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Unexpected adverse reactions during a clinical trial in rural West Africa

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Summary

Ribavirin has been used widely in various clinical trials, without significant adverse effects beyond reversible, mild anemia. Since 1978 intravenous ribavirin has been used to treat Lassa fever in a remote area of Eastern Sierra Leone, West Africa. In March 1991, brief episodes of rigors in patients receiving ribavirin were reported. An immediate investigation found that 27/93 patients (29%) had records in 1990/91 of at least one episode, the strongest association being with survival of Lassa fever ($P=0.0001$). The occurrence or number of rigors in an individual patient was unassociated with sex, age, weight, volume of loading dose, cumulative dose, administration of other drugs, use of intravenous lines or heparin traps. In a review of 12 years of ribavirin administration, 74/2117 injections sampled (3.5%) were associated with a record of rigors. Most occurred before 08.00 h ($P<0.0001$), between 0 and 30 min after injection, lasted 2–45 min, and clustered towards the end of the treatment course ($P<0.0001$). There was no association with drug lot or individual vials. Drug was being given as a bolus (< 1 min). Since slowing the infusion rate, no further episodes have been reported. Epidemiologic techniques are important tools in rapid assessment of unexpected events particularly when conducting trials in remote locations.

Side effect; Ribavirin; Lassa fever; Rigor

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Introduction

Intravenous ribavirin has been established as effective therapy for Lassa virus infections in studies in Sierra Leone (Holmes et al., 1990; Jahrling et al., 1980; McCormick et al., 1986), where more than 1500 patients have now been treated. Lassa fever is an acute viral infection caused by a West African arenavirus (McCormick et al., 1987b). The natural host is *Mastomys natalensis*, a small African rat, in which the infection is clinically silent and persistent. Patients may experience a severe disease with hemorrhage, encephalopathy, acute respiratory distress syndrome and hypovolemic shock. In hospitalized patients, the case fatality is 17% (McCormick et al., 1987a). Therapeutic studies of ribavirin treatment of Lassa fever have been established at the Lassa Fever Research Project (LFRP), Segbwema, Sierra Leone, since 1976. This project is managed jointly by the Sierra Leone Ministry of Health and Special Pathogens Branch, DVRD, Centers for Disease Control, and supported since 1982 by the United States Army Medical Research Institute of Infectious Diseases. Studies of the therapy of Lassa fever commenced in 1978.

Ribavirin is marketed and sold in many areas of the world. In addition to patients with Lassa fever, it has been given to patients in various clinical trials, including patients with AIDS (Laskin et al., 1987; Roberts et al., 1990a,b), disseminated measles (Ross et al., 1990), several hundred with influenza (Ray et al., 1989; Wilson et al., 1984), and 150 with hemorrhagic fever with renal syndrome (Huggins, 1989). Ribavirin by the aerosol route is an established therapy for respiratory syncytial virus (RSV) infections of infants, and the drug is licensed for this application (Smith et al., 1991; Tabert and Knight, 1983). It has also been used for the treatment of RSV infection in immunocompromised patients (Eisenburg, 1990; Englund et al., 1988; Janai et al., 1990). With the exception of a dose-related reduction in parameters reflecting circulating red blood cell numbers, no significant adverse effects have been reported (Canonico et al., 1984; Enria et al., 1987; Roberts et al., 1987; Steele et al., 1988).

During a site visit to the LFRP in March 1991, it became apparent that from June 1990 an acute, but clinically mild syndrome of a few minutes' duration was being seen in Lassa fever patients being treated with intravenous ribavirin. Hitherto, adverse drug reactions observed during the study of 1,547 patients with laboratory-confirmed Lassa fever were limited to consistent but reversible anemia (McCormick et al., 1986). Increased risk of toxicity, which might be expected in patients with impaired liver function on entry to the trial (aspartate transaminase (AST) >900 IU/l), has not been seen (McCormick et al., 1987a). We conducted an immediate on site investigation of this reaction to establish whether it was associated with the drug or with the method of administration.

Materials and Methods

Patients

Patients are admitted to the Lassa Fever Research Project ward, Nixon Hospital, Sebgwema, Sierra Leone, if they have signs and symptoms compatible with a diagnosis of Lassa fever. Intravenous ribavirin treatment is instituted immediately if the serum AST is equal to or greater than 150 IU/l, a prognostic indicator of mortality (McCormick et al., 1986, 1987a). Informed consent is obtained orally in the first language of the patient by project staff according to an approved clinical protocol for this investigational drug. The study protocol includes regular monitoring for hematologic and biochemical abnormalities, and specimens are taken regularly for Lassa virus antibodies and virus isolation.

