(Jpn. J. Hosp. Pharm.)
— 一般論文 —
26(2) 157 — 163 (2000)

Construction and Evaluation of Common Guidelines for Recommended Dosage and Directions for the Use of Drugs in the Hospital —Observing Cases of Carbapenem Antibiotics and Histamine H₂-Receptor Antagonists Administered during Renal Dysfunction—

MITSURU MACHIDA*†¹, KENICHI SAGAWA†¹, SETSUKO MURASE†¹,
HAJIME KAGAYA†², HARUKO KUZUYAMA†³ and SHIGEHICO SHIMADA†³

Department of Pharmacy, Kitasato University Hospital†¹

Department of Pharmacy, Saiseikai Yokohamashi Nambu Hospital†²

School of Pharmaceutical Sciences, Kitasato University†³

(Received June 29, 1999
Accepted December 10, 1999)

The Ministry of Health and Welfare has issued a warning against carbapenem antibiotics regarding, their relationship to central convulsions and renal function, and also against histamine H₂-receptor antagonists as well, regarding their relationship to renal dysfunction, hematological disorders, and other problems. Therefore, the careful administration of such drugs to prevent renal dysfunction is considered particularly important and strict guidelines for use of these drugs have been developed but there has so far been no reports of institutional standardization of these guidelines. The Committee on the Promotion of the Appropriate Use of Medicines, which consists of physicians of various departments in our hospital, prepared unified drug administration guidelines for our hospital, and also examined their usefulness. As a result, these guidelines have proved to be useful, and were found to help reduce the overall health care costs.

Key words — Carbapenem antibiotics, H₂-Receptor antagonists, renal dysfunction, guidelines

Introduction

Physicians of each department design prescriptions suitable for individual patients, but dosage and directions of use for certain organ dysfunction is prescribed based on experience of each physician and information from drug manufacturers at present.

With respect to carbapenem antibiotics, the Ministry of Health and Welfare has issued a warning in the Emergency Safety Information¹⁻³⁾ regarding their relationship to central convulsions and renal function. Regarding histamine H₂-receptor antagonists as well, the Ministry has called attention to their relationship to renal dysfunction and hematological disorders, and other problems several times in the Safety Information of Medicines⁴⁻⁹⁾. For these drugs, administration planning in cases

†¹ 神奈川県相模原市北里1-15-1; 1-15-1, Kitasato, Sagami-hara-shi, Kanagawa, 228-8555 Japan

†² 神奈川県横浜市港南区港南台3-2-10; 3-2-10, Konandai, Konan-ku, Yokohama-shi, Kanagawa, 234-8503 Japan

†³ 東京都港区白金5-9-1; 5-9-1, Shirogane, Minato-ku, Tokyo, 108-8641 Japan

of renal dysfunction is considered particularly important. Side effects of these drugs are frequently attributable to overdosage, or conventional dosage in elderly persons.

In this study, we selected to focus on carbapenem antibiotics and histamine H₂-receptor antagonists, which require appropriate establishment of dosage and directions for use during renal dysfunction, and we surveyed the quantity of these drugs consumed during renal dysfunction in our hospital. Based on the results, we established guidelines for use for physicians to pay attention to appropriate use at the stage of prescription, and prepared guidelines for recommended dosage and directions for use during renal dysfunction, in the Committee on Promotion of Appropriate Use of Medicines organized in our hospital¹⁰⁾. Evaluation of these guidelines are also reported.

Methods

1. The state of use in our hospital (preliminary survey)

During a one-year period (December 1995 to November 1996), the state of use of carbapenem antibiotics (imipenem/cilastatin, panipenem/betamipron, meropenem) and injection of histamine H₂-receptor antagonists (famotidine, ranitidine, cimetidine) was surveyed. The items investigated included daily doses, as well as blood urea nitrogen (BUN) and serum creatinine (S-Cr) from the results of blood tests. Inpatients (renal medical wards, 45 beds) were selected for this study.

2. Preparation of guidelines for recommended dosage and directions for use

The Committee on Promotion of Appropriate Use of Medicines(PAUM), established in 1996 (16 members), prepared guidelines for recommended dosage and directions for use of carbapenem antibiotics and histamine H₂-receptor antagonists during renal dysfunction by collecting information from previous reports¹¹⁻²²⁾, domestic interview forms, and package inserts.

