The metabolic effects of moderately severe upper gastrointestinal haemorrhage in man

K. J. Foster* D.M.
C. Binder§ M.D.
S. J. Karran† F.R.C.S.
S. Talbot† B.Sc.

K. G. M. M. Alberti† F.R.C.P.
G. Holdstock* M.R.C.P.
C. L. Smith* M.D.
D. C. Turnell† B.Sc.

Departments of *Medicine, †Chemical Pathology and Human Metabolism, and §Surgery, University of Southampton and §Hirdor Hospital, Klampenborg, Copenhagen, Denmark

Summary
The metabolic effects of moderately severe gastrointestinal haemorrhage were investigated in man. Before resuscitation, patients had raised circulating concentrations of glucose, lactate, alanine, glycerol and cortisol.

After urgent operation for haemorrhage, metabolite concentrations were similar to those of control patients having elective abdominal surgery, but insulin concentrations were higher and cortisol lower in haemorrhage patients.

There were no significant differences in nitrogen excretion between haemorrhage patients and their controls, but urinary 3-methyl-histidine excretion by haemorrhage patients was lower indicating decreased muscle protein breakdown. Decreased amino acid release from muscle might account for previously reported impaired wound healing after haemorrhage.

Introduction
Upper gastrointestinal haemorrhage is common and is associated with a high mortality (Johnston et al., 1973; Schiller, Truelove and Gwyn-Williams, 1970). The reason for this is not clear, but compared to patients undergoing elective operation, patients requiring urgent surgery for bleeding peptic ulcer have a higher mortality (McKeown, 1973) and a greater incidence of non-infective complications such as wound dehiscence (McGinn, 1976).

Experimental controlled external haemorrhage

Requests for reprints to Mr S. J. Karran

in man and animals has been noted to produce metabolic features of a stress reaction similar to other injuries (Skillman, Hedley-White and Pallotta, 1971; Hiebert and EgdaI, 1972). In animals, experimental haemorrhage has been shown to result in impaired wound healing (McGinn, 1976; Sandberg and Zederfeldt, 1961). Surprisingly, there has been no extensive study of the metabolic effects of gastrointestinal haemorrhage in man and a study is now presented with particular regard to intermediary and nitrogen metabolism after haemorrhage of moderate to severe extent.

Patients and methods
All subjects gave informed consent to the study, which was approved by the local Ethical Committee. Blood concentrations of metabolites and hormones were measured in 12 patients who presented sequentially with acute upper gastrointestinal haemorrhage severe enough to require transfusion therapy (Table 1). The mean blood pressures were 145/82 mmHg supine and 129/67 mmHg sitting or standing, mean supine pulse rate on admission was 96 beats/min and mean haemoglobin concentration 9.5 g/dl (s.e. mean ±0-6). The mean transfusion requirement of the patients was 3.8 units (s.e. mean ±0-4). Two patients were clinically shocked at the time of admission with a supine systolic blood pressure of <100 mmHg.

The diagnoses were gastric erosions, 1 patient; benign gastric ulcer, 4; duodenal ulcer, 5; stomal...
ulcer, 1; carcinoma of the stomach, 1. Patients with liver or endocrine dysfunction and those on concurrent drug therapy which might disturb metabolism (e.g. corticosteroids) were excluded.

Blood samples were drawn immediately on admission before any fluid replacement therapy was commenced, and 24-hr urine collections were also made, starting at 9 a.m. on the day after admission, in 6 patients who took no food until completion of the collection. These latter patients all completed their blood transfusions before the start of the 24-hr urine collection and received infusions of 0.9% (0.15 mol/l) sodium chloride solution during the urine collection.

