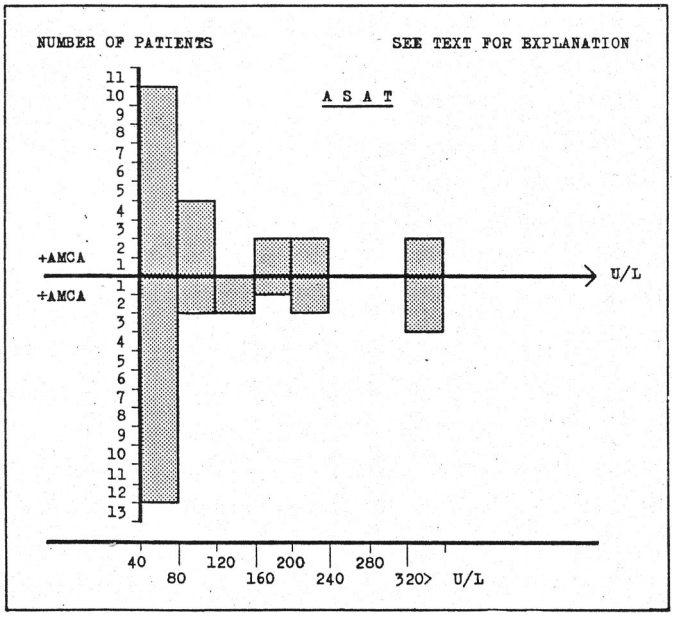

Fig. 3

20 non-treated patients of whom 16 were operated upon (70%) had normalized values at the control visit. Of the 35 patients operated upon, 25 showed a rise in transaminases, 11 of them although only a slight rise. Hypotension was used during 24 operations and in 19 of these patients the enzyme levels were above normal range.

DISCUSSION

A leakage of tissue enzymes from the cells into the general circulation will occur as a result of tissue injury or disease. This damage may thus be caused by trauma, infection, haemolysis, degeneration, infarction and haemorrhage (Elliot and Wilkinson 1963, Rabow 1976, Rabow et al 1971). it may also be induced by different drugs such as anaesthetics, hyper-osmolar solutions and solutions for intravenous nutrition (Rabow and Tibbling 1975). Tissue destruction during surgical procedures is another known cause of rise in serum enzymes (Harrah et al 1969, Rabow and Tibbling 1975). Finally, SAH itself may cause myocardial injury (Greenhoot and Reichenbach 1969).

Among our patients with high levels of serum transaminases, one died from cerebral ischaemia and infarction, two had myocardial infarction, three had pseudomonas pneumonia, 19 had induced hypotension during surgery and 26 were given intralipid intravenously - 15 of which were treated with. AMCA. Blood transfusions did not significantly alter the enzyme activity, which corresponds with the findings of Harrah et al (1969). The highest level of serum enzymes was found in patients who developed severe neurological deficits, as reported by Rabow and Tibbling (1975). However, there was no difference in the levels of LDH, ASAT and ALAT between patients treated with AMCA nad control patients. Increased levels of serum transaminases in combination with muscle pain and weakness and/or myoglobinuria has been reported in several cases after 4-6 weeks treatment with EACA (Bennett 1977, Biswas et al 1980, Brodkin 1980, Frank et al 1977, Gilligan 1973, Kennard et al 1980, Korsan-Bengtsen et al 1969, Lane et al 1979, MacKay et al 1978, Post et al 1977). The reason for this is not known. We did, however, not observe this phenomenon in any of our AMCA-treated patients. Furthermore, we found no evidence that AMCA per se causes a rise in serum transaminases by damaging parenchymatous cells in patients with aneurysmal SAH.

Parenteral water and electrolyte solutions used:

- Fructose - Glucose (ACO) 15%+ 5.5%
- Glucose (ACO) 5.5% or 10%
- Intralipid (Vitrum) contains oleum sojae fractional 10% or 20%
- Invertose (ACO) 10%
- Invertose 10%+electrolytes (ACO) contains also sodium chloride 4.68 g and potassium chloride 2.98 g per 1000 ml.
- Macrodex (Pharmacia) contains dextran 70.6 g and sodium chloride 0.9 g per 100 ml.
- Mannitol(ACO) 0.15 g per ml.
- Normodex (Pharmacia) contains Na^+ 40, K^+ 20, Mg^{2+} 3, Ac^- 23 and Cl^- about 40 mEq:s per 1000 ml.
- Refundex (Pharmacia) contains Na^+. 120, K^+ 10, $Ca2^+$ 5, $Mg2^+$ 3, Ac^- 38 and Cl^- about 100 mEq:s per 1000 ml.
- Rheomacrodex (Pharmacia) contains dextran 40 10 g and sodium chloride 0.9 g per 1000 ml.
- Ringersolution (ACO) contains calcium chloride 0.5 g, potassium chloride 0.3 g and sodium chloride 8.6 g per 1000 ml.
- Ringer-Glucose (ACO) contains calcium chloride 0.25 g, potassium chloride 0.15 g, sodium chloride 4.3 g and glucose 27.5 g per 1000 ml.
- Serum albumin 20% (Kabi).
- Sodium bicarbonate injection (ACO) 14 mg per ml or 50 mg per ml
- Sodium chloride injection (ACO) 9 mg per ml.
- Sodium chloride acetate injection (ACO) contains sodium chloride 5.84 g, sodium acetate 6.80 g, hydrochloric acid and sterile water for injection to 1000 ml.
- Vamin (Vitrum) is a nutritional 7% solution of 18 L-amino acids containing per 1000 ml Na^+ 50, K^+ 20, Ca^{2+} 5, Mg^{2+} 3 and Cl^- 55 mEq:s.

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