only showed gut colonization with this strain but subsequently developed a urinary superinfection with it.

The change in haemoglobin level during cephalixin treatment was -0.3 ± 0.5 g./100 ml. (mean $\pm$ S.E., 12 patients). No change was found in the other laboratory tests.

Discussion

Urinary recovery of cephalixin ranged from 29 to 89% of the daily ingested dose, which is significantly less than that found in healthy volunteers by other workers (Kind *et al.*, 1968; Gower and Dash, 1969). Peak blood levels occurred at half-hour to two hours (Fig. 1 A), and the variable rate of absorption is illustrated by the variation in the one-hour blood levels (Fig. 1 B).

Gower and Dash (1969) suggested that, because of almost complete absorption of cephalixin from the gastrointestinal tract, alteration of bowel flora would be minimal. A significant number of our patients, however, acquired either pseudomonas or proteus in their stools (Table II), which confirms the view (Shooter *et al.*, 1966) that antibiotic therapy may be associated with increased faecal carriage of *Ps. aeruginosa*.

Our results indicate that ingested organisms may replace or displace organisms in the lower gastrointestinal tract. Hötzel and Barnes (1966) suggested that large-bowel flora is determined in the upper alimentary tract, and that this process is influenced by antibiotic therapy. It has been found that large oral doses of pseudomonas are necessary (10^4 – 10^5 organisms) before it can be detected in the faeces but that colonization is aided by ampicillin (Buck and Cooke, 1969). Cephalixin may have a similar and more pronounced effect than ampicillin. This would explain the higher carriage rate of pseudomonas in cephalixin-treated patients compared with those not on antibiotic treatment.

Previous reports suggest that patients may become colonized with *Ps. aeruginosa* ingested in food (Shooter *et al.*,

1969) and that the patient's own gastrointestinal tract may be a source of infection with this organism (Shooter *et al.*, 1966, 1969). We found that four patients became colonized with the same ingested strain (serotype 6, phage type (119x)) and that one patient subsequently developed a urinary infection with this strain. This confirms that food may be a source of infection in hospital. It must be stressed, however, that this may apply only to the present population, who were known to be ingesting repeated doses of pseudomonas. Individuals living at home are probably not exposed to colonization by pseudomonas to the same extent (Buck and Cooke, 1969). Acquisition of proteus may have the same basis.

Cephalixin eliminated the infecting organism in 75% of this small series of patients, and the high urinary concentrations obtained (920–4,700 μ g./ml.) make this an efficient urinary antiseptic. The peak blood levels may also produce a systemic effect.

The pronounced fall in haemoglobin levels found by Meyers *et al.* (1969) has not been confirmed.

Drs. K. O. Black and A. M. Dawson kindly allowed us to study patients under their care, and we are grateful to Professors R. A. Shooter and F. W. O'Grady for helpful advice. Cephalixin assays were performed by Mr. R. Ryden of Eli Lilly and Co. Ltd., who supplied cephalixin.

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Preliminary Communication

Reduction of Reaction due to Iron Dextran Infusion using Chloroquine

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Summary: The use of promethazine and chloroquine sulphate to reduce reaction to total dose infusion of iron dextran (Imferon) is described. The patients chosen for the investigation were anaemic pregnant African women living in the coastal region of East Africa where malaria due to *Plasmodium falciparum* is holoendemic. The results show that promethazine has little value in the reduction of reactions whereas chloroquine appears to be effective.

INTRODUCTION

The treatment of iron-deficiency anaemia with total dose infusion of iron dextran (Imferon) has been reported in all parts of the world. The main advantage of single-dose parenteral iron therapy is that large number of patients can be treated in areas with few hospital beds. The main disadvantage is the incidence of generalized reaction in pregnancy. In tropical areas where malaria is endemic the additional load of iron dextran on the lymphoreticular system may disturb the altered cell-mediated immune mechanisms of pregnancy. This may precipitate clinical malaria.

This paper compares promethazine, an antihistamine, with chloroquine in the reduction of reactions to total dose iron dextran infusion in a region where *Plasmodium falciparum* is holoendemic.