Five patients who underwent urgent surgery for recurrent upper gastrointestinal haemorrhage within 4 days of admission were also studied (Table 2). Only one of these patients was severely shocked at the time of commencement of operation. Blood samples for estimation of venous blood concentra-

Table 1. Characteristics, circulating concentrations of metabolites and hormones and urinary excretion of nitrogenous products in patients admitted with acute upper gastrointestinal haemorrhage and healthy controls. (Mean ± s.e. mean)

<table>
<thead>
<tr>
<th></th>
<th>Haemorrhage patients</th>
<th>Normal control subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Sex ratio (M : F)</td>
<td>10 : 2</td>
<td>4 : 1</td>
</tr>
<tr>
<td>Age (years)</td>
<td>66 (5)</td>
<td>26 (3)***</td>
</tr>
<tr>
<td>Weight (% IBW†)</td>
<td>100 (4)</td>
<td>110 (6)</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>6.2 (0-3)</td>
<td>4.7 (0-1)***</td>
</tr>
<tr>
<td>Lactate (mmol/l)</td>
<td>1.13 (0-15)</td>
<td>0.65 (0-06)**</td>
</tr>
<tr>
<td>Alanine (mmol/l)</td>
<td>0.32 (0-03)</td>
<td>0.24 (0-01)*</td>
</tr>
<tr>
<td>Glycerol (mmol/l)</td>
<td>0.088 (0-011)</td>
<td>0.062 (0-004)*</td>
</tr>
<tr>
<td>Total ketone bodies (mmol/l)</td>
<td>0.44 (0-11)</td>
<td>0.38 (0-04)</td>
</tr>
<tr>
<td>Insulin (μu./l)</td>
<td>6.8 (1-5)</td>
<td>3.7 (0-6)</td>
</tr>
<tr>
<td>Cortisol (nmol/l)</td>
<td>355 (49)</td>
<td>154 (5)**</td>
</tr>
</tbody>
</table>

24-hr urine excretion

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>6</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total nitrogen (mmol/kg/day)</td>
<td>10.0 (0-4)</td>
<td>10.4 (1-3)</td>
<td></td>
</tr>
<tr>
<td>Urea production (mmol/kg/day)</td>
<td>4.4 (0-3)</td>
<td>4.5 (0-5)</td>
<td></td>
</tr>
<tr>
<td>3-methyl-histidine (μmole/kg/day)</td>
<td>1.6 (0-3)</td>
<td>3.1 (0-4)*</td>
<td></td>
</tr>
</tbody>
</table>

*Significant difference between groups  *P<0.05,  **P<0.01,  ***P<0.001.

Blood samples were taken at 9 a.m. on the first 4 postoperative days and also at 9 p.m. on the first postoperative day. Three consecutive 24-hr urine collections were also made in the postoperative period from 9 a.m. on the first postoperative day. These patients received an infusion of 1.5 g glucose/kg body weight/day from the start of the operation and throughout the subsequent study period.

Five healthy subjects (4 male) were controls. The majority of haemorrhage patients were admitted late in the afternoon and usually had not eaten since morning or before. To standardize with patients, blood samples were taken from controls at 6 p.m. after a 10-hr fast. The controls also continued their fast until they had completed a 24-hr urine collection, commencing at 9 a.m. the following day. During this period they remained at rest and took only water by mouth.

The patients undergoing operation for gastrointestinal haemorrhage were compared with 8 surgical control patients previously investigated in a similar manner after elective abdominal surgery (Table 2) (Foster et al., 1980).

Samples of free-flowing venous blood (12 ml) were drawn from resting patients or volunteers for automated fluorimetric assay of blood glucose, lactose, alanine, glycerol and 3-hydroxybutyrate concentrations (Lloyd et al., 1978), for kinetic spectrophotometric assay of blood acetoacetate (Price, Lloyd and Alberti, 1977), and for estimation of serum insulin and cortisol concentrations by double antibody and competitive protein binding
technique respectively (Soeldner and Slone, 1965; Kehlet, Binder and Engbaek, 1974).

Twenty-four hr urine collections were made into 25 ml of 5-mol/l hydrochloric acid as preservative. Total urinary nitrogen excretion was measured using the micro-Kjeldahl technique, urea excretion by the urease-Berthelot method and urinary 3-methyl-histidine with a Technicon TSM amino acid analyser with lithium citrate buffer system.

The sum of the concentrations of acetoacetate and 3-hydroxybutyrate are presented as ‘total ketone bodies’. Urinary excretion of compounds is expressed per kg body weight per day. Urea excretion has been corrected for changes in blood urea and is therefore reported as ‘urea production’ (Lee, 1974). Student’s ‘t’ test was used to compare variables. Results are shown as the mean ± s.e. mean.