3. Evaluation of the prepared guidelines for recommended dosage and directions for use

The number of cases conforming to guidelines for recommended dosage and directions for use and that of nonconforming cases were examined one year after establishment of the guidelines, in August 1998. The items investigated included the number of overdoses among nonconforming cases, and the amount of drug administered and drug price in each overdose.

Results

1. The state of use in our hospital (preliminary survey)

When patients treated with carbapenem antibiotics and histamine H₂-receptor antagonists in renal medical wards during a one-year period (December 1995 to November 1996) were surveyed, the total number of patients receiving carbapenem antibiotics was 69, consisting of 14 patients receiving imipenem/cilastatin, 29 patients receiving panipenem/betamipron, and 26 patients receiving meropenem. Histamine H₂-receptor antagonists were used in 224 patients, including famotidine in 215 patients, ranitidine in 8 patients, and cimetidine in one patient. Both BUN and S-Cr, laboratory parameters indicative of renal function, were beyond the normal range in 12 patients treated with carbapenem antibiotics (17%), and in 56 patients treated with histamine H₂-receptor antagonists (25%). Among these patients, conventional doses were prescribed in 3 patients receiving carbapenem antibiotics (25%), and 15 patients receiving histamine H₂-receptor antagonists (27%)(Table 1).

2. Evaluation of the guidelines for recommended dosage and directions for use

In our hospital, the Committee on PAUM was inaugurated in January 1996 to examine strategies

Table 1. Preliminary Survey

	Carbapenem antibiotics			
	Imipenem/Cilastatin	Panipenem/Betamipron	Meropenem	
The number of patients showing abnormal BUN and S-Cr	12 (17%)			
The number of patients receiving the conventional dose	3 (25%)			
Total number of patients	14	29	26	sum 69

	Histamine H ₂ -receptor antagonists			
	Famotidine	Ranitidine	Cimetidine	
The number of patients showing abnormal BUN and S-Cr	56 (25%)			
The number of patients receiving the conventional dose	15 (27%)			
Total number of patients	215	8	1	sum 224

patients treated with carbapenem antibiotics and histamine H₂-receptor antagonists in renal medical wards during December 1995 to November 1996

for appropriate use of medicines in the hospital in terms of the efficacy, safety and economical efficiency³⁾. This committee surveyed the state of use of carbapenem antibiotics, which are prone to cause nephropathy, and injection drugs of histamine H₂-receptor antagonists, which are frequently used in the hospital. The results suggest the necessity of appropriate use, and therefore, the committee gathered data from domestic package inserts and interview forms, as well as from foreign papers, to prepare standardized guidelines for use during nephropathy in the hospital (Fig. 1).

The collected literature and materials were 9 pieces for carbapenem antibiotics and 10 pieces for histamine H₂-receptor antagonists. There was one package insert and 3 other documents for imipenem/cilastatin, no documents for panipenem/betamipron, and one package insert and 4 other documents for meropenem. There was one package insert and another document for famotidine, one domestic package insert and 5 other documents for ranitidine, and one package insert and another document for cimetidine.

(Carbapenem antibiotics)

Imipenem/Cilastatin

Panipenem/Betamipron

Creatinine clearance (mL/min)	70-50	50-30	30-10
Recommended dose a time	0.5g	0.25-0.5g	0.125-0.25g
Interdosage interval (h)	12	12-24	12

Meropenem

Creatinine clearance (mL/min)	70-50	50-30	30-10
Recommended dose a time	0.25-0.5g	0.25-0.5g	0.25-0.5g
Interdosage interval (h)	8-12	12	24

(Histamine H₂-receptor antagonists)

Cimetidine

Creatinine clearance (mL/min)	50-10	10 or less
Recommended dose a day	75% of the conventional dose	50% of the conventional dose

Famotidine

Creatinine clearance (mL/min)	60 or more	60-31	30 or less
Recommended dose	20mg a time, twice a day	10mg a time, twice a day	10mg a time, once a day

Ranitidine

Creatinine clearance (mL/min)	Below 50
Recommended dose (i.v.)	50mg a time at the interval of 18-24 hours

Fig. 1. Guidelines for Recommended Dosage and Directions for Use of Carbapenem Antibiotics and Histamine H₂-Receptor Antagonists during Renal Dysfunction

