Comparison of the efficacy and safety of isepamicin plus metronidazole and amikacin plus metronidazole in intra-abdominal infections

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Abstrak

Infeksi intra-abdominal akibat luka tembus pada dinding abdomen atau pecahnya saluran cerna merupakan keadaan akut yang memerlukan tindakan bedah serta antibiotika yang tepat. Isepamisin adalah suatu aminoglikosid yang efektif untuk menghambat berbagai kuman Gram negatif penyebab infeksi intra-abdominal. Tujuan penelitian ini adalah untuk mengetahui efektivitas dan keamanan isepamisin (15 mg/kgBB IV sekali sehari) dibandingkan dengan amikasin (7.5 mg/kg BB IV dua kali sehari). Pada kedua rejimen ini ditambahkan metronidazol. Penelitian ini menggunakan desain acak, terbuka, dan paralel, dengan menggunakan rasio jumlah subyek isepamisin:amikasin = 2:1. Dari 50 pasien yang diikutsertakan, 27 pasien memenuhi syarat untuk digolongkan ke dalam populasi keamanan dan efektivitas, sedangkan 46 pasien digolongkan ke dalam populasi intent-to-treat. Dari populasi keamanan dan efektivitas, angka keberhasilan klinik pengobatan kelompok isepamisin dan amikasin tidak berbeda bermakna (masing-masing 95% dan 100%). Dari populasi intent-to-treat, angka keberhasilan klinik pengobatan kelompok isepamisin dan amikasin juga tidak berbeda bermakna (masing-masing 97% dan 100%). Angka eliminasi bakteriologik kedua kelompok tidak berbeda bermakna, baik pada populasi efektivitas dan keamanan (masing-masing 95% dan 100%) maupun pada populasi intent-to-treat (masing-masing 90% dan 93%). Streptokokus dan stafilokokus merupakan patogen yang paling sering (40%) diisolasi dari pus pada penelitian ini, sedangkan Acinetobacter anitratus merupakan kuman yang tersering (55%) diasingkan dari darah penderita. Pada populasi efektivitas dan keamanan, rata-rata lama rawat inap (± SD) di kelompok isepamisin dan amikasin masing-masing adalah 10.7 ±3.9 dan 11.1 ± 3.8 hari. Pada populasi intent-to-treat, angka ini masing-masing ialah 10.1 ± 3.4 dan 10.5 ± 3 hari, Kedua macam aminoglikosid ini ditoleransi dengan baik dan tidak ada pasien yang menghentikan pengobatan karena timbulnya efek samping. Disimpulkan bahwa untuk pengobatan infeksi intra-abdominal, isepamisin dengan dosis tunggal sekali sehari IV memberikan efektivitas yang sama dengan amikasin dua kali sehari IV jika dikombinasi dengan metronidazol. ***(Med J Indones 2001; 10: 88-94)***

Abstract

Intra-abdominal infections due to penetrating wound through the abdominal wall or rupture of the gastrointestinal tract are acute conditions requiring prompt surgical intervention and the use of appropriate antimicrobial agents. Isepamicin is an effective aminoglycoside against various Gram-negative pathogens causing intra-abdominal infections. The objective of the present study is to compare the efficacy and safety of isepamicin (15 mg/kgBW IV o.d.) with amikacin (7.5 mg/kgBB IV b.i.d.), in conjunction with metronidazole for both drugs. An open, randomized, parallel design was applied in this trial. The subject allocation ratio for isepamicin:amikacin is 2:1. Out of 50 patients enrolled in this study, 27 fulfilled the criteria for safety and efficacy population, and 46 for intent-to-treat population. In the safety and efficacy population, the clinical success rate for isepamicin and amikacin group did not differ significantly (i.e., 95% and 100%, respectively). In the intent-to-treat population, the clinical success rates for isepamicin and amikacin group were also insignificantly different (i.e., 97% and 100%, respectively). The rates of bacteriological elimination for isepamicin and amikacin, were 95% and 100%, respectively in the efficacy and safety population, and 90% and 93%, respectively in the intent-to-treat population. Streptococci and staphylococci were the most frequent (40%) pathogens isolated from pus, and Acinetobacter anitratus (55%) was the most common one isolated from blood. In the efficacy and safety population, the mean (± SD) length of hospital stay in the isepamicin and amikacin groups was 10.7 ± 3.9 and 11.1 ± 3.8 days, respectively, while in the intent-to-treat population, the mean (± SD) length of hospital stay in the isepamicin and amikacin groups was 10.1 ± 3.4 and 10.5 ± 3 days, respectively. In the present study, both aminoglycosides were well tolerated and there was no patient withdrawal associated with side effect. It is concluded that for intra-abdominal infections, intravenous isepamicin given once daily is as effective as intravenous amikacin given twice daily in combination with metronidazole. ***(Med J Indones 2001; 10: 88-94)***