Administration of ribavirin

In an ongoing open-label clinical trial, ribavirin (kindly furnished by Virazole, ICN Pharmaceuticals, Covina, CA) is administered by intravenous injection in full-dose and half-dose schedules. The full-dose schedule consists of 32 mg/kg loading dose, followed by 16 mg/kg 6-hourly for 4 days, then 8 mg/kg 8-hourly for a final 6 days. The half-dose schedule is exactly half the full-dose schedule; that is 16 mg/kg loading dose, followed by 8 mg/kg and 4 mg/kg, over the same time period and with the same dosage intervals and schedule so that dose volumes depend on the weight of the patient. After the loading dose (1–24 ml of undiluted drug), dose volumes are usually about 1–3 ml. Sufficient 10-ml vials for the 10-day treatment are allocated to each patient at initiation of treatment, marked with the patient name, accession number, and vial numbers, and used in numerical order, starting with vial no. 1. While the patient is on intravenous fluids (first 2–3 days), the injection is given undiluted as a bolus (<1 min) into the line through a 3-way tap. When the infusion is removed, the patient, who is usually ambulant, is given an indwelling heparinized trap for ribavirin administration (a catheter, or more recently a butterfly needle). Each patient has a 50-ml heparinized saline bag marked with name and number for flushing the trap. Individually packaged disposable needles, catheters, and other materials are in good supply, and fresh equipment is always used. Syringes, needles and other such devices are never reused, but are immediately discarded into 10% hypochloride solution, and then incinerated. Because of the risks of nosocomial Lassa virus transmission, all staff are rigorously trained in barrier nursing techniques, disinfection and sterility.

Review of all patients treated since June 1990

Medical and nursing staff were interviewed. All patient and nursing records were reviewed from June 1990 to March 1991. A data base was developed with information on the nature, duration and timing of any reactions, together with information on each patient, outcome, disease course, ribavirin dosage, additional therapy, use of intravenous lines and concomitant drug therapy.

Retrospective review

Report of acute reactions to ribavirin administration were sought in the clinical records of patients selected randomly over the previous 10 years. An expanded data base was developed and analyzed. For the purposes of this part of the study, an acute reaction was defined as an episode of rigors lasting no longer than 45 min with or without complaints of lumbosacral pain, headache, vomiting, episode of confusion or urticaria, occurring during the course of ribavirin treatment.

Statistical analysis

Unless stated otherwise, Kruskal–Wallis one-way analyses of variance were used.

Results

Responses of medical staff, and examination of clinical records

The reactions initially described by the nursing staff dated only from June 1990 when they received a new shipment of ribavirin, but when they also underwent a review of the project during which the need to pay careful attention to recording potential adverse reactions had been emphasized. They described brief episodes of rigors, sometimes with lumbosacral pain or headache, vomiting, mild urticaria, brief aggressive behavior or a period of confusion. Most reactions occurred within an hour of administration of intravenous ribavirin, and lasted a few minutes, usually in early morning. Most patients were towards the end of their treatment period and convalescing from Lassa fever. All reactions resolved rapidly with aspirin and warm fluids by mouth. There were no deaths.

Ribavirin was being given by rapid intravenous bolus (<1 min), but the speed of administration and drug dilution varied. The reactions appeared random; there was no association with individual patients, intravenous lines, heparin traps, or drug vials. In an attempt to prevent recurrences, medical staff resited lines and changed fluids, needles and catheters without success. No other drugs or intravenous fluids could be implicated.

Analysis of data from June 1990

Ninety patients were treated with intravenous ribavirin from June 1990 to March 1991. Of these 26 (27%) had records of at least one episode of rigors, 7 had one episode, 17 had 2–5, and 2 patients had 8 episodes. Sixty-two had no rigors, and there were no records on two patients. Females (43%) were more likely to be affected than males (20%), ($\chi^2 = 6.91$, $P = 0.0088$). There were 29 deaths due to Lassa virus infection, none of which patients experienced rigors; indeed, the strongest association with an episode of rigors was found to be survival of Lassa infection ($P = 0.0001$). Reactions were inversely associated with maximum AST (with rigors, mean AST 285 IU/l and without rigors, 1155

