a selective surgical policy has been shown by its favourable influence on overall mortality (which can be reduced to about 4%), and the prompt submission of suitable patients to operation is almost certainly an important factor in achieving the best results.

Early barium-meal examination has been adopted in some centres as a means of obtaining useful information. The procedure can be undertaken on the ward using a portable *x*-ray set and without manipulation or the need to move the patient from his bed. Combined with gastroscopy or the use of the fibrescope or gastro-camera it has proved possible to achieve a correct diagnosis of the cause of bleeding in about 80% of patients admitted with haemorrhage from peptic ulcer, usually within 24 or 36 hours from admission. The introduction of the fibrescope or the blind use of the gastro-camera has further minimized the interference and discomfort suffered by the patient, for, unlike gastroscopy, the procedures can be undertaken on the ward and are far less disturbing.

The importance of reaching an early decision as to the surgical treatment of haematemesis cannot be overemphasized; nevertheless, if it is decided to operate, a little time may be allowed to improve the patient's condition by blood transfusion unless bleeding is so profuse as to permit no delay. Chronic gastric ulcer is a particularly strong indication for surgery; bleeding from this source carries a high mortality under medical treatment and its operative arrest by gastrectomy is generally easier than is the surgery of bleeding duodenal ulcer. The indications for surgical intervention in haematemesis and the treatment of bleeding oseophageal varices will be discussed in further contributions to this series.

TODAY'S DRUGS

With the help of expert contributors we publish below notes on a selection of drugs in current use.

Epsilon Aminocaproic Acid

Epsilon aminocaproic acid (E.A.C.A.), marketed by Kabi Pharmaceuticals Ltd. under the name of Epsikapron, is a potent synthetic inhibitor of fibrinolysis. It is used in the treatment of haemorrhagic states.

Chemistry and Pharmacology

E.A.C.A. is a monoamino carboxylic acid structurally related to lysine; its full inhibitory action is dependent on the epsilon position of the amino group. It does not occur naturally but is synthesized as a white crystalline substance, freely soluble in water, with a molecular weight of 131.

E.A.C.A. inhibits the activators which convert the inactive globulin plasminogen into plasmin, the enzyme which normally digests fibrin. At concentrations greater than 10^{-4}M. E.A.C.A. competes with the activators for the enzyme-binding sites of the plasminogen molecule[1] Weak non-competitive inhibition of plasmin occurs only after a hundredfold increase of concentration, and even then no effect is apparent on blood coagulation or platelet aggregation.

Clinically significant effects are seen with a plasma E.A.C.A. concentration of 10^{-3}M.; this can be produced by a dosage of 0.1 g./kg. body weight given either orally or intravenously every four hours.[2]

E.A.C.A. is absorbed rapidly from the gut with peak plasma levels two hours after a single oral dose. The drug is distributed throughout the body water, freely entering the intracellular compartment. The half-life in plasma after a single intravenous injection is of the order of one to three hours; continuous infusion is therefore necessary to maintain adequate blood levels by the intravenous route. Excretion is almost entirely via the kidney, and within 12 hours of a single oral dose 60% to 90% appears unchanged in the urine.[2]

Clinical Indications

The use of E.A.C.A. should be considered when bleeding cannot be controlled by conventional procedures.

Coagulation Disorders, including Haemophilia.—Whenever fibrin formation is deficient, inhibition of even the normal fibrinolytic process may preserve sufficient fibrin to permit adequate haemostasis. The use of E.A.C.A. need not therefore be confined to those cases in which an increase in fibrinolysis can be demonstrated.

In haemophilia treatment with E.A.C.A. has been shown to reduce bleeding after tooth extraction.[3] Patients under treatment with anticoagulants, and patients with von Willebrand's disease, have also been successfully treated, both for tooth extractions and for menorrhagia.

These examples are concerned with bleeding to the exterior. E.A.C.A. may be just as effective in the control of internal bleeding, but great care in the evacuation of blood clot from the body cavities is necessary if residual damage due to formation of fibrous tissue is to be avoided. In cases of haematuria successful results have been claimed, but urinary obstruction is known to be a possibility, and the incidence of this complication has yet to be defined.