Keywords: *Isepamicin, amikacin, intra-abdominal infections*

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Intra-abdominal infections are life-threatening conditions due to contamination of the abdominal cavity by the gut microflora. The most prominent aerobic pathogens causing these infections are *Escherichia coli, Klebsiella sp , Enterobacter,* and *Proteus* spp.[1] *Bacteroides fragilis*, an anaerobic normal flora in the lumen of the gut, is also likely en-countered as a causative pathogen in such infections. Therefore antibiotic combinations used to treat intra-abdominal infections should cover both aerobic and anaerobic pathogens.[2]

Isepamicin is an aminoglycoside with a good activity against aminoglycoside-resistant pathogens. It is not modified by the 2"-aminoglycoside adenylyl-transferase or aminoglycoside acetyltransferases that inactitivate gentamicin. It is also less affected by the 6'-amino-acetyltransferase-I that inactivates amikacin [3].

A previous report from Mexico indicated that isepamicin was as effective as amikacin, in combination with metronidazole, in the treatment of intra-abdominal infection [4].

The objective of the present study is to compare the efficacy and safety of isepamicin plus metronidazole and amikacin plus metronidazole in patients hospitalized with intra-abdominal infections.

METHODS

Study sites

The study was carried out during 1997-1998 at the Department of Surgery, Dr. Cipto Mangunkusumo Hospital, in collaboration with the Pharmacology, Clinical Pathology, and Microbiology Departments, School of Medicine, University of Indonesia, Jakarta. The trial was conducted with the Good Clinical Practice standards and coordinated by PUKO, Clinical Trial Center of the Medical School, University of Indonesia.

Patients

Patients with intra-abdominal infection aged 18 years or more were recruited in the present study. Intra-abdominal infection was characterized by abdominal pain and tenderness, nausea, vomiting, anorexia, decrease or absence of bowel sound, oral temperature of 37.9°C, and leucocyte counts 11.000/mm3 or more. The infection had to be severe enough to require hospitalization.

The patients were excluded if they had a history of hypersensitivity to an aminoglycoside or metronidazole, had received an antibiotic(s) within 72 hours prior to enrollment which was deemed potentially effective against the patient's infection, were considered not requiring any antimicrobial therapy, were pregnant, had renal impairment (serum creatinine > 2 mg/dl or anuria), had liver dysfunction (SGOT or SGPT > 3 times the upper limit of the normal value), had hearing impairment, were immunocompromised, or were likely to die within 24 hours.

Informed consent was obtained from all subjects. The study protocol was approved by the Ethics Committee of the Medical Faculty, University of Indonesia.

Study design

This was a parallel, open-labeled, randomized, controlled study. The subjects were allocated to receive either isepamicin or amikacin in a ratio of 2:1. The treatment group received isepamicin in a daily intravenous dose of 15 mg/kg BW, given in single dose. The control group received amikacin in a daily intravenous dose of 15 mg/kg, given in 2 equally divided doses every 12 hours. The aminoglycosides were given for at least 5 days, but not more than 14 days. Both groups were also given intravenous metronidazole in a dose of 500 mg twelve hourly for the first 3 days, followed by 500-mg intrarectal dose given twelve hourly for the following 6 days.

