Rectal administration of metronidazole in severely ill patients

E M BARKER, J M AITCHISON, J S CRIDLAND, L W BAKER

Abstract

Ten severely ill patients with life threatening sepsis received metronidazole as suppositories and blood concentrations of the drug were measured twice daily over five days. Therapeutic blood concentrations of metronidazole were maintained at all times in all patients.

Rectal administration of metronidazole is accepted as effective prophylaxis against infection associated with surgery and as treatment of established infection. This study shows that in gravely ill patients metronidazole administered as suppositories gives perfectly adequate therapeutic serum concentrations of the drug, but that to achieve these concentrations rapidly the first suppository should be given with an intravenous loading dose.

Introduction

Metronidazole is regarded as the antibacterial agent of choice for proved or suspected infection by anaerobic organisms from the gastrointestinal or female genital tract.\(^1\) -\(^3\) Bacteroides fragilis is the commonest pathogen and most isolates are sensitive to metronidazole.\(^4\) -\(^5\) Metronidazole is satisfactorily absorbed from the rectum when administered as a suppository,\(^6\) -\(^7\) and its use in this form has gained wide acceptance, especially as prophylaxis before and during operations likely to be complicated by anaerobic wound infection.\(^8\) -\(^9\) Although adequate blood concentrations of metronidazole have been shown after administration as a suppository in healthy volunteers,\(^10\) -\(^11\) and patients undergoing major operations,\(^12\) rectal absorption has been thought to be inadequate in seriously ill patients and patients with sepsicaemia and circulatory deficiency.\(^1\) -\(^3\) In such cases it is commonly accepted that only intravenous administration will provide reliably bactericidal serum concentrations.

Intravenous metronidazole is some 10 times dearer than the rectal preparation, and most seriously ill patients need treatment for at least five days. For many hospital services in developing countries cost preclude the use of intravenous metronidazole for major anaerobic sepsis and chloramphenicol is prescribed, despite its attendant risks and less effective anaerobic activity.\(^1\) We decided to see whether therapeutic serum concentrations of metronidazole could be achieved by administering the drug as a suppository in gravely ill patients with sepsis.

Patients and methods

Ten patients were selected for study on the basis of a clinical diagnosis of sepsicaemia or the discovery at emergency operation of intra-abdominal infection of a degree likely to cause sepsicaemia. Many patients were found to be sepsicaemic by blood cultures. Some of the patients experienced episodes of septicemic shock, and most were treated in an intensive care unit. In addition to metronidazole all patients were given other appropriate antimicrobials, usually gentamicin, for aerobic infection. Because we were not certain that rectally administered metronidazole would provide therapeutic serum concentrations in seriously ill patients, additional anaerobic cover was provided by clindamycin in nine patients and by chloramphenicol in one patient with proved typhoid and peritonitis.

Blood, peritoneal exudate, pus, and tissue biopsy specimens were submitted for aerobic and anaerobic culture whenever possible. The anaerobic treatment regimen was as follows: hour 0 and hour 8, metronidazole 500 mg intravenously and 1.0 g as a suppository; hour 16 and eight hourly thereafter, metronidazole 1.0 g as a suppository and clindamycin 600 mg intravenously. Blood was collected for assay of serum concentrations of metronidazole before administration of the second intravenous dose at eight hours and again 33 minutes after this dose was given. Nine further specimens were collected over the next four days (fig 1). Serum concentrations of metronidazole and the hydroxylated methyl metabolite were determined by high performance liquid chromatography.\(^13\)
Results

The table gives the clinical details of the 10 patients, the number of blood samples obtained for assay in each patient, and the lowest and highest recorded serum concentrations of metronidazole. Figure 1 shows the times of drug administration and blood sampling and the serum concentrations of metronidazole.

The lowest serum concentration of the drug recorded after stopping intravenous administration was 8 mg/l and the highest 43 mg/l. Only six of the 98 blood samples assayed contained less than 10 mg/l. Figure 2 shows the serum concentrations of the hydroxylated methyl metabolite relative to the concentrations of metronidazole.

Discussion

The timing of administration of the suppositories and the use of initial intravenous loading doses were dictated by the pharmacokinetic profile of suppository administered metronidozole in healthy volunteers. Peak serum concentrations are not achieved until some eight hours after administration of a 1.0 g suppository. In patients with established and life threatening sepsis it is essential to provide immediate therapeutic serum concentrations, which can be achieved only by intravenous infusion. To avoid delay in reaching these concentrations the first suppository must be given at the time of the first intravenous dose.