PATIENTS AND TREATMENT

Dar-es-Salaam, Tanzania, is in the coastal region of East Africa. Here anaemia in pregnant African women presents a major problem in management. About 10% of these women have haemoglobin levels under 50% (7.4 g./100 ml.). This gives a minimum of 1,500 patients in need of intensive therapy each year.

An investigation of response to iron dextran therapy by total dose infusion was planned. All women with (1) pregnancies of less than 36 weeks having haemoglobin levels of 50% or less, and (2) those with pregnancies estimated to be 36 weeks or more with haemoglobin levels of 60% or less were admitted to hospital for investigation and treatment.

Total dose infusion of iron dextran was given to 1,000 patients, 928 pregnant and 72 in the puerperium. They were divided into four equal groups (A, B, C, and D) for the comparison of reaction to total dose infusion. The treatment given in each group is shown in Table I.

The estimated dose of iron dextran was calculated from the manufacturer's suggested formula: milligrams of elemental iron required = 0.66 WD , where W = body weight in kilograms and D = % haemoglobin deficit. The infusion was started at 20 drops per minute for 30 minutes and if no reaction

occurred the drip rate was increased to 60 drops per minute. Patients stayed in hospital a minimum of 24 hours after the infusion. Patients with a history of allergic response were not included in the series.

Reactions were recorded as immediate or postinfusion. Immediate reactions usually occurred during the test period and produced either dyspnoea or tightness in the chest or both. If these occurred the infusion was discontinued and the patients were excluded from the overall groups. Postinfusion reactions were divided into generalized reactions (pyrexia over 99° F. (37.2° C.), headache, and myalgia) and local reaction in the infusion vein (thrombophlebitis). Before infusion the blood films of all pregnant patients in group A were examined for *P. falciparum*, and the blood films of all pregnant patients in groups A, B, C, and D were examined for *P. falciparum* if a generalized reaction occurred.

RESULTS

Only pregnant patients treated with total dose infusion of iron dextran according to the schedule plan for groups A, B, C, and D were selected for comparison, thus excluding 11 patients with inadequate records and 72 in the puerperium. Thus 231 pregnant patients were in group A, 224 in group B, 235 in group C, and 227 in group D.

The numbers of patients in groups A, B, C, and D who had immediate reaction requiring cessation of the infusion were 5, 3, 2, and 3, an overall incidence of 1.4%.

There was one anaphylactic reaction in the series, and this responded to hydrocortisone sodium succinate 100 mg. intravenously. The incidence of local and general reaction is shown in Table I. Comparison of local reaction occurring in group A and group B, or in group C with group D, shows no significant difference. Comparison of local reactions in group A+B (without chloroquine) with groups C+D (with chloroquine) shows a significant difference of 38 (8.6%) to 5 (1.1%) respectively (S.E.=1.4).

Precipitation of clinical malaria must be considered in generalized reactions. In group A 26 of the 231 patients (11.2%) had *P. falciparum* in the blood films without the clinical presentation of malaria. One of these patients had a generalized reaction. Clinical malaria was considered as a possible cause of the generalized reactions (Table II).

Malarial parasites were found in blood films from 11

patients (28.2%) in group A+B. None were found in group C+D. Exclusion of patients with malarial parasites circulating from the generalized reaction figures in group A+B (without chloroquine) and comparison of the resultant figures with group C+D (with chloroquine) give a significant difference of 28 (6.35%) to 7 (1.5%) respectively (S.E.=1.3). Comparison of the groups treated with and without promethazine in an attempt to reduce reaction showed no significant difference. No generalized reaction to chloroquine sulphate was noted, but occasional rashes did occur.