Specimens (blood and pus) for culture and sensitivity tests were obtained within 48 hours before starting treatment up to 3 hours after the initial dose. During treatment, the patients' clinical status were evaluated daily. This included the rate of wound healing, body temperature, and resolution of symptoms.

To avoid toxicity, peak and trough serum levels of isepamicin and amikacin were measured in all patients on day 2. Blood specimen representing peak level was drawn at 15 minutes following a 30-minute infusion of the aminoglycoside and that of trough level was obtained just prior to the next dose. The presumed safe maximum peak levels for isepamicin and amikacin were 80 mcg/ml and 35 mcg/ml, respectively. The safe maximum trough level for both drugs was < 10 mcg/ml. The aminoglycoside dose was reduced accordingly if the peak or trough level exceeded these maximum levels. Both peak and

Outcome measures

The variables for efficacy included clinical and bacteriological responses at the end of the study. The criteria for clinical response were: cure (resolution of all signs and symptoms of infection), improvement (clinically significant decrease in signs and symptoms), and failure (persistence or worsening of signs and symptoms). The criteria for bacteriological response were the elimination of the causative pathogen(s).

The safety assessment included adverse events and alteration in laboratory values (i.e., hematology, blood chemistry, and urinalysis).

Data analysis

The analysis for efficacy was carried out for both intent-to-treat population (all patients randomised and had received at least one dose of study drug) and efficacy population (the subpopulation fulfilling all criteria for evaluation as stated in the protocol). Unpaired student's t and Chi-squared tests were used to analyze continuous and categorical variables, respectively. A p value of $< .05$ was considered statistically significant.

RESULTS

Demography

A total of 50 patients (36 males and 14 females) were enrolled in the present study. Overall, 20 subjects in the isepamicin group and 7 in the amikacin group were eligible for efficacy and safety evaluation. The other 23 subjects could not fulfill the inclusion criteria due to various reasons, e.g. : 2 under the age limit, 1 for being given radiotherapy for cervical cancer, 1 with history of recent antibiotic treatment, 3 with absence of culture-confirmed intraabdominal infection, 9 with causative pathogens resistant to isepamicin, and the other 7 were resistant to amikacin.

Fourty-six patients (31 in isepamicin and 15 in amikacin group) were considered suitable for analysis in the intent-to-treat population because 4 patients had to be excluded .

Two patients in the isepamicin group died, 1 from respiratory distress and sepsis in the intensive care unit after finishing the study, and the other one from sepsis and acute respiratory distress syndrome (ARDS) in the high care unit.

Demographic data of both the intent-to-treat and efficacy populations is showed in Table I. There were no statistically significant differences in baseline characteristics between treatment groups in either population. The most common primary diagnosis were peritonitis due to appendicular perforation (8 isepamicin, 3 amikacin) and peritonitis due to rupture of small intestine (6 isepamicin, 5 amikacin), followed by gastric and large intestine perforation.

Table 1. Baseline characteristics

	Intent-to-treat population		Efficacy population	
	Isepamicin	Amikacin	Isepamicin	Amikacin
No. of patient	31	15	20	7
Mean age (years)	34.1	33.7	36.8	34.7
Sex : female	8	4	6	2
Male	23	11	14	5
Mean weight (kg)	53.2	55.2	53.7	53.6
Range of SAPS* score	4.8	3.3	4.5	3.86
Primary diagnosis :				
- small intestine perforation	8	3	8	1
- appendix rupture	6	5	3	3
- colon perforation	5	1	0	-
- stomach perforation	8	1	6	1
- cholangitis	1	-	0	-
- strangulated hernia	1	2	1	1
- others	2	3	2	1

EFFICACY EVALUATION

Clinical response

In the efficacy population, clinical response rates (cure + improvement) for isepamicin and amikacin groups were 95% and 100%, respectively. In the intent-to-treat population, clinical response rates for isepamicin and amikacin groups were 96.7 % and 100 %, respectively (Table 2). For both populations, the differences were not statistically significant.

