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Safety analysis of liposomal amphotericin B in adult patients: anaemia, thrombocytopenia, nephrotoxicity, hepatotoxicity and hypokalaemia

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ABSTRACT

Liposomal amphotericin B (L-AmB), which was developed to reduce side effects, has been shown to have a better safety profile than both the deoxycholate and lipid complex forms of amphotericin B; however, the frequency of major side effects is still unclear. Thus, the aim of the present study was to assess retrospectively the frequency of L-AmB-induced anaemia, thrombocytopenia, nephrotoxicity, hepatotoxicity and hypokalaemia as well as the relationship between daily dose of L-AmB and these side effects. A low red blood cell (RBC) count (post-/pre-treatment) and anaemia were observed in 7 and 10 of 21 adult patients, respectively. Thrombocytopenia was observed in 11 of 19 adult patients. Doses of L-AmB that are estimated to cause side effects of a low RBC count, anaemia and thrombocytopenia with 50% probability are 4.0, 3.3 and 3.0 mg/kg/day, respectively. Nephrotoxicity was observed in 6 of 22 patients. Variations of total bilirubin, γ-glutamyl transpeptidase, aspartate aminotransferase and alanine aminotransferase used as indices of hepatotoxicity were observed in 6, 7, 8 and 8 of 22 patients, respectively. Hypokalaemia was observed in 4 of 9 patients; however, nephrotoxicity, hepatotoxicity and hypokalaemia were not caused in a dose-dependent manner. In conclusion, the present analyses showed that L-AmB dose-dependently induced anaemia and thrombocytopenia in adult patients. It is important to pay attention to causing anaemia and thrombocytopenia when patients are receiving L-AmB at doses of >3.3 mg/kg/day and >3.0 mg/kg/day, respectively.

1. Introduction

Amphotericin B deoxycholate (AmBD) is a fungicidal agent active against *Candida*, *Aspergillus*, *Cryptococcus* and other moulds and can be a life-saving drug. Nevertheless, its use is limited by significant toxic reactions, since hypokalaemia and nephrotoxicity occur frequently [1,2]. Unlike amphotericin B (AmB) alone, its liposomal formulation, which was developed to reduce these side effects, has been shown to have a better safety profile than both the deoxycholate and lipid complex forms of AmB and can be given at a higher dose [3–6]. On the other hand, Fischer et al. [7] observed a substantial increase in the risk of hepatotoxicity following receipt of liposomal amphotericin B (L-AmB), which was considerably greater than the increase seen for AmBD. Special attention to hepatotoxicity is needed when L-AmB is administered to a patient. Cornely et al. [8] showed that the most common events leading to L-AmB discontinuation were increases in the creatinine level, abnormal liver test results and hypokalaemia.

Anaemia and thrombocytopenia are other major side effects of AmB. Holeman and Einstein [9] reported that mild or severe anaemia developed in all cases (47 patients receiving intravenous AmB) during therapy. Recently there was also a case report that AmBD caused anaemia [10]. Furthermore, L-AmB-induced thrombocytopenia has been shown as a serious side effect in the package insert in Japan; however, a survey of L-AmB-induced anaemia and thrombocytopenia has not yet been conducted.

Thus, the aim of the present study was to assess retrospectively the frequency of L-AmB-induced anaemia, thrombocytopenia, nephrotoxicity, hepatotoxicity and hypokalaemia in adult patients as well as the relationship between daily dose of L-AmB and these side effects.

2. Patients and methods

2.1. Patients

This study retrospectively assessed data obtained between June 2006 and November 2009 for 22 adult patients who received

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L-AmB once daily at Kagoshima University Hospital (Kagoshima, Japan). The red blood cell (RBC) count, haemoglobin concentration, platelet count, serum creatinine concentration (SCr), total bilirubin (T-Bil), γ-glutamyl transpeptidase (GGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and potassium values were extracted from electronic medical records.

2.2. Assessment of anaemia

One patient was excluded as he had received RBC transfusions during L-AmB therapy. Thus, the data obtained for 21 patients were used in assessment of anaemia.

The RBC ratio [post-/pre-treatment (%)] was used as an index of RBC change caused by L-AmB treatment. A ratio of ≤75% was considered as a clinically significant decrease and was considered as a low RBC count in logistic analysis (absence, 0; presence, 1).

Anaemia was defined if the haemoglobin concentration after completion of L-AmB therapy decreased to less than the lower limit of normal (LLN) at Kagoshima University Hospital (12 g/dL) or the haemoglobin concentration [post-/pre-treatment (%)] decreased to ≤75%. Logistic regression analysis was performed to test whether the L-AmB daily dose is a significant predictor of anaemia (absence, 0; presence, 1).

2.3. Assessment of thrombocytopenia

Three patients were excluded as they had received platelet transfusions during L-AmB therapy. Thus, the data obtained for 19 patients were used in assessment of thrombocytopenia.

Thrombocytopenia was defined if the platelet count after completion of L-AmB therapy decreased to less than the LLN at Kagoshima University Hospital (130 000/mm^3) or the platelet count [post-/pre-treatment (%)] decreased to ≤75%. Logistic regression analysis was performed to test whether the L-AmB daily dose is a significant predictor of thrombocytopenia (absence, 0; presence, 1).