The success of this trial required the cooperation of large numbers of nursing and resident medical staff, who were working under extreme pressure; hence although every effort was made to ensure that drugs were administered and blood samples obtained exactly at the specified times, we were unable to obtain the required 11 samples of blood from more than four of the 10 patients (table). Similarly, the unexpectedly high serum concentrations of metronidazole found eight hours after the first intravenous dose in five patients and the remarkable biphasic grouping of the serum concentrations in those samples (fig 1) suggest that errors may have occurred in the relative timing of blood sampling and drug administration. Despite these shortcomings, the results indicate that in every patient a serum concentration of metronidazole well above the established minimal inhibitory concentration for most anaerobes (6.2 mg/l) was maintained throughout treatment. Eighty-seven of the 98 samples contained between two and seven times the minimal inhibitory concentration, ensuring adequate concentrations in tissues and exudates.

Although the differences did not reach statistical significance, apparently the mean serum concentrations of metronidazole were higher during the early days of suppository administration when patients were severely ill than on days 4 and 5, when clinical improvement was evident in most patients. Contrary to what has been generally accepted, therefore, the concentrations achieved by suppository administration in gravely ill patients were higher than in healthy volunteers. This phenomenon is possibly the result of impaired hepatic and renal function. Maximum serum concentrations of the hydroxylated methyl metabolite were noted between 48 and 72 hours after beginning treatment. Thereafter, as the patients' clinical state improved, concentrations of the metabolite declined at the same rate as those of metronidazole. The highest concentrations of metronidazole (43 mg/l) and the metabolite (20 mg/l) were recorded just before death in the one patient with renal failure. This metabolite has not more than 40% of the biological activity of the parent compound, and its presence in the concentrations recorded in our patients is unlikely to be of therapeutic relevance except in renal failure.

The lack of significant variation in serum concentrations four and eight hours after taking the suppositories suggests that a
satisfactory steady state is achieved by eight hourly administration. Houghton et al showed that administration of the drug as a suppository provides a sustained plateau of serum concentration extending from eight to 16 hours after administration, which suggests that 12 hourly administration may be adequate. The much greater systemic availability of metronidazole from the paediatric (500 mg) suppository than from the 1-g suppository implies that a regimen of 500 mg given as a suppository every 12 hours may be adequate in most patients. Selkon suggested that the dosage of metronidazole recommended at present is excessive and that more metronidazole is being given to patients than is necessary. Further studies are planned to define the optimum treatment regimen.

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References

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Wilson’s disease: a diagnostic dilemma

HISHAM NAZER, V F LARCHER, R J EDE, A P MOWAT, ROGER WILLIAMS

Abstract

A 13 year old boy presented with headache, sore throat, myalgia, and fever and subsequently developed haemolytic anaemia and acute liver failure. Wilson’s disease, a rare cause of acute liver failure, was diagnosed at necropsy.

In such cases Wilson’s disease must be diagnosed at an early stage for treatment to be effective. The most reliable indications are increased urinary and hepatic copper concentrations.

Introduction

Acute liver failure in children is usually the consequence of fulminant viral hepatitis, but if serological tests do not confirm a viral aetiology other causes must be considered. Of these, the most important is Wilson’s disease, whose features mimic a wide range of acute and chronic liver disease, not only because specific treatment may reverse liver damage but also because of the implications of this diagnosis for other members of the family. We report a case in a child in whom Wilson’s disease could not be confirmed in life but in whom the postmortem liver copper content established this diagnosis.

Case report

A 13 year old white boy with unremarkable medical and family histories presented with headache, sore throat, myalgia, and intermittent fever (up to 40°C) and rigors that did not respond to treatment with amoxycillin and soluble aspirin. Ten days later he developed a mild jaundice with pharyngitis and generalised lymphadenopathy but without hepatomegaly. He had an evanescent morbilliform rash. In the third week his condition deteriorated with a swinging fever and hepatosplenomegaly. The serum bilirubin concentration was 77 μmol/l (6-6 mg/100 ml) (mostly conjugated), alanine aminotransferase activity 450 IU/l, alkaline phosphatase activity 118 IU/l, total protein concentration 50 g/l (300 mg/100 ml), and albumin concentration 22 g/l (220 mg/100 ml). He became anaemic (haemoglobin concentration 8·6 g/dl) and had a persistent neutrophil leucocytosis (up to 45 ×10⁹/l (45 000/mm³) and thrombocytopenia (84 ×10⁹/l (84 000/mm³)).

Culture of urine, blood, cerebrospinal fluid, and bone marrow were sterile. There was no serological evidence of hepatitis A or B infection, cytomegalovirus infection, glandular fever, leptospirosis, brucellosis, toxoplasmosis, or streptococcal infection on repeated