Table 2. Clinical response

	Intent-to-treat population		Safety and efficacy population	
	Isepamicin	Amikacin	Isepamicin	Amikacin
No.of patient	31	15	20	7
Cure	29 (93.5%)	15 (100%)	18 (90%)	7 (100%)
Improvement	1 (3.2%)	0	1 (5%)	0
Failure	1 (3.2%)	0	1 (5%)	0

Overall bacteriological elimination rates in the intent-to-treat population in isepamicin and amikacin groups were 90.3 % (28/31) and 93.3 % (14/15), respectively (Table 3). These figures were not significantly different. Bacteriological response was considered indeterminate in 4 patients (i.e., 2 isepamicin and 1 amikacin patients had no growth in the initial microbiological culture; and 1 patient died due to acute respiratory distress syndrome which was unrelated to treatment failure).

Table 3. Bacteriological response

	Intent-to-treat population		Safety and efficacy population	
	Isepamicin	Amikacin	Isepamicin	Amikacin
No.of patient	31	15	20	7
Elimination	28 (90.3%)	14 (93.3%)	19 (95%)	7 (100%)
Elimination with wound infection	5 (16.1%)	1 (6.7%)	4 (20%)	0
Elimination with super infection	2 (6.5%)	0	1 (5%)	0
Elimination with colo nisation	2 (6.5%)	0	2 (10%)	0
Persistance	0	0	0	0
Reinfection	0	0	0	0
Superinfection	0	0	0	0
Indeterminate response	3 (9.7%)	1 (6.7%)	1 (5%)	3 (9.7%)

In the safety and efficacy population, the elimination rates were 95 % (19/20) in isepamicin and 100 % (7/7) in amikacin group. No statistically significant difference was found between these 2 groups.

Fifty-three and 9 strains of microorganisms were isolated from pus and blood, respectively (Table 4). Streptococci (15) and *Staphylococcus epidermidis* (6) were the most commonly isolated pathogens from pus in the present study. These Gram positive cocci constituted 39.6 % (21/53) of the total isolates from pus. The most common pathogen isolated from blood was *Acinetobacter anitratus*, i.e. 55.5 % (5/9).

Table 4. Bacteriologic profile of culture from pus and blood (aerobic)

Pathogens	Number of isolated found in	
	Pus	Blood
Streptococcus α hemolyticus	9	1
Escherichia coli	8	-
Staphylococcus epidermis	6	1
Streptococcus α hemolyticus	5	-
Streptococcus anhemolyticus	1	-
Klebsiella oxytoca	4	1
Klebsiella ozaneae	3	-
Klebsiella pneumoniae	2	-
Pseudomonas aeruginosa	4	-
Acinetobacter anitratus	3	5
Citrobacter freundii	3	-
Proteus mirabilis	3	1
Serratia marcescens	1	-
Actinobacillus sp.	1	-
Total	53	9

The nature and incidences of adverse events of both intent-to-treat and efficacy populations are shown in Table 5. Both isepamicin and amikacin were generally well tolerated and therapy was not withdrawn in any of the 46 patients. In the intent–to-treat population, 8/31 (25.8 %) patients in isepamicin and 2/15 (13.3 %) in amikacin group experienced at least one adverse event during the study. One patient in the isepamicin group became asthmatic and was sent to the Intensive Care Unit for respiratory distress due to broncho-pneumonia. He died later. One had cough which subsided later on without any specific treatment. One with sepsis at admittance was sent to the High Care Unit for acute respiratory distress syndrome with a positive culture of *Pseudomonas aeruginosa*. Perito-nitis was cured in this patient as evidenced by good bowel passage and healing of surgical wound, but he died 9 days after hospitalization because of an ARDS (acute respiratory distress syndrome).