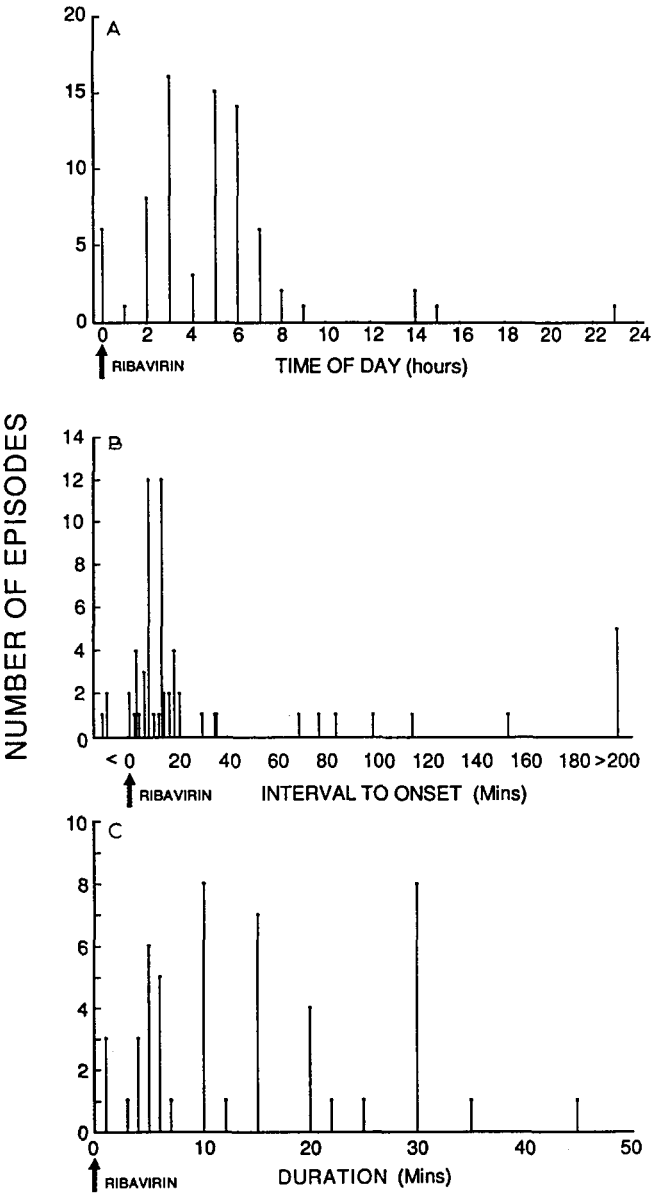

Fig. 1. Timing and duration of episodes of rigors in patients identified in the retrospective review of records from 1978 to 1990, A: time of day; B: interval between ribavirin administration and onset of rigors; C: duration.

IU/l, $P=0.026$), but there was no association with admission AST. There was also no association with laboratory confirmation of Lassa fever. The number of rigors suffered by an individual patient was not associated with the sex, age or

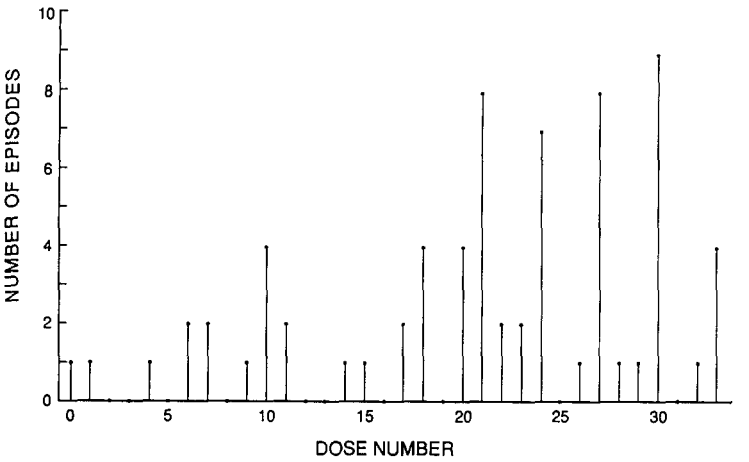

Fig. 2. Dose number associated with episode of rigors in patients identified in the retrospective review of records from 1978 to 1990.

weight of the patient.