2.4. Assessment of nephrotoxicity

Kidney function was accessed by SCr before initiation and after completion of L-AmB therapy. Nephrotoxicity was defined if the value after completion of L-AmB therapy increased to >0.5 mg/dL or SCr increased more than 1.5 times the upper limit of normal (ULN) (SCr, 1.1 mg/dL for men, 0.7 mg/dL for women) before initiation of L-AmB therapy. Logistic regression analysis was performed to test whether the L-AmB daily dose is a significant predictor of nephrotoxicity (absence, 0; presence, 1).

The number of concomitant nephrotoxic drugs (aminoglycoside antibiotic, vancomycin, immunosuppressive agents, cisplatin and foscarnet) was also investigated.

2.5. Assessment of hepatotoxicity

Liver function was assessed by T-Bil, GGT, AST and ALT values before initiation and after completion of L-AmB therapy. Hepatotoxicity was defined if the values after completion of L-AmB therapy increased to more than the ULN at Kagoshima University Hospital (T-Bil, 1.2 mg/dL; GGT, 47 IU/L; AST, 33 IU/L; ALT, 30 IU/L) or each rate increased more than 1.5 times the ULN before initiation of L-AmB therapy. Logistic regression analysis was performed to test whether the L-AmB daily dose is a significant predictor of hepatotoxicity (absence, 0; presence, 1).

2.6. Assessment of hypokalaemia

Thirteen patients were excluded as they had received potassium preparation during L-AmB therapy. Thus, the data obtained for nine patients were used in assessment of hypokalaemia.

Hypokalaemia was defined if potassium values after completion of L-AmB therapy decreased to less than the LLN at Kagoshima University Hospital (3.6 mmol/L) or potassium values [post-/pre-treatment (%)] decreased to ≤75%.

2.7. Creatinine clearance (CL_{Cr})

CL_{Cr} was estimated using the Cockcroft–Gault formula [11].

2.8. Statistical analysis

Regression analysis was performed using SPSS software version 15.0J (SPSS Japan Inc., Tokyo, Japan). DOSE (mg/kg/day) was defined as once-daily administration of L-AmB.

3. Results

Sixteen men and six women [mean ± standard deviation (S.D.) age, 61.0 ± 10.8 years; body weight, 53.0 ± 8.2 kg; and CL_{Cr}, 101.1 ± 34.3 mL/min] were evaluated in the study. The diseases treated with L-AmB were as follows: pulmonary aspergillosis (n = 10); cryptococcal meningitis (n = 6); and probable invasive fungal infection (n = 6). No patient stayed in the Intensive Care Unit. Two patients had received hematopoietic stem cell transplantation (n = 1) or cord blood stem cell transplantation (n = 1). Three patients received carboplatin (n = 1), gemtuzumab ozogamicin (n = 1) or nogitecan (n = 1) as antineoplastic agents for 1 week before initiation of L-AmB therapy. No patient received antineoplastic agents during L-AmB therapy. The mean ± S.D. dose of L-AmB was 3.2 ± 1.0 mg/kg/day and the mean ± S.D. duration of treatment was 18.3 ± 15.5 days.

Fig. 1a shows the relationship between the L-AmB dose and RBC ratio (post-/pre-treatment). A statistically significant (P < 0.05) correlation (r = −0.448) was observed between the L-AmB dose and the RBC ratio. A low RBC count was observed in 7 (33.3%) of 21 patients. The L-AmB dose was a significant predictor of a low RBC count (Fig. 1b) according to the following equation: probability of low RBC count = 1/[1 + exp(−4.91 + 1.22 × DOSE)]. The daily dose of L-AmB that caused a low RBC count with 50% probability was 4.0 mg/kg/day. Next, anaemia was observed in 10 (47.6%) of 21 patients. The L-AmB dose was a significant predictor of anaemia (Fig. 1c) according to the following equation: probability of anaemia = 1/[1 + exp(−4.20 + 1.27 × DOSE)]. The daily dose of L-AmB that caused anaemia with 50% probability was 3.3 mg/kg/day.

Fig. 2 shows the relationship between the daily dose of L-AmB and thrombocytopenia (absence, 0; presence, 1). Thrombocytopenia was observed in 11 (57.9%) of 19 patients. The L-AmB dose was a significant predictor of thrombocytopenia according to the following equation: probability of thrombocytopenia = 1/[1 + exp(−6.86 + 2.30 × DOSE)]. The daily dose of L-AmB that caused thrombocytopenia with 50% probability was 3.0 mg/kg/day.

Nephrotoxicity was observed in 6 (27.3%) of 22 patients. The SCr concentration of only one patient increased to >2 mg/dL (from 0.7 mg/dL to 2.3 mg/dL). The other patients showed mild nephrotoxicity. Variations of T-Bil, GGT, AST and ALT used as indices of hepatotoxicity were observed in 6 (27.3%), 7 (31.8%), 8 (36.4%) and 8 (36.4%) of 22 patients, respectively. The ALT level of only one patient increased to >5 times the ULN or the value before initiation of L-AmB therapy (from 18 IU/L to 210 IU/L). The other patients showed mild hepatotoxicity. Hypokalaemia was observed in four (44.4%) of nine patients. Next, the study investigated whether an increase