Table 5. Adverse events

Adverse events	Intent-to-treat population		Safety and efficacy population	
	Isepamicin	Amikacin	Isepamicin	Amikacin
Asma	1	-	1	-
Broncho-pneumonia	1	-	1	-
Pneumonia	2	1	1	1
Hematemesis	1	-	1	-
Melena	1	-	1	-
Cough	1	-	1	-
Tachycardia	1	-	1	-
Diarrhea	-	1	-	1
Total	8	2	7	2

One patient with stomach perforation experienced hematemesis 2 days after admission and was then recovered with conservative treatment.

Another patient with perforation of the large intestine experienced melena. He recovered spontaneously.

One patient had pneumonia and tachycardia without any cardiac disturbance.

In the amikacin group, one patient with carcinoma of the cervix as concomitant condition got pneumonia. She recovered after being treated. Another patient suffered from diarrhea due to an amikacin-sensitive *Klebsiella oxytoca* and he recovered without any additional treatment.

All adverse events were considered by the authors as unrelated to treatment. Potential biochemical changes including renal function test were comparable between both treatment groups (Table 6). Increased creatinine blood level for more than 3 times normal value was observed in one patient on amikacin.

Table 5. Adverse events

Adverse events	Intent-to-treat population		Safety and efficacy population	
	Isepamicin	Amikacin	Isepamicin	Amikacin
BUN	3/30 (10%)	2/14 (14.3%)	0/20 (0%)	0/7 (0%)
Creatinine	4/31 (12.9%)	2/14 (14.3%)	0/20 (0%)	1/7 (14.2%)
SGOT	4/31 (12.9%)	3/15 (20%)	4/19 (21.1%)	3/7 (42.9%)
SGPT	3/30 (10%)	2/14 (14.3%)	3/19 (15.8%)	2/7 (28.5%)
Alkaline phosphatase	12/31 (38.7%)	3/14 (21.4%)	6/18 (33.3%)	0/7 (0%)
Total bilirubin	5/31 (16.1%)	1/15 (6.7%)	4/20 (20%)	1/7 (14.2%)

Both mean duration of treatment and length of hospitalization were comparable between both treatment groups (Table 7).

Table 7. Duration of treatment and length of hospitalization (days)

	Intent-to-treat population		Safety and efficacy population	
	Isepamicin	Amikacin	Isepamicin	Amikacin
No.of patient	29	15	18	7
Duration of treatment (Mean ± SD)	7.3 ± 2.1	7.3 ± 2.5	7.6 ± 2.3	7.7 ± 3.7
Length of hospitalization (Mean ± SD)	10.1 ± 3.4	10.5 ± 3.0	10.7 ± 3.9	11.1 ± 3.8

In the intent-to-treat population signs and symptoms of peritonitis (i.e., nausea, vomiting, abdominal pain, tenderness, fever, and cessation of bowel sounds) disappeared in approximately the same duration, i.e. 3.3 ± 1.3 days and 3.8 ± 1.1 days for isepamicin and amikacin group, respectively. The difference was not statistically significant. In the efficacy population these figures are 3.7 ± 1.6 and 3.9 ± 0.9 days, respectively. The difference was also not statistically significant.

Mean peak serum concentration (± SD) of isepamicin and amikacin were 52.5 (± 16.2) and 45.5 (± 30.6) mcg/ml, respectively. None of the amikacin group and one of the isepamicin group had antibiotic serum trough levels of more than 10 mcg/ml.