DISCUSSION

The treatment of anaemia in pregnancy in developing countries in the tropics is a major problem of antenatal care. The use of iron dextran in the management of iron-deficiency anaemia in pregnancy in these regions is of considerable value. Both local and general reactions to total dose infusion of iron dextran have been recorded by many authors and the figures vary. Concentrations of iron dextran up to 25% do not appear to alter the incidence of reactions (Roe, 1968). The maximum concentration used in this series was 12%. Pregnancy, however, does appear to give a higher incidence of generalized reactions. Bonnar (1965) described three cases of generalized reaction in a group of 50 pregnant women in contrast to no generalized reactions in 200 non-pregnant patients. Clay *et al.* (1965) described 13 cases, seven of which could be regarded as severe, in a group of 150 pregnant women. Pathak *et al.* (1967), however, recorded only two cases of myalgia in 200 pregnant patients in Jamaica. References to the East African population (Patel and Tulloch, 1967; Roe, 1968) are not specific for pregnancy. Though dextrose 5% is known to cause a higher incidence of local thrombophlebitis (Bonnar, 1965) when used as a diluent, it was used in this series to avoid excess sodium chloride intake in pregnancy. Chloroquine appears to reduce significantly the incidence of local thrombophlebitis whereas a single dose of promethazine does not.

The incidence of *P. falciparum* in the blood of anaemic patients without clinical manifestations of malaria appears to be similar to that among patients in the puerperium, 12.4% (J. Kigardye, personal communication, 1968) and to that among healthy schoolchildren in Dar-es-Salaam, 12.1% (Clyde, 1967).

The initial object of giving chloroquine before the total dose infusion of iron dextran was to stop the development of clinical malaria. After a single dose of chloroquine (300 mg. base) malarial parasites no longer appeared in association with the generalized reactions. In addition to the antimalarial effect there appeared to be a significant reduction of generalized reactions. Promethazine did not have this effect. This suggests a direct suppression of the inflammatory response effects by cell-mediated immune mechanisms similar to that found in autoimmune diseases. Chloroquine therapy was continued through the pregnancy to reduce further the incidence of haemolysis associated with *P. falciparum* that is known to be high in pregnant women in endemic areas (Lawson, 1967).

CONCLUSIONS

Iron dextran given by total dose infusion during pregnancy appears to precipitate a higher incidence of generalized reactions than it does when given to women who are not pregnant. If given to pregnant women in areas where malaria is holoendemic, total dose infusion of iron dextran increases the incidence of circulating malarial parasites. Administration of oral chloroquine before total dose infusion of iron dextran seems to suppress clinical malaria as a reaction and also to reduce the inflammatory response reaction both at the site of the infusion and in the generalized reaction. The mechanism of the anti-inflammatory effect is not understood.

TABLE I.—Incidence of Local and General Reactions after Total Dose Infusion of Iron Dextran in 917 Pregnant Patients

Group	No. of Cases	Treatment	Local Thrombophlebitis	Generalized Reaction
A	231	Iron dextran in 1,000 ml. 5% dextrose	17 (7.35%)	22 (9.55%)
B	224	Iron dextran in 1,000 ml. 5% dextrose Promethazine 50 mg.*	21 (9.35%)	17 (7.60%)
C	235	Iron dextran in 500 ml. 5% dextrose. Chloroquine base 300 mg.*	2 (0.85%)	3 (1.28%)
D	227	Iron dextran in 500 ml. 5% dextrose Promethazine 50 mg.* Chloroquine base 300mg.*	3 (1.32%)	4 (1.76%)

*Given orally one hour before infusion.

TABLE II.—Incidence of *Plasmodium falciparum* in Association with Generalized Reactions as in Table I

Group	Patients with Generalized Reaction	
	<i>P. falciparum</i> Present Only after Infusion	<i>P. falciparum</i> Not Present after Infusion
A. No chloroquine	5 (2.80%)	17 (7.35%)
B. No chloroquine	6 (2.68%)	11 (4.90%)
C. Chloroquine base 300 mg. ..	0	3 (1.28%)
D. Chloroquine base 300 mg. ..	0	4 (1.76%)

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Medical Memoranda

Retroperitoneal Fibrosis Causing Localized Portal Hypertension

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A single case of portal hypertension due to portal vein compression by retroperitoneal fibrosis has been recorded (Eiseman and Yeoh, 1962). We present here the first report of retroperitoneal fibrosis causing localized portal hypertension.