Rigors were not associated with the volume of the loading dose, the total dose received, nor the dose regime allocated to the patient (full or half-dose), but were most frequently recorded following the first dose of the day (Fig. 1a). Similarly the volume of the dose precipitating the rigors and the duration of the rigors themselves were not related to the time between injection and onset of rigors. However, an episode of rigors was more frequent with increasing vial number for the patient ($P=0.002$), i.e. they occurred late in the therapeutic course.

Retrospective examination of records since 1978 for similar reactions

Review of clinical records prior to June 1990 revealed similar episodes had been recorded after injection of ribavirin. Seventy-four of 2117 injections studied (3.5%) were found to have been associated with a record of rigors. Most occurred before 08.00 ($P<0.0000$, FET, Fig. 1a). Fig. 1b shows the reactions clustering between 0 and 30 min following injection. The short duration of the rigors is illustrated in Fig. 1c. Once again, most reactions occurred towards the end of treatment in convalescent patients ($P<0.0000$, FET). Analysis by dose number is illustrated in Fig. 2. The probability of developing a reaction increased with cumulative dose of ribavirin ($P=0.0004$).

Seventy of 74 of the reactions were associated with heparin traps. However, since 71/74 patients had heparin traps, and since accurate information could not be assured on patients without rigors, it was not possible to determine if these traps were significantly associated with the reaction. Five episodes occurred in patients with intravenous lines. No association could be found with administration of other drugs.

Discussion

Ribavirin has been associated with few adverse reactions in patient studies. Most notable and consistent has been a reduction in hematocrit due to reversible anemia, but not occurring until the second week of treatment, and directly related to ribavirin dose (Canonico et al., 1984; Huggins et al., 1991; McCormick et al., 1986). Acute toxic reactions in animal studies, consisting of vomiting and diarrhea, was seen only at doses of over 1000 mg/kg in rhesus monkeys (Canonico et al., 1984; Hillyard, 1980; Tabert and Knight, 1983).

Though the reactions were associated temporally with injection of ribavirin, malaria and other common infectious agents probably explain some episodes. Bacterial contamination of vials, intravenous lines or heparin traps was thought to be unlikely because once a reaction had occurred, a second reaction was not seen with use of the same item or injection site, nor prevented by resiting of the line or trap using new equipment and fresh infusion solutions. The reactions were clinically inconsistent with endotoxic shock. Similarly, no pattern emerged in individual patients to suggest that sensitization to the drug solution could be the cause, nor was there any association found with patient variables except female sex. Similar reactions had been occurring sporadically over the years, and were not associated with a particular drug lot nor with the volume of drug actually given in an individual injection. Raised levels of AST are poor prognosis indicators in Lassa fever (McCormick et al., 1987a), so that the association with low AST is consistent with the associations with favorable outcome and cumulative drug dose.

That most of the reactions were observed late in the disease course may reflect the minor nature of the reaction compared with the severity of Lassa fever, and the association with survival (McCormick et al., 1987a). Patients with severe shock may in fact not be able to mount a response of this nature, and if they do, it would likely not be noticed as unduly abnormal in a very sick patient. The marked association with early morning may be related to the relatively cool temperature at this time of day in equatorial West Africa, when mild shivering is more obvious, and endogenous steroids are at their lowest levels in the very early hours of the morning (Jordan and Kohler, 1990). The daily ward round is at 08.00 so there may be a degree of reporting bias.

The ribavirin injections are usually given by rapid, bolus infusion, particularly into heparin traps by all staff on the project. We were unable to ascertain whether individual members of staff were associated with reactions, and all took turns at early morning shifts and reported using the same procedures. Episodes of rigors have been reported in dogs given rapid intravenous infusions of ribavirin (Clinical Investigators' Brochure, ICN Pharmaceuticals, unpublished). In the early years of the Lassa fever treatment study, a diluted infusion was given over a period of 20 min. We now recommend infusion of a period of 30 min, the procedure used in the study of the treatment of HFRS in China where no similar reactions were observed (Huggins et al., 1991).

Ribavirin is life-saving in Lassa fever. Though the evidence is circumstantial, we reached an on site conclusion that undue speed of administration of ribavirin was the most likely explanation for the reactions, though the random nature of the reactions suggests that some factor other than the patient or the drug (e.g. staff member) may have been involved. We have not been able to explain the sex bias.

The investigation we report took 4 days, was simple and allowed us to give immediate instructions to continue to use the antiviral, but to slow the infusion rate. Subsequently no reactions have been reported. With the expected increase in clinical trials conducted in remote areas with high burden of disease, epidemiologic techniques are important tools in rapid assessment of unexpected events.

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