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Meropenem monotherapy is as effective as and safer than imipenem to treat brain abscesses [☆]

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ABSTRACT

The efficacy of carbapenems versus cefotaxime (8 g/day) + metronidazole (1.5–2 g/day) [combined standard chemotherapy (CSC)] for the treatment of brain abscess was compared. Fifty-nine adult patients with brain abscesses received either imipenem or meropenem (3–4 g/day) or CSC for a mean of 5 weeks, in addition to neurosurgery in most cases. Cure was obtained in 84.7% of cases; 42/47 (89.4%) on carbapenems [18/22 (81.8%) on imipenem versus 24/25 (96.0%) on meropenem] and 8/12 (66.7%) on CSC ($P = 0.06$). Seven patients with multiple abscesses were treated with imipenem (1 died; cure rate 85.7%), five with meropenem (all survived; cure rate 100%) and five with CSC (2 died; cure rate 60%) ($P < 0.4$). Neurosurgery was performed in 43/59 cases (72.9%); 17 (77.3%) in the imipenem group, 21 (84.0%) in the meropenem group and 5 (41.7%) in the CSC group ($P = 0.02$). There was no significant difference in the rate of relapse requiring re-intervention. Treatment with meropenem was associated with a lower mortality than CSC ($P = 0.026$). Seizures were observed only with carbapenems [8/22 (36.4%) for imipenem versus 2/25 (8.0%) for meropenem; $P = 0.03$]. Carbapenems were more effective than CSC for treatment of brain abscesses. Because meropenem induced significantly fewer seizures than imipenem with at least the same clinical efficacy, the former appears to be a better choice to treat this infection.

1. Introduction

Brain abscess is an uncommon infection of the central nervous system with a high morbidity and mortality. It is due primarily to direct spread from an infected paranasal sinus or ear, complication of a neurosurgical procedure or, more rarely, haematogenous dissemination, mostly from the lung and heart [1–3]. It is usually caused by a mixture of microorganisms, with a high proportion of cases due to obligate anaerobes. Broad-spectrum β -lactam antibiotics, and nowadays the combination of cefotaxime + metronidazole, are the standard therapy for empirical treatment of brain abscess, in addition to neurosurgery [4,5].

Carbapenems penetrate well into the cerebrospinal fluid (CSF) and thus are a potential alternative to cephalosporins + metronidazole to treat brain abscesses [6–9]. However, some reports of imipenem-induced seizures, although infrequent, have limited its generalised use [10,11]. Meropenem has shown a much lower convulsive activity than imipenem while retaining the same broad antimicrobial spectrum [12–14].

In this 11-year-old retrospective, non-randomised study, we compared the efficacy and safety of intravenous (i.v.) cefotaxime + metronidazole [combined standard chemotherapy (CSC)] with i.v. meropenem or imipenem monotherapy in addition to neurosurgery in the treatment of brain abscesses in adult patients admitted to the Hospital Universitario Central de Asturias (HUCA), Oviedo, Spain.

2. Patients and methods

Medical records from HUCA from January 1996 to December 2007 were retrospectively reviewed to identify cases of brain abscess. HUCA is a 1500-bed tertiary university hospital in northwestern Spain providing neurosurgical coverage to a population of 1 100 000 people.

The diagnosis of brain abscess was made by microbiological, histological, radiographic, surgical and clinical findings as described previously [2,8]. Brain abscess was diagnosed in 59 patients; surgically and histologically in 43 patients (40 of whom had positive microbiological cultures) and by compatible clinical picture and computed tomography (CT) or magnetic resonance imaging (MRI) findings in 16 patients who did not undergo neurosurgery. The mean incidence of brain abscess was of 4.9 cases/year. Forty-five patients were men and fourteen were women. The age range was 14–80 years (mean age 45.9 ± 18.0 years). Patients with the following conditions were excluded from the study: (i) those who were immunocompromised or who tested positive for human immunodeficiency virus (HIV); (ii) those with subdural and epidural abscesses; and (iii) those with fungal, protozoal or mycobacterial abscesses.

Patients received different antimicrobial treatments in a non-randomised manner according to the preference of the infectious diseases consultant. From 2000 onwards, most of the patients were treated with a carbapenem in addition to neurosurgery. Antibiotics were usually started at the time of diagnosis of

brain abscess, always before neurosurgery, a procedure that could be delayed up to 6 weeks from diagnosis (mean delay 10.5 days; range 0–41 days).