CASE REPORT

This male patient first presented at another hospital in 1964 at the age of 44 complaining of intermittent pain in the left loin. Investigations showed: haemoglobin 6.7 g./100 ml.; serum iron 10 mg./100 ml.; barium meal and barium enema examinations negative, and blood urea 36 mg./100 ml. Intravenous pyelography showed no excretion of contrast medium on the left side, and a retrograde pyelogram showed a left hydronephrosis. A left nephrectomy was therefore performed. Before discharge he had a haematemesis, but repeat barium studies showed nothing abnormal.

In 1967 he was transferred to St. Thomas's Hospital for investigation of oedema of his legs. There was no clinical evidence of cardiac failure. Examination showed haemoglobin 6.9 g./100 ml.; E.S.R. 54 mm./hour; serum iron 35 mg./100 ml.; iron-binding capacity 385 mg./100 ml.; blood urea 62 mg./100.; plasma creatinine 3.5 mg./100 ml.; and creatinine clearance 30 ml./minute. Liver function was normal.

A barium meal examination showed no abnormality, and in particular no evidence of oesophageal varices. An intravenous pyelogram showed dilatation of the calices of the right kidney, and the right ureter was displaced medially. The histology of the left kidney was reviewed. Fibrous tissue was seen to be infiltrating the renal capsule, and a diagnosis of retroperitoneal fibrosis was made. An inferior vena cavagram showed pronounced narrowing at the level of the second lumbar vertebra.

While under investigation he had two further haematemeses, and laparotomy was therefore performed. This revealed a large fibrous plaque obstructing the inferior vena cava, dilated veins over the pylorus and greater curve of the stomach, a small spleen, but no demonstrable splenic vein. A portal venogram through the gastroepiploic vein showed no evidence of obstruction, and the portal venous pressure was 120 mm. of saline. Despite these findings, it seemed that this situation could be best explained on the basis of portal hypertension. A repeat cavagram showed that the inferior vena cava was not suitable for a shunt, and so the patient was managed conservatively.

During the next year he had several more haematemeses requiring transfusion, but otherwise remained well and continued at work. In October 1968 a barium meal showed oesophageal varices. A coeliac axis arteriogram (see Fig.) showed the splenic artery to be tortuous and grossly dilated. A transsplenic portal venogram showed total occlusion of the splenic vein as far as its junction with the portal vein, with extensive varices around the spleen, fundus of stomach, and lower oesophagus.

At a second laparotomy very extensive retroperitoneal fibrosis was found involving the left gastric pedicle, the posterior wall of the stomach, the posterior half of the spleen, and all the vessels in the splenic hilum. There were massive varices over the stomach. A portal venogram showed occlusion of the splenic vein, with

a patent superior mesenteric vein entering the portal vein. The portal pressure was again normal.

The stomach was mobilized with great difficulty; it could not be separated from the spleen, and a splenectomy was therefore carried out. Portoazygos disconnection was then achieved by gastric transection. He made a good initial recovery but later developed peritonitis, and subsequent hepatic and renal failure. These did not respond to medical treatment, including peritoneal dialysis, and he died two weeks after operation.

Necropsy showed breakdown of the suture line of the gastric transection. The liver was macroscopically normal. The splenic artery and vein ran through dense fibrous tissue around the pancreas; the splenic vein was practically obliterated by external compression. The superior mesenteric and portal veins were normal. There was a hydronephrosis of the right kidney, and the ureter was involved in fibrous tissue from just below the kidney. The abdominal aorta and inferior vena cava were surrounded by fibrous tissue from the level of the coeliac axis to just below the pelvic brim. Histology confirmed widespread intra-abdominal retroperitoneal fibrosis. The liver showed evidence of bile stasis, but there were no other gross pathological changes.

COMMENT

In this patient, the rare situation of localized portal hypertension followed involvement of the gastric and splenic veins by retroperitoneal fibrosis with sparing of the portal vein.

Initially the cause of the gastrointestinal haemorrhage could not be established as barium studies were repeatedly negative and oesophageal varices were not seen until very late. While at the first laparotomy a diagnosis of portal hypertension seemed likely, the site of the portal obstruction was not found, and not until a year later, at a second laparotomy, was the diagnosis fully established. The disease process

Selective coeliac axis arteriogram showing considerably dilated and tortuous splenic artery.