Table 2. Conformity to the Guidelines

	Carbapenem antibiotics			sum	
	Imipenem/Cilastatin	Panipenem/Betamipron	Meropenem		
Conforming patients	15 (65%)	22 (81%)	0	37 (74%)	
Nonconforming patients	8 (35%)	5 (19%)	0	13 (26%)	
1) The number of overdoses	3	5	0	8	
2) Amount of drug administered/overdose	1.0g	1.0g			
3) Drug price/overdose	¥4,854	¥4,191.67			
sum	23 (46%)	27 (54%)	0	50	

	Histamine H ₂ -receptor antagonists			sum	Inclusive sum
	Famotidine	Ranitidine	Cimetidine		
Conforming patients	41 (43%)	12 (35%)	3 (10%)	56 (35%)	93 (44%)
Nonconforming patients	54 (57%)	22 (65%)	28 (90%)	104 (65%)	117 (56%)
1) The number of overdoses	26	4	2	32	38
2) Amount of drug administered/overdose	20.769mg	100mg	200mg		
3) Drug price/overdose	¥526.15	¥480	¥216		
sum	95 (60%)	34 (21%)	31 (19%)	160	210

In August 1998, about one year after the standardized guidelines were prepared, the conformity to the guidelines was surveyed and evaluated by examining injection prescriptions in all wards.

Data of these documents suggest the necessity of guidelines for recommended dosage and directions for use during renal dysfunction, and therefore, standardized guidelines were prepared and approved by the Pharmaceutical Affairs Committee. Moreover, we constructed a system in which when physicians select drugs corresponding to the guidelines while ordering prescriptions by computer, they can refer to the guidelines by pressing a single key.

With respect to preparation of the guidelines, opinions of the committee on PAUM's members of each department were considered, but guidelines for use recommended in more than one paper were given priority.

3. Evaluation of the prepared guidelines for recommended dosage and directions for use

In August 1998, about one year after the standardized guidelines were prepared, the conformity to the guidelines was surveyed and evaluated by examining injection prescriptions in all wards (Table 2). The total number of patients investigated was 210, consisting of 50 patients treated with carbapenem antibiotics and 160 patients treated with histamine H₂-receptor antagonists. Among these patients, the guidelines for use were satisfactorily followed in 37 patients (74%) receiving carbapenem antibiotics, including 15 patients (65%) receiving imipenem/cilastatin, 22 patients (81%) receiving panipenem/betamipron, and 0 patients receiving meropenem.

Regarding histamine H₂-receptor antagonists, the guidelines were followed in 56 patients (35%), including 41 patients (43%) receiving famotidine, 12 patients (35%) receiving ranitidine, and 3 patients (10%) receiving cimetidine. The number of overdoses among patients nonconformed to the guidelines were not followed was 6 (46%) for carbapenem antibiotics, consisting of 3 patients (38%) receiving imipenem/cilastatin and 3 patients (60%) receiving panipenem/betamipron, and 32 (31%) for histamine H₂-receptor antagonists, consisting of 26 patients (48%) receiving famotidine, 4 patients (18%) receiving ranitidine, and 2 patients (7%) receiving cimetidine.

Discussion

Physicians prescribe drugs, considering the condition of patients, severity of diseases, and other factors. However, it is very difficult to determine doses of drugs during organ dysfunction, and many physicians experience trouble during such times.

Information from pharmaceutical manufacture alone is insufficient, and we have encountered difficulties in finding relevant foreign literature as well. Recently, as a duty of drug management and guidance, pharmacists have been visiting wards for patient compliance instruction, by which they are able to directly collect information from patients, and feed the information back to physicians and nurses, contributing to the appropriate use of drugs. Simultaneously, pharmacists check prescriptions in individual patients (internal medicines, injection drugs) with the aim of medical and pharmaceutical care that pays more attention to patients. However, sufficient information is not always offered to physicians in all institutions. Therefore, if physicians could easily refer to standardized guidelines for use approved in the hospital when drugs have to be prescribed in case of urgent need, or absence of pharmacists, not only information offered to physicians would be satisfactory, but also malpractice in patients would be prevented. In collaboration with a committee organized by physicians of departments, we prepared standardized guidelines. These guidelines are important to promote appropriate use of drugs, and are useful as well, since required contents can be readily referred to in this system.