E.A.C.A. has also been used in double-blind trials to test its efficacy in reducing the incidence of spontaneous bleeding episodes in haemophilia.[4] Early results are promising but not yet conclusive.

Menorrhagia.—The concentration of plasminogen activators in the endometrium is high and increases as menstruation approaches to reach a maximum on the first day of the period. Double-blind trials have shown that inhibition of fibrinolysis reduces the volume of menstrual flow.[5] If curettage has excluded organic lesions of the uterus and endometrium treatment with E.A.C.A. may be useful for those patients who wish to preserve fertility, especially if hormone therapy has failed or is contraindicated. The drug need be started only when bleeding becomes heavy and need be continued only so long as the flow lasts.

Prostatectomy.—Several trials have shown that the blood loss after prostatectomy can be reduced by giving low doses of E.A.C.A.[6] The incidence of thrombotic complications in the postoperative period is not affected by E.A.C.A. alone. However, a considerable reduction in pulmonary embolic complications has been achieved by the routine prophylactic administration of heparin, made possible by the simultaneous use of E.A.C.A.[7]

Hyperfibrinolysis.—Excessive amounts of plasminogen activators in the blood may provoke bleeding by the release of plasmin in amounts which overwhelm the natural antiplasmins and attack essential clotting factors, reducing their concentration and blocking fibrin formation still further by the anticoagulant effects of the split products of fibrinogen. In these

circumstances E.A.C.A. is one of the ideal treatments, but primary hyperfibrinolysis is difficult to distinguish from other causes of the defibrination syndrome. It is probably rare unless activators such as streptokinase or urokinase are being deliberately administered as a part of thrombolytic therapy.

Defibrination Syndrome.—In complicated obstetrics, major surgical operations, and disseminated cancer massive bleeding may occur suddenly after widespread intravascular clotting has depleted the available clotting factors.[8] A common secondary phenomenon in these cases is an increase in fibrinolysis, which is likely to have a protective effect. For this reason when a low level of circulating fibrinogen is demonstrated E.A.C.A. is probably best held in reserve.

Treatment should begin with controlled replacement of fibrinogen and other missing factors, including platelets. If the stimulus to defibrination persists and bleeding continues heparin may be used as an anticoagulant; once the stimulus to clot formation has been controlled in this way E.A.C.A. may assist haemostasis by preventing the removal of fibrin.[9]

Other Uses.—The list of examples in which E.A.C.A. may be used to assist haemostasis is not exclusive. Other suggested uses include epistaxis, ulcerative colitis, and haematemesis; precise indications have yet to be defined.

An anti-allergic action has been attributed to the drug, which has been said to provide improvement in progressive systemic sclerosis and in eczema.[10] Experimental results are conflicting, and the clinical impressions do not stem from organized trials.

Toxicity and Side-effects

Non-thrombotic.—One large carefully investigated series reports the administration of the drug to 774 patients without serious toxicity.[11] Minor side-effects include nasal congestion, conjunctival suffusion, nausea, vomiting, diarrhoea, maculopapular rashes, and transient hypotension.

Daily injection into pregnant rats has been reported to cause teratogenic effects in the embryos.[12] Although more recent work failed to confirm this finding,[13] E.A.C.A. should not be given in the early stages of pregnancy until further studies are available. E.A.C.A. also inhibits the incorporation of lysine into the proteins of a rat diaphragm preparation,[2] and may slow the growth rate of rats given 100 mg. daily.[14] For these reasons prolonged administration should be avoided during the active growth period of childhood.

High doses have been reported to cause subendocardial haemorrhages in dogs,[10] but no such lesion has been described in man. The intravenous administration of 5 g. of E.A.C.A. per hour, a fivefold increase of the usual dose, causes a small (about 5%) decrease in systolic and diastolic blood pressure, together with a bradycardia, but without any significant change in renal blood flow or glomerular filtration rate.[15] No electrocardiographic changes have been noted. One patient has been reported,[16] who died 32 days after being given E.A.C.A. to control a haemorrhagic state associated with prostatic carcinoma. At necropsy scattered areas of necrosis were found in heart and liver, but their cause was not clear.