For the purpose of the study, patients were divided into three groups: Group 1 comprised 12 patients who received CSC (cefotaxime + metronidazole); Group 2 comprised 22 patients who received i.v. imipenem 1 g/6–8 h; and Group 3 comprised 25 patients treated with i.v. meropenem 1 g/6–8h. No antiepileptic prophylactic therapy was administered prior to or simultaneously with the antibiotics. Treatments lasted a mean of 35.3 ± 16.3 days (range 16–84 days).

Pus from brain abscesses obtained by needle aspiration or surgical debridement in 43 patients was sent in capped syringes to the microbiology laboratory for Gram stain and aerobic and anaerobic cultures. Blood cultures were obtained from all the patients and CSF cultures from 15 patients.

2.1. Statistical analysis

Qualitative variables were compared by χ^2 or Fisher's exact tests as appropriate. The Gaussian distribution of continuous variables was tested with the Kolmogorov–Smirnov test, and the Student's *t*-test or Mann–Whitney *U*-test was used for comparison of these variables accordingly. One-way analysis of variance (ANOVA), with Scheffé post-hoc test, was used for comparison of more than two groups. The independent association of diverse variables with patient survival was assessed by a Cox proportional hazard model. A *P*-value

<0.05 value for a two-tailed test was considered statistically significant. SPSS v.15.0 software (SPSS Inc., Chicago, IL) was used for statistical analysis.

3. Results

3.1. Patients

The characteristics of the patients in the three therapy groups are presented in Table 1. Carbapenems were used to treat brain abscesses after 2000 at HUCA and the annual incidence of the infection was fairly steady throughout the review period, therefore more than twice as many patients were treated with carbapenems than with CSC. In addition, owing to the non-randomised design of the study, patients in the CSC group were not well matched with those receiving carbapenems. In fact, patients receiving CSC were older, more often presented a Glasgow coma scale (GCS) score <7 and more often had multiple abscesses. Patients receiving the two carbapenems were acceptably well matched with regard to the clinical severity of the illness at hospital admission (GCS score, motor weakness, intracranial hypertension), although patients given imipenem were younger. All patients groups were well matched with regard to basic blood and serum determinations such as haemoglobin, total leukocyte count, differential count, platelet count, serum glucose, urea, creatinine and electrolytes ($P = 0.1-0.9$). All antibiotics were administered in a timely manner and at appropriate dosages.

3.2. Number of brain abscesses

Abscesses were single in 42 patients (71.2%) and multiple in 17 patients (28.8%).

3.3. Microbiology and source of entry of the brain abscesses

Positive brain pus cultures were obtained in 27 (62.8%) of 43 cases, positive blood cultures in 15 (25.4%) of 59 cases and positive CSF cultures in 10 (66.7%) of 15 cases. Eleven patients had positive cultures from more than one source. A microbiological diagnosis was based on blood alone in 11 cases (18.6%) and on CSF alone in another 2 cases (3.4%). Anaerobes were isolated in 14 (23.7%) of 59 individuals and they were the most frequent isolates, followed by Gram-positive cocci (12/59; 20.3%), non-anaerobic Gram-negative rods (11/59; 18.6%) and mixed flora (3/59; 5.1%); in 19 patients (32.2%) no microorganisms were obtained from the brain pus or other cultures.

Many of the brain abscesses in this series were secondary to neurosurgical procedures (17/59; 28.8%) or head trauma (2/59; 3.4%), followed by those due to ear, nose and throat infections (14/59; 23.7%). Haematogenous brain abscesses were uncommon (3/59; 5.1%); others were due to other causes (7/59; 11.9%) or were of unknown origin (16/59; 27.1%).

3.4. Clinical outcomes

3.4.1. Cure

Patients remained in hospital on i.v. therapy for a mean of 36.5 ± 22.8 days (range 5–92 days). Overall, cure was achieved in 50/59 cases (84.7%), whereas 9 patients (15.3%) died, mostly due to cranial hypertension and other complications of brain abscess. Four of the patients who died did not undergo neurosurgery. A higher (not statistically significant) cure rate was observed in the carbapenem groups compared with CSC (89.4% of patients on carbapenems compared with 66.6% in the CSC group; $P = 0.06$). Comparing the two carbapenems, meropenem showed a non-significant slightly greater efficacy than imipenem (96.0% cured vs. 81.8%; $P = 0.17$). Meropenem was significantly more effective than CSC [24/25 patients (96.0%) receiving meropenem cured vs. 8/12 (66.7%) receiving CSC; $\chi^2 = 3.72$, odds ratio (OR) = 12.0, 95% confidence interval (CI) 0.98–329.7; $P = 0.03$ by Fisher's exact test] (Table 1). Among the patients with multiple abscesses, seven received imipenem (one died; cure rate 85.7%), five received meropenem (all survived; cure rate 100%) and five received CSC (2 died; cure rate 60%) ($P < 0.4$ for all the comparisons).