To prepare guidelines for recommended dosage and directions for use, cooperation of specialized physicians is crucial, and sufficient search of literature paper is also required. In our hospital, therefore, the Committee on Promotion of Appropriate Use of Medicines organized by physicians in departments was established in 1996, aiming at appropriate use of drugs in the hospital. In accordance with this committee's instruction, the state of use of the guidelines for recommended dosage and directions for use was investigated for one year after the guidelines were prepared. As the preliminary step in this process, an interim survey was carried out in all wards half a year after the guidelines for recommended dosage and directions for use were installed in the computer. During a one-week period between June 15 and June 22, 1997, carbapenem antibiotics had been administered to 33 patients, consisting of 14 patients for imipenem/cilastatin, 11 patients for panipenem/betamipron, and 8 patients for meropenem (Table 3). Injection drugs of histamine H₂-receptor antagonists had been used in 65 patients, including 47 patients for famotidine, 11 patients for ranitidine, and 7 patients for cimetidine. The conformity to the guidelines for recommended dosage and directions for use was evaluated using the daily dose and creatinine clearance at the time of administration. The results showed, among patients receiving carbapenem antibiotics, 6 conforming patients (44%), 4 nonconforming patients (28%), and 4 indistinguishable patients (28%) for imi-

Table 3. Conformity to the Guidelines (interim report)

	Carbapenem antibiotics			sum
	Imipenem/Cilastatin	Panipenem/Betamipron	Meropenem	
Conforming patients	6 (44%)	4 (36%)	2 (25%)	12 (36%)
Nonconforming patients	4 (28%)	2 (18%)	4 (50%)	10 (30%)
Indistinguishable patients	4 (28%)	5 (46%)	11 (34%)	11 (34%)
sum	14 (43%)	11 (33%)	8 (24%)	33

	Histamine H ₂ -receptor antagonists			sum	Inclusive sum
	Famotidine	Ranitidine	Cimetidine		
Conforming patients	26 (42%)	8 (62%)	5 (71%)	39 (60%)	51 (52%)
Nonconforming patients	0	0	0	0	10 (10%)
Indistinguishable patients	21 (58%)	3 (38%)	26 (40%)	26 (40%)	37 (38%)
sum	47 (72%)	11 (17%)	7 (11%)	65	98

An interim survey was carried out in all wards half a year after the guidelines for recommended dosage and directions for use were installed in the computer. During a one-week period between June 15 and June 22, 1997.

penem/cilastatin, 4 conforming patients (36%), 2 nonconforming patients (18%), and 5 indistinguishable patients (45%) for panipenem/betamipron, and 2 conforming patients (25%), 4 nonconforming patients (50%), and 2 indistinguishable patients (25%) for meropenem. With respect to patients receiving histamine H₂-receptor antagonists, there were 26 conforming patients (42%) for famotidine, 12 (35%) for ranitidine, and 3 (10%) for cimetidine. In indistinguishable patients, basic data were too insufficient to calculate the creatinine clearance.

When the conformities at the time of the interim survey and one year later were compared, the conformity to the guideline for carbapenem antibiotics had increased from 36% to 74%, but that for histamine H₂-receptor antagonists was unchanged or decreased. This result is considered to be attributable to differences in the frequency of use of these drugs. Carbapenem antibiotics were consumed in 69 patients per year in one ward (45 beds), while histamine H₂-receptor antagonists were used in 224 patients. In all wards (1,069 beds), carbapenem antibiotics were consumed in 50 patients per month, while histamine H₂-receptor antagonists were used in 210 patients, indicating that the frequency of use of histamine H₂-receptor antagonists is approximately 4 times that of carbapenem antibiotics. The reason was considered to have been due to differences in indications. Namely, histamine H₂-receptor antagonists are among the few drugs that can be indicated in peptic ulcer cases as injection drugs, and are ranked as drugs that are easily prescribed and can induce beneficial effects in the clinic compared with internal medicine. Moreover, differences in the severity of side effects are also considered. Among carbapenem antibiotics, imipenem/cilastatin has been reported to include central convulsions as a side effect in the Emergency Safety Information by the Ministry of Health and Welfare, suggesting a high interest level of physicians in the clinic about these drugs. In contrast, histamine H₂-receptor antagonists have been frequently reported in the Safety Information of Medicines, but the awareness of its exigency is low, causing a lower interest level of physicians in the clinic.