Thrombotic.—Fibrin is necessary to promote haemostasis or repair, but once its immediate purpose has been accomplished it must be removed by the fibrinolytic system, normally in dynamic equilibrium with the coagulation system. Undesirable effects may occur if the balance is disturbed by the administration of E.A.C.A., so that removal of fibrin is prevented.

Fibrin formed from blood within a body cavity may remain to become organized into fibrous tissue. In the pleural space this may form a rigid coating surrounding the lung.[10] Similar persistence of clot within a joint cavity may potentiate residual damage to the joint. If clotting occurs in the urinary passages during treatment of haematuria with E.A.C.A. the indestructible clots may cause permanent obstruction to the urinary outflow tract.[6]

Widespread intravascular fibrin formation is a feature of the defibrination syndrome and also of the later phases of shock. In most of these cases plasminogen activators are released which stimulate endogenous fibrinolysis. If this protective effect is blocked by E.A.C.A. widespread persistence of intravascular thrombi may have fatal results. Examples of such a condition have been found in experimental animals and in man.[17]

Presentation and Dose

For oral use there are sachets of effervescent powder, each containing 3 g. of E.A.C.A. There is also a 30% w/v syrup.

For intravenous use, or local application, a 40% w/v solution may be given diluted at least fourfold in physiological saline or glucose solution.

The usual dose, oral or intravenous, is 0.1 g./kg. body weight repeated every four hours. Intravenous administration is started by giving the calculated dose in 30 minutes, followed by a sustaining infusion. Dosage should be reduced if renal function is impaired. As the drug is concentrated in the urine, 3 g. of E.A.C.A. by mouth every eight hours is sufficient to maintain urinary activity in the adult.

There is no contraindication to the simultaneous administration of heparin or oral anticoagulants.

E.A.C.A. is available as Epsikapron. The basic N.H.S. price of 30 sachets of 3 g. is 39s. 10d., and of 250 ml. of 30% syrup is 35s.

REFERENCES

1. Alkjaersig, N., Fletcher, A. P., and Sherry, S., *J. biol. Chem.*, 1959, **234**, 832.
2. McNicol, G. P., Fletcher, A. P., Alkjaersig, N., and Sherry, S., *J. Lab. clin. Med.*, 1962, **59**, 15.
3. Cooksey, M. W., Perry, C. B., and Raper, A. B., *Brit. med. J.*, 1966, **2**, 1633.
4. Gordon, A. M., McNicol, G. P., Dubber, A. H. C., McDonald, G. A., and Douglas, A. S., ibid., 1965, **1**, 1632.
5. Nilsson, L., and Rybo, G., *Acta obstet. gynaec. scand.*, 1965, **44**, 467.
6. McNicol, G. P., Fletcher, A. P., Alkjaersig, N., and Sherry, S., *J. Urol. (Baltimore)*, 1961, **86**, 829.
7. Andersson, L., *Acta chir. scand.*, 1965, **130**, 393.
8. *Brit. med. J.*, 1965, **2**, 955.
9. Bergin, J. J., *Med. clin. N. Amer.*, 1966, **50**, 1669.
10. McNicol, G. P., and Douglas, A. S., *Brit. med. Bull.*, 1964, **20**, 233.
11. Nilsson, I. M., Andersson, L., and Björkman, S. E., *Acta med. scand.*, 1966, Suppl. No. 448.
12. Johnson, A. J., Skoza, L., and Claus, E., *Thrombos. Diathes. haemorrh. (Stuttg.)*, 1962, **7**, 203.
13. Eneroth, G., and Grant, C. A., *Acta pharm. suec.*, 1966, **3**, 115.
14. Lang, K., and Bitz, H., *Biochem. Z.*, 1953, **324**, 495.
15. Swartz, C., Onesti, G., Ramirez, O., Shah, N., and Brest, A. N., *Curr. ther. Res.*, 1966, **8**, 336.
16. Nour-Eldin, F., and Draisey, T. F., *J. clin. Path.*, 1963, **16**, 61.
17. Naeye, R. L., *Blood*, 1962, **19**, 694.