Current Practice

DISEASE OF THE DIGESTIVE SYSTEM

Bleeding from the Upper Gastrointestinal Tract

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Haematemesis and melaena are symptomatic of haemorrhage into the upper gastrointestinal tract. When such bleeding has occurred the patient will almost always volunteer the information that the blood, if it has been vomited, has come from the stomach. Occasionally the origin of the blood may not be immediately obvious—as when haematemesis occurs as an isolated symptom in a previously healthy person—and there may also be difficulty when the supposed blood vomit has not been kept to be seen by the doctor. Examination of the stools will resolve any such doubts. Haematemesis never occurs without some blood appearing in the stools, and even in the absence of melaena chemical examination of the faeces will show the presence of much more blood than could be accounted for by other means.

Incidence and Mortality

Haematemesis is one of the commonest medical emergencies that may threaten life, and of the complications of peptic ulcer it is the most frequently encountered. Estimates of the clinical incidence of haematemesis vary from a quarter to approximately a third of all patients with peptic ulcer. The tendency to bleed is about the same during the whole course of the disease, with the exception of the first year, in which it is somewhat greater. Most published series show a mortality rate of between 5% and 10% under conservative medical treatment. However, if only examples of massive haemorrhage are considered the death rate is higher. Massive bleeding is defined as haemorrhage that is accompanied by shock, a lowering of the red cell count to 3,000,000/cu. mm. or less, and a haemoglobin level below 50%. With these criteria of selection the mean mortality rate is about 15%, with a range of 4% to 66%.

Though the mortality from haemorrhage in chronic ulcer is considerably higher than in bleeding from acute lesions, the most important correlation is with age. Below 45 years the death rate is small, but it increases sharply after the age of 60; in most western countries haematemesis is steadily increasing both in frequency and severity as the age structure of communities alters with increasing numbers of older people.

Cause of Bleeding

Peptic ulcer is easily the most important cause of haematemesis and melaena, accounting for about 9 out of every 10 admissions, but rather more than a quarter of these patients have no demonstrable radiological abnormality when examined after bleeding has ceased. Nevertheless, gastroscopy or gastrocamera inspection performed in the early stages of illness will reveal the presence of an acute ulcer in over half of this group with negative *x*-ray findings. These lesions heal quickly, and it is in this group that aspirin consumption makes its appreciable contribution to the number of hospital admissions for upper gastrointestinal bleeding.

Haematemesis and melaena are not uncommon complications of carcinoma of the stomach, but the diagnosis has usually been made before the onset of bleeding. In these cases the loss of blood is generally small, though exceptionally, as in the ulcerating type of cancer, it may be profuse. As the blood remains in the stomach for some time before it is vomited, it is generally coffee coloured and mixed with food and mucus.

Haemorrhage from oesophageal varices is not uncommon in cirrhosis of the liver, but confusion in diagnosis may occur since there is often a dyspeptic history and sometimes an associated ulcer. Bleeding from an oesophageal growth is rarely an early symptom and a diagnosis is likely to have been made already on account of dysphagia. Likewise an aortic aneurysm leaking into the oesophagus will almost certainly have given rise to other symptoms and signs to betray its presence. Oesophageal hiatus hernia, sliding or fixed in character, is a common gastroenterological lesion, and bleeding may occur either from an associated oesophagitis or from a gastric ulcer straddling the region of constriction at the level of the diaphragm.

Certain blood dyscrasias may be associated with haematemesis and melaena, but they are infrequent causes of these symptoms. Nevertheless, when the source of bleeding is not obvious nor the history typical the possibility of an underlying haemorrhagic diathesis should always be investigated. Usually a history of bleeding elsewhere will be obtained. Anticoagulants should not be given to patients with known gastroduodenal ulceration, but nevertheless patients on anticoagulant treatment can develop acute ulceration.

Symptoms and Signs

The clinical picture in massive haemorrhage is dominated by the development of shock. The patient is pale both from blood loss and compensatory vasoconstriction. The pulse is rapid and small; there may be marked sweating. One of the first changes to be recorded is a fall in blood pressure, and repeated measurements are essential in estimating cessation of recurrence of bleeding. Restlessness may be extreme, and rapid shallow respirations are of grave import. It is usual for any ulcer pain preceding the bleeding to disappear with the onset of haemorrhage, and the persistence of pain of any severity should always suggest the possibility of concomitant perforation, a particularly lethal combination.

The management of patients with haematemesis and melaena depends to a large extent on the diagnostic probabilities, and an adequate history should be obtained either from the patient or, if he is too ill, from an informed relative. Inquiry should be made for any antecedent history suggestive of peptic ulceration, and any record of perforation or previous radiological confirmation of the existence of an ulcer is extremely valuable.

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The physical examination of these patients should be undertaken with care so as not to exhaust them. The severity of the bleeding will be immediately apparent and should be confirmed by measurement of pulse rate and blood pressure. Abdominal examination must include palpation for an enlarged spleen and an epigastric mass. The existence of a collateral circulation in hepatic cirrhosis is diagnostic of this condition. Malignant disease of the stomach may suggest its presence by a palpable tumour and enlarged glands in the supraclavicular fossa. An assessment of the extent of arteriosclerotic change in older patients is important and demands examination of the superficial arteries and the fundi. Where thrombocytopenic purpura is suspected, a tourniquet test with a sphygmomanometer cuff should be carried out.