Among the different epidemiological, bacteriological, clinical and surgical variables studied, only the GCS score was significantly associated with death ($P = 0.001$).

3.4.2. Neurosurgery

Neurosurgery was performed in 43/59 patients (72.9%); 17/22 (77.3%) on imipenem, 21/25 (84.0%) on meropenem and 5/12 (41.7%) on CSC ($P = 0.02$). Sixteen patients did not undergo neurosurgery; 1/9 (11.1%) of those on carbapenems died and 3/7 (42.9 %) on CSC died ($P = 0.26$ comparing mortality rates of those who did not undergo neurosurgery in the two treatment groups).

Among the 43 patients who underwent neurosurgery, 20 (46.5%) underwent craniotomy and surgical drainage of the brain abscess, 17 (39.5%) underwent needle aspiration of the abscess through a burr hole and 6 (14.0%) had an Ommaya reservoir placed to relieve elevated intracranial hypertension.

3.4.3. Relapse

In total, 12 (20.3%) of the 59 patients relapsed requiring re-intervention; 7/22 (31.8%) on imipenem, 3/25 (12.0%) on meropenem ($P = 0.1$) and 2/12 (16.7%) on CSC ($P < 0.5$). The second surgical procedure was a new abscess puncture in all but three patients. Only four (33.3%) of the patients who underwent a second surgery had multiple abscesses.

3.5. Seizures

Seizures were observed only in those patients treated with carbapenems (10/47; 21.3%) and not in those on CSC ($P = 0.1$). There were significant differences when the three therapeutic groups were considered altogether ($P =$

0.008). However, if imipenem is compared with meropenem, the former induced significantly more seizures [8/22 (36.4%) for imipenem vs. 2/25 (8.0%) for meropenem; $\chi^2 = 4.05$; OR = 6.57, 95% CI 1.04–52.8; $P = 0.03$ by Fisher's exact test]. No other important side effects of antibiotics were reported in the medical charts of patients.

3.6. Multivariate analysis

A Cox multivariate proportional hazard model was used to assess the independent association of different variables with death. The model included variables that were found to be related to patient survival on univariate analysis or that could be clinically relevant to this outcome, such as GCS score, antibiotic treatment and the presence or absence of cranial hypertension and surgical treatment. A GCS score <7 [hazard ratio (HR) = 26.3, 95% CI 2.2–333.3; $P = 0.01$] and treatment with cefotaxime + metronidazole (CSC) compared with meropenem (HR = 0.046, 95% CI 0.003–0.692; $P = 0.026$) were the only variables found to be significantly associated with death (Fig. 1), whereas imipenem treatment ($P = 0.13$), surgical treatment ($P = 0.58$) and cranial hypertension ($P = 0.86$) were not significantly related to this outcome.

4. Discussion

Carbapenem monotherapy proved to be an effective alternative to the standard combination of i.v. cefotaxime + metronidazole (CSC) when used in conjunction with neurosurgery to treat bacterial brain abscesses in this study. Meropenem

showed significantly greater efficacy in univariate analyses than CSC and was independently associated with a favourable outcome by Cox regression. Imipenem-treated patients had the highest incidence of seizures. These observations might make meropenem the best choice for empirical treatment of pyogenic brain abscesses.

This is the largest study of carbapenems for the treatment of brain abscess ever published in the world literature. However, the non-randomised design of the study might have introduced a bias to the results and forces us to be very cautious in interpreting the results. Patients receiving CSC were older, had lower GCS scores, more often had multiple abscesses, less frequently underwent neurosurgery and were admitted before 2000. All these factors, alone or taken together, have been demonstrated to indicate a worse prognosis of brain abscesses in other studies and could work in favour of carbapenems.