DISCUSSION

Forty-six patients with intra-abdominal infections were included in this study. Unfortunately only 27 (20 isepamicin, 7 amikacin) could fulfill the inclusion criteria completely and therefore be analized as efficacy population. The other 19 patients (11 isepamicin, 8 amikacin) failed to meet the inclusion criteria due to either resistance to the treatment drugs or negative cultures. The type of microorganisms found in the present study differed somewhat with those commonly reported to cause intra abdominal infections. This is one possibility why 34.8 % of the pathogens isolated in our study were resistant to the study drugs. Most of our subjects with peritonitis were caused by stab wounds. This could be associated with the high incidence of staphylococcal and streptococcal peritonitis in our series. Streptococci are also known as the predominant microflora in the stomach and the proximal part of the small bowel.[5] Twenty out of 46

(43.5%) patients in the intent-to-treat population had stomach or small intestine perforations. This high incidence of proximal part of gastrointestinal perforations could also contribute to the high incidence of streptococci isolated in the present study.

Negative culture was observed in 4 patients. Since clinical signs of bacterial infection were obvious in all of our patients, it is likely that the negative cultures in these cases were associated with handling of the specimens.

Although 16 out of our 46 patients had pathogens resistant to the study drugs, in general the clinical response were satisfactory. Our findings indicate that antibiotic does not appear to be the single determinant to achieve a successful outcome in the management of intra-abdominal infections. Other major issues in the management of intra abdominal infection include surgical correction, drainage, removal of pus and all necrotic tissues from peritoneal cavity, and adequate fluid therapy.

In the intent-to-treat population, cured or improved patients constitute 96.7% and 100% for isepamicin and amikacin, respectively. In the efficacy population, these figures are 95% and 100% for isepamicin and amikacin, respectively. The differences are not statistically significant. Approximately equal results comparing isepamicin versus amikacin (both were also combined with metronidazole) was reported by Del Rozal.[4] The author found clinical cure or improvement rates were 96.3% and 94.3% for isepamicin and amikacin respectively. Other antimicrobial agents have also been compared to treat intra-abdominal infection such as cefotaxime vs gentamicin + clindamycin,[6] cefoxitin vs tobramycin + clindamycin,[7] and aztreonam+clindamycin vs gentamicin+clindamycin.[8] All the regimens compared in these studies also showed approximately the same satisfactory outcome.

In the intent-to-treat group bacteriological elimination rates were 90.3% and 93.3%, respectively. In the efficacy population the figures were 95% and 100%, respectively. None of these differences was statistically significant.

The incidence of adverse events were 8/31 (25.8 %) for isepamicin and 2/15 (13.3%) for the amikacin group, but these were considered by the investigators as not related to treatment. The most common adverse event was respiratory disturbances such as bronchopneumonia, pneumonia, and cough. These conditions were likely associated with patient care. In another study it was reported that the incidences of drug related adverse events for isepamicin and amikacin were equal, i.e. 6% for both drugs.[4] In the intent-to-treat population in our study, the most relevant laboratory values associated with aminoglycosides (i.e., blood creatinine and BUN levels) were slightly higher in the amikacin group although they were not significantly different from those of the isepamicin group (Table 6).

The Minimal Inhibitory Concentration which inhibited 50% of the isolates (MIC_{50}) of isepamicin for *P. aeruginosa* was in the range of 2-16 mcg/ml depending on the calcium and magnesium content in the culture medium.[9] The mean peak concentration of isepamicin (i.e., 52.5 mcg/ml, respectively) was well above this MIC_{50}. We do not, however, attempt to see whether or not the ratio of mean peak concentration : MIC value in this study is above 10 because the blood samples for peak concentration determination was obtained at 15 minutes after the completion of drug infusion (i.e., the alpha phase of the drug distribution in the body). At this point, the blood concentration was representing the distribution in the intravascular compartment rather than the distribution in the whole body.

It is concluded that in the present study, isepamicin 15 mg/kg once daily plus metronidazole was as effective as amikacin 7.5 mg/kg twice daily plus metronidazole in the treatment of intraabdominal infections.

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