Principles of Treatment

There is no longer any controversy about the advisability of liberal feeding. Most patients tolerate bland diet extremely well, given two-hourly with sufficient fluid to correct dehydration and maintain an adequate urinary output. Confinement to bed is essential if bleeding continues and morphine 15 mg. or sodium phenobarbitone 200 mg. may be given to allay restlessness or anxiety. Pulse rate and blood pressure should be measured hourly and the details recorded, together with any further episode of bleeding, on a chart available at the bedside.

There can be no hard-and-fast rules on when blood transfusion is required. While determinations of blood volume would enable the clinician to assess the amount of blood lost accurately, such techniques are as yet unsuitable for routine use and reasonable indications for transfusion are a pulse rate of 110 or more or a systolic blood pressure of 110 mm. Hg or less. Such patients need transfusion urgently, and prompt action is particularly important in the elderly to prevent the irreversible cerebral damage that may complicate prolonged shock. If severe anaemia is allowed to develop a compensatory increase in venous pressure leads to greater cardiac filling and improved cardiac output. This hyperkinetic phase is shown by the presence of a full, bounding pulse, raised pulse pressure, and jugular venous distension. The venous pressure also rises during the initial stages of transfusion, and though it falls again as the arterial pressure rises overtransfusion carries the risk of precipitating heart failure. Ideally part of the replacement after massive bleeding should consist of packed red cells to minimize the possibility of overloading the circulation and to reduce the risk of pulmonary oedema. Usually gastroduodenal bleeding stops within 12 or 24 hours of admission, most often permanently, and during this time 1,500–3,000 ml. of blood may be given by slow drip transfusion (40 drops per minute). Occasionally there is a continuous slow loss of blood requiring intermittent transfusion, and this seems to happen most commonly in patients bleeding from acute lesions ; the vessels from which an acute ulcer bleeds are mostly small and submucosal, and such bleeding lacks the dramatic quality of arterial haemorrhage from the base of a chronic ulcer. Exceptionally, chronic ulcers bleed so severely that the only hope for the patient lies in intra-arterial transfusion and immediate operation.

Transfusions of 500 ml. are unnecessary and wasteful. Large volumes of blood given rapidly carry risks of citrate intoxication and hyperkalaemia. The former may lead to defective clotting and myocardial failure and it is wise to give 10 ml. of 10% calcium gluconate intravenously after every fourth bottle of blood. Potassium intoxication carries the very real threat of cardiac arrest—particularly if bank-blood near the limit of its expiry is used—when serum potassium levels may reach 25 mEq. Warming the blood before use will encourage the return of potassium to the cells and the danger can be further diminished by the infusion of dextrose solutions. However, when such massive transfusions are in question the need for surgical arrest of haemorrhage should be urgently reviewed.

Medication other than vitamin concentrates is best avoided, though iron may be given by mouth from the start. Constipation is the rule after haematemesis and is usually well tolerated by the patient. Purgatives should not be administered, but there is no contraindication to the giving of an enema or the use of a glycerin or Dulcolax (bisacodyl) suppository.

Time in Bed

There is no reason why the patient whose course is uncomplicated should not be allowed up by the second or third day in hospital. There is no evidence that recovery after haematemesis is hastened by confinement to bed, the dangers of which are obvious, especially in older people with associated degenerative disease.

The management of bleeding from oesophageal varices consequent on cirrhosis will be considered in a separate article. Some of these patients die from haemorrhage long before the reduction of hepatic function has become a threat to life.

Though brisk continued bleeding from peptic ulcer is an indication for surgical treatment, there are a few patients in whom operation is out of the question because of severe associated disease or overwhelming senility. Nevertheless, however unpromising the prognosis may appear, neither hope nor treatment should be abandoned. Distension of the stomach with blood clot may be an important factor preventing the atonic stomach of a shocked patient from arresting the bleeding by contraction. Emptying the stomach with a Senoran's evacuator followed by lavage with ice-cold water may help to stop bleeding. The use of a topical haemostatic such as thrombin after lavage with 1 : 1000 adrenaline has been advocated in the treatment of bleeding acute peptic ulcer. In such cases the stomach should first be emptied through a large bore tube and then washed with 1 : 1000 adrenaline ; finally, thrombin in a suitably viscous vehicle as methylcellulose is instilled into the stomach. Gastric cooling has not won any wide acceptance either for the treatment of bleeding peptic ulcer or for haemorrhage from oesophageal varices using an oesophageal extension of the gastric balloon.

Early Diagnosis in Haematemesis

The difficulty of treating bleeding peptic ulcer largely concerns the detection of those patients in whom the prognosis with medical measures must be considered poor and who will bleed to death unless surgery is employed. The problem, however, is not always easily solved. Acute ulceration or erosion of the stomach or duodenum is a common lesion which usually responds well to medical treatment. Unfortunately this diagnosis is not always obvious, being largely based on negative evidence and frequently confirmed only in retrospect by a negative *x*-ray. The vessels from which an acute ulcer bleeds are mostly small and submucosal, and operation should be undertaken only as a life-saving measure or because a chronic ulcer is suspected.

Extragastric sources of bleeding must also be excluded before patients are submitted to surgery. The history is most valuable in achieving a correct diagnosis ; thus where chronic peptic ulceration is responsible for the bleeding it will be unusual to find such a patient denying previous periodic dyspepsia with relief of his pain by food and alkalis. The shorter the history of preceding dyspepsia, the more likely is the lesion to be acute and therefore susceptible to cure by medical means alone. Unfortunately the diagnosis is not always obvious and the history often misleading.

An attempt to obtain diagnostic information in the acute stages of illness can be helpful in subsequent management, for if chronic peptic ulcer can be diagnosed with confidence surgical treatment is to be recommended for patients over the age of 50 in whom bleeding continues or recurs. The success of such

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