In such circumstances, it is important to call more attention to histamine H₂-receptor antagonists. Furthermore, considering that internal medicines with the same ingredient are sold as over-the-counter drugs, and insufficient explanation to patients has become an object of public concern, it is important that their safety be ensured by medical institutions. The number of conforming patients were 39 in the interim survey, but increased to 56 in the survey one year later, suggesting importance of these guidelines.

When comparing in terms of the economical efficiency, the number of conforming patients increased from 12 to 37 for carbapenem antibiotics, and approximately 112,500 yen of the health care cost was reduced. For histamine H₂-receptor antagonists, taking famotidine for example, the reduction was about 7,800 yen. Since the guideline are values for one year, more money would be saved by these guidelines in the future.

However, overdosage according to these guidelines for recommended dosage and directions for use was noted in 13 patients receiving carbapenem antibiotics and 104 patients treated with histamine H₂-receptor antagonists. The amount of drug administered in each overdose was 1 g for carbapenem antibiotics and 100-200 mg for histamine H₂-receptor antagonists.

Preparation of these guidelines for recommended dosage and directions for use proceeded in accordance with the concept of DUE performed in the United States. It is controversial whether the style of the United States could be adopted in Japan, considering the differences in the medical in-

surance systems. The guidelines for recommended dosage and directions for use approved in the hospital are predicted to sufficiently accommodate to medical system reform in the future. However, it is important that the guidelines for recommended dosage and directions for use be used, repeatedly examined, and evaluated in the future. Construction of standardized guidelines for recommended dosage and directions for use during renal dysfunction in hospitals such as we did is considered crucial to deal with medical system reform in the future and avoid severe side effects.

References

- 1) Emergency Safety Information proposed by the Ministry of Health and Welfare, **10** (1989).
- 2) Information of Adverse Drug Reactions proposed by the Ministry of Health and Welfare, No. **93**, 10 (1988).
- 3) Information of Adverse Drug Reactions proposed by the Ministry of Health and Welfare, No. **99**, 10 (1989).
- 4) Information of Adverse Drug Reactions proposed by the Ministry of Health and Welfare, No. **70**, 12 (1984).
- 5) Information of Adverse Drug Reactions proposed by the Ministry of Health and Welfare, No. **94**, 1 (1989).
- 6) Information of Adverse Drug Reactions proposed by the Ministry of Health and Welfare, No. **58**, 12 (1982).
- 7) Information of Adverse Drug Reactions proposed by the Ministry of Health and Welfare, No. **95**, 3 (1989).
- 8) Information of Adverse Drug Reactions proposed by the Ministry of Health and Welfare, No. **79**, 6 (1986).
- 9) Information of Adverse Drug Reactions proposed by the Ministry of Health and Welfare, No. **94**, 1 (1989).
- 10) The 7 th clinical pharmacy symposium, Abstracts, 95-96 (1998).
- 11) Kumon. H, et al., *Jpn. J. Antibiotics.*, **40** (9), 1571-1583 (1987).
- 12) TP. Gibson, et al., *Am. J. Med.*, **78** (Suppl 6 A), 54-61 (1985).
- 13) GA. Verpooten, et al., *Br. J. Clin. Pharmacol.*, **18**, 183-193 (1984).
- 14) M. Chimata, et al., *Antimicrob Agents Chemother*, **37** (2), 229-233 (1993).
- 15) BA. Christensson, et al., *Antimicrob Agents Chemother*, **36**, 1532-1537 (1992).
- 16) A. Leroy, et al., *Antimicrob Agents Chemother*, **36**, 2794-2798 (1992).
- 17) A. Leroy, et al., *Eur. J. Clin. Pharmacol.*, **42**, 535-538 (1992).
- 18) WM. Bennett, et al., "American College of Physicians", 1987.
- 19) A.Ebihara, *Rinsho Iyaku*, **8**, 11 (1992).
- 20) McGonigle RJS, Williams LC, et al., "Medicine Publishing Foundation", Oxford, 1982, pp.41-47.
- 21) A. Ebihara, et al., *Int. J. Clin. Pharmacol. Res.*, **9**, 1-7 (1989).
- 22) M. Feldman, ME.Burton, *N. Engl. J. Med.*, **323** (24), 1672-1680 (1990).