Meropenem and imipenem penetrate into the CSF and show excellent antimicrobial activity in meningitis caused by different microorganisms [6–10,13]. Imipenem has been shown to be present in high concentrations in brain pus and, although not reported so far, meropenem should behave similarly [9,12,13]. Both drugs should be present at levels that are well above the minimum inhibitory concentration for 90% of microorganisms (MIC_{90}) for isolates from brain abscesses in this study, mostly obligate anaerobes and Gram-positive cocci.

Overall mortality in this study (15.3%) was similar to that reported in our previous work and in larger series [2,8]. Jansson et al. [5] reported a much lower short-term abscess-related mortality (4.5%) and lower relapse rate (8.3%) with i.v. cefotaxime + metronidazole. However, they observed a 6-month mortality of 12%, similar to ours, and 60% of patients had adverse reactions, including a seizures rate at the end of therapy of 11%. No seizures were observed in our patients treated with i.v. cefotaxime + metronidazole at the same dose used by Jansson et al. [5].

Meropenem has been shown to be less epileptogenic than imipenem, with a seizure incidence as low as 0.07% in infections other than meningitis [13]. The convulsive activity of β -lactams is related to inhibition of [3 H]-muscimol binding to the GABA_A receptor in brain tissue. In vitro assays and clinical trials have shown that meropenem induced a much lower seizure activity than imipenem, although it was higher than other newer carbapenems such as doripenem and biapenem [14,15]. This study confirms the lower epileptogenic activity of meropenem compared with imipenem even in patients with a high risk of seizures such as brain abscesses with subsequent neurosurgery.

In many countries, i.v. metronidazole is not available and therefore meropenem could be an alternative. However, the cost of 5 weeks of i.v. therapy has to be considered by the clinician and hospital pharmacist because meropenem is the most expensive regimen (€5177 for i.v. meropenem, €4900 for i.v. imipenem and €1639 for the combination i.v. cefotaxime + metronidazole in Spain).

We conclude that carbapenem monotherapy was more effective than CSC to treat brain abscesses, in addition to neurosurgery, and produced similar relapses. Meropenem, although the most expensive regimen, induced fewer seizures with slightly better clinical efficacy than imipenem and so may prove to be a better choice to treat this neurological infection.

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Competing interests

None declared.

Ethical approval

Not required.

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Fig. 1. Multivariate Cox regression curves to assess the association with death of the antimicrobial therapies received: meropenem vs. cefotaxime + metronidazole (combined standard chemotherapy) ($P = 0.026$); meropenem vs. imipenem ($P = 0.18$); and imipenem vs. cefotaxime + metronidazole ($P = 0.13$).

Table 1

Characteristics of patients with brain abscess in the three therapy groups

	CSC (<i>n</i> = 12)	Imipenem (<i>n</i> = 22)	Meropenem (<i>n</i> = 25)	<i>P</i> -value
Age (years) (mean ± S.D.)	53.0 ± 14.7	37.5 ± 19.3	50.0 ± 15.9	0.016 ^a
Gender (male) [<i>n</i> (%)]	7 (58.3)	18 (81.8)	20 (80.0)	0.3
GCS score <7 [<i>n</i> (%)]	3 (25.0)	6 (27.3)	3 (12.0)	0.4
Motor weakness [<i>n</i> (%)]	2 (16.7)	10 (45.5)	10 (40.0)	0.2
Cranial hypertension [<i>n</i> (%)]	2 (16.7)	2 (9.1)	4 (16.0)	0.7
Multiple abscesses [<i>n</i> (%)]	5 (41.7)	7 (31.8)	5 (20.0)	0.4
No surgery [<i>n</i> (%)]	7 (58.3)	5 (22.7)	4 (16.0)	0.02 ^b
Re-intervention [<i>n</i> (%)]	2 (16.7)	7 (31.8)	3 (12.0)	0.5
Death [<i>n</i> (%)]	4 (33.3)	4 (18.2)	1 (4.0)	0.06 ^c
Days of hospital stay (mean ± S.D.)	31.8 ± 25.4	36.6 ± 20.0	38.8 ± 24.4	0.7

CSC, combined standard chemotherapy (cefotaxime+ metronidazole); S.D., standard deviation; GCS, Glasgow coma scale.

^a Standard therapy versus imipenem ($P = 0.048$) and standard therapy versus meropenem ($P = 0.051$), by Scheffé test.

^b Standard therapy versus imipenem ($P = 0.06$) and standard therapy versus meropenem ($P = 0.018$).

^c Standard therapy versus imipenem ($P = 0.4$) and standard therapy versus meropenem ($P = 0.03$).

Fig.1.