Results

All the patients studied survived their gastrointestinal haemorrhage although some were critically ill for a period. The majority were not shocked at the time of entry into the study, although all had either signs of hypovolaemia including tachycardia and postural hypotension or had a history of syncope related to their haemorrhage, indicating in each case considerable blood loss with a minimum transfusion requirement of 1 litre of whole blood.

Circulating metabolites and urea excretion on admission (Table 1)

The haemorrhage patients studied on admission to hospital were older than the normal control subjects. Compared with controls, the patients had raised circulating concentrations of glucose, lactate, alanine, glycerol and cortisol; insulin concentration also tended to be higher (0-10 > P > 0-05). Urinary excretion of nitrogen and urea production were similar in both groups but 3-methyl-histidine excretion was 50% lower in the patient group.

Metabolism after operation

The 5 subjects studied after operation for gastrointestinal haemorrhage were physically similar to the surgical controls (Table 2). Pre-operative concentrations of metabolites and hormones were also similar.

After operation, mean circulating concentrations of metabolites (Table 3) were similar in haemorrhage patients and surgical control patients. However, mean insulin concentrations were higher and cortisol concentrations lower in the haemorrhage patients. While nitrogen excretion and urea production tended to be greater, 3-methyl-histidine excretion was again markedly decreased in the haemorrhage patients’ group (Table 4).

Discussion

This study confirms that moderately severe gastrointestinal haemorrhage, as frequently encountered clinically, induces a stress reaction similar in some features to that expected from experimental haemorrhage (Skillman et al., 1971; Hiebert and Egdahl, 1972), and traumatic injury (Batstone et al., 1976; Meguid et al., 1974) probably related to increased secretion of cortisol and catecholamines (Batstone et al., 1976). It is important to note, however, that the changes in concentrations of metabolites found in the haemorrhage patients were small. The patients studied presented sequentially and it is believed that they are similar to those studied by other workers and reported to have a high mortality. All required transfusion therapy although shock was observed in only a minority. Nevertheless, the observed changes do not suggest that metabolic decompensation such as severe
hyperglycaemia or lactic acidosis, accounts for the poor prognosis of patients with gastrointestinal haemorrhage, even in the high risk group requiring urgent surgery. Such decomposition might be seen in severe haemorrhagic shock but in the authors’ experience this has been uncommon when milder degrees of shock are treated urgently.

The differences are not accounted for by the age difference between controls and patients studied on admission to hospital (Foster et al., 1978) or by the absorption of blood protein from the gut (Wahren, Felig and Hagenfeldt, 1976). Surprisingly, cortisol concentrations were slightly higher in the control group after operation, although not on admission. However, the authors have previously found rather lower cortisol concentrations amongst other subjects after elective abdominal surgery and this result may be unrepresentative (Foster et al., 1980).

As expected, nitrogen excretion tended to be higher after gastrointestinal haemorrhage. In contrast, 3-methyl-histidine excretion was decreased. The excretion rate of this amino acid provides a quantitative measure of the rate of skeletal muscle breakdown (Haeverberg et al., 1975; Long et al., 1975). Excretion is typically raised in catabolic states such as infection and abdominal surgery but is decreased in starvation (Long et al., 1977; Young et al., 1973; Foster et al., 1979).

The present finding of lowered urinary excretion of 3-methyl-histidine after gastrointestinal haemorrhage is therefore surprising as the dietary states of patients and controls were carefully matched. These observations provide no definite explanation for this anomaly. Patients studied on admission were older than their controls, but the fall in protein turnover with age (Golden and Waterlow, 1977) is too small to account for the difference in 3-methyl-histidine excretion, while those patients studied after operation were the same age as their controls. This decrease in muscle protein breakdown may be of great significance. Muscle acts as a store of protein and release of amino acids from muscle for resynthesis into protein at other sites is of great importance in catabolic situations (Daniel, Pratt and Spargo, 1977). Failure of release of amino acids from muscle after operation for haemorrhage might contribute to the impaired wound healing reported after haemorrhage (McGinn, 1976; Sandberg and Zederfeldt, 1961) if blood protein absorbed from the gut were insufficient or ineffective in promoting tissue repair. The effects of amino acid supply and of insulin on wound healing after haemorrhage deserve further attention.

Acknowledgments

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References


to factors influencing the outcome. *British Medical Journal, 2*, 7.


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